Vaping Dangers 2019: Cigarette Alternative Linked To Heart Attack, High Blood And Others

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By Johnny Vatican April 4, 2019

The electronic cigarette or e-cigarette we know today was invented by a Chinese pharmacist named Hon Lik in 2003.

When first sold in 2004, e-cigarettes were marketed as a healthy alternative to smoking since the e-liquid generating the smoke-like vapor was claimed to contain small quantities of nicotine. Vaping was claimed to help tobacco smokers quit smoking.

In the 15 years since, e-cigarettes are still with us but in enormous numbers, and they are mostly made in China. But the health dangers posed by vaping are now more clearly understood.

The verdict by doctors and scientists based on a growing body of knowledge: Vaping is dangerous to the health of users and might be more dangerous than smoking tobacco in the long run.

Researchers such as Maciej Goniewicz, one of the leading e-cigarette researchers based at Roswell Park Comprehensive Cancer Center New York, are now finding out that e-cigarettes may be more dangerous than expected, especially for the heart, lungs and brain. They're also trying to determine what impact vaping has on developing bodies and brains.

What these researchers agree on is that vapers are overwhelmingly young people who are in their teens up to early 30s. And many vapers weren't even smokers when they started the habit, a clear indication vaping is indeed addictive.

Researchers also agree that vaping is a health danger. And why is this so?

Among the most serious dangers posed by vaping is a probable link to an increased risk of seizures because a lot of e-liquids today, especially Juul (the market leader) contain too much liquid nicotine. Juul has even admitted that one of its e-liquid pods is equal to a pack of cigarettes in terms of nicotine.

The U.S. Food and Drug Administration (FDA) has warned that nicotine-induced seizures could be a side effect of vaping, albeit a rare one. There have been at least 35 reports of seizures in the U.S. over the past decade following e-cigarette use.

Although this number might not seem large, it is disturbing since it opens the possibility that an otherwise healthy user might be stricken by a sudden, life-threatening seizure. Researchers have long known seizures can be a side effect of nicotine poisoning.

"While 35 cases may not seem like much compared to the total number of people using e-cigarettes, we are nonetheless concerned by these reported cases," FDA administrator Dr. Scott Gottlieb said. "We also recognize that not all of the cases may be reported."

Dr. Gottlieb noted the FDA is calling for more investigation into whether there is a connection between vaping and seizures. It urges doctors and the public to come forward if they know about cases.

Doctors also said the nicotine in e-cigarettes may stress the cardiovascular system.

“Nicotine (in e-cigarettes) does the same thing as (tobacco) cigarettes,” Dr. Neal Benowitz, a professor of medicine at the University of California San Francisco who studies the link between e-cigarettes and heart health, said.

The nicotine in an e-liquid can boost the adrenaline in our bodies and activate the sympathetic nervous system (or the “fight or flight” response). This raises blood pressure and accelerates the heart rate, causing the arteries carrying blood away from the heart to narrow.

The U.S. Centers for Disease Control and Prevention (CDC) has never stopped warning about the dangers posed by nicotine to young people, whether this nicotine be in an e-cigarette or in a common tobacco cigarette.

CDC affirmed most e-cigarettes contain nicotine, which can harm the developing adolescent brain. It said the brain keeps developing until about age 25. Using nicotine in adolescence can also harm the parts of the brain that control attention, learning, mood and impulse control.

The center also pointed out that young people who use e-cigarettes might be more likely to smoke cigarettes in the future.

OPINION
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Dr. Marc Siegel: More dangers of e-cigarettes are coming to light



By Dr. Marc Siegel | Fox News

FDA investigating possible correlation between vaping and seizures

U.S. health officials are investigating whether electronic cigarettes may trigger seizures in some people who use the nicotine-vaping devices; insight from Dr. Marc Siegel, Fox News medical contributor.

There was more evidence this week that the electronic cigarettes used by millions of American teens pose **serious health risks**. E-cigarettes are battery-powered devices that in most cases heat a flavored nicotine solution, turning it into a vapor that can be inhaled – a practice known as vaping. The e-cigarettes differ in how much nicotine they deliver.

Dr. Scott Gottlieb, who stepped down Friday as Food and Drug Administration commissioner, issued a powerful statement Wednesday revealing that 35 users of e-cigarettes had **seizures** after vaping between 2010 and this year.

There are many unknowns regarding e-cigarettes. **Now we can add a possible association with seizures to the list.**

DR. SIEGEL: VAPING AMONG TEENS IS SKYROCKETING -- WE MUST DO MORE TO ADDRESS THIS EPIDEMIC

We don't know how many more seizures experienced by users of the devices were never reported. **We don't know** if the process of vaping itself or nicotine from the vapor caused the seizures. **We also don't know** how much vaping in a single session would be enough to cause a potential problem.

Recent studies in animals have shown that high amounts of **nicotine in the brain can trigger seizures and brain injuries.**

There is clearly no free lunch with e-cigarettes. You should not consider them to be harmless devices with no health impacts.

Gottlieb said a recent large toxicology study **showed that the impact of vaping on the lungs includes the development of inflammation and pre-malignant changes.**

There is clearly no free lunch with e-cigarettes. You should not consider them to be harmless devices with no health impacts.

According to the National Youth Tobacco Survey, more than 3.6 million middle and high school students used e-cigarettes in 2018, making the devices the most commonly used tobacco product among this age group**. This turns out to be a stunning 78 percent increase in e-cigarette use among high school students and a 48 percent increase among middle school student use over the previous year.**

The increase comes **despite the fact** that it is illegal to sell e-cigarettes to minors.

Not only is vaping potentially harmful – it is also a gateway drug to tobacco. Studies have shown that teens who vape are **nearly four times more likely to start smoking** cigarettes than those who don't.

Gottlieb has been a key player in the fight against the e-cigarette epidemic among teens. I spoke to him in a final interview as FDA commissioner about the new seizure concern.

"It is a very early signal," Gottlieb told me. "But we are concerned that there are a lot of cases that aren't being reported to us. By going out with this signal now, if there are other similar experiences we are encouraging other doctors and parents to start reporting them to us."

Gottlieb called new information coming to light about e-cigarettes "public health 101." The new report of seizures associated with vaping is a small signal, with no evidence yet of a causal relationship, but raises enough of a concern to prompt additional reporting and study.

In my medical practice, I have developed a somewhat effective approach to recalcitrant smokers. I use a combination of a nicotine patch during the day with e-cigarettes, usually with a tobacco or menthol flavor, for breakthrough urges.

I tell my patients to choose e-cigarettes that look and feel as much like tobacco as possible. Recent studies have confirmed the usefulness of the devices as a smoking cessation tool.

But the problem isn't with adult smokers using e-cigarettes to help them quit. The problem is with our middle schoolers and high schoolers turning to e-cigarettes.

My 14-year-old tells me that some kids use two or three pods of JUUL (the most popular e-cigarette brand) per day, which is the equivalent – in terms of nicotine – of at least two to three packs of traditional cigarettes per day.

Fighting e-cigarette use and nicotine addiction may end up being Gottlieb's most important legacy in his two-year stint as FDA commissioner. Unfortunately, despite his best efforts, the problem continues to grow.

A rare association of e-cigarette use with seizures is just the tip of the iceberg. My prediction is that despite the lung-damaging risks of formaldehyde, propylene glycol, silicate particles and metals found in e-cigarette vapor, the biggest risk of all will always be the link to tobacco use, where the tar in cigarettes directly causes emphysema and lung cancer.

A big thanks should go to now-former FDA Commissioner Scott Gottlieb for calling our attention to the dangers of e-cigarettes, along with his many other accomplishments. He has been an important foot soldier in the war for public health.

CLICK HERE TO READ MORE FROM DR. MARC SIEGEL

Marc Siegel, M.D. is a professor of medicine and medical director of Doctor Radio at NYU Langone Medical Center. He is a Fox News Medical Analyst. Follow him on Twitter @drmarcsiegel.

Article from a member of the public

CERTIFICATION

The following ENDs, HNB and associated nicotine addiction dispenser Gizmos products have been certified for human NRT use by the US FDA, MHRA UK, EMA Europe and TGA Australia for Nicotine Replacement Therapy use and associated health claims:

(as at 01 April 2019)

List of Certified Products:

NONE Certified

Caveat Emptor

Caveat Utilitor



Champix

Procedural steps taken and scientific information after the authorisation

Application number	Scope	Opinion / Notification [1] issued on	Commission Decision Issued [2] / amended on	Product Information affected [3]	Summary
IAIN/0073	C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation	21/09/2018		SmPC and PL	
T/0071	Transfer of Marketing Authorisation	11/07/2018	30/07/2018	SmPC, Labelling and PL	
IB/0070/G	This was an application for a group of variations.	11/04/2018	31/05/2018	Annex II, Labelling and	

[1] Notifications are issued for type I variations and Article 61(3) notifications (unless part of a group including a type II variation or extension application or a worksharing application). Opinions are issued for all other procedures.
[2] A Commission decision (CD) is issued for procedures that affect the terms of the marketing authorisation (e.g. summary of product characteristics, annex II, labelling, package leaflet). The CD is issued within two months of the opinion for variations falling under the scope of Article 23.1a(a) of Regulation (EU) No. 712/2012, or within one year for other procedures.
[3] SmPC (Summary of Product Characteristics), Annex II, Labelling, PL (Package Leaflet).

	B.II.b.1.a - Replacement or addition of a manufacturing site for the FP - Secondary packaging site B.II.b.1.b - Replacement or addition of a manufacturing site for the FP - Primary packaging site B.II.b.1.e - Replacement or addition of a manufacturing site for the FP - Site where any manufacturing operation(s) take place, except batch-release, batch control, primary and secondary packaging, for non-sterile medicinal products B.II.b.2.c.2 - Change to importer, batch release arrangements and quality control testing of the FP - Including batch control/testing B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.3.a - Change in the manufacturing process of the finished or intermediate product - Minor change in the manufacturing process B.II.b.4.z - Change in the batch size (including batch size ranges) of the finished product - Other variation B.II.d.1.z - Change in the specification parameters and/or limits of the finished product - Other variation B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure			PL	

	B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.2.d - Change in test procedure for the finished product - Other changes to a test procedure (including replacement or addition) B.II.d.2.e - Change in test procedure for the finished product - Update of the test procedure to comply with the updated general monograph in the Ph. Eur. B.II.e.2.z - Change in the specification parameters and/or limits of the immediate packaging of the finished product - Other variation B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes				
IB/0069/G	This was an application for a group of variations. B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes B.II.e.5.a.2 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change outside the range of the currently approved pack sizes	12/01/2018	31/05/2018	SmPC, Labelling and PL	
PSUSA/3099/ 201705	Periodic Safety Update EU Single assessment - varenicline	11/01/2018	n/a		PRAC Recommendation - maintenance

IB/0067/G	This was an application for a group of variations. B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.1.i - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Introduction of a new site of micronisation B.I.a.2.a - Changes in the manufacturing process of the AS - Minor change in the manufacturing process of the AS B.I.b.2.a - Change in test procedure for AS or starting material/reagent/intermediate - Minor changes to an approved test procedure B.I.c.1.z - Change in immediate packaging of the AS - Other variation B.I.c.3.a - Change in test procedure for the immediate packaging of the AS - Minor changes to an approved test procedure	13/07/2017	n/a		
II/0066	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	09/06/2017	31/05/2018	SmPC	Section 5.1 of the Summary of Product Characteristics (SmPC) for Champix has been revised and now includes a description of the results of Study A3051148.

II/0064	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	09/06/2017	31/05/2018	SmPC, Labelling and PL	The product information for Champix was amended to include the addition of information regarding Study A3051078 (Varenicline Pregnancy Cohort Study), a prospective population-based cohort study comparing the occurrence of major congenital malformations among infants exposed and not exposed to varenicline in utero in mothers who smoked. Changes were made to Section 4.6 (Fertility, pregnancy and lactation) and Section 5.1 (Pharmacodynamic properties). In particular, to convey that it is preferable to avoid the use of Champix while pregnant, Section 4.6 now reads: “A moderate amount of data on pregnant women indicated no malformative or foetal/neonatal toxicity of varenicline. Animal studies have shown reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of varenicline during pregnancy.”
N/0063	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	28/07/2016	31/05/2018	Labelling and PL	
R/0061	Renewal of the marketing authorisation.	28/04/2016	29/06/2016	SmPC, Annex II, Labelling and PL	Based on the review of data on quality, safety and efficacy, the CHMP considered that the benefit-risk balance of Champix in the approved indication remains favourable and therefore recommended the renewal of the marketing authorisation with unlimited validity.
II/0062	The MAH submitted the final study report of study A3051123 and updated sections 4.4 and 5.1 of the SmPC to reflect the study results. Annex II, package leaflet and Risk Management Plan were also updated accordingly. In addition, the MAH took the opportunity to remove the Black Triangle and to introduce minor	28/04/2016	29/06/2016	SmPC, Annex II, Labelling and PL	Varenicline was evaluated in a randomised, double-blind, active and placebo-controlled study that included subjects with a history of psychiatric disorder (psychiatric cohort, N=4074) and subjects without a history of psychiatric disorder (non-psychiatric cohort, N=3984). The conducted Study A3051123 showed that varenicline had

	amendments to the labelling. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				efficacy both in smokers with or without a prior history of psychiatric disorder. The adverse events profile of varenicline in A3051123 corresponded with the varenicline known safety profile. Varenicline was not associated with a greater risk of suicide-related events, or with a greater risk of other clinically significant neuropsychiatric events, compared to placebo or to bupropion or nicotine replacement therapy. This was the case in smokers with or without a prior history of psychiatric disorder.
IA/0060	A.7 - Administrative change - Deletion of manufacturing sites	03/12/2015	n/a		
N/0059	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	20/11/2015	17/05/2016	Labelling and PL	
N/0058	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	24/06/2015	17/05/2016	PL	
II/0057	Update of sections 4.4 and 5.1 of the SmPC in order to include information on Neuropsychiatric Safety (NPS) analyses of clinical studies and from observational studies. The MAH took the opportunity to implement minor editorial changes in the SmPC. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	21/05/2015	17/05/2016	SmPC	Analyses of clinical trial data did not show evidence of an increased risk of serious neuropsychiatric events with varenicline compared to placebo. In addition, independent observational studies have not supported an increased risk of serious neuropsychiatric events in patients treated with varenicline compared to patients prescribed nicotine replacement therapy (NRT) or bupropion.
II/0056	Update of section 4.5 of the SmPC in order to include further information on alcohol interaction after	21/05/2015	17/05/2016	SmPC and PL	There have been post marketing reports of increased intoxicating effects of alcohol in patients treated with

	analysis of post marketing data. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data				varenicline. A causal relationship between these events and varenicline use has not been established.
PSUV/0054	Periodic Safety Update	04/12/2014	n/a		PRAC Recommendation - maintenance
II/0053	Update of sections 4.2 and 5.1 of the SmPC based on data from Study A3051075, a Phase 4, multi-national, randomized, double-blind, placebo-controlled study to evaluate the efficacy and safety of varenicline compared to placebo for smoking cessation through reduction. The Package Leaflet is updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/11/2014	11/02/2015	SmPC and PL	This variation application is based on data from Study A3051075, a double-blind, placebo-controlled study to evaluate the efficacy and safety of varenicline compared to placebo for smoking cessation through reduction, which enrolled smokers who were not able or willing to quit abruptly. Subjects gradually reduced the number of cigarettes smoked over a 12-week treatment period prior to quitting and to continue with another 12 weeks of treatment. The study demonstrated that a gradual quit approach, with a reduction in the number of cigarettes smoked prior to quitting has efficacy for smokers who will not or cannot quit smoking abruptly. New safety concerns for varenicline use would not be expected using this approach, and the study did not give rise to new safety concerns. The CHMP considered that Champix has a positive benefit/risk balance in smokers who will not/cannot quit smoking abruptly.
IAIN/0055	A.5.a - Administrative change - Change in the name and/or address of a manufacturer/importer responsible for batch release	23/10/2014	11/02/2015	Annex II and PL	
II/0051	Update of Annex II based on submission of the final	25/09/2014	11/02/2015	Annex II	As requested by the CHMP, the MAH has conducted

	Report on Overall Evaluation of Psychiatric Events from pooled data from five clinical studies (A30151072, A3051115, A3051095, A3051122 and A3051139). C.I.11.b - Introduction of, or change(s) to, the obligations and conditions of a marketing authorisation, including the RMP - Implementation of change(s) which require to be further substantiated by new additional data to be submitted by the MAH where significant assessment is required				meta-analyses, pooling data regarding risk of suicide and/or psychiatric symptoms from 5 randomized, placebo controlled studies of varenicline, rating study subjects with the Columbia Suicide Severity Rating Scale, as well as data reported from the total of 18 randomized, placebo controlled varenicline studies. These analyses do not show statistically significant differences between varenicline and placebo in the incidence rates of suicidal ideation or behaviour, in the incidence rate of hostility/aggression, or in the incidence rates of various psychiatric symptoms/disorders with the exception of sleep related symptoms. There were no clinical results reported from the studies that give rise to concern. The results from study A3051122, a study of stable patients with depressive disorder where special emphasis was placed on retrieving information about the incidence of hostility/aggression, suggest that hostility and increased aggression is perhaps more common in subjects treated for smoking tobacco/nicotine dependence than has previously been reported. In study A3051122 the incidence of these symptoms was higher in the varenicline-treated group, but it is plausible that this may in part be a result of varenicline-treated subjects reducing their tobacco/nicotine consumption. Moreover, as stated above, the overall meta-analysis of hostility/aggression does not show an increased risk associated with varenicline compared with placebo. The MAH's obligation to conduct the post-authorisation measure was fulfilled, without new concerns about suicidality or psychiatric events arising. The results do not change the positive benefit-risk balance of varenicline. The

					corresponding obligation was deleted from Annex II.
IA/0052	A.4 - Administrative change - Change in the name and/or address of a manufacturer or an ASMF holder or supplier of the AS, starting material, reagent or intermediate used in the manufacture of the AS or manufacturer of a novel excipient	25/04/2014	n/a		
II/0049	Update of section 4.8 of the SmPC in order to update the safety information, including a re-assessment of the Adverse Reactions profile based on pooled data from 18 placebo-controlled pre- and post-marketing studies with varenicline. The Package Leaflet (section 4) was updated accordingly. C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	20/02/2014	11/02/2015	SmPC and PL	To account for the completion of new clinical studies since approval of Champix in 2006, the MAH conducted an exercise to determine if the profile of Adverse Drug Reactions (ADRs) listed in the Product Information (SmPC and PL) remained accurate. To this end, pooled safety data from 18 placebo-controlled studies including over 5000 patients treated with varenicline were analysed based on the all-causality adverse events set. As a result, 13 side effects had their frequency categorization upgraded and 34 side effects had their frequency categorization downgraded. In addition, 12 new side effects were added to the product information, namely: Conjunctivitis, Angina pectoris, Tachycardia, Hot flush, Upper respiratory tract inflammation, Rhinitis allergic, Toothache, Arthralgia, Myalgia, Back pain, Pollakiuria (frequent daytime urination) and Influenza like illness.
PSUV/0050	Periodic Safety Update	05/12/2013	n/a		Update of section 4.4 and 4.8 of the SmPC with regard to seizure related events. The update included a warning in section 4.4 regarding seizures in patients with or without a history of seizures, and addition of ‘seizures’ in section 4.8, under the class nervous system disorders, with a frequency of uncommon. This frequency was calculated from the clinical trials data set.

					The Package Leaflet was updated accordingly.
II/0047	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	21/11/2013	06/06/2014	SmPC	The effectiveness of re-treatment with varenicline has not previously been studied in full-scale clinical trials. Study A3051139 was designed to compare the efficacy and safety of re-treatment with varenicline with placebo in subjects who had previously taken varenicline and had been unable to stop smoking or who had relapsed. This study provided evidence that re-treatment with varenicline can benefit smokers who either failed to quit while taking varenicline or relapsed after taking it. Re-treatment with varenicline was generally well-tolerated, with a safety profile consistent with previous studies of varenicline-naïve subjects and did not reveal any new safety concerns. The following text was added to section 4.2 of the SmPC: “Patients who are motivated to quit and who did not succeed in stopping smoking during prior Champix therapy, or who relapsed after treatment, may benefit from another quit attempt with Champix”.
IB/0048/G	This was an application for a group of variations. B.II.f.1.b.1 - Stability of FP - Extension of the shelf life of the finished product - As packaged for sale (supported by real time data) B.II.f.1.d - Stability of FP - Change in storage conditions of the finished product or the diluted/reconstituted product	14/11/2013	06/06/2014	SmPC	

IB/0046/G	This was an application for a group of variations. B.II.d.z - Change in control of the Finished Product - Other variation B.II.d.z - Change in control of the Finished Product - Other variation	04/09/2013	n/a		
II/0045	Revision of Section 4.4 Special warnings and precautions for use and Section 5.1 Pharmacodynamic properties of the SmPC to reflect data from a completed clinical study (A3051122) to measure the Safety and Efficacy of Champix for Smoking Cessation in people with depression. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	27/06/2013	06/06/2014	SmPC, Annex II, Labelling and PL	The results of the Study A3051122 showed that varenicline is effective for smoking cessation in patients with major depressive disorder on stable antidepressant treatment and/or who had a major depressive episode in the previous 2 years and were successfully treated. With regards to Safety, the analyses of the psychiatric measurement did not reveal differences between varenicline and placebo and showed no overall worsening of depression in either treatment group. Section 4.4 was updated to reflect the data, and the study results are now presented in Section 5.1.
II/0043/G	This was an application for a group of variations. To add a new specification for a specified impurity. To add a new alternative blister packaging material (PVC/alu) To add new presentations within the range of the currently approved pack sizes with the new alternative blister packaging material (PVC/alu). B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms B.II.d.1.e - Change in the specification parameters and/or limits of the finished product - Change outside	21/02/2013	06/06/2014	SmPC and Labelling	

	the approved specifications limits range B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of				

	the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes B.II.e.5.a.1 - Change in pack size of the finished product - Change in the number of units (e.g. tablets, ampoules, etc.) in a pack - Change within the range of the currently approved pack sizes				
IG/0235/G	This was an application for a group of variations. C.I.z - Changes (Safety/Efficacy) of Human and Veterinary Medicinal Products - Other variation C.I.9.b - Changes to an existing pharmacovigilance system as described in the DDPS - Change in the contact details of the QPPV	06/12/2012	n/a		C.I.z - To replace the Detailed Description of the Pharmacovigilance System (DDPS) with the Pharmacovigilance System Master File (PSMF).
II/0041	Update of sections 4.4 and 5.1 of the SmPC to update the safety information with data emerging from a meta-analysis of Cardiovascular events. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	18/10/2012	19/11/2012	SmPC and PL	This type II variation updated the Summary of Product Characteristics (SmPC) following completion of a pooled analysis of cardiovascular (heart or blood vessel) side effects in controlled varenicline clinical studies. The CHMP supported that the analysis should be mentioned in the SmPC, with a description including its main results and mentioning the fact that the increase in risk observed with Champix was higher in patients with higher cardiovascular risk than in patients with lower cardiovascular risk. The SmPC now details the results of the analysis. The CHMP considered that the data assessed on the cardiovascular effects do not change the benefit-risk balance for Champix in smoking cessation in adults and that the revised wording of the product information adequately reflects the main findings of the CV meta-analysis.

					Section 2 of the Package Leaflet: Information for the User, Take care with CHAMPIX, was amended to reflect changes made to section 4.4 and section 5.1 of the SmPC, and now reads: Cardiovascular symptoms New or worse heart or blood vessel (cardiovascular) problems have been reported primarily in people who already have cardiovascular problems. Tell your doctor if you have any changes in symptoms during treatment with CHAMPIX. Get emergency medical help right away if you have symptoms of a heart attack or stroke.
IG/0169/G	This was an application for a group of variations. C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	08/06/2012	n/a		
II/0039	Following CHMP review of the Risk Management Plan version 6.0 for Champix, it was requested that the results from study A3051070 be provided once completed. With this variation, Section 5.2 (Pharmacokinetics) of the SmPC was updated with the results from this study.	15/03/2012	13/04/2012	SmPC and Annex II	The primary objective of study A3051070 was to characterise the multiple-dose pharmacokinetics of varenicline in adolescent male and female smoking subjects. The information provided in Section 5.2 (Pharmacokinetics) of the SmPC was updated, and now includes the results of both the single-dose and multiple-dose PK studies. However, since efficacy was not an objective of study A3051070 (which

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				was too small for any statistic evaluation of efficacy), the CHMP recommended reiterating the message already given in section 4.2 of the SmPC that efficacy and safety has not been demonstrated in the paediatric population below 18 years of age, and no recommendation on a posology can be made.
IB/0040/G	This was an application for a group of variations. A.7 - Administrative change - Deletion of manufacturing sites B.I.a.1.a - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - The proposed manufacturer is part of the same pharmaceutical group as the currently approved manufacturer B.I.a.1.f - Change in the manufacturer of AS or of a starting material/reagent/intermediate for AS - Changes to quality control testing arrangements for the AS -replacement or addition of a site where batch control/testing takes place B.I.a.3.a - Change in batch size (including batch size ranges) of AS or intermediate - Up to 10-fold increase compared to the currently approved batch size	04/04/2012	n/a		
II/0038	Update of section 4.8 of the SmPC to include reference to 'diabetes', 'hyperglycaemia' and 'somnambulism' further to requests from CHMP following review of PSUR 8. The Package Leaflet updated in accordance. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical,	16/02/2012	21/03/2012	SmPC and PL	Following requests from the CHMP resulting from review of PSUR 8, reference to the side effects "diabetes", "hyperglycaemia" and "somnambulism" was included in the table of side effects in section 4.8 of the SPC with a frequency "Not known". The PL was updated accordingly, and now lists "diabetes", "high blood sugar" and "sleep walking" in its section 4

	clinical or pharmacovigilance data				(Possible side-effects).
II/0036	Update of sections 4.4 (Special warnings and precautions for use) and 5.1 (Pharmacodynamic properties) of the Summary of Product Characteristics (SPC) in order to update the safety information and include a mention of the fact that limited data are available from a single smoking cessation study (A3051072) in patients with stable schizophrenia or schizoaffective disorder. C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	15/12/2011	20/01/2012	SmPC	The CHMP had requested a Safety study to evaluate the risk of Champix treatment in schizophrenic patients as a Follow up measure. Following this request, the MAH conducted a safety study of Champix (varenicline) for smoking cessation in patients with psychosis (Study A3051072). After finalization of Study A3051072, its results were evaluated as part of FUM 008.2. This assessment led to a request for clarification to the MAH, who, within their variation application for this procedure (II/36), provided answers to the points raised by the CHMP and at the same time submitted wording to update the SPC for Champix in accordance to the findings emerging from Study A3051072. The key messages added to the SPC were that “Limited data are available from a single smoking cessation study in patients with stable schizophrenia or schizoaffective disorder” and that “The limited data available from this single smoking cessation study are not sufficient to allow for definitive conclusions to be drawn about the safety in patients with schizophrenia or schizoaffective disorder.”
II/0034	The Product Information for Champix was revised (Section 4.4 Special warnings and precautions for use, Section 4.8 Undesirable effects, Section 5.1 Pharmacodynamic properties of the Summary of Product Characteristics (SPC) and Section 2 (Before you take Champix) and 4 of the Package Leaflet) with information regarding cardiovascular and cerebrovascular events.	20/10/2011	21/11/2011	SmPC and PL	In July 2011, the results of a large pooled data study (meta-analysis) of Champix's side effects affecting the heart and blood vessels were published in the literature. The study, published in the Canadian Medical Association Journal on Monday 4 July, looked at the number of cardiovascular events seen in a total of 8,216 people taking either Champix or placebo in 14 randomised clinical trials lasting up to a year. The events included heart attack, stroke, disruption of the heart rhythm, heart failure and death related to

	C.I.4 - Variations related to significant modifications of the SPC due in particular to new quality, pre-clinical, clinical or pharmacovigilance data				cardiovascular problems. The largest of the studies included over 700 patients with pre-existing cardiovascular disease. The meta-analysis found that events were rare in both groups, but that there was a slightly increased number in the people taking Champix: 1.06% of those taking Champix had an event (52 out of 4,908) compared with 0.82% of those taking placebo (27 out of 3,308). This did not result in a difference in death rates between the two groups. The Committee identified a number of limitations of the meta-analysis, including the low number of events seen, the types of events counted, the higher drop-out rates in people receiving placebo, the lack of information on the timing of events, and the exclusion of studies in which no-one had an event. Because of these limitations, the Committee could not draw robust conclusions from the meta-analysis. However, as recommended by the CHMP, Pfizer, the marketing-authorisation holder for Champix, included more information on cardiovascular events in the medicine's product information, as follows: - Appropriate warnings on risk of cardiovascular events were introduced in section 4.4 (Special warnings and precautions for use). - In Section 4.8 (Undesirable effects) of the SmPC cardiovascular events were previously presented in three different subsections. In order to improve clarity, the events "blood pressure increased, electrocardiogram ST segment depression, electrocardiogram T wave amplitude decreased, heart rate increased" were moved to the appropriate

					subsections. Furthermore, “stroke” was included in the section. - The description in the SmPC (section 5.1) on the study in over 700 subjects with cardiovascular disease has been made more informative in terms of cardiovascular safety. The text has been made more factual by including information on how many subjects experienced cardiovascular events in general and specific events such as myocardial infarction in each treatment group.
IA/0035	B.II.e.1.a.1 - Change in immediate packaging of the finished product - Qualitative and quantitative composition - Solid pharmaceutical forms	10/10/2011	n/a		
II/0033	The purpose of this type II variation was to update Section 4.8 (Undesirable effects) of the Summary of Product Characteristics (SPC) and Section 4 of the Package Leaflet (PL) with frequencies of adverse events reported in study A3051084 a Modified Prescription Event Monitoring (M-PEM) study in response to a request by CHMP made in November 2010 (FU2 034.2). C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	19/05/2011	17/06/2011	SmPC and PL	The Adverse Drug Reactions table in Section 4.8 of the SPC was updated to include the ADRs 'depression', 'anxiety' and 'hallucinations' with the frequency "Uncommon". A footnote was added at the bottom of the table to underline that the frequency "Uncommon" for depression, anxiety and hallucinations had been calculated using a different methodology from the frequencies of the rest of the Adverse Drug Reactions. Section 4 of the Package Leaflet was updated to reflect the SPC.
R/0032	Renewal of the marketing authorisation.	17/03/2011	07/06/2011	SmPC, Annex II, Labelling	Based upon the data that have become available since the granting of the initial Marketing Authorisation, the CHMP

				and PL	considered that the benefit-risk balance of Champix remains positive, but considers that its safety profile is to be closely monitored for the following reasons: A number of safety issues have been identified for Champix, in particular neuropsychiatric changes (most notably depression, suicide-related events and aggressive behaviour) but also cardiovascular events. Given the serious nature of the above issues, their impact on the benefit-risk balance needs to be continuously evaluated. Thus, the CHMP decided that the MAH should continue to submit yearly PSURs until otherwise stated. Therefore, based upon the safety profile of Champix, which requires submission of yearly PSURs, the CHMP concluded that the MAH should submit one additional renewal application in 5 years time.
IG/0044/G	This was an application for a group of variations. C.I.9.e - Changes to an existing pharmacovigilance system as described in the DDPS - Changes in the major contractual arrangements with other persons or organisations involved in the fulfilment of pharmacovigilance obligations and described in the DD C.I.9.g - Changes to an existing pharmacovigilance system as described in the DDPS - Change of the site undertaking pharmacovigilance activities C.I.9.h - Changes to an existing pharmacovigilance system as described in the DDPS - Other change(s) to the DDPS that does not impact on the operation of the pharmacovigilance system	02/03/2011	n/a	Annex II	

II/0030	Update of Sections 4.2 and 5.1 of the SPC and section 3 of the PL further to data emerging from clinical study A3051095. C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	18/11/2010	20/12/2010	SmPC, Annex II and PL	The originally approved prescribing instructions of Champix recommended that the patient should determine a date to stop smoking, and dosing should begin one or two weeks before this date. In clinical study A3051095, the efficacy and safety of Champix was evaluated in smokers who had the flexibility of quitting between weeks 1 and 5 of treatment. The results of the study suggested that the flexible target quit date between week 2-5 may be an alternative option for those patients who are not willing or able to quit early in the treatment. Accordingly, the product information for Champix has been updated to reflect the concept that before starting a course of Champix, patients should usually decide on a date in the second week of treatment (between day 8 and day 14) when to stop smoking. If a patient is not willing or able to set a target quit date within 2 weeks, they may choose their own quit date within 5 weeks after starting treatment.
II/0029	C.I.3.b - Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under Article 45/46, or amendments to reflect a Core SPC - Change(s) with new additional data submitted by the MAH	23/09/2010	25/10/2010	SmPC	The studies presented in the initial Marketing Authorisation Application for Champix included only 'healthy' smokers. The MAH has conducted a post-marketing study in a population with mild to moderate chronic obstructive pulmonary disease (COPD), as this subpopulation has a pronounced need for smoking cessation. The study showed that varenicline is as efficacious and well-tolerated in the treatment of patients with COPD than among healthy smokers. Therefore, the MAH was requested to update the Product Information for Champix as, since smoking cessation is especially relevant in this population, it may be helpful for clinicians to be aware that varenicline could be used in patients with mild-moderate COPD. The following text has

					been added to section 5.1 of the SPC for Champix: "The efficacy and safety of CHAMPIX (1 mg twice daily) for smoking cessation in subjects with mild-moderate COPD was demonstrated in a randomised double-blind placebo-controlled clinical trial. In this 52-week duration study, patients received treatment for 12 weeks, followed by a 40-week non-treatment follow-up phase. The primary endpoint of the study was the CO-confirmed; 4-week Continuous Quit Rate (4W CQR) from week 9 through week 12 and a key secondary endpoint was the Continuous Abstinence (CA) from Week 9 through Week 52. The safety profile of varenicline was comparable to what was reported in other trials in the general population, including pulmonary safety."
IA/0031	B.II.d.2.a - Change in test procedure for the finished product - Minor changes to an approved test procedure	14/09/2010	n/a		
II/0026	Update of section 5.1 (Pharmacodynamic properties) of the SPC with information emerging from a clinical study in patients with stable cardiovascular disease. Update of Summary of Product Characteristics	22/10/2009	03/12/2009	SmPC	The MAH submitted the results of an efficacy/safety study of varenicline in smokers with cardiovascular disease. It was agreed that the information on cardiovascular adverse events in this patient population is of relevance to the prescribers. New text was added to section 5.1, to convey the message that the efficacy and safety of varenicline was evaluated in cardiovascular compromised smokers. Efficacy and safety was similar to that observed in studies with non-cardiovascular compromised smokers.

II/0028	Update of sections 4.4 and 4.8 of the SPC in order to include reference to post-marketing reports of angioedema; severe cutaneous reactions (including Stevens-Johnson Syndrome and Erytema Multiforme) and additional neuropsychiatric events in patients using varenicline. Sections 2 and 4 of the PL have been changed accordingly. Update of Summary of Product Characteristics and Package Leaflet	24/09/2009	30/11/2009	Annex II and PL	Based on comments from the CHMP assessment of PSUR 3 for Champix, a cumulative review of angioedema-related events was performed by the MAH and submitted with PSUR 4. More recently, the MAH's post-marketing database was reviewed again for term Angioedema. As a result, reference to hypersensitivity reactions, including angioedema has been added to the Product Information. Additionally, the post-marketing database was searched for cases reporting severe skin reactions using the term 'Severe Cutaneous Adverse Reactions'. As a result, reference to rare but sever cutaneous reactions has been added to the Product Information. Instructions have been added to the PL to inform patients that they should stop taking Champix and contact their doctor immediately if they develop swelling of the face, mouth or throat, or if their skin starts to peel or blister. A review of all serious events in the Psychiatric Disorders was also performed to ensure that the Product Information appropriately characterises the types of neuropsychiatric events associated with varenicline treatment. This analysis led to inclusion of the following neuropsychiatric event categories in the Product Information: changes in thinking, anxiety, psychosis, mood swings, and aggressive behaviour.
II/0027	Changes to the quality control of the finished product. Update of or change(s) to the pharmaceutical documentation	22/10/2009	05/11/2009		

II/0023	Update of DDPS (Pharmacovigilance) Update of DDPS (Pharmacovigilance)	25/06/2009	27/08/2009	Annex II	The Detailed Description of the Pharmacovigilance System (DDPS) has been updated (version 2.0) in order to reflect various organisational changes as well as the change of the global safety database. Consequently, Annex II has been updated using the standard text including the new version number of the agreed DDPS.
II/0022	Update the the Package Leaflet (PL) for Champix with information concerning suicide related events (SRE) and neuropsychiatric risk, together with guidance for patients in section 2 "Take special care with Champix" of the PL, as recommended by the CHMP in January 2009. Update of Package Leaflet	25/06/2009	27/08/2009	PL	The Package Leaflet has been updated to clearly reflect, in patient-compatible language, the relevant SPC information concerning SRE and neuropsychiatric risk, together with guidance for patients in the "Take special care with CHAMPIX" section of the leaflet. The following new text has been introduced to section 2 of the PL: "There have been reports of depression, suicidal ideation and behaviour and suicide attempts in patients taking CHAMPIX. If you are taking CHAMPIX and develop agitation, depressed mood, changes in behaviour that are of concern to you, your family or doctor or if you develop suicidal thoughts or behaviours you should stop your treatment and contact your doctor immediately." Additionally, in section 4 of the PL, the following sentence has been given prominence by being moved from the end of the section to its beginning: "If you are taking CHAMPIX and develop agitation, depressed mood, changes in behaviour or suicidal thoughts you should stop your treatment and contact your doctor immediately."

IB/0025	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	04/08/2009	04/08/2009	SmPC, Labelling and PL	
II/0024	Update of the SPC and PL according to the outcome of the assessment of the fifth PSUR Update of Summary of Product Characteristics and Package Leaflet	25/06/2009	03/08/2009	SmPC and PL	The fifth PSUR for Champix (covering the period of 10 May 2008 - 9 November 2008), contained a Cumulative Review of episodes of Aggression/Irrational Behaviour. Cases of aggression/Irrational behaviour have been reported, especially in patients with a psychiatric history. Therefore, a request was made by the CHMP for the terms aggression/irrational behaviour to be added the SPC and Package Leaflet. With this variation the terms were introduced to the Product Information, as requested.
II/0021	Update of section 4.8 of the Summary of Product Characteristics (SPC) to include information on "hallucinations" following the CHMP conclusions adopted in November 2008. Additionally, the contact phone numbers for the Irish, Slovenian and UK local representatives have been updated in the Package Leaflet (PL). Update of Summary of Product Characteristics and Package Leaflet	19/02/2009	07/04/2009	SmPC and PL	The CHMP reviewed the data provided by the MAH on the issue of hallucinations observed during treatment with Champix. The CHMP concluded that, as there is at least a reasonable possibility of an association between its occurrence and use of Champix, 'hallucinations' needed to be included in the SPC, although a full causality could not be established for the cases seen. Consequently, the term has been included in section 4.8 of the SPC and section 4 of the PL by means of this variation procedure.
IA/0020	IA_38_a_Change in test procedure of finished product - minor change to approved test procedure	16/12/2008	n/a		
II/0019	Amendment of section 4.8 of the Summary of Product Characteristics (SPC) and section 4 of the Package Leaflet (PL) to include 'hypersensitivity reactions' (angioedema) further to publication of data in the scientific literature and recommendations from the	23/10/2008	25/11/2008	SmPC, Annex II and PL	A report by Thomas J. Moore et al, entitled 'Strong Safety Signals seen for new Varenicline Risks', by the U.S. Institute for Safe Medication Practices (ISMP) with regard to varenicline and new suspected risks was published (May 2008) by the US Institute for Safe Medication (ISMP). This

	CHMP following assessment of PSUR 3 and 4. Additionally, the Detailed Description of the Pharmacovigilance System (DDPS) in Module 1.8.1 of the Champix Marketing Authorisation has been updated, in accordance with the current pharmacovigilance guideline. Finally, the telephone numbers for the local representatives of the Marketing Authorisation Holder in Germany and Ireland in section 6 of the PL have been amended. Update of Summary of Product Characteristics and Package Leaflet				article raised safety concerns in relation to varenicline and its possible association with adverse events such as, amongst others, skin reactions. Further to this, and based on recommendations from the CHMP further to assessment of PSUR 3 and 4 for Champix, the following text has been included to Section 4.8 (Undesirable Effects) of the Champix SPC: "There have also been reports of hypersensitivity reactions, such as angioedema and facial swelling." To reflect the above change, the following text (between inverted commas) has been added to section 4 of the PL: There have been reports of heart attack, depression, suicidal thoughts “and hypersensitivity reactions (such as swollen face or tongue)” in patients attempting to quit smoking with Champix.
II/0016	Amendment of section 4.4 of the Summary of Product Characteristics and section 4 of the Package Leaflet to strengthen the wording regarding suicide-related events (SRE), and to include instructions on stopping Champix under certain circumstances. Update of Summary of Product Characteristics and Package Leaflet	26/06/2008	08/08/2008	SmPC and PL	In the context of a wider discussion on Champix that took place at the May 2008 PhVWP and CHMP meetings, a review of spontaneous reporting data on Suicide-Related Events (SRE) was presented and discussed. As a result of the discussion on SRE, the CHMP considered that updates to section 4.4 of the SPC and section 4 of the PL were required to strengthen the existing warnings with regards to SRE. In particular, mention of the fact that not all patients experiencing depression and suicidal thoughts had a previous history of psychiatric illness or had stopped smoking was added to the SPC. Moreover, instructions on stopping Champix and contacting doctors when patients develop agitation, depressed mood, changes in behaviour or suicidal thoughts were added to the Product Information.

IB/0018	IB_07_c_Replacement/add. of manufacturing site: All other manufacturing operations ex. batch release	01/08/2008	n/a		
IA/0017	IA_32_a_Change in batch size of the finished product - up to 10-fold	15/07/2008	n/a		
IB/0015	IB_33_Minor change in the manufacture of the finished product	13/05/2008	n/a		
IA/0013	IA_05_Change in the name and/or address of a manufacturer of the finished product	08/04/2008	n/a	Annex II and PL	
IB/0012	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	19/03/2008	19/03/2008	SmPC, Labelling and PL	
II/0011	Update of sections 4.4 and 4.8 of the Summary of Products Characteristics (SPC) to include information on depression, suicidal ideation and suicidal attempt. The Package Leaflet (PL) is being updated accordingly. Update of Summary of Product Characteristics and Package Leaflet	24/01/2008	28/02/2008	SmPC and PL	Further to the submission of the second Periodic Safety Assessment Report (PSUR) and additional data provided by the MAH, the CHMP reviewed reported cases of suicidal ideation (thinking about committing suicide) or attempted suicide in patients taking Champix. From the available data, and considering that stopping smoking itself can make people depressed, the CHMP could not definitely conclude on the actual association of the reported cases with Champix. However, the CHMP agreed that the Product Information should be updated to include information in this regard. The following warning was included in section 4.4 (Warnings and Precautions) of the SPC: "Depressed mood may be a symptom of nicotine withdrawal. Depression, rarely including suicidal ideation and suicide attempt, has been reported in patients undergoing a smoking cessation attempt. These

					symptoms have also been reported while attempting to quit smoking with Champix. Clinicians should be aware of the possible emergence of significant depressive symptomatology in patients undergoing a smoking cessation attempt, and should advise patients accordingly." Section 4.8 (Side Effects) of the SPC was also updated to include that "Post-marketing cases of depression and suicidal ideation have been reported in patients taking varenicline". The PL was updated accordingly.
II/0010	Update of section 2 of the Package Leaflet (PL) to include a statement regarding possible exacerbation of psychiatric conditions in connection to smoking cessation, as requested by the CHMP in September 2007. Additionally, a sentence with clarifications regarding smoking after the quit date was added to section 1 of the PL. Finally, contact details of local representatives were also updated. Update of Package Leaflet	24/01/2008	28/02/2008	PL	Section 2 ("Before you take Champix") of the PL has been amended to include information on possible exacerbation of psychiatric conditions in connection to smoking cessation, as previously requested by the CHMP. In addition to this requested change, the MAH included further changes to the leaflet in their application. Specifically, a sentence with clarifications regarding smoking after the 'quit date' was added to section 1 ("What is Champix and what it is used for"). Finally, administrative changes to the details of the local representatives section were implemented.
IB/0008	IB_13_b_Change in test proc. for active substance - other changes (replacement/addition)	15/11/2007	n/a		
IB/0007	IB_38_c_Change in test procedure of finished product - other changes	01/10/2007	n/a		
II/0006	Update of Section 4.8 (Undesirable Effects) of the SPC to include a statement indicating that post-marketing cases of myocardial infarction had been observed in	22/03/2007	26/04/2007	SmPC	Following post-marketing reports of myocardial infarction in patients taking varenicline, the CHMP requested the SPC to be updated with this information. The MAH reviewed the

	patients taking varenicline. Update of Summary of Product Characteristics				post-marketing database and analysed all cases of myocardial infarction related events. From the analysis of the reported cases it can be concluded that the frequency of reported cases does not exceed what could be expected based on current epidemiological knowledge and most cases had coexisting cardiovascular risk factors. However, the presence of cardiovascular risk factors does not exclude an additional contributory risk from the use of varenicline. Therefore, the following information was added to section 4.8 of the SPC: "Post-marketing cases of myocardial infarction have been reported in patients taking varenicline.".
IB/0005	IB_41_a_02_Change in pack size - change in no. of units outside range of appr. pack size	21/03/2007	21/03/2007	SmPC, Labelling and PL	
N/0003	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	06/02/2007	n/a	PL	
IB/0004	IB_10_Minor change in the manufacturing process of the active substance	30/01/2007	n/a		
IB/0002	IB_42_a_01_Change in shelf-life of finished product - as packaged for sale	18/12/2006	n/a	SmPC	
N/0001	Minor change in labelling or package leaflet not connected with the SPC (Art. 61.3 Notification)	14/12/2006	n/a	PL	

CHAMPIX 1 mg film-coated tablets

Summary of Product Characteristics Updated 21-Aug-2018 | Pfizer Limited

1. Name of the medicinal product

CHAMPIX 0.5 mg film-coated tablets

CHAMPIX 1 mg film-coated tablets

2. Qualitative and quantitative composition

Each 0.5 mg film-coated tablet contains 0.5 mg of varenicline (as tartrate).

Each 1 mg film-coated tablet contains 1 mg of varenicline (as tartrate).

For the full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablets

0.5 mg film-coated tablets of 4 mm x 8 mm: White, capsular-shaped, biconvex tablets debossed with "*Pfizer*" on one side and "CHX 0.5" on the other side.

1 mg film-coated tablets of 5 mm x 10 mm: Light blue, capsular-shaped, biconvex tablets debossed with "*Pfizer*" on one side and "CHX 1.0" on the other side.

4. Clinical particulars

4.1 Therapeutic indications

CHAMPIX is indicated for smoking cessation in adults.

4.2 Posology and method of administration

Posology

The recommended dose is 1 mg varenicline twice daily following a 1-week titration as follows:

Days 1 – 3:	0.5 mg once daily
Days 4 – 7:	0.5 mg twice daily
Day 8 – End of treatment:	1 mg twice daily

The patient should set a date to stop smoking. CHAMPIX dosing should usually start at 1-2 weeks before this date (see section 5.1).

Patients should be treated with CHAMPIX for 12 weeks.

For patients who have successfully stopped smoking at the end of 12 weeks, an additional course of 12 weeks treatment with CHAMPIX at 1 mg twice daily may be considered for the maintenance of abstinence (see section 5.1).

A gradual approach to quitting smoking with CHAMPIX should be considered for patients who are not able or willing to quit abruptly. Patients should reduce smoking during the first 12 weeks of treatment and quit by the end of that treatment period. Patients should then continue taking CHAMPIX for an additional 12 weeks for a total of 24 weeks of treatment (see section 5.1).

Patients who are motivated to quit and who did not succeed in stopping smoking during prior CHAMPIX therapy, or who relapsed after treatment, may benefit from another quit attempt with CHAMPIX (see section 5.1).

Patients who cannot tolerate adverse reactions of CHAMPIX may have the dose lowered temporarily or permanently to 0.5 mg twice daily.

In smoking cessation therapy, risk for relapse to smoking is elevated in the period immediately following the end of treatment. In patients with a high risk of relapse, dose tapering may be considered (see section 4.4).

Elderly

No dosage adjustment is necessary for elderly patients (see section 5.2). Because elderly patients are more likely to have decreased renal function, prescribers should consider the renal status of an elderly patient.

Renal impairment

No dosage adjustment is necessary for patients with mild (estimated creatinine clearance > 50 ml/min and ≤ 80 ml/min) to moderate (estimated creatinine clearance ≥ 30 ml/min and ≤ 50 ml/min) renal impairment.

For patients with moderate renal impairment who experience adverse reactions that are not tolerable, dosing may be reduced to 1 mg once daily.

For patients with severe renal impairment (estimated creatinine clearance < 30 ml/min), the recommended dose of CHAMPIX is 1 mg once daily. Dosing should begin at 0.5 mg once daily for the first 3 days then increased to 1 mg once daily. Based on insufficient clinical experience with CHAMPIX in patients with end stage renal disease, treatment is not recommended in this patient population (see section 5.2).

Hepatic impairment

No dosage adjustment is necessary for patients with hepatic impairment (see section 5.2).

Paediatric population

The safety and efficacy of CHAMPIX in children or adolescents below 18 years have not yet been established. Currently available data are described in section 5.2 but no recommendation on a posology can be made.

Method of administration

CHAMPIX is for oral use and the tablets should be swallowed whole with water.

CHAMPIX can be taken with or without food

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Effect of smoking cessation

Physiological changes resulting from smoking cessation, with or without treatment with CHAMPIX, may alter the pharmacokinetics or pharmacodynamics of some medicinal products, for which dosage adjustment may be necessary (examples include theophylline, warfarin and insulin). As smoking induces CYP1A2, smoking cessation may result in an increase of plasma levels of CYP1A2 substrates.

Neuropsychiatric symptoms

Changes in behaviour or thinking, anxiety, psychosis, mood swings, aggressive behaviour, depression, suicidal ideation and behaviour and suicide attempts have been reported in patients attempting to quit smoking with CHAMPIX in the post-marketing experience.

A large randomised, double-blind, active and placebo-controlled study was conducted to compare the risk of serious neuropsychiatric events in patients with and without a history of psychiatric disorder treated for smoking cessation with varenicline, bupropion, nicotine replacement therapy patch (NRT) or placebo. The primary safety endpoint was a composite of neuropsychiatric adverse events that have been reported in post-marketing experience.

The use of varenicline in patients with or without a history of psychiatric disorder was not associated with an increased risk of serious neuropsychiatric adverse events in the composite primary endpoint compared with placebo (see section 5.1 **Pharmacodynamic properties** - *Study in Subjects with and without a History of Psychiatric Disorder*).

Depressed mood, rarely including suicidal ideation and suicide attempt, may be a symptom of nicotine withdrawal.

Clinicians should be aware of the possible emergence of serious neuropsychiatric symptoms in patients attempting to quit smoking with or without treatment. If serious neuropsychiatric symptoms occur whilst on varenicline treatment, patients should discontinue varenicline immediately and contact a healthcare professional for re-evaluation of treatment.

History of psychiatric disorders

Smoking cessation, with or without pharmacotherapy, has been associated with exacerbation of underlying psychiatric illness (e.g. depression).

CHAMPIX smoking cessation studies have provided data in patients with a history of psychiatric disorders (see section 5.1).

In a smoking cessation clinical trial, neuropsychiatric adverse events were reported more frequently in patients with a

history of psychiatric disorders compared to those without a history of psychiatric disorders, regardless of treatment (see section 5.1).

Care should be taken with patients with a history of psychiatric illness and patients should be advised accordingly.

Seizures

In clinical trials and post-marketing experience there have been reports of seizures in patients with or without a history of seizures, treated with CHAMPIX. CHAMPIX should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold.

Treatment discontinuation

At the end of treatment, discontinuation of CHAMPIX was associated with an increase in irritability, urge to smoke, depression, and/or insomnia in up to 3% of patients. The prescriber should inform the patient accordingly and discuss or consider the need for dose tapering.

Cardiovascular events

Patients taking CHAMPIX should be instructed to notify their doctor of new or worsening cardiovascular symptoms and to seek immediate medical attention if they experience signs and symptoms of myocardial infarction or stroke (see section 5.1).

Hypersensitivity reactions

There have been post-marketing reports of hypersensitivity reactions including angioedema in patients treated with varenicline. Clinical signs included swelling of the face, mouth (tongue, lips, and gums), neck (throat and larynx) and extremities. There were rare reports of life-threatening angioedema requiring urgent medical attention due to respiratory compromise. Patients experiencing these symptoms should discontinue treatment with varenicline and contact a health care provider immediately.

Cutaneous reactions

There have also been post-marketing reports of rare but severe cutaneous reactions, including Stevens-Johnson Syndrome and Erythema Multiforme in patients using varenicline. As these skin reactions can be life threatening, patients should discontinue treatment at the first sign of rash or skin reaction and contact a healthcare provider immediately.

4.5 Interaction with other medicinal products and other forms of interaction

Based on varenicline characteristics and clinical experience to date, CHAMPIX has no clinically meaningful drug interactions. No dosage adjustment of CHAMPIX or co-administered medicinal products listed below is recommended.

In vitro studies indicate that varenicline is unlikely to alter the pharmacokinetics of compounds that are primarily metabolised by cytochrome P450 enzymes.

Furthermore since metabolism of varenicline represents less than 10% of its clearance, active substances known to affect the cytochrome P450 system are unlikely to alter the pharmacokinetics of varenicline (see section 5.2) and therefore a dose adjustment of CHAMPIX would not be required.

In vitro studies demonstrate that varenicline does not inhibit human renal transport proteins at therapeutic concentrations. Therefore, active substances that are cleared by renal secretion (e.g., metformin - see below) are unlikely to be affected by varenicline.

Metformin

Varenicline did not affect the pharmacokinetics of metformin. Metformin had no effect on varenicline pharmacokinetics.

Cimetidine

Co-administration of cimetidine, with varenicline increased the systemic exposure of varenicline by 29% due to a reduction in varenicline renal clearance. No dosage adjustment is recommended based on concomitant cimetidine administration in subjects with normal renal function or in patients with mild to moderate renal impairment. In patients with severe renal impairment, the concomitant use of cimetidine and varenicline should be avoided.

Digoxin

Varenicline did not alter the steady-state pharmacokinetics of digoxin.

Warfarin

Varenicline did not alter the pharmacokinetics of warfarin. Prothrombin time (INR) was not affected by varenicline.

Smoking cessation itself may result in changes to warfarin pharmacokinetics (see section 4.4).

Alcohol

There are limited clinical data on any potential interaction between alcohol and varenicline. There have been post marketing reports of increased intoxicating effects of alcohol in patients treated with varenicline. A causal relationship between these events and varenicline use has not been established.

Use with other therapies for smoking cessation

Bupropion

Varenicline did not alter the steady-state pharmacokinetics of bupropion.

Nicotine replacement therapy (NRT)

When varenicline and transdermal NRT were co-administered to smokers for 12 days, there was a statistically significant decrease in average systolic blood pressure (mean 2.6 mmHg) measured on the final day of the study. In this study, the incidence of nausea, headache, vomiting, dizziness, dyspepsia, and fatigue was greater for the combination than for NRT alone.

Safety and efficacy of CHAMPIX in combination with other smoking cessation therapies have not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

A moderate amount of data on pregnant women indicated no malformative or foetal/neonatal toxicity of varenicline (see section 5.1).

Animal studies have shown reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of varenicline during pregnancy (see section 5.1).

Breast-feeding

It is unknown whether varenicline is excreted in human breast milk. Animal studies suggest that varenicline is excreted in breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with CHAMPIX should be made taking into account the benefit of breast-feeding to the child and the benefit of CHAMPIX therapy to the woman.

Fertility

There are no clinical data on the effects of varenicline on fertility.

Non-clinical data revealed no hazard for humans based on standard male and female fertility studies in the rat (see section 5.3).

4.7 Effects on ability to drive and use machines

CHAMPIX may have minor or moderate influence on the ability to drive and use machines. CHAMPIX may cause dizziness, somnolence and transient loss of consciousness, and therefore may influence the ability to drive and use machines. Patients are advised not to drive, operate complex machinery or engage in other potentially hazardous activities until it is known whether this medicinal product affects their ability to perform these activities.

4.8 Undesirable effects

Summary of the safety profile

Smoking cessation with or without treatment is associated with various symptoms. For example, dysphoric or depressed mood; insomnia, irritability, frustration or anger; anxiety; difficulty concentrating; restlessness; decreased heart rate; increased appetite or weight gain have been reported in patients attempting to stop smoking. No attempt has been made in either the design or the analysis of the CHAMPIX studies to distinguish between adverse reactions associated with study drug treatment or those possibly associated with nicotine withdrawal. Adverse drug reactions are based on evaluation of data from pre-marketing phase 2-3 studies and updated based on pooled data from 18 placebo-controlled pre- and post-marketing studies, including approximately 5,000 patients treated with varenicline.

In patients treated with the recommended dose of 1 mg twice daily following an initial titration period the adverse event most commonly reported was nausea (28.6%). In the majority of cases nausea occurred early in the treatment period, was mild to moderate in severity and seldom resulted in discontinuation.

Tabulated summary of adverse reactions

In the table below all adverse reactions, which occurred at an incidence greater than placebo are listed by system organ class and frequency (very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) and rare (≥ 1/10,000 to < 1/1,000)). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	Adverse Drug Reactions
Infections and infestations	
Very common	Nasopharyngitis
Common	Bronchitis, sinusitis
Uncommon	Fungal infection, viral infection
Blood and lymphatic system disorders	
Rare	Platelet count decreased
Metabolism and nutrition disorders	
Common	Weight increased, decreased appetite, increased appetite
Uncommon	Hyperglycaemia
Rare	Diabetes mellitus, polydipsia
Psychiatric disorders	
Very common	Abnormal dreams, insomnia
Uncommon	Suicidal ideation, aggression, panic reaction, thinking abnormal, restlessness, mood swings, depression*, anxiety*, hallucinations*, libido increased, libido decreased
Rare	Psychosis, somnambulism, abnormal behaviour, dysphoria, bradyphrenia
Nervous system disorders	
Very common	Headache
Common	Somnolence, dizziness, dysgeusia
Uncommon	Seizure, tremor, lethargy, hypoaesthesia
Rare	Cerebrovascular accident, hypertonia, dysarthria, coordination abnormal, hypogeusia, circadian rhythm sleep disorder
Not known	Transient loss of consciousness
Eye disorders	
Uncommon	Conjunctivitis, eye pain
Rare	Scotoma, scleral discolouration, mydriasis, photophobia, myopia, lacrimation increased
Ear and labyrinth disorders	
Uncommon	Tinnitus
Cardiac disorders	
Uncommon	Myocardial infarction, angina pectoris, tachycardia, palpitations, heart rate increased

Rare	Atrial fibrillation, electrocardiogram ST segment depression, electrocardiogram T wave amplitude decreased
Vascular disorders	
Uncommon	Blood pressure increased, hot flush
Respiratory, thoracic and mediastinal disorders	
Common	Dyspnoea, cough
Uncommon	Upper respiratory tract inflammation, respiratory tract congestion, dysphonia, rhinitis allergic, throat irritation, sinus congestion, upper- airway cough syndrome, rhinorrhoea
Rare	Laryngeal pain, snoring
Gastrointestinal disorders	
Very common	Nausea
Common	Gastrooesophageal reflux disease, vomiting, constipation, diarrhoea, abdominal distension, abdominal pain, toothache, dyspepsia, flatulence, dry mouth
Uncommon	Haematochezia, gastritis, change of bowel habit, eructation, aphthous stomatitis, gingival pain
Rare	Haematemesis, abnormal faeces, tongue coated
Skin and subcutaneous tissue disorders	
Common	Rash, pruritus
Uncommon	Erythema, acne, hyperhidrosis, night sweats
Rare	Severe cutaneous reactions, including Stevens Johnson Syndrome and Erythema Multiforme, angioedema
Musculoskeletal and connective tissue disorders	
Common	Arthralgia, myalgia, back pain
Uncommon	Muscle spasms, musculoskeletal chest pain
Rare	Joint stiffness, costochondritis
Renal and urinary disorders	
Uncommon	Pollakiuria, nocturia
Rare	Glycosuria, polyuria
Reproductive system and breast disorders	
Uncommon	Menorrhagia
Rare	Vaginal discharge, sexual dysfunction
General disorders and administration site conditions	
Common	Chest pain, fatigue
Uncommon	Chest discomfort, influenza like illness, pyrexia, asthenia, malaise

Rare	Feeling cold, cyst
Investigations	
Common	Liver function test abnormal
Rare	Semen analysis abnormal, C-reactive protein increased, blood calcium decreased
* Frequencies are estimated from a post-marketing, observational cohort study	

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product.

United Kingdom

Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

Ireland

Healthcare professionals are asked to report any suspected adverse reactions via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

No cases of overdose were reported in pre-marketing clinical trials.

In case of overdose, standard supportive measures should be instituted as required.

Varenicline has been shown to be dialyzed in patients with end stage renal disease (see section 5.2), however, there is no experience in dialysis following overdose.

5. Pharmacological properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other nervous system drugs; Drugs used in addictive disorders; Drugs used in nicotine dependence, ATC code: N07BA03

Mechanism of action

Varenicline binds with high affinity and selectivity at the α4β2 neuronal nicotinic acetylcholine receptors, where it acts as a partial agonist - a compound that has both agonist activity, with lower intrinsic efficacy than nicotine, and antagonist activities in the presence of nicotine.

Electrophysiology studies *in vitro* and neurochemical studies in vivo have shown that varenicline binds to the α4β2 neuronal nicotinic acetylcholine receptors and stimulates receptor-mediated activity, but at a significantly lower level than nicotine. Nicotine competes for the same human α4β2 nAChR binding site for which varenicline has higher affinity. Therefore, varenicline can effectively block nicotine's ability to fully activate α4β2 receptors and the mesolimbic dopamine system, the neuronal mechanism underlying reinforcement and reward experienced upon smoking. Varenicline is highly selective and binds more potently to the α4β2 receptor subtype (Ki=0.15 nM) than to other common nicotinic receptors (α3β4 Ki=84 nM, α7 Ki= 620 nM, α1βγδ Ki= 3,400 nM), or to non-nicotinic receptors and transporters (Ki > 1μM, except to 5-HT3 receptors: Ki=350 nM).

Pharmacodynamic effects

The efficacy of CHAMPIX in smoking cessation is a result of varenicline's partial agonist activity at the α4β2 nicotinic receptor where its binding produces an effect sufficient to alleviate symptoms of craving and withdrawal (agonist activity), while simultaneously resulting in a reduction of the rewarding and reinforcing effects of smoking by preventing nicotine binding to α4β2 receptors (antagonist activity).

Clinical efficacy and safety

Smoking cessation therapies are more likely to succeed for patients who are motivated to stop smoking and who are provided with additional advice and support.

The efficacy of CHAMPIX in smoking cessation was demonstrated in 3 clinical trials involving chronic cigarette smokers

(≥ 10 cigarettes per day). Two thousand six hundred nineteen (2619) patients received CHAMPIX 1 mg BID (titrated during the first week), 669 patients received bupropion 150 mg BID (also titrated) and 684 patients received placebo.

Comparative clinical studies

Two identical double-blind clinical trials prospectively compared the efficacy of CHAMPIX (1 mg twice daily), sustained release bupropion (150 mg twice daily) and placebo in smoking cessation. In these 52-week duration studies, patients received treatment for 12 weeks, followed by a 40-week non-treatment phase.

The primary endpoint of the two studies was the carbon monoxide (CO) confirmed, 4-week continuous quit rate (4W-CQR) from week 9 through week 12. The primary endpoint for CHAMPIX demonstrated statistical superiority to bupropion and placebo.

After the 40 week non-treatment phase, a key secondary endpoint for both studies was the Continuous Abstinence Rate (CA) at week 52. CA was defined as the proportion of all subjects treated who did not smoke (not even a puff of a cigarette) from Week 9 through Week 52 and did not have an exhaled CO measurement of > 10 ppm.

The 4W-CQR (weeks 9 through 12) and CA rate (weeks 9 through 52) from studies 1 and 2 are included in the following table:

	Study 1 (n=1022)		Study 2 (n=1023)	
	4W CQR	CA Wk 9-52	4W CQR	CA Wk 9-52
CHAMPIX	44.4%	22.1%	44.0%	23.0%
Bupropion	29.5%	16.4%	30.0%	15.0%
Placebo	17.7%	8.4%	17.7%	10.3%
Odds ratio CHAMPIX vs. placebo	3.91 p < 0.0001	3.13 p < 0.0001	3.85 p < 0.0001	2.66 p < 0.0001
Odds ratio CHAMPIX vs. bupropion	1.96 p < 0.0001	1.45 p = 0.0640	1.89 p < 0.0001	1.72 p = 0.0062

Patient reported craving, withdrawal and reinforcing effects of smoking

Across both Studies 1 and 2 during active treatment, craving and withdrawal were significantly reduced in patients randomised to CHAMPIX in comparison with placebo. CHAMPIX also significantly reduced reinforcing effects of smoking that can perpetuate smoking behaviour in patients who smoke during treatment compared with placebo. The effect of varenicline on craving, withdrawal and reinforcing effects of smoking were not measured during the non-treatment long-term follow-up phase.

Maintenance of abstinence study

The third study assessed the benefit of an additional 12 weeks of CHAMPIX therapy on the maintenance of abstinence. Patients in this study (n=1,927) received open-label CHAMPIX 1 mg twice daily for 12 weeks. Patients who stopped smoking by Week 12 were then randomised to receive either CHAMPIX (1 mg twice daily) or placebo for an additional 12 weeks for a total study duration of 52 weeks.

The primary study endpoint was the CO-confirmed continuous abstinence rate from week 13 through week 24 in the double-blind treatment phase. A key secondary endpoint was the continuous abstinence (CA) rate for week 13 through week 52.

This study showed the benefit of an additional 12-week treatment with CHAMPIX 1 mg twice daily for the maintenance of smoking cessation compared to placebo; superiority to placebo for CA was maintained through week 52. The key results are summarised in the following table:

Continuous Abstinence Rates in Subjects Treated with Champix versus Placebo

	CHAMPIX n=602	Placebo n=604	Difference (95% CI)	Odds ratio (95% CI)

CA* wk 13-24	70.6%	49.8%	20.8% (15.4%, 26.2%)	2.47 (1.95, 3.15)
CA* wk 13-52	44.0%	37.1%	6.9% (1.4%, 12.5%)	1.35 (1.07, 1.70)

*CA: Continuous Abstinence Rate

There is currently limited clinical experience with the use of CHAMPIX among black people to determine clinical efficacy.

Flexible quit date between weeks 1 and 5

The efficacy and safety of varenicline has been evaluated in smokers who had the flexibility of quitting between weeks 1 and 5 of treatment. In this 24-week study, patients received treatment for 12 weeks followed by a 12 week non-treatment follow up phase. The 4 week (week 9-12) CQR for varenicline and placebo was 53.9% and 19.4%, respectively (difference=34.5%, 95% CI: 27.0% - 42.0%) and the CA week 9-24 was 35.2% (varenicline) vs. 12.7% (placebo) (difference=22.5%, 95% CI: 15.8% - 29.1%). Patients who are not willing or able to set the target quit date within 1-2 weeks, could be offered to start treatment and then choose their own quit date within 5 weeks.

Study in subjects re-treated with CHAMPIX

CHAMPIX was evaluated in a double-blind, placebo-controlled trial of 494 patients who had made a previous attempt to quit smoking with CHAMPIX, and either did not succeed in quitting or relapsed after treatment. Subjects who experienced an adverse event of a concern during previous treatment were excluded. Subjects were randomised 1:1 to CHAMPIX 1 mg twice daily (N=249) or placebo (N=245) for 12 weeks of treatment and followed for up to 40 weeks post-treatment. Patients included in this study had taken CHAMPIX for a smoking-cessation attempt in the past (for a total treatment duration of a minimum of two weeks), at least three months prior to study entry, and had been smoking for at least four weeks.

Patients treated with CHAMPIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 and from weeks 9 through 52 compared to subjects treated with placebo. The key results are summarised in the following table:

Continuous Abstinence Rates in Subjects Treated with Champix versus Placebo

	CHAMPIX n=249	Placebo n=245	Odds ratio (95% CI), p value
CA* wk 9-12	45.0%	11.8%	7.08 (4.34, 11.55), p<0.0001
CA* wk 9-52	20.1%	3.3%	9.00 (3.97, 20.41), p<0.0001

*CA: Continuous Abstinence Rate

Gradual approach to quitting smoking

CHAMPIX was evaluated in a 52-week double-blind placebo-controlled study of 1,510 subjects who were not able or willing to quit smoking within four weeks, but were willing to gradually reduce their smoking over a 12 week period before quitting. Subjects were randomised to either CHAMPIX 1 mg twice daily (n=760) or placebo (n=750) for 24 weeks and followed up post-treatment through week 52. Subjects were instructed to reduce the number of cigarettes smoked by at least 50 percent by the end of the first four weeks of treatment, followed by a further 50 percent reduction from week four to week eight of treatment, with the goal of reaching complete abstinence by 12 weeks. After the initial 12-week reduction phase, subjects continued treatment for another 12 weeks. Subjects treated with CHAMPIX had a significantly higher Continuous Abstinence Rate compared with placebo; the key results are summarised in the following table:

Continuous Abstinence Rates in Subjects Treated with Champix versus Placebo

	CHAMPIX n=760	Placebo n=750	Odds ratio (95% CI), p value
CA* wk 15-24	32.1%	6.9%	8.74 (6.09, 12.53), p<0.0001

CA* wk 21-52	27.0%	9.9%	4.02 (2.94, 5.50), p<0.0001
*CA: Continuous Abstinence Rate			

The CHAMPIX safety profile in this study was consistent with that of pre-marketing studies.

Subjects with cardiovascular disease

CHAMPIX was evaluated in a randomised, double-blind, placebo-controlled study of subjects with stable, cardiovascular disease (other than, or in addition to, hypertension) that had been diagnosed for more than 2 months. Subjects were randomised to CHAMPIX 1 mg twice daily (n=353) or placebo (n=350) for 12 weeks and then were followed for 40 weeks post-treatment. The 4 week CQR for varenicline and placebo was 47.3% and 14.3%, respectively and the CA week 9-52 was 19.8% (varenicline) vs. 7.4% (placebo).

Deaths and serious cardiovascular events were adjudicated by a blinded, committee. The following adjudicated events occurred with a frequency ≥ 1% in either treatment group during treatment (or in the 30-day period after treatment): nonfatal myocardial infarction (1.1% vs. 0.3% for CHAMPIX and placebo, respectively), and hospitalisation for angina pectoris (0.6% vs. 1.1%). During non-treatment follow up to 52 weeks, the adjudicated events included need for coronary revascularisation (2.0% vs. 0.6%), hospitalisation for angina pectoris (1.7% vs. 1.1%), and new diagnosis of peripheral vascular disease (PVD) or admission for a PVD procedure (1.4% vs. 0.6%). Some of the patients requiring coronary revascularisation underwent the procedure as part of management of nonfatal MI and hospitalisation for angina. Cardiovascular death occurred in 0.3% of patients in the CHAMPIX arm and 0.6% of patients in the placebo arm over the course of the 52-week study.

A meta-analysis of 15 clinical trials of ≥ 12 weeks treatment duration, including 7002 patients (4190 CHAMPIX, 2812 placebo), was conducted to systematically assess the cardiovascular safety of CHAMPIX. The study in patients with stable cardiovascular disease described above was included in the meta-analysis.

The key cardiovascular safety analysis included occurrence and timing of a composite endpoint of Major Adverse Cardiovascular Events (MACE), defined as cardiovascular death, nonfatal MI, and nonfatal stroke. These events included in the endpoint were adjudicated by a blinded, independent committee. Overall, a small number of MACE occurred during treatment in the trials included in the meta-analysis (CHAMPIX 7 [0.17%]; placebo 2 [0.07%]). Additionally, a small number of MACE occurred up to 30 days after treatment (CHAMPIX 13 [0.31%]; placebo 6 [0.21%]).

The meta-analysis showed that exposure to CHAMPIX resulted in a hazard ratio for MACE of 2.83 (95% confidence interval from 0.76 to 10.55, p=0.12) for patients during treatment and 1.95 (95% confidence interval from 0.79 to 4.82, p=0.15) for patients up to 30 days after treatment. These are equivalent to an estimated increase of 6.5 MACE events and 6.3 MACE events per 1,000 patient-years, respectively of exposure. The hazard ratio for MACE was higher in patients with cardiovascular risk factors in addition to smoking compared with that in patients without cardiovascular risk factors other than smoking. There were similar rates of all-cause mortality (CHAMPIX 6 [0.14%]; placebo 7 [0.25%]) and cardiovascular mortality (CHAMPIX 2 [0.05%]; placebo 2 [0.07%]) in the CHAMPIX arms compared with the placebo arms in the meta-analysis.

Cardiovascular safety assessment study in subjects with and without a history of psychiatric disorder

The cardiovascular (CV) safety of CHAMPIX was evaluated in the Study in Subjects with and without a History of Psychiatric Disorder (parent study; see section 5.1 - *Neuropsychiatric safety*) and its non-treatment extension, the Cardiovascular Safety Assessment Study, which enrolled 4595 of the 6293 subjects who completed the parent study (N=8058) and followed them through week 52. Of all subjects treated in the parent study, 1749 (21.7%) had a medium CV risk and 644 (8.0%) had a high CV risk, as defined by Framingham score.

The primary CV endpoint was the time to major adverse cardiovascular events (MACE), defined as cardiovascular death, non-fatal myocardial infarction or non-fatal stroke during treatment. Deaths and cardiovascular events were adjudicated by a blinded, independent committee.

The following table shows the incidence of MACE and Hazard Ratios vs placebo for all treatment groups during treatment, and cumulative for treatment plus 30 days and through end of study.

	CHAMPIX N=2016	**Bupropion N=2006**	**NRT N=2022**	**Placebo N=2014**
During treatment				
MACE, n (%)	1 (0.05)	2 (0.10)	1 (0.05)	4 (0.20)

Hazard Ratio (95% CI) vs placebo	0.29 (0.05, 1.68)	0.50 (0.10, 2.50)	0.29 (0.05, 1.70)	
During treatment plus 30 days				
MACE, n (%)	1 (0.05)	2 (0.10)	2 (0.10)	4 (0.20)
Hazard Ratio (95% CI) vs placebo	0.29 (0.05, 1.70)	0.51 (0.10, 2.51)	0.50 (0.10, 2.48)	
Through end of study				
MACE, n (%)	3 (0.15)	9 (0.45)	6 (0.30)	8 (0.40)
Hazard Ratio (95% CI) vs placebo	0.39 (0.12, 1.27)	1.09 (0.42, 2.83)	0.75 (0.26, 2.13)	

The use of CHAMPIX, bupropion, and NRT was not associated with an increased risk of CV AEs in smokers treated for up to 12 weeks and followed for up to 1 year compared to placebo, although because of the relatively low number of events overall, an association cannot be entirely ruled out.

Subjects with mild-moderate chronic obstructive pulmonary disease (COPD)

The efficacy and safety of CHAMPIX (1 mg twice daily) for smoking cessation in subjects with mild-moderate COPD was demonstrated in a randomised double-blind placebo-controlled clinical trial. In this 52-week duration study, patients received treatment for 12 weeks, followed by a 40-week non-treatment follow-up phase. The primary endpoint of the study was the CO-confirmed, 4-week Continuous Quit Rate (4W CQR) from week 9 through week 12 and a key secondary endpoint was the Continuous Abstinence (CA) from Week 9 through Week 52. The safety profile of varenicline was comparable to what was reported in other trials in the general population, including pulmonary safety. The results for the 4W CQR (weeks 9 through 12) and CA rate (weeks 9 through 52) are shown in the following table:

	4W CQR	**CA Wk 9-52**
CHAMPIX, (n = 248)	42.3%	18.5%
Placebo, (n = 251)	8.8%	5.6%
Odds ratio (CHAMPIX vs. Placebo)	8.40 p < 0.0001	4.04 p < 0.0001

Study in subjects with a history of major depressive disorder

The efficacy of varenicline was confirmed in a randomised placebo-controlled trial in 525 subjects with a history of major depression in the past two years or under current stable treatment. The cessation rates in this population were similar to those reported in the general population. Continuous abstinence rate between weeks 9-12 was 35.9% in the varenicline treatment group versus 15.6% in the placebo group (OR 3.35 (95% CI 2.16-5.21)) and between weeks 9-52 was 20.3% versus 10.4% respectively (OR 2.36 (95% CI 1.40-3.98)). The most common adverse events (≥ 10%) in subjects taking varenicline were nausea (27.0% vs. 10.4% on placebo), headache (16.8% vs. 11.2%), abnormal dreams (11.3% vs. 8.2%), insomnia (10.9% vs. 4.8%) and irritability (10.9% vs. 8.2%). Psychiatric scales showed no differences between the varenicline and placebo groups and no overall worsening of depression, or other psychiatric symptoms, during the study in either treatment group.

Study in subjects with stable schizophrenia or schizoaffective disorder

Varenicline safety and tolerability was assessed in a double-blind study of 128 smokers with stable schizophrenia or schizoaffective disorder, on antipsychotic medication, randomised 2:1 to varenicline (1 mg twice daily) or placebo for 12 weeks with 12-week non-drug follow-up.

The most common adverse events in subjects taking varenicline were nausea (23.8% vs. 14.0% on placebo), headache (10.7% vs. 18.6% on placebo) and vomiting (10.7% vs. 9.3% on placebo). Among reported neuropsychiatric adverse events, insomnia was the only event reported in either treatment group in ≥ 5% of subjects at a rate higher in the varenicline group than in placebo (9.5% vs. 4.7%).

Overall, there was no worsening of schizophrenia in either treatment group as measured by psychiatric scales and there were no overall changes in extra-pyramidal signs. In the varenicline group compared to placebo, a higher proportion of

subjects reported suicidal ideation or behaviour prior to enrolment (lifetime history) and after the end of active treatment period (on Days 33 to 85 after the last dose of treatment). During the active treatment period, the incidence of suicide-related events was similar between the varenicline-treated and the placebo-treated subjects (11 vs. 9.3%, respectively). The percentage of subjects with suicide-related events in the active treatment phase compared to post-treatment phase was unchanged in the varenicline group; in the placebo group, this percentage was lower in the post-treatment phase. Although there were no completed suicides, there was one suicidal attempt in a varenicline-treated subject whose lifetime history included several similar attempts. The limited data available from this single smoking cessation study are not sufficient to allow for definitive conclusions to be drawn about the safety in patients with schizophrenia or schizoaffective disorder.

Neuropsychiatric Safety

Study in Subjects with and without a History of Psychiatric Disorder: Varenicline was evaluated in a randomised, double-blind, active and placebo-controlled study that included subjects with a history of psychiatric disorder (psychiatric cohort, N=4074) and subjects without a history of psychiatric disorder (non-psychiatric cohort, N=3984). Subjects aged 18-75 years, smoking 10 or more cigarettes per day were randomised 1:1:1:1 to varenicline 1 mg BID, bupropion SR 150 mg BID, nicotine replacement therapy patch (NRT) 21 mg/day with taper or placebo for a treatment period of 12 weeks; they were then followed for another 12 weeks post-treatment.

The primary safety endpoint was a composite of the following neuropsychiatric (NPS) adverse events: severe events of anxiety, depression, feeling abnormal, or hostility, and/or moderate or severe events of agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behaviour or completed suicide.

The following table shows the rates of the composite NPS adverse event primary endpoint by treatment group and the risk differences (RDs) (95% CI) vs placebo in the **non-psychiatric cohort**.

In addition, the table shows the subset of the composite NPS AE endpoint of severe intensity:

	Non-psychiatric Cohort N=3984			
	Varenicline	**Bupropion**	**NRT**	**Placebo**
Number of Patients Treated	990	989	1006	999
Composite NPS AE Primary Endpoint, n (%)	13 (1.3)	22 (2.2)	25 (2.5)	24 (2.4)
RD (95% CI) vs Placebo	-1.28 (-2.40, -0.15)	-0.08 (-1.37, 1.21)	-0.21 (-1.54,1.12)	
Composite NPS AE Endpoint of severe intensity n (%)	1 (0.1)	4 (0.4)	3 (0.3)	5 (0.5)

AE, adverse event; NRT=Nicotine replacement therapy patch

The rates of events in the composite endpoint were low across all treatment groups and were similar or lower for each of the active treatments compared to placebo. The use of varenicline, bupropion and NRT in the non-psychiatric cohort was not associated with a significantly increased risk of NPS adverse events in the composite primary endpoint compared with placebo (95% CIs were lower than or included zero).

The percentage of subjects with suicidal ideation and/or behaviour based on the Columbia-Suicide Severity Rating Scale (C-SSRS) was similar between the varenicline and placebo groups during treatment and in the non- treatment follow-up, as shown in the following table:

	Non-psychiatric Cohort N=3984			
	Varenicline N=990 n (%)	**Bupropion N=989 n (%)**	**NRT N=1006 n (%)**	**Placebo N=999 n (%)**

During treatment				
Number assessed	988	983	996	995
Suicidal behaviour and/or ideation	7 (0.7)	4 (0.4)	3 (0.3)	7 (0.7)
Suicidal behaviour	0	0	1 (0.1)	1 (0.1)
Suicidal ideation	7 (0.7)	4 (0.4)	3 (0.3)	6 (0.6)
During follow up				
Number assessed	807	816	800	805
Suicidal behaviour and/or ideation	3 (0.4)	2 (0.2)	3 (0.4)	4 (0.5)
Suicidal behaviour	0	1 (0.1)	0	0
Suicidal ideation	3 (0.4)	2 (0.2)	3 (0.4)	4 (0.5)

NRT=Nicotine replacement therapy patch

There was one completed suicide, which occurred during treatment in a subject treated with placebo in the non-psychiatric cohort.

The following table shows the rates of the composite NPS adverse event primary endpoint by treatment group and the RDs (95% CI) vs placebo in the **psychiatric cohort**. The individual components of the endpoint are also shown.

In addition, the table shows the subset of the composite NPS AE endpoint of severe intensity:

	Psychiatric Cohort N=4074			
	Varenicline	**Bupropion**	**NRT**	**Placebo**
Number of Patients Treated	1026	1017	1016	1015
Composite NPS AE Primary Endpoint, n (%)	67 (6.5)	68 (6.7)	53 (5.2)	50 (4.9)
RD (95% CI) vs Placebo	1.59 (-0.42, 3.59)	1.78 (-0.24, 3.81)	0.37 (-1.53, 2.26)	
NPS AE Primary Endpoint Components n (%):				
Anxiety[a]	5 (0.5)	4 (0.4)	6 (0.6)	2 (0.2)
Depression[a]	6 (0.6)	4 (0.4)	7 (0.7)	6 (0.6)
Feeling abnormal[a]	0	1 (0.1)	0	0
Hostility[a]	0	0	0	0
Agitation[b]	25 (2.4)	29 (2.9)	21 (2.1)	22 (2.2)
Aggression[b]	14 (1.4)	9 (0.9)	7 (0.7)	8 (0.8)
Delusions[b]	1 (0.1)	1 (0.1)	1 (0.1)	0
Hallucinations[b]	5 (0.5)	4 (0.4)	2 (0.2)	2 (0.2)

Homicidal ideation[b]	0	0	0	0
Mania[b]	7 (0.7)	9 (0.9)	3 (0.3)	6 (0.6)
Panic[b]	7 (0.7)	16 (1.6)	13 (1.3)	7 (0.7)
Paranoia[b]	1 (0.1)	0	0	2 (0.2)
Psychosis[b]	4 (0.4)	2 (0.2)	3 (0.3)	1 (0.1)
Suicidal behaviour[b]	1 (0.1)	1 (0.1)	0	1 (0.1)
Suicidal ideation[b]	5 (0.5)	2 (0.2)	3 (0.3)	2 (0.2)
Completed suicide[b]	0	0	0	0
Composite NPS AE Endpoint of severe intensity n (%)	14 (1.4)	14 (1.4)	14 (1.4)	13 (1.3)

AE, adverse event; [a]Grade = severe intensity AE; [b]Grade = moderate and severe intensity AE; NRT=Nicotine replacement therapy patch

There were more events reported in patients in the psychiatric cohort in each treatment group compared with the non-psychiatric cohort, and the incidence of events in the composite endpoint was higher for each of the active treatments compared to placebo. However, the use of varenicline, bupropion and NRT in the psychiatric cohort was not associated with a significantly increased risk of NPS adverse events in the composite primary endpoint compared with placebo (95% CIs included zero).

In the psychiatric cohort, the percentage of subjects with suicidal ideation and/or behaviour based on the Columbia-Suicide Severity Rating Scale (C-SSRS) was similar between the varenicline and placebo groups during treatment and in the non- treatment follow-up, as shown in the following table:

	Psychiatric Cohort N=4074			
	Varenicline N=1026 n (%)	**Bupropion N=1017 n (%)**	**NRT N=1016 n (%)**	**Placebo N=1015 n (%)**
During treatment				
Number assessed	1017	1012	1006	1006
Suicidal behaviour and/or ideation	27 (2.7)	15 (1.5)	20 (2.0)	25 (2.5)
Suicidal behaviour	0	1 (0.1)	0	2 (0.2)
Suicidal ideation	27 (2.7)	15 (1.5)	20 (2.0)	25 (2.5)
During follow up				
Number assessed	833	836	824	791
Suicidal behaviour and/or ideation	14 (1.7)	4 (0.5)	9 (1.1)	11 (1.4)
Suicidal behaviour	1 (0.1)	0	1 (0.1)	1 (0.1)
Suicidal ideation	14 (1.7)	4 (0.5)	9 (1.1)	11 (1.4)

NRT=Nicotine replacement therapy patch

There were no completed suicides reported in the psychiatric cohort.

The most commonly reported adverse events in subjects treated with varenicline in this study were similar to those observed in premarketing studies.

In both cohorts, subjects treated with varenicline demonstrated statistical superiority of CO-confirmed abstinence during weeks 9 through 12 and 9 through 24 compared to subjects treated with bupropion, nicotine patch and placebo (please see table below).

The key efficacy results are summarised in the following table:

	Non-psychiatric Cohort	**Psychiatric Cohort**
CA 9-12 n/N (%)		
Varenicline	382/1005 (38.0%)	301/1032 (29.2%)
Bupropion	261/1001 (26.1%)	199/1033 (19.3%)
NRT	267/1013 (26.4%)	209/1025 (20.4%)
Placebo	138/1009 (13.7%)	117/1026 (11.4%)
Treatment Comparisons: Odds ratio (95% CI), p value		
Varenicline vs Placebo	4.00 (3.20, 5.00), P<0.0001	3.24 (2.56, 4.11), P<0.0001
Bupropion vs Placebo	2.26 (1.80, 2.85), P<0.0001	1.87 (1.46, 2.39), P<0.0001
NRT vs Placebo	2.30 (1.83, 2.90), P<0.0001	2.00 (1.56, 2.55), P<0.0001
Varenicline vs Bupropion	1.77 (1.46, 2.14), P<0.0001	1.74 (1.41, 2.14), P<0.0001
Varenicline vs NRT	1.74 (1.43, 2.10), P<0.0001	1.62 (1.32, 1.99), P<0.0001
CA 9-24 n/N (%)		
Varenicline	256/1005 (25.5%)	189/1032 (18.3%)
Bupropion	188/1001 (18.8%)	142/1033 (13.7%)
NRT	187/1013 (18.5%)	133/1025 (13.0%)
Placebo	106/1009 (10.5%)	85/1026 (8.3%)
Treatment Comparisons: Odds ratio (95% CI), p value		
Varenicline vs Placebo	2.99 (2.33, 3.83), P<0.0001	2.50 (1.90, 3.29), P<0.0001
Bupropion vs Placebo	2.00 (1.54, 2.59), P<0.0001	1.77 (1.33, 2.36), P<0.0001
NRT vs Placebo	1.96 (1.51, 2.54), P<0.0001	1.65 (1.24, 2.20), P=0.0007
Varenicline vs Bupropion	1.49 (1.20, 1.85), P=0.0003	1.41 (1.11, 1.79), P=0.0047
Varenicline vs NRT	1.52 (1.23, 1.89), P=0.0001	1.51 (1.19, 1.93), P=0.0008

CA = continuous abstinence rate; CI = confidence interval; NRT=Nicotine replacement therapy patch

Neuropsychiatric Safety Meta-analyses and Observational Studies:

Analyses of clinical trial data did not show evidence of an increased risk of serious neuropsychiatric events with varenicline compared to placebo. In addition, independent observational studies have not supported an increased risk of serious neuropsychiatric events in patients treated with varenicline compared to patients prescribed nicotine replacement therapy (NRT) or bupropion.

Treatment discontinuation

The treatment discontinuation rate due to adverse reactions was 11.4% for varenicline compared with 9.7% for placebo. In this group, the discontinuation rates for the most common adverse reactions in varenicline treated patients were as follows: nausea (2.7% vs. 0.6% for placebo), headache (0.6% vs. 1.0% for placebo), insomnia (1.3% vs. 1.2% for placebo), and abnormal dreams (0.2% vs. 0.2% for placebo).

Analyses of Clinical Trials:

A meta-analysis of 5 randomised, double-blind, placebo controlled trials, including 1907 patients (1130 varenicline, 777 placebo), was conducted to assess suicidal ideation and behaviour as reported on the Columbia-Suicide Severity Rating Scale (C-SSRS). This meta-analysis included one trial (N=127) in patients with a history of schizophrenia or schizoaffective disorder and another trial (N=525) in patients with a history of depression. The results showed no increase in the incidence of suicidal ideation and/or behaviour in patients treated with varenicline compared to patients treated with placebo, as shown in the table below. Of the 55 patients who reported suicidal ideation or behaviour, 48 (24 varenicline, 24 placebo) were from the two trials that enrolled patients with a history of schizophrenia/ schizoaffective disorder, or of depression. Few patients reported these events in the other three trials (4 varenicline, 3 placebo).

Number of Patients and Risk Ratio for Suicidal Ideation and/or Behaviour Reported on C-SSRS from a Meta-Analysis of 5 Clinical Trials Comparing Varenicline to Placebo:

	Varenicline (N=1130)	**Placebo** (N=777)
Patients with suicidal ideation and/or behaviour* [n (%)]**	28 (2.5)	27 (3.5)
Patient-years of exposure	325	217
Risk Ratio # (RR; 95% CI)	0.79 (0.46, 1.36)	
* Of these, one patient in each treatment arm reported suicidal behaviour ** Patients with events up to 30 days after treatment; % are not weighted by study # RR of incidence rates per 100 patient years		

A meta-analysis of 18 double-blind, randomised, placebo-controlled clinical trials was conducted to assess the neuropsychiatric safety of varenicline. These trials included the 5 trials described above that used the C-SSRS, and a total of 8521 patients (5072 varenicline, 3449 placebo), some of which had psychiatric conditions. The results showed a similar incidence of combined neuropsychiatric adverse events, other than sleep disorders, in patients treated with varenicline compared to patients treated with placebo, with a risk ratio (RR) of 1.01 (95% CI: 0.89-1.15). Pooled data from these 18 trials showed a similar incidence rate of individual categories of psychiatric events in patients treated with varenicline compared to patients treated with placebo. The table below describes the most frequently (≥ 1%) reported categories of adverse events related to psychiatric safety other than sleep disorders and disturbances.

Psychiatric Adverse Events Occurring in ≥ 1% of Patients from Pooled Data from 18 Clinical Trials:

	Varenicline (N=5072)	**Placebo** (N=3449)
Anxiety disorders and symptoms	253 (5.0)	206 (6.0)
Depressed mood disorders and disturbances	179 (3.5)	108 (3.1)
Mood disorders and disturbances NEC*	116 (2.3)	53 (1.5)
* NEC = Not Elsewhere Classified Counts (percentages) corresponds to the number of patients reporting the event		

Observational Studies

Four observational studies, each including 10,000 to 30,000 users of varenicline in the adjusted analyses, compared the risk of serious neuropsychiatric events, including neuropsychiatric hospitalizations and fatal and non-fatal self-harm, in patients treated with varenicline versus patients prescribed NRT or bupropion. All studies were retrospective cohort

studies and included patients with and without a psychiatric history. All studies used statistical methods to control for confounding factors, including preferential prescribing of varenicline to healthier patients, although there is the possibility of residual confounding.

Two of the studies found no difference in risk of neuropsychiatric hospitalisations between varenicline users and nicotine patch users (Hazard Ratio [HR] 1.14; 95% Confidence Interval [CI]: 0.56–2.34 in the first study, and 0.76; 95% CI: 0.40-1.46 in the second study). The power to detect differences in these two studies was limited. The third study reported no difference in risk of psychiatric adverse events diagnosed during an emergency department visit or inpatient admission between varenicline users and bupropion users (HR 0.85; 95% CI: 0.55-1.30). Based on post marketing reports, bupropion may be associated with neuropsychiatric adverse events.

The fourth study showed no evidence of a higher risk of fatal and non-fatal self- harm (HR of 0.88; 95% CI: 0.52-1.49) in patients prescribed varenicline compared to patients prescribed NRT. The occurrence of detected suicide was rare during the three months after patients initiated any drug treatment (two cases in 31,260 varenicline users and six cases in 81,545 NRT users).

Pregnancy Cohort Study

A population-based cohort study compared infants exposed to CHAMPIX *in utero* (N=335) with infants born to mothers who smoked during pregnancy (N=78,412) and infants born to non-smoking mothers (N=806,438). In this study, infants exposed to CHAMPIX *in utero* as compared to infants born to mothers who smoked during pregnancy had lower rates of congenital malformations (3.6% vs 4.3%), stillbirth (0.3% vs 0.5%), preterm birth (7.5% vs 7.9%), small for gestational age (12.5% vs 17.1%), and premature rupture of membrane (3.6% vs 5.4%).

5.2 Pharmacokinetic properties

Absorption

Maximum plasma concentrations of varenicline occur typically within 3-4 hours after oral administration. Following administration of multiple oral doses to healthy volunteers, steady-state conditions were reached within 4 days. Absorption is virtually complete after oral administration and systemic availability is high. Oral bioavailability of varenicline is unaffected by food or time-of-day dosing.

Distribution

Varenicline distributes into tissues, including the brain. Apparent volume of distribution averaged 415 litres (%CV= 50) at steady-state. Plasma protein binding of varenicline is low (≤ 20%) and independent of both age and renal function. In rodents, varenicline is transferred through the placenta and excreted in milk.

Biotransformation

Varenicline undergoes minimal metabolism with 92% excreted unchanged in the urine and less than 10% excreted as metabolites. Minor metabolites in urine include varenicline N-carbamoylglucuronide and hydroxyvarenicline. In circulation, varenicline comprises 91% of drug-related material. Minor circulating metabolites include varenicline N-carbamoylglucuronide and N-glucosylvarenicline.

In vitro studies demonstrate that varenicline does not inhibit cytochrome P450 enzymes (IC50 > 6,400 ng/ml). The P450 enzymes tested for inhibition were: 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4/5. Also, in human hepatocytes *in vitro*, varenicline was shown to not induce the activity of cytochrome P450 enzymes 1A2 and 3A4. Therefore, varenicline is unlikely to alter the pharmacokinetics of compounds that are primarily metabolised by cytochrome P450 enzymes.

Elimination

The elimination half-life of varenicline is approximately 24 hours. Renal elimination of varenicline is primarily through glomerular filtration along with active tubular secretion via the organic cationic transporter, OCT2 (see section 4.5).

Linearity/Non linearity

Varenicline exhibits linear kinetics when given as single (0.1 to 3 mg) or repeated 1 to 3 mg/day doses.

Pharmacokinetics in special patient populations

There are no clinically meaningful differences in varenicline pharmacokinetics due to age, race, gender, smoking status, or use of concomitant medicinal products, as demonstrated in specific pharmacokinetic studies and in population pharmacokinetic analyses.

Hepatic impairment

Due to the absence of significant hepatic metabolism, varenicline pharmacokinetics should be unaffected in patients with

hepatic impairment. (see section 4.2).

Renal impairment

Varenicline pharmacokinetics were unchanged in subjects with mild renal impairment (estimated creatinine clearance > 50 ml/min and ≤ 80 ml/min). In patients with moderate renal impairment (estimated creatinine clearance ≥ 30 ml/min and ≤ 50 ml/min), varenicline exposure increased 1.5-fold compared with subjects with normal renal function (estimated creatinine clearance > 80 ml/min). In subjects with severe renal impairment (estimated creatinine clearance < 30 ml/min), varenicline exposure was increased 2.1-fold. In subjects with end-stage-renal disease (ESRD), varenicline was efficiently removed by haemodialysis (see section 4.2).

Elderly

The pharmacokinetics of varenicline in elderly patients with normal renal function (aged 65-75 years) is similar to that of younger adult subjects (see section 4.2). For elderly patients with reduced renal function please refer to section 4.2.

Paediatric population

Single and multiple-dose pharmacokinetics of varenicline have been investigated in paediatric patients aged 12 to 17 years old (inclusive) and were approximately dose-proportional over the 0.5 mg to 2 mg daily dose range studied. Steady-state systemic exposure in adolescent patients of bodyweight > 55 kg, as assessed by AUC (0-24), was comparable to that noted for the same doses in the adult population. When 0.5 mg twice daily was given, steady-state daily exposure of varenicline was, on average, higher (by approximately 40%) in adolescent patients with bodyweight ≤ 55 kg compared to that noted in the adult population. Efficacy and safety has not been demonstrated in the paediatric population below 18 years of age and no recommendation on a posology can be made (see section 4.2).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, fertility and embryo-foetal development. In male rats dosed for 2 years with varenicline, there was a dose-related increase in the incidence of hibernoma (tumour of the brown fat). In the offspring of pregnant rats treated with varenicline there were decreases in fertility and increases in the auditory startle response (see section 4.6). These effects were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. Nonclinical data indicate varenicline has reinforcing properties albeit with lower potency than nicotine. In clinical studies in humans, varenicline showed low abuse potential.

6. Pharmaceutical particulars

6.1 List of excipients

Tablets' core

0.5 mg and 1 mg Tablets

Cellulose, Microcrystalline

Calcium Hydrogen Phosphate Anhydrous

Croscarmellose Sodium

Silica, Colloidal Anhydrous

Magnesium Stearate

Film coating

0.5 mg Tablet

Hypromellose

Titanium Dioxide (E171)

Macrogol 400

Triacetin

1 mg Tablet

Hypromellose

Titanium Dioxide (E171)

Indigo Carmine Aluminium Lake E132

Macrogol 400

Triacetin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Bottles: 2 years

Blisters: 3 years

6.4 Special precautions for storage

Blisters: Store below 30°C

HDPE Bottle: This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

Treatment initiation packs

PCTFE/PVC blisters with aluminium foil backing containing one clear blister of 11 x 0.5 mg film-coated tablets and a second clear blister of 14 x 1 mg film-coated tablets in secondary heat sealed card packaging.

PCTFE/PVC blisters with aluminium foil backing containing one clear blister of 11 x 0.5 mg film-coated tablets and a second clear blister containing 14 x 1 mg film-coated tablets in a carton.

PCTFE/PVC blisters with aluminium foil backing containing one clear blister of 11 x 0.5 mg and 14 x 1 mg film-coated tablets and a second clear blister of 28 x 1 mg film-coated tablets in secondary heat sealed card packaging.

PVC blisters with aluminium foil backing containing one clear blister of 11 x 0.5 mg film-coated tablets and a second clear blister of 14 x 1 mg film-coated tablets in secondary heat sealed card packaging.

PVC blisters with aluminium foil backing containing one clear blister of 11 x 0.5 mg film-coated tablets and a second clear blister containing 14 x 1 mg film-coated tablets in a carton.

PVC blisters with aluminium foil backing containing one clear blister of 11 x 0.5 mg and 14 x 1 mg film-coated tablets and a second clear blister of 28 x 1 mg film-coated tablets in secondary heat sealed card packaging.

One outer carton containing:

PCTFE/PVC blisters with aluminium foil backing containing one clear blister of 11 x 0.5 mg and 14 x 1 mg film-coated tablets and a second clear blister of 28 x 1 mg film-coated tablets in one secondary heat sealed card pack and PCTFE/PVC blisters with aluminium foil backing in two secondary heat sealed card packs each containing 56 x 1 mg film-coated tablets.

One outer carton containing:

PVC blisters with aluminium foil backing containing one clear blister of 11 x 0.5 mg and 14 x 1 mg film-coated tablets and a second clear blister of 28 x 1 mg film-coated tablets in one secondary heat sealed card pack and PVC blisters with aluminium foil backing in two secondary heat sealed card packs each containing 56 x 1 mg film-coated tablets.

Maintenance packs

PCTFE/PVC blisters with aluminium foil backing in a pack containing 28 x 0.5 mg film-coated tablets in secondary heat sealed card packaging.

PCTFE/PVC blisters with aluminium foil backing in a pack containing 56 x 0.5 mg film-coated tablets in secondary heat sealed card packaging.

PVC blisters with aluminium foil backing in a pack containing 28 x 0.5 mg film-coated tablets in secondary heat sealed card packaging.

PVC blisters with aluminium foil backing in a pack containing 56 x 0.5 mg film-coated tablets in secondary heat sealed card packaging.

High-density polyethylene (HDPE) bottle with polypropylene child resistant closure and an aluminium foil /polyethylene induction seal containing 56 x 0.5 mg film-coated tablets

PCTFE/PVC blisters with aluminium foil backing in a pack containing 28 x 1 mg film-coated tablets in secondary heat sealed card packaging.

PCTFE/PVC blisters with aluminium foil backing in a pack containing 56 x 1 mg film-coated tablets in secondary heat sealed card packaging.

PCTFE/PVC blisters with aluminium foil backing in a pack containing 28 x 1 mg film-coated tablets in a carton.

PCTFE/PVC blisters with aluminium foil backing in a pack containing 56 x 1 mg film-coated tablets in a carton.

PCTFE/PVC blisters with aluminium foil backing in a pack containing 112 x 1 mg film-coated tablets in a carton.

PCTFE/PVC blisters with aluminium foil backing in a pack containing 140 x 1 mg film-coated tablets in a carton.

PVC blisters with aluminium foil backing in a pack containing 28 x 1 mg film-coated tablets in secondary heat sealed card packaging.

PVC blisters with aluminium foil backing in a pack containing 56 x 1 mg film-coated tablets in secondary heat sealed card packaging.

PVC blisters with aluminium foil backing in a pack containing 28 x 1 mg film-coated tablets in a carton.

PVC blisters with aluminium foil backing in a pack containing 56 x 1 mg film-coated tablets in a carton.

PVC blisters with aluminium foil backing in a pack containing 112 x 1 mg film-coated tablets in a carton.

PVC blisters with aluminium foil backing in a pack containing 140 x 1 mg film-coated tablets in a carton.

High-density polyethylene (HDPE) bottle with polypropylene child resistant closure and an aluminium foil / polyethylene induction seal containing 56 x 1 mg film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. Marketing authorisation holder

Pfizer Europe MA EEIG

Boulevard de la Plaine 17

1050 Bruxelles

Belgium

8. Marketing authorisation number(s)

0.5 mg tablets: EU/1/06/360/001, EU/1/06/360/006, EU/1/06/360/007, EU/1/06/360/017, EU/1/06/360/018

1mg tablets: EU/1/06/360/002, EU/1/06/360/004 EU/1/06/360/005 EU/1/06/360/009 EU/1/06/360/010 EU/1/06/360/011 EU/1/06/360/013, EU/1/06/360/015, EU/1/06/360/016, EU/1/06/360/020, EU/1/06/360/021, EU/1/06/360/022, EU/1/06 /360/024

Treatment initiation packs: EU/1/06/360/003, EU/1/06/360/008, EU/1/06/360/012, EU/1/06/360/014 EU/1/06/360/019, EU/1/06/360/023, EU/1/06/360/025, EU/1/06/360/026

9. Date of first authorisation/renewal of the authorisation

Date of first authorisation: 26 September 2006

Date of latest renewal: 29 June 2016

10. Date of revision of the text

08/2018

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu/

Ref: CI 39_0

Company Contact Details

Pfizer Limited

Address
Ramsgate Road, Sandwich, Kent, CT13 9NJ

Telephone
+44 (0)1304 616 161

Medical Information Direct Line
+44 (0)1304 616161

Medical Information Website
www.pfizermedicalinformation.co.uk

Package leaflet: Information for the user

CHAMPIX 0.5 mg film-coated tablets
CHAMPIX 1 mg film-coated tablets
Varenicline

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What CHAMPIX is and what it is used for
2. What you need to know before you take CHAMPIX
3. How to take CHAMPIX
4. Possible side effects
5. How to store CHAMPIX
6. Contents of the pack and other information

1. What CHAMPIX is and what it is used for

CHAMPIX contains the active substance varenicline. CHAMPIX is a medicine which is used in adults to help them stop smoking.

CHAMPIX can help to relieve the craving and withdrawal symptoms associated with stopping smoking.

CHAMPIX can also reduce the enjoyment of cigarettes if you do smoke when on treatment.

2. What you need to know before you take CHAMPIX

Do not take CHAMPIX:

- If you are allergic to varenicline or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions
Talk to your doctor or pharmacist before taking CHAMPIX.

There have been reports of depression, suicidal ideation and behaviour and suicide attempts in patients taking CHAMPIX. If you are taking CHAMPIX and develop agitation, depressed mood, changes in behaviour that are of concern to you or your family or if you develop suicidal thoughts or behaviours you should stop taking CHAMPIX and contact your doctor immediately for treatment assessment.

The effects of stopping smoking
The effects of changes in your body resulting from stopping smoking, with or without treatment with CHAMPIX, may alter the way other medicines work. Therefore, in some cases an adjustment of the dose may be necessary. See below under 'Other medicines and CHAMPIX' for further details.

For some people, stopping smoking with or without treatment has been associated with an increased risk of experiencing changes in thinking or behaviour, feelings of depression and anxiety and can be associated with a worsening of psychiatric disorder. If you have a history of psychiatric disorder you should discuss this with your doctor.

Heart symptoms
New or worse heart or blood vessel (cardiovascular) problems have been reported primarily in people who already have cardiovascular problems. Tell your doctor if you have any changes in symptoms during treatment with CHAMPIX. Get emergency medical help right away if you have symptoms of a heart attack or stroke.

Seizures
Tell your doctor if you have experienced seizures or have epilepsy before your start CHAMPIX treatment. Some people have reported seizures while taking CHAMPIX.

Hypersensitivity reactions
Stop taking CHAMPIX and tell your doctor immediately if you experience any of the following signs and symptoms that may indicate a serious allergic reaction: swelling of the face, lips, tongue, gums, throat or body and/or difficulty breathing, wheezing.

Skin reactions
Potentially life-threatening skin rashes (Stevens-Johnson syndrome and Erythema Multiforme) have been reported with the use of CHAMPIX. If you develop a rash or if your skin starts to peel or blister you should stop taking CHAMPIX and seek emergency medical help.

Children and adolescents
CHAMPIX is not recommended for use in children or adolescents below 18 years as safety and efficacy have not yet been established.

Other medicines and CHAMPIX
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

In some cases as a result of stopping smoking, with or without CHAMPIX, an adjustment of the dose of other medicines may be necessary. Examples include theophylline (a medicine to treat breathing problems), warfarin (a medicine to reduce blood clotting), and insulin (a medicine to treat diabetes). If in doubt, you should consult your doctor or pharmacist.

If you have severe kidney disease you should avoid taking cimetidine (a medicine used for gastric problems) at the same time as CHAMPIX as this may cause increased blood levels of CHAMPIX.

Use of CHAMPIX with other therapies for smoking cessation
Consult your doctor before using CHAMPIX in combination with other smoking cessation therapies.

CHAMPIX with food and drink
There have been some reports of increased intoxicating effects of alcohol in patients taking CHAMPIX. However, it is not known if CHAMPIX actually increases alcohol intoxication.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

It is preferable to avoid the use of CHAMPIX while you are pregnant. Talk to your doctor if you are intending to become pregnant.

Although it was not studied, CHAMPIX may pass into breast milk. You should ask your doctor or pharmacist for advice before taking CHAMPIX.

Driving and using machines
CHAMPIX may be linked with dizziness, sleepiness and transient loss of consciousness. You should not drive, operate complex machinery or engage in any other potentially hazardous activities until you know whether this medicine affects your ability to perform these activities.

3. How to take CHAMPIX

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

You are more likely to stop smoking if you are motivated to stop. Your doctor and pharmacist can provide advice, support and sources of further information to help ensure your attempt to stop smoking is successful.

Before starting your course of CHAMPIX you should usually decide on a date in the second week of treatment (between day 8 and day 14) when you will stop smoking. If you are not willing or able to set a target quit date within 2 weeks, you may choose your own target quit date within 5 weeks after starting treatment. You should write this date on the pack as a reminder.

CHAMPIX comes as a white tablet (0.5 mg) and a light blue tablet (1 mg). You start with the white tablet and then usually go to the light blue tablet. See the chart below for the usual dosing instructions which you should follow from Day 1.

Week 1	**Dose**
Day 1 - 3	From day 1 to day 3, you should take one white CHAMPIX 0.5 mg film-coated tablet once a day.
Day 4 - 7	From day 4 to day 7, you should take one white CHAMPIX 0.5 mg film-coated tablet twice daily, once in the morning and once in the evening, at about the same time each day.

Week 2	
Day 8 – 14	From day 8 to day 14, you should take one light blue CHAMPIX 1 mg film-coated tablet twice daily, once in the morning and once in the evening, at about the same time each day.

Weeks 3 - 12	
Day 15 - end of treatment	From day 15 until the end of treatment, you should take one light blue CHAMPIX 1 mg film-coated tablet twice daily, once in the morning and once in the evening, at about the same time each day.

After 12 weeks of treatment, if you have stopped smoking, your doctor may recommend an additional 12 weeks of treatment with CHAMPIX 1 mg film-coated tablets twice daily to help avoid returning back to smoking.

If you are not able or willing to quit smoking straight away, you should reduce smoking during the first 12 weeks of treatment and quit by the end of that treatment period. You should then continue to take CHAMPIX 1 mg film-coated tablets twice daily for a further 12 weeks resulting in a total of 24 weeks of treatment.

Should you experience adverse effects that you cannot tolerate your doctor may decide to reduce your dose temporarily or permanently to 0.5 mg twice daily.

If you have problems with your kidneys, you should speak to your doctor before taking CHAMPIX. You may need a lower dose.

Champix is for oral use.
The tablets should be swallowed whole with water and can be taken with or without food.

If you take more CHAMPIX than you should
If you accidentally take more CHAMPIX than your doctor prescribed, you must seek medical advice or go to the nearest hospital casualty department immediately. Take your box of tablets with you.

If you forget to take CHAMPIX
Do not take a double dose to make up for a forgotten tablet. It is important that you take CHAMPIX regularly at the same time each day. If you forget to take a dose, take it as soon as you remember. If, it is within 3-4 hours before your next dose, do not take the tablet that you have missed.

If you stop taking CHAMPIX
It has been shown in clinical trials that taking all doses of your medicine at the appropriate times and for the recommended duration of treatment described above will increase your chances of stopping smoking. Therefore, unless your doctor instructs you to stop treatment, it is important to keep taking CHAMPIX, according to the instructions described in the table above.

In smoking cessation therapy, risk of returning to smoking may be elevated in the period immediately following the end of treatment. You may temporarily experience increased irritability, urge to smoke, depression and/or sleep disturbances when you stop taking CHAMPIX. Your doctor may decide to gradually lower your dose of CHAMPIX at the end of treatment.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Giving up smoking with or without treatment can cause various symptoms. These could include changes of mood (like feeling depressed, irritable, frustrated or anxious), sleeplessness, difficulty concentrating, decreased heart rate and increased appetite or weight gain.

You should be aware of the possible emergence of serious neuropsychiatric symptoms, such as agitation, depressed mood, or changes in behaviour during a quit attempt with or without CHAMPIX and you should contact a doctor or pharmacist if you experience such symptoms.

Serious side effects of either an uncommon or rare frequency have occurred in people attempting to quit smoking with CHAMPIX: seizure, stroke, heart attack, suicidal thoughts, loss of contact with reality and unable to think or judge clearly (psychosis), changes in thinking or behaviour (such as aggression and abnormal behaviour). There have also been reports of severe skin reactions including Erythema Multiforme (a type of rash) and Stevens-Johnson Syndrome (a serious illness with blistering of the skin, mouth, around the eyes or genitals) and serious allergic reactions including angioedema (swelling of the face, mouth, or throat).

- Very common: may affect more than 1 in 10 people

    - Inflammation of the nose and throat, abnormal dreams, difficulty sleeping, headache,
    - Nausea

- Common: may affect up to 1 in 10 people

    - Chest infection, inflammation of the sinuses
    - Increased weight, decreased appetite, increased appetite
    - Sleepiness, dizziness, changes in the way things taste
    - Shortness of breath, cough
    - Heartburn, vomiting, constipation, diarrhoea, feeling bloated, abdominal pain, toothache, indigestion, flatulence, dry mouth
    - Skin rash, itching
    - Joint ache, muscle ache, back pain
    - Chest pain, tiredness

- Uncommon: may affect up to 1 in 100 people

    - Fungal infection, viral infection
    - Feeling of panic, difficulty thinking, restlessness, mood swings, depression, anxiety, hallucinations, changes in sex drive
    - Seizure, tremor, feeling sluggish, less sensitive to touch
    - Conjunctivitis, eye pain
    - Ringing in the ears
    - Angina, rapid heart rate, palpitations, increased heart rate
    - Increased blood pressure, hot flush
    - Inflammation of nose, sinuses and throat, congestion of nose, throat and chest, hoarseness, hay fever, throat irritation, congested sinuses, excess mucous from nose causing cough, runny nose
    - Red blood in stools, irritated stomach, change of bowel habit, belching, mouth ulcers, pain in the gums
    - Reddening of the skin, acne, increased sweating, night sweats
    - Muscle spasms, chest wall pain
    - Abnormally frequent urination, urination at night
    - Increased menstrual flow
    - Chest discomfort, flu like illness, fever, feeling weak or unwell
    - High blood sugar
    - Heart attack
    - Suicidal thoughts
    - Changes in thinking or behaviour (such as aggression)

- Rare: may affect up to 1 in 1,000 people

    - Excessive thirst
    - Feeling unwell or unhappy, slow thinking
    - Stroke
    - Increased muscle tension, difficulty with speech, difficulty with coordination, reduced sense of taste, altered sleep pattern
    - Disturbed vision, eyeball discolouration, dilated pupils, sensitivity to light, shortsightedness, watery eyes
    - Irregular heart beat or heart rhythm disturbances
    - Throat pain, snoring
    - Blood in vomit, abnormal stools, coated tongue
    - Stiff joints, rib pain

- Glucose in urine, increased urine volume and frequency
- Vaginal discharge, changes in sexual ability
- Feeling cold, cyst
- Diabetes
- Sleep walking
- Loss of contact with reality and unable to think or judge clearly (psychosis)
- Abnormal behaviour
- Severe skin reactions including Erythema Multiforme (a type of rash) and Stevens-Johnson Syndrome (a serious illness with blistering of the skin, mouth, around the eyes or genitals)
- Serious allergic reactions including angioedema (swelling of the face, mouth, or throat)

- Not known

  - Transient loss of consciousness

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly (see details below). By reporting side effects you can help provide more information on the safety of this medicine.

United Kingdom
Yellow Card Scheme website: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

Ireland
HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

Malta
ADR Reporting
Website: www.medicinesauthority.gov.mt/adrportal

5. How to store CHAMPIX

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the card packaging or carton after EXP. The expiry date refers to the last day of that month.

Blisters: Store below 30°C
Bottle: This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What CHAMPIX contains
- The active substance is varenicline.
- Each 0.5 mg film-coated tablet contains 0.5 mg of varenicline (as tartrate).

- Each 1 mg film-coated tablet contains 1 mg of varenicline (as tartrate).
- The other ingredients are:

Tablet Core - CHAMPIX 0.5 mg and 1 mg film-coated tablets
Cellulose, Microcrystalline Calcium Hydrogen Phosphate Anhydrous Croscarmellose Sodium Silica, Colloidal Anhydrous Magnesium Stearate

Tablet film coating - CHAMPIX 0.5 mg film-coated tablets
Hypromellose Titanium dioxide (E171) Macrogol 400 Triacetin

Tablet film coating - CHAMPIX 1 mg film-coated tablets
Hypromellose Titanium dioxide (E171) Macrogol 400 Indigo Carmine Aluminium Lake (E132) Triacetin

What CHAMPIX looks like and contents of the pack

- CHAMPIX 0.5 mg film-coated tablets are white, film-coated, modified capsular shaped tablets, marked "*Pfizer*" and "CHX 0.5"

- CHAMPIX 1 mg film-coated tablets are light blue film-coated, modified capsular shaped tablets, marked "*Pfizer*" and "CHX 1.0"

CHAMPIX is available in the following pack presentations:

- A treatment initiation pack containing 2 blisters; 1 clear blister of 11 x CHAMPIX 0.5 mg film-coated tablets and 1 clear blister of 14 x CHAMPIX 1 mg film-coated tablets in card packaging.
- A treatment initiation pack containing 2 blisters; 1 clear blister of 11 x CHAMPIX 0.5 mg and 14 x 1 mg film-coated tablets and 1 clear blister of 28 x CHAMPIX 1 mg film-coated tablets in card packaging.
- A treatment initiation pack in an outer carton containing one pack with 1 clear blister of 11 x CHAMPIX 0.5 mg and 14 x 1 mg film-coated tablets and 1 clear blister of 28 x CHAMPIX 1 mg film-coated tablets in card packaging and two packs each containing 2 clear blisters of 28 x CHAMPIX 1 mg film-coated tablets in card packaging.
- A follow-on (maintenance) pack containing 2 clear blisters of 14 x CHAMPIX 1 mg film-coated tablets in card packaging.
- A follow-on (maintenance) pack containing 2 clear blisters of 28 x CHAMPIX 1 mg film-coated tablets in card packaging.
- A follow-on (maintenance) pack containing 2 clear blisters of 14 x CHAMPIX 0.5 mg film-coated tablets in card packaging.
- A follow-on (maintenance) pack containing 2 clear blisters of 28 x CHAMPIX 0.5 mg film-coated tablets in card packaging.
- A treatment initiation pack containing 2 blisters; 1 clear blister of 11 x CHAMPIX 0.5 mg film-coated tablets and 1 clear blister of 14 x CHAMPIX 1 mg film-coated tablets in a carton.
- A follow-on (maintenance) pack containing 2 clear blisters of 14 x CHAMPIX 1 mg film-coated tablets in a carton.

- A follow-on (maintenance) pack containing 4 clear blisters of 14 x CHAMPIX 1 mg film-coated tablets in a carton.
- A follow-on (maintenance) pack containing 8 clear blisters of 14 x CHAMPIX 1 mg film-coated tablets in a carton.
- A follow-on (maintenance) pack containing 10 clear blisters of 14 x CHAMPIX 1 mg film-coated tablets in a carton.
- A sealed white HDPE bottle pack, with a child resistant screw cap, in a carton, containing 56 x CHAMPIX 1 mg film-coated tablets.
- A sealed white HDPE bottle pack, with a child resistant screw cap, in a carton, containing 56 x CHAMPIX 0.5 mg film-coated tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

Manufacturer
R-Pharm Germany GmbH
Heinrich-Mack-Str. 35, 89257 Illertissen
Germany

or

Pfizer Italia S.r.l.
Località Marino del Tronto,
63100 Ascoli Piceno (AP)
Italy

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

United Kingdom
Pfizer Limited
Tel: + 44 (0) 1304 616161

Ireland
Pfizer Healthcare Ireland
Tel: 1800 633 363 (toll free)
+44 (0) 1304 616161

Malta
V.J. Salomone Pharma Ltd.
Tel: +356 21220174

This leaflet was last revised in 08/2018

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency website: http://www.ema.europa.eu/

SCIENTIFIC DISCUSSION

1. Introduction

The claimed indication for CHAMPIX (varenicline) 0.5 mg and 1 mg film-coated tablets is smoking cessation in adults.

Varenicline is a highly selective partial agonist of the nicotinic acetylcholine receptor α4β2 subtype. In animal models, the α4β2 nicotinic receptor has been shown to be responsible for the reinforcing properties of nicotine. Both nicotine and varenicline bind to this receptor subtype. Binding of nicotine to this receptor subtype causes dopamine release in the mesolimbic "reward" system *(nucleus. accumbens*). It is hypothesized that varenicline, a partial agonist, blocks the full-agonist activity of nicotine by competitive binding. As varenicline has this partial agonistic action it may cause relief of withdrawal and craving symptoms. Withdrawal and craving symptoms are thought to maintain nicotine addiction, and diminishing these symptoms would promote smoking cessation.

The European Commission has estimated that more than 650,000 (i.e. 1 in 7) Europeans die prematurely every year due to smoking related diseases while an additional 13 million suffer from a serious, chronic disease as a result of smoking. The economic burden due to smoking was in EU conservatively estimated at 98-130 billion Euros per year or between 1.04% and 1.39% of the region's Gross Domestic Product for 2000.

According to World Bank estimates the number of smokers worldwide exceeded 1.3 billion in 2003. The worldwide prevalence of smoking was estimated at 47% of men and 10% of women. Smoking prevalence overall and by gender varies by country and/or region). In 2002-2003, the average prevalence of adult smoking in the 25 EU member states was 29% overall, 35% for men and 22% for women. Reducing the current smoking rate by 50% would avoid 20-30 million premature deaths in the first quarter of this century.

Population-based surveys in the United States and United Kingdom indicate that approximately 70% of smokers say they are interested in giving up smoking. Reports indicate that 35% to 45% of smokers actually try to abstain each year but only 3.5% succeed without assistance. Relapse within days to weeks is common and most smokers make multiple attempts to stop, often waiting 2 to 3 years between attempts.

Nicotine has affinity for the nicotinic cholinergic receptors, which are widely spread throughout the brain, the autonomic ganglia, and the neuromuscular junction. The natural ligand for the receptor is acetylcholine. Nicotine may exert both stimulating and inhibiting effects upon different organ systems. Nicotine use induces arterial constriction and affects the cardiovascular tone; nicotine induces nausea in naïve subjects and may induce metabolic changes (hyperglycaemia). Its addictive properties arise from its pre-synaptic actions influencing neurotransmitter release in the brain (dopamine release in the *nucleus accumbens* reward system). The craving and withdrawal symptoms, which include depressed mood, irritability, difficulty concentrating, restlessness, increased appetite, and sleep disturbance, cause significant distress to the smoker and threaten the quit attempt

Current pharmacotherapies for smoking cessation are presently various forms of nicotine replacement therapy (NRT) and the non-nicotinic agent, sustained release bupropion. Meta-analyses of controlled clinical trials have consistently shown that both NRT (any form) and bupropion approximately double the odds of smoking cessation compared with placebo.

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2. Quality aspects

Introduction

Champix is presented as immediate release film-coated tablets containing 0.5 mg and 1 mg of varenicline (as varenicline tartrate) as active substance. The other ingredients are cellulose, microcrystalline, calcium hydrogen phosphate, anhydrous, croscarmellose sodium, silica, colloidal anhydrous and magnesium stearate. The film consists of hypromellose, titanium dioxide, macrogols, Purified Water and colorants.

The film-coated tablets are marketed either in opaque blue-white HDPE bottle with an aluminum foil/polyethylene induction seal and a child-resistant polypropylene closure or in clear PVC / Aclar film with an aluminum foil backing.

Active substance

The drug substance is varenicline as varenicline tartrate and its chemical name is 7,8,9,10-tetrahydro-6,10-methano-6*H*-azepino[4,5-*g*]quinoxaline (2*R*,3*R*)-tartrate according to the IUPAC nomenclature. Varenicline tartrate is white to off-white to slightly yellow solid and is non-hygroscopic. It is moderately soluble in dimethylacetamide, acetronitrile, methanol, hexane and ethyl acetate. Varenicline freebase is an achiral molecule, however varenicline tartrate, which is formed through the reaction of varenicline freebase and L-tartaric acid is optically active, and has the absolute configuration of the counter ion 2R, 3R.

- **Manufacture**

Varenicline is synthesised in six chemical steps followed by purification (filtration) and milling.

The manufacturing process has been adequately described. Critical parameters have been identified and adequate in-process controls included.

Specifications for starting materials, reagents, catalysts and solvents have been provided. Adequate control of critical steps and intermediates have been presented.

Structure elucidation has been performed by infrared absorption spectroscopy, mass spectrometry, ^{1}H-NMR spectroscopy, ^{13}C-NMR spectroscopy, X-ray spectroscopy, ultraviolet spectroscopy and optical rotation spectroscopy, and these data confirm the structure of the active substance. The established structure of varenicline tartrate was in agreement with the method of synthesis, analytical and spectroscopic data. The molecular weight determined by mass spectroscopy was in agreement with the expected molecular weight. Definite proof of structure was provided by X-ray crystallography.

- **Specification**

The active substance specifications include test for Appearance (Visual Inspection), identification (IR and HPLC), assay (98.00 – 102% HPLC), tartaric acid content (HPLC), water content (Karl Fisher), Residue on Ignition, heavy metals, residual solvents (GC) Impurities (HPLC) and particle size.
The specifications reflect all relevant quality attributes of the active substance. The analytical methods which were used in the routine controls were described and their validations are in accordance with the ICH Guidelines. Impurities have been extensively described, classified as process related impurities and possible degradation products, and qualified. Furthermore, some of the genotoxic impurities were reduced resulting in levels in the active substance in accordance with CHMP Guideline on the Limits of Genotoxic Impurities. Residual solvents have been satisfactorily controlled in the active substance. Limits are in accordance with ICH requirements. Batch analysis results for the active substance comply with the specifications and show a good uniformity from batch to batch.

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- **Stability**

The stability results from long-term accelerated and stress studies which were completed according to ICH guidelines demonstrated adequate stability of the active substance. It was confirmed that the active substance is very stable when exposed to a variety of stressed conditions such as acid, base, oxidation, thermal, humidity and light exposure. The results of the long-term and accelerated studies support the retest period.

Finished product

- **Pharmaceutical Development**

All information regarding the choice of the drug substance as a tartaric acid salt and the excipients are sufficiently justified. Well known excipients were used in the formulation, selected based on their suitability for use in a dry granulation process. Microcrystalline cellulose is used as a diluent and binder, anhydrous calcium hydrogen phosphate as a diluent, croscarmellose sodium as a disintegrant, anhydrous colloidal silica as a glidant and magnesium stearate as lubricant. The compatibility of the active substance was demonstrated with the results of stability studies performed on the finished product.
A film-coating system was added and the tablet shape was changed to capsular tablet shape. In order to differentiate the two strengths the colorant use in the film-coating system was slightly different.
The bioequivalence studies which were performed confirmed bioequivalence between the commercial tablets (1 mg) and the phase 3 tablets, as well as between phase 3 tablets and phase 2B tablets (tartrate salt) and phase 2A tablets (succinate salt). The same core formulation (common blend) has been used for the 0.5 mg tablets as has been used for the 1 mg tablets.
Comparative dissolution profiles are presented for the two strengths of six primary stability batches manufactured by the site. All batches demonstrated similar dissolution profiles with nearly 100 % dissolved after 5 minutes.

- **Manufacture of the Product**

The proposed commercial manufacturing process involves standard technology using standard manufacturing process such as blending, milling (deagglomeration), roller compaction and milling, compression, aqueous-based film-coating unit operations. Furthermore the equipment used is commonly available in the pharmaceutical industry. A dry granulation process was selected based on the improved process robustness gained by the resulting properties of the granulate, including improvements to flow and drug uniformity.
The process validation scheme for manufacture commercial batches was provided.

The batch analysis results show that the medicinal product can be manufactured reproducibly according the agreed finished product specifications.

- **Product Specification**

The drug product specifications were established according the ICH guidelines and include the following tests: appearance, identification (TLC and HPLC), content per tablet of the active substance (HPLC), uniformity of dosage units (Ph Eur), disintegration (Ph Eur), water content (Ph Eur), individual degradation products (HPLC), microbial limits (Ph Eur).
All analytical procedures which were used for testing the drug product were properly described. Moreover, all relevant methods were satisfactorily validated in accordance with the CHMP and ICH guidelines.
The batch analysis data obtained from the analysis of six batches for each strength manufactured by the commercial manufacturing process confirmed satisfactory uniformity of the product at release.

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- **Stability of the Product**

The stability studies were conducted according to the ICH guideline. Three production scale batches of each strength have been stored at long term and accelerated conditions in the proposed market packaging.
One production batch per strength was stored under elevated temperature and humidity conditions for 3 months and at ICH photostability conditions and degradation conditions.
Based on available stability data, the proposed shelf life and storage conditions as stated in the SPC are acceptable.

Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture, control of the active substance and the finished product have been presented in a satisfactory manner and justified in accordance with relevant Guidelines. The results of tests carried out indicate satisfactory consistency and uniformity of the finished product. Therefore, this medicinal product should have a satisfactory and uniform performance in the clinic.
At the time of the CHMP opinion, there were a number of minor unresolved quality issues which do not have impact on the Benefit/Risk ratio of the medicinal product. The applicant gave a letter of undertaking and committed to resolve these as Follow Up Measures after the opinion, within the agreed timeframe.

3. Non-clinical aspects

Introduction

The non-clinical programme is in reasonable agreement with EU/ICH guidelines. The majority of safety pharmacology studies were not conducted in compliance with GLP-regulations. The toxicology studies were GLP-compliant. As several pivotal toxicokinetic bioanalyses were performed by a laboratory not listed in the Cumulative Overview of GLP inspections in OECD Member countries of 2001, its GLP-status was verified by the EMEA.

Pharmacology

In vitro varenicline displayed high affinity for the rat cortex $\alpha_4\beta_2$ nicotine receptor in radioligand displacement binding assays with a Ki value of 0.17 nM. It is believed that the nicotinic $\alpha_4\beta_2$ receptor mediates dopamine release in the nucleus accumbens and thus is involved in the motivational effects of smoking. Both nicotine and varenicline both reversibly bind to the same receptor binding site. Considering the 15-fold higher affinity of varenicline for the $\alpha_4\beta_2$ nicotinic acetylcholine receptor as compared with nicotine, very high nicotine brain concentrations would be required to fully displace varenicline and produce nicotine rewarding in the subject.

Ex vivo, varenicline only partially activates the mesolimbic dopamine system, in comparison to activation induced by nicotine: varenicline released ^{3}H-dopamine from rat striatal slices with a maximal response of 51% (relative to the release evoked by nicotine) at 1 μM, indicating that varenicline acts as a partial agonist at the nicotinic acetylcholine receptor. Additionally, 10 μM varenicline reduced the response induced by nicotine by 53%, down to levels induced by varenicline.

An EC_{50} value of 3.5 μM was obtained for varenicline in HEK293 cells expressing human $\alpha_4\beta_2$ receptors. The maximal effect of varenicline was 43% of what was observed for nicotine. Concurrent application of 10 μM varenicline and nicotine reduced the inward current by 53% at steady state.

In vivo microdialysis showed that p.o varenicline treatment caused moderate increases in dopamine release in the nucleus accumbens of freely moving rats. Maximal extracellular dopamine concentrations were reached 2 hours following dosing and the level started to normalise 4 to 5 hours after varenicline administration. The maximal dopamine response of varenicline was around 63% of the full agonist nicotine.

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In drug discrimination studies, varenicline (0.01-1 mg/kg p.o.) dose-dependently generalized to nicotine, with complete generalization at 1 mg/kg. However in self-administration studies, rats self-administered varenicline significantly less than nicotine, demonstrating that varenicline is not as reinforcing as nicotine. Furthermore, varenicline pretreatment (1-3 mg kg s.c.) reduced the amount of nicotine by 50% that rats self-administered.

Varenicline displayed binding affinity towards the 5-HT_{3A}-receptor subunit with a Ki value of 350 nM. The Ki for HT_{3A} is approximately 10-fold higher then the human C_{max}. The HT_3-receptor is involved in the mediation of nausea/emesis and irritable bowel; symptoms which are observed clinically during varenicline treatment. According to the Applicant, varenicline could cause emesis peripherally by affecting afferent signaling pathways from the gastrointestinal tract to the emetic center in the mid-brainstem, most likely by activation of 5-HT_3 receptors and/or $\alpha_3\beta_4$ nAChRs. Furthermore, varenicline could possibly have a central action that contributes to emesis through the activation of $\alpha_4\beta_2$ nAChRs in brain nuclei that control the activity of the emetic center.

- Secondary pharmacodynamics and safety pharmacology

In the safety pharmacology studies, high doses of varenicline induced various CNS effects; however, they all occurred with safety margins of at least 50. The only exception is a treatment-related decrease in body temperature, which occurred with a safety margin of 16.

In vitro, 17 μM varenicline inhibited the hERG current by 17%. Additionally, 10 μM varenicline increased the action potential duration in dog cardiac purkinje fibers. In both cases, the findings occurred with a safety margin of more than 90. When evaluated in six monkeys, there were no significant differences between ECG data obtained during vehicle and varenicline treatment. However, one monkey experienced a 30% decrease in heart rate and a slight increase in P-R-interval. In the repeat-dose toxicity studies conducted in monkeys, no treatment-related effects were observed with respect to heart rate, blood pressure, ECG or respiration rate. Since no effects on ECG were observed in the 9 month repeat dose toxicity study in monkeys at the highest dose (1.2 mg/kg/day), this dose may be considered as NOAEL for QT-prolongation. Comparing clinical C_{max} and C_{max} in the monkeys gives a safety margin of approximately 15. No noteworthy changes in the QT interval or any ECG parameters were observed in the clinical studies and there appears to be no need for further investigations.

A dose-dependent increase in the urinal excretion of sodium and chloride was observed in rats but this finding occurred with a safety margin of 50. An inhibiting effect on gastrointestinal motility was observed with a safety margin of 10. Based on an emesis study conducted in ferrets, varenicline has the potential to induced emesis in humans possible via both a local effect on the gut wall as well as a central effect.

Overall, other pharmacodynamic effects caused by varenicline treatment were observed with large safety margins and the only observations of clinical relevance are nausea and emesis.

- Pharmacodynamic drug interactions

Glaucoma, mydriasis, anti-Parkinson, local anesthetics, anti-psychotics, anti-depressants and anxiolytic/hypnotic drugs show low to very low affinity for the nicotinic α4β2 AChRs. In turn, varenicline displays very low affinity for the target receptors of these classes of drugs. Pharmacodynamic interactions are therefore unlikely to occur.

Pharmacokinetics

Absorption: overall, varenicline is characterised by high absorption, negligible first-pass effect, moderate distribution across many tissues, moderate half-life and extensive renal excretion. In rats and monkeys there was no evidence of gender differences with respect to plasma exposure following repeated p.o. varenicline administration. The systemic exposure (AUC) appeared to be higher following repeated p.o. dosing of rats, indicating that accumulation occurred to a minor extent. Mean

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varenicline C_{max} and AUC values increased in a less than dose-proportional manner following repeated p.o. dosing of rats and monkeys.

Distribution: the percent of drug bound to plasma proteins was 18%, 45%, 19%, 41% and 20% in mouse, rat, dog, monkey and human plasma, respectively. The tissue distribution of varenicline was investigated using whole-body autoradioluminography in male and female Long-Evans rats following oral dosing of ^{14}C-varenicline. In the majority of tissues, maximal radioactivity concentrations were measured at the first sampling point, which was 1 hour post dosing. Varenicline distributed into all collected tissues except the lens and vitreous humor. Still, varenicline displayed a high affinity for ocular tissues since (besides the GI tract) maximal radioactivity was measured in ciliary body, uvea, iris and choroid. Moreover, high concentrations of radioactivity were detected in ocular tissues at the last sampling point (168 hours). There were no apparent gender differences with respect to tissue distribution. Varenicline displays affinity for melanin containing tissues.

Metabolism: the metabolites of varenicline were identified in circulation and in excreta of laboratory animals and healthy human subjects. In mice, rats, monkeys, and humans the vast majority (75%-93%) of drug-related material in circulation and excreta was comprised of unchanged drug, indicating that metabolism is not a primary route of varenicline clearance in these species. In rabbits, metabolites were present in greater abundance than varenicline. A total of 13 metabolites were observed in all species and were products of oxidation and conjugation pathways. Three metabolites in animal studies remain unidentified (designated as M3, M3a, and M6), but all were present at less than 3.3% and none were detected in humans. In excreta, there was no single metabolite that was more than 4.6% of dose in any species, while unchanged varenicline comprised at least 75% or more of dose in excreta in all species. Overall, the metabolism of varenicline in laboratory species and humans is very similar and all metabolites observed in humans were observed in one or more animal species used in preclinical safety evaluations.

Excretion: the organic cation transporter 2 (OCT-2) is involved in renal elimination of varenicline and the risk of pharmacokinetic drug interactions with OCT-2 inhibitors has been evaluated clinically. Drug interactions on the level of CYP mediated metabolism are not likely. In vitro studies showed that glucuronyl transferase 2B7 (UGT2B7) is responsible for the N-carbamoylglucuronidation of varenicline but this pathway represents only a very small portion of the total clearance.

Toxicology

- Single dose toxicity

Single-dose toxicity studies were conducted in Sprague-Dawley rats, Beagle dog and Cynomolgus monkeys. The results are summarised in the Table below. The dose is expressed as free base. All the listed findings were reversible. No mortality was observed after PO administration of 300 mg/kg/day and 0.2 mg/kg/day varenicline to rats and monkeys, respectively.

Study ID	Species/ Number/ Sex/ Group	Dose/ Route	NTEL/ NTEL animal:human Exposure ratio (AUC)	Major findings
97-1545-06 GLP but not TK	rat/3/sex/group	30, 100, 200, 300 mg/kg /PO	100 mg/kg/ 100	≥200 mg/kg: labored respiration, ↓activity, uncoordinated gait, splayed hindlimbs, tremor, ptosis, loose stool, hunched posture, rough haircoat. ↓body weight, ↓WBC, ↓lymphocytes, ↑blood glucose. 300 mg/kg: convulsions (clonic & tonic)
00-1545-26 non-GLP	rat/6/sex/group	3, 30 mg/kg /PO	30 mg/kg/ 50	No toxicity

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97-1545-05 non-GLP Dose escalation study	Dog/1/sex/group	Fasted: 0.05, 0.1, 0.3, 1 mg/kg/PO Fed: 1 mg/kg/PO	<0.05 mg/kg (clinically relevant exposure levels)	≥0.05 mg/kg: multiple episodes of emesis ≥0.1 mg/kg: body tremors, ↓activity, salivation, loose stool, ≥0.3 mg/kg: ↑ALT 1 mg/kg: unsteady gait, prolapsed nictitating membrane, ↑neutrophil, monocytes
98-1545-14 GLP	monkey/2/sex/ group	3 mg/kg/PO	<3 mg/kg (2)	Emesis, recumbency, ↓activity, tremors, ↓food intake Day 1, ↓HR &QT ↑PRQ,
00-1545-27 non-GLP	monkey/2/sex/ group	0.1/day or 0.1 BID/PO	0.1 mg/kg BID/ 0.9	No toxicity
745-03502 GLP but not TK Dose escalation study	monkey/1/sex/ group	Day 1: 80, Day 2: 200, Day 3: 300 µg/kg/day/ IV	80 µg/kg/day (C_{max} ≈ 20.5 – ratio ≈ 2)	200 µg/kg/day: emesis, tremors, ↓activity, muscle rigidity 300 µg/kg/day: as above and generalised tremors (dosing stopped), ↑AST, ALT, ↓total protein, albumin
745-03516 GLP	monkey/4/sex/ group	180 µg/kg /IV	<180 µg/kg (1.5)	↓food consumption, 48(♂)-57(♀)-fold increase in skeletal muscle specific CK, ↑AST, ALT No ECG findings

Human AUC is 194 ng*h/mL following administration of the maximum recommended dose (2 mg/day);The listed exposure ratios have been adjusted for plasma protein binding.

- Repeat dose toxicity (with toxicokinetics)

Repeated dose toxicity of varenicline was evaluated after oral administration in mice, rats, dogs and monkeys. Two studies of 14-days and 3 months duration were conducted in mice, four studies with durations of 10 days, 6 weeks, 3 months and 6 months in rats, one 7-day study in dogs and seven oral studies with durations of 7 days to 9 months were conducted in monkeys. In each study, systemic exposure to varenicline was evaluated for relationship to dose level, sex, and duration of dosing.

Decreased body weight, body weight gain and food consumption were observed in rats at varenicline plasma exposure levels around 50-fold higher than is observed in the clinic. Body weight loss, dehydration and inappetance were dose-limiting factors in the monkey repeat-dose toxicity study, where weight loss and reduced food consumption occurred at AUC values approximately 10 times the human systemic exposure. Anorexia and decreased appetite are uncommon findings in the clinic. In contrast, most patients experience increased appetite, which is commonly observed following cessation of smoking.

Effects on the central nervous system (e g tremors, laboured respiration, unsteady gait) were seen in mice, rats (both at 100 mg/kg/day), and dogs (at ≥0.1 mg/kg/day). At 150mg/kg/day, convulsions were seen in mice. Salivation was a common finding in varenicline-treated rats and monkeys, which occurred at a 6-fold higher AUC values than observed in the clinic.

Gastrointestinal effects (gastric/cecal/colonic dilatation and/or emesis, and loose stools/dehydration) occurred in mice, rats and/or monkeys and were expected findings based on known pharmacological effects of nicotine. Enlarged stomach with or without enlarged pylorus was observed in mice (at 150 mg/kg/day) and jejunal/cecal/colonic dilatation were observed in rats (at ≥30 mg/kg/day, effects that might be related to decreased gastrointestinal transit. One monkey died due to megacolon (at 0.2 BID mg/kg/day). It cannot be excluded that varenicline contributed to pathology in this animal that showed prior to and during treatment various episodes of gastrointestinal disorders. Emesis occurred in dogs (at ≥ 0.05 mg/kg/day) and in monkeys (at ≥0.25 mg/kg/day QD and ≥0.2 mg/kg/day BID). Loose stools and dehydration occurred in rats (at ≥100 mg/kg/day) and dogs (at 1 mg/kg/day). The reduced blood glucose levels, observed in mice (at 150 mg/kg/day) and rats (at ≥10 mg/kg/day), might be secondary and related to the gastrointestinal effects.

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The liver was identified as a target organ in mice and rats on the basis of hepatocellular (single-cell) necrosis and moderate elevations in ALT, AST, total bilirubin and decreased 5'nucleotidase activity at 100 mg/kg/day. Liver weight was also increased by varenicline treatment at 10 mg/kg/day in rat but caused smaller increases in mean transaminase elevations without a microscopic correlate. At 30 mg/kg/day, an increase of hepatic microsomal enzymes was seen (CYP1A, CYP2E, CYP3A). Serious effects like necrosis were only seen at high doses in the short term studies. Elevated liver enzymes were observed at lower doses but still these findings occurred with a large margin of exposure. The lack of similar findings in dogs and monkeys may be due to the dose-limiting emesis observed in these species.

Hematopoietic effects consisted of increases in red blood cell counts (RBC) and haemoglobin levels and decreases in white blood cell counts (WBC) and lymphocyte counts in rats (at 100 mg/kg/day) and decreases in RBC, haemoglobin levels, WBC, and lymphocyte counts in mice (at 100 mg/kg/day). In addition there was minimal to mild cellular depletion of the bone marrow at 30 mg/kg/day in the 3 month rat toxicity study. The bone marrow changes might be related to a decrease in food consumption and body weight. Treatment-related changes in erythroid parameters (decreases in mean RBC count, haemoglobin, and haematocrit; increases in mean corpuscular volume, mean corpuscular haemoglobin, and reticulocyte count in rats (at ≥30 mg/kg/day) and mice (at ≥100 mg/kg/day) might be related to increased RBC turnover. These effects were not seen in dogs and monkeys. An increase in total bilirubin was seen in rats and occasionally also in monkeys.

Based on plasma AUC values obtained at the NOAEL and adjusted for species differences in plasma protein binding, the overall safety margins ranged from 6 to 15 in rats and from 1 to 6 in monkeys.

- Genotoxicity

Varenicline was neither mutagenic nor clastogenic when tested in assays for gene mutations in bacteria and mammalian cells or for chromosome aberrations *in vitro* and *in vivo*.

- Carcinogenicity

Carcinogenic potential was investigated in two-year studies in mice and rats.

In mice no treatment-related increase in tumor incidence was noted at any dose tested. Based on toxicokinetic data from a 3-month study, systemic exposure in the mice of the high dose group (20 mg/kg/day) is estimated to be at least 58 times the expected systemic exposure in humans at the maximum recommended therapeutic dose.

In rats, 1 benign hibernoma (brown fat tissue (BAT) tumour) were seen in the mid-dose males and 2 malignant hibernomas in the high-dose males. According to the applicant, varenicline, at exaggerated multiples of efficacious levels, could act like nicotine, and increase sympathetic stimulation/β-oxidation/UCP-1 expression in brown adipocytes. The resulting sustained stimulation of β-oxidation in mediastinal BAT could lead to the formation of reactive oxygen species may cause sufficient local oxidative damage to DNA and decreased apoptosis for development of BAT neoplasia (hibernoma) in rodents.

The exposure multiple at the NOAEL in the rat carcinogenicity study was 5 and at the mid dose where one benign hibernoma was observed the exposure multiple was 17. In rodents, BAT is present at birth, develops rapidly postnatally, and is important in thermogenesis. In contrast, in humans, BAT is present at maximal amounts at birth, after which its metabolic activity and thermogenic capacity decrease to minimal levels. Based on these arguments it is considered that the risk for humans to develop hibernomas following treatment with varenicline is theoretical and most probably non-existent.

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- Reproduction Toxicity

Varenicline was tested for reproductive and developmental toxicity in conventional studies in the rat (Segment I, II and III) and the rabbit (Segment II). Toxicokinetics were included in all studies. Exposure margins were up to 37-133 times the human C_{max} or AUC at the MRHD.

Separate female and male fertility studies were conducted with varenicline. In either sex, toxicity consisted of decreases in body weights at 15 mg/kg/day. There were no findings on fertility or reproductive parameters in females and no treatment-related effects on copulation, pregnancy rates, reproductive parameters or the reproductive tract in males. Thus, the NTEL for reproduction and fertility was 15 mg/kg/day. Based on the toxicokinetic part of the 6-week rat study, this dose level would correspond to an AUC value of 36 times the AUC at the MRHD.

Varenicline was not teratogenic in rats or rabbits at any of the doses evaluated. In the rat study, maternal toxicity (decrease in body weight) was observed at doses of 5 and 15 mg/kg/day with a NOAEL of 0.3 mg/kg/day. The NTEL for fetotoxicity and teratogenicity was 15 mg/kg/day, corresponding to a safety margin of 36. In the rabbit study, maternal toxicity (decrease in body weight) was observed at 30 mg/kg/day. The only finding was a significant decrease in fetal and placental weights at the maternally toxic dose of 30 mg/kg/day. Thus, the NTEL for fetotoxicity was 10 mg/kg/day, corresponding to a safety margin of 50. Pre- and postnatal development was studied in rats at doses of 0.3, 3 and 15 mg/kg/day. The NTEL for maternal systemic toxicity (reduced body weight and food consumption) was 0.3 mg/kg/day.

Based on the toxicokinetic part of the rat Segment II study, this dose level would correspond to an AUC value of 0.85 times the AUC at the MRHD. In the offspring, treatment-related developmental findings were observed at 15 mg/kg/day and included reduced body weights, a reduction in the number of rearings, increased maximum amplitude of the auditory startle response (ASR) in males only, and reduced fertility; therefore, the NTEL for F_1 developmental toxicity was 3 mg/kg/day. The fertility rate at 15 mg/kg was 80% compared to 95% for the control, which is outside the historical control range (90%-100%). An association between treatment on the one hand and the increase in ASR amplitude and reduced number of successful F_1 mating pairs on the other hand cannot be excluded, but is considered to pose minimal risk to humans as maternal AUC exposures were 36 times the AUC at the MRHD, based on the toxicokinetic part of the rat Segment II study. Moreover, perinatal nicotine exposure also alters postnatal behavioral function in experimental animals and it is well known that maternal smoking is detrimental to human fetal development, with the most notable effect being intra-uterine growth retardation. Therefore, although varenicline is classifiable as a developmental toxicant, this is not considered a cause for concern and it is duly reflected in the SPC.

There are no studies in juvenile animals as a pedriatric indication is not being sought.

- Local tolerance

Varenicline has been tested for dermal toxicity, eye and skin irritation, delayed contact hypersensitivity and phototoxicity. These studies show the drug product to be well tolerated by dermal application, minimally irritating to the skin and eye, unlikely to cause contact dermatitis and devoid of phototoxic potential.

- Other toxicity studies

Antigenicity and immunotoxicity studies were not conducted. Nevertheless, it is known that nicotine alters a wide range of immunological functions and may impair both the immune and inflammatory responses.

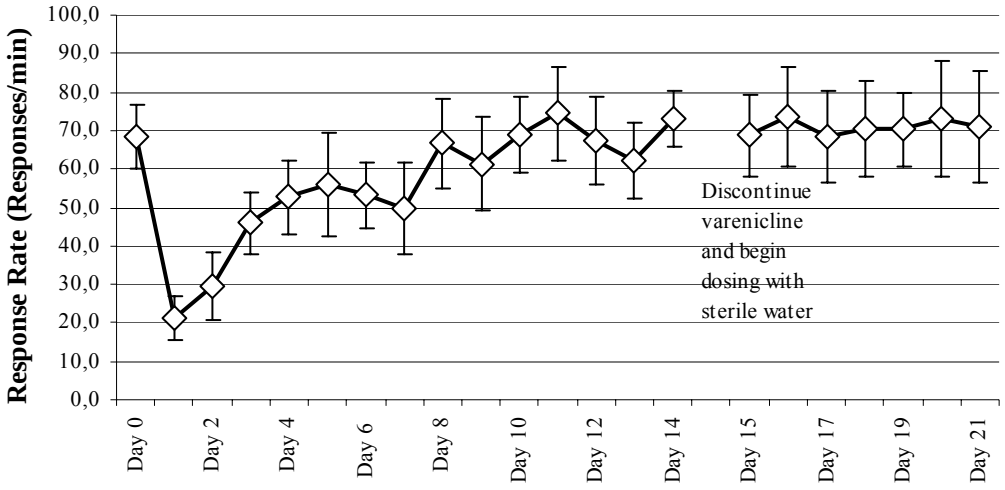
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- Dependence

The comparatively lower release of dopamine in striatal slices, lower dopamine turnover and release in nucleus accumbens and the lower potential of varenicline to maintain self-administration behavior as compared to nicotine suggests that varenicline should have a lower dependence potential when compared to nicotine. Yet, the functional and behavioral effects were not absent and varenicline generalized to nicotine in a drug discrimination study, suggesting varenicline has similar subjective effects as nicotine. Thus, based on the non-clinical studies, it may be concluded that varenicline has dependence potential due to its reinforcing properties.
Male rats were trained to discriminate 0.4 mg/kg SC nicotine from saline. On days with nicotine administration, 30 consecutive responses on the nicotine-associated lever produced a food pellet delivery (reward). On alternate days, vehicle was used and the other lever was activated. After varenicline administration to trained rats, the percentage of responding on the nicotine-associated lever was taken as an indication of the degree of nicotine stimulus exerted. In this model, SC varenicline produced dose-dependent substitution for nicotine with complete substitution at 1.0 mg/kg. Treatment did not compromise the animals' ability to respond. Mecamylamine attenuated the varenicline-treated animals' preference for the nicotine lever.
Varenicline was tested in male rats trained to self-administer (via lever pressing) 30 µg/kg/infusion nicotine through a catheter placed in the jugular vein. The animals were trained according to two different nicotine treatment protocols: 1) reinforcement was allowed after the rats had pressed the lever 5 times (Fixed ratio) and 2) a schedule that investigated how hard an animal would work (lever pressing) for reinforcement (Progressive ratio). Pre-treatment with PO and SC varenicline decreased nicotine intake under a fixed ratio schedule at doses that did not compromise the animals' ability to respond. The reductions in nicotine intake were approximately 50% and 35% following SC and PO administration of 3 mg/kg varenicline, respectively. Similarly, SC pre-treatment with varenicline reduced the number of nicotine infusions earned per minute in animals working on a progressive ratio schedule by up to 50% (at 1.78 and 3.2 mg/kg). Under the progressive ratio schedules, animals worked harder for a nicotine infusion than they did for varenicline. However, animals on the fixed ratio schedule were not able to differentiate between nicotine and varenicline. Consequently, varenicline's reinforcing properties are the same as or lower than nicotine's.

Male rats were trained in a lever-pressing paradigm, where 10 lever presses resulted in a reward food pellet being dispensed. Based on an acute-dose response curve, it was chosen to administer 1.7 mg/kg varenicline (decreased response rate by ~ 50%) daily for 14 days. As expected the response rate was decreased the first days of treatment but tolerance/neuroadaptation to treatment developed and the response rate returned to the baseline level by Day 10 (see Figure below). Potential withdrawal effects were investigated by dosing with sterile water on Days 15 through 21. Discontinuation of varenicline dosing after 14 days and substitution with sterile water on Days 15 through 21 resulted in no change in response rate, and no-observable behavioural effects. Discontinuation of dosing with varenicline did not cause any behaviour that have been observed previously following discontinuation of nicotine, including teeth chattering, chewing, gasping, writhing, head shakes, body shakes, tremors, and ptosis. Additionally, no changes in response rate or body weight were observed during the 1-week abstinence period.

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SC administration of varenicline 1.7 mg/kg produced a reduction of response rate of 78% on Day 1. Dosing was continued for 14 consecutive days, and toleration was achieved by Day 10 and maintained through Day 14. Administration of varenicline was discontinued after Day 14, and rats were dosed with sterile water from Day 15 through Day 21 with no observed effect on response rate or behavior.

Overall, the negative results in the rat withdrawal study and the results obtained at the end of the 9-months monkey toxicology study suggest that varenicline has little or no potential to cause physical dependence. The positive reinforcing effects of varenicline, however, should be judged in view of the chemical-pharmaceutical properties of varenicline (difficulty to synthesize varenicline outside of an industrial setting; bitter taste), clinical experience (emetic properties at higher doses), and the wide availability of a full α4β2 nicotinic receptor agonist (nicotine).

Metabolite, impurity and special studies were not conducted and are not required.

Ecotoxicity/environmental risk assessment

The environmental risk assessment was carried out in accordance with the current draft CHMP guideline. Given a maximum daily dose of 2 mg and a default market penetration of 1%, the calculated $PEC_{surfacewater}$ was equal to the action limit of 0.01 μg/L. As a result, a Phase II fate and effects analysis was provided. Varenicline did not meet the criteria for PBT/PvBv substances. Based on a 7-day survival and reproduction study in *Ceriodaphnia dubia*, the lowest NOEC was 0.003 mg/L and the PEC/PNEC ratio equal to 0.03. Therefore, varenicline is unlikely to represent a risk to the aquatic environment and no further testing or specific labelling is required.

Discussion on the non-clinical aspects

Varenicline plasma levels were not addressed in the submitted pharmacodynamic studies. However, varenicline plasma concentration data are available from the dopamine turnover study (1997-38271). The provided data cover studies were varenicline's intrinsic activity as a nicotinic partial agonist has been investigated. In this study, the oral ED50 for varenicline was derived to be 6 μg/kg and following extrapolation the provided plasma data support the chosen clinical dose.

The CHMP was also concerned as all the safety pharmacology studies (except for cardiac purkinje fiber study IC/001/02), were not performed in compliance with GLP. During the procedure, the Applicant clarified that all safety pharmacology studies (CNS, CV, cardiopulmonary, gastrointestinal and renal) were performed between November 1997-August 1998, i.e. before the release of ICHS7A and data were compiled in a report that was signed off by management on 4 September 1998. After that date additional data were generated (rat colon assay) and/or were repeated (binding assays) and these new data were combined with the safety pharmacology data from 1997-1998 into a new report that was included in the original submission (CP526555/0705/GP).

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Finally, the CHMP was also concerned by the lack of any functional immunological evaluation of varenicline in an animal model and the lack of convincing evidence that the Immunosuppressive effects of nicotine are solely mediated through nicotinic acetylcholine receptors (non-α4β2 subtypes) in human lymphocytes. Therefore, the Applicant will perform a functional immunotoxicity study as a post-approval commitment. The protocol for the study will be provided before the end of 2006. The final report for that study will be provided within one year of the protocol being agreed (see letter of undertaking.

4. Clinical aspects

Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

All plasma samples were analyzed for varenicline concentrations using a fully validated assay employing liquid-liquid extraction followed by HPLC/MS/MS. The analytical methods are suitable for their purposes and well validated. It is agreed, that the results from the two evaluated analytical laboratories are comparable.

Overview of Clinical Pharmacology Studies

The clinical pharmacology program has been studied in healthy volunteers (men and women), in patients with varying degrees of renal or hepatic impairment, in elderly people and in adolescents.

The program consists of:

- 16 clinical pharmacology studies that used only IR formulations;
- 2 clinical pharmacology studies that contained IR arms as part of an evaluation of controlled release (CR) formulations
- 5 bioavailability and bioequivalence studies
- 1 abuse potential study

Table 1- Clinical Pharmacology Program

Type of Study	Study Number
Biopharmaceutics Program	
Relative bioavailability/food effect	A3051001; A3051006[a] (food effect arm); A3051042[b]
Bioequivalence	A3051006[a] (bioequivalence arm); A3051026; A3051030[c]
Clinical Pharmacology Program	
ADME	
Single/multiple dose pharmacokinetics	305-001[a]
Human mass balance	A3051004[a]
Special populations	A3051008[a] (renal impairment); A3051009 (elderly); A3051029 (adolescent); A3051027 and A3051041 (Japanese subjects)
Drug-drug interaction	A3051010 (cimetidine); A3051031 (digoxin); A3051032 (warfarin) A3051033 (NRT patch); A3051034 (Zyban); A3051038 (metformin)
Pharmacodynamics	A3051005 (craving); A3051014, A3051015 (tolerability) A3051012; A3051013
Abuse potential	A3051039[a]

[a]Enrolled nonsmokers (42/102 in single-dose 305-001; 3/6 in A3051004; 10/15 in Study A3051006, 14/30 in Study A3051008; 22/45 in Study A3051039) or exsmokers (2/15 in Study A3051006; 10/30 in Study A3051008)
[b]Definitive food effect study [c]Pivotal bioequivalence study

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Pharmacokinetics

- Absorption

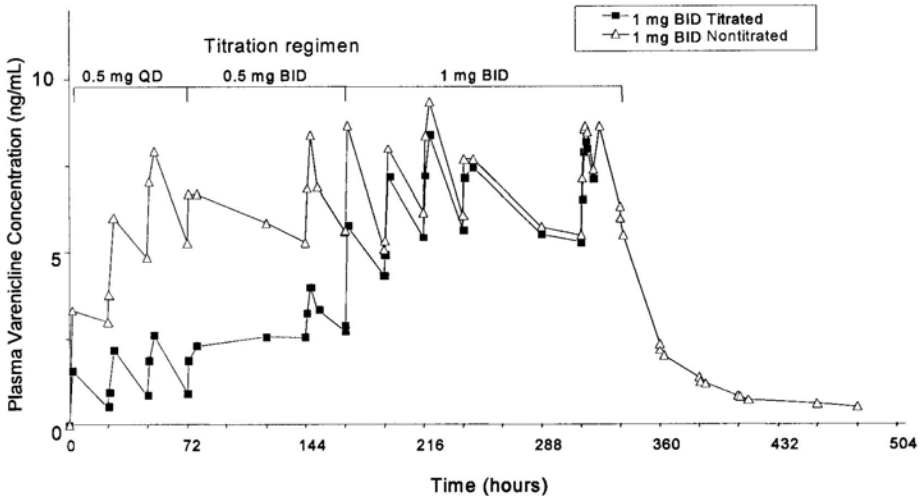
Varenicline (tartrate) oral formulations are virtually completely absorbed. Since varenicline is no substrate for glycoprotein-P transporter enzymes and is practically not metabolised by CYP enzymes in humans, there is no first pass- effect and varenicline is therefore highly available systemically. There was no interaction with food and absorption. Varenicline plasma exposure (AUC, Cmax) is dose-linear.

Table: Multiple dose studies in male and female smokers with normal renal function (mean, SD, for tmax; median, range)

study	dose	$AUC_{0\text{-}inf}$ NG/ML*HR	$AUC_{0\text{-}\tau au}$ NG/ML*HR	$AUC_{0\text{-}t}$ ng/ml*hr	Cmax ng/ml	Tmax h	t½ h
A3051008	0.5 mg QD	NA	56.8 (13.8)	NA	4.13 (1.28)	1(1-2)	34.4 (27.5)
305-001	1 mg QD	271 (75)	144 (24)	NA	7.93 (0.9)	4 (1-8)	23.8 (4.9)
305-001	1 mg BID	504 (101)	105 (16)	NA	10.2 (1)	2 (1-4)	31.5 (7.7)
A3051013	1 mg BID	NA	NA	t=24 h 208 (44.8)	10.8 (2.6)	3 (2-5)	NA
A3051014	1 mg BID	NA	NA	t=8 h 59.3 (10.7) t=24 h 184 (41.3)	8.54 (1.51)	3 (1-8)	NA
A3051014	1.5 mg BID	NA	NA	t=8 h 96.9 (24.6) t=96 h 418 (113)	13.9 (3.3)	3 (1-4)	27.3 (8.5)
A3051015	2 mg QD	NA	188 (31)	-	12.4 (1.9)	3 (2-4)	NA
305-001	2 mg QD	589 (112)	280 (33)	NA	15.1 (1.8)	2 (2-4)	24.8 (2.9)
305-001	3 mg QD	756 (268)	352 (87)	NA	19.8 (3.8)	4 (2-8)	25.2 (3.8)

NA= not available

Figure 2. Mean Plasma Concentration-Time Profiles Following Repeated Oral Administration of 1 mg BID Varenicline Using Titration and Nontitration Dosing Regimens in Healthy Adult Smokers: Study A3051014



Source: Study Report A3051014 Figure 1.1

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- Distribution

Varenicline is a basic amine. In animals, varenicline is distributed throughout the body, including the brain, and varenicline passes the placenta. In rodents, varenicline accumulated in melanine containing cells and the eyes. Whether this also occurs in humans is unknown. Protein binding of varenicline in humans is low (≤20%), and therefore no major interactions regarding protein binding are expected. The volume of distribution (V/F) is estimated as 337 l in adults. Vd was significantly related to body weight. Steady-state is achieved after 4 days repeat dosing.

- Elimination

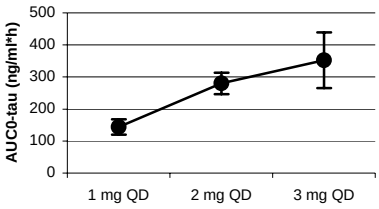
Metabolism: Varenicline is not significantly metabolised oxidatively by liver CYP enzymes. It is therefore not expected that varenicline metabolism and exposure would be affected by hepatic disorders. In minor quantities, conjugates are recovered in plasma and urine (approximately 10% of the total dose). Whether these conjugates are biological active is yet unknown.

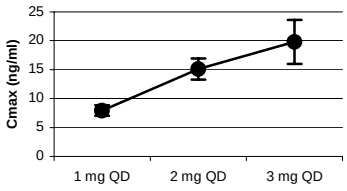
Excretion: Varenicline, and its conjugates, are virtually completely excreted renally, primarily by passive glomerular filtration and to minor extent by active secretion in the proximal tubulus.

- Dose proportionality and time dependencies

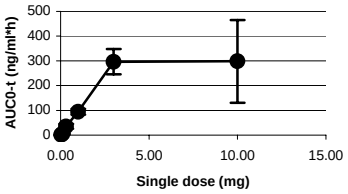
Dose proportionality
In the multiple dose regimen in study 001, varenicline exposure increased linearly with dose (range 1-3 mg QD). In the single dose regimens in the same study, varenicline exposure was dose proportional from 0.01-3 mg. The Cmax and AUC after 10 mg were however similar to 3 mg dose. However, as vomiting was common after the 10 mg single dose, and this may have biased the estimation of Cmax or AUC after 10 mg single dose.

Study 305-001 Multiple dose regimens (n=7-8)





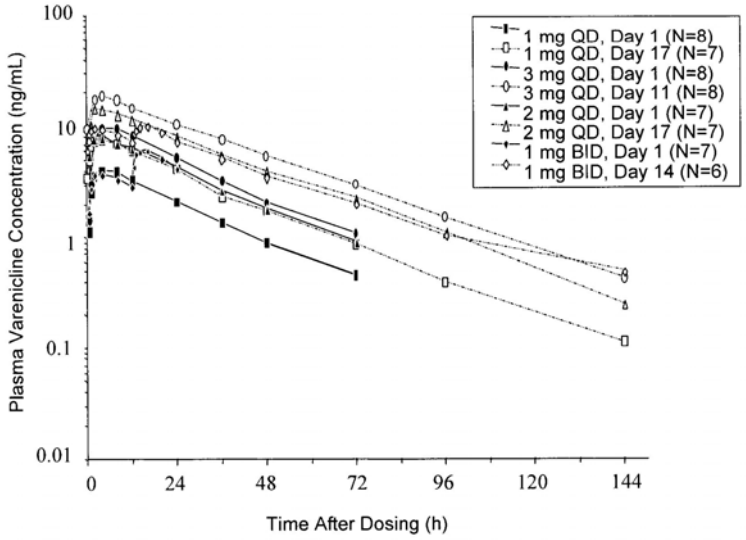
Study 305-001 Single dose regimens, smokers (n=4)





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Figure 1. Mean Varenicline Plasma Concentration-Time Profiles following Single and Multiple Oral Doses given QD or BID: Study 305-001



Exposure of varenicline in plasma is linearly related to the dose.

Time dependency
There was no diurnal variability in varenicline levels. Varenicline exposure was virtually completely similar when a single dose of 2 mg varenicline was administered in the morning or before bedtime (Study A3051015, 90% CI AUC_{0-24} 95-103%)

Renal varenicline clearance was consistent over a study period of 1-14 days. This was confirmed in the population PK model; there were no trends observed in the WRES-time plots.

- Special populations

In the conducted population PK analysis renal function (on systemic clearance, CL/F) and bodyweight (on volume of distribution, V2/F) were the important factors leading to interindividual variability in the pharmacokinetics of varenicline. Plasma concentration time data were fitted to a two-compartmental model, with first-order absorption and elimination. Model parameters were central compartment (V2/F), clearance from central compartment (Cl/F), peripheral compartment (V3/F) and inter-compartmental clearance (Q/F), dosing compartment V1 and absorption constant (Ka) and a lag-time for absorption (Alag).

The table below provides estimated ranges of expected variability in CL/F and V2/F relative to the typical value based on the covariate effects and the observed range of age, weight, and CRCL values in the dataset. Observed covariate factors in the final PK model described a large fraction of the total observed inter-individual variability in both the apparent clearance (44.5%) and central volume of distribution (45.6%) of varenicline.

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Table 16. Covariate Effect Ranges on Varenicline Final Model Pharmacokinetic Parameters

Pharmacokinetic Parameters (units)	Estimated Effect Relative to Typical Parameter Value[a]
CL/F (10.4 L/hr)	
Renal Function (16 - 150 mL/min)[b]	(0.38 - 1.24)
Black	1.16
Other	1.11
V2/F (337 L)	
Body weight (40 - 130 kg)	(0.65 - 1.61)
Age (18-75 yrs)	(0.89 - 1.07)
Black	0.92
Other	0.71
Overall Range (extremes fixed effects)	
CL/F (L/hr)	(0.38 - 1.97)
V2/F (L)	(0.41 - 1.72)
Individual Range (observed fixed effects)	
CL/F (L/hr)	(0.37 - 1.44)
V2/F (L)	(0.50 - 1.58)
Individual Range (observed fixed and	
CL/F (L/hr)	(0.23 - 2.93)
V2/F (L)	(0.31 - 3.99)

[a] Given the reference covariates effects (Caucasian, 45 years old, 70 kg, 100 mL/min)
[b] Estimated glomerular filtration rate (Cockroft-Gault method). Range extends to estimated GFR = 150 mL/min for clinical relevance; the highest value in the dataset was 268 mL/min.

Weight was shown to influence the volume of distribution, thus, plasma concentration fluctuations will be affected by weight.

The clearance of varenicline is linearly related to GFR (glomerular filtration rate), and varenicline exposure increased in patients with limited GFR. It is therefore recommended to adjust the regular varenicline dose if the patient has moderate or severe renal impairment. Varenicline is not recommended in patients with ESRD, based on insufficient clinical experience.

Varenicline was cleared by haemodialysis.

Varenicline plasma exposure was similar in elderly with normal renal function for their age (aged 65-75, creatinine clearance > 70 ml/min) and adults, in different ethnic groups, and between males and females.

In conclusion, there are no major problems expected based on the PK profile of varenicline regarding interactions, gender and ethnicity, though dose adjustments are necessary for patients with severe renal dysfunction.

It should be noted that this product is currently not indicated for children or adolescents. Limited data in adolescents suggests that Cmax was 30% higher than in adults and elimination was 50% shorter, probably because of a limited Vd in adolescents compared to adults.

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- Pharmacokinetic interaction studies

The active tubular secretion is mediated by human organic cation transporter proteins type 2 (hOCT2). Cimetidine is a substrate and inhibitor of this renal transporter, and concomitant use of cimetidine and varenicline caused an increase of varenicline exposure of approximately 30%. Administration of varenicline did not cause inhibition of renal elimination of another hOCT2 substrate, metformin. There were no significant PK interactions found between varenicline and narrow therapeutic drugs like digoxin and warfarin, and other smoking cessation agents like nicotine replacement and bupropion.

Pharmacodynamics

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- Mechanism of action

Varenicline acts as a competitive, partial agonist for nicotine binding to nicotinic acetylcholine receptor α4β2. Both nicotine and varenicline binds to this receptor subtype. In animal models, the α4β2 nicotinic receptor has been shown to be responsible for the reinforcing properties of nicotine. It is hypothesized that varenicline, as it is a partial agonist, blocks the full-agonist activity of nicotine by competitive binding. On the other hand, the partial agonist action of varenicline may cause relief of withdrawal and craving symptoms on its own.

- Primary and Secondary pharmacology

The following pharmacodynamic studies were performed:

Study number	**objective**	**N**	**Dose varenicline (mg)**
A3051005	Proof of concept, relief of craving	40	2 SD
A3051039	Abuse potential	23	1 and 3 SD
A3051014	Tolerability, titration	120 (3x40)	1 BID non-titrated/ 1.5BID non-titrated / 1.5 BID titrated
305-001	*Tolerability, food interaction*	102 SD, 44 MD	SD:0.01-10 MD:1-3 QD,1 BID (14 days)
A3051015	Effect of dosing time on PK/PD (nausea)	44	2 QD 7 days (AM + PM)
A3051033	Drug-Drug Interaction with Nicotine Replacement Therapy (21 mg patch QD)	24	1 BID , 14 days

BID=twice daily/ MD=multiple dose/ SD=Single dose/ QD= once daily/AM=in the morning/ PM=before bedtime

A laboratory craving study was performed in smokers not intending to quit, who were exposed to a smoking related cue after an abstinence period of 12 hours. A single dose of either placebo or 2 mg varenicline was given to each participant. Varenicline significantly reduced the cue-stimulated craving and withdrawal symptoms in comparison with placebo. Results of a PK/PD analysis indicated that increasing plasma varenicline concentration was associated with reduced cigarette craving.
A study was performed to test the abuse potential of varenicline in non-smokers and smokers. Varenicline was compared to amphetamine and placebo in a group of regular amphetamine users, in a double-blind, randomised study. Amphetamine (15/30 mg), varenicline (1/3 mg) or placebo was administered to 21 tobacco smokers + 21 non-smokers. The VAS Drug Liking scale was used to assess the subjective appreciation of the offered drug. Smokers could not distinguish 1 mg varenicline from placebo. The 3 mg varenicline dose could be distinguished from placebo, but the drug was considered as unpleasant. Non-smokers could distinguish 1 mg varenicline from placebo, but like in smokers, the drug was considered unpleasant, especially at 3 mg doses. Varenicline did not induce euphoria in any subject in this study. Higher dose of amphetamine were most appreciated, indicating the validity of the chosen test method. Considering the fact that high doses of varenicline induce nausea and the rewarding effects were low, it is unlikely that varenicline would become a drug of abuse.

Finally, 4 studies were performed in smokers and non-smokers to investigate the maximum tolerated dose and dose titration and timing on dose toleration. The dose-limiting factor was nausea. Smokers were more tolerant to varenicline than non-smokers with respect to nausea. In smokers, the maximum tolerated single dose and multiple dose is 3 mg and 1 mg BID, respectively. Nausea was less severe when varenicline is up-titrated, when varenicline is administered under fed conditions and when the dose was divided over the day. Results from studies A3051014 and A3051015 indicate that the burden of nausea might be reduced by titrating the dose. The results do not enlighten any dose-response effect.

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The incidence of nausea increased when varenicline was concomitantly used with nicotine replacement therapy. The interaction between varenicline and other psychotropic agents like alcohol and benzodiazepines is however only briefly investigated by the Applicant. However, varenicline use induced somnolence and abnormal dreams, indicating that this compound could be psychoactive. This is further addressed in the RMP.

Clinical efficacy

In total, seven Phase II/III studies were performed which provided efficacy data from 5944 subjects. Subjects were eligible if they were current smokers of more than 10 cigarettes per day, willing to quit, and if they had no successful quit attempt that lasted more than 3 months in the year before entrance.

Table: Overview of Phase II Efficacy studies

Study ID	Study location	Study Objectives	Design	duration	Varenicline dose	N ITT population*	Primary Endpoint
A3051007 /18	US	Dose finding Titration	R, PG, DB, PC	12 wks treat + 40 wks non-treat	0.5 mg BID NTitr 0.5 mg BID Titr 1 mg BID NTitr 1 mg BID Titr	VNC 124 VNC 129 VNC 124 VNC 129 Plac 121	4-week CQR (Wks 9-12) CAR wks 9-52
A3051002	US	Dose finding	R,PG,DB,PC, AC	6 wks treat + 45 wks non-treat	0.3 mg QD 1 mg QD 1 mg BID	VNC 126 VNC 126 VNC 125 Bupropion** 126 Plac 123	4-week CQR floating or fixed (Wks 3-6) or (Wks 4-7)
A3051016 /19	US	Dose finding	PC,DB,R	12 wks treat + 40 wks non-treat	Flexible 0.5 QD-1 mg BID	VNC 157 Plac 155	4-week CQR (wks 9-12) CAR Wks 9-52

Table: Overview of Phase III Efficacy Studies

Study ID	Study Location	Study Objectives	Design	duration	Varenicline dose	N ITT population*	Primary Endpoint
A3051028	US	Smoking Cessation	R, PG, DB, PC, AC	12 wks treat + 40-wks non-treat	1 mg BID Titr	VNC 349 Bupropion** 329 Plac. 344	4-week CQR (Wks 9-12)
A3051036	US	Smoking Cessation	R, PG, DB, PC, AC	12 wks treat + 40 wks non-treat	1 mg BID Titr	VNC 343 Bupropion** 340 Plac. 340	4-week CQR (Wks 9-12)
A3051035	US, Eur, Can	Maintenance		12 wks treat OL (I) + 12 wks treat R,DB,PC (II) + 40 wks non-treat	I: 1 mg BID titr II: 1 mg BID	VNC 1927 VNC 602 Plac 604	CAR Wks 13-24
A3051037	US, Aus	Safety	R, DB, PC	52 wks treat	1 mg BID, Titr	VNC 251 Plac 126	7 days PP

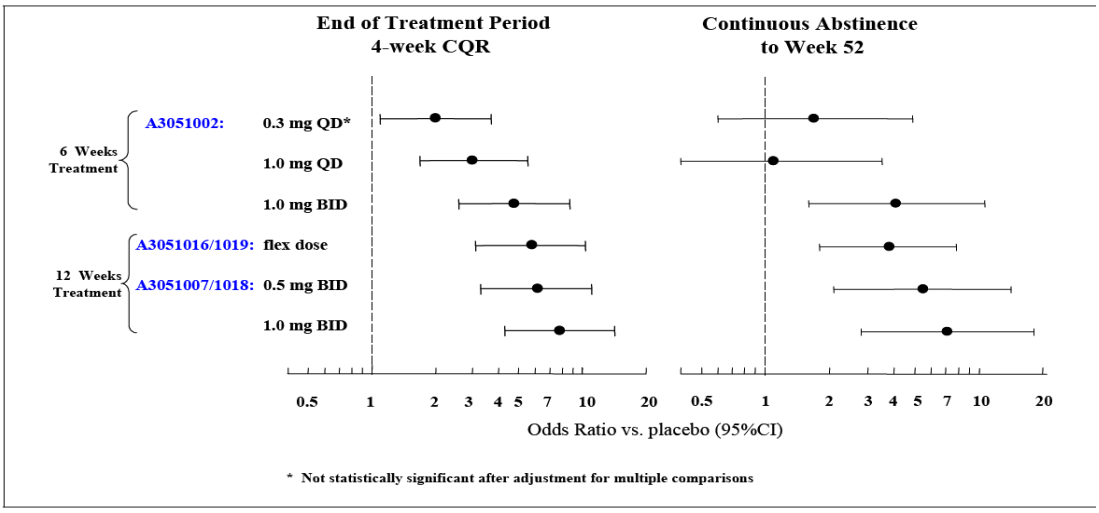
AC = Active-controlled; BID = Twice per day; CAR = Continuous Abstinence Rate; CQR = Continuous Quit Rate; DB = Double-blind; NTitr = Nontitrated; OL = open label; PC = Placebo controlled; Plac = placebo; PG = Parallel Group; PP = 7-days Point Prevalence Abstinence; QD = Once daily; R = Randomized; Titr = Titrated; treat=treatment duration; VNC = varenicline. * all subject who took at least one dosage of study treatment, **Bupropion Dose 150 mg BID

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- Dose response study(ies)

Based on the Phase II dose-finding studies, the following conclusions could be drawn; Varenicline, in dosages > 0.3 mg, was superior to placebo (see figure 17 below). Abstinence-rates were higher after 12-weeks than after 6-weeks continuous varenicline treatment. Dose titration was useful to prevent nausea.

Figure 17. Summary of Treatment Effect (as Odds Ratio) for End of Treatment and Long-Term Abstinence in Phase 2 Dosing Studies A3051002, A3051016/1019, A3051007/1018



In pooled data analyses, continuous cessation rate at the end of treatment at week 12 was approximately 45% in both the 0.5 and 1 mg BID treatment arms (see table III.4.1. below). At week 52, the long-term continuous abstinence rate was 22.6% after 1 mg BID dose and 19.0% after 0.5 mg BID dose.

Table III.4.1.: 4-Week Continuous Quit Rate (CQR) over Week 9-12 and Continuous Abstinence Rate (CAR) over Week 9-24 and Week 9-52 in pooled Phase III studies A3051028 and -36, and -07/18:

	Short term		Long-term			
	1 mg BID (pooled from studies A3051028, -36 and -07/18)					
	CQR Wks 9-12	**OR (95% CI)**	**CQR Wks 9-24**	**OR (95% CI)**	**CAR Wks 9-52**	**OR (95% CI)**
Varenicline	**45.9%** (434/945)	**4.13** (3.29-5.18)	**29.7%** (281/945)	**3.51** (2.6-4.5)	**22.6%** (214/945)	**3.17** (2.36-4.24)
Placebo	**16.9%** (136/805)	-	**10.9%** (88/805)	-	**8.6%** (69/805)	-
0.5 mg BID (study A3051007/1018 only)						
Varenicline	**45.1%** (114/253)	**6.07** (3.32-11.1)	**24.1%** (61/253)	**5.29** (2.3-12.0)	**19.0%** (48/253)	**5.56** (2.1-14.4)
Placebo	**12.4%** (15/121)	-	**5.8%** (7/121)	-	**4.1%** (5/121)	-

In a patient-controlled dosing study (A3051016), patients could choose a dose of 0.5/1/1.5/2 mg a day. The overall median auto-regulated total daily dose was 1.3 mg. At the end of the 12-weeks treatment period, a higher proportion of study participants were taking the 0.5 mg BID dose than the 1 mg BID dose. These data indicate that most patients would benefit from a 1 mg BID dose regime. However, every patient that would stop varenicline use prematurely due to adverse events can be considered as a loss, as varenicline is an effective drug to promote smoking cessation. Intolerant patients should be given the opportunity to change to a regimen of 0.5 mg BID.

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- Main studies

METHODS

Design of pivotal studies: A3051007/1018, A3051028 and A3051036

In Studies A3051028, -36, and –07/18, varenicline was administered for 12 weeks at 1 mg BID with subsequent non-treatment follow-up for one year from the start of treatment. Based on a comparison of titrated and non-titrated regimens in Study A3051007/18, the Phase III studies titrated varenicline from 0.5 mg QD to 1 mg BID during the first week of treatment to improve tolerability. The one-year follow-up period from the start of treatment is an established design element, widely used in the smoking cessation field. Up to 10 minutes of counselling on smoking cessation was provided at each visit in accordance with Agency for Healthcare Research and Quality guidelines.

The identical Phase III trials (A3051028 and -36) were designed to demonstrate the superior efficacy of varenicline compared with bupropion and placebo. Bupropion was selected as an active control because it is an efficacious, widely prescribed, oral pharmacotherapy for smoking cessation. Nicotine replacement therapy was another alternative.

Studies A3051028 and -36 were designed as 52-week, double-blind, placebo-controlled, randomised, multi-centre studies. Varenicline, bupropion or placebo was administered for 12 weeks, followed by a 40 week non-treatment phase. At screening, subjects were requested to select a Target Quit Day to coincide with the Week 1 visit, after the varenicline or bupropion dose had been up-titrated to 1 mg BID and 150 mg BID, respectively.

Clinical visits took place each week during the initial 12 weeks dosing period. At each visit, subjects were asked about cigarette and other nicotine use since the last study visit and in the past 7 days (using the Nicotine Use Inventory). End-expiratory exhaled carbon monoxide was measured at each clinic visit (nonsmoking status being confirmed with a measurement $\leq$ 10 ppm). During the non-treatment follow-up phase, clinical visits took place at weeks 13, 24, 36, 44, and 52. In addition, subjects received a telephone call at weeks 16, 20, 28, 32, 40, and 48. The Nicotine Use Inventory was administered at each visit and at each telephone call during the non-treatment phase.

Adjunctive Counselling: At baseline, candidates were asked to review an educational booklet on smoking cessation by the NCI. At each visit up to 10 minutes of counselling was provided. Counsellors acted according to guidance of the Agency for Healthcare Research and Quality. All subjects were contacted 3 days after the Target Quit Date, as a reminder and support. During the non-treatment phase, additional phone contacts were scheduled between clinic visits to encourage maintenance of abstinence.

Study Participants

Both adult men and women were included and the maximum age was 65 years in Phase II studies and 75 years in Phase III studies. The Phase III protocols were amended to include patients with mild or moderate COPD, hypertension, hyperlipidemia and subjects with a history of cardiovascular diseases (e.g. myocardial infarction, coronary bypass graft, PTCA, angina pectoris) other than in the past 6 months. Subjects treated for hypertension could be included in Phase III studies, provided that hypertension was adequately controlled.

Patients with conditions that are contraindicated for the comparator bupropion were excluded. These conditions were: seizures, diabetes mellitus, hepatic or renal impairment, bipolar disorder, alcoholism (current or in the recent past) and the use of MAO-inhibitors. In addition, chronic and episodic use of antidepressants and antipsychotics, benzodiazepines, naltrexone, systemic steroids (with exception of inhaled steroids), and theophylline was prohibited during the study.

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Patients who had used bupropion in the past were not included into the Zyban-comparator studies. Participants who had used NRT, or other smoking cessation treatment like clonidine and nortryptiline other than the last month could be included.

Treatments

In these parallel placebo-controlled, double-blind, active-comparator studies, varenicline 1 mg BID, placebo or Zyban 150 mg BID was administered for 12 weeks. In week 1, varenicline and Zyban, or their placebo tablets, were titrated according to the following schedule:

varenicline	
Day 1-3	0.5 mg QD
Day 4-7	0.5 mg BID
Day 8-84 (week 12)	1 mg BID

Zyban (bupropion)	
Day 1-3	150 mg QD
Day 4-84 (week 12)	150 mg BID

Objectives

The primary objective of these studies was to compare the efficacy of varenicline to placebo and bupropion regarding smoking cessation at the end of treatment period of 12 weeks.

Secondary objectives were;
-Long term efficacy, till 40 weeks after end of treatment (Week 52)
-The effect on craving and withdrawal
-The effect on weight
-Safety data

Outcomes/endpoints

The primary efficacy outcome was the 4-weeks CQR (Continuous Quit Rate) at the end of treatment between week 9-12. Responders were subjects who remained totally abstinent from weeks 9-12 without a single puff, confirmed by CO-breath test. Key secondary variable was the long term efficacy, the Continuous Abstinence Rate (CAR) during weeks 9-52. Responders were subjects who remained totally abstinent from Weeks 9-52, without a single puff, confirmed by CO-breath test.

Craving, withdrawal and reinforcing effects of smoking were assessed by means of the MNWS (Minnesota Nicotine Withdrawal Scale), the QSU-Brief (Brief Questionnaire of Smoking Urges, measures craving), and SEI (Smoking Effects Inventory). The Urge to Smoke item, and the Negative Affect and Restlessness subscales of the MNWS were prespecified as subscales of primary interest. The Total Craving Score of the QSU-Brief was pre-specified as the endpoint of primary interest for that scale. The SEI included subscales that assessed smoking satisfaction and psychological reward in subjects who smoked since the last time the questionnaires were due.

The MNWS and QSU-Brief questionnaires were filled in by subjects at baseline, and at Week 1-7 and 12 during treatment. The MNWS was also scored at Week 13, one week after end of treatment. The SEI was assessed through Week 7.

Body weight was measured every clinical visit. For the assessment of total weight gain, body weight measured at Week 12 was compared to baseline value in Responders (i.e. Cessators) and the Total Population.

Sample size

Sample sizes were based on the comparison of varenicline 1 mg BID vs. bupropion 150 mg BID, using a continuity-corrected Chi-Squared test with a 0.05 two-sided significance level. The study was intended to be powered to detect differences for both the primary (4-week CQR) and the key secondary CAR endpoint. Sample size calculations were based on the bupropion response rate (varenicline OR of 1.721 over bupropion 4-week CQR of 28.6%). In each study, at least 335 subjects

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per group would be needed to detect a difference between bupropion and varenicline, with 90% power.

Randomisation

Subjects were equally randomised over the 3 study arms (varenicline/bupropion/placebo arm).

Blinding (masking)

This was a double-dummy study, and there were both placebo tablets available for varenicline and Zyban. So patients received either varenicline + Zyban-placebo (varenicline-arm), varenicline - placebo + Zyban (bupropion-arm), or varenicline -placebo + Zyban-placebo (placebo-arm).

Statistical methods

For binary outcome (CQR week 9-12, CAR), logistic regression analysis, with study site and treatment included as fixed factor, was applied. A step-down procedure was employed for the analyses of primary and key secondary endpoints to preserve the family-wise error rate (alpha 0.05). The hierarchy of comparisons was as follows: 1. varenicline versus placebo and 2. varenicline versus Zyban. The withdrawal and craving subscales were analysed by repeated measures Mixed Effect Modelling.

RESULTS

Participant flow

	Study 1028	**1036**
Assessed for Eligibility (n)	1483	1413
Excluded (n)	458	386
Randomised (n)	1025	1027
Allocated to Varenicline (n)	**352 (Varenicline received 349)**	**344 (Varenicline received: 343)**
Allocated to Zyban (n)	**329 (Zyban received 329)**	**342 (Zyban received: 340)**
Allocated to Placebo (n)	**344 (Placebo received 344)**	**341(Placebo received: 340)**
Discontinued Varenicline (n)	**136 (39%)** *During Treatment Phase*: 90 (14 AE, 2 Lack of Efficacy, 4 Protocol Deviation, 23 Refusal, 43 Lost-to-follow-up, 4 Other) *During Follow-Up Phase*: 46 (11 Refusal, 34 Lost-to-follow-up, 1 Other)	**103 (30%)** *During Treatment Phase*: 83 (14 AE, 1 Lack of Efficacy, 2 Protocol Deviation, 28 Refusal, 33 Lost-to-follow-up, 5 Other) *During Follow-Up Phase*: 20 (3 Refusal, 14 Lost-to-follow-up, 3 Other)
Discontinued Zyban (n)	**145 (44%)** *During Treatment Phase*: 104 (34 AE, 1 Lack of Efficacy, 1 Protocol Deviation, 31 Refusal, 36 Lost-to-follow-up, 1 Other) *During Follow-Up Phase*: 41 (1 Protocol Deviation, 10 Refusal, 29 Lost-to-follow-up, 1 Other)	**119 (35%)** *During Treatment Phase*: 100 (16 AE, 0 Lack of Efficacy, 9 Protocol Deviation, 31 Refusal, 39 Lost-to-follow-up, 5 Other) *During Follow-Up Phase*: 19 (1 Death, 2 Protocol Deviation, 6 Refusal, 10 Lost-to-follow-up, 0 Other)
Discontinued Placebo (n)	**157 (46%)** *During Treatment Phase*: 129 (24 AE, 4 Lack of Efficacy, 6 Protocol Deviation, 42 Refusal, 49 Lost-to-follow-up, 4 Other) *During Follow-Up Phase*: 28 (1 Death, 5 Refusal, 22 Lost-to-follow-up)	**136 (40%)** *During Treatment Phase*: 118 (13 AE, 3 Lack of Efficacy, 4 Protocol Deviation, 51 Refusal, 43 Lost-to-follow-up, 4 Other) *During Follow-Up Phase*: 18 (1 Protocol Deviation, 4 Refusal, 12 Lost-to-follow-up, 1 Other)
Analysed: All subjects who received at least 1 dose of:	**Varenicline : 349** **Zyban: 329** **Placebo: 344**	**Varenicline: 343** **Zyban: 340** **Placebo: 340**

The most common reasons for study discontinuation in all three study arms were loss-to-follow-up, refusal to continue participation, and AEs. The discontinuation rate was higher in the placebo arm

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compared to varenicline arm. Probably, this is due to the more severe withdrawal symptoms and because of the lack of efficacy in the placebo arm.
Discontinuation due to adverse events was more common in the Zyban arm (n = 50) and in the placebo-arm (n = 37) than in the varenicline-arm (n = 28).

Recruitment

Smokers were recruited from the general population, and were not referred by medical specialists.

Conduct of the study

Both phase 3 Protocols A3051028 and -36 were amended shortly after study start to allow enrolment of subjects with pre-existing medical conditions typical of the intended patient population.
Both 305A53010 Studies A3051028 and -36 took place in the US, in different study centres.

Baseline data

The demographics and smoking characteristics of subjects in the 2 identical Phase III studies were well balanced across treatment groups.

Demographics: Phase III trials A3051028 and -36 enrolled more men than women (56% versus 44%). The mean age was approximately 42 years (SD 11) in both studies. Approximately 80% of the participants were Caucasian, 10% were African and the remainder were from other ethnical origin. Sixty-two (27 + 35) subjects were older than 65 in study A30510-28 and -36, respectively. Only 17 varenicline treated subjects were 65 years of age or older.
The low number of elderly is a drawback in the assessment of safety. The plasma exposure may be similar in elderly compared to younger adults, but elderly may be more sensitive to side effect of varenicline, and the subgroup is considered too small to make a sound evaluation. This will be reflected in the SPC. Treatment in elderly should be monitored post-approval (see Risk Management Plan).

Concomitant diseases: in subjects who were included, the following present & past medical conditions were noted at screening (pooled data Study A30510-28 and -36):

Cardiac Disorders	2.4%
Dyspnea at exertion	<2%
COPD	<2%
Emphysema	<1%
History of depression	4.4%
History of alcoholism	4.6%

Smoker status: all participants were current smokers, who smoked at least 10 cigarettes a day. The baseline smoking behaviour features were similar in both studies, over all study arms. The mean Fagerström Total Score ranged between 5.16-5.40 (SD±2) across study arms, indicating that the average participant was a moderate smoker.
The mean age at which the subjects started smoking was approximately 17 years, and the average smoking years were approximately 24-25 years in all study arms (range 1-61). In the last month before entrance, the participants smoked on average 21 cigarettes (range 10-80) per day. The majority of participants, about 85%, had at least one serious quit attempt in lifetime.

Numbers analysed

Efficacy analyses occurred in the "All Subjects" group, i.e. all subjects who received at least 1 dose of the relevant study drug (further referred as ITT in this report). To test the robustness of the conclusions from ITT dataset, analyses took also place in "Evaluable Subjects" group, defined as subjects who took study medication at least for 14 days, and Completer Subjects group, i.e. subject who were for at

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least 80% treatment compliant. In this report, efficacy parameters of the ITT population are presented, unless specified otherwise. For details see participant flow table above.
Subjects who withdrew from the study or who were lost to follow-up before the study was completed were considered as non-responders for subsequent smoking evaluations.

Outcomes and estimation

Main results of clinical efficacy

Varenicline at the recommended dosing regimen (1 mg BID for 12 weeks) is superior to placebo for smoking cessation at the end of treatment period and at one year from the start of treatment.

With regard to 4-Week CQR (Weeks 9-12) and Continuous abstinence Weeks 9-24 varenicline was significantly better than bupropion. At Continuous Abstinence Weeks 9-52 varenicline was statistically superior to bupropion in one of the two phase III studies.
The results of primary endpoints in the pivotal Phase III studies (A3051028 and -36) are summarised below in table III.3.2 below:

Table III.3.2 : Continuous Quit Rate (CQR) over Week 9-12 and Continuous Abstinence Rate (CAR) Week 9-52 in pivotal Phase III studies A3051028 and -36:

	Studies A3051028			**Studies A3051036**		
Study arm	**Varenicline 1 mg BID**	**Zyban 150 mg BID**	**Place-bo**	**Varenicline 1 mg BID**	**Zyban 150 mg BID**	**Place-bo**
N	349	329	344	343	340	340
Abstinent Week 9-12	**44.4%**	**29.5%**	**17.7%**	**44.0%**	**30.0%**	**17.6%**
OR ($CI_{95\%}$, p) *versus placebo*	3.91 (2.74-5.59) < 0.0001	2.00 (1.38- 2.89) 0.0002	-	3.85 (2.69- 5.50) <0.0001	2.03 (1.41- 2.94) 0.0001	
versus zyban	1.96 (1.42, 2.72) <0.0001		-	1.89 (1.37 -2.61) <0.0001		
RR ($CI_{95\%}$, p) *versus placebo*	2.50 (1.94- 3.24) < 0.0001	1.66 (1.25 - 2.21) 0.0003	-	2.49 (1.93- 3.23) < 0.0001	1.70 (1.28- 2.25) 0.0002	
versus Zyban	1.51 (1.23- 1.85) 0.0001		-	1.47 (1.20- 1.80) 0.0001		
AR ($CI_{95\%}$, p) *versus placebo*	26.7 (20.1- 33.3) < 0.0001	11.8 (5.4 -18.1) 0.0003	-	26.4 (19.7- 33.0) <0.0001	12.4 (6.01- 18.7) 0.0002	
versus Zyban	14.9 (7.8- 22.1) 0.0001		-	14.0 (6.86- 21.2) 0.0001		
Abstinent over 9-52 wks	**22.1%**	**16.4%**	**8.4%**	**23.0%**	**15.0%**	**10.3%**
OR ($CI_{95\%}$, p) *versus placebo*	3.13 (1.97- 4.97) <0.0001	2.16 (1.33- 3.51) 0.0014	-	2.66 (1.72- 4.11) <0.0001	1.54 (0.97-2.45) 0.0634	
versus Zyban	1.45 (0.98-2.14) 0.0640		-	1.72 (1.16- 2.55) 0.0062		
RR ($CI_{95\%}$, p) *versus placebo*	2.62 (1.75- 3.91) 0.0001	1.94 (1.27- 2.98) 0.0016	-	2.24 (1.55 - 3.23) <0.0001	1.46 (0.97- 2.18) 0.065	
versus Zyban	1.34 (0.98 -1.84) 0.063		-	1.54 (1.12 -2.11) 0.008		
AR ($CI_{95\%}$, p) *versus placebo*	13.6 (8.4 -18.9) 0.0001	8.0 (3.1-12.9) 0.0016	-	12.7 (7.2 - 18.2) < 0.0001	4.7 (-2.8 -9.7) 0.065	
versus Zyban	5.6 (-2.6 - 11.6) 0.063		-	8.0 (2.2 -13.9) 0.008		

AR=additive risk, OR=odds ratio, RR= relative risk

In the individual Phase III studies, varenicline significantly reduced craving, withdrawal characterised by symptoms of negative affect (depressed mood, irritability, frustration, or anger, anxiety, difficulty concentrating) and the reinforcing effects of smoking compared with placebo.

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In the *All Subjects* population, mean weight gain was higher for varenicline than for placebo, while in the *Cessators* population, mean weight gain was lower for varenicline than for placebo.

Table: Change in Body Weight from Baseline (kg) to Week 12
[Mean Change (SE)]Study A3051028 and -36

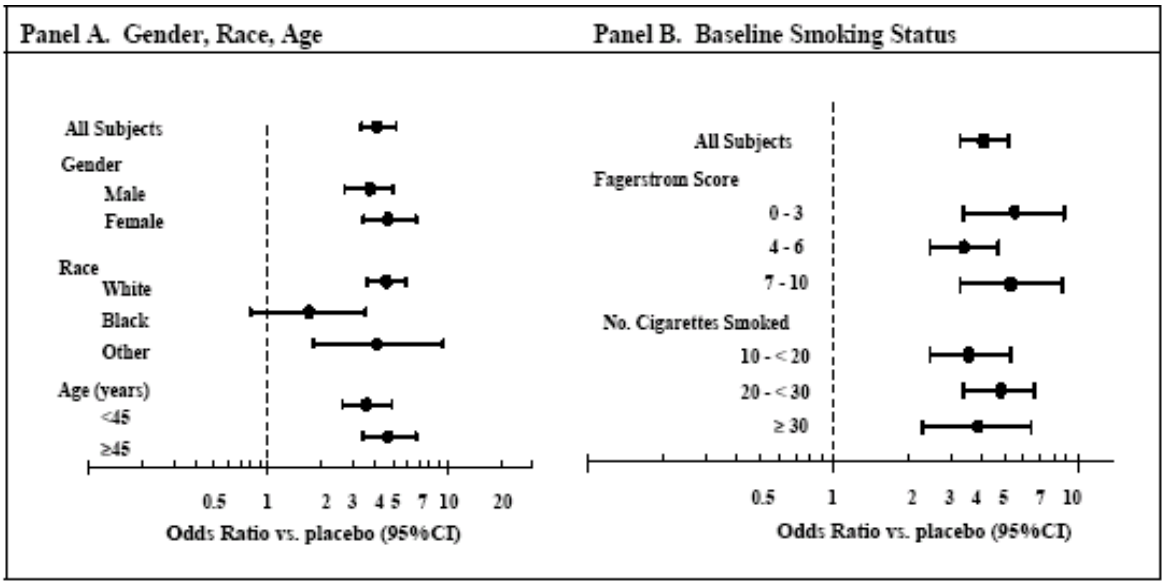
	All Subjects		Cessators[a]	
	N	Mean Change (SE)	N	Mean Change (SE)
		Study A3051028		
Varenicline	236	2.11 (0.18)	144	2.37 (0.23)
Placebo	198	1.40 (0.19)	56	2.92 (0.42)
Zyban	197	1.88 (0.17)	88	2.12 (0.24)
		Study A3051036		
Varenicline	230	2.29 (0.18)	136	2.89 (0.24)
Placebo	195	1.52 (0.21)	51	3.15 (0.53)
Zyban	213	1.32 (0.22)	94	1.88 (0.34)

SE = standard error [a] Cessators = subjects who were responders on the Week 9-12 CQR.

- Analysis performed across trials (pooled analyses and meta-analysis)

Overall, pooled data from studies A3051007/1018, A3051028 and A3051036 showed that varenicline is significantly better that placebo.
Subgroup analysis by age, gender, race, and baseline smoking characteristics.
Post hoc subgroup analyses based on gender, age, race, and baseline smoking characteristics (total Fagerström score and average number of cigarettes smoked during the month prior to study enrolment) were conducted using pooled data from Studies A3051028, -36 and the 1 mg BID arm of Study -07/18 (N = 1750).

Figure: Treatment Effect (as Odds Ratio) for 4-Week CQR (Weeks 9-12) by Gender, Race, Age and Baseline Smoking Status: Pooled Principal Smoking Cessation Studies



Source: Section 2.7.3 Tables A13.1, A13.2, A13.3, A13.4, A13.5
Pooled efficacy data: Studies A3051028, A3051036 and Study A3051007/1018 (1 mg BID varenicline + placebo)

The age analysis split subject ages <45 years and ≥45 years because the small number of subjects ≥65 years (39/1750, 2.2%) precluded a meaningful analysis based on the age groups designated in ICH-E7. No remarkable effects of gender or baseline Total Fagerström score/Average number of cigarettes smoked on either 4-week *CQR* (Weeks 9-12) or *Continuous Abstinence* (Weeks 9-52) were observed.

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In the by-race analysis, the small number of non-White subjects limits the ability to estimate precisely the treatment effect in these subpopulations. The Weeks 9-12 *CQRs* and the *Continuous Abstinence* rates from Weeks 9-24 and Weeks 9-52 were similar in Whites and Other races. Similarly, the estimated treatment effects were strong and similar in these 2 subgroups. Varenicline also increased the rate of smoking cessation in Blacks compared with placebo, however, the Weeks 9-12 *CQR* (Table below) and *Continuous Abstinence* rates over both intervals were lower than those of Whites and Others and the treatment effect was smaller. The finding of a smaller treatment effect in Blacks is consistent with published survey data for the United States showing that fewer Blacks than Whites or Hispanics remained abstinent for at least one month.

Overall, pooled data from these three studies showed that the efficacy of varenicline in the above-mentioned subgroups was generally comparable to that observed in the total ITT population.

Pooled Analysis of Craving, Withdrawal, and the Reinforcing Effects of Smoking.

For pooled studies A3051028 and –36, varenicline significantly reduced craving compared with placebo, as measured by both MNWS Urge to Smoke and QSU-Brief Total Craving Score (see table below). Varenicline was superior to placebo in reducing withdrawal characterised by symptoms of negative affect (depressed mood, irritability, frustration, or anger, anxiety, difficulty concentrating) and the reinforcing effects of smoking in patients who smoked over treatment.

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Table: Craving, Withdrawal, and Reinforcing Effects of Smoking in pooled analysis (Studies A3051028, -36)

	Average of Weeks 1-7		Comparison vs. Placebo			
	LS Mean (SE)	95% CI	Difference (SE)	95% CI	p-value	Effect Size
Craving						
MNWS Urge to Smoke (Item 1)						
Varenicline (N=672)	1.18 (0.03)	1.12, 1.24	-0.51 (0.04)	-0.59, -0.42	<0.0001	-0.65
Zyban (N=646)	1.38 (0.03)	1.32, 1.44	-0.31 (0.04)	-0.39, -0.23	<0.0001	-0.40
Placebo (N=669)	1.69 (0.03)	1.63, 1.74	--	--	--	--
QSU-Brief Total Craving Score						
Varenicline (N=671)	1.73 (0.03)	1.67, 1.80	-0.44 (0.05)	-0.53, -0.35	<0.0001	-0.33
Zyban (N=646)	1.90 (0.03)	1.83, 1.96	-0.28 (0.05)	-0.37, -0.19	<0.0001	-0.21
Placebo (N=670)	2.18 (0.03)	2.11, 2.24	--	--	--	--
Withdrawal						
MNWS Negative Affect (Items 2-5)[a]						
Varenicline (N=672)	0.60 (0.02)	0.56, 0.64	-0.16 (0.03)	-0.22, -0.11	<0.0001	-0.27
Zyban (N=646)	0.62 (0.02)	0.57, 0.66	-0.15 (0.03)	-0.21, -0.09	<0.0001	-0.24
Placebo (N=670)	0.76 (0.02)	0.72, 0.80	--	--	--	--
MNWS Restlessness (Item 6)[b]						
Varenicline (N=671)	0.75 (0.03)	0.70, 0.80	-0.12 (0.04)	-0.19, -0.05	0.0009	-0.14
Zyban (N=644)	0.79 (0.03)	0.74, 0.84	-0.08 (0.04)	-0.16, -0.01	0.0246	-0.10
Placebo (N=669)	0.87 (0.03)	0.82, 0.92	--	--	--	--
Reinforcing Effects of Smoking						
SEI/mCEQ Smoking Satisfaction (Questions 1, 2 &12)[c]						
Varenicline (N=598)	2.57 (0.05)	2.47, 2.67	-0.51 (0.07)	-0.64, -0.38	<0.0001	-0.41
Zyban (N=594)	2.85 (0.05)	2.75, 2.94	-0.24 (0.07)	-0.37, -0.11	0.0004	-0.19
Placebo (N=639)	3.08 (0.05)	3.00, 3.17	--	--	--	--
SEI/mCEQ Psychological Reward (Questions 4-8)[d]						
Varenicline (N=598)	2.14 (0.04)	2.06, 2.22	-0.40 (0.06)	-0.51, -0.29	<0.0001	-0.29
Zyban (N=594)	2.28 (0.04)	2.20, 2.36	-0.26 (0.06)	-0.37, -0.15	<0.0001	-0.19
Placebo (N=639)	2.54 (0.04)	2.47, 2.62	--	--	--	--

Note: Effect Size = LS mean treatment differences / pooled standard deviation at baseline (pooled by center and study)
Scoring: MNWS: Scores ranged from 0 (Not at all) to 4 (Extreme) with higher scores indicating greater intensity; QSU-Brief Scores range from 1 (strongly disagree) to 7 (strongly agree) with higher scores indicating greater craving; SEI/mCEQ: Scores ranged from 1 (not at all) to 7 (extremely) with higher scores indicating greater intensity
[a]Negative Affect scale =average of MNWS items # 2 (depressed mood);#3 (irritability, frustration, or anger); #4 (anxiety) and #5 (difficulty concentrating), [b]Restlessness scale= MNWS item # 6 (restlessness)
[c]Smoking Satisfaction scale =average of SEI/mCEQ questions #1 (Was smoking satisfying?), #2 (Did cigarettes taste good?), and # 12 (Did you enjoy smoking?); [d]Psychological Reward scale=average of SEI/mCEQ questions #4 (Does smoking calm you down?), #5 (Did smoking make you feel more awake?, # 6 (Did smoking make you fell less irritable?), #7 (Did smoking help you concentrate?) and #8 (Did smoking reduce your hunger for food?)

- Clinical studies in special populations

Not applicable.

- Supportive studies

Maintenance Study

Because published literature as well as observations from the varenicline clinical program indicate that most relapses to smoking occur in the first weeks following end of treatment. Study A3051035 examined whether an additional 12 weeks of varenicline treatment at 1 mg BID would increase long-term smoking abstinence rates in subjects who were abstinent for at least the last week of the initial treatment period.

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The primary efficacy endpoint in this study was a comparison between varenicline and placebo in the rate of continuous abstinence for Weeks 13-24 in subjects responding to an initial 12-week course of smoking cessation therapy with varenicline. The rate of continuous abstinence form weeks 13-52 was a secondary endpoint.

Study design: This international multicentre study was conducted in 3 phases: a 12-week open-label phase in which all patients were treated with varenicline at 1 mg BID; a 12-week double-blind phase in which patients were randomised to either varenicline 1 mg BID or placebo (Weeks 13-24); and a non-treatment follow-up phase to Week 52. Patients who were abstinent during the last week of the open-label period were eligible to enter the double-blind treatment phase.

Results: Of the subjects who received open-label varenicline 1 mg BID, 1236 (64.1%) subjects were abstinent for the 7 days prior to and including the Week 12 visit. Of these, 1206 (602 varenicline, 604 placebo) took at least one dose of double-blind study medication and were included in efficacy evaluations.
For the *All Subjects* population, the *Continuous Abstinence* rate from Week 13 through Week 24 was statistically significantly higher for varenicline (425/602, 70.6%) than for placebo (301/604, 49.8%) ($p<0.0001$; odds ratio = 2.47). The Continuous Abstinence rate from Week 13 through Week 52 was significantly higher for subjects treated with double-blind varenicline (265/602, 44.0%) than for subjects treated with double-blind placebo (224/604; 37.1%) ($p = 0.0126$, odds ratio = 1.35).

The Applicant concluded that subjects given an additional 12 weeks of varenicline treatment had significantly higher rates of complete smoking abstinence for Weeks 13 to 24 than subjects given placebo and the treatment effect of the additional 12 weeks of varenicline treatment remained statistically significant at the end of the non-treatment follow-up at Week 52. Based on these findings it was concluded that subjects who successfully quit smoking after 12 weeks treatment should take an additional 12 weeks of treatment in order to maintain abstinence.

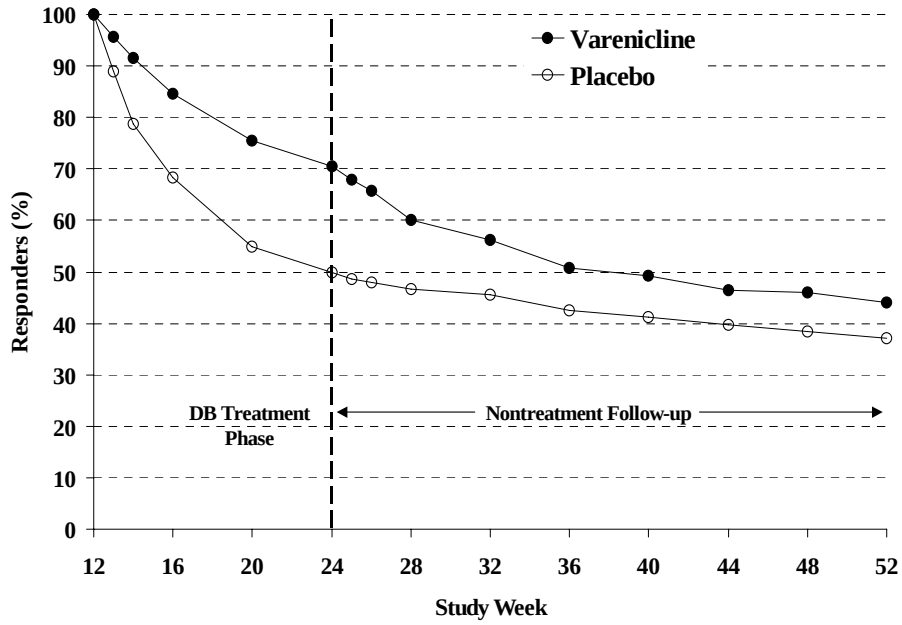
- Discussion on clinical efficacy

The CHMP was concerned by the fact that comparing the response rates for the two groups at a time point where they have been without treatment for the same period of time, the response rates are equal.

Based on the observation of point Week 24 in the placebo group and point Week 36 in the varenicline group, both treatment groups share approximately 50 % response rate. Therefore it can not be ruled out that the two curves are approaching each other resulting in an insignificant difference after a drug free follow up period of 40 weeks.

The additional 12 weeks treatment with varenicline reduced the initial rate of relapse compared with the placebo as shown in the figure below. The abstinence rate in the varenicline group was 70.6% compared with 49.8% in the placebo group at Week 24, but the CHMP questioned whether this comparison was relevant.

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The recommendation for treatment prolongation with another 12 weeks was therefore initially not supported and the Applicant was invited to further argue this issue or to amend the SPC accordingly.

The applicant contested the CHMP's interpretation of the A3051035 results on the following bases:

A: The comparison of the two treatment arms at equal time points after the end of varenicline treatment creates a staggered analysis that violates the principle of a randomized trial, in which study arms should differ solely in the quality of the intervention.

B: The protocol design and data analysis of Study A3051035 conform to the standard approach for smoking relapse prevention studies.

C: The statistically significant treatment effect of the 12 weeks varenicline maintenance treatment at final follow-up (40 weeks after randomization) represents a clinically meaningful impact on long-term health outcomes. Extrapolation of a model fitted to the observed relapse curves shows that a difference between varenicline and placebo lines is likely to persist beyond the observed period.

The CHMP, taking into account the arguments from the Applicant during the oral explanation and the following discussion within the CHMP meeting, agreed to the inclusion of maintenance data in the label to inform discussions of maintenance treatment between physicians and patients.

The CHMP was also concerned by abrupt withdrawal at the end of treatment and suggested that dose-tapering may be useful to prevent increased relapse the first week after stopping varenicline. Both after 12 and 24 week varenicline treatment, a sharp decline in treatment response (i.e. a sharp increase in relapse rate) was observed that is not fully understood. It may be related to withdrawal symptoms of weak AchR agonist activity of varenicline, or a rebound effect.

Although the elimination half-life of varenicline is indeed long, it may not be long enough for nAchRs to adapt to the absence of the partial agonist-antagonist varenicline. Though the exact mechanism underlying this phenomenon may not be fully understood, the initial sharper decline in success rate in varenicline arm is a fact, and it may be tempered by a more gradual decline of the dose.

Based on these observations, the Applicant was asked to discuss the feasibility of a clinical trial comparing the long term efficacy of abrupt discontinuation versus dose –tapering or whether dose – tapering should be proposed as an option for individual patient.

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The applicant noted that there was a slightly higher relapse rate (3-6% compared with placebo or bupropion) in the varenicline group that was limited to the first week after stopping treatment. The Applicant agreed to amend the dosing recommendation in section 4.2 of the SPC to acknowledge that the risk for relapse to smoking is elevated in the period immediately following the end of treatment in smoking cessation therapy and that in patients with a high risk of relapse, dose tapering may be considered. In addition, the Applicant agreed to add a statement in section 4.4 outlining that there was an increase in irritability, urge to smoke, depression, and/or insomnia in up to 3% of patients on discontinuation of Champix and that the prescriber should inform the patient accordingly and discuss or consider the need for dose tapering.

Moreover, the Applicant committed to report back to the CHMP about the feasibility of a clinical trial evaluating dose tapering versus abrupt discontinuation in terms of long-term efficacy, as a post-authorisation follow-up measure.

Clinical safety

The safety profile of varenicline was investigated in a program of 32 studies. These studies included:

1) 8 completed Phase 2/3 studies, with a total of 5944 subjects in all treatment groups
2) 24 completed Phase 1 studies, with a total of 795 subjects in all treatment groups (include 2 studies with controlled release treatment arms)

Serious Adverse Events (SAEs) in subjects receiving the CR formulation are included in the listings of SAEs, but routine safety data from subjects who received only a CR formulation are not included.
A cut-off date of 15 July 2005 has been applied to data from 3 ongoing studies and to the Serious Adverse Event data.

- Patient exposure

As of 15 July 2005, the varenicline clinical development program safety database comprised of 6739 individuals who received at least one dose of study drug (5944 in Phase 2/3 studies; 795 subjects in Phase 1 studies). Of the 3298 subjects who received study drug in the Fixed-dose, Placebo-controlled Studies, 1575 received varenicline, 795 received bupropion (Zyban), and 928 received placebo. In all completed phase 2/3 trials, 3940 subjects received varenicline; 795 received bupropion, and 1209 received placebo.
More than 80% of the 3940 subjects who received varenicline in all completed phase 2/3 studies received the 1 mg BID dose. In the fixed-dose, placebo-controlled studies, 314 subjects received >12 weeks of varenicline at 1 mg BID. In addition, most subjects counted as receiving >11 weeks of the 1 mg BID dose actually completed the full 12 weeks of treatment (i.e. 84 days).

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Table: Estimated subject-days exposure, by study and median duration of exposure by cohort

	Varenicline		Zyban	Placebo
	< 1 mg BID	1 mg BID		
All Completed Phase 2/3 Studies				
Fixed-dose, Placebo-controlled Studies				
Study A3051028	--	23679	20342	21090
Study A3051036	--	23060	22077	21633
Study A3051007	17098	16642	--	7030
Study A3051002	10186	5053	5053	4912
Subject-days[a]	27284	68434	47472	54665
Median Duration days (range)	49 (1-91)	83 (1-102)	83 (1-107)	80 (1-133)
Number of Subjects	505	1070	795	928
Study A3051037	--	60140	--	27967
Study A3051035				
Open-label		132339	--	--
Double-blind		46181	--	
Study A3051016	10980			10159
Study A3051043	1108			
Subject-days All Completed Phase 2/3 Studies[a]	346466		47472	92791
Median Duration days (range)	84 (1-413)		83 (1-107)	83 (1-379)
Number of Subjects	3940		795	1209

Source: Studies A3051002, A3051007, A3051016; A3051028, A3051036, A3051035, A3051037

[a] Subject-days of drug exposure is calculated from first day of dosing to (and including) last day of dosing.

In the All Completed Phase 2/3 Subjects cohort, 456 subjects had >24 weeks of treatment. In addition, many subjects counted as receiving >20 weeks of treatment completed the scheduled 24 weeks of dosing in Study A3051035 but had their final study day prior to Day 169. In Study A3051037, 95 subjects had >52 weeks of varenicline (1 mg BID) treatment, and 112 subjects received varenicline for ≥52 weeks (≥364 days), in compliance with ICH-E1A.

In All Completed Phase 2/3 Studies , approximately equal proportions of men and women received varenicline (49.7% versus 50.3%, respectively) (see table below). A greater proportion of men than women received bupropion (57.2% versus 42.8%) or placebo (54.3% versus 45.7%). The mean age across all groups was 43.4 years; a total of 165 (2.8%) subjects were 65 years of age or older. More than 87% of subjects were White, 7% were Black, and 6% belonged to other racial groups.

These data indicate that the number of subjects (White ≤ 65 years) exposed to varenicline at the dose and duration of exposure proposed in the label is adequate for the safety assessment of the product.

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Table: Demographic Characteristics - All Completed Phase 2/3 Studies

Number (%)[a] of Treated Subjects	Varenicline N= 3940	Zyban N=795	Placebo N=1209
Gender			
Males	1959 (49.7%)	455 (57.2%)	656 (54.3%)
Females	1981 (50.3%)	340 (42.8%)	553 (45.7%)
Age (years):			
<18	0	0	0
18-44	2035 (51.6%)	462 (58.1%)	678 (56.1%)
45-64	1797 (45.6%)	308 (38.7%)	499 (41.3%)
≥65	108 (2.7%)	25 (3.1%)	32 (2.6%)
Mean	43.8±11.0	42.2±11.6	42.9±11.5
Range	18-75	18-75	18-75
Race[b]			
White	3538 (89.8%)	650 (81.8%)	998 (82.5%)
Black	211 (5.4%)	73 (9.2%)	129 (10.7%)
Other	191 (4.8%)	72 (9.1%)	82 (6.8%)
Weight (kg), Males			
N	1953	454	656
Mean±SD	85.4 ±14.7	85.5 ± 14.3	85.4±14.9
Weight (kg), Females			
N	1978	339	550
Mean±SD	69.4±13.3	70.9 ±14.2	70.8 ± 13.8

Protocols included: A3051002, A3051007, A3051016, A3051028, A3051035, A3051036 A3051037, A3051043

[a]: Percentages may not add to 100% due to rounding.

[b]: CRFs for some studies listed racial categories in addition to White, Black, and Other. Subjects in those additional racial categories are included in this summary as "Other".

- Adverse events

The ability to characterize the adverse event profile of varenicline is confounded by the fact that some subjects may continue to smoke while taking smoking cessation pharmacotherapy; and/or smoking cessation may be associated with symptoms of nicotine withdrawal (e.g. depressed mood, insomnia, irritability/frustration/anger, restlessness, difficulty concentrating). No attempt was made in the analysis of varenicline safety data to distinguish between adverse events associated with study drug treatment and those possibly associated with either of the two conditions mentioned above.

In the fixed-dose, placebo-controlled trials, varenicline-treated subjects most commonly reported treatment-emergent (and treatment-related) gastrointestinal, central nervous system and/or psychiatric system events. Nausea was the single most frequently reported adverse event among varenicline-treated subjects. In addition to nausea, the treatment-emergent adverse events most commonly reported (≥5% and ≥1.5 times placebo) by varenicline-treated subjects (1 mg BID) were gastrointestinal disorders (specifically, constipation, flatulence, dyspepsia, and vomiting). The treatment-emergent adverse events that increased in frequency with increasing varenicline dose were nausea, constipation, vomiting, abnormal dreams, and sleep disorder. These common treatment-emergent (and treatment-related) events were mild or moderate in severity in more than 98% of cases.

The percentage of varenicline-treated subjects (1 mg BID) reporting severe adverse events exceeded 1% only for nausea (1.3% vs. 0.4% for placebo) and headache (1.2% vs. 0.9% for placebo). Among the common treatment-emergent adverse events, the only two leading to discontinuation from 1 mg BID varenicline treatment at a rate ≥1% were nausea (3.1% vs. 0.5% placebo) and insomnia (1.2% vs. 1.1% placebo).

The adverse event profile in the all completed phase 2/3 Studies was similar to the Fixed-dose Placebo-controlled Studies, indicating that the safety and tolerability profile in subjects receiving 12 weeks treatment accurately reflected the overall varenicline safety experience (see table below).

The incidence of gastrointestinal disorders is high compared to the placebo group. However no weight loss was observed in the Cessator subjects who completed the studies.

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Table: Most frequent all causality adverse events (≥5% in any treatment group) - All Completed Phase 2/3 Studies

MedDRA System Organ Class Preferred term[a] Subject-days of drug exposure[b]	Varenicline N= 3940 346466	Zyban N= 795 47472	Placebo N= 1209 92791
		n (%)	
Any adverse event	3274 (83.1)	633 (79.6)	925 (76.5)
Adverse event resulting in permanent discontinuation from treatment	510 (12.9)[c]	114 (14.3)[d]	109 (9.0)[e]
Gastrointestinal Disorders	**2081 (52.8)**	**270 (34.0)**	**363 (30.0)**
Constipation	325 (8.2)	62 (7.8)	38 (3.1)
Dry mouth	176 (4.5)	70 (8.8)	50 (4.1)
Dyspepsia	275 (7.0)	27 (3.4)	38 (3.1)
Flatulence	382 (9.7)	21 (2.6)	39 (3.2)
Nausea	1260 (32.0)	92 (11.6)	121 (10.0)
General Disorders and Administration Site Conditions	**582 (14.8)**	**82 (10.3)**	**143 (11.8)**
Fatigue	280 (7.1)	29 (3.6)	62 (5.1)
Infections & Infestations	**1155 (29.3)**	**201 (25.3)**	**367 (30.4)**
Nasopharyngitis	362 (9.2)	45 (5.7)	100 (8.3)
Upper respiratory tract infection	277 (7.0)	67 (8.4)	135 (11.2)
Metabolism & Nutrition Disorders	**318 (8.1)**	**56 (7.0)**	**53 (4.4)**
Increased appetite	220 (5.6)	27 (3.4)	27 (2.2)
Nervous System	**1325 (33.6)**	**244 (30.7)**	**359 (29.7)**
Dizziness	216 (5.5)	55 (6.9)	82 (6.8)
Dysgeusia	252 (6.4)	49 (6.2)	48 (4.0)
Headache	698 (17.7)	111 (14.0)	182 (15.1)
Psychiatric Disorders	**1632 (41.4)**	**335 (42.1)**	**340 (28.1)**
Abnormal dreams	545 (13.8)	53 (6.7)	61 (5.0)
Anxiety	120 (3.0)	44 (5.5)	54 (4.5)
Irritability	256 (6.7)	46 (5.8)	75 (6.2)
Insomnia	754 (19.1)	180 (22.6)	146 (12.1)
Sleep disorder	145 (3.7)	46 (5.8)	28 (2.3)

Protocols included: A3051028, A3051036, A3051037, A3051035, A3051002, A3051007, A3051016, A3051043

[a] Includes MedDRA Preferred Terms for adverse events present in ≥5% of any treatment group

[b] Subject-days of drug exposure is calculated from first day of dosing to (and including) last day of dosing.

[c] Total does not include one subject (Subject 103510321036) with an adverse event resulting in permanent discontinuation from treatment.

[d] Total includes one subject (Subject 102810181055) counted as permanently discontinued but was temporarily discontinued.

[e] Total includes one subject (Subject 102810131027) counted as permanently discontinued but was no action taken and one subject (Subject 103710061017) counted as no action taken but was permanently discontinued.

The treatment emergent adverse events observed in varenicline-treated subjects in the pooled Phase 1 studies were similar to those in Fixed-dose Placebo-controlled Studies with nausea, headache, and vomiting being the most commonly reported adverse events. The relatively high incidences of vomiting in the 2 mg and >2 mg daily dose groups (8.7% and 21.4%, respectively) may reflect the higher varenicline doses used in the Phase 1 studies (e.g. up to a 10 mg single dose in Study 305-001). The incidence of gastrointestinal disorders is high compared to the placebo group.

In Phase 2/3 studies, no weight loss was observed in the Cessator subjects who completed the studies.

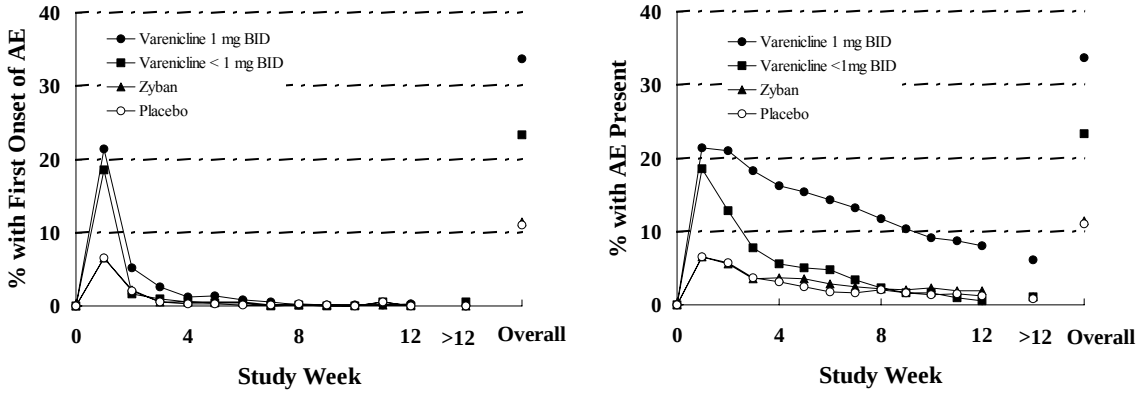
Time to onset and persistence

The time to onset of first occurrence of an adverse event and the presence of that adverse event over time were assessed using the Fixed-dose, Placebo-controlled Studies dataset. The majority of subjects who experienced nausea reported the first occurrence during the first week of treatment. The proportion of subjects reporting nausea as "present" was greatest at Week 1 then decreased over time. Among subjects receiving varenicline at doses less than 1 mg BID, the percent reporting nausea approached placebo levels as early as Week 4. Among subjects receiving varenicline at 1 mg BID, the proportion with nausea decreased by about 50% over the 12 weeks of study treatment. The median duration of a nausea event for subjects receiving the 1 mg BID dose was 10 days.

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This pattern of onset and presence is representative of that of other common AE.

Panel A. First Onset of Nausea, by Week **Panel B. Presence of Nausea, by Week**



Study A3051037 investigated the safety of 1 mg BID varenicline administered for 52 weeks. Adverse events that occurred in ≥5% of varenicline-treated subjects are summarized here:

Table:Long-Term Safety Study A3051037 : Most Frequent All Causality Adverse Events (≥ 5% in Any Treatment Group)

MedDRA System Organ Class Preferred term[a]	**Varenicline N=251**	**Placebo N=126**
	n (%)	
Any adverse event	242 (96.4)	104 (82.5)
Adverse event resulting in permanent discontinuation from treatment	71 (28.3)	12 (9.5) [b]
Gastrointestinal Disorders	**179 (71.3)**	**48 (38.1)**
Constipation	31 (12.4)	9 (7.1)
Diarrhea	20 (8.0)	12 (9.5)
Dry mouth	11 (4.4)	8 (6.3)
Dyspepsia	33 (13.1)	3 (2.4)
Flatulence	31 (12.4)	12 (9.5)
Nausea	101 (40.2)	10 (7.9)
Vomiting	17 (6.8)	2 (1.6)
General Disorders and Administration Site Conditions	**42 (16.7)**	**20 (15.9)**
Fatigue	6 (2.4)	8 (6.3)
Infections & Infestations	**123 (49.0)**	**58 (46.0)**
Bronchitis	3 (1.2)	7 (5.6)
Influenza	15 (6.0)	3 (2.4)
Nasopharyngitis	38 (15.1)	20 (15.9)
Sinusitis	17 (6.8)	8 (6.3)
Upper respiratory tract infection	34 (13.5)	12 (9.5)
Investigations	**50 (19.9)**	**12 (9.5)**
Weight increased	17 (6.8)	5 (4.0)
Metabolism & Nutrition Disorders	**28 (11.2)**	**8 (6.3)**
Increased appetite	13 (5.2)	4 (3.2)
Musculoskeletal & Connective Tissue Disorders	**65 (25.9)**	**25 (19.8)**
Arthralgia	18 (7.2)	7 (5.6)
Back Pain	16 (6.4)	6 (4.8)
Nervous System	**108 (43.0)**	**45 (35.7)**
Dizziness	19 (7.6)	6 (4.8)
Dysgeusia	27 (10.8)	3 (2.4)
Headache	43 (17.1)	26 (20.6)
Psychiatric Disorders	**109 (43.4)**	**39 (31.0)**
Abnormal dreams	57 (22.7)	9 (7.1)
Insomnia	48 (19.1)	12 (9.5)
Irritability	13 (5.2)	7 (5.6)
Vascular Disorders	**26 (10.4)**	**11 (8.7)**
Hypertension	15 (6.0)	5 (4.0)

[a] Includes MedDRA Preferred Terms for adverse events present in ≥5% of any treatment group
[b] Total includes one subject (Subject 103710061017) counted as no action taken but was permanently discontinued .

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While the overall incidence of adverse events in subjects receiving varenicline for up to for 52 weeks (Study A3051037) was higher than in studies with 6- or 12-weeks varenicline treatment, no additional adverse events emerged that suggested an increase in risk with increased duration of exposure.

No clinically meaningful changes in laboratory test results were observed in the clinical trials nor were there any noteworthy changes in the QT/QTc interval or any other ECG parameter in either preclinical or clinical studies.

- Serious adverse event/deaths/other significant events

The SAE safety database included 134 cases (count includes deaths).

There were five deaths (3 varenicline, 1 bupropion, 1 placebo) reported in the safety database, no deaths were reported in ongoing studies. All deaths occurred post-treatment in Phase 3 studies. The bupropion and placebo deaths occurred outside the 30-day post-treatment reporting window. None of the deaths were considered treatment-related.

Table: Deaths in completed varenicline studies

Age/Race/ Gender[a]	Treatment/ Dose	Day of Death	Total exposure (days)	Cause[b]
Varenicline				
61/W/M	Varenicline 1 mg BID	Day 196 (post-therapy Day 27)	169 days	Suicide
71/W/M	Varenicline 1 mg BID	Day 188 (post-therapy Day 19)	169 days	Massive pericardial exudate Lung cancer Lymph node metastasis Right side pneumonia Cardiac arrest
29/W/M	Varenicline 1 mg BID	Day 218 [c] (post-therapy Day 197)	15 days	Rectal sarcoma
Zyban				
46/W/M	Bupropion 150 mg BID	Day 222[d] (post-therapy Day 137)	85 days	Accidental death (fatal motorcycle accident)
Placebo				
64/W/M	Placebo	Day 352[d] (post-therapy Day 239)	N/A	Death unexplained (fall, collapse of lung, elbow fracture)

N/A = not applicable.

[a] Race: W = White, Gender: M = male..

[b] Investigator's term(s).

[c] Although the death occurred on Day 218, the subject was diagnosed with rectal sarcoma <30 days after varenicline treatment.

[d] Event occurred beyond the required reporting period but is included for completeness.

A total of 134 SAE cases were reported in completed Phase 1, 2, and 3 varenicline studies. Of the 134 SAE cases, 120 (86 varenicline, 15 bupropion, 19 placebo) occurred while subjects were either on treatment or within 30 days of the last dose of study drug. The majority of SAE cases were single events. Among patients treated with varenicline, two SAE cases in Phase 1 and 7 cases in Phase 2/3 were considered treatment-related by the investigator. Among these 9 cases, no pattern was evident in either the event terms or the time to onset of event from the beginning of treatment. A summary of the serious adverse events by treatment group is provided below.

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Table: Incidence of serious adverse events in completed varenicline studies by system organ class (All Causality and Treatment Related)

	Number of Events: All Causality (Treatment Related)			
	Varenicline	Varenicline/ Placebo[a]	Bupropion	Placebo
Cardiac Disorders	24 (2)	0	0	4
Neoplasms, benign, malignant and unspecified	12	0	1	2
Infections and infestations	11	1	3	4
Nervous system disorders	11 (2)	1	6 (5)	1
Gastrointestinal disorders	9 (2)	1	1 (1)	1
General disorders and administration site conditions	7 (3)	0	1	3
Psychiatric disorders	6 (1)	0	0	2
Vascular disorders	6	0	0	1
Eye disorders	5 (3)	0	0	0
Injury poisoning and procedural complications	6	0	3 (1)	5
Investigations	5 (1)	0	0	0
Musculoskeletal and connective tissue disorders	4	0	1	0
Metabolism and nutrition disorders	3	0	0	0
Renal and urinary disorders	3	0	0	0
Hepatobiliary disorders	2	1	1	0
Pregnancy, puerperium and perinatal conditions	2	0	2	0
Reproductive system and breast disorders	2	2	0	1
Respiratory, thoracic and mediastinal disorders	2 (1)	0	0	2
Ear and labyrinth disorders	1 (1)	0	0	0
Immune system disorder	0	0	0	1 (1)
Skin and subcutaneous tissue disorders	0	0	1 (1)	0

Note: Where present, numbers in parentheses are the number of treatment-related cases; if not present, no cases were treatment related.

[a] SAEs listed in this column occurred in those subjects who received placebo in the double-blind phase of Study A3051035.

Thirteen (8 varenicline, 4 bupropion, 1 placebo) of the 16 subjects with treatment-related SAEs discontinued treatment due to the SAE. In addition, 35 (23 varenicline, 4 Zyban, 8 placebo) subjects permanently discontinued treatment for SAEs not considered related to study drug. Of the 23 varenicline-treated subjects, 6 were discontinued for Cardiac Disorders (tachycardia; angina unstable; atrial fibrillation; acute coronary syndrome; myocardial infarction; coronary artery disease), 2 for Gastrointestinal Disorders (duodenal ulcer; abdominal pain), 6 for Nervous System Disorders (grand mal convulsion (2 cases); headache; cerebral infarct, cerebral thrombosis; loss of consciousness; multiple sclerosis); 3 for Neoplasms (cholesteatoma; adenocarcinoma; lung and brain neoplasm malignant); and 6 for SAEs affecting other body systems (chest pain; meningitis aseptic; back pain; calculus ureteric; epistaxis; acute psychosis, affect lability). No pattern was observed in either the event terms or the time to onset of event from the start of treatment.

Neither the number of deaths nor the number and severity of SAE are of concern from a safety perspective.

- Laboratory findings

Liver function

The clinical laboratory test database was reviewed for liver enzyme abnormalities based on non-clinical findings of hepatic changes and microscopic evidence of hepatocellular necrosis in rats given 100 mg/kg/day in a 10-day study. Few subjects (≤0.8% in any group) demonstrated clinically significant elevations in liver function tests (LFT) (AST and ALT (>3xULN), bilirubin (>1.5xULN). The proportion of varenicline-treated subjects with elevated LFTs was generally comparable to that in the placebo group. Additionally, there was no apparent relationship between dose and the incidence of elevated LFTs. Increasing the size of the safety database to All Completed Phase 2/3 Studies had no notable effect on the incidence of liver function test abnormalities in spite of including longer-term Studies A3051035 and A3051037.

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Electrocardiogram
The effects of varenicline on the ECG and the QT/QTc interval were assessed in both non-clinical and clinical studies.

In the Phase 1 clinical program, on-treatment ECGs were collected in 19 of the 24 studies and manually read by a centralized ECG reader in 7 of those studies. Two of the 7 studies (A3051012 and A3051014) employed rigorous methods for assessing QT/QTc following single dose and multiple dose administration of varenicline, respectively. These two studies were among the 7 Phase 1 studies in which QT intervals from electronic ECG tracings were measured by a blinded centralized reader. Both performed baseline and post-baseline measurements in triplicate, measured QTc at the approximate Tmax, standardized the timing of ECGs with regard to meals, enrolled both males and females, included a within subject placebo control group and included pharmacokinetic sampling to provide for ECG/PK time matched pairs. Study A3051014 is particularly noteworthy for the number of subjects (n=120, 40 per treatment regimen) studied, and also for including a 1.5 mg BID dose, i.e., higher than the recommended dose of 1 mg BID. In these studies, the placebo-adjusted mean changes from baseline in QTcF were generally 0 msec or less, with isolated increases of <4 msec. For all measurements the nominal 90% confidence interval excluded 10 msec, the threshold of concern proposed in the ICH E14 guidance.

Additionally, because of the extensive collection of data in healthy male and female subjects, smokers and non-smokers, treated with both single- and multiple-doses of varenicline or placebo, a model-based analysis was performed to evaluate the exposure-response relationship between varenicline concentration and the heart rate corrected QT interval (QTc). The results of this analysis show that no concentration-related effect of varenicline on QT/QTc prolongation was detected in male and female subjects, as evidenced by a mean slope estimate near zero and an upper bound of the 95% confidence interval predicting a maximum mean effect on QTc of about 0.3 msec at the recommended 1 mg BID dose. Even with factors that can influence the pharmacokinetics of varenicline such as renal function, the upper extremes of predicted probability distributions for mean QTc prolongation do not exceed 2 msec.

Blood pressure and heart rate
Varenicline produced no clinically meaningful changes in standing/sitting diastolic or systolic blood pressure or pulse rate in Phase 1/2/3 studies. In Fixed-dose, Placebo-controlled Studies, median changes in blood pressure and pulse rate were comparable in the varenicline and placebo groups. The presence of an additional cardiovascular risk factor did not affect median change of either variable. The proportion of subjects with blood pressure or pulse rate measurements meeting categorical thresholds was small (≤1.5%) and showed no consistent pattern.

Lipids
Approximately 25 % of the subject had elevated non-fasting triglycerides without regard to baseline values. There were no differences between the varenicline, bupropion and placebo groups.

Renal function
Clinical laboratory assessments of renal function included BUN, creatinine, and qualitative urinalysis tests. No varenicline-treated subjects in the Phase 2/3 Fixed-Dose, Placebo-Controlled Studies had a clinically significant elevation of BUN or creatinine. Among the 3940 varenicline-treated subjects in the Phase 2/3 studies, 3 had clinically significant elevations of BUN, and none had clinically significant elevations of creatinine.

- Safety in special populations

Safety in subgroups
Analyses of the safety data revealed that the safety and tolerability profile of varenicline was independent of gender, age, race or presence of cardiovascular risk factors (additional to smoking) and within each of these subgroups there was a similar pattern of events in varenicline-treated subjects compared with placebo subjects. No children younger than 12 years have been treated with

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varenicline. No systematic studies on the use of varenicline in pregnant or lactating women have been conducted.

It should be noticed that only a small percentage of the study population had any concurrent cardiovascular disease at study entrance (<3%), and most of them were mild of nature. The lack of experience in this special patient group is compensated for by the applicant´s commitment to perform further studies

Because of the use of bupropion as comparator, many specific populations could not be included in the clinical studies. Varenicline is not investigated in subjects with a history of seizures, diabetes mellitus, hepatic or renal impairment, bipolar disorder, alcoholism (current or in the recent past). Neither was varenicline investigated in combination with MAO-inhibitors, antidepressants, antipsychotics, benzodiazepines, naltrexon, systemic steroids (with exception of inhaled steroids), and theophylline. Cholinergic agents are known to induce psychoses. There were only two cases of acute psychosis (one possible drug-related) reported during varenicline use. In addition, there were 3 cases of seizures reported after varenicline use, but none of them was deemed to be drug-related. Despite the low incidence of psychoses and seizures, one should realise that patients at risk had not been included. Since there is no clinical experience in these special groups, no clear conclusion could be drawn concerning the risk of varenicline treatment in these patients.

- Safety related to drug-drug interactions and other interactions

In anticipation of probable co-administration in clinical practice, NRT was selected for drug interaction study. In Study A3051033 varenicline (1 mg BID) and NRT (patch, 21 mg/day) were co-administered to smokers for 12 days. A statistically significant decrease (mean = 2.6 mmHg) in systolic blood pressure was measured on the final day of the study. In this study, the incidences of nausea, headache, fatigue, vomiting, dizziness, and dyspepsia were greater for the combination than for NRT alone. Aside from this interaction, no evidence for clinically important pharmacokinetic interactions between varenicline and the other tested drugs were observed. Furthermore no other safety concerns were observed.

- Abuse potential

Examination of abuse-potential adverse event terms in all Phase 2/3 fixed-dose, placebo controlled studies showed that the only preferred term with an incidence in the varenicline groups higher than in the placebo group was somnolence (4.4% and 4.0% for varenicline <1 mg BID and 1 mg BID, respectively versus 2.6% for placebo). In study A3051002, where subjects were treated with varenicline for six weeks followed by one week placebo, subjects did not experience immediate relapse with the withdrawal of therapy nor was there any indication that subjects needed to smoke additional cigarettes to manage craving and withdrawal symptoms. This observation is consistent with the observations in rats and monkeys that varenicline does not produce physiological dependence. Study A3051016 demonstrated that when subjects were permitted to adjust their daily dose ad libitum between 0.5 mg and 2 mg, the mean modal dose for varenicline peaked at approximately 1.5 mg at Week 2 and declined to just above 1.0 mg at Week 12, supporting the claim that there is no pattern of abuse in subjects treated with varenicline and no psychic dependence liability.
The objective of the A3051039 study was to evaluate the abuse potential of varenicline relative to amphetamine in a population of recreational stimulant using subjects. The pattern of effects for both smokers and non-smokers is consistent with the profile of a drug that while having pharmacologic activity (i.e. some known action), has a dose-response profile unlike amphetamine and the general pattern for other drugs of abuse. This is based on the multivariate analysis of primary measures of abuse potential and further evaluation of secondary parameters, including physiological effects. For smokers, the data provide evidence that subjects are unmotivated to abuse varenicline. For non-smokers, 1 mg varenicline differentiated from placebo in the multivariate analysis, specifically with respect to the peak values for the VAS High and ARCI/Cole Abuse Potential scales. The VAS High measure, while capturing the sensation of receiving an active drug, was associated with a disliking of the sensation, especially compared with their liking of amphetamine. No reinforcing effects were

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identified for varenicline as evidenced by the lack of significant difference from placebo on the multiple choice procedure.

The clinical and non-clinical data collected to date, taken together, indicate that varenicline is unlikely to be a substance of abuse.

- Discontinuation due to adverse events

In all completed phase 1 and 2/3 studies, 535 among 4748 varenicline treated subject discontinued due to AE. Most of the events resulting in discontinuation from treatment were gastrointestinal, nervous, and/or psychiatric system events. The median number of days to discontinuation was 28 days for the varenicline 1 mg BID in the fixed-dose, placebo-controlled trials. Few laboratory abnormalities resulted in treatment discontinuation for more than one subject in the Phase 2/3 Fixed-dose Studies. Most of the discontinuations resulted from abnormalities in liver function tests (LFTs). Fifteen varenicline-treated subjects in Phase 2/3 Fixed-dose, Placebo-controlled studies and 23 varenicline treated subjects in All Completed Phase 2/3 Studies were permanently discontinued due to clinically significant elevations in LFT values.
31 varenicline treated subjects discontinued treatment due to an SAE. Eight varenicline-treated subjects were discontinued due to SAEs that were considered treatment related: 3 subjects experienced altered visual acuity/transient loss of vision; 2 subjects were characterized by chest/abdominal pain; 2 subjects experienced multiple treatment-related SAEs affecting two or more organ systems; and 1 experienced acute psychosis. Additionally, one varenicline-treated subject had atrial fibrillation which was considered treatment related but was not noted until the Week 12 visit (end of treatment).

- Post marketing experience

NA

- Discussion on clinical safety

Overall, the analysis of routine adverse events identified no serious safety concerns in smokers receiving varenicline at doses up to 1 mg BID for up to 12 weeks.

The Applicant recommends 1 mg BID dose for all patients, except for patients with severe renal dysfunction. However, every patient that would stop varenicline use prematurely due to adverse events can be considered as a loss, as varenicline is an effective drug to promote smoking cessation. Therefore the CHMP considered that intolerant patients should be given the opportunity to change to a regimen of 0.5 mg BID. The Applicant was asked to introduce the 0.5 mg tablets as a separate pack size to accommodate the need for dosing of patients intolerant of 1.0 mg. The Applicant has implemented the requested measure.

Regarding carcinogenicity, the concern was raised by the fact that hibernomas were identified in rats. It is agreed that the risk for humans to develop hibernomas following treatment with varenicline is theoretical and most probably non-existent. Furthermore, it also agreed that the potential benefit of smoking cessation due to treatment with varenicline, which would prevent additional exposure to known carcinogens from smoking, would be expected to outweigh a hypothetical risk arising from the non clinical hibernoma finding. This is taken into account in the Section 5.3 of the SPC.

Concerning the cardiovascular effects, although there seems to be no suggestion for an increased risk for cardiovascular adverse reactions, the population of patients who stop smoking is a population at risk and therefore cardiovascular effects should be included in the safety specifications and be monitored. The applicant proposed that the specific Cardiovascular Study and monitoring for cardiovascular adverse events in the COPD and Psychosis Studies address the request for cardiovascular monitoring; the RMP will be updated as part of the follow-up measures.

Concerning the issue relating to rebound, withdrawal and dependence, this is a general issue for centrally acting products intended for smoking cessation, and therefore will be included in the safety specifications. A label change to address this issue can be found in Section 4.4 of the SPC where it

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states: "At the end of treatment, discontinuation of CHAMPIX was associated with an increase in irritability, urge to smoke, depression, and insomnia in up to 3% of patients. The prescriber should inform the patient accordingly."

Concerning patients on antidepressants, antipsychotic agents, benzodiazepines, anticonvulsants, naltrexone, oral hypoglycaemic agents, insulin, steroids and theophylline, it is agreed that these drugs show low to very low affinity for the nicotinic α4β2 AchRs and that in turn, varenicline displays very low affinity for the target receptors of these classes of drugs. Pharmacodynamic interactions are therefore unlikely to occur. Nevertheless, the Applicant agreed to monitor for adverse events associated with drug-drug interactions in the Cardiovascular, COPD and Psychosis studies and modify the RMP accordingly.

As is the case with many medicinal products, there are very limited data from the clinical program on the use of varenicline in pregnant women. The Applicant recognized that some pregnant women may potentially be exposed to varenicline as they attempt to stop smoking. To assess the safety of varenicline exposure during pregnancy, the Applicant committed to conducting a prospective cohort study post-approval to compare women who use varenicline while pregnant to women who smoke while pregnant with respect to birth outcomes.

The Applicant will submit a study protocol to the EMEA within three months of the approval and a study report at the time of varenicline renewal.
The varenicline RMP has been updated to include the above proposed prospective cohort study in pregnant women.

5. Pharmacovigilance

Detailed description of the Pharmacovigilance system

In the data submitted the applicant has provided information which ensure that the necessary resources and systems are in place to support routine pharmacovigilance activities that meet the needs for this product.

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

Risk Management Plan

The MAA submitted a risk management plan, which included a risk minimisation plan.

Based on the results from the non-clinical and clinical development program, the Applicant identified areas of potential risk and areas with limited information, for continued pharmacovigilance.

Potential Risks: Effects of smoking cessation

Areas with Limited Information: Very elderly subjects (≥75 years old); cardiovascular Patients; COPD Patients; Psychosis Patients; Pregnancy; Adolescents and Overdose.

Post-launch safety monitoring activities will include routine periodic database searches for any varenicline report of a Designated Medical Event (DME, a predetermined list of medical events considered to be clinically important and frequently associated with drug use), adverse events reported in patients with severe renal impairment and/or aged 75 years or older. In addition, reviews of all events received post-launch will be conducted periodically and following the cut-off date of each Periodic safety Update Report (PSUR).

Routine pharmacovigilance will be employed. The Applicant will provide reviews of adverse events associated with the use of varenicline, and specific reviews of events reported in patients with severe renal impairment, in patients older than 74 years of age or younger than 18 years of age, overdose and

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effects of use during pregnancy (mother and child) in PSURs. In addition, specific studies in cardiovascular, COPD, and psychosis subjects, adolescents and the prospective cohort study in pregnancy also will be conducted.

These activities are noted in Table RM-1 below:

Risks	**SPC**	**Patient Leaflet**	**Psychosis Clinical Trial**	**COPD Clinical Trial**	**Cardio-vascular Clinical Trial**	**Adolescent PK and Safety and Efficacy Trials**	**Pregnancy Prospective Cohort Study**	**PV**
Adverse Events associated Smoking Cessation	√	√						√
Limited Information								
Very Elderly	√	√						√
Cardiovascular Disease			√	√	√			√
COPD				√				√
Psychosis			√					√
Pregnancy - Lactation	√	√					√	√
Adolescents	√	√				√		√
Overdose	√	√						√

Studies proposed by the Applicant are summarized in the table below:

Study	**Ongoing**	**New**	**Estimated Start Date**	**Estimated End Date**
Cardiovascular Disease subjects	√			2008
COPD subjects	√			2008
Psychosis subjects		√	2007	2010
Pregnancy Prospective Cohort		√	2007	2011
Adolescent Multi-dose PK		√	2008	2010
Adolescent Efficacy and Safety		√	2010	2012

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Table Summary of the risk management plan

Safety concern	Proposed pharmacovigilance activities	Proposed risk minimisation activities
Adverse events associated with smoking cessation	Routine pharmacovigilance	Wording in Section 4.4 and 4.8 of the SPC and in the Package Leaflet in Section 2.
Limited Information		
Very Elderly	Routine pharmacovigilance	Noted in Section 5.2 of the SPC
Cardiovascular disease	Routine pharmacovigilance and an efficacy and safety study in subjects with cardiovascular disease ongoing	-
COPD	Routine pharmacovigilance and an efficacy and safety study in subjects with COPD ongoing	-
Psychosis	Routine pharmacovigilance and a study in subjects with psychosis planned	-
Pregnancy/Lactation	Routine pharmacovigilance and a prospective cohort study to compare women who use varenicline while pregnant to women who smoke while pregnant with respect to birth outcomes planned	Wording in Section 4.6 of the SPC and Section 2 of the Package Leaflet
Adolescents	Routine pharmacovigilance; a multi-dose pharmacokinetic study and an efficacy and safety study are planned	Wording in Sections 4.2 and 5.2 of the SPC
Overdose	Routine pharmacovigilance	Recommendation in Section 4.9 of the SPC and Section 3 of the Package Leaflet

The CHMP, having considered the data submitted in the application, is of the opinion that no additional risk minimisation activities are required beyond those included in the product information.

2.1 Overall conclusions, risk/benefit assessment and recommendation

Quality

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

Non-clinical pharmacology and toxicology

Non-clinical pharmacology and toxicology were sufficiently documented in the non-clinal studies program, except for the functional immunological evaluation of varenicline in an animal model. Therefore, the Applicant will perform a functional immunotoxicity study as a post-approval commitment.

Efficacy

One thousand one hundred ninety-eight (1198) subjects were treated with varenicline and 805 were treated with placebo for up to 12 weeks in Studies A3051028, -36, -07/18. Six hundred ninety-two (692) and 669 subjects were treated with varenicline or bupropion, respectively, in Phase III trials

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A3051028 and –36. In Study A3051035, 1927 subjects were treated with open-label varenicline for up to 12 weeks; of these 1236 (64.1%) had stopped smoking by Week 12. One thousand two hundred six (1206) subjects (602 varenicline, 604 placebo) were subsequently randomised and received up to 12 additional weeks of double-blind treatment.

Across the above-mentioned 12-week trials, varenicline was superior to placebo for smoking cessation at doses of 0.5 mg BID and 1 mg BID: Approximately 46% of the smokers in the 0.5 mg BID and 1 mg BID varenicline groups had stopped smoking over the last 4 weeks of treatment (Weeks 9-12), compared with 17% in the placebo arm.

Varenicline was also superior to bupropion at the end of the 12 weeks treatment. In pooled Studies A3051028, and -36, 44% of subjects treated with varenicline at 1 mg BID stopped smoking at Weeks 9-12 compared with 30% of bupropion-treated subjects.

In the pooled Studies A3051028, -36, and –07/18, 23% of subjects treated with varenicline at 1 mg BID were still abstinent at Week 52 compared with 9% in the placebo arm. In pooled Studies A3501028 and –36, 23% of varenicline treated subjects remained abstinent at Week 52 compared with 16% in the bupropion group.
In Study A3051035, subjects who received varenicline for an additional 12 weeks had higher abstinence rates at both Weeks 13-24 (71%) and Weeks 13-52 (44%) than the placebo group at the corresponding intervals (50% and 37%, respectively).

Safety

A total of 5944 subjects (3940 varenicline, 795 bupropion, 1209 placebo) comprised the varenicline Phase 2/3 safety database. In all completed Phase 2/3 studies, 1531 subjects have received varenicline 1 mg BID for >12 weeks, 456 subjects for >24 weeks and 112 subjects for ≥ 52 weeks.

The most commonly observed (≥10%) treatment-related adverse events (AEs) in varenicline-treated subjects in all completed Phase 2/3 studies were nausea, insomnia, abnormal dreams, and headache. Overall, 10.7% of varenicline-treated subjects discontinued treatment due to a treatment-related adverse event; 12.9% of varenicline-treated subjects discontinued treatment due to an all causality adverse event.

Some other special patients' groups were eligible for the varenicline trials, such as elderly and patients with cardiovascular diseases, but only low numbers were included. It is therefore difficult to draw conclusions concerning safety for these special patients' groups, and these patients should be monitored when varenicline is prescribed (see Risk Management Plan).

Overall, the well-established risks of smoking use outweigh the risks of varenicline, and this product is considered favourable from a safety point of view.

The safety profile of varenicline is considered acceptable, since the majority of AEs were reversible and not in need of acute medical attention. Most subjects became tolerant to nausea in due time.

From the safety database all the adverse reactions reported in clinical trials have been included in the Summary of Product Characteristics.

- User consultation

The applicant has provided detailed results of readability testing performed according to the European Commission Guideline on Packaging Information of Medicinal Products for Human Use Authorised by the Community and as per guidance provided by the EC "Guideline on the readability of the label and package leaflet (PL) of medicinal products for human use"

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The Package Leaflet fully conforms to the standards set. The applicant has performed readability testing according to the "readability guideline" and has subsequently taken appropriate measures to improve the readability.

Risk-benefit assessment

Tobacco smoke is a major preventable factor in the development of a number of life-threatening diseases such as ischaemic heart disease, cancers and COPD. Nicotine is a strong addictive agent which is reflected in the low spontaneous quitting rate and rate of continuous abstinence among quitters not using any pharmacological aid. Nicotine replacement therapy and bupropion roughly doubles the chances for a successful attempt to quit as compared to no pharmacological aid, but there is still a need for therapies to aid smoking cessation in both healthy smokers and especially in patients with smoking-related diseases.

In three 12-week trials, varenicline at 1 mg BID was superior to placebo for stopping smoking at both the end of treatment and at one year from the start of the study. Forty-six percent (46%) of subjects treated with varenicline at 0.5 mg BID or 1 mg BID stopped smoking during the last 4 weeks of a 12-week treatment period (versus 17% in the placebo arm); the long-term abstinence rate (ie to 1 year from the start of the study) was 23% in subjects treated with varenicline compared with 9% in placebo-treated subjects.

The most common treatment-related adverse events were nausea (reported by approximately 30% of patients), insomnia, abnormal dreams, and headache. Most of these symptoms, including nausea, decreased over time. Overall, 10.7% of varenicline-treated subjects discontinued treatment due to a treatment-related adverse event; 12.9% discontinued treatment due to an all causality adverse event.

Some other special patients' groups were eligible for the varenicline trials, such as elderly and patients with cardiovascular diseases, but only low numbers were included. Therefore these patients will bemonitored post marketing (see Risk Management Plan).

Efficacy was demonstrated, and overall, the well-established risks of smoking outweigh the risks of varenicline.

A risk management plan was submitted. The CHMP, having considered the data submitted, was of the opinion that:

- pharmacovigilance activities in addition to the use of routine pharmacovigilance were needed to investigate further some of the safety concerns

and

- the following follow-up measures were needed:
  - an immunotoxicity study in an appropriate model, will be performed;
  - a prospective cohort study to compare women who use varenicline while pregnant to women who smoke while pregnant with respect to birth outcomes will be conducted;
  - a protocol for a study in patients with psychosis will be provided
  - information on the feasibility of performing a study for evaluating dose tapering versus abrupt discontinuation in terms of efficacy will be provided
  - final results of on-going clinical studies will be reported
  - the Risk management Plan will be updated, in line with the CHMP Guideline on Risk Management Systems for medicinal products for human use

Recommendation

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considered by consensus decision that the risk-benefit balance of Champix in approved indication of smoking cessation was favourable and therefore recommended the granting of the marketing authorisation.

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MA (EU) number	(Invented) name	Strength	Pharmaceutical Form	Route of Administration	Immediate Packaging	Pack size
EU/1/06/360/001	Champix	0.5 mg	Film-coated tablet	Oral use	bottle (HDPE)	56 tablets
EU/1/06/360/002	Champix	1 mg	Film-coated tablet	Oral use	bottle (HDPE)	56 tablets
EU/1/06/360/003	Champix	0.5 mg and 1 mg	Film-coated tablet	Oral use	blister (Aclar/PVC/alu) in a card	Initiation pack: 11 x 0.5 mg + 14 x 1 mg tablets
EU/1/06/360/004	Champix	1 mg	Film-coated tablet	Oral use	blister (Aclar/PVC/alu) in a card	28 tablets
EU/1/06/360/005	Champix	1 mg	Film-coated tablet	Oral use	blister (Aclar/PVC/alu) in a card	56 tablets
EU/1/06/360/006	Champix	0.5 mg	Film-coated tablet	Oral use	blister (Aclar/PVC/alu) in a card	28 tablets
EU/1/06/360/007	Champix	0.5 mg	Film-coated tablet	Oral use	blister (Aclar/PVC/alu) in a card	56 tablets
EU/1/06/360/008	Champix	0.5 mg and 1 mg	Film-coated tablet	Oral use	blister (Aclar/PVC/alu) in a carton	Initiation pack: 11 x 0.5 mg + 14 x 1 mg tablets
EU/1/06/360/009	Champix	1 mg	Film-coated tablet	Oral use	blister (Aclar/PVC/alu) in a carton	28 tablets
EU/1/06/360/010	Champix	1 mg	Film-coated tablet	Oral use	blister (Aclar/PVC/alu) in a carton	56 tablets
EU/1/06/360/011	Champix	1 mg	Film-coated tablet	Oral use	blister (Aclar/PVC/alu) in a carton	112 tablets
EU/1/06/360/012	Champix	0.5 mg and 1 mg	Film-coated tablet	Oral use	blister (Aclar/PVC/alu) in a card	Initiation pack: 11 x 0.5 mg + 14 x 1 mg tablets + 28 x 1 mg tablets
EU/1/06/360/013	Champix	1 mg	Film-coated tablet	Oral use	blister (Aclar/PVC/alu) in a carton	140 tablets
EU/1/06/360/014	Champix	0.5 mg and 1 mg	Film-coated tablet	Oral use	blister (PVC/alu) in a card	Initiation pack: 11 x 0.5 mg + 14 x 1 mg tablets
EU/1/06/360/015	Champix	1 mg	Film-coated tablet	Oral use	blister (PVC/alu) in a card	28 tablets
EU/1/06/360/016	Champix	1 mg	Film-coated tablet	Oral use	blister (PVC/alu) in a card	56 tablets
EU/1/06/360/017	Champix	0.5 mg	Film-coated tablet	Oral use	blister (PVC/alu) in a card	28 tablets
EU/1/06/360/018	Champix	0.5 mg	Film-coated tablet	Oral use	blister (PVC/alu) in a card	56 tablets
EU/1/06/360/019	Champix	0.5 mg and 1 mg	Film-coated tablet	Oral use	blister (PVC/alu) in a carton	Initiation pack: 11 x 0.5 mg + 14 x 1 mg tablets
EU/1/06/360/020	Champix	1 mg	Film-coated tablet	Oral use	blister (PVC/alu) in a carton	28 tablets

MA (EU) number	(Invented) name	Strength	Pharmaceutical Form	Route of Administration	Immediate Packaging	Pack size
EU/1/06/360/021	Champix	1 mg	Film-coated tablet	Oral use	blister (PVC/alu) in a carton	56 tablets
EU/1/06/360/022	Champix	1 mg	Film-coated tablet	Oral use	blister (PVC/alu) in a carton	112 tablets
EU/1/06/360/023	Champix	0.5 mg and 1 mg	Film-coated tablet	Oral use	blister (PVC/alu) in a card	Initiation pack: 11 x 0.5 mg + 14 x 1 mg tablets + 28 x 1 mg tablets
EU/1/06/360/024	Champix	1 mg	Film-coated tablet	Oral use	blister (PVC/alu) in a carton	140 tablets
EU/1/06/360/025	Champix	0.5 mg and 1 mg	Film-coated tablet	Oral use	blister (Aclar/PVC/alu) in a card	Initiation pack: 11 x 0.5 mg + 14 x 1 mg tablets + 28 x 1 mg tablets +2 x 56 x 1 mg tablets
EU/1/06/360/026	Champix	0.5 mg and 1 mg	Film-coated tablet	Oral use	blister (PVC/alu) in a card	Initiation pack: 11 x 0.5 mg + 14 x 1 mg tablets + 28 x 1 mg tablets +2 x 56 x 1 mg tablets

ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 0.5 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 0.5 mg of varenicline (as tartrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet of 4 mm x 8 mm

White, capsular-shaped, biconvex tablets debossed with "*Pfizer*" on one side and "CHX 0.5" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CHAMPIX is indicated for smoking cessation in adults.

4.2 Posology and method of administration

Posology

The recommended dose is 1 mg varenicline twice daily following a 1-week titration as follows:

Days 1 – 3:	0.5 mg once daily
Days 4 – 7:	0.5 mg twice daily
Day 8 – End of treatment:	1 mg twice daily

The patient should set a date to stop smoking. CHAMPIX dosing should usually start at 1-2 weeks before this date (see section 5.1). Patients should be treated with CHAMPIX for 12 weeks.

For patients who have successfully stopped smoking at the end of 12 weeks, an additional course of 12 weeks treatment with CHAMPIX at 1 mg twice daily may be considered for the maintenance of abstinence (see section 5.1).

A gradual approach to quitting smoking with CHAMPIX should be considered for patients who are not able or willing to quit abruptly. Patients should reduce smoking during the first 12 weeks of treatment and quit by the end of that treatment period. Patients should then continue taking CHAMPIX for an additional 12 weeks for a total of 24 weeks of treatment (see section 5.1).

Patients who are motivated to quit and who did not succeed in stopping smoking during prior CHAMPIX therapy, or who relapsed after treatment, may benefit from another quit attempt with CHAMPIX (see section 5.1).

Patients who cannot tolerate adverse reactions of CHAMPIX may have the dose lowered temporarily or permanently to 0.5 mg twice daily.

In smoking cessation therapy, risk for relapse to smoking is elevated in the period immediately following the end of treatment. In patients with a high risk of relapse, dose tapering may be considered (see section 4.4).

Elderly
No dosage adjustment is necessary for elderly patients (see section 5.2). Because elderly patients are more likely to have decreased renal function, prescribers should consider the renal status of an elderly patient.

Renal impairment
No dosage adjustment is necessary for patients with mild (estimated creatinine clearance > 50 ml/min and ≤ 80 ml/min) to moderate (estimated creatinine clearance ≥ 30 ml/min and ≤ 50 ml/min) renal impairment.

For patients with moderate renal impairment who experience adverse reactions that are not tolerable, dosing may be reduced to 1 mg once daily.

For patients with severe renal impairment (estimated creatinine clearance < 30 ml/min), the recommended dose of CHAMPIX is 1 mg once daily. Dosing should begin at 0.5 mg once daily for the first 3 days then increased to 1 mg once daily. Based on insufficient clinical experience with CHAMPIX in patients with end stage renal disease, treatment is not recommended in this patient population (see section 5.2).

Hepatic impairment
No dosage adjustment is necessary for patients with hepatic impairment (see section 5.2).

Paediatric population
The safety and efficacy of CHAMPIX in children or adolescents below 18 years have not yet been established. Currently available data are described in section 5.2 but no recommendation on a posology can be made.

Method of administration

CHAMPIX is for oral use and the tablets should be swallowed whole with water.
CHAMPIX can be taken with or without food

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Effect of smoking cessation

Physiological changes resulting from smoking cessation, with or without treatment with CHAMPIX, may alter the pharmacokinetics or pharmacodynamics of some medicinal products, for which dosage adjustment may be necessary (examples include theophylline, warfarin and insulin). As smoking induces CYP1A2, smoking cessation may result in an increase of plasma levels of CYP1A2 substrates.

Neuropsychiatric symptoms

Changes in behaviour or thinking, anxiety, psychosis, mood swings, aggressive behaviour, depression, suicidal ideation and behaviour and suicide attempts have been reported in patients attempting to quit smoking with CHAMPIX in the post-marketing experience.

A large randomised, double-blind, active and placebo-controlled study was conducted to compare the risk of serious neuropsychiatric events in patients with and without a history of psychiatric disorder treated for smoking cessation with varenicline, bupropion, nicotine replacement therapy patch (NRT) or placebo. The primary safety endpoint was a composite of neuropsychiatric adverse events that have been reported in post-marketing experience.

The use of varenicline in patients with or without a history of psychiatric disorder was not associated with an increased risk of serious neuropsychiatric adverse events in the composite primary endpoint compared with placebo (see section 5.1 **Pharmacodynamic properties** - *Study in Subjects with and without a History of Psychiatric Disorder*).

Depressed mood, rarely including suicidal ideation and suicide attempt, may be a symptom of nicotine withdrawal.

Clinicians should be aware of the possible emergence of serious neuropsychiatric symptoms in patients attempting to quit smoking with or without treatment. If serious neuropsychiatric symptoms occur whilst on varenicline treatment, patients should discontinue varenicline immediately and contact a healthcare professional for re-evaluation of treatment.

History of psychiatric disorders

Smoking cessation, with or without pharmacotherapy, has been associated with exacerbation of underlying psychiatric illness (e.g. depression).

CHAMPIX smoking cessation studies have provided data in patients with a history of psychiatric disorders (see section 5.1).

In a smoking cessation clinical trial, neuropsychiatric adverse events were reported more frequently in patients with a history of psychiatric disorders compared to those without a history of psychiatric disorders, regardless of treatment (see section 5.1).

Care should be taken with patients with a history of psychiatric illness and patients should be advised accordingly.

Seizures

In clinical trials and post-marketing experience there have been reports of seizures in patients with or without a history of seizures, treated with CHAMPIX. CHAMPIX should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold.

Treatment discontinuation

At the end of treatment, discontinuation of CHAMPIX was associated with an increase in irritability, urge to smoke, depression, and/or insomnia in up to 3% of patients. The prescriber should inform the patient accordingly and discuss or consider the need for dose tapering.

Cardiovascular events

Patients taking CHAMPIX should be instructed to notify their doctor of new or worsening cardiovascular symptoms and to seek immediate medical attention if they experience signs and symptoms of myocardial infarction or stroke (see section 5.1).

Hypersensitivity reactions

There have been post-marketing reports of hypersensitivity reactions including angioedema in patients treated with varenicline. Clinical signs included swelling of the face, mouth (tongue, lips, and gums), neck (throat and larynx) and extremities. There were rare reports of life-threatening angioedema requiring urgent medical attention due to respiratory compromise. Patients experiencing these symptoms should discontinue treatment with varenicline and contact a health care provider immediately.

Cutaneous reactions

There have also been post-marketing reports of rare but severe cutaneous reactions, including Stevens-Johnson Syndrome and Erythema Multiforme in patients using varenicline. As these skin reactions can be life threatening, patients should discontinue treatment at the first sign of rash or skin reaction and contact a healthcare provider immediately.

4.5 Interaction with other medicinal products and other forms of interaction

Based on varenicline characteristics and clinical experience to date, CHAMPIX has no clinically meaningful drug interactions. No dosage adjustment of CHAMPIX or co-administered medicinal products listed below is recommended.

In vitro studies indicate that varenicline is unlikely to alter the pharmacokinetics of compounds that are primarily metabolised by cytochrome P450 enzymes.

Furthermore since metabolism of varenicline represents less than 10% of its clearance, active substances known to affect the cytochrome P450 system are unlikely to alter the pharmacokinetics of varenicline (see section 5.2) and therefore a dose adjustment of CHAMPIX would not be required.

In vitro studies demonstrate that varenicline does not inhibit human renal transport proteins at therapeutic concentrations. Therefore, active substances that are cleared by renal secretion (e.g., metformin - see below) are unlikely to be affected by varenicline.

Metformin

Varenicline did not affect the pharmacokinetics of metformin. Metformin had no effect on varenicline pharmacokinetics.

Cimetidine

Co-administration of cimetidine, with varenicline increased the systemic exposure of varenicline by 29% due to a reduction in varenicline renal clearance. No dosage adjustment is recommended based on concomitant cimetidine administration in subjects with normal renal function or in patients with mild to moderate renal impairment. In patients with severe renal impairment, the concomitant use of cimetidine and varenicline should be avoided.

Digoxin

Varenicline did not alter the steady-state pharmacokinetics of digoxin.

Warfarin

Varenicline did not alter the pharmacokinetics of warfarin. Prothrombin time (INR) was not affected by varenicline. Smoking cessation itself may result in changes to warfarin pharmacokinetics (see section 4.4).

Alcohol

There are limited clinical data on any potential interaction between alcohol and varenicline. There have been post marketing reports of increased intoxicating effects of alcohol in patients treated with varenicline. A causal relationship between these events and varenicline use has not been established.

Use with other therapies for smoking cessation

Bupropion
Varenicline did not alter the steady-state pharmacokinetics of bupropion.

Nicotine replacement therapy (NRT)
When varenicline and transdermal NRT were co-administered to smokers for 12 days, there was a statistically significant decrease in average systolic blood pressure (mean 2.6 mmHg) measured on the final day of the study. In this study, the incidence of nausea, headache, vomiting, dizziness, dyspepsia, and fatigue was greater for the combination than for NRT alone.

Safety and efficacy of CHAMPIX in combination with other smoking cessation therapies have not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

A moderate amount of data on pregnant women indicated no malformative or foetal/neonatal toxicity of varenicline (see section 5.1).

Animal studies have shown reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of varenicline during pregnancy (see section 5.1).

Breast-feeding

It is unknown whether varenicline is excreted in human breast milk. Animal studies suggest that varenicline is excreted in breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with CHAMPIX should be made taking into account the benefit of breast-feeding to the child and the benefit of CHAMPIX therapy to the woman.

Fertility

There are no clinical data on the effects of varenicline on fertility.

Non-clinical data revealed no hazard for humans based on standard male and female fertility studies in the rat (see section 5.3).

4.7 Effects on ability to drive and use machines

CHAMPIX may have minor or moderate influence on the ability to drive and use machines. CHAMPIX may cause dizziness, somnolence and transient loss of consciousness, and therefore may influence the ability to drive and use machines. Patients are advised not to drive, operate complex

machinery or engage in other potentially hazardous activities until it is known whether this medicinal product affects their ability to perform these activities.

4.8 Undesirable effects

Summary of the safety profile

Smoking cessation with or without treatment is associated with various symptoms. For example, dysphoric or depressed mood; insomnia, irritability, frustration or anger; anxiety; difficulty concentrating; restlessness; decreased heart rate; increased appetite or weight gain have been reported in patients attempting to stop smoking. No attempt has been made in either the design or the analysis of the CHAMPIX studies to distinguish between adverse reactions associated with study drug treatment or those possibly associated with nicotine withdrawal. Adverse drug reactions are based on evaluation of data from pre-marketing phase 2-3 studies and updated based on pooled data from 18 placebo-controlled pre- and post-marketing studies, including approximately 5,000 patients treated with varenicline.

In patients treated with the recommended dose of 1 mg twice daily following an initial titration period the adverse event most commonly reported was nausea (28.6%). In the majority of cases nausea occurred early in the treatment period, was mild to moderate in severity and seldom resulted in discontinuation.

Tabulated summary of adverse reactions

In the table below all adverse reactions, which occurred at an incidence greater than placebo are listed by system organ class and frequency (very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) and rare (≥ 1/10,000 to < 1/1,000)). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	**Adverse Drug Reactions**
Infections and infestations	
Very common	Nasopharyngitis
Common	Bronchitis, sinusitis
Uncommon	Fungal infection, viral infection
Blood and lymphatic system disorders	
Rare	Platelet count decreased
Metabolism and nutrition disorders	
Common	Weight increased, decreased appetite, increased appetite
Uncommon	Hyperglycaemia
Rare	Diabetes mellitus, polydipsia
Psychiatric disorders	
Very common	Abnormal dreams, insomnia
Uncommon	Suicidal ideation, aggression, panic reaction, thinking abnormal, restlessness, mood swings, depression*, anxiety*, hallucinations*, libido increased, libido decreased
Rare	Psychosis, somnambulism, abnormal behaviour, dysphoria, bradyphrenia
Nervous system disorders	
Very common	Headache
Common	Somnolence, dizziness, dysgeusia
Uncommon	Seizure, tremor, lethargy, hypoaesthesia
Rare	Cerebrovascular accident, hypertonia, dysarthria, coordination abnormal, hypogeusia, circadian rhythm sleep disorder
Not known	Transient loss of consciousness

System Organ Class	Adverse Drug Reactions
Eye disorders	
Uncommon	Conjunctivitis, eye pain
Rare	Scotoma, scleral discolouration, mydriasis, photophobia, myopia, lacrimation increased
Ear and labyrinth disorders	
Uncommon	Tinnitus
Cardiac disorders	
Uncommon	Myocardial infarction, angina pectoris, tachycardia, palpitations, heart rate increased
Rare	Atrial fibrillation, electrocardiogram ST segment depression, electrocardiogram T wave amplitude decreased
Vascular disorders	
Uncommon	Blood pressure increased, hot flush
Respiratory, thoracic and mediastinal disorders	
Common	Dyspnoea, cough
Uncommon	Upper respiratory tract inflammation, respiratory tract congestion, dysphonia, rhinitis allergic, throat irritation, sinus congestion, upper-airway cough syndrome, rhinorrhoea
Rare	Laryngeal pain, snoring
Gastrointestinal disorders	
Very common	Nausea
Common	Gastrooesophageal reflux disease, vomiting, constipation, diarrhoea, abdominal distension, abdominal pain, toothache, dyspepsia, flatulence, dry mouth
Uncommon	Haematochezia, gastritis, change of bowel habit, eructation, aphthous stomatitis, gingival pain
Rare	Haematemesis, abnormal faeces, tongue coated
Skin and subcutaneous tissue disorders	
Common	Rash, pruritus
Uncommon	Erythema, acne, hyperhidrosis, night sweats
Rare	Severe cutaneous reactions, including Stevens Johnson Syndrome and Erythema Multiforme, angioedema
Musculoskeletal and connective tissue disorders	
Common	Arthralgia, myalgia, back pain
Uncommon	Muscle spasms, musculoskeletal chest pain
Rare	Joint stiffness, costochondritis
Renal and urinary disorders	
Uncommon	Pollakiuria, nocturia
Rare	Glycosuria, polyuria
Reproductive system and breast disorders	
Uncommon	Menorrhagia
Rare	Vaginal discharge, sexual dysfunction
General disorders and administration site conditions	
Common	Chest pain, fatigue
Uncommon	Chest discomfort, influenza like illness, pyrexia, asthenia, malaise
Rare	Feeling cold, cyst
Investigations	
Common	Liver function test abnormal
Rare	Semen analysis abnormal, C-reactive protein increased, blood calcium decreased
* Frequencies are estimated from a post-marketing, observational cohort study	

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No cases of overdose were reported in pre-marketing clinical trials.

In case of overdose, standard supportive measures should be instituted as required.

Varenicline has been shown to be dialyzed in patients with end stage renal disease (see section 5.2), however, there is no experience in dialysis following overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other nervous system drugs; Drugs used in addictive disorders; Drugs used in nicotine dependence, ATC code: N07BA03

Mechanism of action

Varenicline binds with high affinity and selectivity at the α4β2 neuronal nicotinic acetylcholine receptors, where it acts as a partial agonist - a compound that has both agonist activity, with lower intrinsic efficacy than nicotine, and antagonist activities in the presence of nicotine.

Electrophysiology studies *in vitro* and neurochemical studies in vivo have shown that varenicline binds to the α4β2 neuronal nicotinic acetylcholine receptors and stimulates receptor-mediated activity, but at a significantly lower level than nicotine. Nicotine competes for the same human α4β2 nAChR binding site for which varenicline has higher affinity. Therefore, varenicline can effectively block nicotine's ability to fully activate α4β2 receptors and the mesolimbic dopamine system, the neuronal mechanism underlying reinforcement and reward experienced upon smoking. Varenicline is highly selective and binds more potently to the α4β2 receptor subtype (Ki=0.15 nM) than to other common nicotinic receptors (α3β4 Ki=84 nM, α7 Ki= 620 nM, α1βγδ Ki= 3,400 nM), or to non-nicotinic receptors and transporters (Ki > 1μM, except to 5-HT3 receptors: Ki=350 nM).

Pharmacodynamic effects

The efficacy of CHAMPIX in smoking cessation is a result of varenicline's partial agonist activity at the α4β2 nicotinic receptor where its binding produces an effect sufficient to alleviate symptoms of craving and withdrawal (agonist activity), while simultaneously resulting in a reduction of the rewarding and reinforcing effects of smoking by preventing nicotine binding to α4β2 receptors (antagonist activity).

Clinical efficacy and safety

Smoking cessation therapies are more likely to succeed for patients who are motivated to stop smoking and who are provided with additional advice and support.

The efficacy of CHAMPIX in smoking cessation was demonstrated in 3 clinical trials involving chronic cigarette smokers (≥ 10 cigarettes per day). Two thousand six hundred nineteen

(2619) patients received CHAMPIX 1 mg BID (titrated during the first week), 669 patients received bupropion 150 mg BID (also titrated) and 684 patients received placebo.

Comparative clinical studies
Two identical double-blind clinical trials prospectively compared the efficacy of CHAMPIX (1 mg twice daily), sustained release bupropion (150 mg twice daily) and placebo in smoking cessation. In these 52 week duration studies, patients received treatment for 12 weeks, followed by a 40 week non-treatment phase.

The primary endpoint of the two studies was the carbon monoxide (CO) confirmed, 4 week continuous quit rate (4W-CQR) from week 9 through week 12. The primary endpoint for CHAMPIX demonstrated statistical superiority to bupropion and placebo.

After the 40 week non-treatment phase, a key secondary endpoint for both studies was the Continuous Abstinence Rate (CA) at week 52. CA was defined as the proportion of all subjects treated who did not smoke (not even a puff of a cigarette) from Week 9 through Week 52 and did not have an exhaled CO measurement of > 10 ppm.

The 4W-CQR (weeks 9 through 12) and CA rate (weeks 9 through 52) from studies 1 and 2 are included in the following table:

	Study 1 (n=1022)		Study 2 (n=1023)	
	4W CQR	CA Wk 9-52	4W CQR	CA Wk 9-52
CHAMPIX	44.4%	22.1%	44.0%	23.0%
Bupropion	29.5%	16.4%	30.0%	15.0%
Placebo	17.7%	8.4%	17.7%	10.3%
Odds ratio CHAMPIX vs. placebo	3.91 $p < 0.0001$	3.13 $p < 0.0001$	3.85 $p < 0.0001$	2.66 $p < 0.0001$
Odds ratio CHAMPIX vs. bupropion	1.96 $p < 0.0001$	1.45 $p = 0.0640$	1.89 $p < 0.0001$	1.72 $p = 0.0062$

Patient reported craving, withdrawal and reinforcing effects of smoking
Across both Studies 1 and 2 during active treatment, craving and withdrawal were significantly reduced in patients randomised to CHAMPIX in comparison with placebo. CHAMPIX also significantly reduced reinforcing effects of smoking that can perpetuate smoking behaviour in patients who smoke during treatment compared with placebo. The effect of varenicline on craving, withdrawal and reinforcing effects of smoking were not measured during the non-treatment long-term follow-up phase.

Maintenance of abstinence study
The third study assessed the benefit of an additional 12 weeks of CHAMPIX therapy on the maintenance of abstinence. Patients in this study (n=1,927) received open-label CHAMPIX 1 mg twice daily for 12 weeks. Patients who stopped smoking by Week 12 were then randomised to receive either CHAMPIX (1 mg twice daily) or placebo for an additional 12 weeks for a total study duration of 52 weeks.

The primary study endpoint was the CO-confirmed continuous abstinence rate from week 13 through week 24 in the double-blind treatment phase. A key secondary endpoint was the continuous abstinence (CA) rate for week 13 through week 52.

This study showed the benefit of an additional 12-week treatment with CHAMPIX 1 mg twice daily for the maintenance of smoking cessation compared to placebo; superiority to placebo for CA was maintained through week 52. The key results are summarised in the following table:

Continuous Abstinence Rates in Subjects Treated with Champix versus Placebo

	CHAMPIX n=602	Placebo n=604	Difference (95% CI)	Odds ratio (95% CI)
CA* wk 13-24	70.6%	49.8%	20.8% (15.4%, 26.2%)	2.47 (1.95, 3.15)
CA* wk 13-52	44.0%	37.1%	6.9% (1.4%, 12.5%)	1.35 (1.07, 1.70)

*CA: Continuous Abstinence Rate

There is currently limited clinical experience with the use of CHAMPIX among black people to determine clinical efficacy.

Flexible quit date between weeks 1 and 5
The efficacy and safety of varenicline has been evaluated in smokers who had the flexibility of quitting between weeks 1 and 5 of treatment. In this 24-week study, patients received treatment for 12 weeks followed by a 12 week non-treatment follow up phase. The 4 week (week 9-12) CQR for varenicline and placebo was 53.9% and 19.4%, respectively (difference=34.5%, 95% CI: 27.0% - 42.0%) and the CA week 9-24 was 35.2% (varenicline) vs. 12.7% (placebo) (difference=22.5%, 95% CI: 15.8% - 29.1%). Patients who are not willing or able to set the target quit date within 1-2 weeks, could be offered to start treatment and then choose their own quit date within 5 weeks.

Study in subjects re-treated with CHAMPIX
CHAMPIX was evaluated in a double-blind, placebo-controlled trial of 494 patients who had made a previous attempt to quit smoking with CHAMPIX, and either did not succeed in quitting or relapsed after treatment. Subjects who experienced an adverse event of a concern during previous treatment were excluded. Subjects were randomised 1:1 to CHAMPIX 1 mg twice daily (N=249) or placebo (N=245) for 12 weeks of treatment and followed for up to 40 weeks post-treatment. Patients included in this study had taken CHAMPIX for a smoking-cessation attempt in the past (for a total treatment duration of a minimum of two weeks), at least three months prior to study entry, and had been smoking for at least four weeks.

Patients treated with CHAMPIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 and from weeks 9 through 52 compared to subjects treated with placebo. The key results are summarised in the following table:

Continuous Abstinence Rates in Subjects Treated with Champix versus Placebo

	CHAMPIX n=249	Placebo n=245	Odds ratio (95% CI), p value
CA* wk 9-12	45.0%	11.8%	7.08 (4.34, 11.55), p<0.0001
CA* wk 9-52	20.1%	3.3%	9.00 (3.97, 20.41), p<0.0001

*CA: Continuous Abstinence Rate

Gradual approach to quitting smoking
CHAMPIX was evaluated in a 52-week double-blind placebo-controlled study of 1,510 subjects who were not able or willing to quit smoking within four weeks, but were willing to gradually reduce their smoking over a 12 week period before quitting. Subjects were randomised to either CHAMPIX 1 mg twice daily (n=760) or placebo (n=750) for 24 weeks and followed up post-treatment through week 52. Subjects were instructed to reduce the number of cigarettes smoked by at least 50 percent by the end of the first four weeks of treatment, followed by a further 50 percent reduction from week four to week eight of treatment, with the goal of reaching complete abstinence by 12 weeks. After the

initial 12-week reduction phase, subjects continued treatment for another 12 weeks. Subjects treated with CHAMPIX had a significantly higher Continuous Abstinence Rate compared with placebo; the key results are summarised in the following table:

Continuous Abstinence Rates in Subjects Treated with Champix versus Placebo

	CHAMPIX n=760	Placebo n=750	Odds ratio (95% CI), p value
CA* wk 15-24	32.1%	6.9%	8.74 (6.09, 12.53), p<0.0001
CA* wk 21-52	27.0%	9.9%	4.02 (2.94, 5.50), p<0.0001

*CA: Continuous Abstinence Rate

The CHAMPIX safety profile in this study was consistent with that of pre-marketing studies.

Subjects with cardiovascular disease
CHAMPIX was evaluated in a randomised, double-blind, placebo-controlled study of subjects with stable, cardiovascular disease (other than, or in addition to, hypertension) that had been diagnosed for more than 2 months. Subjects were randomised to CHAMPIX 1 mg twice daily (n=353) or placebo (n=350) for 12 weeks and then were followed for 40 weeks post-treatment. The 4 week CQR for varenicline and placebo was 47.3% and 14.3%, respectively and the CA week 9-52 was 19.8% (varenicline) vs. 7.4% (placebo).

Deaths and serious cardiovascular events were adjudicated by a blinded, committee. The following adjudicated events occurred with a frequency ≥ 1% in either treatment group during treatment (or in the 30-day period after treatment): nonfatal myocardial infarction (1.1% vs. 0.3% for CHAMPIX and placebo, respectively), and hospitalisation for angina pectoris (0.6% vs. 1.1%). During non-treatment follow up to 52 weeks, the adjudicated events included need for coronary revascularisation (2.0% vs. 0.6%), hospitalisation for angina pectoris (1.7% vs. 1.1%), and new diagnosis of peripheral vascular disease (PVD) or admission for a PVD procedure (1.4% vs. 0.6%). Some of the patients requiring coronary revascularisation underwent the procedure as part of management of nonfatal MI and hospitalisation for angina. Cardiovascular death occurred in 0.3% of patients in the CHAMPIX arm and 0.6% of patients in the placebo arm over the course of the 52-week study.

A meta-analysis of 15 clinical trials of ≥ 12 weeks treatment duration, including 7002 patients (4190 CHAMPIX, 2812 placebo), was conducted to systematically assess the cardiovascular safety of CHAMPIX. The study in patients with stable cardiovascular disease described above was included in the meta-analysis.

The key cardiovascular safety analysis included occurrence and timing of a composite endpoint of Major Adverse Cardiovascular Events (MACE), defined as cardiovascular death, nonfatal MI, and nonfatal stroke. These events included in the endpoint were adjudicated by a blinded, independent committee. Overall, a small number of MACE occurred during treatment in the trials included in the meta-analysis (CHAMPIX 7 [0.17%]; placebo 2 [0.07%]). Additionally, a small number of MACE occurred up to 30 days after treatment (CHAMPIX 13 [0.31%]; placebo 6 [0.21%]).

The meta-analysis showed that exposure to CHAMPIX resulted in a hazard ratio for MACE of 2.83 (95% confidence interval from 0.76 to 10.55, p=0.12) for patients during treatment and 1.95 (95% confidence interval from 0.79 to 4.82, p=0.15) for patients up to 30 days after treatment. These are equivalent to an estimated increase of 6.5 MACE events and 6.3 MACE events per 1,000 patient-years, respectively of exposure. The hazard ratio for MACE was higher in patients with cardiovascular risk factors in addition to smoking compared with that in patients without cardiovascular risk factors other than smoking. There were similar rates of all-cause mortality

(CHAMPIX 6 [0.14%]; placebo 7 [0.25%]) and cardiovascular mortality (CHAMPIX 2 [0.05%]; placebo 2 [0.07%]) in the CHAMPIX arms compared with the placebo arms in the meta-analysis.

Cardiovascular safety assessment study in subjects with and without a history of psychiatric disorder
The cardiovascular (CV) safety of CHAMPIX was evaluated in the Study in Subjects with and without a History of Psychiatric Disorder (parent study; see section 5.1 - *Neuropsychiatric safety*) and its non-treatment extension, the Cardiovascular Safety Assessment Study, which enrolled 4595 of the 6293 subjects who completed the parent study (N=8058) and followed them through week 52. Of all subjects treated in the parent study, 1749 (21.7%) had a medium CV risk and 644 (8.0%) had a high CV risk, as defined by Framingham score.

The primary CV endpoint was the time to major adverse cardiovascular events (MACE), defined as cardiovascular death, non-fatal myocardial infarction or non-fatal stroke during treatment. Deaths and cardiovascular events were adjudicated by a blinded, independent committee.

The following table shows the incidence of MACE and Hazard Ratios vs placebo for all treatment groups during treatment, and cumulative for treatment plus 30 days and through end of study.

	CHAMPIX N=2016	**Bupropion N=2006**	**NRT N=2022**	**Placebo N=2014**
During treatment				
MACE, n (%)	1 (0.05)	2 (0.10)	1 (0.05)	4 (0.20)
Hazard Ratio (95% CI) vs placebo	0.29 (0.05, 1.68)	0.50 (0.10, 2.50)	0.29 (0.05, 1.70)	
During treatment plus 30 days				
MACE, n (%)	1 (0.05)	2 (0.10)	2 (0.10)	4 (0.20)
Hazard Ratio (95% CI) vs placebo	0.29 (0.05, 1.70)	0.51 (0.10, 2.51)	0.50 (0.10, 2.48)	
Through end of study				
MACE, n (%)	3 (0.15)	9 (0.45)	6 (0.30)	8 (0.40)
Hazard Ratio (95% CI) vs placebo	0.39 (0.12, 1.27)	1.09 (0.42, 2.83)	0.75 (0.26, 2.13)	

The use of CHAMPIX, bupropion, and NRT was not associated with an increased risk of CV AEs in smokers treated for up to 12 weeks and followed for up to 1 year compared to placebo, although because of the relatively low number of events overall, an association cannot be entirely ruled out.

Subjects with mild-moderate chronic obstructive pulmonary disease (COPD)
The efficacy and safety of CHAMPIX (1 mg twice daily) for smoking cessation in subjects with mild-moderate COPD was demonstrated in a randomised double-blind placebo-controlled clinical trial. In this 52-week duration study, patients received treatment for 12 weeks, followed by a 40-week non-treatment follow-up phase. The primary endpoint of the study was the CO-confirmed, 4-week Continuous Quit Rate (4W CQR) from week 9 through week 12 and a key secondary endpoint was the Continuous Abstinence (CA) from Week 9 through Week 52. The safety profile of varenicline was comparable to what was reported in other trials in the general population, including pulmonary safety. The results for the 4W CQR (weeks 9 through 12) and CA rate (weeks 9 through 52) are shown in the following table:

	4W CQR	CA Wk 9-52
CHAMPIX, (n = 248)	42.3%	18.5%
Placebo, (n = 251)	8.8%	5.6%
Odds ratio (CHAMPIX vs. Placebo)	8.40 p < 0.0001	4.04 p < 0.0001

Study in subjects with a history of major depressive disorder
The efficacy of varenicline was confirmed in a randomised placebo-controlled trial in 525 subjects with a history of major depression in the past two years or under current stable treatment. The cessation rates in this population were similar to those reported in the general population. Continuous abstinence rate between weeks 9-12 was 35.9% in the varenicline treatment group versus 15.6% in the placebo group (OR 3.35 (95% CI 2.16-5.21)) and between weeks 9-52 was 20.3% versus 10.4% respectively (OR 2.36 (95% CI 1.40-3.98)). The most common adverse events (≥ 10%) in subjects taking varenicline were nausea (27.0% vs. 10.4% on placebo), headache (16.8% vs. 11.2%), abnormal dreams (11.3% vs. 8.2%), insomnia (10.9% vs. 4.8%) and irritability (10.9% vs. 8.2%). Psychiatric scales showed no differences between the varenicline and placebo groups and no overall worsening of depression, or other psychiatric symptoms, during the study in either treatment group.

Study in subjects with stable schizophrenia or schizoaffective disorder
Varenicline safety and tolerability was assessed in a double-blind study of 128 smokers with stable schizophrenia or schizoaffective disorder, on antipsychotic medication, randomised 2:1 to varenicline (1 mg twice daily) or placebo for 12 weeks with 12-week non-drug follow-up.

The most common adverse events in subjects taking varenicline were nausea (23.8% vs. 14.0% on placebo), headache (10.7% vs. 18.6% on placebo) and vomiting (10.7% vs. 9.3% on placebo). Among reported neuropsychiatric adverse events, insomnia was the only event reported in either treatment group in ≥ 5% of subjects at a rate higher in the varenicline group than in placebo (9.5% vs. 4.7%).

Overall, there was no worsening of schizophrenia in either treatment group as measured by psychiatric scales and there were no overall changes in extra-pyramidal signs. In the varenicline group compared to placebo, a higher proportion of subjects reported suicidal ideation or behaviour prior to enrolment (lifetime history) and after the end of active treatment period (on Days 33 to 85 after the last dose of treatment). During the active treatment period, the incidence of suicide-related events was similar between the varenicline-treated and the placebo-treated subjects (11 vs. 9.3%, respectively). The percentage of subjects with suicide-related events in the active treatment phase compared to post-treatment phase was unchanged in the varenicline group; in the placebo group, this percentage was lower in the post-treatment phase. Although there were no completed suicides, there was one suicidal attempt in a varenicline-treated subject whose lifetime history included several similar attempts. The limited data available from this single smoking cessation study are not sufficient to allow for definitive conclusions to be drawn about the safety in patients with schizophrenia or schizoaffective disorder.

Neuropsychiatric safety
Study in Subjects with and without a History of Psychiatric Disorder: Varenicline was evaluated in a randomised, double-blind, active and placebo-controlled study that included subjects with a history of psychiatric disorder (psychiatric cohort, N=4074) and subjects without a history of psychiatric disorder (non-psychiatric cohort, N=3984). Subjects aged 18-75 years, smoking 10 or more cigarettes per day were randomised 1:1:1:1 to varenicline 1 mg BID, bupropion SR 150 mg BID, nicotine replacement therapy patch (NRT) 21 mg/day with taper or placebo for a treatment period of 12 weeks; they were then followed for another 12 weeks post-treatment.

The primary safety endpoint was a composite of the following neuropsychiatric (NPS) adverse events: severe events of anxiety, depression, feeling abnormal, or hostility, and/or moderate or severe events of agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behaviour or completed suicide.

The following table shows the rates of the composite NPS adverse event primary endpoint by treatment group and the risk differences (RDs) (95% CI) vs placebo in the **non-psychiatric cohort**.

In addition, the table shows the subset of the composite NPS AE endpoint of severe intensity:

	Non-psychiatric Cohort N=3984			
	Varenicline	**Bupropion**	**NRT**	**Placebo**
Number of Patients Treated	990	989	1006	999
Composite NPS AE Primary Endpoint, n (%)	13 (1.3)	22 (2.2)	25 (2.5)	24 (2.4)
RD (95% CI) vs Placebo	-1.28 (-2.40, -0.15)	-0.08 (-1.37, 1.21)	-0.21 (-1.54,1.12)	
Composite NPS AE Endpoint of severe intensity n (%)	1 (0.1)	4 (0.4)	3 (0.3)	5 (0.5)

AE, adverse event; NRT=Nicotine replacement therapy patch

The rates of events in the composite endpoint were low across all treatment groups and were similar or lower for each of the active treatments compared to placebo. The use of varenicline, bupropion and NRT in the non-psychiatric cohort was not associated with a significantly increased risk of NPS adverse events in the composite primary endpoint compared with placebo (95% CIs were lower than or included zero).

The percentage of subjects with suicidal ideation and/or behaviour based on the Columbia-Suicide Severity Rating Scale (C-SSRS) was similar between the varenicline and placebo groups during treatment and in the non- treatment follow-up, as shown in the following table:

	Non-psychiatric Cohort N=3984			
	Varenicline N=990 n (%)	**Bupropion N=989 n (%)**	**NRT N=1006 n (%)**	**Placebo N=999 n (%)**
During treatment				
Number assessed	988	983	996	995
Suicidal behaviour and/or ideation	7 (0.7)	4 (0.4)	3 (0.3)	7 (0.7)
Suicidal behaviour	0	0	1 (0.1)	1 (0.1)
Suicidal ideation	7 (0.7)	4 (0.4)	3 (0.3)	6 (0.6)
During follow up				
Number assessed	807	816	800	805
Suicidal behaviour and/or ideation	3 (0.4)	2 (0.2)	3 (0.4)	4 (0.5)

Suicidal behaviour	0	1 (0.1)	0	0
Suicidal ideation	3 (0.4)	2 (0.2)	3 (0.4)	4 (0.5)

NRT=Nicotine replacement therapy patch

There was one completed suicide, which occurred during treatment in a subject treated with placebo in the non-psychiatric cohort.

The following table shows the rates of the composite NPS adverse event primary endpoint by treatment group and the RDs (95% CI) vs placebo in the **psychiatric cohort**. The individual components of the endpoint are also shown.

In addition, the table shows the subset of the composite NPS AE endpoint of severe intensity:

	Psychiatric Cohort N=4074			
	Varenicline	**Bupropion**	**NRT**	**Placebo**
Number of Patients Treated	1026	1017	1016	1015
Composite NPS AE Primary Endpoint, n (%)	67 (6.5)	68 (6.7)	53 (5.2)	50 (4.9)
RD (95% CI) vs Placebo	1.59 (-0.42, 3.59)	1.78 (-0.24, 3.81)	0.37 (-1.53, 2.26)	
NPS AE Primary Endpoint Components n (%):				
Anxiety[a]	5 (0.5)	4 (0.4)	6 (0.6)	2 (0.2)
Depression[a]	6 (0.6)	4 (0.4)	7 (0.7)	6 (0.6)
Feeling abnormal[a]	0	1 (0.1)	0	0
Hostility[a]	0	0	0	0
Agitation[b]	25 (2.4)	29 (2.9)	21 (2.1)	22 (2.2)
Aggression[b]	14 (1.4)	9 (0.9)	7 (0.7)	8 (0.8)
Delusions[b]	1 (0.1)	1 (0.1)	1 (0.1)	0
Hallucinations[b]	5 (0.5)	4 (0.4)	2 (0.2)	2 (0.2)
Homicidal ideation[b]	0	0	0	0
Mania[b]	7 (0.7)	9 (0.9)	3 (0.3)	6 (0.6)
Panic[b]	7 (0.7)	16 (1.6)	13 (1.3)	7 (0.7)
Paranoia[b]	1 (0.1)	0	0	2 (0.2)
Psychosis[b]	4 (0.4)	2 (0.2)	3 (0.3)	1 (0.1)
Suicidal behaviour[b]	1 (0.1)	1 (0.1)	0	1 (0.1)
Suicidal ideation[b]	5 (0.5)	2 (0.2)	3 (0.3)	2 (0.2)
Completed suicide[b]	0	0	0	0
Composite NPS AE Endpoint of severe intensity n (%)	14 (1.4)	14 (1.4)	14 (1.4)	13 (1.3)

AE, adverse event; [a]Grade = severe intensity AE; [b]Grade = moderate and severe intensity AE; NRT=Nicotine replacement therapy patch

There were more events reported in patients in the psychiatric cohort in each treatment group compared with the non-psychiatric cohort, and the incidence of events in the composite endpoint was higher for each of the active treatments compared to placebo. However, the use of varenicline, bupropion and NRT in the psychiatric cohort was not associated with a significantly increased risk of NPS adverse events in the composite primary endpoint compared with placebo (95% CIs included zero).

In the psychiatric cohort, the percentage of subjects with suicidal ideation and/or behaviour based on the Columbia-Suicide Severity Rating Scale (C-SSRS) was similar between the varenicline and placebo groups during treatment and in the non- treatment follow-up, as shown in the following table:

	Psychiatric Cohort N=4074			
	Varenicline N=1026 n (%)	**Bupropion N=1017 n (%)**	**NRT N=1016 n (%)**	**Placebo N=1015 n (%)**
During treatment				
Number assessed	1017	1012	1006	1006
Suicidal behaviour and/or ideation	27 (2.7)	15 (1.5)	20 (2.0)	25 (2.5)
Suicidal behaviour	0	1 (0.1)	0	2 (0.2)
Suicidal ideation	27 (2.7)	15 (1.5)	20 (2.0)	25 (2.5)
During follow up				
Number assessed	833	836	824	791
Suicidal behaviour and/or ideation	14 (1.7)	4 (0.5)	9 (1.1)	11 (1.4)
Suicidal behaviour	1 (0.1)	0	1 (0.1)	1 (0.1)
Suicidal ideation	14 (1.7)	4 (0.5)	9 (1.1)	11 (1.4)

NRT=Nicotine replacement therapy patch

There were no completed suicides reported in the psychiatric cohort.

The most commonly reported adverse events in subjects treated with varenicline in this study were similar to those observed in premarketing studies.

In both cohorts, subjects treated with varenicline demonstrated statistical superiority of CO-confirmed abstinence during weeks 9 through 12 and 9 through 24 compared to subjects treated with bupropion, nicotine patch and placebo (please see table below).

The key efficacy results are summarised in the following table:

	Non-psychiatric Cohort	**Psychiatric Cohort**
CA 9-12 n/N (%)		
Varenicline	382/1005 (38.0%)	301/1032 (29.2%)
Bupropion	261/1001 (26.1%)	199/1033 (19.3%)
NRT	267/1013 (26.4%)	209/1025 (20.4%)
Placebo	138/1009 (13.7%)	117/1026 (11.4%)
Treatment Comparisons: Odds ratio (95% CI), p value		
Varenicline vs Placebo	4.00 (3.20, 5.00), P<0.0001	3.24 (2.56, 4.11), P<0.0001
Bupropion vs Placebo	2.26 (1.80, 2.85), P<0.0001	1.87 (1.46, 2.39), P<0.0001
NRT vs Placebo	2.30 (1.83, 2.90), P<0.0001	2.00 (1.56, 2.55), P<0.0001
Varenicline vs Bupropion	1.77 (1.46, 2.14), P<0.0001	1.74 (1.41, 2.14), P<0.0001
Varenicline vs NRT	1.74 (1.43, 2.10), P<0.0001	1.62 (1.32, 1.99), P<0.0001

CA 9-24 n/N (%)		
Varenicline	256/1005 (25.5%)	189/1032 (18.3%)
Bupropion	188/1001 (18.8%)	142/1033 (13.7%)
NRT	187/1013 (18.5%)	133/1025 (13.0%)
Placebo	106/1009 (10.5%)	85/1026 (8.3%)
Treatment Comparisons: Odds ratio (95% CI), p value		
Varenicline vs Placebo	2.99 (2.33, 3.83), P<0.0001	2.50 (1.90, 3.29), P<0.0001
Bupropion vs Placebo	2.00 (1.54, 2.59), P<0.0001	1.77 (1.33, 2.36), P<0.0001
NRT vs Placebo	1.96 (1.51, 2.54), P<0.0001	1.65 (1.24, 2.20), P=0.0007
Varenicline vs Bupropion	1.49 (1.20, 1.85), P=0.0003	1.41 (1.11, 1.79), P=0.0047
Varenicline vs NRT	1.52 (1.23, 1.89), P=0.0001	1.51 (1.19, 1.93), P=0.0008

CA = continuous abstinence rate; CI = confidence interval; NRT=Nicotine replacement therapy patch

Neuropsychiatric Safety Meta-analyses and Observational Studies:
Analyses of clinical trial data did not show evidence of an increased risk of serious neuropsychiatric events with varenicline compared to placebo. In addition, independent observational studies have not supported an increased risk of serious neuropsychiatric events in patients treated with varenicline compared to patients prescribed nicotine replacement therapy (NRT) or bupropion.

Treatment discontinuation
The treatment discontinuation rate due to adverse reactions was 11.4% for varenicline compared with 9.7% for placebo. In this group, the discontinuation rates for the most common adverse reactions in varenicline treated patients were as follows: nausea (2.7% vs. 0.6% for placebo), headache (0.6% vs. 1.0% for placebo), insomnia (1.3% vs. 1.2% for placebo), and abnormal dreams (0.2% vs. 0.2% for placebo).

Analyses of Clinical Trials:

A meta-analysis of 5 randomised, double-blind, placebo controlled trials, including 1907 patients (1130 varenicline, 777 placebo), was conducted to assess suicidal ideation and behaviour as reported on the Columbia-Suicide Severity Rating Scale (C-SSRS). This meta-analysis included one trial (N=127) in patients with a history of schizophrenia or schizoaffective disorder and another trial (N=525) in patients with a history of depression. The results showed no increase in the incidence of suicidal ideation and/or behaviour in patients treated with varenicline compared to patients treated with placebo, as shown in the table below. Of the 55 patients who reported suicidal ideation or behaviour, 48 (24 varenicline, 24 placebo) were from the two trials that enrolled patients with a history of schizophrenia/ schizoaffective disorder, or of depression. Few patients reported these events in the other three trials (4 varenicline, 3 placebo).

Number of Patients and Risk Ratio for Suicidal Ideation and/or Behaviour Reported on C-SSRS from a Meta-Analysis of 5 Clinical Trials Comparing Varenicline to Placebo:

	Varenicline (N=1130)	**Placebo** (N=777)
Patients with suicidal ideation and/or behaviour* [n (%)]**	28 (2.5)	27 (3.5)
Patient-years of exposure	325	217
Risk Ratio # (RR; 95% CI)	0.79 (0.46, 1.36)	

* Of these, one patient in each treatment arm reported suicidal behaviour

** Patients with events up to 30 days after treatment; % are not weighted by study

RR of incidence rates per 100 patient years

A meta-analysis of 18 double-blind, randomised, placebo-controlled clinical trials was conducted to assess the neuropsychiatric safety of varenicline. These trials included the 5 trials described above that used the C-SSRS, and a total of 8521 patients (5072 varenicline, 3449 placebo), some of which had psychiatric conditions. The results showed a similar incidence of combined neuropsychiatric

adverse events, other than sleep disorders, in patients treated with varenicline compared to patients treated with placebo, with a risk ratio (RR) of 1.01 (95% CI: 0.89-1.15). Pooled data from these 18 trials showed a similar incidence rate of individual categories of psychiatric events in patients treated with varenicline compared to patients treated with placebo. The table below describes the most frequently (≥ 1%) reported categories of adverse events related to psychiatric safety other than sleep disorders and disturbances.

Psychiatric Adverse Events Occurring in ≥ 1% of Patients from Pooled Data from 18 Clinical Trials:

	Varenicline (N=5072)	**Placebo** (N=3449)
Anxiety disorders and symptoms	253 (5.0)	206 (6.0)
Depressed mood disorders and disturbances	179 (3.5)	108 (3.1)
Mood disorders and disturbances NEC*	116 (2.3)	53 (1.5)

* NEC = Not Elsewhere Classified

Counts (percentages) corresponds to the number of patients reporting the event

Observational Studies

Four observational studies, each including 10,000 to 30,000 users of varenicline in the adjusted analyses, compared the risk of serious neuropsychiatric events, including neuropsychiatric hospitalizations and fatal and non-fatal self-harm, in patients treated with varenicline versus patients prescribed NRT or bupropion. All studies were retrospective cohort studies and included patients with and without a psychiatric history. All studies used statistical methods to control for confounding factors, including preferential prescribing of varenicline to healthier patients, although there is the possibility of residual confounding.

Two of the studies found no difference in risk of neuropsychiatric hospitalisations between varenicline users and nicotine patch users (Hazard Ratio [HR] 1.14; 95% Confidence Interval [CI]: 0.56-2.34 in the first study, and 0.76; 95% CI: 0.40-1.46 in the second study). The power to detect differences in these two studies was limited. The third study reported no difference in risk of psychiatric adverse events diagnosed during an emergency department visit or inpatient admission between varenicline users and bupropion users (HR 0.85; 95% CI: 0.55-1.30). Based on post marketing reports, bupropion may be associated with neuropsychiatric adverse events.

The fourth study showed no evidence of a higher risk of fatal and non-fatal self- harm (HR of 0.88; 95% CI: 0.52-1.49) in patients prescribed varenicline compared to patients prescribed NRT. The occurrence of detected suicide was rare during the three months after patients initiated any drug treatment (two cases in 31,260 varenicline users and six cases in 81,545 NRT users).

Pregnancy Cohort Study

A population-based cohort study compared infants exposed to CHAMPIX *in utero* (N=335) with infants born to mothers who smoked during pregnancy (N=78,412) and infants born to non-smoking mothers (N=806,438). In this study, infants exposed to CHAMPIX *in utero* as compared to infants born to mothers who smoked during pregnancy had lower rates of congenital malformations (3.6% vs 4.3%), stillbirth (0.3% vs 0.5%), preterm birth (7.5% vs 7.9%), small for gestational age (12.5% vs 17.1%), and premature rupture of membrane (3.6% vs 5.4%).

5.2 Pharmacokinetic properties

Absorption

Maximum plasma concentrations of varenicline occur typically within 3-4 hours after oral administration. Following administration of multiple oral doses to healthy volunteers, steady-state

conditions were reached within 4 days. Absorption is virtually complete after oral administration and systemic availability is high. Oral bioavailability of varenicline is unaffected by food or time-of-day dosing.

Distribution

Varenicline distributes into tissues, including the brain. Apparent volume of distribution averaged 415 litres (%CV= 50) at steady-state. Plasma protein binding of varenicline is low (≤ 20%) and independent of both age and renal function. In rodents, varenicline is transferred through the placenta and excreted in milk.

Biotransformation

Varenicline undergoes minimal metabolism with 92% excreted unchanged in the urine and less than 10% excreted as metabolites. Minor metabolites in urine include varenicline N-carbamoylglucuronide and hydroxyvarenicline. In circulation, varenicline comprises 91% of drug-related material. Minor circulating metabolites include varenicline N-carbamoylglucuronide and N-glucosylvarenicline.

In vitro studies demonstrate that varenicline does not inhibit cytochrome P450 enzymes (IC50 > 6,400 ng/ml). The P450 enzymes tested for inhibition were: 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4/5. Also, in human hepatocytes *in vitro*, varenicline was shown to not induce the activity of cytochrome P450 enzymes 1A2 and 3A4. Therefore, varenicline is unlikely to alter the pharmacokinetics of compounds that are primarily metabolised by cytochrome P450 enzymes.

Elimination

The elimination half-life of varenicline is approximately 24 hours. Renal elimination of varenicline is primarily through glomerular filtration along with active tubular secretion via the organic cationic transporter, OCT2 (see section 4.5).

Linearity/Non linearity

Varenicline exhibits linear kinetics when given as single (0.1 to 3 mg) or repeated 1 to 3 mg/day doses.

Pharmacokinetics in special patient populations

There are no clinically meaningful differences in varenicline pharmacokinetics due to age, race, gender, smoking status, or use of concomitant medicinal products, as demonstrated in specific pharmacokinetic studies and in population pharmacokinetic analyses.

Hepatic impairment
Due to the absence of significant hepatic metabolism, varenicline pharmacokinetics should be unaffected in patients with hepatic impairment (see section 4.2).

Renal impairment
Varenicline pharmacokinetics were unchanged in subjects with mild renal impairment (estimated creatinine clearance > 50 ml/min and ≤ 80 ml/min). In patients with moderate renal impairment (estimated creatinine clearance ≥ 30 ml/min and ≤ 50 ml/min), varenicline exposure increased 1.5-fold compared with subjects with normal renal function (estimated creatinine clearance > 80 ml/min). In subjects with severe renal impairment (estimated creatinine clearance < 30 ml/min), varenicline exposure was increased 2.1-fold. In subjects with end-stage-renal disease (ESRD), varenicline was efficiently removed by haemodialysis (see section 4.2).

Elderly
The pharmacokinetics of varenicline in elderly patients with normal renal function (aged 65-75 years) is similar to that of younger adult subjects (see section 4.2). For elderly patients with reduced renal function please refer to section 4.2.

Paediatric population
Single and multiple-dose pharmacokinetics of varenicline have been investigated in paediatric patients aged 12 to 17 years old (inclusive) and were approximately dose-proportional over the 0.5 mg to 2 mg daily dose range studied. Steady-state systemic exposure in adolescent patients of bodyweight > 55 kg, as assessed by AUC (0-24), was comparable to that noted for the same doses in the adult population. When 0.5 mg twice daily was given, steady-state daily exposure of varenicline was, on average, higher (by approximately 40%) in adolescent patients with bodyweight ≤ 55 kg compared to that noted in the adult population. Efficacy and safety has not been demonstrated in the paediatric population below 18 years of age and no recommendation on a posology can be made (see section 4.2).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, fertility and embryo-foetal development. In male rats dosed for 2 years with varenicline, there was a dose-related increase in the incidence of hibernoma (tumour of the brown fat). In the offspring of pregnant rats treated with varenicline there were decreases in fertility and increases in the auditory startle response (see section 4.6). These effects were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. Nonclinical data indicate varenicline has reinforcing properties albeit with lower potency than nicotine. In clinical studies in humans, varenicline showed low abuse potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablets' core

Cellulose, Microcrystalline
Calcium Hydrogen Phosphate Anhydrous
Croscarmellose Sodium
Silica, Colloidal Anhydrous
Magnesium Stearate

Film coating

Hypromellose
Titanium Dioxide (E171)
Macrogol 400
Triacetin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Bottles: 2 years
Blisters: 3 years

6.4 Special precautions for storage

Blisters: Store below 30°C
HDPE Bottle: This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

Maintenance packs

PCTFE/PVC blisters with aluminium foil backing in a pack containing 28 x 0.5 mg film-coated tablets in secondary heat sealed card packaging.

PCTFE/PVC blisters with aluminium foil backing in a pack containing 56 x 0.5 mg film-coated tablets in secondary heat sealed card packaging.

PVC blisters with aluminium foil backing in a pack containing 28 x 0.5 mg film-coated tablets in secondary heat sealed card packaging.

PVC blisters with aluminium foil backing in a pack containing 56 x 0.5 mg film-coated tablets in secondary heat sealed card packaging.

High-density polyethylene (HDPE) bottle with polypropylene child resistant closure and an aluminium foil/polyethylene induction seal containing 56 x 0.5 mg film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/360/001
EU/1/06/360/006
EU/1/06/360/007
EU/1/06/360/017
EU/1/06/360/018

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 September 2006
Date of latest renewal: 29 June 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu/

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 1 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 1 mg of varenicline (as tartrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet of 5 mm x 10 mm

Light blue, capsular-shaped, biconvex tablets debossed with "*Pfizer*" on one side and "CHX 1.0" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CHAMPIX is indicated for smoking cessation in adults.

4.2 Posology and method of administration

Posology

The recommended dose is 1 mg varenicline twice daily following a 1-week titration as follows:

Days 1 – 3:	0.5 mg once daily
Days 4 – 7:	0.5 mg twice daily
Day 8 – End of treatment:	1 mg twice daily

The patient should set a date to stop smoking. CHAMPIX dosing should usually start 1-2 weeks before this date (see section 5.1). Patients should be treated with CHAMPIX for 12 weeks.

For patients who have successfully stopped smoking at the end of 12 weeks, an additional course of 12 weeks treatment with CHAMPIX at 1 mg twice daily may be considered for the maintenance of abstinence (see section 5.1).

A gradual approach to quitting smoking with CHAMPIX should be considered for patients who are not able or willing to quit abruptly. Patients should reduce smoking during the first 12 weeks of treatment and quit by the end of that treatment period. Patients should then continue taking CHAMPIX for an additional 12 weeks for a total of 24 weeks of treatment (see section 5.1).

Patients who are motivated to quit and who did not succeed in stopping smoking during prior CHAMPIX therapy, or who relapsed after treatment, may benefit from another quit attempt with CHAMPIX (see section 5.1).

Patients who cannot tolerate adverse reactions of CHAMPIX may have the dose lowered temporarily or permanently to 0.5 mg twice daily.

In smoking cessation therapy, risk for relapse to smoking is elevated in the period immediately following the end of treatment. In patients with a high risk of relapse, dose tapering may be considered (see section 4.4).

Elderly
No dosage adjustment is necessary for elderly patients (see section 5.2). Because elderly patients are more likely to have decreased renal function, prescribers should consider the renal status of an elderly patient.

Renal impairment
No dosage adjustment is necessary for patients with mild (estimated creatinine clearance > 50 ml/min and ≤ 80 ml/min) to moderate (estimated creatinine clearance ≥ 30 ml/min and ≤ 50 ml/min) renal impairment.

For patients with moderate renal impairment who experience adverse reactions that are not tolerable, dosing may be reduced to 1 mg once daily.

For patients with severe renal impairment (estimated creatinine clearance < 30 ml/min), the recommended dose of CHAMPIX is 1 mg once daily. Dosing should begin at 0.5 mg once daily for the first 3 days then increased to 1 mg once daily. Based on insufficient clinical experience with CHAMPIX in patients with end stage renal disease, treatment is not recommended in this patient population (see section 5.2).

Hepatic impairment
No dosage adjustment is necessary for patients with hepatic impairment (see section 5.2).

Paediatric population
The safety and efficacy of CHAMPIX in children or adolescents below 18 years have not yet been established. Currently available data are described in section 5.2 but no recommendation on a posology can be made

Method of administration

CHAMPIX is for oral use and the tablets should be swallowed whole with water.
CHAMPIX can be taken with or without food

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Effect of smoking cessation

Physiological changes resulting from smoking cessation, with or without treatment with CHAMPIX, may alter the pharmacokinetics or pharmacodynamics of some medicinal products, for which dosage adjustment may be necessary (examples include theophylline, warfarin and insulin). As smoking induces CYP1A2, smoking cessation may result in an increase of plasma levels of CYP1A2 substrates.

Neuropsychiatric symptoms

Changes in behaviour or thinking, anxiety, psychosis, mood swings, aggressive behaviour, depression, suicidal ideation and behaviour and suicide attempts have been reported in patients attempting to quit smoking with CHAMPIX in the post-marketing experience.

A large randomised, double-blind, active and placebo-controlled study was conducted to compare the risk of serious neuropsychiatric events in patients with and without a history of psychiatric disorder treated for smoking cessation with varenicline, bupropion, nicotine replacement therapy patch (NRT) or placebo. The primary safety endpoint was a composite of neuropsychiatric adverse events that have been reported in post-marketing experience.

The use of varenicline in patients with or without a history of psychiatric disorder was not associated with an increased risk of serious neuropsychiatric adverse events in the composite primary endpoint compared with placebo (see section 5.1 **Pharmacodynamic properties** - *Study in Subjects with and without a History of Psychiatric Disorder*).

Depressed mood, rarely including suicidal ideation and suicide attempt, may be a symptom of nicotine withdrawal.

Clinicians should be aware of the possible emergence of serious neuropsychiatric symptoms in patients attempting to quit smoking with or without treatment. If serious neuropsychiatric symptoms occur whilst on varenicline treatment, patients should discontinue varenicline immediately and contact a healthcare professional for re-evaluation of treatment.

History of psychiatric disorders
Smoking cessation, with or without pharmacotherapy, has been associated with exacerbation of underlying psychiatric illness (e.g. depression).

CHAMPIX smoking cessation studies have provided data in patients with a history of psychiatric disorders (see section 5.1).

In a smoking cessation clinical trial, neuropsychiatric adverse events were reported more frequently in patients with a history of psychiatric disorders compared to those without a history of psychiatric disorders, regardless of treatment (see section 5.1).

Care should be taken with patients with a history of psychiatric illness and patients should be advised accordingly.

Seizures

In clinical trials and post-marketing experience there have been reports of seizures in patients with or without a history of seizures, treated with CHAMPIX. CHAMPIX should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold.

Treatment discontinuation

At the end of treatment, discontinuation of CHAMPIX was associated with an increase in irritability, urge to smoke, depression, and/or insomnia in up to 3% of patients. The prescriber should inform the patient accordingly and discuss or consider the need for dose tapering.

Cardiovascular events

Patients taking CHAMPIX should be instructed to notify their doctor of new or worsening cardiovascular symptoms and to seek immediate medical attention if they experience signs and symptoms of myocardial infarction or stroke (see section 5.1).

Hypersensitivity reactions

There have been post-marketing reports of hypersensitivity reactions including angioedema in patients treated with varenicline. Clinical signs included swelling of the face, mouth (tongue, lips, and gums), neck (throat and larynx) and extremities. There were rare reports of life-threatening angioedema requiring urgent medical attention due to respiratory compromise. Patients experiencing these symptoms should discontinue treatment with varenicline and contact a health care provider immediately.

Cutaneous reactions

There have also been post-marketing reports of rare but severe cutaneous reactions, including Stevens-Johnson Syndrome and Erythema Multiforme in patients using varenicline. As these skin reactions can be life threatening, patients should discontinue treatment at the first sign of rash or skin reaction and contact a healthcare provider immediately.

4.5 Interaction with other medicinal products and other forms of interaction

Based on varenicline characteristics and clinical experience to date, CHAMPIX has no clinically meaningful drug interactions. No dosage adjustment of CHAMPIX or co-administered medicinal products listed below is recommended.

In vitro studies indicate that varenicline is unlikely to alter the pharmacokinetics of compounds that are primarily metabolised by cytochrome P450 enzymes.

Furthermore since metabolism of varenicline represents less than 10% of its clearance, active substances known to affect the cytochrome P450 system are unlikely to alter the pharmacokinetics of varenicline (see section 5.2) and therefore a dose adjustment of CHAMPIX would not be required.

In vitro studies demonstrate that varenicline does not inhibit human renal transport proteins at therapeutic concentrations. Therefore, active substances that are cleared by renal secretion (e.g., metformin - see below) are unlikely to be affected by varenicline.

Metformin

Varenicline did not affect the pharmacokinetics of metformin. Metformin had no effect on varenicline pharmacokinetics.

Cimetidine

Co-administration of cimetidine, with varenicline increased the systemic exposure of varenicline by 29% due to a reduction in varenicline renal clearance. No dosage adjustment is recommended based on concomitant cimetidine administration in subjects with normal renal function or in patients with mild to moderate renal impairment. In patients with severe renal impairment, the concomitant use of cimetidine and varenicline should be avoided.

Digoxin

Varenicline did not alter the steady-state pharmacokinetics of digoxin.

Warfarin

Varenicline did not alter the pharmacokinetics of warfarin. Prothrombin time (INR) was not affected by varenicline. Smoking cessation itself may result in changes to warfarin pharmacokinetics (see section 4.4).

Alcohol

There are limited clinical data on any potential interaction between alcohol and varenicline. There have been post marketing reports of increased intoxicating effects of alcohol in patients treated with varenicline. A causal relationship between these events and varenicline use has not been established.

Use with other therapies for smoking cessation

Bupropion
Varenicline did not alter the steady-state pharmacokinetics of bupropion.

Nicotine replacement therapy (NRT)
When varenicline and transdermal NRT were co-administered to smokers for 12 days, there was a statistically significant decrease in average systolic blood pressure (mean 2.6 mmHg) measured on the final day of the study. In this study, the incidence of nausea, headache, vomiting, dizziness, dyspepsia, and fatigue was greater for the combination than for NRT alone.

Safety and efficacy of CHAMPIX in combination with other smoking cessation therapies have not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

A moderate amount of data on pregnant women indicated no malformative or foetal/neonatal toxicity of varenicline (see section 5.1).

Animal studies have shown reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of varenicline during pregnancy (see section 5.1).

Breast-feeding

It is unknown whether varenicline is excreted in human breast milk. Animal studies suggest that varenicline is excreted in breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with CHAMPIX should be made taking into account the benefit of breast-feeding to the child and the benefit of CHAMPIX therapy to the woman.

Fertility

There are no clinical data on the effects of varenicline on fertility.

Non-clinical data revealed no hazard for humans based on standard male and female fertility studies in the rat (see section 5.3).

4.7 Effects on ability to drive and use machines

CHAMPIX may have minor or moderate influence on the ability to drive and use machines. CHAMPIX may cause dizziness, somnolence and transient loss of consciousness, and therefore may influence the ability to drive and use machines. Patients are advised not to drive, operate complex machinery or engage in other potentially hazardous activities until it is known whether this medicinal product affects their ability to perform these activities.

4.8 Undesirable effects

Summary of the safety profile

Smoking cessation with or without treatment is associated with various symptoms. For example, dysphoric or depressed mood; insomnia, irritability, frustration or anger; anxiety; difficulty concentrating; restlessness; decreased heart rate; increased appetite or weight gain have been reported in patients attempting to stop smoking. No attempt has been made in either the design or the analysis of the CHAMPIX studies to distinguish between adverse reactions associated with study drug treatment or those possibly associated with nicotine withdrawal. Adverse drug reactions are based on evaluation of data from pre-marketing phase 2-3 studies and updated based on pooled data from 18 placebo-controlled pre- and post-marketing studies, including approximately 5,000 patients treated with varenicline.

In patients treated with the recommended dose of 1 mg twice daily following an initial titration period the adverse event most commonly reported was nausea (28.6%). In the majority of cases nausea occurred early in the treatment period, was mild to moderate in severity and seldom resulted in discontinuation.

Tabulated summary of adverse reactions

In the table below all adverse reactions, which occurred at an incidence greater than placebo are listed by system organ class and frequency (very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) and rare (≥ 1/10,000 to < 1/1,000)). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	Adverse Drug Reactions
Infections and infestations	
Very common	Nasopharyngitis
Common	Bronchitis, sinusitis
Uncommon	Fungal infection, viral infection
Blood and lymphatic system disorders	
Rare	Platelet count decreased
Metabolism and nutrition disorders	
Common	Weight increased, decreased appetite, increased appetite
Uncommon	Hyperglycaemia
Rare	Diabetes mellitus, polydipsia
Psychiatric disorders	
Very common	Abnormal dreams, insomnia
Uncommon	Suicidal ideation, aggression, panic reaction, thinking abnormal, restlessness, mood swings, depression*, anxiety*, hallucinations*, libido increased, libido decreased
Rare	Psychosis, somnambulism, abnormal behaviour, dysphoria, bradyphrenia
Nervous system disorders	
Very common	Headache
Common	Somnolence, dizziness, dysgeusia
Uncommon	Seizure, tremor, lethargy, hypoaesthesia
Rare	Cerebrovascular accident, hypertonia, dysarthria, coordination abnormal, hypogeusia, circadian rhythm sleep disorder
Not known	Transient loss of consciousness
Eye disorders	
Uncommon	Conjunctivitis, eye pain
Rare	Scotoma, scleral discolouration, mydriasis, photophobia, myopia, lacrimation increased

System Organ Class	Adverse Drug Reactions
Ear and labyrinth disorders	
Uncommon	Tinnitus
Cardiac disorders	
Uncommon	Myocardial infarction, angina pectoris, tachycardia, palpitations, heart rate increased
Rare	Atrial fibrillation, electrocardiogram ST segment depression, electrocardiogram T wave amplitude decreased
Vascular disorders	
Uncommon	Blood pressure increased, hot flush
Respiratory, thoracic and mediastinal disorders	
Common	Dyspnoea, cough
Uncommon	Upper respiratory tract inflammation, respiratory tract congestion, dysphonia, rhinitis allergic, throat irritation, sinus congestion, upper-airway cough syndrome, rhinorrhoea
Rare	Laryngeal pain, snoring
Gastrointestinal disorders	
Very common	Nausea
Common	Gastrooesophageal reflux disease, vomiting, constipation, diarrhoea, abdominal distension, abdominal pain, toothache, dyspepsia, flatulence, dry mouth
Uncommon	Haematochezia, gastritis, change of bowel habit, eructation, aphthous stomatitis, gingival pain
Rare	Haematemesis, abnormal faeces, tongue coated
Skin and subcutaneous tissue disorders	
Common	Rash, pruritus
Uncommon	Erythema, acne, hyperhidrosis, night sweats
Rare	Severe cutaneous reactions, including Stevens Johnson Syndrome and Erythema Multiforme, angioedema
Musculoskeletal and connective tissue disorders	
Common	Arthralgia, myalgia, back pain
Uncommon	Muscle spasms, musculoskeletal chest pain
Rare	Joint stiffness, costochondritis
Renal and urinary disorders	
Uncommon	Pollakiuria, nocturia
Rare	Glycosuria, polyuria
Reproductive system and breast disorders	
Uncommon	Menorrhagia
Rare	Vaginal discharge, sexual dysfunction
General disorders and administration site conditions	
Common	Chest pain, fatigue
Uncommon	Chest discomfort, influenza like illness, pyrexia, asthenia, malaise
Rare	Feeling cold, cyst
Investigations	
Common	Liver function test abnormal
Rare	Semen analysis abnormal, C-reactive protein increased, blood calcium decreased
* Frequencies are estimated from a post-marketing, observational cohort study	

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No cases of overdose were reported in pre-marketing clinical trials.

In case of overdose, standard supportive measures should be instituted as required.

Varenicline has been shown to be dialyzed in patients with end stage renal disease (see section 5.2), however, there is no experience in dialysis following overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other nervous system drugs ; Drugs used in addictive disorders, Drugs used in nicotine dependence, ATC code: N07BA03

Mechanism of action

Varenicline binds with high affinity and selectivity at the α4β2 neuronal nicotinic acetylcholine receptors, where it acts as a partial agonist - a compound that has both agonist activity, with lower intrinsic efficacy than nicotine, and antagonist activities in the presence of nicotine.

Electrophysiology studies *in vitro* and neurochemical studies in vivo have shown that varenicline binds to the α4β2 neuronal nicotinic acetylcholine receptors and stimulates receptor-mediated activity, but at a significantly lower level than nicotine. Nicotine competes for the same human α4β2 nAChR binding site for which varenicline has higher affinity. Therefore, varenicline can effectively block nicotine's ability to fully activate α4β2 receptors and the mesolimbic dopamine system, the neuronal mechanism underlying reinforcement and reward experienced upon smoking. Varenicline is highly selective and binds more potently to the α4β2 receptor subtype (Ki=0.15 nM) than to other common nicotinic receptors (α3β4 Ki=84 nM, α7 Ki= 620 nM, α1βγδ Ki= 3,400 nM), or to non-nicotinic receptors and transporters (Ki > 1μM, except to 5-HT3 receptors: Ki=350 nM).

Pharmacodynamic effects

The efficacy of CHAMPIX in smoking cessation is a result of varenicline's partial agonist activity at the α4β2 nicotinic receptor where its binding produces an effect sufficient to alleviate symptoms of craving and withdrawal (agonist activity), while simultaneously resulting in a reduction of the rewarding and reinforcing effects of smoking by preventing nicotine binding to α4β2 receptors (antagonist activity).

Clinical efficacy and safety

Smoking cessation therapies are more likely to succeed for patients who are motivated to stop smoking and who are provided with additional advice and support.

The efficacy of CHAMPIX in smoking cessation was demonstrated in 3 clinical trials involving chronic cigarette smokers (≥ 10 cigarettes per day). Two thousand six hundred nineteen (2619)

patients received CHAMPIX 1 mg BID (titrated during the first week), 669 patients received bupropion 150 mg BID (also titrated) and 684 patients received placebo.

Comparative clinical studies
Two identical double-blind clinical trials prospectively compared the efficacy of CHAMPIX (1 mg twice daily), sustained release bupropion (150 mg twice daily) and placebo in smoking cessation. In these 52-week duration studies, patients received treatment for 12 weeks, followed by a 40-week non-treatment phase.

The primary endpoint of the two studies was the carbon monoxide (CO) confirmed, 4-week continuous quit rate (4W-CQR) from week 9 through week 12. The primary endpoint for CHAMPIX demonstrated statistical superiority to bupropion and placebo.

After the 40 week non-treatment phase, a key secondary endpoint for both studies was the Continuous Abstinence Rate (CA) at week 52. CA was defined as the proportion of all subjects treated who did not smoke (not even a puff of a cigarette) from Week 9 through Week 52 and did not have an exhaled CO measurement of > 10 ppm. The 4W-CQR (weeks 9 through 12) and CA rate (weeks 9 through 52) from studies 1 and 2 are included in the following table:

	Study 1 (n=1022)		Study 2 (n=1023)	
	4W CQR	CA Wk 9-52	4W CQR	CA Wk 9-52
CHAMPIX	44.4%	22.1%	44.0%	23.0%
Bupropion	29.5%	16.4%	30.0%	15.0%
Placebo	17.7%	8.4%	17.7%	10.3%
Odds ratio CHAMPIX vs. placebo	3.91 $p < 0.0001$	3.13 $p < 0.0001$	3.85 $p < 0.0001$	2.66 $p < 0.0001$
Odds ratio CHAMPIX vs. bupropion	1.96 $p < 0.0001$	1.45 $p = 0.0640$	1.89 $p < 0.0001$	1.72 $p = 0.0062$

Patient reported craving, withdrawal and reinforcing effects of smoking
Across both Studies 1 and 2 during active treatment, craving and withdrawal were significantly reduced in patients randomised to CHAMPIX in comparison with placebo. CHAMPIX also significantly reduced reinforcing effects of smoking that can perpetuate smoking behaviour in patients who smoke during treatment compared with placebo. The effect of varenicline on craving, withdrawal and reinforcing effects of smoking were not measured during the non-treatment long-term follow-up phase.

Maintenance of abstinence study
The third study assessed the benefit of an additional 12 weeks of CHAMPIX therapy on the maintenance of abstinence. Patients in this study (n=1,927) received open-label CHAMPIX 1 mg twice daily for 12 weeks. Patients who stopped smoking by Week 12 were then randomised to receive either CHAMPIX (1 mg twice daily) or placebo for an additional 12 weeks for a total study duration of 52 weeks.

The primary study endpoint was the CO-confirmed continuous abstinence rate from week 13 through week 24 in the double-blind treatment phase. A key secondary endpoint was the continuous abstinence (CA) rate for week 13 through week 52.

This study showed the benefit of an additional 12-week treatment with CHAMPIX 1 mg twice daily for the maintenance of smoking cessation compared to placebo; superiority to placebo for CA was maintained through week 52. The key results are summarised in the following table:

Continuous Abstinence Rates in Subjects Treated with Champix versus Placebo

	CHAMPIX n=602	Placebo n=604	Difference (95% CI)	Odds ratio (95% CI)
CA* wk 13-24	70.6%	49.8%	20.8% (15.4%, 26.2%)	2.47 (1.95, 3.15)
CA* wk 13-52	44.0%	37.1%	6.9% (1.4%, 12.5%)	1.35 (1.07, 1.70)

*CA: Continuous Abstinence Rate

There is currently limited clinical experience with the use of CHAMPIX among black people to determine clinical efficacy.

Flexible quit date between weeks 1 and 5
The efficacy and safety of varenicline has been evaluated in smokers who had the flexibility of quitting between weeks 1 and 5 of treatment. In this 24-week study, patients received treatment for 12 weeks followed by a 12 week non-treatment follow up phase. The 4 week (week 9-12) CQR for varenicline and placebo was 53.9% and 19.4%, respectively (difference=34.5, 95% CI: 27.0% - 42.0%) and the CA week 9-24 was 35.2% (varenicline) vs. 12.7% (placebo) (difference=22.5%, 95% CI: 15.8% - 29.1%). Patients who are not willing or able to set the target quit date within 1-2 weeks, could be offered to start treatment and then choose their own quit date within 5 weeks.

Study in subjects re-treated with CHAMPIX
CHAMPIX was evaluated in a double-blind, placebo-controlled trial of 494 patients who had made a previous attempt to quit smoking with CHAMPIX, and either did not succeed in quitting or relapsed after treatment. Subjects who experienced an adverse event of a concern during previous treatment were excluded. Subjects were randomised 1:1 to CHAMPIX 1 mg twice daily (N=249) or placebo (N=245) for 12 weeks of treatment and followed for up to 40 weeks post-treatment. Patients included in this study had taken CHAMPIX for a smoking-cessation attempt in the past (for a total treatment duration of a minimum of two weeks), at least three months prior to study entry, and had been smoking for at least four weeks.

Patients treated with CHAMPIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 and from weeks 9 through 52 compared to subjects treated with placebo. The key results are summarised in the following table:

Continuous Abstinence Rates in Subjects Treated with Champix versus Placebo

	CHAMPIX n=249	Placebo n=245	Odds ratio (95% CI), p value
CA* wk 9-12	45.0%	11.8%	7.08 (4.34, 11.55), p<0.0001
CA* wk 9-52	20.1%	3.3%	9.00 (3.97, 20.41), p<0.0001

*CA: Continuous Abstinence Rate

Gradual approach to quitting smoking
CHAMPIX was evaluated in a 52-week double-blind placebo-controlled study of 1,510 subjects who were not able or willing to quit smoking within four weeks, but were willing to gradually reduce their smoking over a 12 week period before quitting. Subjects were randomised to either CHAMPIX 1 mg twice daily (n=760) or placebo (n=750) for 24 weeks and followed up post-treatment through week 52. Subjects were instructed to reduce the number of cigarettes smoked by at least 50 percent by the end of the first four weeks of treatment, followed by a further 50 percent reduction from week four to week eight of treatment, with the goal of reaching complete abstinence by 12 weeks. After the initial 12-week reduction phase, subjects continued treatment for another 12 weeks. Subjects treated with

CHAMPIX had a significantly higher Continuous Abstinence Rate compared with placebo; the key results are summarised in the following table:

Continuous Abstinence Rates in Subjects Treated with Champix versus Placebo

	CHAMPIX n=760	Placebo n=750	Odds ratio (95% CI), p value
CA* wk 15-24	32.1%	6.9%	8.74 (6.09, 12.53) p<0.0001
CA* wk 21-52	27.0%	9.9%	4.02 (2.94, 5.50) p<0.0001

*CA: Continuous Abstinence Rate

The CHAMPIX safety profile in this study was consistent with that of pre-marketing studies.

Subjects with cardiovascular disease
CHAMPIX was evaluated in a randomised, double-blind, placebo-controlled study of subjects with stable, cardiovascular disease (other than, or in addition to, hypertension) that had been diagnosed for more than 2 months. Subjects were randomised to CHAMPIX 1 mg twice daily (n=353) or placebo (n=350) for 12 weeks and then were followed for 40 weeks post-treatment. The 4 week CQR for varenicline and placebo was 47.3% and 14.3%, respectively and the CA week 9-52 was 19.8% (varenicline) vs. 7.4% (placebo).

Deaths and serious cardiovascular events were adjudicated by a blinded, committee. The following adjudicated events occurred with a frequency ≥ 1% in either treatment group during treatment (or in the 30-day period after treatment): nonfatal myocardial infarction (1.1% vs. 0.3% for CHAMPIX and placebo, respectively), and hospitalisation for angina pectoris (0.6% vs. 1.1%). During non-treatment follow up to 52 weeks, the adjudicated events included need for coronary revascularisation (2.0% vs. 0.6%), hospitalisation for angina pectoris (1.7% vs. 1.1%), and new diagnosis of peripheral vascular disease (PVD) or admission for a PVD procedure (1.4% vs. 0.6%). Some of the patients requiring coronary revascularisation underwent the procedure as part of management of nonfatal MI and hospitalisation for angina. Cardiovascular death occurred in 0.3% of patients in the CHAMPIX arm and 0.6% of patients in the placebo arm over the course of the 52-week study.

A meta-analysis of 15 clinical trials of ≥ 12 weeks treatment duration, including 7002 patients (4190 CHAMPIX, 2812 placebo), was conducted to systematically assess the cardiovascular safety of CHAMPIX. The study in patients with stable cardiovascular disease described above was included in the meta-analysis.

The key cardiovascular safety analysis included occurrence and timing of a composite endpoint of Major Adverse Cardiovascular Events (MACE), defined as cardiovascular death, nonfatal MI, and nonfatal stroke. These events included in the endpoint were adjudicated by a blinded, independent committee. Overall, a small number of MACE occurred during treatment in the trials included in the meta-analysis (CHAMPIX 7 [0.17%]; placebo 2 [0.07%]). Additionally, a small number of MACE occurred up to 30 days after treatment (CHAMPIX 13 [0.31%]; placebo 6 [0.21%]).

The meta-analysis showed that exposure to CHAMPIX resulted in a hazard ratio for MACE of 2.83 (95% confidence interval from 0.76 to 10.55, p=0.12) for patients during treatment and 1.95 (95% confidence interval from 0.79 to 4.82, p=0.15) for patients up to 30 days after treatment. These are equivalent to an estimated increase of 6.5 MACE events and 6.3 MACE events per 1,000 patient-years, respectively of exposure. The hazard ratio for MACE was higher in patients with cardiovascular risk factors in addition to smoking compared with that in patients without cardiovascular risk factors other than smoking. There were similar rates of all-cause mortality

(CHAMPIX 6 [0.14%]; placebo 7 [0.25%]) and cardiovascular mortality (CHAMPIX 2 [0.05%]; placebo 2 [0.07%]) in the CHAMPIX arms compared with the placebo arms in the meta-analysis.

Cardiovascular safety assessment study in subjects with and without a history of psychiatric disorder
The cardiovascular (CV) safety of CHAMPIX was evaluated in the Study in Subjects with and without a History of Psychiatric Disorder (parent study; see section 5.1 - *Neuropsychiatric safety*) and its non-treatment extension, the Cardiovascular Safety Assessment Study, which enrolled 4595 of the 6293 subjects who completed the parent study (N=8058) and followed them through week 52. Of all subjects treated in the parent study, 1749 (21.7%) had a medium CV risk and 644 (8.0%) had a high CV risk, as defined by Framingham score.

The primary CV endpoint was the time to major adverse cardiovascular events (MACE), defined as cardiovascular death, non-fatal myocardial infarction or non-fatal stroke during treatment. Deaths and cardiovascular events were adjudicated by a blinded, independent committee.

The following table shows the incidence of MACE and Hazard Ratios vs placebo for all treatment groups during treatment, and cumulative for treatment plus 30 days and through end of study.

	CHAMPIX N=2016	**Bupropion N=2006**	**NRT N=2022**	**Placebo N=2014**
During treatment				
MACE, n (%)	1 (0.05)	2 (0.10)	1 (0.05)	4 (0.20)
Hazard Ratio (95% CI) vs placebo	0.29 (0.05, 1.68)	0.50 (0.10, 2.50)	0.29 (0.05, 1.70)	
During treatment plus 30 days				
MACE, n (%)	1 (0.05)	2 (0.10)	2 (0.10)	4 (0.20)
Hazard Ratio (95% CI) vs placebo	0.29 (0.05, 1.70)	0.51 (0.10, 2.51)	0.50 (0.10, 2.48)	
Through end of study				
MACE, n (%)	3 (0.15)	9 (0.45)	6 (0.30)	8 (0.40)
Hazard Ratio (95% CI) vs placebo	0.39 (0.12, 1.27)	1.09 (0.42, 2.83)	0.75 (0.26, 2.13)	

The use of CHAMPIX, bupropion, and NRT was not associated with an increased risk of CV AEs in smokers treated for up to 12 weeks and followed for up to 1 year compared to placebo, although because of the relatively low number of events overall, an association cannot be entirely ruled out.

Subjects with mild-moderate chronic obstructive pulmonary disease (COPD)
The efficacy and safety of CHAMPIX (1 mg twice daily) for smoking cessation in subjects with mild-moderate COPD was demonstrated in a randomised double-blind placebo-controlled clinical trial. In this 52-week duration study, patients received treatment for 12 weeks, followed by a 40-week non-treatment follow-up phase. The primary endpoint of the study was the CO-confirmed, 4-week Continuous Quit Rate (4W CQR) from week 9 through week 12 and a key secondary endpoint was the Continuous Abstinence (CA) from Week 9 through Week 52. The safety profile of varenicline was comparable to what was reported in other trials in the general population, including pulmonary safety. The results for the 4W CQR (weeks 9 through 12) and CA rate (weeks 9 through 52) are shown in the following table:

	4W CQR	CA Wk 9-52
CHAMPIX, (n = 248)	42.3%	18.5%
Placebo, (n = 251)	8.8%	5.6%
Odds ratio (CHAMPIX vs. Placebo)	8.40 p < 0.0001	4.04 p < 0.0001

Study in subjects with a history of major depressive disorder
The efficacy of varenicline was confirmed in a randomised placebo-controlled trial of 525 subjects with a history of major depression in the past two years or under current stable treatment. The cessation rates in this population were similar to those reported in the general population. Continuous abstinence rate between weeks 9-12 was 35.9% in the varenicline treatment group versus 15.6% in the placebo group (OR 3.35 (95% CI 2.16-5.21)) and between weeks 9-52 was 20.3% versus 10.4% respectively (OR 2.36 (95% CI 1.40-3.98)). The most common adverse events (≥ 10%) in subjects taking varenicline were nausea (27.0% vs. 10.4% on placebo), headache (16.8% vs. 11.2%), abnormal dreams (11.3% vs. 8.2%), insomnia (10.9% vs. 4.8%) and irritability (10.9% vs. 8.2%). Psychiatric scales showed no differences between the varenicline and placebo groups and no overall worsening of depression, or other psychiatric symptoms, during the study in either treatment group.

Study in subjects with stable schizophrenia or schizoaffective disorder
Varenicline safety and tolerability was assessed in a double-blind study of 128 smokers with stable schizophrenia or schizoaffective disorder, on antipsychotic medication, randomised 2:1 to varenicline (1 mg twice daily) or placebo for 12 weeks with 12-week non-drug follow-up.

The most common adverse events in subjects taking varenicline were nausea (23.8% vs. 14.0% on placebo), headache (10.7% vs. 18.6% on placebo) and vomiting (10.7% vs. 9.3% on placebo). Among reported neuropsychiatric adverse events, insomnia was the only event reported in either treatment group in ≥ 5% of subjects at a rate higher in the varenicline group than in placebo (9.5% vs. 4.7%).

Overall, there was no worsening of schizophrenia in either treatment group as measured by psychiatric scales and there were no overall changes in extra-pyramidal signs. In the varenicline group compared to placebo, a higher proportion of subjects reported suicidal ideation or behaviour prior to enrolment (lifetime history) and after the end of active treatment period (on Days 33 to 85 after the last dose of treatment). During the active treatment period, the incidence of suicide-related events was similar between the varenicline-treated and the placebo-treated subjects (11 vs. 9.3%, respectively). The percentage of subjects with suicide-related events in the active treatment phase compared to post-treatment phase was unchanged in the varenicline group; in the placebo group, this percentage was lower in the post-treatment phase. Although there were no completed suicides, there was one suicidal attempt in a varenicline-treated subject whose lifetime history included several similar attempts. The limited data available from this single smoking cessation study are not sufficient to allow for definitive conclusions to be drawn about the safety in patients with schizophrenia or schizoaffective disorder.

Neuropsychiatric Safety Study in Subjects with and without a History of Psychiatric Disorder:
Varenicline was evaluated in a randomised, double-blind, active and placebo-controlled study that included subjects with a history of psychiatric disorder (psychiatric cohort, N=4074) and subjects without a history of psychiatric disorder (non-psychiatric cohort, N=3984). Subjects aged 18-75 years, smoking 10 or more cigarettes per day were randomised 1:1:1:1 to varenicline 1 mg BID, bupropion SR 150 mg BID, nicotine replacement therapy patch (NRT) 21 mg/day with taper or placebo for a treatment period of 12 weeks; they were then followed for another 12 weeks post-treatment.

The primary safety endpoint was a composite of the following neuropsychiatric (NPS) adverse events: severe events of anxiety, depression, feeling abnormal, or hostility, and/or moderate or severe events of agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behaviour or completed suicide.

The following table shows the rates of the composite NPS adverse event primary endpoint by treatment group and the risk differences (RDs) (95% CI) vs placebo in the **non-psychiatric cohort**.

In addition, the table shows the subset of the composite NPS AE endpoint of severe intensity:

	Non-psychiatric Cohort N=3984			
	Varenicline	**Bupropion**	**NRT**	**Placebo**
Number of Patients Treated	990	989	1006	999
Composite NPS AE Primary Endpoint, n (%)	13 (1.3)	22 (2.2)	25 (2.5)	24 (2.4)
RD (95% CI) vs Placebo	-1.28 (-2.40, -0.15)	-0.08 (-1.37, 1.21)	-0.21 (-1.54,1.12)	
Composite NPS AE Endpoint of severe intensity n (%)	1 (0.1)	4 (0.4)	3 (0.3)	5 (0.5)

AE, adverse event; NRT=Nicotine replacement therapy patch

The rates of events in the composite endpoint were low across all treatment groups and were similar or lower for each of the active treatments compared to placebo. The use of varenicline, bupropion and NRT in the non-psychiatric cohort was not associated with a significantly increased risk of NPS adverse events in the composite primary endpoint compared with placebo (95% CIs were lower than or included zero).

The percentage of subjects with suicidal ideation and/or behaviour based on the Columbia-Suicide Severity Rating Scale (C-SSRS) was similar between the varenicline and placebo groups during treatment and in the non- treatment follow-up, as shown in the following table:

	Non-psychiatric Cohort N=3984			
	Varenicline N=990 n (%)	**Bupropion N=989 n (%)**	**NRT N=1006 n (%)**	**Placebo N=999 n (%)**
During treatment				
Number assessed	988	983	996	995
Suicidal behaviour and/or ideation	7 (0.7)	4 (0.4)	3 (0.3)	7 (0.7)
Suicidal behaviour	0	0	1 (0.1)	1 (0.1)
Suicidal ideation	7 (0.7)	4 (0.4)	3 (0.3)	6 (0.6)
During follow up				
Number assessed	807	816	800	805
Suicidal behaviour and/or ideation	3 (0.4)	2 (0.2)	3 (0.4)	4 (0.5)
Suicidal behaviour	0	1 (0.1)	0	0
Suicidal ideation	3 (0.4)	2 (0.2)	3 (0.4)	4 (0.5)

NRT=Nicotine replacement therapy patch

There was one completed suicide, which occurred during treatment in a subject treated with placebo in the non-psychiatric cohort.

The following table shows the rates of the composite NPS adverse event primary endpoint by treatment group and the RDs (95% CI) vs placebo in the **psychiatric cohort**. The individual components of the endpoint are also shown.

In addition, the table shows the subset of the composite NPS AE endpoint of severe intensity:

	Psychiatric Cohort N=4074			
	Varenicline	**Bupropion**	**NRT**	**Placebo**
Number of Patients Treated	1026	1017	1016	1015
Composite NPS AE Primary Endpoint, n (%)	67 (6.5)	68 (6.7)	53 (5.2)	50 (4.9)
RD (95% CI) vs Placebo	1.59 (-0.42, 3.59)	1.78 (-0.24, 3.81)	0.37 (-1.53, 2.26)	
NPS AE Primary Endpoint Components n (%):				
Anxiety[a]	5 (0.5)	4 (0.4)	6 (0.6)	2 (0.2)
Depression[a]	6 (0.6)	4 (0.4)	7 (0.7)	6 (0.6)
Feeling abnormal[a]	0	1 (0.1)	0	0
Hostility[a]	0	0	0	0
Agitation[b]	25 (2.4)	29 (2.9)	21 (2.1)	22 (2.2)
Aggression[b]	14 (1.4)	9 (0.9)	7 (0.7)	8 (0.8)
Delusions[b]	1 (0.1)	1 (0.1)	1 (0.1)	0
Hallucinations[b]	5 (0.5)	4 (0.4)	2 (0.2)	2 (0.2)
Homicidal ideation[b]	0	0	0	0
Mania[b]	7 (0.7)	9 (0.9)	3 (0.3)	6 (0.6)
Panic[b]	7 (0.7)	16 (1.6)	13 (1.3)	7 (0.7)
Paranoia[b]	1 (0.1)	0	0	2 (0.2)
Psychosis[b]	4 (0.4)	2 (0.2)	3 (0.3)	1 (0.1)
Suicidal behaviour[b]	1 (0.1)	1 (0.1)	0	1 (0.1)
Suicidal ideation[b]	5 (0.5)	2 (0.2)	3 (0.3)	2 (0.2)
Completed suicide[b]	0	0	0	0
Composite NPS AE Endpoint of severe intensity n (%)	14 (1.4)	14 (1.4)	14 (1.4)	13 (1.3)

AE, adverse event; [a]Grade = severe intensity AE; [b]Grade = moderate and severe intensity AE; NRT=Nicotine replacement therapy patch

There were more events reported in patients in the psychiatric cohort in each treatment group compared with the non-psychiatric cohort, and the incidence of events in the composite endpoint was higher for each of the active treatments compared to placebo. However, the use of varenicline, bupropion and NRT in the psychiatric cohort was not associated with a significantly increased risk of NPS adverse events in the composite primary endpoint compared with placebo (95% CIs included zero).

In the psychiatric cohort, the percentage of subjects with suicidal ideation and/or behaviour based on the Columbia-Suicide Severity Rating Scale (C-SSRS) was similar between the varenicline and placebo groups during treatment and in the non- treatment follow-up, as shown in the following table:

	Psychiatric Cohort N=4074			
	Varenicline **N=1026** **n (%)**	**Bupropion** **N=1017** **n (%)**	**NRT** **N=1016** **n (%)**	**Placebo** **N=1015** **n (%)**
During treatment				
Number assessed	1017	1012	1006	1006
Suicidal behaviour and/or ideation	27 (2.7)	15 (1.5)	20 (2.0)	25 (2.5)
Suicidal behaviour	0	1 (0.1)	0	2 (0.2)
Suicidal ideation	27 (2.7)	15 (1.5)	20 (2.0)	25 (2.5)
During follow up				
Number assessed	833	836	824	791
Suicidal behaviour and/or ideation	14 (1.7)	4 (0.5)	9 (1.1)	11 (1.4)
Suicidal behaviour	1 (0.1)	0	1 (0.1)	1 (0.1)
Suicidal ideation	14 (1.7)	4 (0.5)	9 (1.1)	11 (1.4)

NRT=Nicotine replacement therapy patch

There were no completed suicides reported in the psychiatric cohort.

The most commonly reported adverse events in subjects treated with varenicline in this study were similar to those observed in premarketing studies.

In both cohorts, subjects treated with varenicline demonstrated statistical superiority of CO-confirmed abstinence during weeks 9 through 12 and 9 through 24 compared to subjects treated with bupropion, nicotine patch and placebo (please see table below).

The key efficacy results are summarised in the following table:

	Non-psychiatric Cohort	**Psychiatric Cohort**
CA 9-12 n/N (%)		
Varenicline	382/1005 (38.0%)	301/1032 (29.2%)
Bupropion	261/1001 (26.1%)	199/1033 (19.3%)
NRT	267/1013 (26.4%)	209/1025 (20.4%)
Placebo	138/1009 (13.7%)	117/1026 (11.4%)
Treatment Comparisons: Odds ratio (95% CI), p value		
Varenicline vs Placebo	4.00 (3.20, 5.00), P<0.0001	3.24 (2.56, 4.11), P<0.0001
Bupropion vs Placebo	2.26 (1.80, 2.85), P<0.0001	1.87 (1.46, 2.39), P<0.0001
NRT vs Placebo	2.30 (1.83, 2.90), P<0.0001	2.00 (1.56, 2.55), P<0.0001
Varenicline vs Bupropion	1.77 (1.46, 2.14), P<0.0001	1.74 (1.41, 2.14), P<0.0001
Varenicline vs NRT	1.74 (1.43, 2.10), P<0.0001	1.62 (1.32, 1.99), P<0.0001
CA 9-24 n/N (%)		
Varenicline	256/1005 (25.5%)	189/1032 (18.3%)
Bupropion	188/1001 (18.8%)	142/1033 (13.7%)
NRT	187/1013 (18.5%)	133/1025 (13.0%)
Placebo	106/1009 (10.5%)	85/1026 (8.3%)

Treatment Comparisons: Odds ratio (95% CI), p value		
Varenicline vs Placebo	2.99 (2.33, 3.83), P<0.0001	2.50 (1.90, 3.29), P<0.0001
Bupropion vs Placebo	2.00 (1.54, 2.59), P<0.0001	1.77 (1.33, 2.36), P<0.0001
NRT vs Placebo	1.96 (1.51, 2.54), P<0.0001	1.65 (1.24, 2.20), P=0.0007
Varenicline vs Bupropion	1.49 (1.20, 1.85), P=0.0003	1.41 (1.11, 1.79), P=0.0047
Varenicline vs NRT	1.52 (1.23, 1.89), P=0.0001	1.51 (1.19, 1.93), P=0.0008

CA = continuous abstinence rate; CI = confidence interval; NRT=Nicotine replacement therapy patch

Neuropsychiatric Safety Meta-analyses and Observational Studies:
Analyses of clinical trial data did not show evidence of an increased risk of serious neuropsychiatric events with varenicline compared to placebo. In addition, independent observational studies have not supported an increased risk of serious neuropsychiatric events in patients treated with varenicline compared to patients prescribed nicotine replacement therapy (NRT) or bupropion.

Treatment discontinuation
The treatment discontinuation rate due to adverse reactions was 11.4% for varenicline compared with 9.7% for placebo. In this group, the discontinuation rates for the most common adverse reactions in varenicline treated patients were as follows: nausea (2.7% vs. 0.6% for placebo), headache (0.6% vs. 1.0% for placebo), insomnia (1.3% vs. 1.2% for placebo), and abnormal dreams (0.2% vs. 0.2% for placebo).

Analyses of Clinical Trials:

A meta-analysis of 5 randomised, double-blind, placebo controlled trials, including 1907 patients (1130 varenicline, 777 placebo), was conducted to assess suicidal ideation and behaviour as reported on the Columbia-Suicide Severity Rating Scale (C-SSRS). This meta-analysis included one trial (N=127) in patients with a history of schizophrenia or schizoaffective disorder and another trial (N=525) in patients with a history of depression. The results showed no increase in the incidence of suicidal ideation and/or behaviour in patients treated with varenicline compared to patients treated with placebo, as shown in the table below. Of the 55 patients who reported suicidal ideation or behaviour, 48 (24 varenicline, 24 placebo) were from the two trials that enrolled patients with a history of schizophrenia/ schizoaffective disorder, or of depression. Few patients reported these events in the other three trials (4 varenicline, 3 placebo).

Number of Patients and Risk Ratio for Suicidal Ideation and/or Behaviour Reported on C-SSRS from a Meta-Analysis of 5 Clinical Trials Comparing Varenicline to Placebo:

	Varenicline (N=1130)	**Placebo** (N=777)
Patients with suicidal ideation and/or behaviour* [n (%)]**	28 (2.5)	27 (3.5)
Patient-years of exposure	325	217
Risk Ratio # (RR; 95% CI)	0.79 (0.46, 1.36)	

* Of these, one patient in each treatment arm reported suicidal behaviour

** Patients with events up to 30 days after treatment; % are not weighted by study

RR of incidence rates per 100 patient years

A meta-analysis of 18 double-blind, randomised, placebo-controlled clinical trials was conducted to assess the neuropsychiatric safety of varenicline. These trials included the 5 trials described above that used the C-SSRS, and a total of 8521 patients (5072 varenicline, 3449 placebo), some of which had psychiatric conditions. The results showed a similar incidence of combined neuropsychiatric adverse events, other than sleep disorders, in patients treated with varenicline compared to patients treated with placebo, with a risk ratio (RR) of 1.01 (95% CI: 0.89-1.15). Pooled data from these 18 trials showed a similar incidence rate of individual categories of psychiatric events in patients treated with varenicline compared to patients treated with placebo. The table below describes the most

frequently (≥ 1%) reported categories of adverse events related to psychiatric safety other than sleep disorders and disturbances.

Psychiatric Adverse Events Occurring in ≥ 1% of Patients from Pooled Data from 18 Clinical Trials:

	Varenicline (N=5072)	**Placebo** (N=3449)
Anxiety disorders and symptoms	253 (5.0)	206 (6.0)
Depressed mood disorders and disturbances	179 (3.5)	108 (3.1)
Mood disorders and disturbances NEC*	116 (2.3)	53 (1.5)

* NEC = Not Elsewhere Classified

Counts (percentages) corresponds to the number of patients reporting the event

Observational Studies

Four observational studies, each including 10,000 to 30,000 users of varenicline in the adjusted analyses, compared the risk of serious neuropsychiatric events, including neuropsychiatric hospitalizations and fatal and non-fatal self-harm, in patients treated with varenicline versus patients prescribed NRT or bupropion. All studies were retrospective cohort studies and included patients with and without a psychiatric history. All studies used statistical methods to control for confounding factors, including preferential prescribing of varenicline to healthier patients, although there is the possibility of residual confounding.

Two of the studies found no difference in risk of neuropsychiatric hospitalisations between varenicline users and nicotine patch users (Hazard Ratio [HR] 1.14; 95% Confidence Interval [CI]: 0.56–2.34 in the first study, and 0.76; 95% CI: 0.40-1.46 in the second study). The power to detect differences in these two studies was limited. The third study reported no difference in risk of psychiatric adverse events diagnosed during an emergency department visit or inpatient admission between varenicline users and bupropion users (HR 0.85; 95% CI: 0.55-1.30). Based on post marketing reports, bupropion may be associated with neuropsychiatric adverse events.

The fourth study showed no evidence of a higher risk of fatal and non-fatal self- harm (HR of 0.88; 95% CI: 0.52-1.49) in patients prescribed varenicline compared to patients prescribed NRT. The occurrence of detected suicide was rare during the three months after patients initiated any drug treatment (two cases in 31,260 varenicline users and six cases in 81,545 NRT users).

Pregnancy Cohort Study

A population-based cohort study compared infants exposed to CHAMPIX *in utero* (N=335) with infants born to mothers who smoked during pregnancy (N=78,412) and infants born to non-smoking mothers (N=806,438). In this study, infants exposed to CHAMPIX *in utero* as compared to infants born to mothers who smoked during pregnancy had lower rates of congenital malformations (3.6% vs 4.3%), stillbirth (0.3% vs 0.5%), preterm birth (7.5% vs 7.9%), small for gestational age (12.5% vs 17.1%), and premature rupture of membrane (3.6% vs 5.4%).

5.2 Pharmacokinetic properties

Absorption

Maximum plasma concentrations of varenicline occur typically within 3-4 hours after oral administration. Following administration of multiple oral doses to healthy volunteers, steady-state conditions were reached within 4 days. Absorption is virtually complete after oral administration and systemic availability is high. Oral bioavailability of varenicline is unaffected by food or time-of-day dosing.

Distribution

Varenicline distributes into tissues, including the brain. Apparent volume of distribution averaged 415 litres (%CV= 50) at steady-state. Plasma protein binding of varenicline is low (≤ 20%) and independent of both age and renal function. In rodents, varenicline is transferred through the placenta and excreted in milk.

Biotransformation

Varenicline undergoes minimal metabolism with 92% excreted unchanged in the urine and less than 10% excreted as metabolites. Minor metabolites in urine include varenicline N-carbamoylglucuronide and hydroxyvarenicline. In circulation, varenicline comprises 91% of drug-related material. Minor circulating metabolites include varenicline N-carbamoylglucuronide and N-glucosylvarenicline.

In vitro studies demonstrate that varenicline does not inhibit cytochrome P450 enzymes (IC50 > 6,400 ng/ml). The P450 enzymes tested for inhibition were: 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4/5. Also, in human hepatocytes *in vitro*, varenicline was shown to not induce the activity of cytochrome P450 enzymes 1A2 and 3A4. Therefore, varenicline is unlikely to alter the pharmacokinetics of compounds that are primarily metabolised by cytochrome P450 enzymes.

Elimination

The elimination half-life of varenicline is approximately 24 hours. Renal elimination of varenicline is primarily through glomerular filtration along with active tubular secretion via the organic cationic transporter, OCT2 (see section 4.5).

Linearity/Non linearity

Varenicline exhibits linear kinetics when given as single (0.1 to 3 mg) or repeated 1 to 3 mg/day doses.

Pharmacokinetics in special patient populations

There are no clinically meaningful differences in varenicline pharmacokinetics due to age, race, gender, smoking status, or use of concomitant medicinal products, as demonstrated in specific pharmacokinetic studies and in population pharmacokinetic analyses.

Hepatic impairment
Due to the absence of significant hepatic metabolism, varenicline pharmacokinetics should be unaffected in patients with hepatic impairment. (see section 4.2).

Renal impairment
Varenicline pharmacokinetics were unchanged in subjects with mild renal impairment (estimated creatinine clearance > 50 ml/min and ≤ 80 ml/min). In patients with moderate renal impairment (estimated creatinine clearance ≥ 30 ml/min and ≤ 50 ml/min), varenicline exposure increased 1.5-fold compared with subjects with normal renal function (estimated creatinine clearance > 80 ml/min). In subjects with severe renal impairment (estimated creatinine clearance < 30 ml/min), varenicline exposure was increased 2.1-fold. In subjects with end-stage-renal disease (ESRD), varenicline was efficiently removed by haemodialysis (see section 4.2).

Elderly
The pharmacokinetics of varenicline in elderly patients with normal renal function (aged 65-75 years) is similar to that of younger adult subjects (see section 4.2). For elderly patients with reduced renal function please refer to section 4.2.

Paediatric population
Single and multiple-dose pharmacokinetics of varenicline have been investigated in paediatric patients aged 12 to 17 years old (inclusive) and were approximately dose-proportional over the 0.5 mg to 2 mg daily dose range studied. Steady-state systemic exposure in adolescent patients of bodyweight > 55 kg, as assessed by AUC (0-24), was comparable to that noted for the same doses in the adult population. When 0.5 mg twice daily was given, steady-state daily exposure of varenicline was, on average, higher (by approximately 40%) in adolescent patients with bodyweight ≤ 55 kg compared to that noted in the adult population. Efficacy and safety has not been demonstrated in the paediatric population below 18 years of age and no recommendation on a posology can be made (see section 4.2).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, fertility and embryo-foetal development. In male rats dosed for 2 years with varenicline, there was a dose-related increase in the incidence of hibernoma (tumour of the brown fat). In the offspring of pregnant rats treated with varenicline there were decreases in fertility and increases in the auditory startle response (see section 4.6). These effects were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. Nonclinical data indicate varenicline has reinforcing properties albeit with lower potency than nicotine. In clinical studies in humans, varenicline showed low abuse potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablets' core

Cellulose, Microcrystalline
Calcium Hydrogen Phosphate Anhydrous
Croscarmellose Sodium
Silica, Colloidal Anhydrous
Magnesium Stearate

Film coating

Hypromellose
Titanium Dioxide (E171)
Macrogol 400
Indigo Carmine Aluminium Lake E132
Triacetin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Bottles: 2 years
Blisters: 3 years

6.4 Special precautions for storage

Blisters: Store below 30°C

HDPE Bottle: This medicinal product does not require any special storage conditions

6.5 Nature and contents of container

Maintenance packs

PCTFE/PVC blisters with aluminium foil backing in a pack containing 28 x 1 mg film-coated tablets in secondary heat sealed card packaging.

PCTFE/PVC blisters with aluminium foil backing in a pack containing 56 x 1 mg film-coated tablets in secondary heat sealed card packaging.

PCTFE/PVC blisters with aluminium foil backing in a pack containing 28 x 1 mg film-coated tablets in a carton.

PCTFE/PVC blisters with aluminium foil backing in a pack containing 56 x 1 mg film-coated tablets in a carton.

PCTFE/PVC blisters with aluminium foil backing in a pack containing 112 x 1 mg film-coated tablets in a carton.

PCTFE/PVC blisters with aluminium foil backing in a pack containing 140 x 1 mg film-coated tablets in a carton.

PVC blisters with aluminium foil backing in a pack containing 28 x 1 mg film-coated tablets in secondary heat sealed card packaging.

PVC blisters with aluminium foil backing in a pack containing 56 x 1 mg film-coated tablets in secondary heat sealed card packaging.

PVC blisters with aluminium foil backing in a pack containing 28 x 1 mg film-coated tablets in a carton.

PVC blisters with aluminium foil backing in a pack containing 56 x 1 mg film-coated tablets in a carton.

PVC blisters with aluminium foil backing in a pack containing 112 x 1 mg film-coated tablets in a carton.

PVC blisters with aluminium foil backing in a pack containing 140 x 1 mg film-coated tablets in a carton.

High-density polyethylene (HDPE) bottle with polypropylene child resistant closure and an aluminium foil / polyethylene induction seal containing 56 x 1 mg film-coated tablets

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/360/002
EU/1/06/360/004
EU/1/06/360/005
EU/1/06/360/009
EU/1/06/360/010
EU/1/06/360/011
EU/1/06/360/013
EU/1/06/360/015
EU/1/06/360/016
EU/1/06/360/020
EU/1/06/360/021
EU/1/06/360/022
EU/1/06/360/024

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 September 2006
Date of latest renewal: 29 June 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu/

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 0.5 mg film-coated tablets
CHAMPIX 1 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 0.5 mg film-coated tablet contains 0.5 mg of varenicline (as tartrate).
Each 1 mg film-coated tablet contains 1 mg of varenicline (as tartrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablets

0.5 mg film-coated tablets of 4mm x 8mm: White, capsular-shaped, biconvex tablets debossed with "*Pfizer*" on one side and "CHX 0.5" on the other side.

1 mg film-coated tablets of 5mm x 10mm: Light blue, capsular-shaped, biconvex tablets debossed with "*Pfizer*" on one side and "CHX 1.0" on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

CHAMPIX is indicated for smoking cessation in adults.

4.2 Posology and method of administration

Posology

The recommended dose is 1 mg varenicline twice daily following a 1-week titration as follows:

Days 1 – 3:	0.5 mg once daily
Days 4 – 7:	0.5 mg twice daily
Day 8 – End of treatment:	1 mg twice daily

The patient should set a date to stop smoking. CHAMPIX dosing should usually start at 1-2 weeks before this date (see section 5.1). Patients should be treated with CHAMPIX for 12 weeks.

For patients who have successfully stopped smoking at the end of 12 weeks, an additional course of 12 weeks treatment with CHAMPIX at 1 mg twice daily may be considered for the maintenance of abstinence (see section 5.1).

A gradual approach to quitting smoking with CHAMPIX should be considered for patients who are not able or willing to quit abruptly. Patients should reduce smoking during the first 12 weeks of treatment and quit by the end of that treatment period. Patients should then continue taking CHAMPIX for an additional 12 weeks for a total of 24 weeks of treatment (see section 5.1).

Patients who are motivated to quit and who did not succeed in stopping smoking during prior CHAMPIX therapy, or who relapsed after treatment, may benefit from another quit attempt with CHAMPIX (see section 5.1).

Patients who cannot tolerate adverse reactions of CHAMPIX may have the dose lowered temporarily or permanently to 0.5 mg twice daily.

In smoking cessation therapy, risk for relapse to smoking is elevated in the period immediately following the end of treatment. In patients with a high risk of relapse, dose tapering may be considered (see section 4.4).

Elderly
No dosage adjustment is necessary for elderly patients (see section 5.2). Because elderly patients are more likely to have decreased renal function, prescribers should consider the renal status of an elderly patient.

Renal impairment
No dosage adjustment is necessary for patients with mild (estimated creatinine clearance > 50 ml/min and ≤ 80 ml/min) to moderate (estimated creatinine clearance ≥ 30 ml/min and ≤ 50 ml/min) renal impairment.

For patients with moderate renal impairment who experience adverse reactions that are not tolerable, dosing may be reduced to 1 mg once daily.

For patients with severe renal impairment (estimated creatinine clearance < 30 ml/min), the recommended dose of CHAMPIX is 1 mg once daily. Dosing should begin at 0.5 mg once daily for the first 3 days then increased to 1 mg once daily. Based on insufficient clinical experience with CHAMPIX in patients with end stage renal disease, treatment is not recommended in this patient population (see section 5.2).

Hepatic impairment
No dosage adjustment is necessary for patients with hepatic impairment (see section 5.2).

Paediatric population
The safety and efficacy of CHAMPIX in children or adolescents below 18 years have not yet been established. Currently available data are described in section 5.2 but no recommendation on a posology can be made.

Method of administration

CHAMPIX is for oral use and the tablets should be swallowed whole with water.
CHAMPIX can be taken with or without food

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Effect of smoking cessation

Physiological changes resulting from smoking cessation, with or without treatment with CHAMPIX, may alter the pharmacokinetics or pharmacodynamics of some medicinal products, for which dosage adjustment may be necessary (examples include theophylline, warfarin and insulin). As smoking induces CYP1A2, smoking cessation may result in an increase of plasma levels of CYP1A2 substrates.

Neuropsychiatric symptoms

Changes in behaviour or thinking, anxiety, psychosis, mood swings, aggressive behaviour, depression, suicidal ideation and behaviour and suicide attempts have been reported in patients attempting to quit smoking with CHAMPIX in the post-marketing experience.

A large randomised, double-blind, active and placebo-controlled study was conducted to compare the risk of serious neuropsychiatric events in patients with and without a history of psychiatric disorder treated for smoking cessation with varenicline, bupropion, nicotine replacement therapy patch (NRT) or placebo. The primary safety endpoint was a composite of neuropsychiatric adverse events that have been reported in post-marketing experience.

The use of varenicline in patients with or without a history of psychiatric disorder was not associated with an increased risk of serious neuropsychiatric adverse events in the composite primary endpoint compared with placebo (see section 5.1 **Pharmacodynamic properties** - *Study in Subjects with and without a History of Psychiatric Disorder*).

Depressed mood, rarely including suicidal ideation and suicide attempt, may be a symptom of nicotine withdrawal.

Clinicians should be aware of the possible emergence of serious neuropsychiatric symptoms in patients attempting to quit smoking with or without treatment. If serious neuropsychiatric symptoms occur whilst on varenicline treatment, patients should discontinue varenicline immediately and contact a healthcare professional for re-evaluation of treatment.

History of psychiatric disorders

Smoking cessation, with or without pharmacotherapy, has been associated with exacerbation of underlying psychiatric illness (e.g. depression).

CHAMPIX smoking cessation studies have provided data in patients with a history of psychiatric disorders (see section 5.1).

In a smoking cessation clinical trial, neuropsychiatric adverse events were reported more frequently in patients with a history of psychiatric disorders compared to those without a history of psychiatric disorders, regardless of treatment (see section 5.1).

Care should be taken with patients with a history of psychiatric illness and patients should be advised accordingly.

Seizures

In clinical trials and post-marketing experience there have been reports of seizures in patients with or without a history of seizures, treated with CHAMPIX. CHAMPIX should be used cautiously in patients with a history of seizures or other conditions that potentially lower the seizure threshold.

Treatment discontinuation

At the end of treatment, discontinuation of CHAMPIX was associated with an increase in irritability, urge to smoke, depression, and/or insomnia in up to 3% of patients. The prescriber should inform the patient accordingly and discuss or consider the need for dose tapering.

Cardiovascular events

Patients taking CHAMPIX should be instructed to notify their doctor of new or worsening cardiovascular symptoms and to seek immediate medical attention if they experience signs and symptoms of myocardial infarction or stroke (see section 5.1).

Hypersensitivity reactions

There have been post-marketing reports of hypersensitivity reactions including angioedema in patients treated with varenicline. Clinical signs included swelling of the face, mouth (tongue, lips, and gums), neck (throat and larynx) and extremities. There were rare reports of life-threatening angioedema requiring urgent medical attention due to respiratory compromise. Patients experiencing these symptoms should discontinue treatment with varenicline and contact a health care provider immediately.

Cutaneous reactions

There have also been post-marketing reports of rare but severe cutaneous reactions, including Stevens-Johnson Syndrome and Erythema Multiforme in patients using varenicline. As these skin reactions can be life threatening, patients should discontinue treatment at the first sign of rash or skin reaction and contact a healthcare provider immediately.

4.5 Interaction with other medicinal products and other forms of interaction

Based on varenicline characteristics and clinical experience to date, CHAMPIX has no clinically meaningful drug interactions. No dosage adjustment of CHAMPIX or co-administered medicinal products listed below is recommended.

In vitro studies indicate that varenicline is unlikely to alter the pharmacokinetics of compounds that are primarily metabolised by cytochrome P450 enzymes.

Furthermore since metabolism of varenicline represents less than 10% of its clearance, active substances known to affect the cytochrome P450 system are unlikely to alter the pharmacokinetics of varenicline (see section 5.2) and therefore a dose adjustment of CHAMPIX would not be required.

In vitro studies demonstrate that varenicline does not inhibit human renal transport proteins at therapeutic concentrations. Therefore, active substances that are cleared by renal secretion (e.g., metformin - see below) are unlikely to be affected by varenicline.

Metformin

Varenicline did not affect the pharmacokinetics of metformin. Metformin had no effect on varenicline pharmacokinetics.

Cimetidine

Co-administration of cimetidine, with varenicline increased the systemic exposure of varenicline by 29% due to a reduction in varenicline renal clearance. No dosage adjustment is recommended based on concomitant cimetidine administration in subjects with normal renal function or in patients with

mild to moderate renal impairment. In patients with severe renal impairment, the concomitant use of cimetidine and varenicline should be avoided.

Digoxin

Varenicline did not alter the steady-state pharmacokinetics of digoxin.

Warfarin

Varenicline did not alter the pharmacokinetics of warfarin. Prothrombin time (INR) was not affected by varenicline. Smoking cessation itself may result in changes to warfarin pharmacokinetics (see section 4.4).

Alcohol

There are limited clinical data on any potential interaction between alcohol and varenicline. There have been post marketing reports of increased intoxicating effects of alcohol in patients treated with varenicline. A causal relationship between these events and varenicline use has not been established.

Use with other therapies for smoking cessation

Bupropion
Varenicline did not alter the steady-state pharmacokinetics of bupropion.

Nicotine replacement therapy (NRT)
When varenicline and transdermal NRT were co-administered to smokers for 12 days, there was a statistically significant decrease in average systolic blood pressure (mean 2.6 mmHg) measured on the final day of the study. In this study, the incidence of nausea, headache, vomiting, dizziness, dyspepsia, and fatigue was greater for the combination than for NRT alone.

Safety and efficacy of CHAMPIX in combination with other smoking cessation therapies have not been studied.

4.6 Fertility, pregnancy and lactation

Pregnancy

A moderate amount of data on pregnant women indicated no malformative or foetal/neonatal toxicity of varenicline (see section 5.1).

Animal studies have shown reproductive toxicity (see section 5.3). As a precautionary measure, it is preferable to avoid the use of varenicline during pregnancy (see section 5.1).

Breast-feeding

It is unknown whether varenicline is excreted in human breast milk. Animal studies suggest that varenicline is excreted in breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with CHAMPIX should be made taking into account the benefit of breast-feeding to the child and the benefit of CHAMPIX therapy to the woman.

Fertility

There are no clinical data on the effects of varenicline on fertility.

Non-clinical data revealed no hazard for humans based on standard male and female fertility studies in the rat (see section 5.3).

4.7 Effects on ability to drive and use machines

CHAMPIX may have minor or moderate influence on the ability to drive and use machines. CHAMPIX may cause dizziness, somnolence and transient loss of consciousness, and therefore may influence the ability to drive and use machines. Patients are advised not to drive, operate complex machinery or engage in other potentially hazardous activities until it is known whether this medicinal product affects their ability to perform these activities.

4.8 Undesirable effects

Summary of the safety profile

Smoking cessation with or without treatment is associated with various symptoms. For example, dysphoric or depressed mood; insomnia, irritability, frustration or anger; anxiety; difficulty concentrating; restlessness; decreased heart rate; increased appetite or weight gain have been reported in patients attempting to stop smoking. No attempt has been made in either the design or the analysis of the CHAMPIX studies to distinguish between adverse reactions associated with study drug treatment or those possibly associated with nicotine withdrawal. Adverse drug reactions are based on evaluation of data from pre-marketing phase 2-3 studies and updated based on pooled data from 18 placebo-controlled pre- and post-marketing studies, including approximately 5,000 patients treated with varenicline.

In patients treated with the recommended dose of 1 mg twice daily following an initial titration period the adverse event most commonly reported was nausea (28.6%). In the majority of cases nausea occurred early in the treatment period, was mild to moderate in severity and seldom resulted in discontinuation.

Tabulated summary of adverse reactions

In the table below all adverse reactions, which occurred at an incidence greater than placebo are listed by system organ class and frequency (very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100) and rare (≥ 1/10,000 to < 1/1,000)). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

System Organ Class	Adverse Drug Reactions
Infections and infestations	
Very common	Nasopharyngitis
Common	Bronchitis, sinusitis
Uncommon	Fungal infection, viral infection
Blood and lymphatic system disorders	
Rare	Platelet count decreased
Metabolism and nutrition disorders	
Common	Weight increased, decreased appetite, increased appetite
Uncommon	Hyperglycaemia
Rare	Diabetes mellitus, polydipsia
Psychiatric disorders	
Very common	Abnormal dreams, insomnia
Uncommon	Suicidal ideation, aggression, panic reaction, thinking abnormal, restlessness, mood swings, depression*, anxiety*, hallucinations*, libido increased, libido decreased
Rare	Psychosis, somnambulism, abnormal behaviour, dysphoria, bradyphrenia
Nervous system disorders	
Very common	Headache
Common	Somnolence, dizziness, dysgeusia

System Organ Class	Adverse Drug Reactions
Uncommon	Seizure, tremor, lethargy, hypoaesthesia
Rare	Cerebrovascular accident, hypertonia, dysarthria, coordination abnormal, hypogeusia, circadian rhythm sleep disorder
Not known	Transient loss of consciousness
Eye disorders	
Uncommon	Conjunctivitis, eye pain
Rare	Scotoma, scleral discolouration, mydriasis, photophobia, myopia, lacrimation increased
Ear and labyrinth disorders	
Uncommon	Tinnitus
Cardiac disorders	
Uncommon	Myocardial infarction, angina pectoris, tachycardia, palpitations, heart rate increased
Rare	Atrial fibrillation, electrocardiogram ST segment depression, electrocardiogram T wave amplitude decreased
Vascular disorders	
Uncommon	Blood pressure increased, hot flush
Respiratory, thoracic and mediastinal disorders	
Common	Dyspnoea, cough
Uncommon	Upper respiratory tract inflammation, respiratory tract congestion, dysphonia, rhinitis allergic, throat irritation, sinus congestion, upper-airway cough syndrome, rhinorrhoea
Rare	Laryngeal pain, snoring
Gastrointestinal disorders	
Very common	Nausea
Common	Gastrooesophageal reflux disease, vomiting, constipation, diarrhoea, abdominal distension, abdominal pain, toothache, dyspepsia, flatulence, dry mouth
Uncommon	Haematochezia, gastritis, change of bowel habit, eructation, aphthous stomatitis, gingival pain
Rare	Haematemesis, abnormal faeces, tongue coated
Skin and subcutaneous tissue disorders	
Common	Rash, pruritus
Uncommon	Erythema, acne, hyperhidrosis, night sweats
Rare	Severe cutaneous reactions, including Stevens Johnson Syndrome and Erythema Multiforme, angioedema
Musculoskeletal and connective tissue disorders	
Common	Arthralgia, myalgia, back pain
Uncommon	Muscle spasms, musculoskeletal chest pain
Rare	Joint stiffness, costochondritis
Renal and urinary disorders	
Uncommon	Pollakiuria, nocturia
Rare	Glycosuria, polyuria
Reproductive system and breast disorders	
Uncommon	Menorrhagia
Rare	Vaginal discharge, sexual dysfunction
General disorders and administration site conditions	
Common	Chest pain, fatigue
Uncommon	Chest discomfort, influenza like illness, pyrexia, asthenia, malaise
Rare	Feeling cold, cyst
Investigations	
Common	Liver function test abnormal
Rare	Semen analysis abnormal, C-reactive protein increased, blood calcium decreased

System Organ Class	Adverse Drug Reactions
* Frequencies are estimated from a post-marketing, observational cohort study	

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

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4.9 Overdose

No cases of overdose were reported in pre-marketing clinical trials.

In case of overdose, standard supportive measures should be instituted as required.

Varenicline has been shown to be dialyzed in patients with end stage renal disease (see section 5.2), however, there is no experience in dialysis following overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other nervous system drugs; Drugs used in addictive disorders; Drugs used in nicotine dependence, ATC code: N07BA03

Mechanism of action

Varenicline binds with high affinity and selectivity at the α4β2 neuronal nicotinic acetylcholine receptors, where it acts as a partial agonist - a compound that has both agonist activity, with lower intrinsic efficacy than nicotine, and antagonist activities in the presence of nicotine.

Electrophysiology studies *in vitro* and neurochemical studies in vivo have shown that varenicline binds to the α4β2 neuronal nicotinic acetylcholine receptors and stimulates receptor-mediated activity, but at a significantly lower level than nicotine. Nicotine competes for the same human α4β2 nAChR binding site for which varenicline has higher affinity. Therefore, varenicline can effectively block nicotine's ability to fully activate α4β2 receptors and the mesolimbic dopamine system, the neuronal mechanism underlying reinforcement and reward experienced upon smoking. Varenicline is highly selective and binds more potently to the α4β2 receptor subtype (Ki=0.15 nM) than to other common nicotinic receptors (α3β4 Ki=84 nM, α7 Ki= 620 nM, α1βγδ Ki= 3,400 nM), or to non-nicotinic receptors and transporters (Ki > 1μM, except to 5-HT3 receptors: Ki=350 nM).

Pharmacodynamic effects

The efficacy of CHAMPIX in smoking cessation is a result of varenicline's partial agonist activity at the α4β2 nicotinic receptor where its binding produces an effect sufficient to alleviate symptoms of craving and withdrawal (agonist activity), while simultaneously resulting in a reduction of the rewarding and reinforcing effects of smoking by preventing nicotine binding to α4β2 receptors (antagonist activity).

Clinical efficacy and safety

Smoking cessation therapies are more likely to succeed for patients who are motivated to stop smoking and who are provided with additional advice and support.

The efficacy of CHAMPIX in smoking cessation was demonstrated in 3 clinical trials involving chronic cigarette smokers (≥ 10 cigarettes per day). Two thousand six hundred nineteen (2619) patients received CHAMPIX 1 mg BID (titrated during the first week), 669 patients received bupropion 150 mg BID (also titrated) and 684 patients received placebo.

Comparative clinical studies
Two identical double-blind clinical trials prospectively compared the efficacy of CHAMPIX (1 mg twice daily), sustained release bupropion (150 mg twice daily) and placebo in smoking cessation. In these 52-week duration studies, patients received treatment for 12 weeks, followed by a 40-week non-treatment phase.

The primary endpoint of the two studies was the carbon monoxide (CO) confirmed, 4-week continuous quit rate (4W-CQR) from week 9 through week 12. The primary endpoint for CHAMPIX demonstrated statistical superiority to bupropion and placebo.

After the 40 week non-treatment phase, a key secondary endpoint for both studies was the Continuous Abstinence Rate (CA) at week 52. CA was defined as the proportion of all subjects treated who did not smoke (not even a puff of a cigarette) from Week 9 through Week 52 and did not have an exhaled CO measurement of > 10 ppm. The 4W-CQR (weeks 9 through 12) and CA rate (weeks 9 through 52) from studies 1 and 2 are included in the following table:

	Study 1 (n=1022)		Study 2 (n=1023)	
	4W CQR	CA Wk 9-52	4W CQR	CA Wk 9-52
CHAMPIX	44.4%	22.1%	44.0%	23.0%
Bupropion	29.5%	16.4%	30.0%	15.0%
Placebo	17.7%	8.4%	17.7%	10.3%
Odds ratio CHAMPIX vs. placebo	3.91 $p < 0.0001$	3.13 $p < 0.0001$	3.85 $p < 0.0001$	2.66 $p < 0.0001$
Odds ratio CHAMPIX vs. bupropion	1.96 $p < 0.0001$	1.45 $p = 0.0640$	1.89 $p < 0.0001$	1.72 $p = 0.0062$

Patient reported craving, withdrawal and reinforcing effects of smoking

Across both Studies 1 and 2 during active treatment, craving and withdrawal were significantly reduced in patients randomised to CHAMPIX in comparison with placebo. CHAMPIX also significantly reduced reinforcing effects of smoking that can perpetuate smoking behaviour in patients who smoke during treatment compared with placebo. The effect of varenicline on craving, withdrawal and reinforcing effects of smoking were not measured during the non-treatment long-term follow-up phase.

Maintenance of abstinence study

The third study assessed the benefit of an additional 12 weeks of CHAMPIX therapy on the maintenance of abstinence. Patients in this study (n=1,927) received open-label CHAMPIX 1 mg twice daily for 12 weeks. Patients who stopped smoking by Week 12 were then randomised to receive either CHAMPIX (1 mg twice daily) or placebo for an additional 12 weeks for a total study duration of 52 weeks.

The primary study endpoint was the CO-confirmed continuous abstinence rate from week 13 through week 24 in the double-blind treatment phase. A key secondary endpoint was the continuous abstinence (CA) rate for week 13 through week 52.

This study showed the benefit of an additional 12-week treatment with CHAMPIX 1 mg twice daily for the maintenance of smoking cessation compared to placebo; superiority to placebo for CA was maintained through week 52. The key results are summarised in the following table:

Continuous Abstinence Rates in Subjects Treated with Champix versus Placebo

	CHAMPIX n=602	Placebo n=604	Difference (95% CI)	Odds ratio (95% CI)
CA* wk 13-24	70.6%	49.8%	20.8% (15.4%, 26.2%)	2.47 (1.95, 3.15)
CA* wk 13-52	44.0%	37.1%	6.9% (1.4%, 12.5%)	1.35 (1.07, 1.70)

*CA: Continuous Abstinence Rate

There is currently limited clinical experience with the use of CHAMPIX among black people to determine clinical efficacy.

Flexible quit date between weeks 1 and 5
The efficacy and safety of varenicline has been evaluated in smokers who had the flexibility of quitting between weeks 1 and 5 of treatment. In this 24-week study, patients received treatment for 12 weeks followed by a 12 week non-treatment follow up phase. The 4 week (week 9-12) CQR for varenicline and placebo was 53.9% and 19.4%, respectively (difference=34.5%, 95% CI: 27.0% - 42.0%) and the CA week 9-24 was 35.2% (varenicline) vs. 12.7% (placebo) (difference=22.5%, 95% CI: 15.8% - 29.1%). Patients who are not willing or able to set the target quit date within 1-2 weeks, could be offered to start treatment and then choose their own quit date within 5 weeks.

Study in subjects re-treated with CHAMPIX
CHAMPIX was evaluated in a double-blind, placebo-controlled trial of 494 patients who had made a previous attempt to quit smoking with CHAMPIX, and either did not succeed in quitting or relapsed after treatment. Subjects who experienced an adverse event of a concern during previous treatment were excluded. Subjects were randomised 1:1 to CHAMPIX 1 mg twice daily (N=249) or placebo (N=245) for 12 weeks of treatment and followed for up to 40 weeks post-treatment. Patients included in this study had taken CHAMPIX for a smoking-cessation attempt in the past (for a total treatment duration of a minimum of two weeks), at least three months prior to study entry, and had been smoking for at least four weeks.

Patients treated with CHAMPIX had a superior rate of CO-confirmed abstinence during weeks 9 through 12 and from weeks 9 through 52 compared to subjects treated with placebo. The key results are summarised in the following table:

Continuous Abstinence Rates in Subjects Treated with Champix versus Placebo

	CHAMPIX n=249	Placebo n=245	Odds ratio (95% CI), p value
CA* wk 9-12	45.0%	11.8%	7.08 (4.34, 11.55), p<0.0001
CA* wk 9-52	20.1%	3.3%	9.00 (3.97, 20.41), p<0.0001

*CA: Continuous Abstinence

Gradual approach to quitting smoking
CHAMPIX was evaluated in a 52-week double-blind placebo-controlled study of 1,510 subjects who were not able or willing to quit smoking within four weeks, but were willing to gradually reduce their smoking over a 12 week period before quitting. Subjects were randomised to either CHAMPIX 1 mg twice daily (n=760) or placebo (n=750) for 24 weeks and followed up post-treatment through week 52. Subjects were instructed to reduce the number of cigarettes smoked by at least 50 percent by the end of the first four weeks of treatment, followed by a further 50 percent reduction from week four to week eight of treatment, with the goal of reaching complete abstinence by 12 weeks. After the initial 12-week reduction phase, subjects continued treatment for another 12 weeks. Subjects treated with CHAMPIX had a significantly higher Continuous Abstinence Rate compared with placebo; the key results are summarised in the following table:

Continuous Abstinence Rates in Subjects Treated with Champix versus Placebo

	CHAMPIX n=760	Placebo n=750	Odds ratio (95% CI), p value
CA* wk 15-24	32.1%	6.9%	8.74 (6.09, 12.53) p<0.0001
CA* wk 21-52	27.0%	9.9%	4.02 (2.94, 5.50) p<0.0001

*CA: Continuous Abstinence Rate
The CHAMPIX safety profile in this study was consistent with that of pre-marketing studies.

Subjects with cardiovascular disease
CHAMPIX was evaluated in a randomised, double-blind, placebo-controlled study of subjects with stable, cardiovascular disease (other than, or in addition to, hypertension) that had been diagnosed for more than 2 months. Subjects were randomised to CHAMPIX 1 mg twice daily (n=353) or placebo (n=350) for 12 weeks and then were followed for 40 weeks post-treatment. The 4 week CQR for varenicline and placebo was 47.3% and 14.3%, respectively and the CA week 9-52 was 19.8% (varenicline) vs. 7.4% (placebo).

Deaths and serious cardiovascular events were adjudicated by a blinded, committee. The following adjudicated events occurred with a frequency ≥ 1% in either treatment group during treatment (or in the 30-day period after treatment): nonfatal myocardial infarction (1.1% vs. 0.3% for CHAMPIX and placebo, respectively), and hospitalisation for angina pectoris (0.6% vs. 1.1%). During non-treatment follow up to 52 weeks, the adjudicated events included need for coronary revascularisation (2.0% vs. 0.6%), hospitalisation for angina pectoris (1.7% vs. 1.1%), and new diagnosis of peripheral vascular disease (PVD) or admission for a PVD procedure (1.4% vs. 0.6%). Some of the patients requiring coronary revascularisation underwent the procedure as part of management of nonfatal MI and hospitalisation for angina. Cardiovascular death occurred in 0.3% of patients in the CHAMPIX arm and 0.6% of patients in the placebo arm over the course of the 52-week study.

A meta-analysis of 15 clinical trials of ≥ 12 weeks treatment duration, including 7002 patients (4190 CHAMPIX, 2812 placebo), was conducted to systematically assess the cardiovascular safety of CHAMPIX. The study in patients with stable cardiovascular disease described above was included in the meta-analysis.

The key cardiovascular safety analysis included occurrence and timing of a composite endpoint of Major Adverse Cardiovascular Events (MACE), defined as cardiovascular death, nonfatal MI, and nonfatal stroke. These events included in the endpoint were adjudicated by a blinded, independent committee. Overall, a small number of MACE occurred during treatment in the trials included in the meta-analysis (CHAMPIX 7 [0.17%]; placebo 2 [0.07%]). Additionally, a small number of MACE occurred up to 30 days after treatment (CHAMPIX 13 [0.31%]; placebo 6 [0.21%]).

The meta-analysis showed that exposure to CHAMPIX resulted in a hazard ratio for MACE of 2.83 (95% confidence interval from 0.76 to 10.55, p=0.12) for patients during treatment and 1.95 (95% confidence interval from 0.79 to 4.82, p=0.15) for patients up to 30 days after treatment. These are equivalent to an estimated increase of 6.5 MACE events and 6.3 MACE events per 1,000 patient-years, respectively of exposure. The hazard ratio for MACE was higher in patients with cardiovascular risk factors in addition to smoking compared with that in patients without cardiovascular risk factors other than smoking. There were similar rates of all-cause mortality (CHAMPIX 6 [0.14%]; placebo 7 [0.25%]) and cardiovascular mortality (CHAMPIX 2 [0.05%]; placebo 2 [0.07%]) in the CHAMPIX arms compared with the placebo arms in the meta-analysis.

Cardiovascular safety assessment study in subjects with and without a history of psychiatric disorder
The cardiovascular (CV) safety of CHAMPIX was evaluated in the Study in Subjects with and without a History of Psychiatric Disorder (parent study; see section 5.1 - *Neuropsychiatric safety*) and its non-treatment extension, the Cardiovascular Safety Assessment Study, which enrolled 4595 of the 6293 subjects who completed the parent study (N=8058) and followed them through week 52. Of all subjects treated in the parent study, 1749 (21.7%) had a medium CV risk and 644 (8.0%) had a high CV risk, as defined by Framingham score.

The primary CV endpoint was the time to major adverse cardiovascular events (MACE), defined as cardiovascular death, non-fatal myocardial infarction or non-fatal stroke during treatment. Deaths and cardiovascular events were adjudicated by a blinded, independent committee.

The following table shows the incidence of MACE and Hazard Ratios vs placebo for all treatment groups during treatment, and cumulative for treatment plus 30 days and through end of study.

	CHAMPIX N=2016	**Bupropion N=2006**	**NRT N=2022**	**Placebo N=2014**
During treatment				
MACE, n (%)	1 (0.05)	2 (0.10)	1 (0.05)	4 (0.20)
Hazard Ratio (95% CI) vs placebo	0.29 (0.05, 1.68)	0.50 (0.10, 2.50)	0.29 (0.05, 1.70)	
During treatment plus 30 days				
MACE, n (%)	1 (0.05)	2 (0.10)	2 (0.10)	4 (0.20)
Hazard Ratio (95% CI) vs placebo	0.29 (0.05, 1.70)	0.51 (0.10, 2.51)	0.50 (0.10, 2.48)	
Through end of study				
MACE, n (%)	3 (0.15)	9 (0.45)	6 (0.30)	8 (0.40)
Hazard Ratio (95% CI) vs placebo	0.39 (0.12, 1.27)	1.09 (0.42, 2.83)	0.75 (0.26, 2.13)	

The use of CHAMPIX, bupropion, and NRT was not associated with an increased risk of CV AEs in smokers treated for up to 12 weeks and followed for up to 1 year compared to placebo, although because of the relatively low number of events overall, an association cannot be entirely ruled out.

Subjects with mild-moderate chronic obstructive pulmonary disease (COPD)
The efficacy and safety of CHAMPIX (1 mg twice daily) for smoking cessation in subjects with mild-moderate COPD was demonstrated in a randomised double-blind placebo-controlled clinical trial. In this 52-week duration study, patients received treatment for 12 weeks, followed by a 40-week non-treatment follow-up phase. The primary endpoint of the study was the CO-confirmed, 4-week Continuous Quit Rate (4W CQR) from week 9 through week 12 and a key secondary endpoint was the Continuous Abstinence (CA) from Week 9 through Week 52. The safety profile of varenicline was comparable to what was reported in other trials in the general population, including pulmonary safety.

The results for the 4W CQR (weeks 9 through 12) and CA rate (weeks 9 through 52) are shown in the following table:

	4W CQR	**CA Wk 9-52**
CHAMPIX, (n = 248)	42.3%	18.5%
Placebo, (n = 251)	8.8%	5.6%
Odds ratio (CHAMPIX vs. Placebo)	8.40 p < 0.0001	4.04 p < 0.0001

Study in subjects with a history of major depressive disorder
The efficacy of varenicline was confirmed in a randomised placebo-controlled trial in 525 subjects with a history of major depression in the past two years or under current stable treatment. The cessation rates in this population were similar to those reported in the general population. Continuous abstinence rate between weeks 9-12 was 35.9% in the varenicline treatment group versus 15.6% in the placebo group (OR 3.35 (95% CI 2.16-5.21)) and between weeks 9-52 was 20.3% versus 10.4% respectively (OR 2.36 (95% CI 1.40-3.98)). The most common adverse events (≥ 10%) in subjects taking varenicline were nausea (27.0% vs. 10.4% on placebo), headache (16.8% vs. 11.2%), abnormal dreams (11.3% vs. 8.2%), insomnia (10.9% vs. 4.8%) and irritability (10.9% vs. 8.2%). Psychiatric scales showed no differences between the varenicline and placebo groups and no overall worsening of depression, or other psychiatric symptoms, during the study in either treatment group.

Study in subjects with stable schizophrenia or schizoaffective disorder
Varenicline safety and tolerability was assessed in a double-blind study of 128 smokers with stable schizophrenia or schizoaffective disorder, on antipsychotic medication, randomised 2:1 to varenicline (1 mg twice daily) or placebo for 12 weeks with 12-week non-drug follow-up.

The most common adverse events in subjects taking varenicline were nausea (23.8% vs. 14.0% on placebo), headache (10.7% vs. 18.6% on placebo) and vomiting (10.7% vs. 9.3% on placebo). Among reported neuropsychiatric adverse events, insomnia was the only event reported in either treatment group in ≥ 5% of subjects at a rate higher in the varenicline group than in placebo (9.5% vs. 4.7%).

Overall, there was no worsening of schizophrenia in either treatment group as measured by psychiatric scales and there were no overall changes in extra-pyramidal signs. In the varenicline group compared to placebo, a higher proportion of subjects reported suicidal ideation or behaviour prior to enrolment (lifetime history) and after the end of active treatment period (on Days 33 to 85 after the last dose of treatment). During the active treatment period, the incidence of suicide-related events was similar between the varenicline-treated and the placebo-treated subjects (11 vs. 9.3%, respectively). The percentage of subjects with suicide-related events in the active treatment phase compared to post-treatment phase was unchanged in the varenicline group; in the placebo group, this percentage was lower in the post-treatment phase. Although there were no completed suicides, there was one suicidal attempt in a varenicline-treated subject whose lifetime history included several similar attempts. The limited data available from this single smoking cessation study are not sufficient to allow for definitive conclusions to be drawn about the safety in patients with schizophrenia or schizoaffective disorder.

Neuropsychiatric Safety Study in Subjects with and without a History of Psychiatric Disorder: Varenicline was evaluated in a randomised, double-blind, active and placebo-controlled study that included subjects with a history of psychiatric disorder (psychiatric cohort, N=4074) and subjects without a history of psychiatric disorder (non-psychiatric cohort, N=3984). Subjects aged 18-75 years, smoking 10 or more cigarettes per day were randomised 1:1:1:1 to varenicline 1 mg BID, bupropion SR 150 mg BID, nicotine replacement therapy patch (NRT) 21 mg/day with taper or placebo for a treatment period of 12 weeks; they were then followed for another 12 weeks post-treatment.

The primary safety endpoint was a composite of the following neuropsychiatric (NPS) adverse events: severe events of anxiety, depression, feeling abnormal, or hostility, and/or moderate or severe events of agitation, aggression, delusions, hallucinations, homicidal ideation, mania, panic, paranoia, psychosis, suicidal ideation, suicidal behaviour or completed suicide.

The following table shows the rates of the composite NPS adverse event primary endpoint by treatment group and the risk differences (RDs) (95% CI) vs placebo in the **non-psychiatric cohort**.

In addition, the table shows the subset of the composite NPS AE endpoint of severe intensity:

	Non-psychiatric Cohort N=3984			
	Varenicline	**Bupropion**	**NRT**	**Placebo**
Number of Patients Treated	990	989	1006	999
Composite NPS AE Primary Endpoint, n (%)	13 (1.3)	22 (2.2)	25 (2.5)	24 (2.4)
RD (95% CI) vs Placebo	-1.28 (-2.40, -0.15)	-0.08 (-1.37, 1.21)	-0.21 (-1.54,1.12)	
Composite NPS AE Endpoint of severe intensity n (%)	1 (0.1)	4 (0.4)	3 (0.3)	5 (0.5)

AE, adverse event; NRT=Nicotine replacement therapy patch

The rates of events in the composite endpoint were low across all treatment groups and were similar or lower for each of the active treatments compared to placebo. The use of varenicline, bupropion and NRT in the non-psychiatric cohort was not associated with a significantly increased risk of NPS adverse events in the composite primary endpoint compared with placebo (95% CIs were lower than or included zero).

The percentage of subjects with suicidal ideation and/or behaviour based on the Columbia-Suicide Severity Rating Scale (C-SSRS) was similar between the varenicline and placebo groups during treatment and in the non- treatment follow-up, as shown in the following table:

	Non-psychiatric Cohort N=3984			
	Varenicline N=990 n (%)	**Bupropion N=989 n (%)**	**NRT N=1006 n (%)**	**Placebo N=999 n (%)**
During treatment				
Number assessed	988	983	996	995
Suicidal behaviour and/or ideation	7 (0.7)	4 (0.4)	3 (0.3)	7 (0.7)
Suicidal behaviour	0	0	1 (0.1)	1 (0.1)

Suicidal ideation	7 (0.7)	4 (0.4)	3 (0.3)	6 (0.6)
During follow up				
Number assessed	807	816	800	805
Suicidal behaviour and/or ideation	3 (0.4)	2 (0.2)	3 (0.4)	4 (0.5)
Suicidal behaviour	0	1 (0.1)	0	0
Suicidal ideation	3 (0.4)	2 (0.2)	3 (0.4)	4 (0.5)

NRT=Nicotine replacement therapy patch

There was one completed suicide, which occurred during treatment in a subject treated with placebo in the non-psychiatric cohort.

The following table shows the rates of the composite NPS adverse event primary endpoint by treatment group and the RDs (95% CI) vs placebo in the **psychiatric cohort**. The individual components of the endpoint are also shown.

In addition, the table shows the subset of the composite NPS AE endpoint of severe intensity:

	Psychiatric Cohort N=4074			
	Varenicline	**Bupropion**	**NRT**	**Placebo**
Number of Patients Treated	1026	1017	1016	1015
Composite NPS AE Primary Endpoint, n (%)	67 (6.5)	68 (6.7)	53 (5.2)	50 (4.9)
RD (95% CI) vs Placebo	1.59 (-0.42, 3.59)	1.78 (-0.24, 3.81)	0.37 (-1.53, 2.26)	
NPS AE Primary Endpoint Components n (%):				
Anxiety[a]	5 (0.5)	4 (0.4)	6 (0.6)	2 (0.2)
Depression[a]	6 (0.6)	4 (0.4)	7 (0.7)	6 (0.6)
Feeling abnormal[a]	0	1 (0.1)	0	0
Hostility[a]	0	0	0	0
Agitation[b]	25 (2.4)	29 (2.9)	21 (2.1)	22 (2.2)
Aggression[b]	14 (1.4)	9 (0.9)	7 (0.7)	8 (0.8)
Delusions[b]	1 (0.1)	1 (0.1)	1 (0.1)	0
Hallucinations[b]	5 (0.5)	4 (0.4)	2 (0.2)	2 (0.2)
Homicidal ideation[b]	0	0	0	0
Mania[b]	7 (0.7)	9 (0.9)	3 (0.3)	6 (0.6)
Panic[b]	7 (0.7)	16 (1.6)	13 (1.3)	7 (0.7)
Paranoia[b]	1 (0.1)	0	0	2 (0.2)
Psychosis[b]	4 (0.4)	2 (0.2)	3 (0.3)	1 (0.1)
Suicidal behaviour[b]	1 (0.1)	1 (0.1)	0	1 (0.1)
Suicidal ideation[b]	5 (0.5)	2 (0.2)	3 (0.3)	2 (0.2)
Completed suicide[b]	0	0	0	0
Composite NPS AE Endpoint of severe intensity n (%)	14 (1.4)	14 (1.4)	14 (1.4)	13 (1.3)

AE, adverse event; [a]Grade = severe intensity AE; [b]Grade = moderate and severe intensity AE; NRT=Nicotine replacement therapy patch

There were more events reported in patients in the psychiatric cohort in each treatment group compared with the non-psychiatric cohort, and the incidence of events in the composite endpoint was higher for each of the active treatments compared to placebo. However, the use of varenicline, bupropion and NRT in the psychiatric cohort was not associated with a significantly increased risk of NPS adverse events in the composite primary endpoint compared with placebo (95% CIs included zero).

In the psychiatric cohort, the percentage of subjects with suicidal ideation and/or behaviour based on the Columbia-Suicide Severity Rating Scale (C-SSRS) was similar between the varenicline and placebo groups during treatment and in the non- treatment follow-up, as shown in the following table:

	Psychiatric Cohort N=4074			
	Varenicline **N=1026** **n (%)**	**Bupropion** **N=1017** **n (%)**	**NRT** **N=1016** **n (%)**	**Placebo** **N=1015** **n (%)**
During treatment				
Number assessed	1017	1012	1006	1006
Suicidal behaviour and/or ideation	27 (2.7)	15 (1.5)	20 (2.0)	25 (2.5)
Suicidal behaviour	0	1 (0.1)	0	2 (0.2)
Suicidal ideation	27 (2.7)	15 (1.5)	20 (2.0)	25 (2.5)
During follow up				
Number assessed	833	836	824	791
Suicidal behaviour and/or ideation	14 (1.7)	4 (0.5)	9 (1.1)	11 (1.4)
Suicidal behaviour	1 (0.1)	0	1 (0.1)	1 (0.1)
Suicidal ideation	14 (1.7)	4 (0.5)	9 (1.1)	11 (1.4)

NRT=Nicotine replacement therapy patch

There were no completed suicides reported in the psychiatric cohort.

The most commonly reported adverse events in subjects treated with varenicline in this study were similar to those observed in premarketing studies.

In both cohorts, subjects treated with varenicline demonstrated statistical superiority of CO-confirmed abstinence during weeks 9 through 12 and 9 through 24 compared to subjects treated with bupropion, nicotine patch and placebo (please see table below).

The key efficacy results are summarised in the following table:

	Non-psychiatric Cohort	Psychiatric Cohort
CA 9-12 n/N (%)		
Varenicline	382/1005 (38.0%)	301/1032 (29.2%)
Bupropion	261/1001 (26.1%)	199/1033 (19.3%)
NRT	267/1013 (26.4%)	209/1025 (20.4%)
Placebo	138/1009 (13.7%)	117/1026 (11.4%)
Treatment Comparisons: Odds ratio (95% CI), p value		
Varenicline vs Placebo	4.00 (3.20, 5.00), P<0.0001	3.24 (2.56, 4.11), P<0.0001
Bupropion vs Placebo	2.26 (1.80, 2.85), P<0.0001	1.87 (1.46, 2.39), P<0.0001
NRT vs Placebo	2.30 (1.83, 2.90), P<0.0001	2.00 (1.56, 2.55), P<0.0001
Varenicline vs Bupropion	1.77 (1.46, 2.14), P<0.0001	1.74 (1.41, 2.14), P<0.0001
Varenicline vs NRT	1.74 (1.43, 2.10), P<0.0001	1.62 (1.32, 1.99), P<0.0001
CA 9-24 n/N (%)		
Varenicline	256/1005 (25.5%)	189/1032 (18.3%)
Bupropion	188/1001 (18.8%)	142/1033 (13.7%)
NRT	187/1013 (18.5%)	133/1025 (13.0%)
Placebo	106/1009 (10.5%)	85/1026 (8.3%)
Treatment Comparisons: Odds ratio (95% CI), p value		
Varenicline vs Placebo	2.99 (2.33, 3.83), P<0.0001	2.50 (1.90, 3.29), P<0.0001
Bupropion vs Placebo	2.00 (1.54, 2.59), P<0.0001	1.77 (1.33, 2.36), P<0.0001
NRT vs Placebo	1.96 (1.51, 2.54), P<0.0001	1.65 (1.24, 2.20), P=0.0007
Varenicline vs Bupropion	1.49 (1.20, 1.85), P=0.0003	1.41 (1.11, 1.79), P=0.0047
Varenicline vs NRT	1.52 (1.23, 1.89), P=0.0001	1.51 (1.19, 1.93), P=0.0008

CA = continuous abstinence rate; CI = confidence interval; NRT=Nicotine replacement therapy patch

Neuropsychiatric Safety Meta-analyses and Observational Studies:
Analyses of clinical trial data did not show evidence of an increased risk of serious neuropsychiatric events with varenicline compared to placebo. In addition, independent observational studies have not supported an increased risk of serious neuropsychiatric events in patients treated with varenicline compared to patients prescribed nicotine replacement therapy (NRT) or bupropion.

Treatment discontinuation
The treatment discontinuation rate due to adverse reactions was 11.4% for varenicline compared with 9.7% for placebo. In this group, the discontinuation rates for the most common adverse reactions in varenicline treated patients were as follows: nausea (2.7% vs. 0.6% for placebo), headache (0.6% vs. 1.0% for placebo), insomnia (1.3% vs. 1.2% for placebo), and abnormal dreams (0.2% vs. 0.2% for placebo).

Analyses of Clinical Trials:

A meta-analysis of 5 randomised, double-blind, placebo controlled trials, including 1907 patients (1130 varenicline, 777 placebo), was conducted to assess suicidal ideation and behaviour as reported on the Columbia-Suicide Severity Rating Scale (C-SSRS). This meta-analysis included one trial (N=127) in patients with a history of schizophrenia or schizoaffective disorder and another trial (N=525) in patients with a history of depression. The results showed no increase in the incidence of suicidal ideation and/or behaviour in patients treated with varenicline compared to patients treated with placebo, as shown in the table below. Of the 55 patients who reported suicidal ideation or behaviour, 48 (24 varenicline, 24 placebo) were from the two trials that enrolled patients with a history of schizophrenia/ schizoaffective disorder, or of depression. Few patients reported these events in the other three trials (4 varenicline, 3 placebo).

Number of Patients and Risk Ratio for Suicidal Ideation and/or Behaviour Reported on C-SSRS from a Meta-Analysis of 5 Clinical Trials Comparing Varenicline to Placebo:

	Varenicline (N=1130)	**Placebo** (N=777)
Patients with suicidal ideation and/or behaviour* [n (%)]**	28 (2.5)	27 (3.5)
Patient-years of exposure	325	217
Risk Ratio # (RR; 95% CI)	0.79 (0.46, 1.36)	

* Of these, one patient in each treatment arm reported suicidal behaviour

** Patients with events up to 30 days after treatment; % are not weighted by study

RR of incidence rates per 100 patient years

A meta-analysis of 18 double-blind, randomised, placebo-controlled clinical trials was conducted to assess the neuropsychiatric safety of varenicline. These trials included the 5 trials described above that used the C-SSRS, and a total of 8521 patients (5072 varenicline, 3449 placebo), some of which had psychiatric conditions. The results showed a similar incidence of combined neuropsychiatric adverse events, other than sleep disorders, in patients treated with varenicline compared to patients treated with placebo, with a risk ratio (RR) of 1.01 (95% CI: 0.89-1.15). Pooled data from these 18 trials showed a similar incidence rate of individual categories of psychiatric events in patients treated with varenicline compared to patients treated with placebo. The table below describes the most frequently (≥ 1%) reported categories of adverse events related to psychiatric safety other than sleep disorders and disturbances.

Psychiatric Adverse Events Occurring in ≥ 1% of Patients from Pooled Data from 18 Clinical Trials:

	Varenicline (N=5072)	**Placebo** (N=3449)
Anxiety disorders and symptoms	253 (5.0)	206 (6.0)
Depressed mood disorders and disturbances	179 (3.5)	108 (3.1)
Mood disorders and disturbances NEC*	116 (2.3)	53 (1.5)

* NEC = Not Elsewhere Classified

Counts (percentages) corresponds to the number of patients reporting the event

Observational Studies

Four observational studies, each including 10,000 to 30,000 users of varenicline in the adjusted analyses, compared the risk of serious neuropsychiatric events, including neuropsychiatric hospitalizations and fatal and non-fatal self-harm, in patients treated with varenicline versus patients prescribed NRT or bupropion. All studies were retrospective cohort studies and included patients with and without a psychiatric history. All studies used statistical methods to control for confounding factors, including preferential prescribing of varenicline to healthier patients, although there is the possibility of residual confounding.

Two of the studies found no difference in risk of neuropsychiatric hospitalisations between varenicline users and nicotine patch users (Hazard Ratio [HR] 1.14; 95% Confidence Interval [CI]: 0.56–2.34 in the first study, and 0.76; 95% CI: 0.40-1.46 in the second study). The power to detect differences in these two studies was limited. The third study reported no difference in risk of psychiatric adverse events diagnosed during an emergency department visit or inpatient admission between varenicline users and bupropion users (HR 0.85; 95% CI: 0.55-1.30). Based on post marketing reports, bupropion may be associated with neuropsychiatric adverse events.

The fourth study showed no evidence of a higher risk of fatal and non-fatal self- harm (HR of 0.88; 95% CI: 0.52-1.49) in patients prescribed varenicline compared to patients prescribed NRT. The

occurrence of detected suicide was rare during the three months after patients initiated any drug treatment (two cases in 31,260 varenicline users and six cases in 81,545 NRT users).

Pregnancy Cohort Study

A population-based cohort study compared infants exposed to CHAMPIX *in utero* (N=335) with infants born to mothers who smoked during pregnancy (N=78,412) and infants born to non-smoking mothers (N=806,438). In this study, infants exposed to CHAMPIX *in utero* as compared to infants born to mothers who smoked during pregnancy had lower rates of congenital malformations (3.6% vs 4.3%), stillbirth (0.3% vs 0.5%), preterm birth (7.5% vs 7.9%), small for gestational age (12.5% vs 17.1%), and premature rupture of membrane (3.6% vs 5.4%).

5.2 Pharmacokinetic properties

Absorption

Maximum plasma concentrations of varenicline occur typically within 3-4 hours after oral administration. Following administration of multiple oral doses to healthy volunteers, steady-state conditions were reached within 4 days. Absorption is virtually complete after oral administration and systemic availability is high. Oral bioavailability of varenicline is unaffected by food or time-of-day dosing.

Distribution

Varenicline distributes into tissues, including the brain. Apparent volume of distribution averaged 415 litres (%CV= 50) at steady-state. Plasma protein binding of varenicline is low ($\leq$ 20%) and independent of both age and renal function. In rodents, varenicline is transferred through the placenta and excreted in milk.

Biotransformation

Varenicline undergoes minimal metabolism with 92% excreted unchanged in the urine and less than 10% excreted as metabolites. Minor metabolites in urine include varenicline N-carbamoylglucuronide and hydroxyvarenicline. In circulation, varenicline comprises 91% of drug-related material. Minor circulating metabolites include varenicline N-carbamoylglucuronide and N-glucosylvarenicline.

In vitro studies demonstrate that varenicline does not inhibit cytochrome P450 enzymes (IC50 > 6,400 ng/ml). The P450 enzymes tested for inhibition were: 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, and 3A4/5. Also, in human hepatocytes *in vitro*, varenicline was shown to not induce the activity of cytochrome P450 enzymes 1A2 and 3A4. Therefore, varenicline is unlikely to alter the pharmacokinetics of compounds that are primarily metabolised by cytochrome P450 enzymes.

Elimination

The elimination half-life of varenicline is approximately 24 hours. Renal elimination of varenicline is primarily through glomerular filtration along with active tubular secretion via the organic cationic transporter, OCT2 (see section 4.5).

Linearity/Non linearity

Varenicline exhibits linear kinetics when given as single (0.1 to 3 mg) or repeated 1 to 3 mg/day doses.

Pharmacokinetics in special patient populations

There are no clinically meaningful differences in varenicline pharmacokinetics due to age, race, gender, smoking status, or use of concomitant medicinal products, as demonstrated in specific pharmacokinetic studies and in population pharmacokinetic analyses.

Hepatic impairment
Due to the absence of significant hepatic metabolism, varenicline pharmacokinetics should be unaffected in patients with hepatic impairment. (see section 4.2).

Renal impairment
Varenicline pharmacokinetics were unchanged in subjects with mild renal impairment (estimated creatinine clearance > 50 ml/min and ≤ 80 ml/min). In patients with moderate renal impairment (estimated creatinine clearance ≥ 30 ml/min and ≤ 50 ml/min), varenicline exposure increased 1.5-fold compared with subjects with normal renal function (estimated creatinine clearance > 80 ml/min). In subjects with severe renal impairment (estimated creatinine clearance < 30 ml/min), varenicline exposure was increased 2.1-fold. In subjects with end-stage-renal disease (ESRD), varenicline was efficiently removed by haemodialysis (see section 4.2).

Elderly
The pharmacokinetics of varenicline in elderly patients with normal renal function (aged 65-75 years) is similar to that of younger adult subjects (see section 4.2). For elderly patients with reduced renal function please refer to section 4.2.

Paediatric population
Single and multiple-dose pharmacokinetics of varenicline have been investigated in paediatric patients aged 12 to 17 years old (inclusive) and were approximately dose-proportional over the 0.5 mg to 2 mg daily dose range studied. Steady-state systemic exposure in adolescent patients of bodyweight > 55 kg, as assessed by AUC (0-24), was comparable to that noted for the same doses in the adult population. When 0.5 mg twice daily was given, steady-state daily exposure of varenicline was, on average, higher (by approximately 40%) in adolescent patients with bodyweight ≤ 55 kg compared to that noted in the adult population. Efficacy and safety has not been demonstrated in the paediatric population below 18 years of age and no recommendation on a posology can be made (see section 4.2).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, fertility and embryo-foetal development. In male rats dosed for 2 years with varenicline, there was a dose-related increase in the incidence of hibernoma (tumour of the brown fat). In the offspring of pregnant rats treated with varenicline there were decreases in fertility and increases in the auditory startle response (see section 4.6). These effects were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use. Nonclinical data indicate varenicline has reinforcing properties albeit with lower potency than nicotine. In clinical studies in humans, varenicline showed low abuse potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablets' core

0.5 mg and 1 mg Tablets
Cellulose, Microcrystalline
Calcium Hydrogen Phosphate Anhydrous
Croscarmellose Sodium
Silica, Colloidal Anhydrous
Magnesium Stearate

Film coating

0.5 mg Tablet
Hypromellose
Titanium Dioxide (E171)
Macrogol 400
Triacetin

1 mg Tablet

Hypromellose
Titanium Dioxide (E171)
Indigo Carmine Aluminium Lake E132
Macrogol 400
Triacetin

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

Blisters: 3 years

6.4 Special precautions for storage

Store below 30°C

6.5 Nature and contents of container

Treatment initiation packs

PCTFE/PVC blisters with aluminium foil backing containing one clear blister of 11 x 0.5 mg film-coated tablets and a second clear blister of 14 x 1 mg film-coated tablets in secondary heat sealed card packaging.

PCTFE/PVC blisters with aluminium foil backing containing one clear blister of 11 x 0.5 mg film-coated tablets and a second clear blister containing 14 x 1 mg film-coated tablets in a carton.

PCTFE/PVC blisters with aluminium foil backing containing one clear blister of 11 x 0.5 mg and 14 x 1 mg film-coated tablets and a second clear blister of 28 x 1 mg film-coated tablets in secondary heat sealed card packaging.

PVC blisters with aluminium foil backing containing one clear blister of 11 x 0.5 mg film-coated tablets and a second clear blister of 14 x 1 mg film-coated tablets in secondary heat sealed card packaging.

PVC blisters with aluminium foil backing containing one clear blister of 11 x 0.5 mg film-coated tablets and a second clear blister containing 14 x 1 mg film-coated tablets in a carton.

PVC blisters with aluminium foil backing containing one clear blister of 11 x 0.5 mg and 14 x 1 mg film-coated tablets and a second clear blister of 28 x 1 mg film-coated tablets in secondary heat sealed card packaging.

One outer carton containing:

PCTFE/PVC blisters with aluminium foil backing containing one clear blister of 11 x 0.5 mg and 14 x 1 mg film-coated tablets and a second clear blister of 28 x 1 mg film-coated tablets in one secondary heat sealed card pack and PCTFE/PVC blisters with aluminium foil backing in two secondary heat sealed card packs each containing 56 x 1 mg film-coated tablets.

One outer carton containing:

PVC blisters with aluminium foil backing containing one clear blister of 11 x 0.5 mg and 14 x 1 mg film-coated tablets and a second clear blister of 28 x 1 mg film-coated tablets in one secondary heat sealed card pack and PVC blisters with aluminium foil backing in two secondary heat sealed card packs each containing 56 x 1 mg film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

Treatment initiation packs:

EU/1/06/360/003
EU/1/06/360/008
EU/1/06/360/012
EU/1/06/360/014
EU/1/06/360/019
EU/1/06/360/023
EU/1/06/360/025
EU/1/06/360/026

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 26 September 2006
Date of latest renewal: 29 June 2016

10. DATE OF REVISION OF THE TEXT

Detailed information on this product is available on the website of the European Medicines Agency http://www.ema.europa.eu/

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

R-Pharm Germany GmbH
Heinrich-Mack-Str. 35, 89257 Illertissen
Germany

Pfizer Italia S.r.l.
Località Marino del Tronto, 63100
Ascoli Piceno (AP)
Italy

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
  Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Obligation to conduct post-authorisation measures**

Not Applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Maintenance pack
Heat sealed card pack containing either 2 blister packs of 14 x 0.5 mg varenicline film-coated tablets or 2 blister packs of 28 x 0.5 mg varenicline film-coated tablets– inner and outer labelling

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 0.5 mg
Film-coated tablets
Varenicline

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 0.5 mg varenicline (as tartrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Maintenance pack containing
28 film-coated tablets
56 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use
numbers 1 to 14
numbers 1 to 28
sun as symbol
moon as symbol

Do not use if box has been opened.

Keep the package intact

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

Store below 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/360/006
EU/1/06/360/007
EU/1/06/360/017
EU/1/06/360/018

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CHAMPIX 0.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister Pack of 14 x 0.5 mg and 28 x 0.5 mg varenicline film-coated tablets, Heat Sealed Card

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 0.5 mg
Varenicline

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG (as MA Holder Logo)

3. EXPIRY DATE

EXP: MM/YYYY

4. BATCH NUMBER

Lot:

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Maintenance pack
Heat sealed card pack containing either 2 blister packs of 14 x 1 mg varenicline film-coated tablets or 2 blister packs of 28 x 1 mg varenicline film-coated tablets– inner and outer labelling

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 1 mg
Film-coated tablets
Varenicline

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 1 mg varenicline (as tartrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Maintenance pack containing
28 film-coated tablets
56 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use
Read the package leaflet before use
numbers 1 to 14
numbers 1 to 28
sun as symbol
moon as symbol

Do not use if box has been opened.

Keep the package intact

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

Store below 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/360/004
EU/1/06/360/005
EU/1/06/360/015
EU/1/06/360/016

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CHAMPIX 1 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister Pack of 14 x 1 mg and 28 x 1 mg varenicline film-coated tablets, Heat Sealed Card

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 1 mg
Varenicline

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG (as MA Holder Logo)

3. EXPIRY DATE

EXP: MM/YYYY

4. BATCH NUMBER

Lot:

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Maintenance pack
Carton Pack containing 2 blister packs of 14 x 1 mg varenicline film-coated tablets or 4 blister packs of 14 x 1 mg varenicline film-coated tablets or 8 blister packs of 14 x 1 mg varenicline film-coated tablets or 10 blister packs of 14 x 1 mg varenicline film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 1 mg
Film-coated tablets
Varenicline

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 1 mg varenicline (as tartrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

28 Film-coated tablets
56 Film-coated tablets
112 Film-coated tablets
140 Film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

Do not use if box has been opened.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

Store below 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/360/009
EU/1/06/360/010
EU/1/06/360/011
EU/1/06/360/013
EU/1/06/360/020
EU/1/06/360/021
EU/1/06/360/022
EU/1/06/360/024

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CHAMPIX 1 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister Pack of 14 x 1 mg varenicline film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 1 mg
Varenicline

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG (as MA Holder Logo)

3. EXPIRY DATE

EXP: MM/YYYY

4. BATCH NUMBER

Lot:

5. OTHER

sun as symbol
moon as symbol

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

2-week treatment initiation pack
Heat sealed card pack containing 1 blister pack of 11 x 0.5 mg varenicline film-coated tablets and 1 blister pack of 14 x 1 mg varenicline film-coated tablets – inner and outer labelling

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 0.5 mg
CHAMPIX 1 mg
Film-coated tablets
Varenicline

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 0.5 mg or 1 mg varenicline (as tartrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Initiation pack containing
Film-coated tablets
11 x 0.5 mg and 14 x 1 mg

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

Start at day 1
The day you stop smoking should usually be between day 8 and day 14.
To quit gradually, please refer to package leaflet for dosing instructions.

Week 1
Week 2

Numbers 1 to 14
sun as symbol
moon as symbol

Do not use if box has been opened.

Keep the package intact
Does not contain a tablet

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

Store below 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/360/003
EU/1/06/360/014

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CHAMPIX
0.5 mg
1 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister Pack of 11 x 0.5 mg varenicline film-coated tablets, Heat Sealed Card

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 0.5 mg
Varenicline

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG (as MA Holder Logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister Pack of 14 x 1 mg varenicline film-coated tablets, Heat Sealed Card

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 1 mg
Varenicline

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG (as MA Holder Logo)

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

Treatment initiation pack
Carton pack with 1 blister pack of 11 x 0.5 mg varenicline film-coated tablets and 1 blister pack of 14 x 1 mg varenicline film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 0.5 mg
CHAMPIX 1 mg
Film-coated tablets
Varenicline

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 0.5 mg or 1 mg varenicline (as tartrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets
11 x 0.5 mg and 14 x 1 mg

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

Do not use if box has been opened.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

Store below 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/360/008
EU/1/06/360/019

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CHAMPIX
0.5 mg
1 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister Pack of 11 x 0.5 mg varenicline film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 0.5 mg
Varenicline

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG (as MA Holder Logo)

3. EXPIRY DATE

EXP: MM/YYYY

4. BATCH NUMBER

Lot:

5. OTHER

sun as symbol
moon as symbol

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister Pack of 14 x 1 mg varenicline film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 1 mg
Varenicline

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG (as MA Holder Logo)

3. EXPIRY DATE

EXP: MM/YYYY

4. BATCH NUMBER

Lot:

5. OTHER

sun as symbol
moon as symbol

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

4-week treatment initiation pack
Heat sealed card pack containing 1 blister pack of 11 x 0.5 mg and 14 x 1 mg varenicline film-coated tablets and 1 blister pack of 28 x 1 mg varenicline film-coated tablets – inner and outer labelling

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 0.5 mg
CHAMPIX 1 mg
Film-coated tablets
Varenicline

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 0.5 mg or 1 mg varenicline (as tartrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

4-week treatment initiation pack containing:
11 x 0.5 mg film-coated tablets
and
42 x 1 mg film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

Start at Day 1
The day you stop smoking should usually be between day 8 and day 14.
To quit gradually, please refer to package leaflet for dosing instructions.

Week 1
Week 2-4

Numbers 1 to 28
sun as symbol
moon as symbol

Do not use if box has been opened.

Keep the package intact
Does not contain any tablets

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

Store below 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/360/012
EU/1/06/360/023

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CHAMPIX
0.5 mg
1 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister Pack of 11 x 0.5 mg and 14 x 1 mg varenicline film-coated tablets, Heat Sealed Card

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 0.5 mg
CHAMPIX 1 mg
Varenicline

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG (as MA Holder Logo)

3. EXPIRY DATE

EXP: MM/YYYY

4. BATCH NUMBER

Lot:

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister Pack of 28 x 1 mg varenicline film-coated tablets, Heat Sealed Card

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 1 mg
Varenicline

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG (as MA Holder Logo)

3. EXPIRY DATE

EXP: MM/YYYY

4. BATCH NUMBER

Lot:

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

12-week Treatment Initiation Pack
One Outer Carton Pack containing:
1 x heat sealed card pack containing 11 x 0.5 mg and 14 x 1 mg varenicline film-coated tablets and 1 blister pack of 28 x 1 mg varenicline film-coated tablets and 2 x heat sealed card packs each containing 2 blister packs of 28 x 1 mg varenicline film-coated tablets – outer and inner labelling.

Contains Blue Box

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 0.5 mg
CHAMPIX 1 mg
Film-coated tablets
Varenicline

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 0.5 mg or 1 mg varenicline (as tartrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

12-week Treatment Initiation Pack
containing:
11 x 0.5 mg film-coated tablets
and
154 x 1 mg film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

Start at Day 1
The day you stop smoking should usually be between day 8 and day 14.
To quit gradually, please refer to package leaflet for dosing instructions.

Do not use if box has been opened.

Keep the package intact

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

Store below 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/360/025
EU/1/06/360/026

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CHAMPIX
0.5 mg
1 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON
4-week treatment initiation pack
Heat sealed card pack containing 1 blister pack of 11 x 0.5 mg and 14 x 1 mg varenicline film-coated tablets and 1 blister pack of 28 x 1 mg varenicline film-coated tablets – inner and outer labelling.

Contains No Blue Box

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 0.5 mg
CHAMPIX 1 mg
Film-coated tablets
Varenicline

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 0.5 mg or 1 mg varenicline (as tartrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

4-week treatment initiation pack containing:
11 x 0.5 mg film-coated tablets
and
42 x 1 mg film-coated tablets

Can’t be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

Start at Day 1
The day you stop smoking should usually be between day 8 and day 14.
To quit gradually, please refer to package leaflet for dosing instructions.

Week 1
Week 2-4

Numbers 1 to 28
sun as symbol
moon as symbol

Do not use if box has been opened.

Keep the package intact
Does not contain any tablets

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

Store below 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/360/025
EU/1/06/360/026

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CHAMPIX
0.5 mg
1 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

Not Applicable

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

Not Applicable

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister Pack of 11 x 0.5 mg and 14 x 1 mg varenicline film-coated tablets, Heat Sealed Card

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 0.5 mg
CHAMPIX 1 mg
Varenicline

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG (as MA Holder Logo)

3. EXPIRY DATE

EXP: MM/YYYY

4. BATCH NUMBER

Lot:

5. OTHER

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister Pack of 28 x 1 mg varenicline film-coated tablets, Heat Sealed Card

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 1 mg
Varenicline

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG (as MA Holder Logo)

3. EXPIRY DATE

EXP: MM/YYYY

4. BATCH NUMBER

Lot:

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INTERMEDIATE CARTON
Maintenance pack
Heat sealed card pack containing 2 blister packs of 28 x 1 mg varenicline film-coated tablets– inner and outer labelling

Contains No Blue Box

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 1 mg
Film-coated tablets
Varenicline

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 1 mg varenicline (as tartrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

Maintenance pack containing
56 film-coated tablets

Can't be sold separately.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.
numbers 1 to 14
numbers 1 to 28
sun as symbol
moon as symbol

Do not use if box has been opened.

Keep the package intact

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

Store below 30°C

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/360/025
EU/1/06/360/026

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CHAMPIX 1 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

Not Applicable

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

Not Applicable

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

Blister Pack of 28 x 1 mg varenicline film-coated tablets, Heat Sealed Card

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 1 mg
Varenicline

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG (as MA Holder Logo)

3. EXPIRY DATE

EXP: MM/YYYY

4. BATCH NUMBER

Lot:

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

High-density polyethylene (HDPE) bottle packaging for 56 x 0.5 mg varenicline film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 0.5 mg
Film-coated tablets
Varenicline

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 0.5 mg varenicline (as tartrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

56 Film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/360/001

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CHAMPIX 0.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE THE IMMEDIATE PACKAGING

High-density polyethylene (HDPE) bottle label for 56 x 0.5 mg varenicline film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 0.5 mg
Film-coated tablets
Varenicline

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 0.5 mg varenicline (as tartrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

56 Film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG (as MA Holder Logo)

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/360/001

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

Not Applicable

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

Not Applicable

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

High-density polyethylene (HDPE) bottle packaging for 56 x 1 mg varenicline film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 1 mg
Film-coated tablets
Varenicline

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 1 mg varenicline (as tartrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

56 Film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/360/002

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

CHAMPIX 1 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE THE IMMEDIATE PACKAGING

High-density polyethylene (HDPE) bottle label for 56 x 1 mg varenicline film-coated tablets

1. NAME OF THE MEDICINAL PRODUCT

CHAMPIX 1 mg
Film-coated tablets
Varenicline

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 1 mg varenicline (as tartrate).

3. LIST OF EXCIPIENTS

4. PHARMACEUTICAL FORM AND CONTENTS

56 Film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Oral use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP: MM/YYYY

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Pfizer Europe MA EEIG (as MA Holder Logo)

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/06/360/002

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

Not Applicable

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

Not Applicable

B. PACKAGE LEAFLET

Package leaflet: Information for the user

CHAMPIX 0.5 mg film-coated tablets
CHAMPIX 1 mg film-coated tablets
Varenicline

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What CHAMPIX is and what it is used for
2. What you need to know before you take CHAMPIX
3. How to take CHAMPIX
4. Possible side effects
5. How to store CHAMPIX
6. Contents of the pack and other information

1. What CHAMPIX is and what it is used for

CHAMPIX contains the active substance varenicline. CHAMPIX is a medicine which is used in adults to help them stop smoking.

CHAMPIX can help to relieve the craving and withdrawal symptoms associated with stopping smoking.

CHAMPIX can also reduce the enjoyment of cigarettes if you do smoke when on treatment.

2. What you need to know before you take CHAMPIX

Do not take CHAMPIX:

- If you are allergic to varenicline or any of the other ingredients of this medicine (listed in section 6)

Warnings and precautions
Talk to your doctor or pharmacist before taking CHAMPIX.

There have been reports of depression, suicidal ideation and behaviour and suicide attempts in patients taking CHAMPIX. If you are taking CHAMPIX and develop agitation, depressed mood, changes in behaviour that are of concern to you or your family or if you develop suicidal thoughts or behaviours you should stop taking CHAMPIX and contact your doctor immediately for treatment assessment.

The effects of stopping smoking
The effects of changes in your body resulting from stopping smoking, with or without treatment with CHAMPIX, may alter the way other medicines work. Therefore, in some cases an adjustment of the dose may be necessary. See below under 'Other medicines and CHAMPIX' for further details.

For some people, stopping smoking with or without treatment has been associated with an increased risk of experiencing changes in thinking or behaviour, feelings of depression and anxiety and can be associated with a worsening of psychiatric disorder. If you have a history of psychiatric disorder you should discuss this with your doctor.

Heart symptoms
New or worse heart or blood vessel (cardiovascular) problems have been reported primarily in people who already have cardiovascular problems. Tell your doctor if you have any changes in symptoms during treatment with CHAMPIX. Get emergency medical help right away if you have symptoms of a heart attack or stroke.

Seizures
Tell your doctor if you have experienced seizures or have epilepsy before your start CHAMPIX treatment. Some people have reported seizures while taking CHAMPIX.

Hypersensitivity reactions
Stop taking CHAMPIX and tell your doctor immediately if you experience any of the following signs and symptoms that may indicate a serious allergic reaction: swelling of the face, lips, tongue, gums, throat or body and/or difficulty breathing, wheezing.

Skin reactions
Potentially life-threatening skin rashes (Stevens-Johnson syndrome and Erythema Multiforme) have been reported with the use of CHAMPIX. If you develop a rash or if your skin starts to peel or blister you should stop taking CHAMPIX and seek emergency medical help.

Children and adolescents
CHAMPIX is not recommended for use in children or adolescents below 18 years as safety and efficacy have not yet been established.

Other medicines and CHAMPIX
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

In some cases as a result of stopping smoking, with or without CHAMPIX, an adjustment of the dose of other medicines may be necessary. Examples include theophylline (a medicine to treat breathing problems), warfarin (a medicine to reduce blood clotting), and insulin (a medicine to treat diabetes). If in doubt, you should consult your doctor or pharmacist.

If you have severe kidney disease you should avoid taking cimetidine (a medicine used for gastric problems) at the same time as CHAMPIX as this may cause increased blood levels of CHAMPIX.

Use of CHAMPIX with other therapies for smoking cessation
Consult your doctor before using CHAMPIX in combination with other smoking cessation therapies.

CHAMPIX with food and drink
There have been some reports of increased intoxicating effects of alcohol in patients taking CHAMPIX. However, it is not known if CHAMPIX actually increases alcohol intoxication.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

It is preferable to avoid the use of CHAMPIX while you are pregnant. Talk to your doctor if you are intending to become pregnant.

Although it was not studied, CHAMPIX may pass into breast milk. You should ask your doctor or pharmacist for advice before taking CHAMPIX.

Driving and using machines
CHAMPIX may be linked with dizziness, sleepiness and transient loss of consciousness. You should not drive, operate complex machinery or engage in any other potentially hazardous activities until you know whether this medicine affects your ability to perform these activities.

3. How to take CHAMPIX

Always take this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

You are more likely to stop smoking if you are motivated to stop. Your doctor and pharmacist can provide advice, support and sources of further information to help ensure your attempt to stop smoking is successful.

Before starting your course of CHAMPIX you should usually decide on a date in the second week of treatment (between day 8 and day 14) when you will stop smoking. If you are not willing or able to set a target quit date within 2 weeks, you may choose your own target quit date within 5 weeks after starting treatment. You should write this date on the pack as a reminder.

CHAMPIX comes as a white tablet (0.5 mg) and a light blue tablet (1 mg). You start with the white tablet and then usually go to the light blue tablet. See the chart below for the usual dosing instructions which you should follow from Day 1.

Week 1	**Dose**
Day 1 - 3	From day 1 to day 3, you should take one white CHAMPIX 0.5 mg film-coated tablet once a day.
Day 4 - 7	From day 4 to day 7, you should take one white CHAMPIX 0.5 mg film-coated tablet twice daily, once in the morning and once in the evening, at about the same time each day.

Week 2	
Day 8 – 14	From day 8 to day 14, you should take one light blue CHAMPIX 1 mg film-coated tablet twice daily, once in the morning and once in the evening, at about the same time each day.

Weeks 3 - 12	
Day 15 - end of treatment	From day 15 until the end of treatment, you should take one light blue CHAMPIX 1 mg film-coated tablet twice daily, once in the morning and once in the evening, at about the same time each day.

After 12 weeks of treatment, if you have stopped smoking, your doctor may recommend an additional 12 weeks of treatment with CHAMPIX 1 mg film-coated tablets twice daily to help avoid returning back to smoking.

If you are not able or willing to quit smoking straight away, you should reduce smoking during the first 12 weeks of treatment and quit by the end of that treatment period. You should then continue to

take CHAMPIX 1 mg film-coated tablets twice daily for a further 12 weeks resulting in a total of 24 weeks of treatment.

Should you experience adverse effects that you cannot tolerate your doctor may decide to reduce your dose temporarily or permanently to 0.5 mg twice daily.

If you have problems with your kidneys, you should speak to your doctor before taking CHAMPIX. You may need a lower dose.

Champix is for oral use.
The tablets should be swallowed whole with water and can be taken with or without food.

If you take more CHAMPIX than you should
If you accidentally take more CHAMPIX than your doctor prescribed, you must seek medical advice or go to the nearest hospital casualty department immediately. Take your box of tablets with you.

If you forget to take CHAMPIX
Do not take a double dose to make up for a forgotten tablet. It is important that you take CHAMPIX regularly at the same time each day. If you forget to take a dose, take it as soon as you remember. If, it is within 3-4 hours before your next dose, do not take the tablet that you have missed.

If you stop taking CHAMPIX
It has been shown in clinical trials that taking all doses of your medicine at the appropriate times and for the recommended duration of treatment described above will increase your chances of stopping smoking. Therefore, unless your doctor instructs you to stop treatment, it is important to keep taking CHAMPIX, according to the instructions described in the table above.

In smoking cessation therapy, risk of returning to smoking may be elevated in the period immediately following the end of treatment. You may temporarily experience increased irritability, urge to smoke, depression and/or sleep disturbances when you stop taking CHAMPIX. Your doctor may decide to gradually lower your dose of CHAMPIX at the end of treatment.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Giving up smoking with or without treatment can cause various symptoms. These could include changes of mood (like feeling depressed, irritable, frustrated or anxious), sleeplessness, difficulty concentrating, decreased heart rate and increased appetite or weight gain.

You should be aware of the possible emergence of serious neuropsychiatric symptoms, such as agitation, depressed mood, or changes in behaviour during a quit attempt with or without CHAMPIX and you should contact a doctor or pharmacist if you experience such symptoms.

Serious side effects of either an uncommon or rare frequency have occurred in people attempting to quit smoking with CHAMPIX: seizure, stroke, heart attack, suicidal thoughts, loss of contact with reality and unable to think or judge clearly (psychosis), changes in thinking or behaviour (such as aggression and abnormal behaviour). There have also been reports of severe skin reactions including Erythema Multiforme (a type of rash) and Stevens-Johnson Syndrome (a serious illness with blistering of the skin, mouth, around the eyes or genitals) and serious allergic reactions including angioedema (swelling of the face, mouth, or throat).

- Very common: may affect more than 1 in 10 people

    - Inflammation of the nose and throat, abnormal dreams, difficulty sleeping, headache,
    - Nausea

- Common: may affect up to 1 in 10 people

    - Chest infection, inflammation of the sinuses
    - Increased weight, decreased appetite, increased appetite
    - Sleepiness, dizziness, changes in the way things taste
    - Shortness of breath, cough
    - Heartburn, vomiting, constipation, diarrhoea, feeling bloated, abdominal pain, toothache, indigestion, flatulence, dry mouth
    - Skin rash, itching
    - Joint ache, muscle ache, back pain
    - Chest pain, tiredness

- Uncommon: may affect up to 1 in 100 people

    - Fungal infection, viral infection
    - Feeling of panic, difficulty thinking, restlessness, mood swings, depression, anxiety, hallucinations, changes in sex drive
    - Seizure, tremor, feeling sluggish, less sensitive to touch
    - Conjunctivitis, eye pain
    - Ringing in the ears
    - Angina, rapid heart rate, palpitations, increased heart rate
    - Increased blood pressure, hot flush
    - Inflammation of nose, sinuses and throat, congestion of nose, throat and chest, hoarseness, hay fever, throat irritation, congested sinuses, excess mucous from nose causing cough, runny nose
    - Red blood in stools, irritated stomach, change of bowel habit, belching, mouth ulcers, pain in the gums
    - Reddening of the skin, acne, increased sweating, night sweats
    - Muscle spasms, chest wall pain
    - Abnormally frequent urination, urination at night
    - Increased menstrual flow
    - Chest discomfort, flu like illness, fever, feeling weak or unwell
    - High blood sugar
    - Heart attack
    - Suicidal thoughts
    - Changes in thinking or behaviour (such as aggression)

- Rare: may affect up to 1 in 1,000 people

    - Excessive thirst
    - Feeling unwell or unhappy, slow thinking
    - Stroke
    - Increased muscle tension, difficulty with speech, difficulty with coordination, reduced sense of taste, altered sleep pattern
    - Disturbed vision, eyeball discolouration, dilated pupils, sensitivity to light, shortsightedness, watery eyes
    - Irregular heart beat or heart rhythm disturbances
    - Throat pain, snoring
    - Blood in vomit, abnormal stools, coated tongue
    - Stiff joints, rib pain
    - Glucose in urine, increased urine volume and frequency

- Vaginal discharge, changes in sexual ability
- Feeling cold, cyst
- Diabetes
- Sleep walking
- Loss of contact with reality and unable to think or judge clearly (psychosis)
- Abnormal behaviour
- Severe skin reactions including Erythema Multiforme (a type of rash) and Stevens-Johnson Syndrome (a serious illness with blistering of the skin, mouth, around the eyes or genitals)
- Serious allergic reactions including angioedema (swelling of the face, mouth, or throat)

- Not known

  - Transient loss of consciousness

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store CHAMPIX

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the card packaging or carton after EXP. The expiry date refers to the last day of that month.

Blisters: Store below 30°C
Bottle: This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What CHAMPIX contains
- The active substance is varenicline.
- Each 0.5 mg film-coated tablet contains 0.5 mg of varenicline (as tartrate).
- Each 1 mg film-coated tablet contains 1 mg of varenicline (as tartrate).
- The other ingredients are:

Tablet Core - CHAMPIX 0.5 mg and 1 mg film-coated tablets
Cellulose, Microcrystalline Calcium Hydrogen Phosphate Anhydrous Croscarmellose Sodium Silica, Colloidal Anhydrous Magnesium Stearate

Tablet film coating - CHAMPIX 0.5 mg film-coated tablets
Hypromellose Titanium dioxide (E171) Macrogol 400

Triacetin

Tablet film coating - CHAMPIX 1 mg film-coated tablets
Hypromellose Titanium dioxide (E171) Macrogol 400 Indigo Carmine Aluminium Lake (E132) Triacetin

What CHAMPIX looks like and contents of the pack

- CHAMPIX 0.5 mg film-coated tablets are white, film-coated, modified capsular shaped tablets, marked "*Pfizer*" and "CHX 0.5"

- CHAMPIX 1 mg film-coated tablets are light blue film-coated, modified capsular shaped tablets, marked "*Pfizer*" and "CHX 1.0"

CHAMPIX is available in the following pack presentations:

- A treatment initiation pack containing 2 blisters; 1 clear blister of 11 x CHAMPIX 0.5 mg film-coated tablets and 1 clear blister of 14 x CHAMPIX 1 mg film-coated tablets in card packaging.
- A treatment initiation pack containing 2 blisters; 1 clear blister of 11 x CHAMPIX 0.5 mg and 14 x 1 mg film-coated tablets and 1 clear blister of 28 x CHAMPIX 1 mg film-coated tablets in card packaging.
- A treatment initiation pack in an outer carton containing one pack with 1 clear blister of 11 x CHAMPIX 0.5 mg and 14 x 1 mg film-coated tablets and 1 clear blister of 28 x CHAMPIX 1 mg film-coated tablets in card packaging and two packs each containing 2 clear blisters of 28 x CHAMPIX 1 mg film-coated tablets in card packaging.
- A follow-on (maintenance) pack containing 2 clear blisters of 14 x CHAMPIX 1 mg film-coated tablets in card packaging.
- A follow-on (maintenance) pack containing 2 clear blisters of 28 x CHAMPIX 1 mg film-coated tablets in card packaging.
- A follow-on (maintenance) pack containing 2 clear blisters of 14 x CHAMPIX 0.5 mg film-coated tablets in card packaging.
- A follow-on (maintenance) pack containing 2 clear blisters of 28 x CHAMPIX 0.5 mg film-coated tablets in card packaging.
- A treatment initiation pack containing 2 blisters; 1 clear blister of 11 x CHAMPIX 0.5 mg film-coated tablets and 1 clear blister of 14 x CHAMPIX 1 mg film-coated tablets in a carton.
- A follow-on (maintenance) pack containing 2 clear blisters of 14 x CHAMPIX 1 mg film-coated tablets in a carton.
- A follow-on (maintenance) pack containing 4 clear blisters of 14 x CHAMPIX 1 mg film-coated tablets in a carton.
- A follow-on (maintenance) pack containing 8 clear blisters of 14 x CHAMPIX 1 mg film-coated tablets in a carton.
- A follow-on (maintenance) pack containing 10 clear blisters of 14 x CHAMPIX 1 mg film-coated tablets in a carton.
- A sealed white HDPE bottle pack, with a child resistant screw cap, in a carton, containing 56 x CHAMPIX 1 mg film-coated tablets.
- A sealed white HDPE bottle pack, with a child resistant screw cap, in a carton, containing 56 x CHAMPIX 0.5 mg film-coated tablets.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Pfizer Europe MA EEIG
Boulevard de la Plaine 17
1050 Bruxelles
Belgium

Manufacturer
R-Pharm Germany GmbH
Heinrich-Mack-Str. 35, 89257 Illertissen
Germany

or

Pfizer Italia S.r.l.
Località Marino del Tronto, 63100
Ascoli Piceno (AP)
Italy

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

België/Belgique/Belgien
Pfizer S.A./N.V.
Tél/Tel: + 32 (0)2 554 62 11

Lietuva
Pfizer Luxembourg SARL filialas Lietuvoje
Tel. +3705 2514000

България
Пфайзер Люксембург САРЛ,
Клон България
Тел.: +359 2 970 4333

Luxembourg/Luxemburg
Pfizer S.A.
Tél/Tel: + 32 (0)2 554 62 11

Česká republika
Pfizer PFE, spol. s r.o.
Tel: + 420 283 004 111

Magyarország
Pfizer Kft.
Tel.: +36 1 488 37 00

Danmark
Pfizer ApS
Tlf: + 45 44 20 11 00

Malta
V.J. Salomone Pharma Ltd.
Tel : +356 21220174

Deutschland
Pfizer Pharma GmbH
Tel: +49 (0)30 550055-51000

Nederland
Pfizer bv
Tel: +31 (0)10 406 43 01

Eesti
Pfizer Luxembourg SARL Eesti filiaal
Tel: +372 666 7500

Norge
Pfizer Norge AS
Tlf: +47 67 52 61 00

Ελλάδα
PFIZER ΕΛΛΑΣ Α.Ε.,
Τηλ.: +30 210 67 85 800

Österreich
Pfizer Corporation Austria Ges.m.b.H.
Tel.: +43 (0)1 521 15-0

España
Pfizer, S.L.
Tel: + 34 91 490 99 00

Polska
Pfizer Polska Sp. z o.o.
Tel.: + 48 22 335 61 00

France
Pfizer
Tél: + 33 (0)1 58 07 34 40

Hrvatska
Pfizer Croatia d.o.o.
Tel: + 385 1 3908 777

Ireland
Pfizer Healthcare Ireland

Tel: 1800 633 363 (toll free)
+44 (0) 1304 616161

Ísland
Icepharma hf.
Simi: +354 540 8000

Italia
Pfizer S.r.l.
Tel: +39 06 33 18 21

Κύπρος
PFIZER ΕΛΛΑΣ A.E. (CYPRUS BRANCH),
Τηλ: +357 22 817690

Latvija
Pfizer Luxembourg SARL filiāle Latvijā
Tel: + 371 670 35 775

Portugal
Pfizer Biofarmacêutica, Sociedade Unipessoal Lda
Tel: +351 21 423 5500

România
Pfizer România S.R.L.
Tel: +40 (0)21 207 28 00

Slovenija
Pfizer Luxembourg SARL, Pfizer, podružnica za svetovanje s področja farmacevtske dejavnosti, Ljubljana
Tel: + 386 (0) 1 52 11 400

Slovenská republika
Pfizer Luxembourg SARL, organizačná zložka
Tel: +421-2-3355 5500

Suomi/Finland
Pfizer Oy
Puh/Tel: + 358 (0)9 43 00 40

Sverige
Pfizer Innovations AB
Tel: + 46 (0)8 550 520 00

United Kingdom
Pfizer Limited
Tel: + 44 (0) 1304 616161

This leaflet was last revised in

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu/

EMA/163166/2014
EMEA/H/C/00699

EPAR summary for the public

Champix

varenicline

This is a summary of the European public assessment report (EPAR) for Champix. It explains how the Committee for Medicinal Products for Human Use (CHMP) assessed the medicine to reach its opinion in favour of granting a marketing authorisation and its recommendations on the conditions of use for Champix.

What is Champix?

Champix is a medicine that contains the active substance varenicline. It is available as tablets (0.5 and 1 mg).

What is Champix used for?

Champix is used in adults to help them stop smoking.

The medicine can only be obtained with a prescription.

How is Champix used?

Treatment with Champix is more likely to succeed in smokers who are motivated to stop smoking and who are also receiving additional advice and support. Patients set themselves a target date for quitting and will usually start taking Champix one to two weeks before this date. Patients who are unwilling or unable to set a target date within one to two weeks could be offered the treatment first and then later choose their target date to fall within five weeks of starting treatment.

Treatment with Champix lasts for 12 weeks. The tablets are swallowed whole with water. In the first week the patient takes one 0.5 mg tablet once a day for three days, followed by one 0.5 mg tablet twice a day for four days. For the remaining 11 weeks of treatment, the patient takes one 1 mg tablet twice a day. Reduced doses may be used in patients who do not tolerate the medicine or who have kidney problems.

For patients who have successfully stopped smoking after 12 weeks of treatment, doctors may choose to carry on treatment for another 12 weeks.

How does Champix work?

People who smoke become addicted to nicotine, a chemical in tobacco. Nicotine acts in the nervous system, where it binds to receptors and triggers the release of a chemical messenger, dopamine, which plays a part in the pleasure derived from smoking.

The active substance in Champix, varenicline, can bind to some of these receptors, the α4β2 nicotinic acetylcholine receptors. When binding to these receptors, varenicline acts in two ways: it acts like nicotine (partial agonist) and this helps to relieve craving symptoms, but it also acts against nicotine (antagonist), by taking its place, and this helps to reduce the pleasurable effects of smoking.

How has Champix been studied?

In two main studies 2,052 smokers received 12-week treatment with Champix, bupropion (another non-nicotine medicine) or placebo (a dummy treatment). The patients' target date for quitting was set at one week after starting treatment and the patients were followed up for a further 40 weeks after their treatment to see if they started smoking again. The main measure of effectiveness was the number of patients who had completely stopped smoking for four weeks (between week 9 and week 12 of the study), confirmed by laboratory testing of the patients' breath for signs of smoking.

Another study compared Champix with placebo in patients who were allowed to choose their own target dates for quitting, which could be between one week and five weeks of starting treatment.

What benefit has Champix shown during the studies?

In both studies, Champix was more effective than bupropion or placebo in helping patients to stop smoking. The percentage of patients who had not smoked at all during weeks 9-12 was 44% with Champix, 30% with bupropion, and 18% with placebo. More patients remained non-smokers after treatment with Champix than after placebo: 40 weeks after the end of the treatment period, the percentage of patients who were still non-smokers was 23% among those who had taken Champix, and 9% among those who had taken a placebo. The percentage in the patients who had taken bupropion was 16%.

In the study where patients were allowed to set their own target dates, Champix was also shown to be effective in helping patients to quit.

What is the risk associated with Champix?

The most common side-effects with Champix (seen in more than 1 patient in 10) are nausea (feeling sick), insomnia (difficulty sleeping), abnormal dreams, headache and nasopharyngitis (inflammation of the nose and throat). For the full list of all side effects and restrictions with Champix, see the package leaflet.

Why has Champix been approved?

The CHMP concluded that the benefits of Champix outweigh its risks and recommended that it be given marketing authorisation.

What measures are being taken to ensure the safe and effective use of Champix?

A risk management plan has been developed to ensure that Champix is used as safely as possible. Based on this plan, safety information has been included in the summary of product characteristics and the package leaflet for Champix, including the appropriate precautions to be followed by healthcare professionals and patients.

Other information about Champix

The European Commission granted a marketing authorisation valid throughout the European Union for Champix on 26 September 2006.

The full EPAR for Champix can be found on the Agency's website ema.europa.eu/Find medicine/Human medicines/European Public Assessment Reports. For more information about treatment with Champix, read the package leaflet (also part of the EPAR) or contact your doctor or pharmacist.

This summary was last updated in 03-2014.

Champix

ema.europa.eu/en/medicines/human/EPAR/champix

September 17, 2018

varenicline

Authorised

This medicine is authorised for use in the European Union.

Overview

List item

Champix : EPAR - Summary for the public
(PDF/86.46 KB)

More detail is available in the summary of product characteristics

This EPAR was last updated on 12/11/2018

Authorisation details

Name	Champix
Agency product number	EMEA/H/C/000699
Active substance	varenicline
International non-proprietary name (INN) or common name	varenicline
Therapeutic area (MeSH)	Tobacco Use Cessation
Anatomical therapeutic chemical (ATC) code	N07BA03
Marketing-authorisation holder	Pfizer Europe MA EEIG
Revision	33
Date of issue of marketing authorisation valid throughout the European Union	25/09/2006

Contact address

Boulevard de la Plaine
17
1050 Bruxelles
Belgium

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Electronic Cigarette Use and Smoking Initiation in Taiwan: Evidence from the First Prospective Study in Asia

Yu-Ning Chien [1,2], Wayne Gao [3], Mattia Sanna [3], Ping-Ling Chen [4], Yi-Hua Chen [2], Stanton Glantz [5] and Hung-Yi Chiou [2,*]

1 Chung-Hua Institution for Economic Research, Taipei 106, Taiwan; chienyuning@cier.edu.tw
2 College of Public Health, Taipei Medical University, Taipei 110, Taiwan; yichen@tmu.edu.tw
3 Master's Program in Global Health and Development, Taipei Medical University, Taipei 110, Taiwan; waynegao@tmu.edu.tw (W.G.); msanna@tmu.edu.tw (M.S.)
4 Graduate Institute of Injury Prevention and Control, Taipei Medical University, Taipei 110, Taiwan; plchen@tmu.edu.tw
5 Department of Medicine, Center for Tobacco Control Research and Education, University of California San Francisco, San Francisco, CA 94117, USA; Stanton.Glantz@ucsf.edu
* Correspondence: hychiou@tmu.edu.tw

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Abstract: A growing literature indicates that electronic cigarette use increases the risk of subsequent initiation of conventional smoking among cigarette-naïve adolescents in several Western countries. This research assesses the same relationship in an Asian country, Taiwan. The Taiwan Adolescent to Adult Longitudinal Study is a school-based survey that was carried out in two waves in 2014 (baseline) and in 2016 (follow-up). It employs probability sampling to create nationally representative samples of students in junior high school (mean age 13, 7th grade at baseline) and in senior high school (mean age 16, 10th grade at baseline). Data from this survey were analyzed via logistic regression to estimate the association between ever use of e-cigarettes at baseline and smoking initiation at follow-up, accounting for susceptibility to smoking, socio-demographic profile, depression status, and peer support. Among the 12,954 cigarette-naïve students surveyed, those with e-cigarette experience at baseline exhibited higher odds of smoking initiation at follow-up (Odds Ratio = 2.14, 95% CI (1.66, 2.75), $p < 0.001$). For the first time, we confirmed, through a longitudinal survey, a prospective association between ever use of e-cigarettes and smoking initiation in an Asian adolescent population. The restrictive policy on e-cigarettes currently in force in Taiwan is justified to prevent both e-cigarette and cigarette use among adolescents.

Keywords: e-cigarette; smoking initiation; prospective study; Asian youth; Taiwan

1. Introduction

The popularity of electronic cigarettes among teenagers and adolescents is increasing in the U.S. [1] and other developed countries [2–4], raising concerns in the public health community and in many governments [5,6], particularly when youth who have never smoked cigarettes are involved. Longitudinal studies conducted in the U.S. [7–14], Canada [15,16], Germany [17], and the U.K. [18–20] have demonstrated that never cigarette smoking youth who have tried e-cigarettes are more likely to initiate at a later point [7,8,10,13,20–24] and that e-cigarette users are more inclined towards other substance use [25]. In accordance with these findings, the European Tobacco Products Directive stated: "*Electronic cigarettes can develop into a gateway to nicotine addiction and ultimately traditional tobacco consumption, as they mimic and normalize the action of smoking*" [26], while the Australian National

Health and Medical Research Council concluded that actions should be taken to minimize the harm of e-cigarettes to users and bystanders and to protect vulnerable groups such as young people [27].

As of 2018, in Taiwan, e-cigarette liquid with nicotine is classified as an illegal pharmaceutical product and advertising nicotine-free e-cigarettes as smoking cessation devices is prohibited. The current regulation is seemingly strict, but in fact has loopholes and has raised unsolved controversies [4], with the result that vaping products are still readily available, especially over the Internet. As for age distribution, e-cigarettes are more widespread among youth (2.5% among junior high school students and 4.5% among senior high school students in 2017 [28]) than among adults (0.5% in 2017 [29]).

Even though e-cigarette use has been significantly increasing in many Asian countries, the effects on Asian youth have only been investigated through cross-sectional studies [3,30,31]. Thus, this research aimed to examine the impact of ever using e-cigarettes on smoking initiation among cigarette-naïve individuals in a longitudinal sample of Taiwanese students.

2. Materials and Methods

2.1. Dataset

Data were retrieved from the Taiwan Adolescent to Adult Longitudinal Study (TAALS) [32], a school-based nationally representative longitudinal survey with wave 1 in 2014 (baseline) and wave 2 in 2016 (follow-up). School was the primary sampling unit and the first wave included 18,064 first-year students from junior high school (N = 6667, 7th grade, mean age 13), senior high school (N = 4689, 10th grade, mean age 16), and vocational high school (N = 6708, 10th grade, mean age 16). The 15,795 students (87%) who completed the follow-up questionnaire two years later were used as the primary data set. The TAALS was approved by the Joint Institutional Review Board of Taipei Medical University, Taiwan (TMU-JIRB-201410043).

Table 1 shows the sample characteristics by ever-smoking status at follow-up. Among the 12,954 students who had never smoked at baseline, 1115 (8.6%) were ever smokers at 2-year follow-up. The attrition analysis additionally performed to assess whether baseline never smokers lost at follow-up were different from those retained with respect to the measures assessed at baseline indicates that in terms of age, gender, father's education, and mother's ethnicity the two groups are extremely similar (see Appendix A—Table A1).

Table 1. Sample characteristics by ever smoking status at follow-up, among never smokers at baseline—unweighted data.

		Ever Smokers at Follow-Up (N = 1115)		Never Smokers at Follow-Up (N = 11,839)	
		n	% [n/N]	n	% [n/N]
Gender	Male	704	63.1%	4957	41.9%
	Female	4957	444.6%	6882	58.1%
Days of Smoking in the Past 30 Days	0	814	73.0%	11,837	100.0%
	1–5	156	14.0%	0	0.0%
	6–9	25	2.2%	0	0.0%
	10–19	29	2.6%	0	0.0%
	>20	90	8.1%	0	0.0%
School	Junior High	471	42.2%	5012	42.3%
	Senior High	644	57.8%	6827	57.7%
Ever Used E-Cigarettes at Baseline	Entire Dataset	118	10.6%	543	4.6%
	Junior High Students *	54	4.8%	253	2.1%
	Senior High Students †	64	5.7%	290	2.4%
Never Used E-Cigarettes at Baseline	Entire Dataset	209	18.7%	670	5.7%
	Junior High Students	96	8.6%	286	2.4%
	Senior High Students	113	10.1%	384	3.2%

Table 1. *Cont.*

		Ever Smokers at Follow-Up (N = 1115)		Never Smokers at Follow-Up (N = 11,839)	
		n	**% [*n*/*N*]**	***n***	**% [*n*/*N*]**
Susceptible to Smoking at Baseline	Entire Dataset	209	18.7%	670	5.7%
	Junior High Students	96	8.6%	286	2.4%
	Senior High Students	113	10.1%	384	3.2%
Father's Education	Below Junior High School	247	22.2%	2036	17.2%
	Senior or Vocational High School	452	40.5%	4396	37.1%
	Above College	295	26.5%	4298	36.3%
Mother's Ethnicity	Native	939	84.2%	10,451	88.3%
	Indigenous	52	4.7%	337	2.8%
	Foreigner	106	9.5%	896	7.6%
Parents' Employment Status	Full-time Job	1021	91.6%	11,093	93.7%
	Part-time Job	31	2.8%	211	1.8%
	Unemployed	51	4.6%	411	3.5%
Family Living Arrangement	Parents or Extended Family	794	71.2%	9433	79.7%
	Single Parents	242	21.7%	1886	15.9%
	Grandparents	33	3.0%	245	2.1%
	Other Relatives	46	4.1%	275	2.3%
		Average	**SD**	**Average**	**SD**
CES-D Scale		3.8	3.0	3.3	2.7
Peer Support Score		13.3	2.4	13.5	2.2

* 13 years old at baseline; † 16 years old at baseline. CES-D Scale: Center for Epidemiologic Studies Depression Scale.

2.2. E-Cigarette Use and Smoking Status at Baseline

At baseline, all participants were asked to answer "Yes" or "No" to the following questions: "Have you ever tried e-cigarettes?", and "Have you ever smoked cigarettes, even one or two puffs?".

2.3. Outcome Variable: Cigarette Smoking Initiation at Follow-Up

All students who responded "No" to having tried conventional cigarettes at baseline were asked again whether they had ever smoked at follow-up. Those who responded "Yes" were classified as having initiated smoking.

Due to the low number of established smokers in our dataset, it was not possible to take into account regular smoking (i.e., daily, weekly, or monthly). In Taiwan, smoking initiation occurs later than in Western countries [33]. Moreover, any smoking in adolescence predicts smoking in young adulthood [34].

2.4. Susceptibility to Smoking at Baseline

In case of cigarette-naïve individuals, susceptibility to smoking at baseline, defined as "absence of a firm decision not to smoke" [35], was assessed by asking "If one of your best friends offered you a cigarette would you smoke it?" and "At any time during the next 12 months do you think you will smoke a cigarette?" (answer options were "Definitely No", "Probably No", "Probably Yes", and "Definitely Yes"). Participants who responded "Definitely No" to both questions were classified as not susceptible to smoking at baseline; all others were classified as susceptible.

2.5. Socio-Demographic Profile

The socio-demographic profile of each student was defined by age in years at the time of the survey, father's education, mother's ethnicity, parents' employment status (full-time job, part-time job, or unemployed), and family living arrangement.

Only mother's ethnicity was assessed because most Taiwanese newborns with one foreign parent are given birth by mothers of foreign origin (10% to 13% of the total number of newborns between

2001 and 2007 [36]), while very few newborns have fathers of foreign origin. Moreover, mothers from foreign countries may face different challenges (in terms of language and/or cultural and social networking) that may affect their children's health behaviors, such as their willingness to try smoking. The education level of each parent is an important factor as well but due to limited questions allowed in the questionnaire, father's education was chosen as representative of the educational level in the household.

2.6. Depression Status and Peer Support

The depression status of each participant was measured using the Center for Epidemiologic Studies Depression Scale (CES-D) [37]. The CES-D scale consists of 20 self-report items developed to measure depressive symptoms in the general population. The response choices for each item are "Not at all" (0 Points), "A little" (1 point), "Some" (2 points), and "A lot" (3 points). Items reflecting positive affect and behavior score reversely as 0 points for answering "A lot", 1 point for "Some", 2 points for "A little", and 3 points for "Not at all". The CES-D scale then ranges from 0 to 60. Peer support, i.e., the degree of support provided by friends (e.g., "During the past 6 months, were your friends there for you whenever you needed help?"), was quantified using a 5-item questionnaire developed by the U.S. Centers for Disease Control and Prevention, CDC [38]. Item responses were rated on a 4-point scale ranging from zero to three and were summed to calculate the total score. The index ranges from 0 to 15, and higher scores indicate stronger peer support.

2.7. Statistical Analysis

Data were weighted to be nationally representative of the Taiwanese student population. The following post-stratification weighting procedure was used. For each type of school (junior, senior, and vocational), we divided the sample into 24 groups, one for each combination of geographic area (North, South, Center, East), school size (small, medium, large), and gender. Then for each group we calculated a specific weight as follows:

$$W_{g,s,x} = \left(N_{g,s,x}/N\right)/\left(n_{g,s,x}/n\right)$$

where $n_{g,s,x}$ is the number of individuals in the sample of gender x attending schools of size s located in the geographic area g and $N_{g,s,x}$ is the number of individuals in the population of gender x attending schools of size s located in the geographic area g. n is the size of the entire sample, and N is the size of the entire population (junior, senior, or vocational students). Further details can be found in a study by Chien et al. [32] We then applied complex survey logistic regression to determine whether students who had never smoked at baseline but had already used e-cigarettes were more likely to initiate smoking at 2-year follow-up than those who had not used e-cigarettes. Two models were considered: an unadjusted model just considering the crude relationship between ever use of e-cigarettes and smoking initiation, and an adjusted model including the following covariates: smoking susceptibility at baseline, socio-demographic profile, psychological status, and peer support. The interaction effect between school grade and ever use of e-cigarettes was initially analyzed and found to be not statistically significant ($p = 0.93$ for interaction). For this reason, the regression analyses were performed on the entire dataset.

A sensitivity analysis was also conducted to assess whether students lost to follow-up were different from those retained, and whether these differences might have influenced the results. In detail, we ran the above described regression analyses under two opposite scenarios: all the students lost at follow-up were non-smokers and all the students lost at follow-up were smokers. The Odds Ratios under the two scenarios were very similar (Appendix A—Tables A2 and A3), leading us to conclude that respondents lost at follow-up may be different from those who retained, but this difference did not affect our main results significantly.

The statistical analysis was conducted using the "svyset" command in STATA statistical software (version 12, StataCorp LLC, College Station, TX, USA) and a $p < 0.05$ was considered significant.

3. Results

The unadjusted and adjusted logistic regressions provided similar results (Table 2), demonstrating that the effect of e-cigarette ever use on cigarette smoking initiation is independent of other determinants of smoking and that confounding is unlikely to be a problem. Students who had already tried e-cigarettes at baseline exhibited significantly higher odds of starting smoking in the following two years than those who never tried e-cigarettes; the odds ratios (ORs) being 2.44 (95% CI 1.94–3.09) with the unadjusted model and 2.14 (95% CI 1.66–2.75) with the adjusted model.

Table 2. Logistic regression output for smoking initiation—weighted estimates (observations: 11,615).

		Entire Dataset	
		ORs	**95% CI**
Unadjusted Model			
Ever Use of E-cigarettes at Baseline		2.44 ***	(1.94–3.09)
Adjusted Model			
Ever Use of E-cigarettes at Baseline		2.14 ***	(1.66–2.75)
Susceptibility to Smoking at Baseline		3.61 ***	(2.99–4.36)
Father's Education	Below Junior High School	1.00	
	Senior or Vocational High School	0.91	(0.78–1.07)
	Above College	0.65 ***	(0.53–0.79)
Mother's Ethnicity	Native	1.00	
	Indigenous	1.73 ***	(1.22–2.45)
	Foreigner	1.18	(0.93–1.49)
Parents' Employment Status	Full-time Job	1.00	
	Part-time Job	1.29	(0.84–1.99)
	Unemployed	1.10	(0.78–1.57)
Family Living Arrangement	Parents or Extended Family	1.00	
	Single Parents	1.26 ***	(1.08–1.47)
	Grandparents	2.06 ***	(1.50–2.82)
	Other Relatives	1.53 *	(1.06–2.22)
Age (in years)		1.01	(0.96–1.07)
CES-D Scale		1.04 ***	(1.02–1.06)
Peer Support Score		0.98	(0.95–1.01)
Constant		0.07 ***	(0.02–0.21)

*** denotes p value < 0.001; ** denotes p value < 0.01; * denotes p value < 0.05. ORs: Odds Ratios.

4. Discussion

In accordance with previous results in Western countries [7,23,24,39], our study shows that cigarette-naïve Taiwanese adolescents who had ever used e-cigarettes at baseline were more likely to initiate smoking 2 years later. In other words, starting to use e-cigarettes increased the odds of progressing to conventional cigarettes, which in Asian countries like Taiwan are still more affordable and ubiquitously available than e-cigarettes, which remain de facto illegal.

Smoking cessation is one reason that youth use e-cigarettes in Korea [3] and the USA [40]. In particular, Korean adolescents who tried to quit smoking are more likely to use e-cigarettes but less likely to no longer smoke, which suggests that e-cigarettes inhibit rather than promote cessation [3]. It has been argued that the observation that e-cigarettes increase the likelihood of subsequent cigarette smoking initiation merely reflects the fact that some users may share a similar propensity toward two

behaviors [41]; however, our results seem to exclude the existence of other major confounders, as the odds ratios in our adjusted models were statistically significant.

The odds ratios found in our study are smaller than those reported in Western countries [14,16,17,20,23]. This difference could be due to the restrictive e-cigarette policy in Taiwan: the government has not yet approved any legal nicotine-based product and marketing of e-cigarettes is not allowed. In the current regulatory context, without visible marketing, frequent vaping scenes on TV, and exposure in daily life, adolescents may be less likely to use e-cigarettes.

The consistent finding of a prospective association between e-cigarette use and cigarette smoking in all the available longitudinal studies [7,15,23,24,39] suggests the need for policies to make e-cigarettes less attractive to youth. The European Union has recommended that a restrictive approach should be adopted towards advertising e-cigarettes and refill containers [26], while the availability of a wide range of refill flavors has been identified as an important motive for smoking e-cigarettes among young users [25], indicating that banning fruit-, mint-, and candy-flavored liquids would be a good starting point for prevention, as well as implementing the same restrictions on marketing currently applied to conventional cigarettes.

The results of Taiwan's Global Youth Survey also revealed that smoking prevalence among youth has continued to decline, reaching historical lows in 2017 (8.3% among senior high school students, 2.7% among junior high school students), while at the same time e-cigarette use has increased [28]. Nicotine dependence may be the major reason pushing young "vapers" towards conventional smoking [39], especially given that cigarettes are largely affordable in Taiwan [42].

There are several strengths of this work. First, previous prospective studies on the association between e-cigarette use and subsequent smoking have all been from Western countries; our longitudinal study contributes to filling this gap for Asian youth [15]. Even though our findings come from a single medium-sized country, they are particularly important since other Asian countries share many similarities with Taiwan in terms of tobacco control, including former or current government-owned tobacco monopolies [43], high male smoking rate [44], lagged tobacco endemic transition, as well as tobacco control endeavors comparable to the Western countries. Second, the longitudinal design of the study ensures that e-cigarette use preceded initiation of cigarette smoking among never smoking adolescents. Third, our results are based on a national representative sample, with a low loss to follow-up. Fourth, the sensitivity analysis we performed to evaluate the possible impact of attrition revealed that even under two opposite scenarios (all the lost students were smokers and all the lost students were non-smokers) the ORs of initiating smoking were substantially identical: in the all-non-smokers case, 2.19 ($p < 0.0001$) with the unadjusted model and 2.03 ($p < 0.0001$) with the adjusted model; in the all-smokers case, 1.94 ($p < 0.0001$) with the unadjusted model and 2.03 ($p < 0.0001$) with the adjusted model. Fifth, no major changes in tobacco control occurred during the study period, hence external factors influencing smoking patterns remained mostly constant.

Nonetheless, there are also some limitations to this research. First, we were not able to determine if students referred to e-cigarettes containing nicotine or not, but about 80% of the 3062 e-cigarettes examined by Taiwan's Food and Drug Administration in 2016 contained nicotine [45]. Second, while important covariates were included, rebellion, sensation seeking propensity, e-cigarette use and smoking by friends and parents, alcohol and other drugs use were not assessed in the survey. In particular, a recent study shows that sensation seeking is significantly related to experimentation with e-cigarettes, similarly to what happens with conventional cigarettes among adolescents [46], while Wills et al. (2016) found no significant association between prior use of e-cigarettes and subsequent initiation of smoking among youth after the inclusion of mediating variables such as marijuana use [47], contradicting previous results [11]. However, illicit substance use among adolescents in Taiwan is low (0.52% in 2014), with club drugs like N_2O being the most popular [48]. In conclusion, other overlooked variables might explain the association between initial e-cigarette use and subsequent smoking.

One of the most plausible pathways for this sequential relationship is that adolescents who never smoked cigarettes are first exposed to addictive nicotine with e-cigarettes, thanks to sophisticated strategies of targeted marketing based on abundant attractive flavors and "less harmful" claims [49]; then, once nicotine use is established, adolescents become more open to conventional smoking.

5. Conclusions

We confirmed the prospective association of e-cigarette use with smoking initiation that has been observed in Western countries in an Asian population, with the largest effect among students exhibiting low susceptibility to initiating nicotine use with conventional cigarettes. With prevalence of e-cigarette smoking still relatively low in Taiwan, it is a good public health practice to maintain a restrictive and cautious policy towards e-cigarettes. Such measures are needed to prevent e-cigarettes from serving as a new gateway to conventional smoking for Asian youths, who are already exposed to a stronger smoking culture than their Western counterparts.

Author Contributions: Y.-N.C.: the first author who designed the initial analysis, drafted a preliminary version of the Methods section, collected, organized, analyzed the data, and critically reviewed the manuscript. W.G.: co-first author, conceived the study, designed the analysis, interpreted the results, and drafted the manuscript. M.S. contributed to designing the analysis and interpreted the results, drafted, reviewed and revised the manuscript. S.G. provided crucial feedback on both the methodology and data interpretation; moreover, he critically reviewed the manuscript. P.-L.C. and Y.-H.C. conceptualized the survey on whose data this study is based, discussed the results, and critically reviewed the manuscript. H.-Y.C. was in charge of the overall direction and planning of the study. All the authors reviewed and approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

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Conflicts of Interest: The authors declare no conflict of interest.

Appendix A Attrition and Sensitivity Analysis

Table A1. Output of the attrition analysis performed on never smokers at baseline and at follow-up.

		Baseline Cohort (*N* = 14,587)		Follow-Up Cohort (*N* = 13,108)		RRF * (95% CI)
		n	% [*n*/*N*]	*n*	% [*n*/*N*]	
Gender	Male	6439	44.14	5738	43.77	0.99 (0.989–1.007)
	Female	8148	55.86	7370	56.23	1.01 (1.009–1.011)
School	Junior High (13 years old at baseline)	5915	40.55	5544	42.29	1.04 (1.039–1.041)
	Senior High (16 years old at baseline)	8672	59.45	7564	57.71	0.97 (0.969–0.971)
Father's Education	Below Junior High School	2621	17.97	2310	17.62	0.98 (0.979–0.981)
	Senior or Vocational High School	5475	37.53	4901	37.39	1.00 (0.999–1.001)
	Above College	5099	34.96	4646	35.44	1.01 (1.009–1.011)
	Missing	1387	9.51	1247	9.51	1.00 (0.998–1.002)

Table A1. *Cont.*

		Baseline Cohort (*N* = 14,587)		Follow-Up Cohort (*N* = 13,108)		RRF * (95% CI)
		n	% [*n*/*N*]	*n*	% [*n*/*N*]	
Mother's Ethnicity	Native	12,787	87.66	11,526	87.93	1.00 (1.000–1.000)
	Indigenous	483	3.31	394	3.01	0.91 (0.906–0.914)
	Foreigner	1130	7.75	1013	7.73	1.00 (0.998–1.002)
	Missing	178	1.22	167	1.27	1.04 (1.035–1.045)

* The Ratios of Relative Frequencies (RRFs) were calculated based on [50].

Table A2. Sensitivity Analysis: regression output assuming all the students lost at follow-up were non-smokers—weighted estimates (observations: 12,921).

	OR	Lin. Std. Err.	*t*	$p > \|t\|$	95% CI
Unadjusted Model					
Ever Use of E-cigarettes at Baseline	2.30	0.27	7.08	0.00	1.82−2.89
Constant	0.08	0.00	−49.60	0.00	0.07−0.09
Adjusted Model					
Ever Use of E-cigarettes at Baseline	2.00	0.25	5.49	0.00	1.56−2.56
Susceptibility to Smoking at Baseline	3.32	0.32	12.50	0.00	2.75−4.01
Parents' Employment Status (Part-time Job)	1.23	0.27	0.97	0.33	0.81−1.88
Parents' Employment Status (Unemployed)	1.05	0.18	0.29	0.77	0.75−1.48
Father's Education (Senior or Vocational High School)	0.94	0.07	−0.80	0.43	0.8−1.1
Father's Education (Above College)	0.68	0.07	−3.93	0.00	0.56−0.82
Family Living Arrangement (Single Parents)	1.20	0.10	2.25	0.03	1.02−1.4
Family Living Arrangement (Grandparents)	2.04	0.32	4.49	0.00	1.49−2.79
Family Living Arrangement (Other Relatives)	1.51	0.28	2.23	0.03	1.05−2.18
Mother's Ethnicity (Indigenous)	1.46	0.25	2.23	0.03	1.04−2.04
Mother's Ethnicity (Foreigner)	1.19	0.14	1.44	0.15	0.94−1.5
CES-D Scale	1.03	0.01	2.90	0.00	1.01−1.06
Age (in years)	0.98	0.03	−0.58	0.56	0.93−1.04
Peer Support Score	1.00	0.02	−0.02	0.98	0.97−1.03

Table A3. Sensitivity Analysis: regression output assuming all the students lost at follow-up were smokers—weighted estimates (observations: 12,921).

	OR	Lin. Std. Err.	*t*	$p > \|t\|$	95% CI
Unadjusted Model					
Ever Use of E-cigarettes at Baseline	1.97	0.17	7.95	0.00	1.66–2.33
Constant	0.21	0.01	−30.62	0.00	0.19–0.23
Adjusted Model					
Ever Use of E-cigarettes at Baseline	1.80	0.17	6.41	0.00	1.5–2.16
Susceptibility to Smoking at Baseline	2.44	0.19	11.18	0.00	2.08–2.85
Parents' Employment Status (Part-time Job)	1.31	0.20	1.73	0.09	0.96–1.78
Parents' Employment Status (Unemployed)	1.30	0.16	2.15	0.03	1.02–1.66
Father's Education (Senior or Vocational High School)	0.93	0.06	−1.12	0.27	0.83–1.05
Father's Education (Above College)	0.75	0.05	−3.92	0.00	0.66–0.87
Family Living Arrangement (Single Parents)	1.29	0.07	4.73	0.00	1.16–1.43
Family Living Arrangement (Grandparents)	1.51	0.19	3.23	0.00	1.17–1.94

Table A3. *Cont.*

	OR	Lin. Std. Err.	*t*	$p > \|t\|$	95% CI
Family Living Arrangement (Other Relatives)	1.33	0.17	2.27	0.03	1.04–1.71
Mother's Ethnicity (Indigenous)	2.20	0.29	6.07	0.00	1.7–2.84
Mother's Ethnicity (Foreigner)	1.07	0.09	0.78	0.44	0.9–1.27
CES-D Scale	1.03	0.01	3.44	0.00	1.01–1.05
Age (in years)	1.17	0.03	6.08	0.00	1.11–1.23
Peer Support Score	0.91	0.01	−8.57	0.00	0.89–0.93

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Short Communication Open Access

Heated Tobacco Products Create Side-Stream Emissions: Implications for Regulation

Grant O'Connell[1], Peter Wilkinson[1], Kerstin MM Burseg[2], Stephen J Stotesbury[1], John D Pritchard[1]*

[1]*Imperial Tobacco Ltd, 121 Winterstoke Road, Bristol, BS3 2LL, UK*
[2]*Reemtsma Cigarettenfabriken GmbH - Imperial Tobacco Group, Albert-Einstein-Ring 7, D-22761, Hamburg, Germany*

Abstract

A number of tobacco manufacturers are promoting products where the tobacco is reportedly "heated" rather than burned. It has been claimed that certain heated tobacco products produce only mainstream and no side-stream emissions. In this study we investigated these claims for a commercially available heated tobacco product and, by using a simple experimental design, investigated whether the high temperature heating of the tobacco matrix during product activation and use results in the generation of side-stream emissions. By way of comparison, the Nicorette® inhalator and a leading e-cigarette brand were also investigated. Our findings indicated that a large number of different chemical compounds were released into the airspace around the heated tobacco product when switched on and during consumer use indicating the generation of side-stream emissions. As the public health community has concluded there is no safe level of exposure to tobacco-containing product emissions, this would be of concern and warrants further investigation. Based on our data showing side-stream emissions from the tobacco matrix, the use of heated tobacco products in indoor public places should fall under the same regulations as cigarettes.

Keywords: Heated tobacco; Heat-not-burn; E-cigarette; Nicorette; Side-stream emissions; Second-hand smoke; Nicotine; Tobacco

Introduction

It is well known that when tobacco burns, many thousands of chemicals are released from the tobacco matrix and are inhaled by consumers and bystanders [1,2]. It has been stated that the majority of smoking-related diseases are caused not by nicotine but by the generation of harmful or potentially harmful smoke constituents (HPHCs) from the burning of tobacco [3,4]. In response, a number of tobacco manufacturers are promoting products where the tobacco is reportedly "heated" rather than burned in an attempt to reduce HPHC emissions [5-7]. This is not a new concept, as cigarette-based heated tobacco products were first marketed in the USA in the 1980s and proved to be commercially unsuccessful. Heated tobacco products are now being revived and repositioned as an alternative for smokers who may not wish to replace conventional cigarettes with non-tobacco products such as electronic cigarettes (e-cigarettes). While some manufacturers claim heated tobacco products do not produce side-stream emissions, the major component of 'second-hand smoke', this has yet to be independently verified [8-12]. Since the World Health Organisation has stated "*there is no safe level of exposure to second-hand tobacco smoke*" [13] and the British Medical Association (BMA) has stated that "*almost 85 per cent of second-hand smoke is in the form of invisible, odourless gases*" [14], claims of an absence of side-stream emissions from heated tobacco products warrants investigation. To that end, we sought to investigate whether or not side-stream emissions were generated by a commercially available heated tobacco product. For comparative purposes, we also investigated the Nicorette® inhalator and a leading e-cigarette.

Experimental Section

The analytical technique Proton Transfer Reaction-Mass Spectrometry (PTR-MS) was used to sample and analyze for any side-stream emissions released to the airspace around an iQOS heated tobacco product with regular Marlboro *HeatSticks* (manufacturer, Philip Morris International) when activated by the user (but not puffed) and also during product use. Additionally, sampling was conducted for a Nicorette® inhalator (15 mg nicotine replacement aid; manufacturer, McNeil Consumer Healthcare Ltd) and Blu™ closed system e-cigarette (18 mg nicotine; manufacturer, Fontem Ventures B.V.) All products used in this study were used in accordance with manufacturer's instructions and consumed *ad libitum* i.e., there was no pre-defined consumption requirement. For each of the different products, a number of replicate puffs were made and representative data from a single puff is shown. In short, the PTR-MS instrument ionizes volatile organic compounds (VOCs) in the gas phase through their reaction with H_3O^+ to form protonated VOCs ($VOCH^+$) which can then be detected by a mass spectrometer [15]. This process can be run on air samples with or without dilution as normal air gases (e.g., N_2, O_2, CO_2) have a proton affinity less than water and thus are not ionized. Most VOCs have a proton affinity greater than water and therefore are readily ionized and detected [15]. Analyses with PTR-MS can be conducted in real-time and continuously without the need for sample preparation [15]. Airspace analysis was conducted by connecting the PTR-MS inlet to the test chamber and sampling directly. PTR-MS operating conditions were as follows: drift tube voltage, 500 V; drift tube pressure, 2.3 mbar; drift tube temperature, 120°C; drift tube length, 9.3 cm; *E/N* ratio, 130 Td (Townsends; where *E* is electric field and *N* is the number density of the gas in the drift tube; 1 Td=10^{-17} cm^2 V $molecule^{-1}$); inlet temperature, 120°C. The experimental set-up is outlined in Figure 1.

Results and Discussion

Qualitative characterization of side-stream emissions

Following activation of the iQOS heated tobacco product, as per the manufacturer's instructions, a large number of different VOC species across a range of masses were released into the airspace (Figure 2A). This clearly indicates the generation of side-stream emissions when the device is activated but not puffed by the consumer, which

***Corresponding author:** John D Pritchard, Imperial Tobacco Ltd, 121 Winterstoke Road, Bristol, BS3 2LL, UK, Tel: 440117-933-7556; E-mail: john.pritchard@uk.imptob.com

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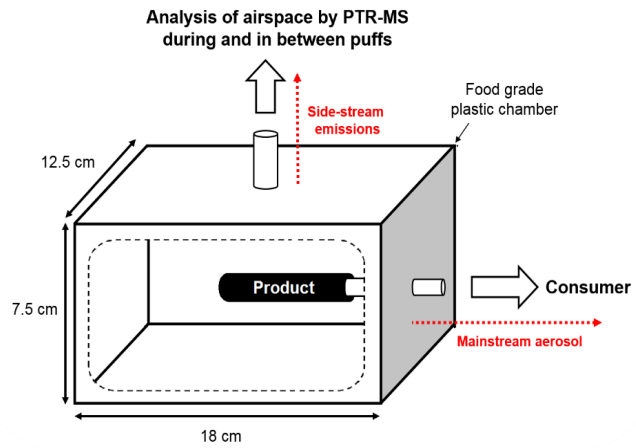


Figure 1: Schematic representation showing experimental set-up and the side-stream emissions capture chamber.

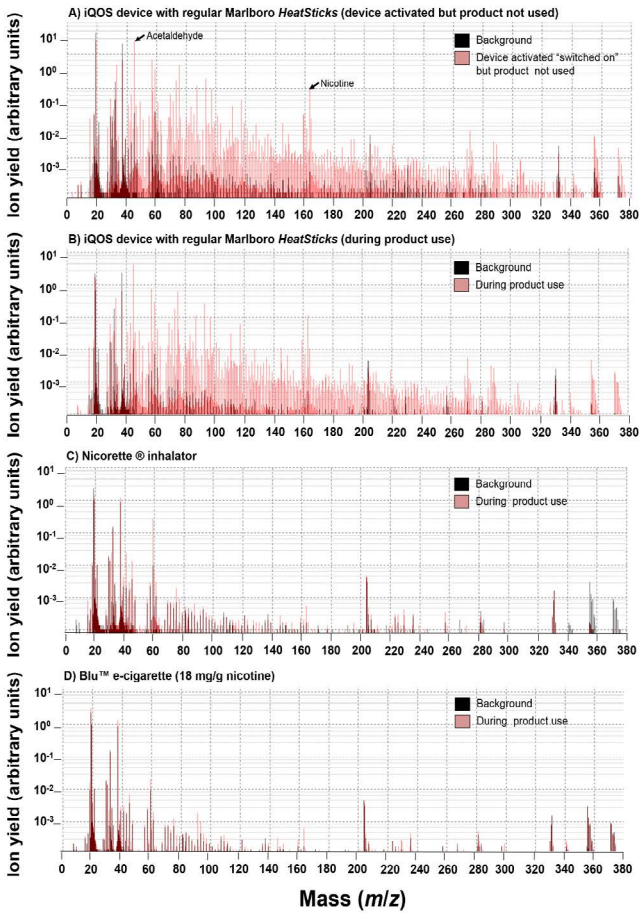


Figure 2: Representative PTR-MS mass spectra of the VOCs released to the airspace for (**A**) iQOS with regular Marlboro *HeatStick* when activated "switched on" but product not actively puffed and (**B**) during consumer use of the iQOS device with regular Marlboro *HeatSticks*; (**C**) during consumer use of the Nicorette® inhalator; and (**D**) during consumer use of the Blu™ e-cigarette. Specific compound (peaks) at *m/z* 45 is protonated acetaldehyde and *m/z* 163 is protonated nicotine and is labelled with arrowheads in (**A**).

would be released into the ambient air, raising potential concerns for bystanders. Furthermore, during active puffing on the heated tobacco product, side-stream emissions are also released (Figure 2B). These chemicals are being released from the high temperature heating of the tobacco matrix in the *HeatSticks*. Given the similarities of the Marlboro branded *HeatStick* used in the iQOS device to a conventional cigarette, the detection of side-stream emissions is perhaps not surprising even though it has been stated that such products produce no side-stream aerosol/smoke [8-12]. Given the findings presented in this pilot study, this requires further investigation.

The PTR-MS mass spectra of the VOCs in the airspace around the Nicorette® inhalator (Figure 2C) and the e-cigarette (Figure 2D) during product use are virtually indistinguishable. Moreover, the Nicorette® inhalator and the e-cigarette profiles are entirely distinct from that of the heated tobacco product, as may be anticipated given these products do not contain tobacco. The Nicorette® inhalator was selected as an appropriate comparator in this study as the UK Medicines and Healthcare products Regulatory Agency (MHRA) has indicated this should be used as a reference product, if manufacturers intend to license e-cigarettes as medicinal products [16].

Future investigations

PTR-MS is a one dimensional technique that characterizes VOCs via their mass; to enable identification of the chemicals in the side-stream emissions from the heated tobacco product it is necessary to further calibrate the machine for identification and quantification of compounds of regulatory interest e.g., HPHCs in tobacco products and tobacco smoke as developed by the US Food and Drug Administration (FDA) [17]. We will therefore determine the identities of the many different VOCs released to the airspace, and by extension to the bystander's breathing space, from the heated tobacco product when activated and used by the consumer. Moreover, it is also conceivable that differences in side-stream emissions may be observed under varying user consumption topographies. Further research in these areas will be informative.

Conclusions

The release of side-stream emissions from heated tobacco products has been observed by PTR-MS using the simple method presented here. These emissions are generated by the high temperature heating of the *HeatSticks* tobacco matrix inserted within the iQOS device.

The public health community has stated that there is no safe level of exposure to tobacco-containing product emissions [13,18], and so the side-stream constituents including nicotine, released during activation and use of the iQOS heated tobacco product can lead to exposure to bystanders; this would be of concern to public health authorities and warrants further investigation.

It is conceivable that based on these findings and the conclusions of public health community regarding tobacco product emissions, the use of heated tobacco products should be included in smoke-free legislation.

Conflicts of Interest

The work in this short communication was supported by Imperial Tobacco Group. Imperial Tobacco Group is the parent company of Fontem Ventures B.V., the manufacturer of the e-cigarette used in this study.

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PMI's own in vivo clinical data on biomarkers of potential harm in Americans show that IQOS is not detectably different from conventional cigarettes

Stanton A Glantz[1,2]

[1]Department of Medicine/Division of Cardiology, University of California San Francisco, San Francisco, CA 94143-1390, USA
[2]Center for Tobacco Control Research and Education, University of California San Francisco, San Francisco, CA 94143-1390, USA

Correspondence to
Professor Stanton A Glantz, Department of Medicine/Cardiology, University of California San Francisco, San Francisco, CA 94143-1390, USA; glantz@medicine.ucsf.edu

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ABSTRACT

Introduction New 'heated tobacco products' are being marketed in several countries with claims that they expose users to lower levels of toxins than conventional cigarettes which could be read as being less likely to cause health problems than conventional cigarettes. In the USA, Philip Morris International (PMI) has submitted an application to the Food and Drug Administration for permission to market its heated tobacco product, IQOS, with reduced exposure and reduced risk claims.

Methods Analysis of detailed results on 24 biomarkers of potential harm in PMI studies of humans using IQOS compared with humans using conventional cigarettes.

Results Among American adults, there is no statistically detectable difference between IQOS and conventional cigarette users for 23 of the 24 biomarkers of potential harm in PMI's studies. In Japan, there were no significant differences between people using IQOS and conventional cigarettes in 10 of 13 biomarkers of potential harm. It is likely that some of the significant differences are false positives.

Conclusion Despite delivering lower levels of some toxins than conventional cigarettes, PMI's own data fail to show consistently lower risks of harm in humans using its heated tobacco product, IQOS, than conventional cigarettes.

INTRODUCTION

Nicotine is the addictive drug in tobacco. Burning the tobacco generates an aerosol of ultrafine particles that carries nicotine deep into smokers' lungs, where it is absorbed and rapidly reaches the brain. That burning yields toxic chemicals that cause disease. Ever since people started understanding in the 1950s that smoking kills, millions have struggled to stop smoking. The tobacco companies, desperate to keep and expand their customers, have been trying to make 'safer cigarettes' since the 1960s.[1] They have also developed products that avoided burning, including e-cigarettes,[2] nicotine replacement therapy,[3] and products that heat the tobacco without setting it on fire. As of January 2018 all the major multinational tobacco companies had developed, or were in the process of developing, so-called 'heated tobacco products' (HTP; also called 'heat-not-burn' tobacco products). Because these devices generate their nicotine aerosols by heating a stick of ground tobacco and chemicals without setting the tobacco on fire, they generally produce fewer toxic chemicals than a conventional cigarette, which is promoted as meaning or implying that these products are not as dangerous as conventional cigarettes.

In 2015, Philip Morris International (PMI) started test marketing its IQOS HTP outside the USA on the grounds that it is not as bad as a cigarette because 'the tobacco is heated and not burned, the levels of harmful chemicals are significantly reduced compared to cigarette smoke.'[4]

Because IQOS is a new tobacco product, PMI needs to obtain premarket authorisation from the US Food and Drug Administration (FDA) to sell it in the USA. In particular, PMI wants to market IQOS with reduced risk claims, what US law calls a 'modified risk tobacco product' (MRTP). To obtain authorisation to market IQOS with reduced risk claims, PMI submitted an application to the FDA in December 2016.[5] As required by law, FDA has made most of the application available for the public to review. The application includes comparisons of the levels of 24 biomarkers of potential harm in human smokers, including comparisons with people who smoke conventional cigarettes. These biomarkers include measures of inflammation, oxidative stress, cholesterol and triglycerides, blood pressure and lung function. This paper uses information in the PMI application to evaluate this comparison and concludes that in people who actually use IQOS, the levels of these biomarkers of potential harm are not detectably different from conventional cigarettes.

METHODS

The results analysed in this paper are from PMI's 'Three-month Reduced Exposure in a confined and ambulatory setting' studies (ZRHR-REXA-07-JP in Japan and ZRHM-REXA-08-US in the USA) that present human clinical studies of non-cancer biomarkers of potential harm presented in PMI's MRTP application's[5] Executive Summary, Module 6: Summaries of All Research Findings, and Module 7.3.1: Scientific Studies and Analyses (Studies in Adult Human Studies: Clinical Studies), specifically the data on 24 biomarkers of potential harm *in human users* derived from two of their 'Reduced Exposure' studies: ZRHR-REXA-07-JP in Japan and ZRHM-REXA-08-US in the USA.

As described in Section 6.1.4.3.2 of the application, cigarette smokers were randomised, controlled, open-label, three-arm parallel group studies in which smokers were randomised to IQOS (menthol), continued smoking their current brand of cigarettes or smoking abstinence. Baseline data were collected on day 0 immediately before randomisation, people were held during a 5-day confinement period then released to the ambulatory setting and observed at 90 (±3 (range)) days

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after randomisation. (Some variables were measured during confinement and before 90 days, but are not considered in this analysis.) During the confinement period, product use was directed and monitored by the study staff and participating smokers were controlled for product compliance. Subjects assigned to conventional cigarettes or IQOS used the products without restriction (ad libitum) during an extended daily time window (16 hours); dual use of conventional cigarettes and IQOS was not permitted. The 3-month ambulatory phase was designed to reflect a near real-world environment where dual use of IQOS and conventional cigarettes or other tobacco products could occur. PMI selected a 3-month extended ambulatory follow-up period so that the study would be long enough to assess the initial changes in some of the clinical risk endpoints that have been shown to be reversible within 2 weeks to 3 months.

The final sample (table 1) consisted of people who were adherent with their assigned study product and without major protocol deviations that impacted the validity of the evaluation of the study results. This sample was designed to assess the maximum exposure reduction achievable (what PMI characterised as the 'optimal effect') in subjects who were using IQOS ad libitum and exclusively or at least predominantly, rather than the effect in the full population representing a heterogeneous exposure (eg, as mixed product use, or non-use of the assigned product).

The point estimates and 95% confident intervals (CIs) at day 90 were computed using least squares means from an analysis of covariance with study arm as a factor adjusting for baseline value, sex and average daily conventional cigarette consumption over the last 4 weeks as reported during screening. (Thus, the width of the CIs for the differences between IQOS and conventional cigarette use in table 1 benefits from the information in the smoking abstinence group even though those subjects are not directly involved in the point estimates being compared.) Endpoints that were not normally distributed were log-transformed (base e) prior to analysis, then back-transformed to calculate least squares means ratios to compare IQOS with conventional cigarettes.

Both trials were registered with ClinTrials.gov.

Specific results are based on measures of inflammation in Section 6.1.4.4.2; cholesterol, triglycerides and physiological measures related to heart disease in Section 6.1.4.4.4; and lung function in Section 6.1.4.4.5.

RESULTS

Among American adults, there is no statistically detectable difference between IQOS and conventional cigarettes for 23 of the 24 biomarkers of potential harm in PMI's studies (table 1). This is indicated by the fact that 23 of the 95% CIs include zero (ie, no statistically significant difference). Moreover, when using the conventional 95% confidence standard for statistical hypothesis testing, one would expect 5% of the tests to yield false positives. Five per cent of 24 tests is 1.2 tests, which means that one would expect one false positive result. PMI had one positive result (soluble intercellular adhesion molecule (ICAM)), which is what one would expect by chance.

PMI also reported the results on 13 biomarkers of potential harm among Japanese people (table 1). There were significant improvements in 4/13 of these biomarkers, 3 markers of inflammation (white cell count, prostaglandin F2 alpha and soluble ICAM) and 1 measure of cholesterol (high-density lipoprotein cholesterol). When using the conventional 95% confidence standard one would expect 0.65 positive tests, which means one would expect one false positive test.

Table 1 Summary of Philip Morris studies of changes in biomarkers in IQOS users compared with conventional cigarette smokers after 90 days of product use (95% CIs in parenthesis)

	Japan	USA
Inflammation (6.1.4.4.2**)		
White cell count	**−0.57 GI/L (−1.04 to −0.10)**	0.17 GI/L (−0.47 to 0.81)
C-reactive protein (CRP)	6.41% ↓ (−40.75 to 37.77)	16.23% ↓ (−21.69 to 42.33)
Soluble ICAM (sICAM-1)	**8.72% ↓ (2.05 to 14.94)**	**10.59% ↓ (4.03 to 16.71)**
Fibrinogen	5.42% ↓ (−1.80 to 12.13)	1.63% ↓ (−6.42 to 9.08)
Oxidative stress (6.1.4.4.3)		
Prostaglandin F2 alpha (8-epi-PGF2α)	**12.71% ↓ (2.55 to 21.81)**	13.46% ↓ (−1.95 to 23.61)
11-dehydrothromboxane B2 (11DTXB2)	5.42% ↓ (−1.80 to 12.13)	3.56% ↓ (−23.31 to 24.57)
Cholesterol and triglycerides (6.1.4.4.4)		
High-density lipoprotein cholesterol (HDL-C)	**4.53** mg/dL **(1.17 to 7.88)**	1.4 mg/dL (−2.3 to 5.0)
Low-density lipoprotein cholesterol (LDL-C)	0.87 mg/dL (−6.55 to 8.30)	−3.3 mg/dL (−12.0 to 5.4)
Total cholesterol	2.00 mg/dL (−6.68 to 10.67)	−4.0 mg/dL (−13.3 to 5.2)
Triglycerides	−6.25 mg/dL (−21.20 to 8.69)	0.9 mg/dL (−12.8 to 14.6)
Apolipoprotein A1 (apoA1)	NA	3.1 mg/dL (−4.6 to 10. 7)
Apolipoprotein B (apoB)	NA	−1.6 mg/dL (−7.24 to 4.03)
Physiological measures		
Systolic blood pressure	−0.59 mm Hg (−3.80 to 2.62)	−0.7 mm Hg (−4.5 to 3.1)
Diastolic blood pressure	−0.68 mm Hg (−3.04 to 1.69)	0.2 mm Hg (−3.7 to 4.0)
Lung function (6.1.4.4.5)		
Forced expiratory volume in 1 s (FEV_1)	1.91 %Pred (−0.14 to 3.97)	0.53 %Pred (−2.09 to 3.00) 0.05 L (−0.06 to 0.15)
FEV_1/FVC (forced vital capacity)	NA	0.00 (−0.02 to 0.02)
Mid-expiratory flow (MEF 25–75) (L/s)	NA	−0.67 (−6.33 to 4.99)
Diffusion capacity for lung CO (DLCO) (mL/min/mm Hg)	NA	0.31 (−1.09 to 1.72)
Rate constant of CO (KCO) (mmol/min/kPa/L)	NA	0.05 (−0.02 to 0.12)
Total lung capacity (TLC) (L)	NA	0.09 (−0.25 to 0.43)
Functional residual volume (FRV) (L)	NA	−0.09 (−0.31 to 0.13)
Inspiratory capacity (IC) (L)	NA	0.21 (−0.08 to 0.51)
Vital capacity (VC) (L)	NA	0.10 (0.00 to 0.21)
Summary		
Number of biomarkers tested	13	24
Number significantly improved	3	1
Number expected by chance	1	1

Continued

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Table 1 Continued

	Japan	USA
Sample sizes		
IQOS	70	47†
Conventional cigarettes	41	32‡
Smoking abstinence	37	9§

The results are either IQOS:CC or IQOS-CC (conventional cigarettes).
Bold results are statistically significant differences (p<05).
*Section of Philip Morris International's Modified Risk Tobacco Product application.
†n=45 for fibrinogen, 8-epi-PGF2α, 11DTXB2, systolic blood pressure, diastolic blood pressure, DCLO and KCO.
‡n=30 for FEV_1, FEV_1/FVC, MEF 25–75, DLCO, KCO, TLC, FRV, IC and VC.
§n=8 for DLCO and 7 for KCO.
ICAM, intercellular adhesion molecule; NA, not applicable.

DISCUSSION

These human data are important information because they represent direct evidence on how IQOS affects people who use the product. They show that, despite the evidence that PMI submitted that the levels of some toxins in IQOS aerosol are lower than in conventional cigarettes,[5] fewer toxic chemicals, however, do not necessarily translate into lower harm when people use the product.

In its MRTP application, PMI did not discuss the results of the conventional statistical tests described in the Results section, which are routine for such scientific analysis. Rather, they simply emphasise the direction of changes while ignoring the fact that these differences are within what would be expected based on simple randomness. No tobacco company would tolerate such assertions made by the FDA or other public health authorities.

The results reported in PMI's application (and in a published paper[6]) for Japan are slightly more positive for IQOS, with 4 of 13 biomarkers showing differences from conventional cigarettes (where one would expect one false positive by chance). These results are not strong enough to warrant drawing a conclusion of reduced risk. The conclusion of no significant difference on biomarkers of potential harm is based on taking PMI's results at face value despite the tobacco companies' (including Philip Morris) long record of manipulating the design, analysis and presentation of their published scientific studies <<ED: Citation should be "7-12" no "7-13".>>.[7–13]

Like cigarettes (and e-cigarettes), IQOS uses an aerosol of ultrafine particles to deliver the nicotine. These ultrafine particles cause heart and lung disease. The adverse health effects of these particles and many of the other toxins do not drop in proportion to reducing the dose, so even low levels of exposure can be dangerous.[13] This effect is why smoke-free environment laws are followed by big drops in heart attacks and other diseases despite the fact that secondhand smokers breathe in much less smoke that the smokers.[14] In addition, while the IQOS does not set the tobacco stick on fire, it heats it to 350°C (660°F), which is still hot enough to cause pyrolysis. There is already independent evidence that IQOS compromises functioning of arteries,[15] a key risk factor for heart disease and heart attacks, as badly as a cigarette.

The clinical studies that PMI reported appropriately did not include cancer because carcinogenic effects take much longer to be manifest than cardiovascular and pulmonary effects. Even if the levels of carcinogens delivered by IQOS are lower than conventional cigarettes on a per-puff basis, these lower exposure levels may not yield proportionately lower cancer risks because both the intensity and duration of exposure impact cancer risk.[16–18]

The purpose of this paper is to assess the data on biomarkers of potential harm of the Philip Morris IQOS HTP system in people who were actually using the system compared with people who smoke conventional cigarettes based on the information submitted to the US FDA in PMI's MRTP application for IQOS. On 31 March 2018, the author conducted a PubMed search using the search term '(IQOS or 'heat not burn' or 'heated tobacco product') and (health or harm) and (human or clinical)'. This search returned 33 papers, none of which reported on comparisons of in vivo biomarkers of potential harm in people using IQOS (or any other HTP system) compared with conventional cigarettes. Thus, as of 9 July 2018, the data in the PMI MRTP application remained the only publicly available evidence on the in vivo human clinical effects of IQOS compared with conventional cigarettes.

While this analysis is limited to the data presented in PMI's IQOS MRTP application to the FDA, it is likely that the effects of other HTPs being developed by other tobacco companies will have similar effects because the fundamental principles behind all these products are the same.

On 15 June 2018, PMI issued a press release, 'Philip Morris (PM) Announces Positive Results from New Clinical Study on IQOS,'[19] that said, 'all eight of the primary clinical risk endpoints moved in the same direction as observed for smoking cessation in the group who switched to IQOS, with statistically significant changes in five of the eight endpoints compared with on-going smoking.' While PMI did not release any detailed results, examining the protocol (on ClinicalTrials.gov) revealed that this new study only examined six clinical measures, compared with the 24 in MRTP application (table 1). (The other two were biomarkers of exposure.) PMI did not say which of the changes were statistically significant, raising the possibility that the protocol and analysis were manipulated to achieve positive results.[8 9] PMI increased the sample size from 88 in the original US study to 984. While bigger studies are better, the fact is that making the sample size big enough will increase the power to the point that almost any difference will reach statistical significance regardless of whether it is clinically significant or not. The true measure of reduced risk would be statistically significant changes that were large enough to be clinically significant in enough biomarkers of potential harm to be meaningful.

PMI's failure to show significant improvements in these biomarkers of potential harm is consistent with the data PMI reported on the levels of toxicants in IQOS mainstream aerosol compared with mainstream smoke of 3R4F reference cigarettes.[20] While many toxicants were lower in IQOS aerosol, 56 others were higher in IQOS emissions and 22 were more than twice as high, and 7 were more than an order of magnitude higher.

In short, PMI's results in humans failed to meet the legal requirement that IQOS 'as it is actually used by consumers, will significantly reduce harm and the risk of tobacco-related disease to individual users' that US law requires before the FDA can approve a reduced risk claim. In the USA, PMI wants to sell IQOS with claims that 'Scientific studies have shown that switching completely from cigarettes to the IQOS system can reduce the risks of tobacco-related diseases' and 'Switching completely to IQOS presents less risk of harm than continuing to smoke cigarettes'[5]; these claims are not substantiated by PMI's own data.

On 25 January 2018, based in part on the information in this paper (which had been submitted to FDA as a public comment) showing gaps in PMI's scientific evidence, the FDA's Tobacco Products Scientific Advisory Committee voted that PMI had failed to demonstrate that its proposed modified (reduced) risk labelling and advertising claims for IQOS were demonstrated by scientific evidence.[21]

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What this paper adds

- Heated tobacco products are being marketed in several countries with claims of reduced exposure to toxins compared with conventional cigarettes.
- Studies conducted in people using Philip Morris International's IQOS heated tobacco product did not reveal detectably better measures of biomarkers of potential harm than conventional cigarettes in human tests.
- These products should not be permitted to be marketed with claims that state or imply reduced risks compared with conventional cigarettes.

Based on the data in the PMI MRTP application for IQOS, neither the US FDA nor comparable authorities elsewhere in the world should permit such claims to be made. All companies wishing to market HTPs with reduced risk claims should be held to the same standard, and their claims independently verified.

Contributors SAG is the sole author of this article.

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Data sharing statement All data are available in the PMI MRTP application on the FDA website.

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IQOS: examination of Philip Morris International's claim of reduced exposure

Gideon St.Helen,[1,2] Peyton Jacob III,[1,2] Natalie Nardone,[1] Neal L Benowitz[1,2,3]

[1]Division of Clinical Pharmacology, Department of Medicine, University of California San Francisco, San Francisco, California, USA
[2]Center for Tobacco Control Research and Education, University of California, San Francisco, California, USA
[3]Department of Bioengineering and Therapeutic Sciences, University of California San Francisco, San Francisco, California, USA

Correspondence to
Dr Gideon St.Helen, Division of Clinical Pharmacology and Experimental Therapeutics, University of California San Francisco, San Francisco, CA 94143-1220, USA;
Gideon.StHelen@ucsf.edu

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ABSTRACT

Background New electronic heated tobacco products are being introduced in the global market and are gaining popularity. In 2016, Philip Morris International, Inc. (PMI) submitted a modified risk tobacco product (MRTP) application to the Food and Drug Administration (FDA) to market IQOS in the USA with claims of reduced exposure and reduced risk.

Methods We examined PMI's MRTP application, specifically sections on aerosol chemistry and human exposure assessment, to assess the validity of PMI's claims of reduced exposure and risk.

Findings PMI reported levels for only 40 of 93 harmful and potentially harmful constituents (HPHCs) on FDA's HPHC list in IQOS mainstream aerosol. All substances in PMI's list of 58 constituents (PMI-58) were lower in IQOS emissions compared with mainstream smoke of 3R4F reference cigarettes. However, levels of 56 other constituents, which are not included in the PMI-58 list or FDA's list of HPHCs, were higher in IQOS emissions; 22 were >200% higher and seven were >1000% higher than in 3R4F reference cigarette smoke. PMI's studies also show significantly lower systemic exposure to some HPHCs from use of IQOS compared with smoking combustible cigarettes.

Conclusion PMI's data appear to support PMI's claim that IQOS reduces exposure to HPHCs. However, PMI's data also show significantly higher levels of several substances that are not recognised as HPHCs by the FDA in IQOS emissions compared with combustible cigarette smoke. The impact of these substances on the overall toxicity or harm of IQOS is not known.

INTRODUCTION

Many alternative tobacco products have entered the USA market in the last three decades. These include electronic cigarettes that heat a nicotine solution[1] as well as products that heat tobacco without combustion called heated tobacco products (HTPs) or heat-not-burn (HNB) products. A 2000 internal R J Reynolds document gave the rationale for the pursuit of an acceptable HTP:

> Given that no particular agent or group of agents can be definitely assigned the carcinogenic risk associated with cigarettes, the most effective strategy for reducing lung cancer risk in the smoking population is an overall reduction in both the number and concentration of particulate and vapor phase components. This strategy can be achieved by primarily heating, rather than burning, tobacco to form cigarette smoke aerosol.[2]

R J Reynolds first released Premier in 1988,[3] which was followed by Eclipse, a paper-encased tobacco plug heated by a carbon element.[4] Independent studies showed that use of Eclipse decreased tobacco cigarette consumption without causing withdrawal symptoms, maintained blood nicotine concentrations and decreased exposure to the carcinogenic tobacco-specific nitrosamine, 4-(methylnitrosamino)−1-(3-pyridyl)−1-butanone, but increased exposure to carbon monoxide (CO).[5–7] Other HTPs included Philip Morris' Accord, which was a combination of a handheld device that heated specially constructed cigarettes. One independent study showed that use of Accord suppressed withdrawal symptoms and reduced CO exposure.[8] Each iteration of HTPs was commercially unsuccessful, and most products were discontinued shortly after their introduction.[9]

Despite repeated failures at producing a commercially viable HTP, tobacco companies continue to research and develop these products. R J Reynolds launched a revamped Eclipse, rebranded as 'Revo', in November 2014. Revo was briefly test marketed in Wisconsin but pulled off the market.[10] Other current HTPs include British American Tobacco's Glo iFuse, a hybrid of HTP and e-cigarettes. It consists of a heating element, a liquid tank (like e-cigarettes) and a tobacco cavity through which the e-cigarette-like aerosol passes and is infused with tobacco flavour.[11] Japan Tobacco's Ploom Tech, which entered the Japanese market in 2016,[12] consists of a liquid cartridge and a capsule of granulated tobacco leaves that the vapour passes through.

Philip Morris Products S.A., a subsidiary of Philip Morris International, Inc. (PMI), developed IQOS ('I Quit Ordinary Smoking') as an HTP.[9 10] IQOS consists of a tobacco stick (HeatStick) and a battery-powered tobacco heating device.[13] As of May 2018, IQOS is currently sold in over 37 countries, including Japan, the UK and Canada.[14] Philip Morris Products S.A. filed a modified risk tobacco product (MRTP) application with the US Food and Drug Administration (FDA) in December 2016[15 16] to market IQOS in the USA with reduced exposure and reduced risk claims. The FDA's Tobacco Products Scientific Advisory Committee (TPSAC) reviewed the MRTP application in January 2018. The TPSAC committee approved, in an 8 to 1 vote, PMI's statement '*Scientific studies have shown that switching completely from cigarettes to the IQOS system significantly reduces your body's exposure to harmful or potentially harmful chemicals [HPHCs]*' was true.[17] Of the eight committee members who agreed with PMI's claim that IQOS significantly reduced exposure to HPHCs, a majority (five of eight) voted that PMI has not '*demonstrated that the reductions in exposure are reasonably likely to translate to a measurable and substantial reduction in morbidity and/or mortality*'.[17]

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Examination of PMI's studies, results and interpretation of data to support claims of reduced exposure and risk is critically important before FDA approval in order to protect public health, particularly as PMI's MRTP application and approval may set the precedent for other MRTP applications of similar products. This paper examines PMI's reported studies on IQOS aerosol chemistry and human exposure assessment, and we assessed whether they support PMI's claims of reduced exposure.

METHODS

We examined studies presented in PMI's MRTP application,[16] namely those in Module 6.1.1: *Aerosol Chemistry*; Module 6.1.3.1: *Justification of Selection of Biomarkers of Exposure*; and Module 6.1.3.2: *Summary of Biomarkers of Exposure Assessments*. We also reviewed data presented in the document, *Addendum to FDA Briefing Document: January 24–25, 2018*,[18] which was prepared by FDA's Center for Tobacco Products for the TPSAC meeting on IQOS held on 24 and 25 January 2018.

To examine the aerosol chemistry of IQOS, mainstream aerosol from IQOS HeatSticks (regular and menthol) and smoke from 3R4F reference cigarettes were generated according to the Health Canada Intense machine-smoking regimen on a Borgwaldt linear smoking machine type LM20X (Borgwaldt KC GmbH, Hamburg, Germany) for most analytes and Burghart rotary smoking machine type RMB 20 (Burghart Tabaktechnik GmbH, Wedel, Germany) for elements.[19] Methods for chemical analyses have been described previously.[19]

PMI conducted four clinical studies to examine whether human exposure to harmful substances are statistically significantly reduced with IQOS (Module 6.1.3.2).[16] All studies were randomised, controlled, open-label, three-arm, parallel group, single-centre studies. Studies ZRHR-REXC-03-EU (conducted in Poland) and ZRHR-REXC-04-JP (conducted in Japan) were conducted over 5 days in confinement. Each study included 160 combustible cigarette smokers who were randomly assigned to one of three arms, namely, IQOS with regular HeatSticks, commercially available combustible cigarettes or smoking abstinence. Use of IQOS or combustible cigarettes was from 06:30 to 23:00 and was ad libitum. Studies ZRHM-REXA-07-JP (conducted in Japan) and ZRHM-REXA-08-US (conducted in the USA) were conducted over 3 months, during which 160 participants were randomised to one of three arms in each study, namely, IQOS with menthol HeatSticks, commercially available menthol combustible cigarettes or smoking abstinence. These two studies included 5 days in confinement followed by 85 or 86 days, respectively, in an ambulatory setting. Participants in the IQOS or combustible cigarettes arms used each product ad libitum in confinement (06:30–23:00) and in the ambulatory setting. Compliance with study protocol could not be enforced during the ambulatory phase.

For the two 5-day confinement studies, it was evaluated whether reductions of 50% or more in 24 hours urine concentrations of mercapturic acid metabolites of 1,3-butadiene, acrolein and benzene and carboxyhaemoglobin in blood were observed in smokers assigned to IQOS compared with smokers who continued smoking combustible cigarettes. Levels of selected biomarkers of exposure over the 5-day exposure period were also compared between smokers who switched to IQOS and those who continued smoking and the maximum reduction in biomarker levels in abstinent smokers was assessed. For the two 3-month studies, they examined whether the geometric mean levels of biomarkers of exposure for IQOS (menthol) were lower relative to combustible cigarette (menthol) use. Differences in mercapturic acid metabolites of 1,3-butadiene, acrolein and benzene and carboxyhaemoglobin in blood were tested on day 5 and total 4-(methylnitrosamino)−1-(3-pyridyl)−1-butanol on day 90.

RESULTS

PMI reported the levels of 58 constituents (which PMI refers to as 'PMI-58') in mainstream aerosol generated from IQOS and 3R4F reference cigarettes (Module 6.1.1).[16] The PMI-58 list includes 40 (43%) out of the 93 harmful or potentially harmful constituents (HPHCs) on FDA's list of HPHCs.[20] The PMI-58 list included 18 additional constituents that do not appear on FDA's list of HPHCs, including water, total particulate matter, pyrene and nitrogen oxides. PMI concluded that the levels of HPHCs on the PMI-58 list were reduced by >92% on a stick basis and >89% on a normalised for nicotine basis for the regular tobacco stick, and >93% on a stick basis and >88% on a normalised for nicotine basis for the mentholated tobacco stick compared to 3R4F reference cigarette (Module 6.1.1, p. 45).[16]

Importantly, the addendum to the briefing document for the 24 and 25 January 2018 TPSAC meeting, prepared by FDA's Center for Tobacco Products,[18] presented additional data from PMI studies that showed higher levels of many substances in IQOS emissions compared with 3R4F cigarette smoke (table 1). The addendum consisted of data from Module 3.3.2 and section 6.1.1.3.4 of the MRTP application and appendix A of an amendment to the MRTP application. The addendum reported levels of 113 constituents, including 56 of the 58 constituents on the PMI-58 list (total particulate matter and nicotine-free dry particulate matter were the two exclusions) and 57 constituents that do not appear on the PMI-58 list. Fifty-six of the 57 non-PMI-58 constituents were higher in IQOS emission than in 3R4F smoke (median, 154% higher; range, undefined to 13 650% higher in IQOS aerosol vs 3R4F mainstream smoke); tar was the exception. Twenty-two of the non-PMI-58 constituents were at least 200% higher while seven were at least 1000% higher in IQOS emission compared with 3R4F mainstream smoke (table 1).

PMI characterised the droplet size distribution of IQOS aerosol by measuring the mass median aerodynamic diameter (MMAD) (the diameter at which 50% of the particles by mass are larger and 50% are smaller) and geometric standard deviation (presented in Module 6.1.1).[16] The MMAD for the various IQOS products tested (regular and menthol) ranged between 0.54 µm to 0.75 µm and fell within the respirability region, based on the respirability upper threshold defined at 2.5 µm. The range of MMAD for IQOS appears slightly larger than those of e-cigarettes and conventional tobacco cigarettes, which one report showed were about 0.15 µm and 0.17 µm, respectively.[21]

Regarding the human exposure studies, 11 of the 17 HPHCs measured are included in a list of 18 HPHCs that FDA recommends to be measured and reported in users of tobacco products.[20] PMI assessed systemic exposure to pyrene, which is not included in FDA's list of HPHCs, as a proxy for exposure to polycyclic aromatic hydrocarbons (PAHs) using 1-hydroxypyrene. PMI did not assess systemic exposure to inorganic compounds, phenols and metals.

Biomarkers of HPHCs measured were statistically significantly lower with IQOS use compared with combustible cigarette use (Module 6.1.3.2).[16] Reductions of at least 50% in levels of biomarkers of exposure to HPHCs were reported when smokers switched from combustible cigarettes to IQOS during 5 days of confinement; these reductions were sustained during the 85/86 days in ambulatory settings (Module 6.1.3.2, p. 145).

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Table 1 Compounds in mainstream aerosol of Marlboro HeatSticks compared with 3R4F reference cigarette

PMI product	Unit	PMI-58	IQOS HeatStick	3R4F	Change (%) with 3R4F on stick basis
1,2,3-Propanetriol, diacetate (diacetin)	µg/stick	No	1.23	0.381	↑ 223
1,2-Propanediol, 3-chloro	µg/stick	No	9.94	5.93	↑ 68
1,4-Dioxane, 2-ethyl-5-methyl-	µg/stick	No	0.055	0.0004	↑ 13 650
12,14-Labdadiene-7,8-diol, (8a,12E)	µg/stick	No	1.43	0.064	↑ 2134
1 hour-Indene, 2,3-dihydro-1,1,5,6-tetramethyl-	µg/stick	No	0.026	0.014	↑ 86
1-Hydroxy-2-butanone	µg/stick	No	0.947	0.465	↑ 104
1-Hydroxy-2-propanone(1,2-Propenediol)	µg/stick	No	162	96.8	↑ 67
2 (5H)-Furanone	µg/stick	No	5.32	1.99	↑ 167
2,3-Dihydro-5-hydroxy-6-methyl-4 hour-pyran-4-one	µg/stick	No	0.231	0.135	↑ 71
2,4-Dimethylcyclopent-4-ene-1,3-dione	µg/stick	No	0.333	0.193	↑ 73
2-Cyclopentene-1,4-dione	µg/stick	No	3.8	0.764	↑ 397
2-Formyl-1-methylpyrrole	µg/stick	No	0.128	0.064	↑ 100
2-Furancarboxaldehyde,5-methyl-	µg/stick	No	11.1	2.94	↑ 278
2-Furanmethanol	µg/stick	No	39.2	7	↑ 460
2-Furanmethanol, 5-methyl-	µg/stick	No	0.123	0.029	↑ 324
2 hour-Pyran-2-one,tetrahydro-5-hydroxy	µg/stick	No	4.45	3.11	↑ 43
2-Methylcyclobutane-1,3-dione	µg/stick	No	2.78	0.71	↑ 292
2-Propanone, 1-(acetyloxy)-	µg/stick	No	16.9	8.01	↑ 111
3 (2H)-Furanone, dihydro-2-methyl-	µg/stick	No	0.326	0.119	↑ 174
3-Methylvaleric acid	µg/stick	No	5.1	3.63	↑ 40
4(H)-Pyridine, N-acetyl-	µg/stick	No	0.296	0.112	↑ 164
5-Methylfurfural	µg/stick	No	0.995	0.632	↑ 57
Anhydro linalool oxide	µg/stick	No	0.457	0.291	↑ 57
Benzene, 1,2,3,4-tetramethyl-4-(1-methylethenyl)-	µg/stick	No	0.006	0.005	↑ 20
Benzenemethanol, 4-hydroxy-	µg/stick	No	0.011	0	↑
Benzoic acid, 2,5-dihydroxy-methyl	µg/stick	No	4.55	2.18	↑ 109
Butylated hydroxytoluene	µg/stick	No	0.132	0.007	↑ 1786
Butyrolactone	µg/stick	No	4.08	0.728	↑ 460
Cis-sesquisabinene hydrate	µg/stick	No	0.061	0	↑
Cyclohexane, 1,2-dioxo-	µg/stick	No	0.083	0.046	↑ 80
Cyclohexane-1,2-dione, 3-methyl-	µg/stick	No	0.101	0.073	↑ 38
Eicosane, 2-methyl-	µg/stick	No	0.05	0.014	↑ 257
Ergosterol	µg/stick	No	3.18	1.58	↑ 101
Ethyl 2,4-dioxohexanoate	µg/stick	No	6.73	3.57	↑ 89
Ethyl dodecanoate (ethyl laurate)	µg/stick	No	0.023	0	↑
Ethyl linoleate	µg/stick	No	0.135	0.008	↑ 1588
Ethyl linolenate	µg/stick	No	0.614	0.153	↑ 301
Furfural	µg/stick	No	31.1	25.9	↑ 20
Glycerol	mg/stick	No	5.02	2.08	↑ 141
Glycidol	µg/stick	No	5.71	1.76	↑ 224
Heneicosane, 2-methyl-	µg/stick	No	0.063	0.021	↑ 200
Hexadecanoic acid, ethyl ester	µg/stick	No	0.491	0.008	↑ 6038
Isolinderanolide	µg/stick	No	4.99	1.85	↑ 170
Isoquinoline, 3-methyl	µg/stick	No	6.29	4.99	↑ 26
Labdane-8,15-diol, (13S)	µg/stick	No	0.143	0.015	↑ 853
Lanost-8-en-3-ol, 24-methylene-, (3beta)	µg/stick	No	6.3	1.61	↑ 291
Maltoxazine	µg/stick	No	0.077	0.038	↑ 103
Methyl furoate	µg/stick	No	0.147	0.029	↑ 407
Phenylacetaldehyde	µg/stick	No	1.41	0.529	↑ 167
p-Menthan-3-ol	µg/stick	No	0.786	0.322	↑ 144
Propylene glycol	µg/stick	No	175	23.7	↑ 638
Pyranone	µg/stick	No	6.54	5.07	↑ 29
Pyranone	µg/stick	No	9.26	5.84	↑ 59
Pyridoxin	µg/stick	No	0.699	0.526	↑ 33

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Table 1 Continued

PMI product	Unit	PMI-58	IQOS HeatStick	3R4F	Change (%) with 3R4F on stick basis
Stearate, ethyl-	µg/stick	No	0.074	0.003	↑ 2367
Tar	mg/stick	No	19.4	25	↓ 22
Trans-4-hydroxymethyl-2-methyl-1,3-dioxolane	µg/stick	No	2.09	0.044	↑ 4650
1,3-Butadiene	µg/stick	Yes	0.21	89.2	↓ 99.8
1-Aminonaphthalene	ng/stick	Yes	0.043	20.9	↓ 99.8
2-Aminonaphthalene	ng/stick	Yes	0.022	17.5	↓ 99.9
3-Aminobiphenyl	ng/stick	Yes	0.007	4.6	↓ 99.8
4-Aminobiphenyl	ng/stick	Yes	0.009	3.21	↓ 99.7
Acetaldehyde	µg/stick	Yes	192	1602	↓ 88
Acetamide	µg/stick	Yes	2.96	13	↓ 77
Acetone	µg/stick	Yes	30.7	653	↓ 95
Acrolein	µg/stick	Yes	8.32	158	↓ 95
Acrylamide	µg/stick	Yes	1.58	4.5	↓ 65
Acrylonitrile	µg/stick	Yes	0.145	21.2	↓ 99.3
Ammonia	µg/stick	Yes	12.2	33.2	↓ 63
Arsenic	ng/stick	Yes	<0.36	<7.49	NA
Benz[a]anthracene	ng/stick	Yes	2.65	28.4	↓ 91
Benzene	µg/stick	Yes	0.45	77.3	↓ 99.4
Benzo[a]pyrene	ng/stick	Yes	0.736	13.3	↓ 94
Butyraldehyde	µg/stick	Yes	20.7	81.3	↓ 74
Cadmium	ng/stick	Yes	<0.28	89.2	↓ >99.7
Carbon monoxide	mg/stick	Yes	0.35	29.4	↓ 99
Catechol	µg/stick	Yes	14	84.1	↓ 83
Chromium	ng/stick	Yes	<11.0	<11.9	NA
Crotonaldehyde	µg/stick	Yes	<3.29	49.3	↓ >93
Dibenz[a,h] anthracene	ng/stick	Yes	<0.124	<0.689	NA
Ethylene oxide	µg/stick	Yes	<0.119	16	↓ >99.3
Formaldehyde	µg/stick	Yes	14.1	79.4	↓ 82
Hydrogen cyanide	µg/stick	Yes	<1.75	329	↓ >99.5
Hydroquinone	µg/stick	Yes	6.55	94.5	↓ 93
Isoprene	µg/stick	Yes	1.51	891	↓ 99.8
Lead	ng/stick	Yes	2.23	31.2	↓ 93
m-Cresol	µg/stick	Yes	0.042	4.24	↓ 99
Mercury	ng/stick	Yes	1.38	3.68	↓ 63
Methyl-ethyl-ketone	µg/stick	Yes	10.1	183	↓ 94
Nickel	ng/stick	Yes	<15.9	<12.9	NA
Nicotine	mg/stick	Yes	1.29	1.74	↓ 26
Nitric oxide	µg/stick	Yes	12.6	484	↓ 97
Nitro benzene	µg/stick	Yes	<0.011	<0.038	NA
Nitrogen oxides	µg/stick	Yes	14.2	538	↓ 97
N-nitrosoanabasine	ng/stick	Yes	2.35	29	↓ 92
N-nitrosoanatabine	ng/stick	Yes	14.7	254	↓ 94
NNK	ng/stick	Yes	7.8	244.7	↓ 97
NNN	ng/stick	Yes	10.1	271	↓ 96
o-Cresol	µg/stick	Yes	0.078	4.81	↓ 98
o-Toluidine	ng/stick	Yes	1.1	96.2	↓ 99
p-Cresol	µg/stick	Yes	0.071	9.6	↓ 99
Phenol	µg/stick	Yes	1.47	15.6	↓ 91
Propionaldehyde	µg/stick	Yes	10.8	109	↓ 90
Propylene oxide	ng/stick	Yes	142.3	896	↓ 84
Pyrene	ng/stick	Yes	8.2	79.2	↓ 90
Pyridine	µg/stick	Yes	6.58	30.9	↓ 79
Quinoline	µg/stick	Yes	<0.011	0.43	↓ >98
Resorcinol	µg/stick	Yes	<0.055	1.72	↓ >97

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Table 1 Continued

PMI product	Unit	PMI-58	IQOS HeatStick	3R4F	Change (%) with 3R4F on stick basis
Selenium	ng/stick	Yes	1.27	<4.42	NA
Styrene	µg/stick	Yes	0.58	13.9	↓ 96
Toluene	µg/stick	Yes	1.42	129	↓ 99
Vinyl chloride	ng/stick	Yes	<0.657	93.4	↓ >99
Water	mg/stick	Yes	30.2	14.7	↑ 105

Notes: presented in table 1 of *Addendum to FDA Briefing Document, January 24-25, 2018*, Meeting of the Tobacco Products Scientific Advisory Committee; sata source: section 3.3.2 and section 6.1.1.3.4 of the Modified Risk Tobacco Product application (MRTPAs) and appendix A of an amendment to the MRTPAs submitted on 8 December 2017. Total particulate matter and nicotine-free dry particulate matter, two constituents on the PMI-58 list were not reported by PMI in this table.
↑, higher in IQOS; ↓, lower in IQOS.
PMI, Philip Morris International; PMI-58, PMI's list of 58 constituents.

DISCUSSION

According to FDA's draft guidance, an MRTP is 'any tobacco product that is sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products'.[22] FDA may issue an order allowing a product to be marketed as a modified risk product if it is demonstrated that the product: (A) significantly reduces harm and the risk of tobacco-related disease to individual tobacco users; and (B) benefits the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products. PMI's data show that IQOS significantly reduces emissions and exposure to several HPHCs compared with combustible cigarettes. However, PMI's data also show that IQOS emissions contain higher levels of many other substances compared with combustible cigarettes. The impact of these substances on IQOS toxicity and harm are not known.

Over 7000 distinct substances have been identified in tobacco smoke, many of which are toxic or carcinogenic.[23] HPHCs in tobacco or tobacco smoke have been proposed by several public health authorities, such as the FDA,[20] as possible causes of tobacco-related morbidity and mortality. Elimination or reduction of exposure to these HPHCs may potentially reduce health risks, which is the premise of HTP technology. Schaller and colleagues[19] described five criteria used by PMI to select HPHCs to measure in IQOS aerosol for comparison with 3R4F reference cigarette. Criterion 1 includes smoke constituents determined by International Organization for Standardization (ISO) methods, such as total particulate matter, nicotine and CO. Criterion 2 includes priority toxicants in tobacco smoke selected from the lists issued by regulatory bodies or proposed by cognizant authorities, such as volatile organic compounds like acrylonitrile, 1,3-butadiene and benzene. Criterion 3 includes toxicants for which there is an established biomarker of exposure. Criterion 4 includes toxicants that are predominantly formed below 400°C and that are not included under 'Criterion 2', such as acrylamide and acetamide. Criterion 5 includes toxicants that are predominantly formed above 400°C and that are not included under 'Criterion 1' and 'Criterion 2', such as dibenz[a,h]anthracene and benz[a]anthracene.

PMI's conclusion that IQOS reduces exposure to HPHCs, which TPSAC agreed with,[17] is based, in part, on evidence of lower levels of PMI-58 substances in IQOS emissions compared with 3R4F reference cigarette smoke. However, the PMI-58 list is selective (based on PMI's criteria described before); PMI did not report levels of 53 HPHCs on FDA's list of 93 HPHCs. Of the 53 FDA HPHCs not measured, 50 are carcinogenic (eg, 2,6-dimethylaniline, benz[j]aceanthrylene, ethylbenzene and furan).[20] In addition to the PMI-58 substances, PMI measured levels of 57 other substances in IQOS emissions (non-PMI-58 substances). Importantly, 56 of these 57 non-PMI-58 substances were higher in IQOS aerosol compared with 3R4F mainstream cigarette smoke. It appears that IQOS reduces exposure to some toxicants but elevates exposure to other substances.

Given the elevated levels of the non-PMI-58 substances in IQOS aerosol compared with reference cigarette smoke, their inherent toxicities could play a role in the overall harm of IQOS. A number of these substances, including several that were more than 50% higher in IQOS aerosol, belong to chemical classes that are known to have significant toxicity, such as α,β-unsaturated carbonyl compounds (eg, 2-cyclopentene-1,4-dione),[24] 1,2-dicarbonyl compounds (eg, cyclohexane, 1,2-dioxo-),[25] furans (eg, 2 (5H)-furanone)[26] and epoxides (eg, anhydro linalool oxide).[27] There is limited information on the toxicity of many of the non-PMI-58 substances. We speculate that some of these substances are components of flavour additives in IQOS or thermal degradation compounds. For example, anhydro linalool oxide is listed among flavouring ingredients that are generally regarded as safe (for oral ingestion) by the Flavor and Extract Manufacturers' Association.[28]2 (5H)-Furanone is a food additive that suppresses appetite and/or food intake and has been shown to induce cellular DNA damage in vitro.[29 30] 2-Furanmethanol is a flavouring agent with a flavour profile of burnt, caramel or cooked.[31] 2-Furanmethanol also causes eye, nose, throat and skin irritation and has central nervous system effects.[31] 2-Cyclopentene-1,4-dione is likely generated from thermal breakdown of sugars.[32] 1-Hydroxy-2-butanone, a flavouring ingredient found in coffee and coffee products, is also a degradation product of polysaccharides.[33] Some compounds appear to be contaminants. 3-Chloro-1,2-propanediol (or 1,2-propanediol, 3-chloro), a food contaminant,[34] has not been shown to be genotoxic in vivo,[35] but mutagenic effects were observed at high concentrations in vitro experiments.[36] A 2-year study found increased incidence for the development of tumours in kidney and testis in male rats exposed to 3-chloro-1,2-propanediol.[37] 1,2,3-Propanetriol, diacetate (diacetin) is a solvent used for decaffeinating coffee.

PMI's MRTP application fails to address the important question of whether the aerosol generation process for IQOS produces toxic substances not found in the smoke of combustible cigarettes, which could have been answered through non-targeted chemical analysis. Combustible tobacco cigarettes reach about 900°C during a puff and smoulder at about 400°C between puffs.[23] The burning process, substances emitted and their levels vary at different temperatures.[38] Distillation, the process during which

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nicotine and aromas are transferred from tobacco to smoke, occurs below 300°C; pyrolysis occurs at about 300°C–700°C, entails the decomposition of biopolymers, proteins, and other organic materials and generates the majority of substances emitted in smoke; and combustion occurs above 750°C and results in the generation of carbon dioxide, CO and water.[38] HeatSticks are heated to a maximum of 350°C,[19] a temperature sufficient to enable pyrolytic decomposition of some organic materials. Formation of toxic volatile organic compounds, including formaldehyde, acetaldehyde and acrolein, via dehydration and oxidation of the humectants, propylene glycol and glycerin, have been reported in e-cigarette aerosols at similar temperatures as IQOS.[39–42] In addition, flavouring chemicals in e-cigarettes undergo thermal degradation and contribute significantly to levels of toxic aldehydes emitted in e-cigarette aerosol.[43] Since the constituents of HeatSticks may be different from that of combustible cigarettes, including flavourants and additives, it is plausible that the IQOS aerosol may contain substances not present in tobacco smoke.

A study by Klupinski and colleagues[44] reported that unique substances, such as ambrox, 3-methylbutanenitrile and 4-methylimidazole, were found in little cigar smoke that were not found in cigarette smoke, indicating that different tobacco products can have different chemical fingerprints and lead to different exposure and toxicological profiles. The study by Klupinski and colleagues describes methodology for 'non-targeted' analysis of tobacco smoke aerosol, and the authors suggest that 'the same approach could also be applied to other samples to characterize constituents associated with tobacco product classes or specific tobacco products of interest'. FDA should recommend that manufacturers of HTPs undertake 'non-targeted' analyses (along with targeted analysis), comparing HTP aerosol with smoke from combustible tobacco products to identify potentially toxic chemicals in HTP emissions that may not be present in tobacco smoke.

Although smoking machine studies are appropriate for examining the relative differences in emissions between products, they do not predict use patterns and systemic exposure to toxicants. PMI reported systemic exposure to 17 HPHCs in its human exposure studies. PMI did not assess systemic exposure to any inorganic compounds, phenols and metals, possibly due to the fact that there are no valid biomarkers for some substances or that the time course of the biomarkers may not be optimal for studies of the duration used by PMI. PMI used 1-hydroxypyrene, a metabolite of pyrene (a PAH) as a biomarker of PAHs. Pyrene is not included as an HPHC on FDA's list. We have previously demonstrated that 1-hydroxypyrene is not a selective measure of tobacco-related PAH exposure and is weakly related to nicotine intake and tobacco-specific nitrosamine exposure.[45] Instead, we found that monohydroxylated metabolites of fluorene (particularly 1-hydroxyfluorene) and 2-naphthol (a naphthalene metabolite) were more selective of tobacco smoke exposure. In characterising PAH exposure from HNB products, manufacturers should include biomarkers with relatively high selectivity for tobacco.

In conclusion, PMI's data show that IQOS emissions have significantly lower levels of several HPHCs compared with combustible cigarettes. Furthermore, PMI's data from human studies show that use of IQOS is associated with significantly lower systemic exposure to some HPHCs compared with smoking combustible cigarettes. These data appear to support PMI's claim that IQOS is a reduced exposure product. However, PMI's data also show significantly higher levels of other substances in IQOS emissions compared with combustible cigarette smoke. The impact of these substances on the overall toxicity or harm of IQOS is not known.

What this paper adds

- Studies conducted by Philip Morris International, Inc. (PMI) show that IQOS emissions contain lower levels of many harmful or potentially harmful constituents (HPHCs) compared with combustible tobacco smoke.
- PMI's studies show that use of IQOS results in significantly lower systemic exposure to several HPHCs compared with combustible cigarette smoking.
- PMI's own data also show that IQOS emissions contain many other substances, some of which are potentially toxic, at higher levels than in combustible cigarette smoke.

Contributors All authors were involved in interpretation of data and writing and revising the manuscript. All authors approve this version of the manuscript for publication.

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Competing interests NLB has served on smoking cessation advisory boards for Pfizer and has been an occasional consultant to McNeil and Achieve Life Sciences and has served as a paid expert witness in litigation against tobacco companies.

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Light and mild redux: heated tobacco products' reduced exposure claims are likely to be misunderstood as reduced risk claims

Lucy Popova,[1] Lauren Kass Lempert,[2] Stanton A Glantz[2,3]

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[1]School of Public Health, Georgia State University, Atlanta, Georgia, USA
[2]Center for Tobacco Control Research & Education, University of California, San Francisco, California, USA
[3]Department of Medicine, Cardiovascular Research Institute, Philip R. Lee Institute for Health Policy Studies, Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, San Francisco, California, USA

Correspondence to
Dr Lucy Popova, School of Public Health, Georgia State University, Atlanta, GA 30302, USA; lpopova1@gsu.edu

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ABSTRACT

Introduction Heated tobacco products (HTPs) are being marketed in several countries around the world with claims that they are less harmful than combusted cigarettes, based on assertions that they expose users to lower levels of toxicants. In the USA, Philip Morris International (PMI) has submitted an application to the Food and Drug Administration (FDA) in 2016 seeking authorisation to market its HTPs, IQOS, with reduced risk and reduced exposure claims.

Methods We examined the PMI's Perception and Behavior Assessment Studies evaluating perceptions of reduced risk claims that were submitted to the FDA and made publicly available.

Results Qualitative and quantitative studies conducted by PMI demonstrate that adult consumers in the USA perceive reduced exposure claims as reduced risk claims.

Conclusion The data in the PMI modified risk tobacco product IQOS application do not support reduced risk claims and the reduced exposure claims are perceived as reduced risk claims, which is explicitly prohibited by the FDA. Allowing PMI to promote IQOS as reduced exposure would amount to a legally sanctioned repeat of the 'light' and 'mild' fraud which, for conventional cigarettes, is prohibited by the US law and the WHO Framework Convention on Tobacco Control.

INTRODUCTION

Heated tobacco products (HTPs), also called heat-not-burn products, are tobacco products that heat tobacco to temperatures that avoid combustion and produce a nicotine aerosol that is inhaled by smokers and may also generate side-stream emissions.[1] As of February 2018, HTP entrants into the global market included Philip Morris International's (PMI)'s 'IQOS', British American Tobacco's 'Glo', Japan Tobacco's 'Ploom Tech' and RJ Reynolds' revamped 'Eclipse'. Because of the growing evidence of severe negative health effects of smoking and smokers' concerns about their health, tobacco companies have been motivated to create 'safer cigarettes' since the 1960s, and in 1988 they first introduced HTPs, marketing them as less harmful than combusted cigarettes. While HTPs produce different toxic chemicals than combusted cigarettes,[2] the human health effects of HTPs are not completely understood and the evidence that PMI submitted to the US Food and Drug Administration (FDA) revealed that, in terms of the clinical biomarkers of disease[3] or pulmonary and immune toxicity,[4] IQOS was not significantly different from cigarettes.

As of February 2018, the new HTPs, like PMI's IQOS, were being sold in multiple countries around the world in minimalist high-tech looking stores that resemble Apple stores.[5–7] Advertisements and marketing materials for IQOS emphasise both its superiority over combustible cigarettes (in terms of cleanliness and customisability) and similarity to them (in terms of product's taste, size and providing similar behavioural experience).[6] Claims about health benefits or lower risks of IQOS are not emphasised in the marketing materials and some of the materials carry minimal health warnings, such as 'This tobacco product can harm your health and is addictive'[6] or it is 'not risk-free or a safe alternative to cigarettes but it is a much better choice than smoking.'[7] Before IQOS is introduced into the US market, PMI needs the FDA's permission. The 2009 Family Smoking Prevention and Tobacco Control Act[8] (FSPTCA) assigns the FDA authority to regulate the manufacturing, marketing and distribution of tobacco products in the USA. Tobacco manufacturers may seek authorisation from FDA to market products with claims that they reduce risks of tobacco-related diseases compared with other tobacco products currently on the market.

To obtain FDA authorisation to market a product as a 'modified risk tobacco product' (MRTP), a company must submit an MRTP application to FDA. FDA may issue one of two types of orders permitting such marketing: (1) a 'risk modification order' or (2) an 'exposure modification order'.[9 10] For a *risk modification* order, a company must provide scientific evidence that the product 'as actually used by consumers will (1) significantly reduce harm and the risk of tobacco-related disease to individual users and (2) benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products.'[10] When such scientific evidence is not available and cannot be obtained without long-term epidemiological studies, an *exposure modification* order can be issued if the company demonstrates that such an order would be appropriate for promoting public health (once again taking into account both users and non-users) and that lower levels of harmful chemicals in the product will likely result in reduced death and disease among individual tobacco users. Under the exposure modification order, the marketing claim can only state that the product has lower levels of or is free of a certain substance. Furthermore, a company needs to demonstrate that "consumers will not be misled into believing that the product is […] less harmful or presents […] less of a risk of disease than

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one or more other commercially marketed tobacco products."[9] The FSPTCA puts the burden on the MRTP applicant, not the FDA, to demonstrate that the product presents reduced risk or reduced exposure and to demonstrate that consumers do not perceive reduced exposure claims as reduced risk claims.

Long before the MRTP process was enacted in 2009, tobacco companies had been misleading the public with reduced exposure claims since the 1950s, asserting that filtered and low-tar cigarettes[11] gave smokers 'less tar and nicotine',[12] a reduced exposure claim. 'Light' and 'mild' cigarettes have been marketed to smokers concerned about their health and positioned as an alternative to quitting smoking.[13–15] Even though advertisements for light and mild cigarettes almost never explicitly stated that they would reduce risk of tobacco-related disease, people who saw these advertisements with reduced exposure claims perceived these cigarettes to have lower health risks than regular cigarettes.[16 17]

Furthermore, these cigarettes did not result in lower levels of exposure to harmful chemicals for users. Tobacco companies created them with microscopic ventilation holes in the filters to draw in air and reduce machine-measured tar and nicotine, which gave the appearance that these products delivered lower emissions to the user.[18 19] However, the cigarette companies designed these products so that smokers would compensate for dilution of the smoke by blocking ventilation holes with their lips, taking larger puffs or taking more frequent puffs.[20–23]

This inherently deceptive nature of reduced exposure and reduced risk ('light' and 'mild') marketing claims was at the core of the US Department of Justice's Racketeer Influenced and Corrupt Organization (RICO) Act lawsuit against the major cigarette companies for defrauding the public about the dangers of smoking and which essentially became the basis of the FSPTCA's MRTP provisions. In August 2006, Federal Judge Gladys Kessler held[24] that the tobacco companies, including Philip Morris, violated RICO by fraudulently covering up the health risks associated with smoking and for marketing their products to children. Judge Kessler found that the companies "have engaged in and executed – and *continue to engage in and execute* -- a massive 50 year scheme to defraud the public, including consumers of cigarettes, in violation of RICO [emphasis added]." In her 1683-page opinion with extensive Findings of Fact, Judge Kessler found, among other fraudulent acts, that Philip Morris and other tobacco companies deceptively marketed cigarettes characterised as 'light' or 'low tar', while knowing that those cigarettes were at least as hazardous as 'full flavoured' cigarettes; misled smokers, former smokers and non-smokers to believe that these cigarettes were safer and deliberately targeted the youth market (see table 1 for examples of relevant findings). Importantly, the court found that there was a reasonable likelihood that defendants would continue to violate RICO in future.

Following the 2006 RICO decision, in 2009, Congress recognised and described the tobacco companies' use of reduced exposure claims to mislead the public and Judge Kessler's findings in 14 of the 49 Findings for the FSPTCA.[10] Of particular relevance, Congressional Finding 40 states: "The dangers of products sold or distributed as modified risk tobacco products that do not in fact reduce risk are so high that there is a compelling governmental interest in ensuring that statements about modified risk tobacco products are complete, accurate, and relate to the overall disease risk of the product."

Given the long history of the tobacco industry using reduced exposure claims to mislead consumers into believing that the products in question have reduced risk, most notably through the use of 'light' and 'mild' cigarette claims, it is important to evaluate to what extent the modified risk claims for the new HTP products are based on scientific evidence and whether reduced exposure claims are perceived by consumers as reduced risk claims. This paper uses the materials in the PMI MRTP application made public by the FDA to evaluate these claims.

Table 1 Relevant findings from Racketeer Influenced and Corrupt Organization case

"According to [Brand Manager of Marlboro from 1969 to 1972, James] Morgan, Philip Morris made a calculated decision to use the phrase 'lower tar and nicotine' even though its own marketing research indicated that consumers interpreted that phrase as meaning that the cigarettes not only contained comparatively less tar and nicotine, but also that they were a healthier option."	[24] Para 2402, p. 888
"Morgan, who later became CEO of Philip Morris, further explained in 2002 that rather than relying on the tar and nicotine numbers from the FTC Method, 'the major influence in people's perceptions in the tar of a cigarette would have come from the marketing positioning of a brand as opposed to people literally reading the FTC [tar and nicotine figures]."	[24] Para 2403, p. 888
Philip Morris and the other tobacco companies knew that "many smokers who were concerned and anxious about the health risks from smoking would rely on the health claims made for low tar cigarettes as a reason, or excuse, for not quitting smoking"	[24] Para 2627, p. 971

METHODS

We examined the materials in the PMI MRTP applications to FDA[25] for its HTP IQOS system and Heatstick products (PMI also refers to IQOS as Tobacco Heating System (THS) 2.2 in these materials). On 5 December 2016, PMI submitted its MRTP applications asking the FDA to authorise marketing of IQOS with reduced risk and reduced exposure claims. Our analysis is based on the Executive Summary[26] and Module 7: Scientific Studies and Analyses,[27] specifically Section 7.3 Studies in Adult Human Subject (7.3.2 Perception and Behavior Assessment (PBA) Studies), studies THS-PBA-02-US, THS-PBA-03-US, THS-PBA-04-US and THS-PBA-05-REC-US. We report PMI's findings on the consumer perceptions of reduced exposure claims.

RESULTS

To develop and evaluate marketing messages and materials with reduced risks and reduced exposure claims, PMI conducted Consumer PBA Studies (table 2). Participants were recruited by phone from proprietary databases maintained by local research agencies, which include people interested in participating in market research. Participants' smoking status was based on self-report.

Qualitative studies

PMI's qualitative studies (THS-PBA-02-US and THS-PBA-04-US) were conducted by TNS Qualitative. Focus groups and individual interviews were conducted in person, in facilities with one-way mirrors with PMI representatives observing the studies. They followed discussion guides and employed 'visual aids' to position products on relative risk and interest to use scales. Focus groups lasted 2.5 hours, while individual interviews took 1.5 hours. Participants evaluated various messages containing either reduced exposure or reduced risk claims. In THS-PBA-02-US, they evaluated 13 messages in focus groups in Phase 1 (Online Supplementary 1), which were subsequently modified

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Table 2 Philip Morris International's (PMI)'s Consumer Perception and Behavior Assessment (PBA) Studies in the USA

Study name	Methodology	Location	Study year	Participants	Age	Materials
THS-PBA-02-US	Qualitative 20 focus groups (n=113) 37 individual interviews	Boston, MA Chicago, IL Charlotte, NC Phoenix, AZ	Oct–Dec 2013	S-NITQ, S-ITQ, FS, NS*	21+	Nine potential 'plain text'† messages‡
THS-PBA-03-US	Quantitative (n=1713)	Chicago, IL Marlton, NJ Phoenix, AZ Atlanta, GA	Oct–Dec 2014	S-NITQ, S-ITQ, FS, NS	LA+	Three potential 'plain text'† messages selected from THS-PBA-02-US
THS-PBA-04-US	Qualitative 28 individual interviews	Chicago, IL Phoenix, AZ	Dec 2014	AS, FS, NS	18+	Five potential branded§ communication materials with claims selected from THS-PBA-02-US
THS-PBA-05-RRC-US	Quantitative (n=2255)	Paramus, NJ Dallas, TX St Louis, MO Los Angeles, CA	Jul 2015	S-NITQ, S-ITQ, FS, NS	LA+	Three branded§ communication materials with claim #1 'Reduced risks of tobacco-related diseases'
THS-PBA-05-RRC2-US	Quantitative (n=2247)	Marlton, NJ Chicago, IL Tampa, FL Denver, CO	Sep 2015	S-NITQ, S-ITQ, FS, NS	LA+	Three branded§ communication materials with the claim #2—'Reduced risk of harm'
THS-PBA-05-REC-US	Quantitative (n=2272)	Framingham, MA San Diego, CA St Louis, MO Baltimore, MD	Dec 2015	S-NITQ, S-ITQ, FS, NS	LA+	Three branded§ communication materials with the claim #3 'Reduced body's exposure to harmful and potentially harmful chemicals'

*Never smokers participated only in Phase 2 of THS-PBA-02-US.
†'Plain text' message describes the information communicated on the product.
‡The table in the PMI document says nine messages, but the file (Online Supplementary 1) for Phase 1 shows 13 messages because there are two versions of some (A1, A2, B, C1, C2, D and so on). Phase 2 tested seven messages (Online Supplementary 2).
§The branded communication materials were brochure, pack and direct mail piece with iQOS commercial name and the Tobacco Sticks as HeatSticks with the Marlboro Brand.
AS, adult smokers; FS, adult former smokers; LA, legal smoking age; NS, adult never smokers; S-ITQ, adult smokers with the Intention to quit; S-NITQ, adult smokers with no intention to quit.
Source: adapted from table 1 Overview of the Studies from PMI Research and Development[51] (p. 7).

into seven messages for testing with individual interviews in Phase 2 (Online Supplementary 2).

Participants frequently equated reduced exposure claims with reduced risk, conflating the reduction in chemicals with lower chances of developing tobacco-related health issues. For example, female smoker (21–34 years old, Phoenix) stated: "It reduces your body's exposure to the chemicals… that would be my biggest take-away… it suggests that it is better for you than a traditional cigarette." When asked to clarify: (Better—In what way?), she specified: "It's the lesser of two evils; it's a better bad choice… It reduces harmful chemicals which is likely to reduce your chances of getting a tobacco-related disease."

While the PMI's claims that reduced exposure does not mean reduced harm tried to address this issue, some people found this juxtaposition of a claim of reduced exposure and no reduced harm confusing and hard to believe, which reduced credibility of the message source. Female smoker (21–35 years old, Boston) explained: "It says to me that if you smoke this or if you use this thing, you're still at risk of getting all those diseases that they claim it reduces your exposure to… The way it's worded… I'm not buying into it. It's kind of doubletalk… […] It's flip flopping, saying it will reduce but you still might get it, or … It's just weird, it doesn't make me want to use it at all, now that I'm reading this… This makes me less likely to use it, because I'm… almost mad that it tries to claim that it… has benefits, but it really doesn't."

The THS-PBA-02-US Study report concludes that all messages (both reduced risk and reduced exposure claims) were perceived by participants as statements about lower harm. In Phase 2, three out of seven messages were reduced exposure claims. For all three reduced exposure messages, the PMI's report stated that participants perceived IQOS to be a lower risk than conventional cigarettes because the tobacco is heated, not burned, which results in reduced 'exposure to harmful chemicals' (pp. 31, 34) and 'the absence of smoke and second-hand smoke' (p. 37).[28] For the four reduced risk messages, the report similarly concluded that the product was 'perceived to be a lower risk than conventional cigarettes' (pp. 40, 42, 44, 46) by 'reducing the production of harmful chemicals found in cigarette smoke and providing a possible chance of reducing the risk of tobacco-related diseases' (pp. 44, 46).[28]

The fact that PMI's report does not distinguish perception of reduced risk and reduced exposure provides additional evidence that reduced exposure claims are viewed as reduced risk claims.

The findings from the second qualitative study (THS-PBA-04-US) that assessed reduced risk and reduced exposure claims in the context of marketing materials (brochure, pack and direct mail) portray a similar picture. The study report concludes that "There is a clear recognition that this is an innovative product that heats, rather than burns, the tobacco using electronic technology combining the tobacco taste satisfaction of CC's [conventional cigarettes] with hygiene benefits (less odor, no ash, less mess) and the potential to reduce the risk to health compared to smoking conventional cigarettes."[29] Also, "Understanding is generally consistent across all label, labeling and marketing material and subject groups."[29]

In this second qualitative study, reduced exposure claims in combination with the information that IQOS does not reduce risk of tobacco-related disease (presented as 'Important Warning') were also perceived as confusing and contradictory, but still made participants rate the risk as moderate, below the

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risk of conventional cigarettes. Some participants were able to articulate that reduced exposure does not mean reduced risk:

> "It's still as risky as smoking a cigarette. It does not mean a reduction in the risk of developing tobacco related diseases… Tobacco related diseases are what you get from smoking cigarettes. It's telling me that even though it scientifically reduces my body's exposure to these chemicals, I have the exact same risk of developing a tobacco-related disease." (female adult smoker, 26–35 years old, Chicago).

Yet others were still very optimistic about the product that offers reduced risk, particularly appreciating the implications of reduced exposure as the ability to use HTPs in smoke-free places:

> "There's still a risk, so we all know we can't get anywhere besides-you can't get anywhere, you can't even hide from that, so there's going to be risk. But it's just a better way of smoking a cigarette. It gives you a better option. 'Real tobacco, no fire, tobacco heating system', so obviously trying to make it a better way of smoking, make it better for you to smoke at your workplace, school, anywhere. So yeah, that's what I get from it. Well, they give you the less odor, no fire. It even tells you-it gives you a little hint that it will be better for the people that's around you worrying about affecting them, so that's good." (male adult smoker, 18–25 years old, Phoenix).

In summary, PMI's qualitative studies demonstrate that US adults understand reduced exposure claim to mean that the lower levels of harmful chemicals in the product means reduced risk of health harms.

Quantitative studies

PMI reports results of two quantitative studies (THS-PBA-03-US and THS-PBA-05-REC-US, see table 2 for details) that were conducted by Covance Market Access Service. Quantitative studies were five-arm parallel group experiments, where each arm corresponded to the different message condition tested in the study. Studies used computer-assisted self-interviews (with computer-assisted personal interviews for more in-depth questions in THS-PBA-03-US) and lasted 45 min on average. The outcome measures used in these studies are presented in table 3. For the purpose of our study, we focus on the measures PMI used to assess global comprehension and risk perceptions because they indicate to what extent reduced exposure claims are perceived as reduced risk claims.

In THS-PBA-03-US, five different text-based messages were evaluated: four contained reduced exposure claims and one had a reduced risk claim (figure 1). Participants were randomised into five groups, where each group saw one of the messages. For the measure of global comprehension, the proportion selecting the answer 'Reduces the risk of tobacco-related diseases' was 18% for reduced exposure Message 3, 28% (Message 2), 32% (Message 1) and 35% (Message 4). For all perceived risk measures (health risk to self (figure 3), addiction risk and risk to others), participants rated IQOS lower in risk than cigarettes for all messages, whether it was a reduced exposure message or a reduced risk message.

In THS-PBA-05-REC-US, participants evaluated marketing materials with a reduced exposure warning: a brochure, a pack

Table 3 Outcome measures in quantitative studies

Construct	Instrument	Example question
Intent to Use	The Intent to Use Questionnaire ► Intention to Try (ie, to sample at least once; two items) ► Intention to Use (ie, for continued usage; two items) (Answers on 6-point scale from 'Definitely Not' to 'Definitely').	Based on what you know about IQOS, how likely or unlikely are you to try IQOS? If you try IQOS and like it, and taking into consideration the prices that are shown on the material, how likely or unlikely are you to use IQOS regularly?
Change in Intention to Quit Smoking	Yes/No questions based on Prochaska and DiClemente's Stages of Change model (Prochaska and DiClemente 1982) measured before and after exposure to THS 2.2 message to determine change in Intention to Quit Smoking (four items).	Are you seriously considering quitting smoking within the next 6 months?
Comprehension	1. 'Global comprehension': overall comprehension of the THS 2.2 message on exposure to harmful chemicals and risk of tobacco-related diseases of using THS 2.2. 2. 'Specific comprehension': comprehension of three specific parts of the THS 2.2 message: the Intended Users Statement, Evidence Statement and Warning Statement. Both types of comprehension were assessed with multiple choice questions; five response options were presented, with one correct option, three incorrect options and an option for 'don't know'.	1. Thinking about all of the information on the card, would you say that compared with cigarettes, using THS 2.2: a. Has a greater risk of tobacco-related diseases b. Reduces the risk of tobacco-related diseases c. Has not been demonstrated to reduce the risk of tobacco-related diseases (correct) d. Eliminates the risk of tobacco-related diseases e. Don't know 2. What happens to tobacco when IQOS is used? a. It is burned b. It remains at room temperature c. It is cooled d. It is heated but not burned (correct) e. Don't know
Risk Perception	The Perceived Risk Instrument-Personal Risk comprised of two domains, each measured by a unidimensional scale: 1. Perceived Health Risk 18-item scale 2. Perceived Addiction Risk 7-item scale 3. Perceived Harm to Others (two separate questions) Answers were no risk, low risk, moderate risk, high risk, very high risk and don't know and were later converted into a 0–100 scale (0=no risk and 100=very high risk).	1. If you were to start using IQOS, what do you think would be the risk, if any, to you personally of getting the following (sometime during your lifetime) because you use IQOS… losing some sense of taste, having heart disease, an earlier death, having sores of the mouth or throat and so on. 2. If you were to start using IQOS, what do you think would be the risk, if any, to you personally of experiencing the following because you use IQOS… being unable to quit cigarettes, feeling like you have to smoke cigarettes and so on. 3. If you were to start using IQOS, what do you think would be the risk, if any, to others because you use IQOS… harming others through your secondhand smoke, harming unborn baby.

Source: adapted from table 17 in the Executive Summary, p. 121.[26]

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Message 1	Message 2	Message 3	Message 4	Message 5
Evidence Statement 1 (reduced exposure)	Evidence Statement 1 (reduced exposure)	Evidence Statement 2 (reduced exposure)	Evidence Statement 2 (reduced exposure)	Evidence Statement 3 (reduced risk)
• When tobacco is burned, it produces many harmful or potentially harmful chemicals. • THS 2.2 heats tobacco but does not burn it • With the except ion of nicotine, with THS 2.2 there is a significant reduction in the production of harmful or potentially harmful chemicals	• When tobacco is burned, it produces many harmful or potentially harmful chemicals. • THS 2.2 heats tobacco but does not burn it • With the except ion of nicotine, with THS 2.2 there is a significant reduction in the production of harmful or potentially harmful chemicals	• THS 2.2 heats tobacco but does not burn it • This significantly reduces the production of harmful or potentially harmful chemicals • Scientific studies have shown that switching completely from cigarettes to THS 2.2 significantly reduces your body's exposure to harmful or potentially harmful chemicals	• THS 2.2 heats tobacco but does not burn it • This significantly reduces the production of harmful or potentially harmful chemicals • Scientific studies have shown that switching completely from cigarettes to THS 2.2 significantly reduces your body's exposure to harmful or potentially harmful chemicals	• THS 2.2 heats tobacco but does not burn it • This significantly reduces the production of harmful or potentially harmful chemicals • Scientific studies have shown that switching completely from cigarettes to THS 2.2 can reduce the risks of tobacco-related diseases
WARNING A	Warning B1	WARNING A	Warning B2	Warning C
• **It has not been demonstrated** that switching to THS 2.2 reduces the risk of developing tobacco-related diseases compared to smoking cigarettes • THS 2.2 tobacco sticks contain nicotine which is addictive • Using THS 2.2 can harm your health	• A significant reduction in the production of harmful chemicals, compared to cigarettes, **does not mean a reduction in the risk of tobacco-related diseases** • THS 2.2 tobacco sticks contain nicotine which is addictive • Using THS 2.2 can harm your health	• **It has not been demonstrated** that switching to THS 2.2 reduces the risk of • developing tobacco-related diseases compared to smoking cigarettes • THS 2.2 tobacco sticks contain nicotine which is addictive • Using THS 2.2 can harm your health	• A significant reduction in the your body's exposure to harmful chemicals compared to cigarettes, **does not mean a reduction in the risk of tobacco-related diseases** • THS 2.2 tobacco sticks contain nicotine which is addictive • Using THS 2.2 can harm your health	• Reduced risk **does not mean no risk**. The best way to reduce your risk of tobacco-related diseases is to completely quit tobacco use • THS 2.2 tobacco sticks contain nicotine which is addictive • Using THS 2.2 can harm your health

Figure 1 Reduced exposure and reduced risk messages used in study THS-PBA-03-US. Note: same messages are indicated by the same colour. PBA, Perception and Behavior Assessment.

and a direct mail piece (figure 2). In this study, all materials had a reduced exposure claim, but it was paired with either a Surgeon General (SG) warning for cigarettes or a PMI-developed warning for IQOS communicating that reduced exposure does not mean reduced risk, that IQOS contains addictive nicotine and that IQOS can be harmful ('PMI Important Warning' in figure 2). Participants were randomised into five groups: (1) brochure with SG warning, (2) brochure with PMI warning, (3) pack with the SG warning, (4) pack with PMI warning and (5) direct mail piece with PMI warning.

Between 26% of participants (brochure with a PMI warning) and 58% (pack with SG warning) selected an answer that using IQOS reduces the risk of tobacco-related diseases for the global comprehension measure. An additional 0.8–2.6% answered that it 'eliminates the risk of tobacco-related diseases.' The proportion of participants who answered 'don't know' was 3.1–12.3%. In sum, a large proportion of participants who saw the reduced exposure messages selected answers indicating that tobacco-related disease risk is reduced by switching from cigarettes to IQOS.

For the measures of perceived risk to self, IQOS was rated lower than cigarettes. IQOS was rated similar in perceived risks to e-cigarettes for all measures of perceived risk (figure 3).

Participants also consistently rated IQOS as lower in perceived risk of addiction than combusted cigarettes, even though the marketing brochure did not contain any information on how IQOS compared with cigarettes in terms of addiction risk. PMI's report speculated that participants might be inferring lower perceived addiction risk for IQOS based on the information about reduced exposure to harmful chemicals.[30]

PMI's study report[31] concluded, "In general, reduced exposure messages may present a greater challenge than reduced risk messages on comprehension of disease risk" (p. 74). "It appears likely that consumers will typically infer a degree of reduced disease risk, even where such inferences are explicitly contradicted by warning statements" (p. 76).[31] The report suggested that reduced exposure claims for IQOS "may present an apparent contradiction between (1) reductions in HPHCs [harmful or potentially harmful chemicals identified by the FDA in conventional cigarettes] and (2) a lack of reduced risk for disease" where participants have a hard time reconciling these claims. The report referred the FDA MRTP Draft Guidance, which also acknowledged that "there may be challenges to constructing appropriate claim language that conveys the potential benefits of the product to tobacco users and does not convey that the product is less harmful than other tobacco products.[9] In summary, PMI's quantitative studies corroborated the findings from qualitative studies that US adults perceive reduced exposure claims as reduced risk claims.

DISCUSSION

PMI proposed to market IQOS with reduced exposure and reduced risk claims in the USA. PMI's own qualitative and quantitative studies consistently show that reduced exposure claims are likely to be perceived as reduced risk claims and will,

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Reduced Exposure Claim (REC) and associated Warnings (Tested in study THS-PBA-05-REC-US)

AVAILABLE EVIDENCE TO DATE:

- The *iQOS* system heats tobacco but does not burn it.
- This significantly reduces the production of harmful and potentially harmful chemicals.
- Scientific studies have shown that switching completely from cigarettes to the *iQOS* system significantly reduces your body's exposure to harmful or potentially harmful chemicals.

SURGEON GENERAL'S WARNINGS:

- Smoking Causes Lung Cancer, Heart Disease, Emphysema, And May Complicate Pregnancy.
- Quitting Smoking Now Greatly Reduces Serious Risks to Your Health.
- Smoking By Pregnant Women May Result in Fetal Injury, Premature Birth, And Low Birth Weight.
- Cigarette Smoke Contains Carbon Monoxide.

PMI IMPORTANT WARNING:

- It has not been demonstrated that switching to the *iQOS* system reduces the risk of developing tobacco-related diseases compared to smoking cigarettes.
- *HeatSticks* contain nicotine, which is addictive.
- Using the *iQOS* system can harm your health.



Figure 2 Reduced exposure message and an example of marketing materials from study THS-PBA-05-REC-US. In study THS-PBA-05-REC-US, all marketing materials carried a reduced exposure claim. PBA, Perception and Behavior Assessment; PMI, Philip Morris International.

therefore, mislead the public. While few studies outside the tobacco industry evaluated consumer perceptions of reduced risk or reduced exposure claims for non-cigarette tobacco products,[32–34] the results were similar. El-Toukhy *et al*[34] found that modified exposure claims reduced perceived risks of snus and e-cigarette products among adults and adolescents. These results indicate that perceptions of exposure and risk are highly correlated and communication about one— either lower risk or lower exposure—reduces perceptions of both risk and chemical exposure.

The conclusion that consumers interpret reduced exposure information as reduced harm seems to hold across different contexts and tobacco products. The tobacco industry's 'reduced exposure' claims are perceived as indicators of lower harm, as demonstrated by the PMI's studies reviewed here and by research on 'light' and 'mild' descriptors.[16 17] Furthermore, studies on different ways to communicate amounts of harmful chemicals in cigarettes consistently show that consumers misinterpret quantities of harmful chemicals as indicators of health risks.[35 36] This misperception holds regardless of the way the information on reduced exposure is presented: graphically, numbers only, or numbers with additional information, such as common use of these chemicals.[37]

The tobacco industry has a long history of using reduced exposure claims to mislead consumers into believing that the products in question have reduced risk, most notably through the use of 'light' and 'mild' cigarette claims.[24] Therefore, it is particularly important that the FDA and comparable authorities elsewhere in the world take care not to give legal sanction for PMI or other tobacco companies to market their IQOS or other similar products to mislead the public in the same way that it and other tobacco companies have done with earlier products. In particular, IQOS and other HTPs should not be permitted to be marketed with labelling or advertising that claims or implies modified exposure because the PMI's own studies demonstrate that consumers perceive reduced exposure claims as reduced risk claims. Both US law (FSPTCA, 911(g) and 903)[10] and the Framework Convention on Tobacco Control[38] (FCTC) and FCTC's

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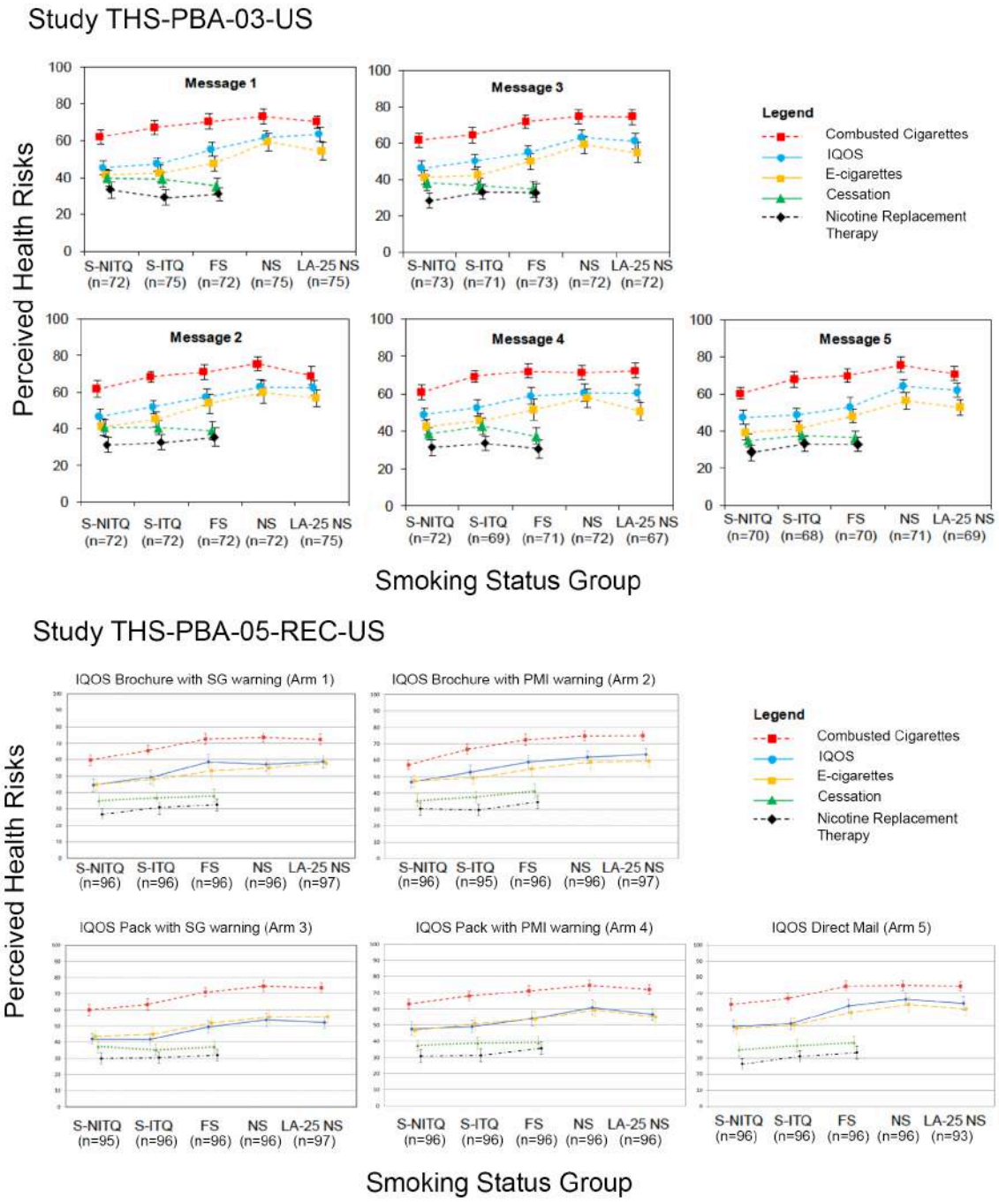


Figure 3 Participants in a quantitative study (THS-PBA-03-US, top panel) perceived health risk of IQOS to be significantly lower than health risks of combusted cigarettes, regardless of whether they saw a reduced exposure claim (Messages 1–4) or a reduced risk claim (Message 5)[31] (p. 68). Similarly, participants in THS-PBA-05-REC-US (bottom panel) rated perceived health risks of IQOS lower than combusted cigarettes for all marketing materials with reduced exposure claim[30] (pp. 56, 72, 86). Note: answers were no risk, low risk, moderate risk, high risk, very high risk and don't know and were later converted into a 0–100 scale (0=no risk and 100=very high risk). Error bars represent 95% CIs from the mean. Connecting lines are only to highlight clustering of outcomes for each comparator along the y-axis across IQOS messages. Abbreviations for Smoking Status Group: FS , adult former smokers; LA-25 NS , adult never smokers aged between their state legal smoking age (18 or 21) to 25 years; NS , adult never smokers; PBA, Perception and Behavior Assessment; PMI, Philip Morris International; SG, Surgeon General; S-ITQ, adult smokers with the intention to quit combusted cigarettes; S-NITQ, adult smokers with no intention to quit combusted cigarettes.

Guidelines for Implementation[39] prohibit tobacco product labelling that is false or misleading, especially labelling that would mislead consumers to believe that the product is less harmful than other products.[40]

Even though tobacco companies almost never marketed light and mild cigarettes with explicit claims of reduced health risks, promotions focused on reduced exposure (lower tar and nicotine) made smokers believe they were reducing their health risks

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by switching to light cigarettes.[13–17] Later, tobacco companies went further to promote light and mild cigarettes with aspirational messages, linking light cigarettes to highly desirable places and situations, such as style, relaxation and sophistication.[41] PMI is using the same playbook in marketing IQOS around the world by promoting IQOS as sophisticated and aspirational,[7]emphasising the themes of cleanliness, customisation and sociability.[6] Based on what we have learnt from marketing of light cigarettes and natural tobacco,[42–44] as well as the results of PMI's own research, it is likely that these claims will also be understood by consumers as reduced risk claims.[34]

Limitations and directions for future research

We report findings from PMI's qualitative and quantitative studies, relying primarily on the summary reports for each study rather than re-analysing the raw data. Our study is limited by the shortcomings of the original studies. For example, it is possible that participants in the qualitative studies perceived reduced exposure claims as reduced risk claims in part because they were exposed to all claims during their focus groups or interviews. These studies focused on more intensive message processing under conditions of participants paying attention to the messages. In the real world, these claims might be processed differently, and the resultant perceptions might be different. Future research should investigate how understanding of reduced exposure and reduced risk claims varies under situations of limited attention and unmotivated processing. Combining reduced risk/exposure claims with warning information that comes from a different source (such as the government) might result in differential processing by various people and more studies need to be done with warnings attributed to various sources to evaluate whether the findings were the artefacts of these specific claims.

Another area worth examining is the role of the source of modified risk information. The PMI's studies do not report on who the consumers attributed the claims to; however, given what we know, understanding whether consumers think this information comes from FDA or from tobacco companies would play an important role. Past research found that consumers (including tobacco users) generally trust FDA and generally distrust tobacco companies.[45] Furthermore, attributing reduced risk claims to FDA might make consumers mistakenly believe that the government endorsed these products and further reduce their risk perceptions, resulting in less informed decision making in the marketplace.[33]

CONCLUSION

PMI's MRTP application for IQOS makes reduced risk claims about IQOS that, like its earlier 'light' and 'mild' claims that were deemed fraudulent in the RICO case, are not substantiated by PMI's own internal research reported in its application.[2–4] Several of the other papers in this supplement indicate that IQOS is not significantly less harmful than combusted cigarettes[2–4 46 47] and that while IQOS had lower levels of pulmonary cytotoxicity[48] and carcinogens[49] than combusted cigarettes, they were higher than those of e-cigarettes. Therefore, the limited evidence on the health risks of HTPs does not support the much lower levels of perceived harm that PMI's consumer studies found. Even the evidence for the reduced exposure claim is questionable because PMI's data show *higher* levels of exposure than conventional cigarettes to some toxins.[2]

In the MRPT application, PMI makes an argument that the 'reduction in exposure to toxicants provides the foundation for the reduced harm rationale for this product as an MRTP', which further indicates that they do not currently have evidence aside from the data on reduced emissions to demonstrate effects on health. However, this is exactly what FDA says is not sufficient to show reduced risk, that is, to demonstrate that IQOS 'significantly reduce[s] harm and the risk of tobacco-related disease to individual users.' On 25 January 2018, the FDA Tobacco Products Scientific Advisory Committee (TPSAC) voted not to accept Philip Morris' claims that IQOS is less harmful than cigarettes (with 8 'No's and 1 'Abstain'). The TPSAC found (on an 8 to 1 vote) that the evidence presented by PMI demonstrated its reduced exposure claim, but unanimously rejected the idea that PMI demonstrated that consumers accurately understand the risks of IQOS. The important point is that the evidence from consumer studies clearly indicates that even a reduced exposure claim does not meet the regulatory criteria because consumers will understand such a claim as a reduced risk claim.

PMI's reduced exposure claims in its labelling and marketing for IQOS and similar claims for HTPs made by other companies are likely to be misunderstood as reduced risk claims. Therefore, FDA and other regulatory agencies in other countries should not permit PMI or any other tobacco company to market IQOS with reduced exposure claims. If PMI and other tobacco companies are allowed to make confusing (if not deliberately deceptive) claims in its labelling and/or advertising, it is likely to result in consumers being misled into believing HTPs are endorsed by regulatory agencies or into misunderstanding HTP's harmfulness.[50] In short, despite PMI's contradictory statements,[26] the actual reports, transcripts and data submitted by PMI to FDA provide substantial evidence that consumers perceive reduced exposure claims as reduced risk claims. Allowing PMI to promote IQOS as reduced exposure would amount to a legally sanctioned repeat of the 'light' and 'mild' fraud which, for conventional cigarettes, is prohibited by the US law and the FCTC.

What this paper adds

- The US Food and Drug Administration can authorise marketing of tobacco products as causing less exposure to harmful chemicals or lowering health risks. The law requires that claims of lower exposure do not mislead the public into believing the product presents reduced risk of health harm.
- The evidence in Philip Morris International's qualitative and quantitative studies submitted as part of its modified risk tobacco product application reveals that adult consumers in the USA perceive reduced exposure claims as reduced risk claims.
- Without evidence of reduced risk, claims of lower exposure are inherently misleading because they will be interpreted as reduced risk claims even if they do not explicitly make reduced risk claims.

Contributors All authors conceptualised the study, contributed to the writing and revision and approved the final version of the manuscript. LP and LKL analysed the data.

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Short Communication Open Access

Heated Tobacco Products Create Side-Stream Emissions: Implications for Regulation

Grant O'Connell[1], Peter Wilkinson[1], Kerstin MM Burseg[2], Stephen J Stotesbury[1], John D Pritchard[1]*

[1]*Imperial Tobacco Ltd, 121 Winterstoke Road, Bristol, BS3 2LL, UK*
[2]*Reemtsma Cigarettenfabriken GmbH - Imperial Tobacco Group, Albert-Einstein-Ring 7, D-22761, Hamburg, Germany*

Abstract

A number of tobacco manufacturers are promoting products where the tobacco is reportedly "heated" rather than burned. It has been claimed that certain heated tobacco products produce only mainstream and no side-stream emissions. In this study we investigated these claims for a commercially available heated tobacco product and, by using a simple experimental design, investigated whether the high temperature heating of the tobacco matrix during product activation and use results in the generation of side-stream emissions. By way of comparison, the Nicorette® inhalator and a leading e-cigarette brand were also investigated. Our findings indicated that a large number of different chemical compounds were released into the airspace around the heated tobacco product when switched on and during consumer use indicating the generation of side-stream emissions. As the public health community has concluded there is no safe level of exposure to tobacco-containing product emissions, this would be of concern and warrants further investigation. Based on our data showing side-stream emissions from the tobacco matrix, the use of heated tobacco products in indoor public places should fall under the same regulations as cigarettes.

Keywords: Heated tobacco; Heat-not-burn; E-cigarette; Nicorette; Side-stream emissions; Second-hand smoke; Nicotine; Tobacco

Introduction

It is well known that when tobacco burns, many thousands of chemicals are released from the tobacco matrix and are inhaled by consumers and bystanders [1,2]. It has been stated that the majority of smoking-related diseases are caused not by nicotine but by the generation of harmful or potentially harmful smoke constituents (HPHCs) from the burning of tobacco [3,4]. In response, a number of tobacco manufacturers are promoting products where the tobacco is reportedly "heated" rather than burned in an attempt to reduce HPHC emissions [5-7]. This is not a new concept, as cigarette-based heated tobacco products were first marketed in the USA in the 1980s and proved to be commercially unsuccessful. Heated tobacco products are now being revived and repositioned as an alternative for smokers who may not wish to replace conventional cigarettes with non-tobacco products such as electronic cigarettes (e-cigarettes). While some manufacturers claim heated tobacco products do not produce side-stream emissions, the major component of 'second-hand smoke', this has yet to be independently verified [8-12]. Since the World Health Organisation has stated "*there is no safe level of exposure to second-hand tobacco smoke*" [13] and the British Medical Association (BMA) has stated that "*almost 85 per cent of second-hand smoke is in the form of invisible, odourless gases*" [14], claims of an absence of side-stream emissions from heated tobacco products warrants investigation. To that end, we sought to investigate whether or not side-stream emissions were generated by a commercially available heated tobacco product. For comparative purposes, we also investigated the Nicorette® inhalator and a leading e-cigarette.

Experimental Section

The analytical technique Proton Transfer Reaction-Mass Spectrometry (PTR-MS) was used to sample and analyze for any side-stream emissions released to the airspace around an iQOS heated tobacco product with regular Marlboro *HeatSticks* (manufacturer, Philip Morris International) when activated by the user (but not puffed) and also during product use. Additionally, sampling was conducted for a Nicorette® inhalator (15 mg nicotine replacement aid; manufacturer, McNeil Consumer Healthcare Ltd) and Blu™ closed system e-cigarette (18 mg nicotine; manufacturer, Fontem Ventures B.V.) All products used in this study were used in accordance with manufacturer's instructions and consumed *ad libitum* i.e., there was no pre-defined consumption requirement. For each of the different products, a number of replicate puffs were made and representative data from a single puff is shown. In short, the PTR-MS instrument ionizes volatile organic compounds (VOCs) in the gas phase through their reaction with H_3O^+ to form protonated VOCs ($VOCH^+$) which can then be detected by a mass spectrometer [15]. This process can be run on air samples with or without dilution as normal air gases (e.g., N_2, O_2, CO_2) have a proton affinity less than water and thus are not ionized. Most VOCs have a proton affinity greater than water and therefore are readily ionized and detected [15]. Analyses with PTR-MS can be conducted in real-time and continuously without the need for sample preparation [15]. Airspace analysis was conducted by connecting the PTR-MS inlet to the test chamber and sampling directly. PTR-MS operating conditions were as follows: drift tube voltage, 500 V; drift tube pressure, 2.3 mbar; drift tube temperature, 120°C; drift tube length, 9.3 cm; *E/N* ratio, 130 Td (Townsends; where *E* is electric field and *N* is the number density of the gas in the drift tube; 1 Td=10^{-17} cm^2 V $molecule^{-1}$); inlet temperature, 120°C. The experimental set-up is outlined in Figure 1.

Results and Discussion

Qualitative characterization of side-stream emissions

Following activation of the iQOS heated tobacco product, as per the manufacturer's instructions, a large number of different VOC species across a range of masses were released into the airspace (Figure 2A). This clearly indicates the generation of side-stream emissions when the device is activated but not puffed by the consumer, which

***Corresponding author:** John D Pritchard, Imperial Tobacco Ltd, 121 Winterstoke Road, Bristol, BS3 2LL, UK, Tel: 440117-933-7556; E-mail: john.pritchard@uk.imptob.com

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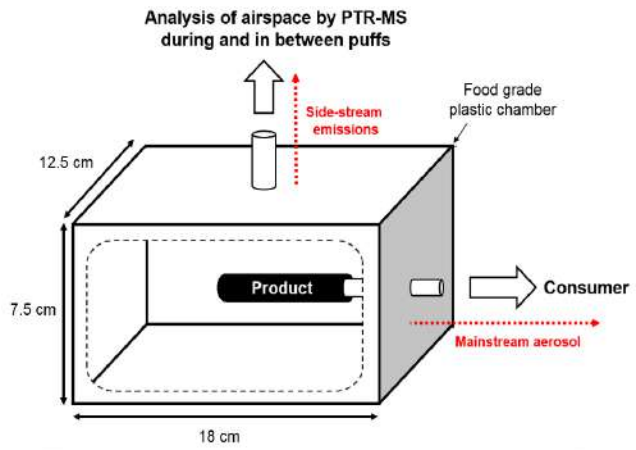


Figure 1: Schematic representation showing experimental set-up and the side-stream emissions capture chamber.

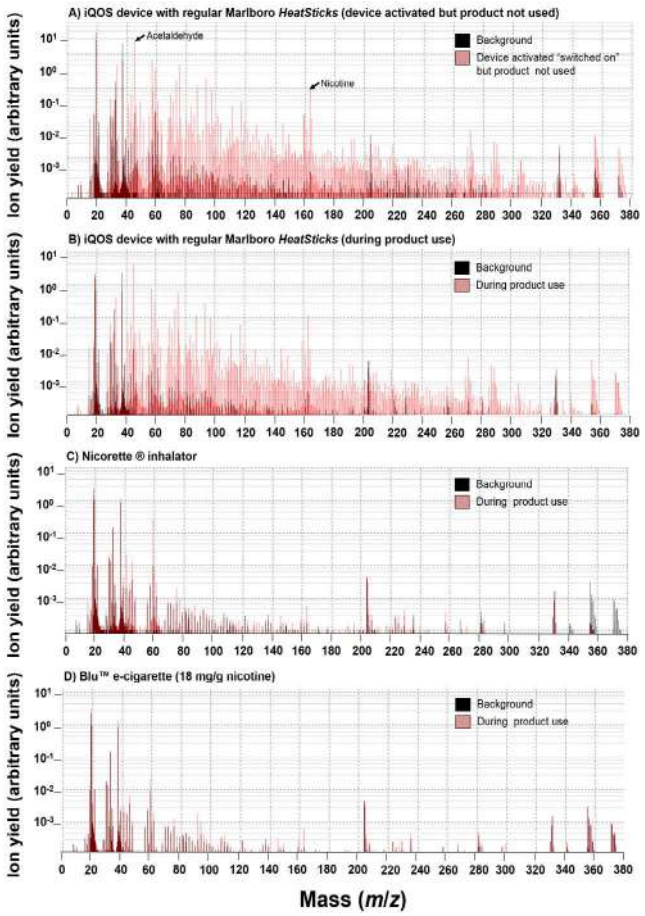


Figure 2: Representative PTR-MS mass spectra of the VOCs released to the airspace for (**A**) iQOS with regular Marlboro *HeatStick* when activated "switched on" but product not actively puffed and (**B**) during consumer use of the iQOS device with regular Marlboro *HeatSticks*; (**C**) during consumer use of the Nicorette® inhalator; and (**D**) during consumer use of the Blu™ e-cigarette. Specific compound (peaks) at *m/z* 45 is protonated acetaldehyde and *m/z* 163 is protonated nicotine and is labelled with arrowheads in (**A**).

would be released into the ambient air, raising potential concerns for bystanders. Furthermore, during active puffing on the heated tobacco product, side-stream emissions are also released (Figure 2B). These chemicals are being released from the high temperature heating of the tobacco matrix in the *HeatSticks*. Given the similarities of the Marlboro branded *HeatStick* used in the iQOS device to a conventional cigarette, the detection of side-stream emissions is perhaps not surprising even though it has been stated that such products produce no side-stream aerosol/smoke [8-12]. Given the findings presented in this pilot study, this requires further investigation.

The PTR-MS mass spectra of the VOCs in the airspace around the Nicorette® inhalator (Figure 2C) and the e-cigarette (Figure 2D) during product use are virtually indistinguishable. Moreover, the Nicorette® inhalator and the e-cigarette profiles are entirely distinct from that of the heated tobacco product, as may be anticipated given these products do not contain tobacco. The Nicorette® inhalator was selected as an appropriate comparator in this study as the UK Medicines and Healthcare products Regulatory Agency (MHRA) has indicated this should be used as a reference product, if manufacturers intend to license e-cigarettes as medicinal products [16].

Future investigations

PTR-MS is a one dimensional technique that characterizes VOCs via their mass; to enable identification of the chemicals in the side-stream emissions from the heated tobacco product it is necessary to further calibrate the machine for identification and quantification of compounds of regulatory interest e.g., HPHCs in tobacco products and tobacco smoke as developed by the US Food and Drug Administration (FDA) [17]. We will therefore determine the identities of the many different VOCs released to the airspace, and by extension to the bystander's breathing space, from the heated tobacco product when activated and used by the consumer. Moreover, it is also conceivable that differences in side-stream emissions may be observed under varying user consumption topographies. Further research in these areas will be informative.

Conclusions

The release of side-stream emissions from heated tobacco products has been observed by PTR-MS using the simple method presented here. These emissions are generated by the high temperature heating of the *HeatSticks* tobacco matrix inserted within the iQOS device.

The public health community has stated that there is no safe level of exposure to tobacco-containing product emissions [13,18], and so the side-stream constituents including nicotine, released during activation and use of the iQOS heated tobacco product can lead to exposure to bystanders; this would be of concern to public health authorities and warrants further investigation.

It is conceivable that based on these findings and the conclusions of public health community regarding tobacco product emissions, the use of heated tobacco products should be included in smoke-free legislation.

Conflicts of Interest

The work in this short communication was supported by Imperial Tobacco Group. Imperial Tobacco Group is the parent company of Fontem Ventures B.V., the manufacturer of the e-cigarette used in this study.

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PMI left a lot of important things out of its toxicology studies of IQOS submitted to the FDA

tobacco.ucsf.edu/pmi-left-lot-important-things-out-its-toxicology-studies-iqos-submitted-fda

My colleagues at the UCSF TCOS just put this public comment in on Phlilip Morris' MRTP application for IQOS. The tracking number is 1k1-902j-m8kv. A PDF of the comment is available here.

Because PMI application did not report the full range of HPHCs in IQOS aerosol, characterize HPHCs in sidestream emissions, include a non-targeted analysis of chemicals in emissions, or conduct clinical studies to describe exposure to toxicants during dual use with other tobacco products, FDA must deny PMI's application

Gideon St.Helen, PhD1,2; Peyton Jacob III, PhD1,2; Natalie Nardone, PhD1,2;
Neal L. Benowitz, MD1,2,3
1Division of Clinical Pharmacology, Department of Medicine, University of California San Francisco; 2UCSF Tobacco Center of Regulatory Science; 3Department of Bioengineering and Therapeutic Sciences, University of California San Francisco
Docket Number: FDA-2017-D-3001
November 29, 2017

Philip Morris Products SA, a subsidiary of Philip Morris International (collectively referred to as PMI hereafter), has recently submitted a "modified risk tobacco product" (MRTP) application to the FDA for review and approval of IQOS. (We refer to the product as IQOS in this comment in place of tobacco heating system, THS 2.2.) According to FDA's draft guidance, an MRTP is "any tobacco product that is sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products."[1] FDA may issue an order allowing a product to be marketed as a modified risk product if it is demonstrated that the product: (1) significantly reduces harm and the risk of tobacco-related disease to individual tobacco users; and, (2) benefits the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products.

We recognize the possible benefit to individuals and public health of marketing tobacco products with substantially reduced risks profiles compared to currently marketed products such as combustible cigarettes, cigars, and some smokeless tobacco products. Given FDA's mission to protect Americans from tobacco-related diseases and death by regulating tobacco, it is critically important that FDA undergo a thorough science-based review of PMI's application to market IQOS as an MRTP. ***The PMI MRTP application lacks important information needed for the FDA to determine that IQOS should be marketed as an MRTP, so should deny the application until PMI presents the information necessary to demonstrate that any product permitted to be marketed as an MRTP actually reduces risk.***

1. **Aerosol Chemistry (Module 6.1.1.):**

1. ***PMI should report emission levels of all 93 HPHCs in IQOS aerosol .*** According to the FDA, harmful and potentially harmful constituents (HPHCs) are "chemicals or chemical compounds in tobacco products or tobacco smoke that cause or could cause harm to smokers or nonsmokers."[2] The FDA has an established list of 93 HPHCs.[3] Quantifying levels of HPHCs in aerosol/smoke of tobacco products that deliver nicotine through the pulmonary route is critical to understanding the potential health risks associated with these products. PMI measured the levels of 58 HPHCs, which they referred to as PMI-58, in mainstream IQOS aerosol. PMI claims that this list contains "chemical constituent representatives of all major toxicologically relevant chemical classes of compounds present in both the particulate-phase and gas/vapor-phase of cigarette smoke," (Module 6.1.1 Aerosol Chemistry p. 6). They also claim that it contains the 18 HPHCs subject to reporting on FDA's abbreviated list. No rationale for leaving out the other 35 HPHCs on the FDA's established list was given. The public (and the FDA) cannot assume that these 35 HPHCs are not important or that they are at much lower levels in IQOS emissions compared to other tobacco products. Since PMI is attempting to market IQOS as a reduced risk product, a more extensive rather than limited analysis of HPHCs is needed.
2. ***PMI should report levels of HPHCs in IQOS sidestream emissions .*** PMI's analysis of the PMI-58 HPHCs was done in mainstream IQOS aerosol. The implicit assumption is that IQOS has no sidestream emissions. However, research on IQOS by Imperial Tobacco Ltd. found "a large number of different VOC [volatile organic compound] species across a range of masses were released into the airspace" when IQOS was activated but not puffed on.[4] In order to protect non-users of tobacco products, FDA must insist that PMI fully characterizes HPHC levels in sidestream emissions from IQOS.
3. ***PMI should report results of non-targeted analyses of constituents in mainstream and sidestream IQOS emissions, in addition to their current targeted analysis.***

The MRTP application reports the results of analyses comparing the emissions of HPHCs from IQOS and a reference cigarette (Module 6.1.1 pp 13-19). The analyses reported by PMI show significant reductions in most of the HPHCs that were measured compared to emissions from a reference 3R4F cigarette.

Significantly, the reported studies fail to address the important question "does the aerosol generation process for IQOS produce substances not found in the smoke of conventional cigarettes, and if so, are any of these substances harmful or potentially harmful?" The main rationale for the development of IQOS and other heat-not-burn products is that combustion, meaning incomplete combustion of many organic materials, including tobacco, produces highly toxic substances such as some on the HPHC lists. The heat-not-burn products generate an inhalable aerosol without combustion, thereby purportedly eliminating or reducing the levels of substances that are generally formed as combustion by-products. ***Nevertheless, the heat required to generate the aerosol in IQOS will likely produce substances not detected in cigarette smoke. Substances in the IQOS (from tobacco or the numerous additives) could undergo heat-induced reactions to form new substances that***

might not survive in the higher temperature and strong oxidizing conditions in a combusted tobacco product.

There are reasons to suspect that the temperatures produced in IQOS are sufficient to cause chemical reactions to occur, as have been demonstrated with e-cigarettes. [5] In other words, substances in the aerosol may not be limited to those present in the tobacco prior to aerosol generation. E-cigarettes use heat to generate an inhalable aerosol without combustion, in a fashion similar to aerosol generation in a heat-not-burn product, and it is well known that numerous chemical reactions occur during the "vaping" process. For example, formation of toxic aldehydes, including formaldehyde, acetaldehyde, and acrolein, via dehydration and oxidation of the vehicles propylene glycol and glycerin is of particular concern.[6],[7] In addition, flavoring chemicals in e-cigarettes undergo thermal degradation and contribute significantly to levels of toxic aldehydes emitted in e-cigarette aerosol.[8]

Similarly, one would expect chemical reactions to occur during aerosol generation in IQOS, and ***there is no reason to expect that all of the substances formed, or that survive during aerosol generation, would be the same as those found in cigarette smoke.*** In fact, even among combusted tobacco products, the composition of the aerosols may differ. A recent study by Klupinski and colleagues reported that unique substances, such as ambrox, 3-methylbutanenitrile, and 4-methylimidazole, were found in little cigar smoke that were not found in cigarette smoke.[9] The study describes methodology for "non-targeted" analysis of tobacco smoke aerosol, and the authors suggest that "the same approach could also be applied to other samples to characterize constituents associated with tobacco product classes or specific tobacco products of interest. Such analyses are critical in identifying tobacco-related exposures that may affect public health." ***PMI should undertake such studies and report the full results.***

In addition to the "targeted" analyses for specific HPHCs that were carried out, PMI should carry out "non-targeted" analyses comparing IQOS aerosol with smoke from combustible tobacco products in an attempt to identify potentially toxic chemicals in IQOS aerosol that may not be present in tobacco smoke. The aforementioned study by Klupinski et al. constitutes "proof of concept" for the feasibility of such chemical analyses.

4. ***PMI should compare aerosol constituents of IQOS to that of other combustible tobacco products and e-cigarettes.*** While PMI's application focuses primarily on comparisons between IQOS emissions and combustible cigarette smoke, it is unlikely that IQOS will only be used by combustible cigarette smokers. Instead, the likely scenario is that at least some users of other combustible and non-combustible tobacco products will switch to IQOS. Unless PMI can guarantee that their product be marketed and sold to current combustible cigarette smokers only, it makes no sense that their comparison is limited to cigarettes. FDA should at least insist that PMI reports comparisons of HPHC emissions between IQOS and all combustible products and electronic nicotine delivery products. This set of data is critical for an accurate assessment of the relative safety/risks of IQOS ***as actually used*** compared to and in conjunction with (i.e., dual use) other tobacco products.
5. ***PMI should characterize free radical emissions in IQOS aerosol.*** Free radicals are

associated with oxidative stress, an underlying mechanism of many disease outcomes, including cardiovascular disease and cancer. Previous research has demonstrated high free radical emissions from e-cigarettes.[10] FDA should insist that PMI compares free radical emissions from IQOS with combustible tobacco products and e-cigarettes.

2. **Justification of selection of biomarkers of exposure (Module 6.1.3.1):**

1. ***PMI should expand the list of HPHCs for which systemic exposure was assessed.***

PMI used 1-hydroxypyrene, a metabolite of pyrene (a polycyclic aromatic hydrocarbon, PAH) as a biomarker of PAHs. We have previously demonstrated that 1-hydroxypyrene is not a selective measure of tobacco-related PAH exposure and is not highly related to nicotine intake and tobacco-specific nitrosamine exposure.[11] Instead, we found that monohydroxylated metabolites of fluorene (particularly 1-hydroxyfluorene) and 2-naphthol (a naphthalene metabolite) were more selective of tobacco smoke exposure. Given the link between PAH exposure and cancer, it is important that PMI reports PAH biomarkers that are more selective of tobacco smoke than 1-hydroxypyrene.

Further, PMI's list of 17 HPHCs, for which systemic exposure were assessed, do not include any inorganic compounds, phenols, and metals. Systemic exposure to these chemicals, especially metals, should be included in PMI's MRTP. One risk assessment model estimated that metals, such as cadmium, chromium (hexavalent), and arsenic, accounted for a significant fraction of the cancer and non-cancer disease risk indices of tobacco smoking.[12] For this reason, FDA should insist that PMI report exposure to metals from IQOS use.

3. **Summary of biomarkers of exposure assessments (Module 6.1.3.2.):**

PMI conducted four clinical studies to "demonstrate that the level of exposure to harmful substances has been statistically significantly reduced," based on FDA MRTP draft guidance. Two of the studies were 5-day studies in confinement, where smokers of combustible tobacco cigarettes were randomly assigned to either switch to IQOS, continue their own brand of cigarettes, or abstain from using tobacco products. The two other studies were 3-month studies consisting of 5 days of confinement followed by up to 3 months in their naturalistic environments (Module 6.1.3.2. p. 9). The first two studies were done in Poland and Japan and the latter two in Japan and the U.S. All studies contained 160 subjects, each. All four studies are of acceptable design, and included biomarker analysis in 24-hour urine (a strength).
However, there are some concerns:

1. ***PMI should present results of statistical tests.*** In figures such as Figure 1, 3, and 5 (Module 6.1.3.2. pp. 15, 20, and 25) comparisons of reduction in biomarkers of exposure to HPHCs are given for smokers who switch to IQOS and those who were in the abstinence arm. Simply stating the percentage reduction in exposure when a smoker moves from cigarettes to IQOS or from cigarettes to abstinence is not

sufficient. Important to our understanding of the relative safety/risks of IQOS is information on the magnitude of the exposure to toxicants when using IQOS compared to during abstinence. FDA should insist that results of statistical tests be presented for comparisons of reductions with IQOS compared to abstinence.

2. ***Clinical studies lacked racial diversity. PMI should investigate the effect of race on use patterns and biomarkers of exposure.*** The studies were conducted with either Japanese or Caucasians. As such, these studies are most likely not representative of the U.S. population, which is diverse racially. Metabolism of and reaction to the absorbed constituents of tobacco products,[13],[14] as well as attitudes, perceptions, preferences, and tobacco use patterns may differ across racial/ethnic groups. For example, we have observed racial differences in the manner in which combustible tobacco cigarettes are smoked and how cigarettes per day related to exposure biomarkers.[15] African Americans tend to smoke each cigarette much more intensely than Caucasian smokers do. African Americans and Native Indians have been shown to be more susceptible to lung cancer than Caucasians.[16] These previous observations underscore the need to include a racially diverse sample in assessing tobacco use patterns and toxicant exposures, and to conduct clinical studies with a sample that is representative of the U.S. population.
3. ***Noncompliance during outpatient (ambulatory) product use reduces the validity of conclusions made regarding reduced toxicant exposure from IQOS.*** The two 3-month studies included 5 days in a controlled setting and 85 or 86 days in their naturalistic environment. They compared the use of IQOS with combustible cigarette smoking and smoking abstinence. PMI implied that both studies showed significant reductions in HPHC biomarkers with use of IQOS, but did not present any associated P values to compare reductions in HPHC biomarkers during IQOS use and smoking abstinence. The results are presented together in Figure 5 (Module 6.1.3.2. p. 25) and Figure 8 (Module 6.1.3.2. p. 32), and are most likely meant to convey the message that IQOS use results in reductions in HPHCs comparable to smoking abstinence. To be a valid comparison, it is important that study participants complied with the assigned product/regime allocation, particularly those of the smoking abstinence arm. If participants in the abstinence arm smoked cigarettes (going against the study regime), percentage reductions in biomarkers of HPHCs would be lower, and most likely be comparable to that of reductions among participants in the IQOS arm, i.e. the study would show comparable reductions in HPHC exposure with IQOS and abstinence. It is not clear from the application how compliance was determined. Compliance was said to be “particularly high” for the first study. This is a relative term and needs to be quantified in the application. For the second study, PMI reports “good” compliance of subjects in the IQOS arm but “poor” compliance in the abstinence arm. With only 7-9 out of 41 subjects from the smoking abstinence arm being included in the “PP set” (it was not clear what PP set meant), comparisons of HPHC exposure reduction between IQOS use and smoking abstinence are not valid. PMI noted that “in light of the limited number of subjects in the [smoking abstinence] arm and the increased variability, the results obtained using the [smoking abstinence] arm should be interpreted with caution.” ***FDA has to ensure that PMI follows its own advice in interpreting the findings with caution. Until it does, FDA cannot rely on the data presented in the application.***

4. ***PMI should describe exposure biomarkers among dual use groups.*** Most e-cigarette users also smoke combustible cigarettes.[17] The most likely scenario if IQOS is allowed into the U.S. market is high prevalence of dual use of IQOS and tobacco cigarettes or other tobacco products. It is unknown if dual use would result in decreased exposure to tobacco smoke toxicants in the context of nicotine titration (harm reduction), or additive exposure to toxicants from cigarettes and IQOS. It is therefore imperative that FDA insist that PMI conducts studies to assess exposure to toxicants during periods of dual IQOS-tobacco cigarette use.

Conclusion

In summary, to ensure that IQOS is truly a modified risk tobacco product with net benefits to individual users and the population as a whole, before acting favorably on an MRTP application for ICOS, FDA should require that: (1) PMI expands the list of reported HPHCs tested in IQOS emissions and those included in biomarker analysis; (2) characterize HPHC emissions in sidestream aerosol from IQOS; (3) conduct non-targeted analysis to identify other potentially toxic constituents of IQOS emissions that may be unique to IQOS (in addition to reported targeted analysis); (4) compare aerosol constituents from IQOS with that of other combustible tobacco products such as cigars in addition to cigarettes; (5) characterize free radical emissions in IQOS aerosol; (6) conduct clinical studies with samples that are representative of the U.S. population (e.g. racial diversity); and, (7) conduct studies to describe exposure biomarkers during periods of dual use. Section 911(g) of the Family Smoking Prevention and Tobacco Control Act is clear and unambiguous: **FDA may issue an MRTP order *only if* PMI has demonstrated that IQOS, *as actually used by consumers*, will "(A) significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and (B) benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products." Since PMI has failed to make this required showing, FDA is not authorized to issue an MRTP order.**

[1] Guidance for Industry. Modified Risk Tobacco Product Applications. Draft Guidance.

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Comparative assessment of the side-stream aerosols emitted from heat-not-burn tobacco devices, e-cigarettes and traditional cigarettes

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Abstract

Consumption of e-cigarettes has increased significantly in recent years, necessitating further research on the potential health risks/benefits of these devices. Recently, Philip Morris International entered the e-cigarette market with the launch of “iQOS”, a “heat-not-burn” cigarette that has been described as a hybrid between traditional and electronic cigarettes. In a recent study (Saffari et al. 2014, Environ. Sci. Process Impacts, 2259-2267), we presented exposure to particulate metals and organic compounds from e-cigarettes. In this study, we have used a similar approach to further expand our previous analyses by characterizing the iQOS. Black carbon (BC) in addition to particle mass and number concentration were measured using continuous monitors, inside of an office environment during e-cigarette and iQOS consumption sessions. Additionally, particle-bound metals and organic compounds as well as gas-phase aldehydes were quantified using time-integrated chemical analysis methods. Moreover, indoor emission rate of these chemical species were quantified by conducting parallel outdoor measurements followed by development of an indoor mass balance model. Our results indicated a substantial decrease in the emission of metals (with the exception of Ni and Cr), BC and organic compounds in e-cigarettes compared to traditional cigarettes. Analysis of the same species in the iQOS

side-stream smoke, however, indicated that while PAHs were mostly non-detected in the iQOS smoke, certain n-alkanes, organic acids were still emitted in substantial levels from iQOS.

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iQOS: evidence of pyrolysis and release of a toxicant from plastic

Barbara Davis, Monique Williams, Prue Talbot

Department of Molecular, Cell and Systems Biology, University of California, Riverside, California, USA

Correspondence to
Dr Prue Talbot, Department of Molecular, Cell and Systems Biology, University of California, Riverside, CA 92521, USA; talbot@ucr.edu

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ABSTRACT

Objective To evaluate performance of the I quit original smoking (iQOS) heat-not-burn system as a function of cleaning and puffing topography, investigate the validity of manufacturer's claims that this device does not burn tobacco and determine if the polymer-film filter is potentially harmful.

Methods iQOS performance was evaluated using five running conditions incorporating two different cleaning protocols. Heatsticks were visually and stereomicroscopically inspected preuse and postuse to determine the extent of tobacco plug charring (from pyrolysis) and polymer-film filter melting, and to elucidate the effects of cleaning on charring. Gas chromatography–mass spectrometry headspace analysis was conducted on unused polymer-film filters to determine if potentially toxic chemicals are emitted from the filter during heating.

Results For all testing protocols, pressure drop decreased as puff number increased. Changes in testing protocols did not affect aerosol density. Charring due to pyrolysis (a form of organic matter thermochemical decomposition) was observed in the tobacco plug after use. When the manufacturer's cleaning instructions were followed, both charring of the tobacco plug and melting of the polymer-film filter increased. Headspace analysis of the polymer-film filter revealed the release of formaldehyde cyanohydrin at 90°C, which is well below the maximum temperature reached during normal usage.

Discussion Device usage limitations may contribute to decreases in interpuff intervals, potentially increasing user's intake of nicotine and other harmful chemicals. This study found that the tobacco plug does char and that charring increases when the device is not cleaned between heatsticks. Release of formaldehyde cyanohydrin is a concern as it is highly toxic at very low concentrations.

INTRODUCTION

With the rise of smoking alternatives, the electronic nicotine delivery systems market has boomed, with electronic cigarettes (EC) being among the most popular worldwide.[1 2] However, there are still a number of conventional (combustible) cigarette smokers who would welcome a cigarette-like tobacco-containing/nicotine-containing product that is devoid of or has a significantly reduced toxicity compared with conventional cigarettes.[1] To appeal to this demographic, Philip Morris International (PMI) has released a new product called the iQOS (I quit original smoking), which is a 'heat-not-burn' system,[3] as an alternative to conventional cigarettes and EC. The iQOS system uses a flange, called the 'heater', which is composed of a silver, gold, platinum, ceramic coating,[4] to heat a rolled, cast-leaf sheet of tobacco impregnated with glycerin, thereby creating an aerosol without combustion.[3] This aerosolisation process is proposed to reduce the user's exposure to toxic and carcinogenic chemicals produced by the combustion of tobacco.[5 6] Thus, the consumer gets the 'harm reduction' component of EC along with the mouth/throat feel of a conventional cigarette. The iQOS system has been well received in Japan and Italy. The iQOS is currently sold in 26 markets by PMI with plans to expand to over 30 countries, including the USA.[7]

Although this product has been extensively evaluated by the manufacturer,[3 5 6 8–13] these studies appeared in a journal that may have a deficient review process,[14] emphasising the need for independent evaluation of the iQOS. As our initial study, we have evaluated the performance of the iQOS system under various conditions, tested the effects of cleaning on performance and pyrolysis and determined the composition of and potential health risk from the polymer-film filter.

MATERIALS AND METHODS

iQOS product acquisition and storage

Four iQOS tobacco heating system kits, manufactured by Philip Morris Products S.A. (Switzerland), were purchased online at eBay (https://www.ebay.com/) from sellers with a 98% or higher satisfaction rating. Kits arrived sealed and in excellent condition. Kits were inventoried, and the components of each kit were placed into individual plastic containers and stored in a dry area at 22°C when not in use.

Cartons of Marlboro (blue box) heatsticks, manufactured by Philip Morris Brands Sàrl (Italy), were purchased in Japan and shipped to us via a personal shopper. Each carton was individually sealed and in excellent condition. Heatsticks were stored, unopened, in a dry, dark area at 22°C in their cartons until used. Unused heatsticks from opened packs were stored in an airtight bag in their carton.

Cleaning the iQOS

iQOS holders were tested using two cleaning regimens: (1) the 'per-use' cleaning protocol in which the device was thoroughly cleaned after each heatstick using the cleaning sticks to remove residual fluid and tobacco plug debris from the heater and surrounding base and to clean out the cap and (2) the manufacturer's recommended cleaning instructions in which the cleaning cycle was used after every 20 heatsticks before using the brush cleaners. When heatstick fragments were left behind, the cleaning hook was used to remove these pieces, as

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necessary, and the holder cap was cleaned by a 5 min warm water immersion. The instructions clearly state that the holder itself is not to be wetted.

Performance evaluation

Pressure drop, which measures the draw resistance of the heatstick, aerosol absorbance (density), a measure of particulate matter trapped within the aerosol, and puff number were evaluated for iQOS products using equipment and protocols described previously.[15–17] Pressure drop across heatsticks was evaluated using a Cole-Parmer Masterflex L/S peristaltic pump (Vernon Hills, Illinois, USA) connected to a U-tube water manometer to detect the change in differential pressure for each puff. Airflow rates were precalculated/precalibrated to the appropriate pump speed using a conversion factor provided by the pump head manufacturer, and flow rate was verified using a Brooks Instruments Sho-Rate flow meter (Hatfield, Pennsylvania, USA). Aerosol density was evaluated by capturing aerosols in a tubular cuvette, and absorbance was measured immediately at 420 nm using a Bausch & Lomb spectrophotometer (120 V, 0.9 A, Rochester, New York, USA).

iQOS devices were evaluated with five operating conditions; four (conditions 1–4) used the per-use cleaning protocol and one (condition 5) used the manufacturer's recommended cleaning instructions. The pump head, tubing set-up and running conditions were as follows: (1) low airflow rate 2 s protocol—the peristaltic pump was outfitted with a Cole-Parmer Masterflex Model 7015-21 pump head (standard pump head) using Masterflex Tygon E-LFL (tubing size 15) tubing to generate a flow rate of 7 mL/s with a 2 s puff duration for a total puff volume of 14 mL, 14 puffs were taken at 25 s intervals; (2) low airflow rate 4 s protocol—the same pump set-up and running conditions as for condition 1 with a 4 s puff duration generating a 28 mL puff volume; (3) International Organization for Standardization (ISO)—the pump was outfitted with a Cole-Parmer Masterflex L/S Easy-Load II Model 77200-52 high-performance pump head with Masterflex Tygon E-LFL (tubing size 15) producing a 17.5 mL/s flow rate with a 2 s puff duration, generating a total puff volume of 35 mL, with a total of six puffs taken, one puff every minute; (4) the Health Canada standard (HCI)—a Cole-Parmer Masterflex L/S Easy-Load II Model 77200-52 high-performance pump head was used with Masterflex Tygon E3603 (tubing size 36) tubing for a flow rate of 27.5 mL/s, with a 2 s puff for a total puff volume of 55 mL, 12 puffs were taken at 30 s intervals; (5) manufacturer's recommended cleaning (HCI), the same pump set-up and running conditions as described for condition 4 but in the absence of per-use cleaning; for this protocol the manufacturer's recommended cleaning instructions were followed (table 1). For conditions 1–4, three different iQOS devices were evaluated with each device being tested in triplicate, that is, a new heatstick was used for each experiment; condition 5 employed a single device in which 10 heatsticks were tested without cleaning between each stick.

Effect of use on the tobacco plug and polymer-film filter

The condition of the tobacco plugs was evaluated by visual and microscopic inspection and imaged using a Nikon C-LEDS stereomicroscope equipped with a Nikon Digital Sight DS-Vi1 camera head (Nikon, Minato, Tokyo, Japan) before and after use. Some heatsticks were dissected before and after use to further evaluate residual char (referred to as 'char' only) of the tobacco plugs and the condition of the polymer-film filter.

Gas chromatography–mass spectrometry analysis of iQOS heatstick polymer-film filters

Gas chromatography–mass spectrometry (GC–MS) using a qualitative wide-scope screening method was performed using an Agilent 7890B GC coupled with a 5977A MSD equipped with a

Table 1 Performance of iQOS heat-not-burn holders

Holder	Puff duration	Puff interval	Airflow rate (mL/s)	Puff volume (mL)	Total number of puffs	Average pressure drop (mm H_2O)	Average absorbance
Low airflow rate 2 s protocol*							
A	2	25	7	14	14	13±5	0.42±0.08
B	2	25	7	14	14	13±4	0.45±0.08
C	2	25	7	14	14	18±7	0.46±0.06
Low airflow rate 4 s protocol†							
A	4	25	7	28	14	9±4	0.41±0.05
B	4	25	7	28	14	11±4	0.46±0.09
C	4	25	7	28	14	10±4	0.49±0.04
ISO standard‡							
A	2	60	17.5	35	6	62±5	0.49±0.10
B	2	60	17.5	35	6	65±8	0.54±0.09
C	2	60	17.5	35	6	57±5	0.49±0.04
HCI standard§							
A	2	30	27.5	55	12	103±9	0.26±0.03
B	2	30	27.5	55	12	100±9	0.41±0.05
C	2	30	27.5	55	12	105±13	0.42±0.05
Manufacturer's recommended cleaning (HCI)¶							
E	2	30	27.5	55	12	103±12	0.46±0.06

*Per-use cleaning protocol, standard pump head with Tygon 15 tubing.
†Per-use cleaning protocol, standard pump head with Tygon 15 tubing.
‡Per-use cleaning protocol, high-performance pump head with Tygon 15 tubing.
§Per-use cleaning protocol, high-performance pump head with Tygon 36 tubing.
¶Manufacturer's recommended cleaning, HCI, high-performance pump head with Tygon 36 tubing.
HCI, Health Canada Standard ; ISO, International Organization for Standardization; iQOS, I quit original smoking.

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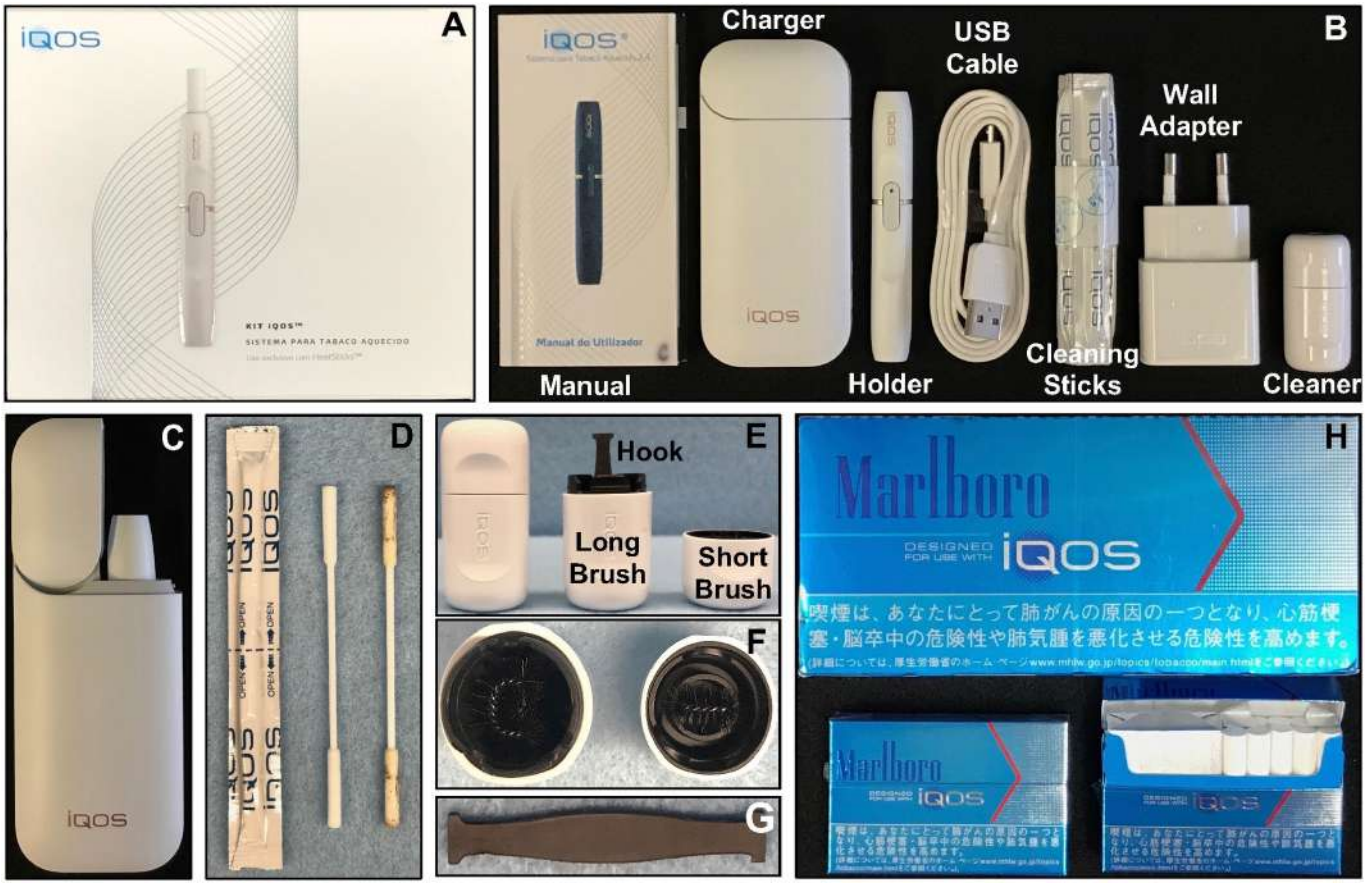


Figure 1 The I quit original smoking (iQOS) heat-not-burn system. (A) An iQOS starter kit. (B) The kit consists of an instruction manual, iQOS pocket charger, iQOS holder, USB cable, iQOS cleaning sticks, wall charging adapter and iQOS cleaner. (C) Profile view of iQOS holder inside a pocket charger. (D) Individual pack of iQOS cleaning sticks with an example of an unused stick and a stick after a single use per end. (E) A closed and opened iQOS cleaner; the larger end contains the long brush and protruding cleaning hook, and the shorter end contains the short brush. (F) Internal view of the iQOS cleaner showing the two brushes (long brush on the left, short brush on the right). (G) The cleaning hook removed from the iQOS cleaner. (H) Marlboro iQOS Heat Stick carton (containing 10 individual packs), sealed individual pack and opened pack exposing heatsticks.

7698A Headspace Sampler (Santa Clara, California, USA). Evaluation of iQOS aerosols was performed using headspace analysis. Chromatographic separation was accomplished using an Agilent J&W HP-5ms Ultra Inert GC Column (30 mx0.25 mmx0.25 µm) and ultra-pure helium (>99.999% purity) as the carrier gas at a flow rate of 1.5 mL/min. For headspace analysis, three unused heatsticks were dissected, polymer-film filters were removed, and a 3 mm portion (16.7%) closest to the tobacco plug were excised and placed into 20 mL headspace vials. All samples were analysed with a split ratio of 50:1, a solvent delay of 2 min, with blank analysis between each sample. GC ramp conditions were as follows: 40°C for 5 min, 45°C for 5 min, 90°C for 5 min, 130°C for 5 min, 135°C for 5 min, 165°C for 5 min, 190°C for 2 min, all temperature ramps were at 10°C/min. Ionisation of compounds was performed using electron impact ionisation at 70 eV in positive mode, the ion source maintained at 250°C and chemicals were identified using the National Institue of Standards and Technology mass spectral library (Gaithersburg, Maryland, USA), only chemicals with an 85% or higher probably match were listed as identifiable.

RESULTS

Components in the iQOS heat-not-burn system

The iQOS kit (figure 1A–G) consists of an instruction manual written in German, English, Portuguese and Italian, a pocket charger, the holder (device), a Universal Serial Bus (USB) cable and a European wall adapter plug for charging, moist cleaning sticks to clean the holder and cap, and the cleaner, which contains a long brush for cleaning the inside of the holder, where the heater is housed, a short brush for cleaning the cap and a hook for removing pieces of tobacco plug left in the holder/cap. A universal power adapter was purchased from Amazon (https://www.amazon.com/) and used to charge the pocket charger unit. Each carton of iQOS heatsticks contained 10 individually wrapped packs, and each pack had 20 heatsticks (figure 1H).

The iQOS kit components had an overall feel of good craftsmanship. The fabrication of the tobacco plug cast-leaf demonstrates a waste not want not strategy in that the plug is fabricated from pulverised tobacco remnants/waste materials, including tobacco stems, torn leaf material and leaf dust.[18] These items are reconstituted with natural adhesives and glycerin (a solvent that is used in EC fluids to produce aerosol) and processed into sheets forming cast-leaf, which is rolled and used as the tobacco plug.[3]

Cleaning of iQOS device

The interior chamber of the holder contained a heating element, referred to in the iQOS instruction manual as the silver, gold, platinum, ceramic-coated heater (figure 2). Unused holders were clean and debris-free with a white base and white heater with a metallic coil in its centre (figure 2A–C). Used holders

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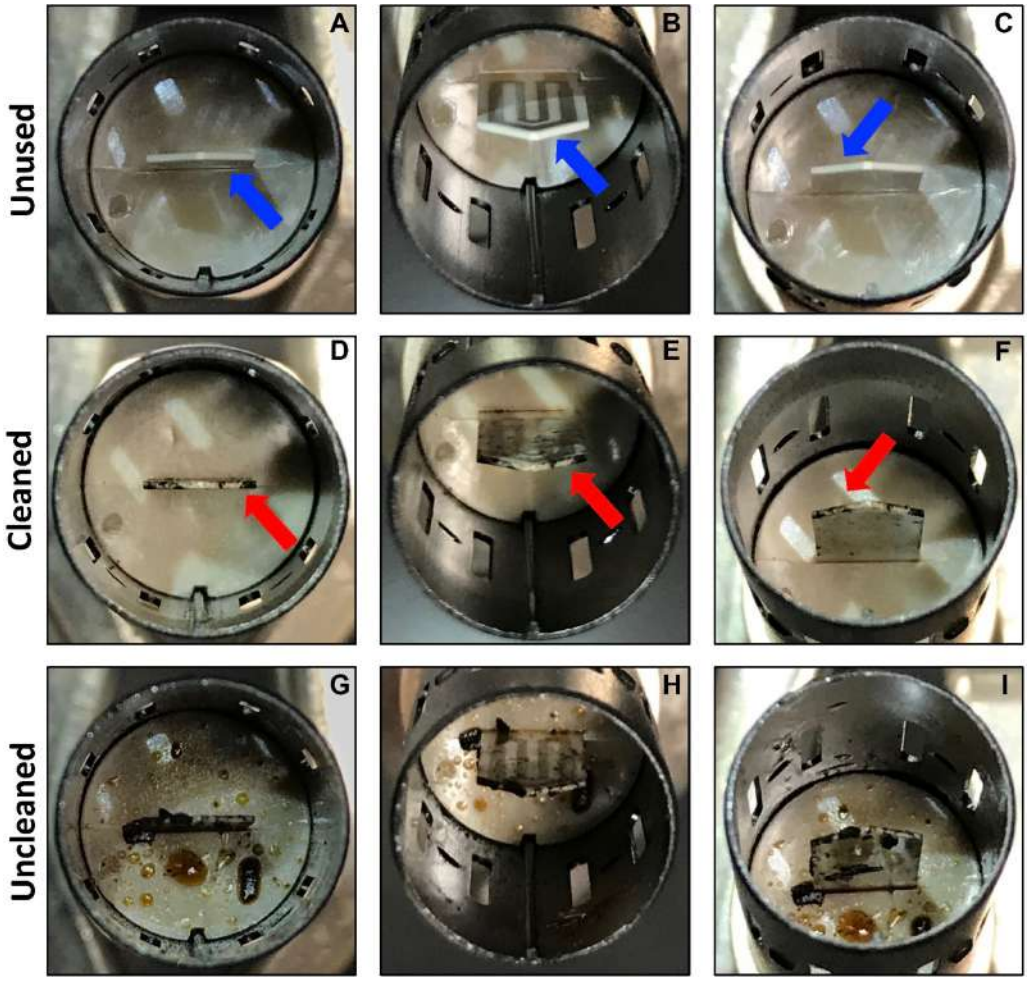


Figure 2 Internal view of the I quit original smoking holder. (A–C) Clean, unused holder showing heater (blue arrows). (D–F) Used holder that was cleaned after every use; black residue remains on heater (red arrows). (G–I) Used holder that was not cleaned between uses (10 uses).

that were thoroughly cleaned with the cleaning sticks between each heatstick were generally similar to the unused holder, except that the heating element had deposits of hardened dark debris that was not removed by the cleaning stick, cleaning cycle of the pocket charger or long brush (figure 2D–F). In the used holder that was not cleaned between heatsticks (manufacturer's recommended cleaning), brown liquid and particulates covered the base, walls and heater (figure 2G–I). With continued use in the absence of cleaning, the volume of liquid and debris increased, and the pieces of debris became darker and appeared more charred (figure 2D–I were taken after the 10th heatstick was used).

iQOS performance

The iQOS gives users a maximum of 14 puffs during a 6 min window per heatstick, after which it must be recharged before it can be used again. Performance of the iQOS was evaluated using five puffing protocols (figure 3, table 1). For protocols 1–4, three different iQOS devices (holders A, B and C) were tested in triplicate, that is, a new heatstick was used for each experiment, and each device underwent an intensive cleaning between each heatstick. For protocol 5, a single device (holder E) was used, and it was not cleaned between 10 heatsticks (average of the first three heatsticks is shown in figure 3I,J). For all testing protocols, pressure drop decreased as puff number increased. Aerosol density readings increased with use, peaking around puffs 7–9 and then begin to decrease. Although pump set-up affected pressure drop, it did not affect aerosol absorbance which remained similar under all running conditions, However, differences in testing conditions may lead to alterations in the chemical constituents present within the aerosol without altering aerosol density. Not cleaning did not affect performance except that pressure drop was more variable during the first four puffs in the uncleaned trials.

Tobacco plug charring

Dissection of unused and used heatsticks showed tobacco plug charring (figure 4A). Stereomicroscopic comparison of unused (figure 4B) and used (figure 4C) tobacco plugs confirmed charring or blackening of the cast-leaf. Visual and stereomicroscopic inspection of used heatsticks show the effects cleaning had on device heat production. Comparison of the first and 10th used heatstick from holder A (per-use cleaning) shows that with regular cleaning the charred area surrounding the heater, referred to as the zone of charring, does not increase with use (figure 4D,E). The effects of cleaning on heating were most evident during the course of the manufacturer's recommended cleaning (HCI) testing. Comparison of these heatsticks to unused and per-use cleaned heatsticks showed that in the absence of regular cleaning, the zone of charring increased as the number of heatsticks tested increased (figure 4H–L).

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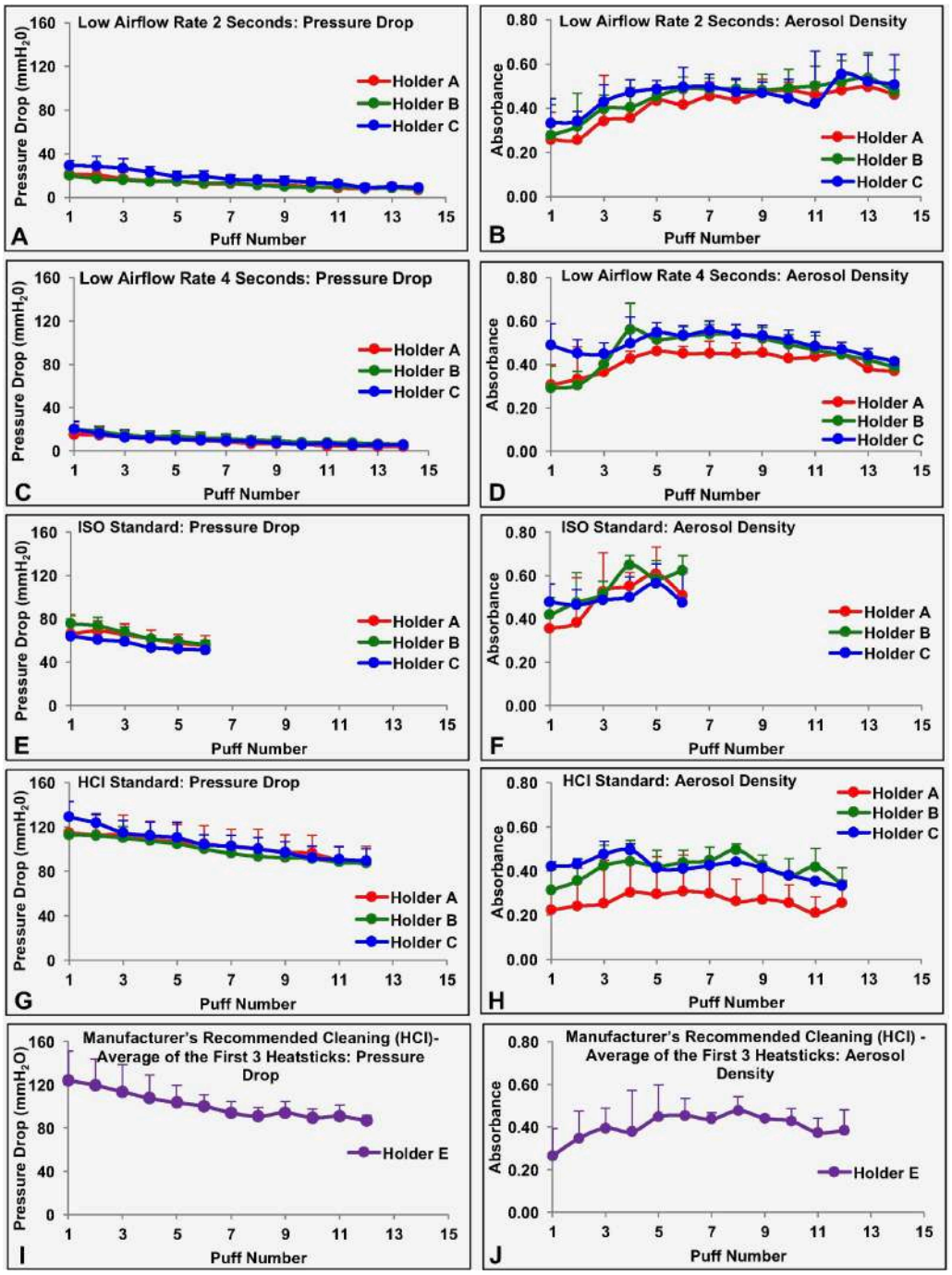


Figure 3 Performance characteristics of the I quit original smoking heat-not-burn system. (A, C, E, G and I) Pressure drop is plotted versus the puff number for five puffing protocols. (B, D, F, H and J) Absorbance is plotted versus puff number for the five puffing protocols. Each line of the graph represents the average of three heatsticks for an individual holder (holder A=red, holder B=green, holder C=blue and holder E=purple). HCI, Health Canada Standard ; ISO, International Organization for Standardization.

Polymer-film melting

Effects of cleaning on heating were not exclusive to the tobacco plug; figure 4A shows that the polymer-film filter (labeled 2), which is separated from the tobacco plug (condition 4) by the hollow acetate filter (condition 3), was adversely effected. The aerosol produced by the iQOS was hot enough to melt the polymer-film filter, which could allow release of potentially hazardous chemicals. Melting of the polymer-film filter was evident by slight yellowing of the filter, as well as by narrowing of the end closest to the tobacco plug (figure 4A indicated by black arrow). This melting and subsequent cooling of the filter caused it to harden, preventing it from being longitudinally dissected. Comparison of unused and used polymer-film filters from both per-use and manufacturer's recommended cleaning experiments showed the relationship between cleaning and increased heat generation. First (figure 4F) and 10th (figure 4G) filters from cleaned devices showed similar discoloration and melting to that of the first filter from the uncleaned device (figure 4N). Comparison of these heatsticks to subsequent manufacturer's recommended cleaning used heatsticks showed discoloration and melting of the polymer-film filter increased with increased use (figure 4M–Q).

Headspace analysis of unused polymer-film filters

GC–MS headspace analysis of unused polymer-film filters showed the presence of ε-caprolactone and lactide, common

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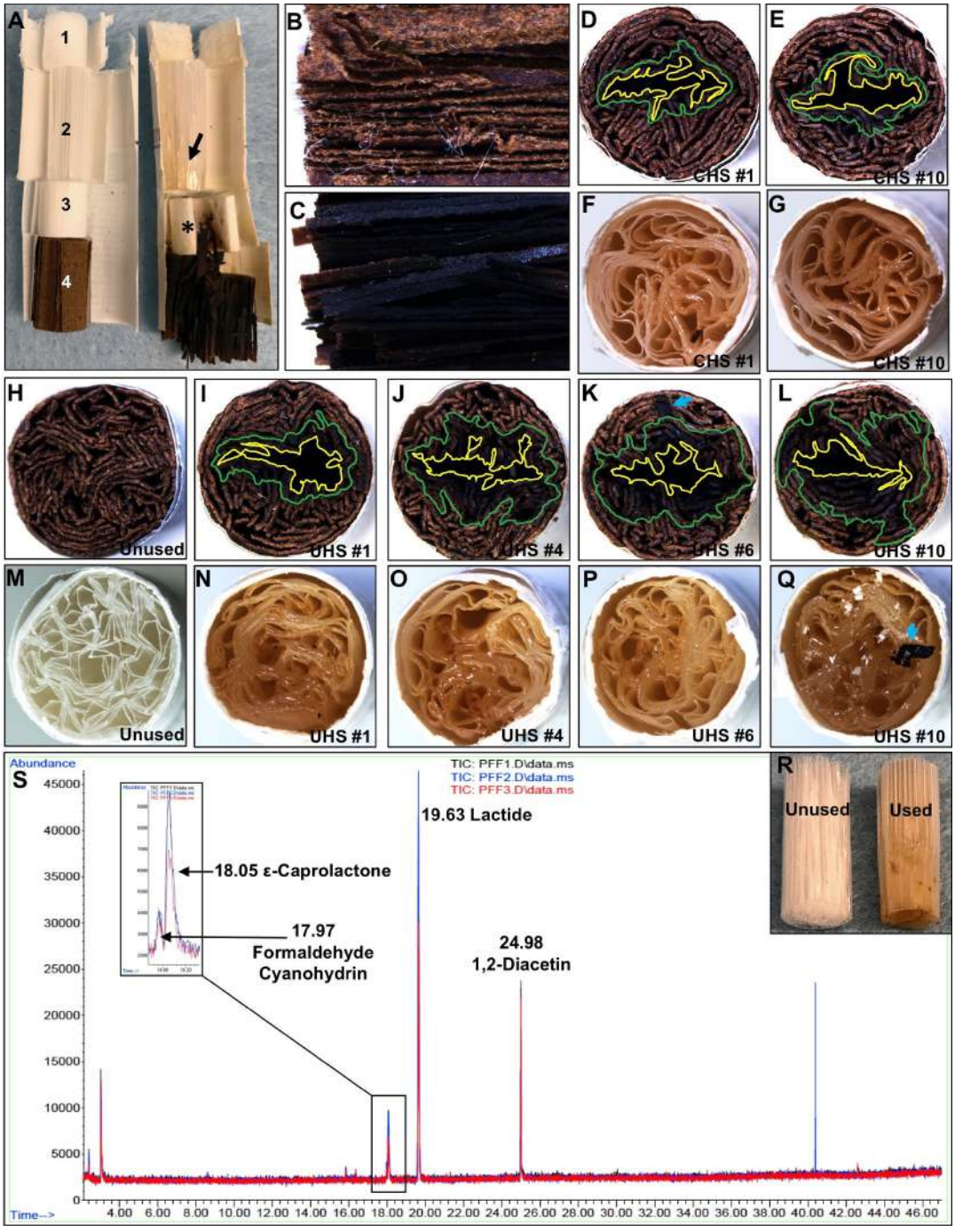


Figure 4 Charring of tobacco plug and melting of polymer-film filter. (A) Dissected heatsticks, each heatstick is composed of: (1) the low-density cellulose mouthpiece filter, (2) polymer-film filter, (3) hollow acetate tube and (4) tobacco plug. Heatsticks from left to right are unused stick with the paper overwrap peeled away, and used stick with the paper overwrap removed with the mouthpiece filter and hollow acetate tube sliced open; black arrow indicates melted region of the polymer-film filter, black asterisk denotes tobacco plug fragments that have been drawn into the hollow acetate tube. (B) An unused tobacco plug. (C) Used tobacco plug showing charring/darkening with use. (D,E) Cross sections of tobacco plugs from the first (D) and 10th (E) heatstick of holder A of the cleaned experiment. Yellow outlined area indicates a void in the cast-leaf left by the heater, the area between the yellow and green outlines are the charred portions of the tobacco plug. (F,G) Cross sections of polymer-film filter from the first (F) and 10th (G) heat stick. Polymer-film filter images shown coincide with tobacco plug images (D) and (E). (For D–G, CHS=cleaned device heatstick.) (H–L) Cross sections of tobacco plugs before use (H) and after use from the first, fourth, sixth and 10th heatstick of the uncleaned experiment (I–L). Yellow outlined area indicates a void in the cast-leaf left by the heater, area between the yellow and green outlines are the charred portions of the tobacco plug. (M–Q) Cross sections of polymer-film filter before (M) and after use (N–Q). Polymer-film filter images shown coincide with tobacco plug images (H–L). Blue arrowheads show charred pieces of cast-leaf that are affixed to the tobacco plug (K) and polymer-film filter (Q). (For (I–L) and (N–Q), UHS=uncleaned device heatstick). (R) Unused and used whole polymer-film filters showing discoloration and film melting, as demonstrated by the narrowing of the used filter. (S) Gas chromatography–mass spectrometry headspace analysis of unused polymer-film filter. Chromatogram shows an overlay of three runs, relative abundance was plotted versus retention time in minutes, unidentifiable peaks were unlabelled. Inset shows a magnified view of peaks with close retention times.

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components in plastics, as well as 1,2-diacetin, a plasticiser (figure 4S). However, of most concern was the presence of formaldehyde cyanohydrin (glycolonitrile), an acute toxicant often used in the production of synthetic resins and used as a solvent.[19] Formaldehyde cyanohydrin was eluted at 17.97 min, when the column reached 90°C.

DISCUSSION

Unlike some EC, which often show significant variation in craftsmanship and performance within and between brands,[15 20] the iQOS appearance, design and performance data are consistent with a product that is well manufactured. However, some design features of the iQOS, such the limited time allowed per heatstick and the need to consume the entire heatstick within this time or alternatively waste part of it, will affect user's topography and may lead to unwanted exposure to potentially toxic chemicals emitted from melting plastic and from pyrolysis of tobacco.

In contrast to tobacco and EC, which usually have no constraints on puffing, the iQOS only operates for 6 min, at which time it automatically shuts off and requires charging before it can be used again. Since a maximum of 14 puffs can be taken from each iQOS heatstick, puffing needs to be done at about 25 s intervals to take full advantage of each heatstick; used heatsticks that have not been fully exhausted cannot be used again as reinsertion would cause the delicate cast-leaf tobacco plug to crumble. This may not appeal to all users, and users who puff less frequently would have a lower number of puffs/heatstick. For users wishing to maximise each heatstick, this limitation will force them to alter their smoking topography by decreasing the interpuff interval and/or accelerating the rate at which they puff, leading to larger volumes of aerosol inhalation.

The manufacturer's cleaning instructions were not fully developed in the instruction manual. The cleaning protocol recommended using the cleaning function of the charger followed by cleaning with the brushes after 20 heatsticks and removing any large fragments of tobacco plug with the hook if necessary. The iQOS kit was equipped with cleaning sticks (figure 1B,D), yet their use was not mentioned in the instruction manual. Our data show that use of one heatstick left a significant amount of debris, fluid and fragments of cast-leaf in the holder (figure 2).

While iQOS heatsticks do not produce a flame, they were always charred after use, which we interpret to be a result of pyrolysis. The zone of charring was greater when cleaning was not performed between heatsticks, suggesting that build-up of fluid and debris in the holder increases pyrolytic temperatures. These data are consistent with the idea that despite similarities in performance characteristics, the cleanliness of the device plays a critical role in thermal regulation. Pyrolysis of tobacco is an endothermic reaction which occurs at temperatures between 200°C and 600°C, during which the majority of volatile and semivolatile components of cigarette smoke are formed.[21 22] Although the Philip Morris study indicated that the aerosol produced by iQOS devices reduce the amount of chemicals found on the Food and Drug Administration's Harmful and Potentially Harmful Constituents list by limiting tobacco pyrolysis,[5] our study, showing charring, in conjunction with a study by Auer *et al*, which confirmed the presence of volatile organic compounds, polycyclic aromatic hydrocarbons, carbon dioxide and nitric oxide,[23] contradict the claim that tobacco pyrolysis is minimised in iQOS. Although iQOS operates at temperatures less than 350°C, this does not negate the formation of volatile and semivolatile harmful constituents of tobacco smoke, which tend to have boiling points that range from 70°C to 300°C.[21 22]

Heatsticks used in this experiment were dissected and the severity of polymer-film filter melting was examined. The function of the polymer-film filter is to cool the aerosol,[3] thus, it would seem that the polymer composing the film should be heat resistant, although, ε-caprolactone, also known as polycaprolactone, tends to have a low-melting point which is thickness dependent.[24] The intensity of the heat produced by the iQOS, under both cleaned and uncleaned conditions, was sufficient to melt the polymer-film filter, even though it was not in direct contact with the heater. The amount of damage to the film (increase in melt and alteration of coloration) increased with each heatstick when cleaning was done per the manufacturer's recommended procedure (after 20 heatsticks). Discoloration may be a product of heating and/or staining from the brown fluid that is expelled from the tobacco plug during use.

Our GC–MS data indicate that components of the polymer-film filter are aerosolised at relatively low temperatures. GC–MS headspace analysis of unused filters suggests the polymer-film filter is a combination of ε-caprolactone, lactide, 1,2-diacetin and other unidentified chemicals. The chemicals released from the film filter during heating may not be suitable for inhalation. Thus, it is unknown if the film filter material is safe for use in products where it would undergo intense cycles of heating and cooling. Of greatest concern was the release from the polymer filter of formaldehyde cyanohydrin, a highly toxic chemical that is metabolised in the liver and broken down into formaldehyde and cyanide.[19] Formaldehyde cyanohydrin can be fatal to humans,[19 25 26] with studies showing mouse inhalation LD_{Lo}, the lowest dose of a toxicant that causes the death of an animal,[27] values as 27 ppm/8 hour.[28 29] iQOS holders operate at temperatures between 330°C and 349°C,[3 23] and as a safety feature, the device shuts off when temperatures reach 350°C. The release of formaldehyde cyanohydrin from unused filters during GC–MS analysis occurred at 90°C, a temperature that all users will exceed.

In conclusion, the iQOS appears to be well manufactured, and performance data were consistent between heatsticks. However, the product has limitations that will affect user topography and the application of standard smoking protocols, such as the ISO 3308, which could not be used for more than six puffs with this product. Users may be forced to smoke at a rapid pace in order to fully maximise heatsticks. Decreasing the interpuff interval could lead to an increase in intake of nicotine[30] and carbonyls.[31] This study also showed that the iQOS is not strictly a

What this paper adds

- Performance characteristics were generally uniform between devices and heatsticks.
- I quit original smoking (iQOS) device usage limitations make modifications to some current smoking standards necessary for proper evaluation of products.
- Device limitations may decrease users' interpuff intervals, increasing possible toxic exposures.
- iQOS holders heat hot enough to cause charring of the tobacco plug via pyrolysis and melting of the polymer-film filter.
- iQOS holder cleanliness affects and contributes to increased charring of the tobacco plug and melting of the polymer-film filter.
- Formaldehyde cyanohydrin, a toxicant, was released from the polymer-film filter at 90°C.

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'heat-not-burn' tobacco product. The iQOS tobacco appeared to char without ignition, and charring increased when cleaning was not done after each use. This study also showed the potential dangers that the polymer-film filter poses. This thin plastic sheet, readily melts during iQOS use and releases formaldehyde cyanohydrin, a dangerous toxicant. This study has shown that the iQOS system may not be as harm-free as claimed and also emphasises the urgent need for further safety testing as the popularity and user base of this product is growing rapidly.

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iQOS: evidence of pyrolysis and release of a toxicant from plastic

Barbara Davis, Monique Williams and Prue Talbot

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Heat-Not-Burn Tobacco Cigarettes: Smoke by Any Other Name

The tobacco industry's most recent response to the documented harms of cigarette smoking was to launch new heat-not-burn (HNB) tobacco cigarettes.[1] Philip Morris International (PMI) created IQOS (I-Quit-Ordinary-Smoking): disposable tobacco sticks soaked in propylene glycol, which are inserted in a holder in the HNB cigarette. The tobacco is heated with an electric blade at 350°C. The cigarettes are marketed by PMI as a "revolutionary technology that heats tobacco without burning it, giving you the true taste of tobacco, with no smoke, no ash and less smell."[2] In many countries, laws that protect people from passive smoke only apply to smoked tobacco products. Philip Morris International claims that IQOS releases no smoke because the tobacco does not combust and the tobacco leaves are only heated not burned. However, there can be smoke without fire. The harmful components of tobacco cigarette smoke are products of incomplete combustion (pyrolysis) and the degradation of tobacco cigarettes through heat (thermogenic degradation). Complete combustion occurs at a high temperature (>1300°C), higher than the heat generated by smoking a tobacco cigarette (<800°C). Typical markers of pyrolysis and thermogenic degradation of tobacco cigarettes are acetaldehyde, an irritant carcinogenic volatile organic compound, benzo[a]pyrene, a carcinogenic polycyclic aromatic hydrocarbon, and carbon monoxide.

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Pilot programs for IQOS began in 2014 in Japan and in 2015 in Switzerland and Italy. An internet survey in Japan published in 2015 suggested that younger individuals (15 to 39 years of age) were more likely to use IQOS, as were former smokers and current smokers.[3] Since 2016, a total of 19 countries have allowed the sale of IQOS cigarettes. In June 2016, data from PMI revealed that IQOS had captured 2.2% of the cigarette market in Japan. IQOS is not yet sold in the United States, but in December 2016, PMI submitted a modified risk tobacco product application to the US Food and Drug Administration. If successful, PMI will be less restricted in its marketing for the IQOS than for conventional tobacco cigarettes. Smokers and nonsmokers need accurate information about toxic compounds released in IQOS smoke. This information should come from sources independent of the tobacco industry, but the only analyses we found were from PMI and PMI competitors.[1]

Methods | We compared the contents of IQOS (IQOS Holder, IQOS Pocket Charger, Marlboro HeatSticks [regular], and Heets, Philipp Morris SA) smoke with the contents of conventional cigarettes (Lucky Strike Blue Lights). We used a smoking device designed and tested in our facility to capture the mainstream aerosol and developed to meet standards for common cigarettes and e-cigarettes.[4] We followed the International Organization for Standardization standards for puff volume (35 mL) at 2 puffs per minute, based on observation of IQOS smokers, who took a mean of 14 puffs during 5 to 6 minutes. We analyzed volatile organic compounds and nicotine by gas chromatography coupled to a flame ionization detector and polycyclic aromatic hydrocarbons using high-performance liquid chromatography coupled to a fluorescence detector, as previously described.[4] We trapped polycyclic aromatic hydrocarbons from IQOS cigarette smoke in a glass filter (Whatman 37 mm Ø GF/B) mounted in line with an XAD2 cartridge. For each sampling, 10 IQOS cigarettes were smoked. Each sampling support was desorbed in 10 mL of acetonitrile and sonicated for 1 hour. The eluate was evaporated in a vacuum concentrator (Speed Vac SC-200, ThermoFisher Scientific) set with 30 millibars and 27*g* until the residue was almost dry to prevent evaporation of the most volatile polycyclic aromatic hydrocarbons. The residue was filtered with polytetrafluoroethylene membrane (Acrodisc CR 13 mm, 0.45 µm, Pall Life Sciences) before it was analyzed with a high-performance liquid chromatography device (Ultimate 3000, ThermoFisher Scientific) equipped with a fluorescence detector (FLD-3000RS), UV detector (VWD-3000), and a separation column Nucleodur EC 150 × 3 mm C18 3 µm (Macherey-Nagel) under isocratic conditions (1.2 mL · min^{-1}). We injected 2 µL into the high-performance liquid chromatography chain; methanol/water (70/30) with acetonitrile was the eluent solvent at an initial ratio of 100% to 0% (4 minutes) and a linear gradient up to 100% acetonitrile (12 minutes). We did not analyze polycyclic aromatic hydrocarbons generated by conventional cigarettes and present the mean values in the 35 best-selling cigarettes brands in the United States, as reported by Vu et al.[5] We monitored the temperature near the heater blade inside the IQOS holder and the core of the conventional cigarette at a sampling rate of 3 Hz with a type k thermocouple.

Results | Volatile organic compounds, polycyclic aromatic hydrocarbons, and carbon monoxide were present in IQOS smoke (**Table**). The temperature of the IQOS was lower (330°C) than the conventional cigarette (684°C).[5] The IQOS smoke had 84% of the nicotine found in conventional cigarette smoke.

Discussion | The smoke released by IQOS contains elements from pyrolysis and thermogenic degradation that are the same harmful constituents of conventional tobacco cigarette smoke. International experts were invited by PMI to describe the IQOS aerosol; one expert claims that "less than 2% by weight of the aerosol components may derive from the pyrolysis of the tobacco substrate which would not be sufficient to characterize the aerosol as 'smoke.'"[6(p 2)] In contrast, our analyses reveal that advertising slogans such as "heat-not-burn" are

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Table. Concentrations of 8 Volatile Organic Compounds, 16 Polycyclic Aromatic Hydrocarbons, 3 Inorganic Compounds, and Nicotine in Mainstream Aerosol and Temperature of the HNB IQOS Cigarette and Conventional Cigarettes

Analyzed Compound	HNB Cigarette		Conventional Cigarette		Proportion of the Chemical in HNB and Conventional Cigarettes, %
	Amount, Mean (SD)	No. of Replications for Each Assay	Amount, Mean (SD)	No. of Replications for Each Assay	
Volatile organic compounds, µg per cigarette[a]					
Acetaldehyde	133 (35)	5	610[b]	1	22
Acetone	12.0 (12.9)	5	95.5 (13.5)	2	13
Acroleine	0.9 (0.6)	2	1.1	1	82
Benzaldehyde	1.2 (1.4)	5	2.4 (2.6)	2	50
Crotonaldehyde	0.7 (0.9)	5	17.4	1	4
Formaldehyde	3.2 (2.7)	5	4.3 (0.4)	2	74
Isovaleraldehyde	3.5 (3.1)	5	8.5 (10.8)	2	41
Propionaldehyde	7.8 (4.3)	5	29.6 (36.6)	2	26
Polycyclic aromatic hydrocarbons, ng per cigarette[c]					
Naphthalene	1.6 (0.5)	4	1105 (269)	7	0.1
Acenaphthylene	1.9 (0.6)	4	235 (39)	7	0.8
Acenaphthene	145 (54)	4	49 (9)	7	295
Fluorene	1.5 (0.6)	4	371 (56)	7	0.4
Anthracene	0.3 (0.1)	4	130 (18)	7	0.2
Phenanthrene	2.0 (0.2)	4	292 (44)	7	0.7
Fluoranthene	7.3 (1.1)	4	123 (18)	7	6
Pyrene	6.4 (1.1)	4	89 (15)	7	7
Benz[a]anthracene	1.8 (0.4)	4	33 (4.2)	7	6
Chrysene	1.5 (0.3)	4	48 (6.2)	7	3
Benzo[b]fluoranthene	0.5 (0.2)	4	24 (2.9)	7	2
Benzo[k]fluoranthene	0.4 (0.2)	4	4.3 (2.8)	7	9
Benzo[a]pyrene	0.8 (0.1)	4	20 (2.9)	7	4
Indeno[1,2,3-cd]pyrene	ND	4	NA	NA	NA
Benzo[ghi]perylene	ND	4	NA	NA	NA
Dibenzo[a,h]anthracene	ND	4	NA	NA	NA
Inorganics, ppm in the mainstream smoke[d]					
Carbon dioxide	3057 (532)	5	>9000	3	NA
Carbon monoxide	328 (76)	5	>2000	3	NA
Nitric oxide	5.5 (1.5)	5	89.4 (71.6)	3	6
Other measures					
Nicotine, µg per cigarette[a]	301 (213)	4	361	1	84
Temperature, °C	330 (10)	2	684 (197)	1	NA
Puff total count	12.6 (2.4)	32	13.3 (3.1)	6	NA

Abbreviations: HNB, heat-not-burn; NA, not analyzed; ND, not detected.

[a] We applied the methods described previously in Varlet et al[4] to analyze volatile organic compounds and nicotine.

[b] Because there was only 1 replication, no SD can be computed.

[c] We present values reported from Vu et al[5] for the ISO smoking regimen and for a mean of the 35 top-selling US cigarette brands.

[d] Carbon dioxide was measured with a Testo 535 (Testo), and carbon monoxide and nitric oxide were measured with a Pac 7000 that detected carbon monoxide (Draeger). The apparatus measured the smoke when it was released from the syringe pump.

no substitute for science. Dancing around the definition of smoke to avoid indoor-smoking bans is unethical. Principle 1 for implementing article 8 of the World Health Organization convention on tobacco control highlights that we should reject ideas that there is a threshold value for toxic effects from second-hand smoke. Independent studies should further evaluate the health effects of the IQOS. In the meantime, heated tobacco products such as IQOS should fall under the same indoor-smoking bans as for conventional tobacco cigarettes.

Reto Auer, MD, MAS
Nicolas Concha-Lozano, PhD
Isabelle Jacot-Sadowski, MD
Jacques Cornuz, MD, MPH
Aurélie Berthet, PhD

Author Affiliations: Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland (Auer); Department of Ambulatory Care and Community Medicine, University of Lausanne, Lausanne, Switzerland (Auer, Jacot-Sadowski, Cornuz); Institute for Work and Health, University of Lausanne and Geneva, Lausanne, Switzerland (Concha-Lozano, Berthet).

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Corresponding Author: Reto Auer, MD, MAS, Institute of Primary Health Care (BIHAM), University of Bern, Gesellschaftsstrasse 49, 3012 Bern, Switzerland (reto.auer@biham.unibe.ch).

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Study concept and design: Auer, Concha-Lozano, Jacot-Sadowski, Berthet.
Acquisition, analysis, or interpretation of data: Auer, Concha-Lozano, Jacot-Sadowski, Cornuz, Berthet.
Drafting of the manuscript: Auer, Concha-Lozano, Berthet.
Critical revision of the manuscript for important intellectual content: Concha-Lozano, Jacot-Sadowski, Cornuz.
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Editor's Note

No Smoke—Just Cancer-Causing Chemicals

Heat-not-burn tobacco products are for sale around the world. Although they are not yet on the market in the United States, Phillip Morris International has applied to the US Food and Drug Administration (FDA) to sell these products. These products threaten the progress that has been made on decreasing the harms of second-hand smoke because existing bans may not apply to these heat-not-burn products. However, as convincingly reported by Auer and colleagues,[1] although these products may or may not produce smoke, they release cancer-causing chemicals. As shown in their table, heat-not-burn cigarettes release similar levels of many volatile organic compounds and nicotine as conventional cigarettes and higher levels of the polycyclic aromatic hydrocarbon acenaphthene than conventional cigarettes. They are bad for health because they release cancer-causing chemicals, and I hope the FDA will not approve them for that important reason. If the FDA does approve the sale of these products, existing smoking bans should be amended to include these products.

Mitchell H. Katz, MD

Author Affiliations: Los Angeles County Department of Health Services, Los Angeles, California; Deputy Editor, *JAMA Internal Medicine*.

Corresponding Author: Mitchell H. Katz, MD, Los Angeles County Department of Health Services, 313 N Figueroa St, Rm 912, Los Angeles, CA 90012 (mkatz@dhs.lacounty.gov).

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COMMENT & RESPONSE

Neuroleptics for Delirium: More Research Is Needed

To the Editor We read with interest the Original Investigation in a recent issue of *JAMA Internal Medicine* by Agar et al[1] on the management of delirium in the palliative care setting. Delirium is one of the most common and disturbing syndromes at the end of life,[2] and there are few well-designed studies to inform practice.[3] Because data from geriatrics and other populations cannot be extrapolated to the palliative care setting, this important study[1] provides unique insights into the role of haloperidol and risperidone compared with placebo; however, several issues regarding the study design complicate its interpretation.

We wonder if the composite subscore of the Nursing Delirium Screening Scale (NuDesc) is an appropriate primary outcome. Although NuDesc has been validated, this subscore has not been studied before, and the minimal clinical important difference has not been defined. While haloperidol and risperidone arms were associated with statistically significant worse NuDesc subscores, the magnitude of change may not be clinically meaningful based on the investigator-defined cutoff (<1 point).

If haloperidol and risperidone were indeed ineffective, could the low medication doses explain it? In our acute palliative care unit, daily haloperidol doses of more than 8 mg were often needed for patients who were agitated.[4,5] We are also curious that despite the low dose and short duration of neuroleptic use, Agar et al[1] reported shortened survival with risperidone. Given the large number of secondary outcomes, these findings should be considered as hypothesis-generating, and further studies are needed.

These are confusing times. Clinicians caring for patients with agitated delirium have to grapple with the dilemma of uncertain benefits and potential risks with neuroleptics for a distressing condition for which few other proven interventions are available. While identification of reversible causes and nonpharmacological measures seem intuitive, these interventions need to be standardized and tested formally in the palliative care setting in which delirium is often severe, progressive, and irreversible. For the large portion of patients who do not respond to these measures, neuroleptics may still have a role for refractory agitation. This study also reopens the debate on whether benzodiazepines alone should be considered for delirium. Given this is a single study enrolling predominantly patients with mild delirium (median Memorial Delirium Assessment Scale score, 13-15), it is premature to close the chapter on neuroleptics in palliative care as suggested by the authors and the accompanying editorial.[1] Instead, this study highlights the tremendous opportunities

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New heated tobacco device causes same damage to lung cells as e-cigs and smoking, study finds

Date: February 11, 2019

Source: European Lung Foundation

Summary: A new study that directly compares new heated tobacco devices with vaping and traditional cigarettes shows that all three are toxic to human lung cells.

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FULL STORY

A new study that directly compares new heated tobacco devices with vaping and traditional cigarettes shows that all three are toxic to human lung cells.

The study published in *ERJ Open Research* suggests that the new device, which heats solid tobacco instead of an e-liquid, is no less toxic to the cells than ordinary cigarette smoke.

Researchers say the study adds to evidence that these newer electronic nicotine delivery devices may not be a safer substitute for cigarette smoking.

The study was led by Dr Pawan Sharma, a researcher at the University of Technology Sydney and the Woolcock Institute of Medical Research, Sydney, Australia.

He said: "Smoking is the leading cause of preventable death, and with the introduction of e-cigarettes in the last decade, the trend of nicotine uptake is not going to slow down in the near future. If the current trend continues, tobacco use will cause more than eight million deaths annually by 2030 around the world.

"The latest addition in this emerging trend is the planned and vigorous in-

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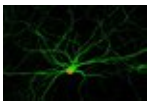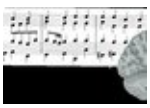


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troduction of heated tobacco devices. They are commonly called next generation or heat-not-burn products. We know very little about the health effects of these new devices, so we designed this research to compare them with cigarette smoking and vaping."

Researchers tested the effects of all three nicotine sources on two types of cells taken from the human airways: epithelial cells and smooth muscle cells. In healthy lungs, epithelial cells act as the first line of defence to any foreign particles entering the airway while smooth muscle cells maintain the structure of the airway. However, smoking can lead to difficulty in breathing primarily by hampering the normal functions of these cells.

Dr Sharma and his team exposed the cells to different concentrations of cigarette smoke, e-cigarette vapour and vapour from a heated tobacco device, and measured whether this was damaging to cells and whether it affected the cells' normal functions.

The researchers found that cigarette smoke and heated tobacco vapour were highly toxic to the cells both at lower and higher concentrations while e-cigarette vapour demonstrated toxicity mainly at higher concentrations. Researchers say that these concentrations represent the levels of nicotine found in chronic smokers.

Dr Sukhwinder Sohal, a researcher at the University of Tasmania, Launceston, Australia, and leading author on the study, said: "We observed different levels of cellular toxicity with all forms of exposures in human lung cells. What came out clearly was that the newer products were in no way less toxic to cells than conventional cigarettes or e-cigarette vaping."

Dr Sharma added: "Our results suggest that all three are toxic to the cells of our lungs and that these new heated tobacco devices are as harmful as smoking traditional cigarettes.

"It took us nearly five decades to understand the damaging effects of cigarette smoke and we don't yet know the long-term impact of using e-cigarettes. These devices that heat solid tobacco are relatively new and it will be decades before we will fully understand their effects on human health.

"What we do know is that damage to these two types of lung cells can destroy lung tissue leading to fatal diseases such as chronic obstructive pulmonary disease, lung cancer and pneumonia, and can increase the risk of developing asthma, so we should not assume that these devices are a safer option."

Dr Sharma hopes his results will stimulate more research on heated tobacco devices and he plans to continue this work by studying the effects of nicotine devices on more sophisticated models of lung tissue and in mice.

Professor Charlotta Pisinger is Chair of the European Respiratory Society's Tobacco Control Committee and was not involved in the research. She said: "These new heated tobacco devices are marketed as produc-



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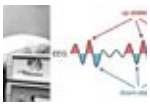
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ing 95% low er levels of toxic compounds because the tobacco is heated, not burned. How ever, the first independent studies have show n that combustion is taking place and toxic and carcinogenic compounds are released, some in low er levels than in conventional cigarette smoke, others in higher levels. A review of the tobacco industry's ow n data on these devices has show n that, in rats, there is evidence of lung inflammation, and there is no evidence of improvement in lung inflammation and function in smokers w ho sw itch to heated tobacco.

"The introduction and vigorous marketing of new devices is very tempting to smokers w ho w ant to stop smoking and mistakenly believe they can sw itch to another harmless tobacco product. It is also opening another avenue for attracting young people to use and become addicted to nicotine. This study adds to evidence that these new devices are not the safe substitute to cigarette smoking they are promoted to be."

Story Source:

Materials provided by **European Lung Foundation**. *Note: Content may be edited for style and length.*

Journal Reference:

1. Sukhw inder Singh Sohal, Mathew Suji Eapen, Vegi G.M. Naidu, Paw an Sharma. **IQOS exposure impairs human airway cell homeostasis: direct comparison w ith traditional cigarette and e-cigarette**. *ERJ Open Research*, 2019; 5 (1): 00159-2018 DOI: 10.1183/23120541.00159-2018

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ORIGINAL RESEARCH LETTER

IQOS exposure impairs human airway cell homeostasis: direct comparison with traditional cigarette and e-cigarette

To the Editor:

While cigarette smoking still remains one of the most pressing global health issues of our time, newer forms of smoking device have been introduced across the globe in the last decade [1]. Electronic nicotine/non-nicotine delivery systems commonly known as electronic cigarettes (eCig) heat a solution (e-liquid) to create vapour [2]; the latest addition to this list is the introduction of heat-not-burn (HNBs) tobacco products branded as IQOS [3]. HNBs are hybrids between eCigs and traditional cigarettes *i.e.* they are equipped with a device that heats the product, without burning to generate aerosol and the product being heated is not a liquid but real tobacco [4, 5]. eCig vaping is comparatively new but its use is increasing at an alarming rate; it is believed it will surpass the use of traditional cigarettes in next 5 years, with global sales reaching US$10 billion [6]. Since its launch in Italy and Japan in 2014, IQOS has become the leader in the HNB market [4, 7]. To date, IQOS is available in 41 countries, including 22 from the WHO-European region, and its market share has now reached the level of cigars in Italy [4]. Emerging data shows that eCig use, particularly in the young, is associated with future cigarette use [8]. Similarly, over half of the people interested in IQOS are never-smokers [4]. Therefore, both eCigs and IQOS may represent a gateway for nicotine addiction among never-smokers rather than a substitute used for harm-reduction purposes in current smokers [4]. It is now clear that eCig vapour contains high levels of toxic compounds [9], which adversely affect respiratory, gastrointestinal and cardiovascular systems both *in vitro* and *in vivo* [10–12]. It is also important to recognise that IQOS products are comparatively new but emerging research suggests that IQOS emits substantially high levels of carbonyls [13]. There is as yet no published comparison between the effect of eCigs, IQOS and tobacco smoke on human lungs. Here, we examine whether exposure to IQOS has the same damaging effect on human airway epithelial and smooth muscle cells as traditional tobacco cigarette and eCigs *in vitro*.

We used human bronchial epithelial cells (Beas-2B, ATCC CRL-9609) and primary human airway smooth muscle (ASM) cells (ATCC PCS-130-010). eCig vapour was generated using an eCig device (KangerTech 3rd Generation; KangerTech, Shenzhen, China) and e-liquid (Blu, Charlotte, NC, USA) (1.2% nicotine); IQOS aerosol was generated using HNB heat-sticks (Philip Morris, Tokyo, Japan) (1.4 mg nicotine); and cigarette-smoke-extract (CSE) was generated using Marlboro Red cigarettes (Philip Morris, Washington, DC, USA) (1.2 mg nicotine). eCig vapour/IQOS aerosol/cigarette smoke was "bubbled" through a T-75 flask containing 25-mL media at a constant rate with modification [14–18]. This freshly generated (100%) eCig vapour, IQOS aerosol and CSE were diluted to the final working concentration and used immediately. Beas-2B or primary human ASM cells were treated with increasing concentrations of CSE, eCig vapour or IQOS aerosol for 72 h, and cell cytotoxicity (Thaizolyl blue tetrazolium bromide (MTT) and lactate dehydrogenase (LDH)), chemokine release (CXCL8), extracellular matrix (ECM) (collagen 1 and fibronectin) release and mitochondrial respiration (glycolysis and proton leak) were measured.

GraphPad (La Jolla, CA, USA) was used for statistical analysis using one-way ANOVA followed by Bonferroni's multiple comparison test.

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Heat-not-burn (HNB) devices can alter vital physiological functions in the lung. HNB devices may not be a safer option than cigarette smoking or eCig vaping; this does not support the recommendation of their use over other nicotine delivery products. http://ow.ly/wZ5P30ng8bU

Cite this article as: Sohal SS, Eapen MS, Naidu VGM, *et al.* IQOS exposure impairs human airway cell homeostasis: direct comparison with traditional cigarette and e-cigarette. *ERJ Open Res* 2019; 5: 00159-2018 [https://doi.org/10.1183/23120541.00159-2018].

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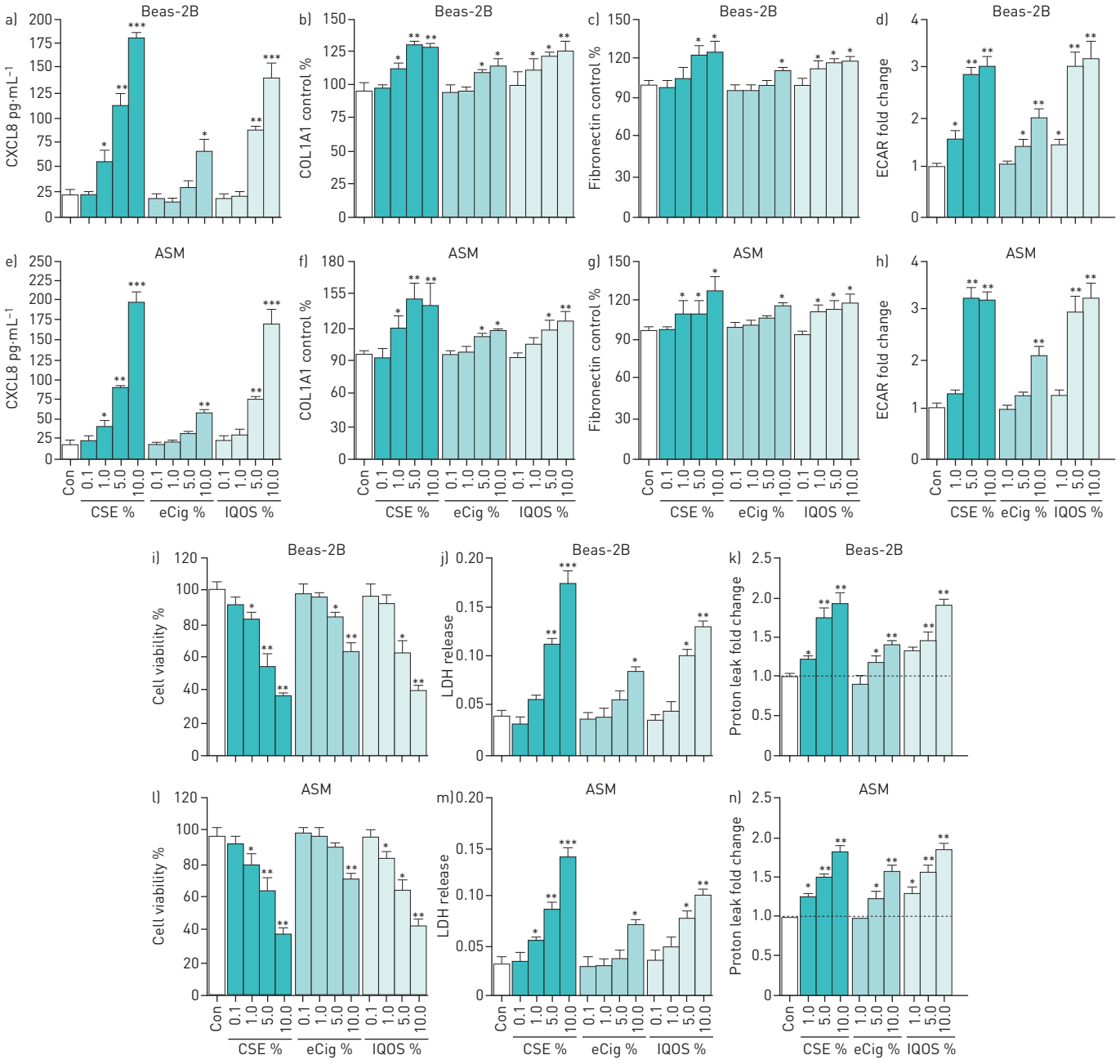


FIGURE 1 a–h) Comparison of the effects of cigarette smoke extract (CSE), electronic cigarette (eCig) vapour and IQOS aerosol exposure on a–d) human airway epithelial (Beas-2B) and e–h) human airway smooth muscle (ASM) cells. a and e) show the release of CXCL8 from Beas-2B and ASM cells. The concentration of CXCL8 in supernatant from Beas-2B and ASM cells after 72 h of stimulation with CSE, eCig vapour or IQOS aerosol exposure was measured using ELISA. Deposition of b and f) collagen I alpha 1 (COL1A1) and c and g) fibronectin from Beas-2B and human ASM cells after 72 h of stimulation with CSE, eCig vapour or IQOS aerosol exposure was measured using extracellular matrix (ECM) ELISA at an absorbance of 450 nm and 570 nm, respectively. d and h) The level of glycolysis was determined in Beas-2B and ASM cells using a seahorse analyser, and extracellular acidification rate (ECAR); an index of glycolysis was measured after 72 h of stimulation with CSE, eCig vapour or IQOS aerosol exposure. Data are presented as mean±SEM (n=5–7). i–n) The effect of CSE, eCig and IQOS exposure on cellular toxicity and respiration. The cell viability (i and l), the lactate dehydrogenase (LDH) release (j and m) and the mitochondrial respiration (k and n) from Beas-2B and human ASM cells was measured using Thaizolyl blue tetrazolium bromide (MTT) and LDH assays at an absorbance of 570 nm and 490 nm, respectively. k and n) Mitochondrial respiration was measured in Beas-2B and ASM cells using a mito-stress kit on a seahorse analyser (Agilent Technologies Inc., Santa Clara, CA, USA), and proton leak was measured as oxygen consumption rate shown as fold change to control. Cells were stimulated with serial dilution of CSE, eCig vapour or IQOS aerosol for 72 h (n=5). Data are presented as mean±SEM. A one-way ANOVA plus Bonferroni post-test was used to determine statistical significance. *: p<0.05 compared with control; **: p<0.01 compared with control; ***: p<0.001 compared with control.

Using two different cytotoxicity assays (MTT and LDH), CSE, eCig or IQOS exposure showed cellular toxicity with increasing concentration (figure 1a–h). A CSE concentration of >10% is highly toxic; therefore, we only used concentrations <10% in our experiments, which is also used widely in many

studies [14–18]. In both Beas-2B and ASM cells, we found that CSE exposure significantly reduced cell viability and increased LDH release at 1, 5 and 10% (figure 1i–n). eCig exposure showed similar toxicity at 5 and 10% exposure. Interestingly, IQOS exposure was as toxic as CSE at 1, 5 and 10%. It is evident that both CSE and eCig vapour can induce inflammation in the lung [18, 19], and as shown in figure 1a–h), CSE exposure in a concentration-dependent manner induced the release of CXCL8 in Beas-2B (figure 1a) and ASM cells (figure 1e). eCig exposure induced CXCL8 release at the highest concentration, whereas IQOS exposure showed a similar induction to CSE, suggesting that IQOS is as effective as CSE in inducing chemokine release from both types of airway cells. Next, we measured the induction of ECM proteins with airway cells; CSE, eCig and IQOS exposure in a concentration-dependent manner increased collagen 1 (figure 1b and f) and fibronectin (figure 1c and g) release with both Beas-2B (figure 1b and c) and ASM (figure 1c and g) cells. Finally, we measured mitochondrial respiration using a seahorse analyser, and found that CSE, eCig and IQOS exposure increased the extracellular acidification rate (a measure of glycolysis) (figure 1a–h) and proton leak (a measure of mitochondrial uncoupling) (figure 1i–n) in both Beas-2B (figure 1d) and ASM (figure 1h) cells, respectively.

Cigarette smoking has been linked to chronic lung diseases such as chronic obstructive pulmonary disease (COPD), asthma, pulmonary fibrosis, cancer and related comorbidities [1]. It took us nearly five decades to understand the detrimental effects of cigarette smoke on humans. Long-term eCig-exposure studies in humans are currently sparse, limiting our understanding of its direct effect(s) on both disease development and progression. eCig vaping is already at its highest level globally, and many countries are imposing stringent regulations in light of the emerging evidence showing the adverse effects of vaping on human health. IQOS use is comparatively new; it will take years before we start to know its detrimental effect on human health. We demonstrate here for the first time that IQOS exposure is as detrimental as cigarette smoking and vaping to human lung cells. Persistent allergic, smoke or environmental-triggered inflammation leads to airway remodelling/scarring through re-organisation of ECM and airway cell proliferation, and mitochondrial dysfunction plays a pivotal role in this process. These are the principal causes for airflow limitation in asthma and COPD. Here, we have analysed all of these mechanisms: inflammation (CXCL8), ECM release (collagen 1 and fibronectin) and mitochondrial respiration (glycolysis and proton leak). We observed collagen-1 and fibronectin induction by both Beas-2B and ASM cells to CSE, eCig and IQOS exposure. ECM proteins facilitate the conversion of mesenchymal cells to ECM secreting active myofibroblasts and epithelial mesenchymal transition (EMT) in chronic lung disease [20, 21]. Our data suggests that like eCigs and traditional cigarettes, IQOS exposure contributes to altered mitochondrial function which can further exaggerate airway inflammation, airway remodelling and lung cancer through active EMT, as seen in smokers [22]. It is widely understood that mitochondria of airway epithelium and mesenchymal cells play differential roles, consistent with their contributions to disease and essential for cell existence. Mitochondrial dysfunction also underpins many normal physiological processes and in certain pathological conditions, such as obesity or with an oxidant trigger such as smoke, eCigs and IQOS, it may impact lung diseases. Cigarette smoking and eCigs can exaggerate respiratory infections by increasing microbial adherence to the airways [23, 24]; IQOS may increase respiratory infections through similar mechanisms.

Given our current findings and those of previous studies, in a manner very similar to cigarette smoke and eCigs, IQOS has the potential to increase oxidative stress and inflammation, infections, airway remodelling and initiate EMT-related changes in the airways of users of these devices. However, prospective clinical studies must be conducted to verify our *in vitro*, cell-based but highly important and novel findings on IQOS.

Sukhwinder Singh Sohal[1], Mathew Suji Eapen[1], Vegi G.M. Naidu[2] and Pawan Sharma[3,4]
[1]Respiratory Translational Research Group, Dept of Laboratory Medicine, School of Health Sciences, University of Tasmania, Launceston, Australia. [2]Dept of Pharmacology, National Institute of Pharmaceutical Education & Research, Guwahati, India. [3]Medical Sciences, School of Life Sciences, Faculty of Science, University of Technology, Sydney, Australia. [4]Woolcock Emphysema Centre, Woolcock Institute of Medical Research, The University of Sydney, Sydney, Australia.

Correspondence: Pawan Sharma, The University of Technology Sydney, 15 Broadway, NSW 2007, Australia. E-mail: Pawan.Sharma@uts.edu.au

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Conflict of interest: None declared.

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Study finds electronic tobacco devices emit more tar than regular cigarettes

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IQOS and Lil cigarettes found as key perpetrators



Models of the IQOS, an electronic heat-not-burn tobacco device, are displayed at convenience store in Seoul's Mapo district. (Lee Jeong-a, staff photographer)

A South Korean government study has found that some heat-not-burn tobacco devices that are being sold in South Korea contain more tar, a harmful substance, than ordinary cigarettes.

On June 7, South Korea's Ministry of Food and Drug Safety (MFDS) released the findings of an analysis of 11 harmful ingredients, including nicotine and tar, in the smokeless cigarettes released by three companies: IQOS by Philip Morris Korea, Glo by British American Tobacco and Lil by KT&G.

In a three-day analysis consisting of three tests per day (in line with the standards of the International Organization for Standardization), the Testing Analysis and Assessment Committee, which is composed of experts in tobacco and environmental analysis, found that IQOS and Lil cigarettes emitted an average of 9.3mg and 9.1mg of tar, respectively. That was higher than the tar content (4.3–5.8mg) of the five kinds of ordinary cigarettes most commonly sold in the country.

"There are no grounds for arguing that heat-not-burn tobacco devices are less harmful than ordinary cigarettes. However, ordinary cigarettes and heat-not-burn tobacco devices may include different kinds of tar, which limits the utility of comparing harmfulness based

on the detected amount," the MFDS said, based on its analytical findings.

These three products had a similar average nicotine content to ordinary cigarettes. When analysts scanned for nine substances other than nicotine and tar that the World Health Organization advises people to reduce their intake of, including Group 1 carcinogens, eight of those substances (all except for 1,3-Butadiene) were detected. On average, the content of these eight substances was lower than in regular cigarettes.

Philip Morris Korea argued that the MFDS's analytical findings "demonstrate once again our basic research findings that these products contain fewer harmful materials [than regular cigarettes]."

By Park Hyun-jung, staff reporter

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June 7, 2018

The Ministry of Food and Drug Safety Thursday dispelled the misconception of heat-not-burn cigarettes being healthier than ordinary cigarettes, publishing the results of an independent st udy done in Korea.

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The Ministry of Food and Drug Safety published study findings on heat-not-burn cigarettes that found them not less harmful than ordinary tobacco.

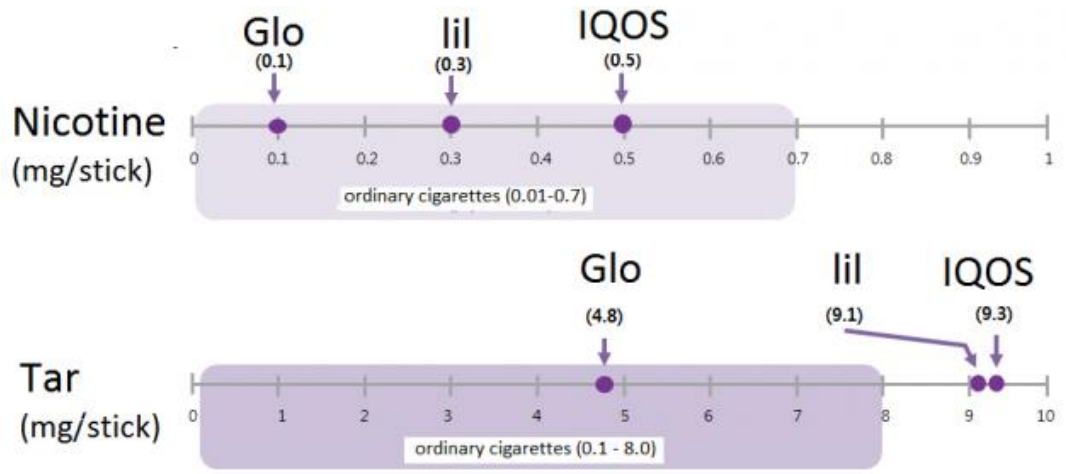
Heat-not-burn cigarettes, which the public has often perceived as being less harmful to health than ordinary tobacco, were found to have more tar than the latter, and have the same nicotin e content, the ministry said. “There were no evidence to show heat-not-burn cigarettes to be l ess harmful than ordinary cigarettes,” it added.

The study, aimed to provide correct information about heat-not-burn cigarettes substances fo r the public, screened six carcinogens and 11 other harmful substances, including nicotine an d tar, excreted from 3 heat-not-burn cigarettes on the Korean market -- Philip Morris’s IQOS, British American Tobacco’s Glo and KT&G’s Lil.

Researchers used the standards of the International Organization for Standardization and the method employed by Health Canada and had results verified by an independent evaluation co mmittee composed of 11 professors, the ministry said.

Findings showed heat-not-burn cigarettes had up to five human carcinogens, including benzo pyrene and benzene. The ministry pointed out that heat-not-burn cigarettes, like ordinary toba cco, can cause various illnesses, such as cancer.

Heat-not-burn cigarettes also had similar levels of nicotine as conventional products while tw o brands of e-cigs had higher tar content. Philip Morris' iQOS had the highest nicotine and tar levels out of the three, the ministry noted.



Source: Ministry of Food and Drug Safety

"The tar content of two heat-not-burn cigarettes was higher than ordinary tobacco, which indi cates they could have other harmful substances not found in the latter," it said.

The ministry also said heat-not-burn cigarettes do not help people quit smoking as nicotine is an addictive substance. The overall harmfulness of e-cigs additionally depends on factors su ch as duration and amount of smoking, inhaling amount and depth as well as other smoking habits, it said.

yjc@docdocdoc.co.kr

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PLAY AUDIO

June 08,2018



A researcher at the Ministry of Food and Drug Safety demonstrates the analysis of substances produced from heat-not-burn cigarettes at a lab in Cheongju, North Chungcheong, on Thursday. [YONHAP]

Heat-not-burn cigarettes are no safer than ordinary cigarettes, according to government test results, and produce harmful substances related to cancer - and possibly even more tar.
Tobacco makers disagreed and claimed the results will only confuse smokers.

On Thursday, the Ministry of Food and Drug Safety announced the results of an 11-month investigation of the safety of heat-not-burn cigarettes.

There are currently three heat-not-burn cigarettes being sold in Korea: Philip Morris Korea’s IQOS, British American Tobacco’s glo and KT&G’s lil. While ordinary cigarettes burn tobacco leaves to make smoke, heat-not-burn cigarettes produce vapor by steadily heating the leaves at a lower temperature.

Manufacturers have promoted the product as a less harmful alternative to conventional cigarettes, a claim the government refuted on Thursday.

The smoke produced from the three brands of heat-not-burn cigarettes was analyzed to measure nicotine, tar and nine harmful substances the World Health Organization has criticized in cigarettes.

Tar collectively refers to substances produced during combustion, except for water and nicotine. The government test results showed that the three heat-not-burn products produced levels of tar between 4.8 and 9.3 milligrams. IQOS and lil produced more tar than some of the most popular ordinary cigarettes, which normally produce less than 8 milligrams.

The nicotine content of the heat-not-burn cigarettes was between 0.1 and 0.5 milligrams. Ordinary cigarettes produce between 0.01 and 0.7 milligrams.

Regarding the nine other harmful substances, heat-not-burn cigarettes produced levels between zero to 30 percent of the amount produced by ordinary cigarettes.

“Two heat-not-burn cigarettes produced more tar than conventional cigarettes,” said a government statement, adding that they may contain harmful substances not found in conventional cigarettes.

It also said that heat-not-burn cigarettes can’t be used to help quit smoking if they produce similar levels of nicotine, an addictive substance, and that heat-not-burn cigarettes can cause diseases like cancer.

“We plan to effectively use the test results to supervise cigarette products and establish antismoking policies,” the government said in its statement.

Heat-not-burn manufacturers rebutted the claims, sticking to the stance that the products are much safer than ordinary cigarettes. Their main point was that it is wrong to deem heat-not-burn cigarettes as dangerous based on the total amount of tar.

“Tar itself is not a harmful substance; it’s a term referring to all substances in the cigarette smoke aside from nicotine and water,” Philip Morris Korea said in a statement.

“Vapor from heat-not-burn cigarettes and smoke from combustible cigarettes are fundamentally different,” it continued. “Therefore the comparison should be based not simply on the total amount of tar, but specifically the content of harmful substances.”

Philip Morris Korea and British American Tobacco Korea (BAT) both said that in terms of harmful substances, the government’s report aligns with their research as the nine substances defined as harmful by the WHO had all been detected in much smaller amounts than ordinary cigarettes.

“We can’t define all of the substances [that constitute vapor or smoke], which is why the WHO designated certain substances [to regulate] that are the most harmful,” said a BAT Korea spokesman. “They are harmful substances defined by credible global institutes and that’s what we should judge health effects upon.”

Regarding the government’s criticism of nicotine content, both companies said that they never said heat-not-burn cigarettes were nicotine-free.

BY SONG KYOUNG-SON [song.kyoungson@joongang.co.kr]

Gov’t denies hiding results of IQOS toxicity tests

theinvestor.co.kr/view.php

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검색폼

The Korea Herald

Retail & Consumer

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[**THE INVESTOR**] The Ministry of Food and Drug Safety said on Feb. 26 it is still conducting tests to fully analyze the harmful ingredients contained in tobacco giant Philip Morris International’s heat-not-burn cigarettes IQOS, refuting a recent news report saying it intentionally hid the results on harmful effects vis-a-vis conventional cigarettes.

"Tests to identify the toxic substances in IQOS, such as tar, are still underway,” a spokesperson from the ministry told The Investor, adding it is not true that the Food Ministry tried to conceal the results. “As soon as the tests are completed, we will announce the results and testing methods.”

The official added they took a great deal of time just to establish the testing methods for the HNB cigarettes, and to consult with experts.


iQOS
iQOS
iQOS
HEETS
This tobacco product damages your health and is addictive
iQOS
iQOS

The ministry began a series of tests in July last year to verify the ingredients of the vapor created by HNB cigarettes. There have been rumors that the ministry's tests were based on Health Canada and the International Standards Organization's analytic methods that are usually for conventional cigarettes.

After deciding that new methods are required for testing HNB cigarettes, the ministry has reportedly formulated a new testing system.

The government spokesperson said the ongoing analysis is aimed at identifying the nine ingredients contained in tar, including benzopyrene, cadmium, nickel and arsenic, which, according to the World Health Organization, can cause cancer or lung diseases.

The tests are drawing much attention as HNB cigarettes have been gaining popularity here. Launched in June last year, IQOS's market share stood at over 9 percent in Korea as of January, according to industry data. Independently conducted tests by Philip Morris show the levels of toxic chemicals found in IQOS vapor to be 90 percent or less compared to those of the convention cigarettes.

By Kim Young-won (wone0102@heraldcorp.com)

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STANTON A. GLANTZ, PhD
Professor of Medicine (Cardiology)
Truth Initiative Distinguished Professor of Tobacco Control
Director, Center for Tobacco Control Research and Education

530 Parnassus Suite 366
San Francisco, CA 94143-1390
Phone: (415) 476-3893
Fax: (415) 514-9345
Stanton.Glantz@ucsf.edu

December 21, 2018

FDA Center for Tobacco Products
c/o Regulations.gov

RE: PMI's 6-month study "Evaluation of Biological and Functional Changes in Healthy Smokers After Switching to THS 2.2 for 26 Weeks (ZRHR-ERS-09 US) submitted in PMI IQOS MRTP June 8, 2018 amendment to FDA-2017-D-3001-0002 does not support claims of reduced risk.

PMI's MRTP application included their 3-month study of 24 non-cancer biomarkers of potential harm (which PMI calls "clinical risk endpoints," CRE) in humans using IQOS compared to conventional cigarettes. These biomarkers include measures of inflammation, oxidative stress, lipids, blood pressure, and lung function. (PMI did separate studies of biomarkers of exposure, several of which are carcinogens.) While PMI's application emphasizes that these biomarkers generally changed in positive directions, the data they submitted revealed no statistically detectable difference between IQOS and conventional cigarettes for 23 of the 24 BOPH in Americans and 10 of 13 in Japanese,[1] with the few significant differences were false positives. ***Thus, despite delivering lower levels of some toxicants, PMI's own data failed to show consistently lower risks of harm in humans using IQOS compared to conventional cigarettes.***

Their undated response, "The Difference between IQOS and Continued Smoking,"[2] presents two arguments against this conclusion:

- The original study submitted to FDA was "NOT DESIGNED to serve as the sole pivotal evidence with regards to CRE's and to show statistically significant changes in the CREs."
- PMI has a new, larger study 6-month human study comparing IQOS with conventional cigarettes that concluded that IQOS is less risky than conventional cigarettes.[3]

With regard to the first point, one is left with the question of why PMI submitted and represented data in the original MRTP application, when it now admits that the study was not designed to provide key evidence. They did not question the specific conclusions[1] that I drew about their 3-month study.

The new 6-month study (ZRHR-ERS-09 US) differs from the study presented in the original MRTP application in several important ways.

First, it is much larger (984 people in the new study compared to 79 in the US study and 112 in the Japanese study cited in the MRTP application). Making the study larger increases statistical power and makes it more likely to declare a difference statistically significant. This is a good thing.

Second, and of greater concern, the new study only considers 6 of the 24 non-cancer biomarkers in the earlier study, leaving the question of why PMI did not measure the other 18. (The 2 other biomarkers in the new study are biomarkers of exposure [CO and NNAL], which were not included in the earlier study and are not at issue in my paper.) Most of the things that they leave out are determined from blood tests, but they had to draw blood to measure the biomarkers they do report. The others are more detailed measures of lung function than the one reported in the new study and easily measured measures of blood pressure.

PMI should be expanding not dropping clinical endpoints because of evidence that IQOS is different from cigarettes.[4,5] For example, the data they presented in the MRTP application suggested that IQOS may be causing liver damage not observed in cigarettes.[6] Given the millions of dollars PMI's application represents, cost does not justify dropping these routine clinical measures. Their detailed presentation on the new study[3] does not address this question.

Third, PMI uses an arcane, little-used statistical method, the Hailperin-Rüger method, that was developed to *confirm* earlier studies.[7] (Neither I nor two biostatistics colleagues have seen this used in any recent clinical trials. A *PubMed* search with the keyword "Hailperin-Rüger" conducted on December 19, 2018, resulted in just one study.[8] The basic argument of the Hailperin-Rüger method is that it is overly cautious to require that all observed changes be statistically significant in order to *confirm* that a therapy works, and that if some lesser number of the variables change significantly, that should be good enough for a global test. The number of significant changes is specified in advance and the probability of a chance finding is adjusted.

PMI decided that if 5 of the 8 biomarkers (6 clinical risk and 2 exposure) changed in the direction of less risk, that would be enough to conclude that IQOS was less risky than conventional cigarettes. They do not provide a clear explanation of why they used 5, other than it was "more than half."

PMI justified using Hailperin-Rüger because "the probability of finding five significant tests ($p<0.05$) by chance alone is extremely low (0.006%)." This is a misleading statement because this low probability would only be the case a chance finding if *none* of the five variables actually changed. The probabilities are much higher when there are real changes.

So, in the new study, PMI went from considering changes in 24 clinical risk biomarkers in the original study to 8 in the new study to only requiring 5 to be statistically significant. That is a pretty major drop in the level of evidence PMI now suggests is sufficient to demonstrate that IQOS is less risky than cigarettes.

In the new study 5 of the changes were statistically significant, so PMI concluded that, overall, IQOS was better. Had they picked 6 in their plan, the overall results would not have been significant, even under the Hailperin-Rüger method's relaxed standards.

There are other problems with using the Hailperin-Rüger method. First, it is designed to *confirm* results of earlier studies. The earlier study did not convincingly show that IQOS was better than conventional cigarettes. Second, the usual way that Hailperin-Rüger is used is when you have several measures *of the same thing.* (For example, the one paper[8] located in PubMed that used Hailperin-Rüger assessed 10 different measures of neurological function and pre-specified that if 5 of the 10 were statistically significant, the global test would be considered statistically significant.)

The idea is that requiring all of them to change significantly is being too stringent a requirement to identify a change in lung function. In this case, PMI mixed apples and oranges by applying the text to a set of 6 clinical variables and 2 exposure that were measuring different underlying physiological processes.

PMI also used a one-tail test that assumes that one only need worry above improvements in the biomarkers without any concern for the possibility that they might worsen the biomarkers. (As noted above, PMI presented – but did not emphasize – other evidence in their MRTP application showing that IQOS caused problems not observed in cigarettes.[6]) I tell my students that, with rare exceptions, one should always do two-tail tests. Two-tail tests require larger differences to reach statistical significance, so by using a one-tail test, PMI made it easier to conclude changes were statistically significant. In this case the overall conclusion would have been the same with a two-tail test, so this bias did not make any practical difference, but they should have not used a one-tail test.

PMI's use of a one-tailed test was especially hypocritical since back in the early 1990's the tobacco companies sued the US EPA for using a one-tail test in their risk assessment that concluded that secondhand smoke caused lung cancer.[9] EPA used a one-tail test because they said it was inconceivable that secondhand smoke exposure would protect against lung cancer (the other tail). The irony there was that EPA would have reached the same conclusion using a two-tailed test.

All this raises the question of whether PMI manipulated the experimental design and analysis to get the desired conclusion, as they have done in the past.[10]

The law requires the MRTP applicant PMI to demonstrate, among other things, that IQOS, as it is actually used by consumers, will "significantly reduce harm and the risk of tobacco-related disease to individual tobacco users." Neither the original 3 month study nor the newer 6 month study meet this standard.

FDA should not rely on PMI's new study to support a conclusion that IQOS is less risky than conventional cigarettes.

Thank you for your consideration.



Stanton A. Glantz, PhD
Professor of Medicine
Truth Initiative Distinguished Professor in Tobacco Control
Director, Center for Tobacco Control Research and Education

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Heated tobacco products: the example of IQOS

Stanton A Glantz

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Correspondence to
Professor Stanton A Glantz, Department of Medicine, Center for Tobacco Control Research and Education, Cardiovascular Research Institute, Philip R. Lee Institute for Health Policy Studies, Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, San Francisco, CA 94143-1390, USA; glantz@medicine.ucsf.edu

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Heated tobacco products (HTP) represent the latest in a long line of products tobacco companies have developed and marketed as less dangerous than conventional cigarettes, beginning with so-called 'safer cigarettes' in the 1960s.[1 2] HTP (figure 1) heat tobacco to generate an inhaled nicotine aerosol and are marketed using messages that explicitly or implicitly claim they are safer than cigarettes.[3–8]

In 2018, HTP were available in many countries (table 1). In the USA, before marketing new tobacco products, the Family Smoking Prevention and Tobacco Control Act[9] (FSPTCA) requires premarket review by the Food and Drug Administration (FDA) to demonstrate that marketing them would be 'appropriate for the protection of the public health' (FSPTCA sections 910 and 905(j)). Additionally, to market any new tobacco product in the USA with claims of reduced risk or reduced exposure to toxins compared to other tobacco products ('Modified Risk Tobacco Product'; MRTP), the company must first obtain an MRTP marketing order from the FDA. In December 2016, Philip Morris International (PMI) submitted an application to market IQOS, one of its HTP, with MRTP claims.[10] PMI's MRTP application included extensive details about the product, the chemistry of the aerosol it produces, related toxicology, effects on clinical measures in people, perceptions of the product and its packaging (including warning labels), and behavioural factors. This application sought FDA approval of PMI's claims that smokers who switched completely to IQOS would reduce their health risks or exposure to dangerous substances compared with smoking cigarettes.

As of November 2017, there were 31 studies of HTP published in the peer reviewed literature, 20 of which were affiliated with the tobacco industry.[11] The 11 independent studies focused on awareness, use, and secondhand emissions of HTP, while the industry affiliated papers examined nicotine delivery and mainstream emissions and exposures to selected toxicants. The fact that the literature has been dominated by industry is particularly concerning because tobacco companies have a record of publishing incomplete or manipulated information and presenting it to governments.[12–16] For example, PMI[17–20] and British American Tobacco[21–23] (BAT) conducted and published studies arguing that additives did not increase cigarettes' toxicities. However, internal PMI documents and analysis of PMI's data done by people independent of the tobacco industry revealed that many toxicants increased when additives—notably menthol—were present.[15]

PMI's IQOS MRTP application (the 'application') provides an opportunity to analyse PMI's data. This supplement to *Tobacco Control* includes eight papers that present analyses of PMI's application by researchers independent of the tobacco industry and 12 papers that provide independent assessments of HTP effects, including their political and policy implications. Together, these papers provide insights into IQOS (and, in broad terms, other HTP) and support the January 2018 vote by the FDA Tobacco Product Scientific Advisory Committee that PMI's application did not demonstrate it reduced risk claims for IQOS[24] (online supplementary table S1). These papers also put HTP in the overall context of the tobacco companies' plans to maintain and grow their markets in the future and outline regulatory responses.

HEALTH EFFECTS

The fundamental justification for introducing HTP is the claim that they are substantially less dangerous than conventional cigarettes. PMI's application includes PMI's 3-month study of 24 non-cancer biomarkers of potential harm (BOPH) in humans using IQOS compared with conventional cigarettes. These biomarkers include measures of inflammation, oxidative stress, cholesterol and triglycerides, blood pressure, and lung function. (PMI did separate studies of biomarkers of exposure, several of which are carcinogens.) While PMI's application emphasises that these biomarkers generally changed in positive directions, Glantz's[25] examination of the data revealed no statistically detectable difference between IQOS and conventional cigarettes for 23 of the 24 BOPH in Americans and 10 of 13 in Japanese. Moreover, it is likely that the few significant differences were false positives. Thus, despite delivering lower levels of some toxicants, PMI's own data fail to show consistently lower risks of harm in humans using IQOS compared with conventional cigarettes.

In June, 2018 PMI issued a press release[26] announcing that a 6-month human study comparing IQOS with conventional cigarettes found eight biomarkers improved in those who switched to IQOS. PMI did not provide specific results. In contrast to the application, PMI's new study only examined six BOPH (plus two biomarkers of exposure). Further, PMI did not report the full range of biomarkers used in the earlier study although they can be measured in a blood sample or simple physiological test. This additional study raises questions about PMI manipulating the experimental design or data analysis as it and other companies have a history of doing.[15]

While HTP are presented as 'new', they are simply the latest incarnation of a technology tobacco companies have been developing for decades. Elias *et al*[2]analysed previously secret PMI documents, public communications and the

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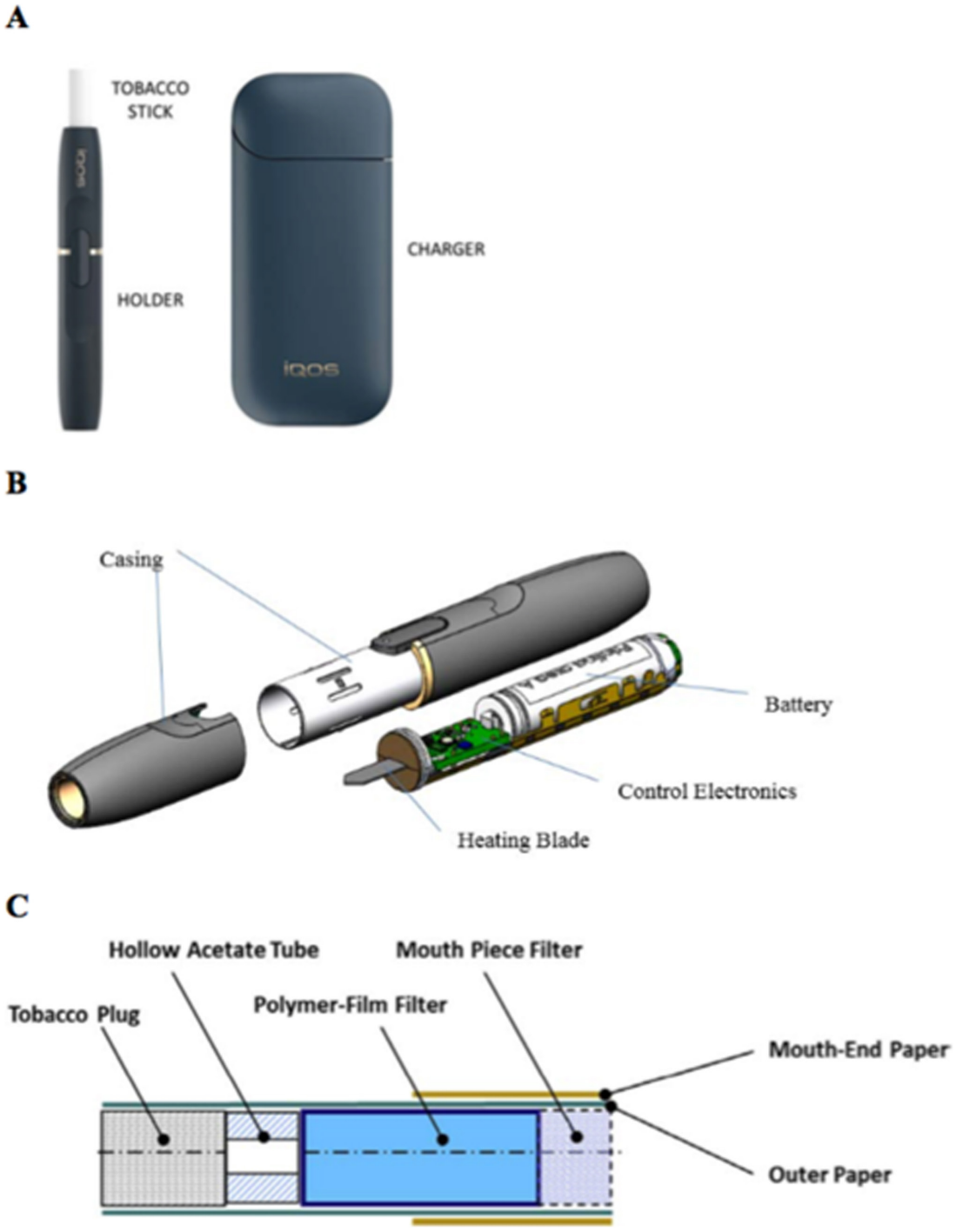


Figure 1 (A) The Philip Morris International IQOS charger, holder and HeetStick (tobacco stick). (B) Schematic drawing of holder. (C) Schematic of HeetStick tobacco stick.[10]

application to compare IQOS to Accord, an earlier HTP that PMI unsuccessfully marketed in the USA and Japan in 1998 and 2006, respectively. PMI's public statements seemed contradictory, claiming that Accord reduced exposure to harmful constituents while consistently emphasising that the reductions did not mean Accord was safer than conventional cigarettes. In terms of aerosol chemistry, Accord had lower levels than IQOS of some toxicants and higher levels of others. PMI appears to be capitalising on the MRTP process to make reduced exposure claims for IQOS despite the fact that overall toxicant exposures are not, on average, different than Accord.

Discussion of HTP (as well as e-cigarettes) has focused on cancer even though cardiovascular and metabolic disease kill about as many smokers as cancer.[27] Unlike cancer, the dose–response relationship for cardiovascular effects is highly non-linear, with large effects at low doses.[28] An important pathway through which tobacco use increases the risk of heart disease is by impairing the ability of arteries to enlarge when needed to accommodate increases in blood flow (flow mediated dilation, FMD). Nabavizadeh *et al*[29] tested whether exposure to IQOS aerosol impaired FMD in a well-established experimental model in which rats inhale IQOS aerosol from a single

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Table 1 Availability of heated tobacco product by major cigarette company and country of availability (January 2018)

Company	Product	Year launched	Countries/comments
British American Tobacco	iFuse* glo	2015 2016	Romania, Japan, Switzerland, Canada, South Korea, Russia.
China National Tobacco Corporation/State Tobacco Monopoly Administration (STMA)	Not reported	Not launched	A few of the companies claim to have over 30 patents of HTP and continue to be engaged in research and development of these products. But none yet are in the market.
Imperial Brands	Not reported	Not launched	Focusing on e-cigarettes at the moment, claims to have options to launch when it deems that time is right.
Japan Tobacco International	Ploom TECH†	2016	Japan, Switzerland.
KT&G Corp	lil	2017	South Korea
Philip Morris International‡	IQOS TEEPS§	2014 Not yet launched	Canada, Guatemala, Colombia, Czech Republic, Denmark, France, Germany, Greece, Israel, Italy, Kazakhstan, Lithuania, Monaco, Netherlands, Poland, Portugal, Romania, Russia, Serbia, Slovak Republic, Slovenia, Spain, Switzerland, Ukraine, United Kingdom, South Africa, South Korea, Japan, New Zealand.

Source: Bialous and Glantz.[49]
*It is unclear that iFuse will remain in the market in Romania, where glo was introduced in 2018.
†Ploom TECH is described as a hybrid between an HTP and a vaporiser. It is to be used with Mevius capsules. Mevius is one of JTI's best-selling cigarette brands. The capsules contain tobacco that are then heated by vapour.
‡PMI website states that it is developing a new heated nicotine delivery product that has no tobacco, STEEM, among other 'reduced risk' products.
§We do not know what TEEPS stands for, it is not included in the product's description (https://www.pmi.com/smoke-free-products/teeps-carbon-heated-tobacco-product).
HTP, heated tobacco product; JTI, Japan Tobacco International;PMI, Philip Morris International.

HeetStick (the IQOS tobacco stick), mainstream smoke from a single Marlboro Red cigarette, or clean air. In contrast with PMI's application claiming that IQOS causes less impairment than conventional cigarettes, Nabavizadeh *et al*[29] showed IQOS aerosol's acute effects impaired vascular endothelial function (measured with FMD) comparably with cigarette smoke.

Moazed *et al*[30] found data in PMI's application raising significant concerns about IQOS' pulmonary effects. Rats exposed to IQOS suffered pulmonary inflammation and immunomodulation. Although PMI did not report any direct measures of pulmonary inflammation in humans, they measured pulmonary function and found no evidence of improvement in cigarette smokers who switched to IQOS. PMI's application also ignores the effect of dual use and secondhand aerosol exposure.

Independent research confirmed adverse effects of IQOS aerosol on lung cells. Leigh *et al*[31] exposed human bronchial epithelial cells in vitro to aerosols from three PMI products: IQOS (tobacco flavour), an e-cigarette (MarkTen, tobacco flavour) and a conventional cigarette (Marlboro Red) at comparable nicotine levels at the air–liquid interface. IQOS showed significantly higher cytotoxicity than e-cigarettes, but less than combustible cigarettes. These observations have important legal implications in the USA because to authorise marketing IQOS with reduced risk claims, the FDA would have to find that IQOS would benefit the public health and significantly reduce harm or reduce exposure to harmful substances 'compared to the similar types of tobacco products then on the market' (FSPTCA section 911(g)(2)(B)(ii)), and e-cigarettes were currently on the market at the time that PMI submitted its application.

Reinforcing the need to compare HTP to e-cigarettes rather than cigarettes, Leigh *et al*[32] compared the levels of carcinogenic tobacco specific nitrosamines (TSNA) in IQOS aerosols to MarkTen e-cigarettes and Marlboro Red 100 conventional cigarettes at comparable nicotine delivery levels. TSNA yields per puff in IQOS aerosol was an order of magnitude lower than in Marlboro cigarette smoke, but an order of magnitude higher than in MarkTen e-cigarettes. In short, IQOS does not reduce exposure to these important carcinogens nearly as much as e-cigarettes.

Most discussion of the toxicants in non-cigarette tobacco products compare them to cigarettes on the assumption that if the non-cigarette products deliver lower levels of toxicants than cigarettes, the products would be less dangerous. However, St Helen *et al*[33] found that PMI's data only support its claim that IQOS reduces exposure to some (40 of 93) harmful and potentially harmful constituents (HPHCs) identified by the FDA. PMI's data also show significantly higher levels of many toxicants not on the FDA HPHC list in IQOS aerosol compared with cigarette smoke, with 22 over twice as high and 7 over 10 times higher. Therefore, it is important to expand chemical assessment of emissions from HTP and other new tobacco products beyond those found in cigarette smoke.

It is possible that HTP could cause some diseases not caused by conventional cigarettes. Chun *et al*[34] identified animal and human studies in PMI's application suggesting that IQOS may cause liver toxicity not observed in cigarette users. PMI compared liver toxicity in rats exposed to IQOS or cigarette smoke, and found that several measures of liver toxicity (liver weights, blood levels of alanine aminotransferase and hepatocellular vacuolisation) increased more in female (but not male) rats exposed to IQOS than cigarettes. PMI's human clinical data also suggested the possibility of increased liver injury in one of their studies: following 5 days of using IQOS, conventional cigarettes, or smoking abstinence, plasma bilirubin was higher in IQOS users than conventional smokers or abstainers. PMI Science posted a response to this paper on its website stating that "based on an analysis of our toxicological studies and clinical studies performed according to international standards of good practice, there is *no evidence* that IQOS use leads to hepatotoxicity [emphasis added]."[35] In contrast to this unequivocal statement, the point that Chun et al make is not that the data PMI submitted to the FDA prove hepatotoxicity, but that the combination of animal data and some of the human data constitute a pattern worth careful consideration, especially in light of the short duration of the studies and lack of additional potential insults to the liver including alcohol use and other drug use that is common in smokers.

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IQOS (and likely HTP generally) are simply *different* from conventional cigarettes and deliver less of some toxicants and more of others, so that IQOS may pose lower, the same or higher health risks than cigarettes depending on the disease. IQOS emits more of several important toxins with more adverse health effects than e-cigarettes.

PERCEPTIONS OF THE PRODUCT AND WARNING LABELS

Despite the evidence discussed above, in 2018 IQOS and other HTP were being marketed around the world with claims that they are less harmful than cigarettes because they expose users to lower levels of some toxicants. Popova *et al*[36] examined the qualitative and quantitative Perception and Behavior Assessment Studies in PMI's application which revealed that consumers perceive even reduced exposure claims as reduced risk claims. Allowing PMI to promote IQOS with reduced exposure claims would amount to permitting the kind of 'light' and 'mild' fraud that the FSPTCA and WHO Framework Convention on Tobacco Control (FCTC) expressly prohibit for other tobacco products.

This misunderstanding of reduced exposure as reduced risk bears directly on how IQOS should be labelled so as not to mislead consumers. McKelvey *et al*[37] examined PMI's application focusing on the statements that switching completely from cigarettes to IQOS reduces risk. PMI failed to demonstrate that current smokers will understand what 'switching completely' means, and therefore failed to demonstrate that their IQOS will not decrease smokers' intentions to quit smoking, or that IQOS users will 'switch completely' (PMI's other studies showed most people use IQOS and cigarettes concurrently, so-called dual users.) Additionally, PMI's study design and measurement instruments suffered design flaws, and their reporting of associated findings is misleading. Experience with other products such as e-cigarettes suggests consumers will not understand that they must completely quit smoking cigarettes to achieve the claimed health benefits of IQOS. Rather, consumers will likely misunderstand unsupported claims of reduced risks to mean IQOS are risk-free.

Independently confirming PMI's results, El-Toukhy *et al*[38] examined the impact of reduced exposure and reduced harm MRTP claims in a national sample of US adults and adolescents. They found that communicating lower risk in MRTP claims led to lower perceived risk among adults and adolescents and increased the likelihood that adults would use the product. Reduced exposure claims led to lower perceived chemical quantity and lower perceived risk, but had no effect on likelihood of product use. Adults and adolescents misinterpreted reduced exposure claims as communicating lower risk, even when no explicit reduced risk claims were made. Because reduced exposure MRTP claims are not permissible under US law if they mislead the public to believe the product presents less risk of harm, these studies demonstrate that reduced exposure claims for IQOS are impermissible.

These concerns are particularly acute for adolescents who are susceptible to using novel tobacco products. E-cigarettes provide a cautionary tale for any new tobacco product coming to market: e-cigarettes have attracted youth at low risk of initiating nicotine use with cigarettes,[39] many of whom then proceed to cigarettes.[40] McKelvey *et al*[41] found that PMI's application failed to provide any evidence regarding the effect IQOS and its marketing will have on the likelihood that adolescents who are not tobacco users or who are former tobacco users will start nicotine use with IQOS. Instead, PMI conducted studies of adults that relied on 'behavioural intention' as a proxy to predict IQOS use, ignoring evidence that these models do not accurately predict tobacco use. Of added concern, the IQOS name, packaging and retail shops resemble popular cell phones that attract youth.[42] PMI's data and independent scientific studies regarding novel tobacco products (including e-cigarettes) marketing suggest IQOS will attract adolescent and young adult non-users to initiate tobacco use with IQOS and could also increase polyuse of different tobacco products.

Hair *et al*[43] examined IQOS marketing in Japan and Switzerland and studied consumer perceptions, attitudes and behaviours. Expert interviews and IQOS packaging and marketing analyses revealed that IQOS was marketed as a clean, chic and pure product which resonated in cultures that value cleanliness, exclusivity and high-tech appearances. Japanese consumers used IQOS for socialising with non-smokers. Focus group participants in both Japan and Switzerland reported lower levels of satisfaction with IQOS than cigarettes, although many found the packaging appealing. Few participants reported potential health benefits compared with cigarettes.

PMI introduced IQOS to Korea in May 2017. Three months later, Kim *et al*[44] conducted an online survey of young adults including current, ever and non-users. Rather than switching from conventional cigarettes to IQOS, all current IQOS users continued to use cigarettes or e-cigarettes. There were no IQOS-only users. Current users believed IQOS less harmful or useful to stop smoking. The observation that all the current IQOS users were dual users of conventional cigarettes or e-cigarettes contradicts PMI's assumption that cigarette smokers would switch to HTP.

As of July 2018, the FDA had not authorised HTP for sale in the USA, but awareness and use were increasing. Nyman *et al*[45] assessed awareness and use of HTP in the USA. From 2016 to 2017, adult awareness of HTP increased from 9.3% to 12.4%, ever use increased from 1.4% to 2.2% and current use doubled from 0.5% to 1.1%. Non-white adults, cigarette smokers, and both current and former users of e-cigarettes were more likely to use HTP.

POLICY, POLITICS AND LAW

Tobacco companies have promoted 'harm reduction' for decades. Although tobacco harm reduction proponents take British psychologist Michael Russell's 1976 idea that 'people smoke for nicotine but they die from the tar'[46] as an article of faith, he simply presented it as a 'hypothesis'. Elias and Ling[47] examined tobacco industry documents and found that Russell collaborated with BAT on two 'safer cigarette' studies and received £55 000 (£300 850 or $398 000 in 2018) to study medium-nicotine low-tar cigarettes. The most prominent early HTP was RJ Reynolds' (RJR) Premier, introduced in the USA in 1988. Russell engaged extensively with RJR about Premier's 'positive aspects' and published an unsigned 1991 *Lancet* editorial[48] endorsing Premier as a 'near-perfect low tar cigarette' 2 years after RJR stopped marketing Premier without disclosing his conflict of interest. Although Premier failed, RJR saw future business opportunities for novel products if endorsed by health authorities, making conflicts of interest highly important considerations in assessing product endorsements, including those published by high-impact medical journals.

It is important to consider HTP in the context of multinational tobacco companies' product mix and response to the tightening regulatory environment promoted by FCTC. Bialous and Glantz[49] describe how HTP extend the industry's strategies to undermine government regulation by reframing tobacco companies from part of the problem to part of the solution. Under the 'harm reduction' moniker, companies are attempting

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to rehabilitate their reputations to more effectively influence governments to roll back existing tobacco control policies or create exemptions for HTP. Where regulations are absent or loopholes exempt HTP from existing regulations, companies' market HTP to increase social acceptability for all their tobacco products. Governments must ensure that HTP are regulated or banned, and reject partnerships with tobacco companies to promote 'harm reduction'. Doing so requires governments in countries where HTP are not available to keep them out or, if allowed in the market, strictly regulate them under the FCTC.

Israel illustrates how PMI took advantage of regulatory ambiguity to implement an aggressive campaign promoting IQOS as safer than conventional cigarettes. Rosen and Kislev[50] describe how PMI promoted IQOS as part of its 'Smoke-Free Israel vision' after launching IQOS in December 2016. The campaign began with quiet pre-market meetings with government officials, followed by meetings in Israel's Parliament and an intense campaign in the printed press to promote harm reduction and PMI's 'Smoke-Free Israel vision'. The public campaign included digital and print marketing aimed at young people to promote PMI's 'Smoke-Free Israel vision' and harm reduction using the theme 'IQOS Changes Everything', that stressed IQOS was clean with less smell and no ash. PMI's campaign initially resulted in IQOS' exemption from tobacco regulations. These policies were later reversed after three petitions to the Supreme Court, pressure from health organisations and leading politicians, and wide press coverage of PMI's influence on Parliament's decision-making process. Israel's weak and poorly enforced advertising restrictions, however, have allowed PMI to continue its marketing claims.

In determining whether any new tobacco product may be sold, including HTP, the FDA must consider the product's overall population health impact. Importantly, in addition to any changes in specific toxicity for current smokers who switch from cigarettes to HTP, the availability of HTP affects nicotine and cigarette initiation and cessation. For products that have not been on the market to empirically answer these questions, modelling is an important element of the decision-making process. Max *et al*[51] evaluated PMI's Population Health Impact Model (PHIM), as used in its application, in comparison with other available models. Although similar to many published models, PHIM includes assumptions likely to lead to a positive assessment of IQOS' population health impact. PHIM does not consider impacts on morbidity, underestimates mortality, does not include impacts on non-users, ignores the impact of IQOS on nicotine product initiation among never smokers and does not use the latest US data to set the model's parameters. Because PHIM systematically underestimates the impact of IQOS on the population as a whole, it cannot adequately justify marketing IQOS as 'appropriate to protect public health'.

The most important change in the policy environment since the tobacco companies were last actively promoting HTP in the 1980s and 1990s is the advent of formal regulatory regimes for tobacco products through the FSPTCA in the USA and the FCTC globally. Lempert and Glantz[52] analysed laws and obligations that apply to the introduction, labelling and marketing of IQOS under FSPTCA and FCTC. PMI's premarket tobacco application and MRTP application for IQOS do not meet FSPTCA requirements on reduced harm or net public health benefit. The FDA can only authorise sale of new products through the new tobacco product pathway that are better for public health than products currently on the market, and e-cigarettes, currently sold in the USA, should probably be the comparator product. FCTC obligates parties to implement laws to reduce tobacco use and nicotine addiction, and the introduction of any new tobacco product must be assessed against this goal. PMI's aggressive marketing techniques for IQOS using targeted customer interventions and sophisticated technologies to capture data and monitor use directly from the IQOS device via the internet[53] should concern privacy and public health advocates. Moreover, nothing in the US law or FCTC prevents authorities from prohibiting HTP. If not banned, all HTP components should be regulated as stringently as tobacco products, including restrictions on labelling, advertising, sales to minors, price and taxation policies, and smoke-free measures, and these laws should be aggressively enforced.

CONCLUSION

HTP are the latest effort by tobacco companies to adapt to a changing regulatory landscape to maintain and expand their customer base amid declining social acceptability of tobacco use and declining cigarette consumption. IQOS and other HTP are the newest in a long string of products designed to retain customers and protect tobacco companies' reputations and political influence. Because US law required PMI to provide detailed results of their IQOS research for its MRTP application, it was possible to independently assess their research. PMI's own data do not support its claims that IQOS is less dangerous than cigarettes. While IQOS may expose users to lower levels of some toxicants than cigarettes, they also expose users to higher levels of other toxicants. Likewise, IQOS likely exposes users to lower risks of some diseases and higher risks of others. PMI's research, confirmed by independent research, also highlights the fact that reduced exposure claims are misunderstood as reduced harm claims. These facts raise serious concerns that HTP and their marketing will harm youth and young adults and undermine cessation among smokers without providing health benefits to smokers who use them.

Fortunately, regulatory tools are in place to make rational, evidence-based decisions about these products. The question is whether public health advocates will ensure that policy-makers prioritise protecting public health and prevent tobacco companies from again using their extensive public relations and political resources to avoid regulation and protect profits. Policy makers should give greater weight to the advice provided by public health scientists than to submissions from industry when it comes to regulating tobacco products such as HTP.

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PMI SCIENCE
PHILIP MORRIS INTERNATIONAL

The Difference between *IQOS* and Continued Smoking

Response to the article entitled "PMI's own in vivo clinical data on biomarkers of potential harm in Americans show that *IQOS* is not detectably different from conventional cigarettes," by Stanton Glantz, 2018[1]

Gizelle Baker, Christelle Haziza, Matthew Hankins, Nicola Lama, Serge Maeder, Patrick Picavet, Maurice Smith, Patrick Vanscheeuwijck, and Manuel C. Peitsch[2]

Philip Morris International R&D

[1] Department of Medicine/Division of Cardiology, University of California San Francisco, San Francisco, CA, USA; Center for Tobacco Control Research and Education, University of California San Francisco, San Francisco, CA, USA

[2] PMI Research and Development, Philip Morris Products S.A., Quai Jeanrenaud 5, 2000 Neuchâtel, Switzerland. Authors are listed in alphabetical order.

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EXECUTIVE SUMMARY

The Department of Medicine, University of California, San Francisco, California, USA has recently published an article in *Tobacco Control* raising concerns that "*PMI's own in vivo clinical data on biomarkers of potential harm in Americans show that IQOS is not detectably different from conventional cigarettes*" [1]. The main conclusion reported by the author of this article is that "*the application [Philip Morris International's {PMI's} Modified Risk Tobacco Product Application {MRTPA} for IQOS] includes comparisons of the levels of 24 biomarkers of potential harm in human smokers, including comparisons with people who smoke conventional cigarettes…[…]…and that in people who actually use IQOS, the levels of these biomarkers of potential harm are not detectably different from conventional cigarettes*." This is considered to be "*consistent with the data PMI reported on the levels of toxicants in IQOS mainstream aerosol compared with mainstream smoke of 3R4F reference cigarettes. While many toxicants were lower in IQOS aerosol, 56 others were higher in IQOS emissions and 22 were more than twice as high, and 7 were more than an order of magnitude higher*." Furthermore, the author states that "*IQOS uses an aerosol of ultrafine particles to deliver the nicotine. These ultrafine particles cause heart and lung disease*."

In short, the statements made by the author are incorrect and misleading, and do not take into consideration good scientific practice. They ignore the overarching assessment approach required for candidate Modified Risk Tobacco Products (MRTP) such as the Tobacco Heating System (THS; marketed in various countries under the brand name IQOS). Furthermore they do not consider the study designs and objectives and ignore the totality of evidence available to date.

PMI's assessment approach for THS is in line with the MRTP draft guidance from the U.S. Food and Drug Administration (FDA) Center for Tobacco Products (CTP). There is no single endpoint or study that is considered to prove risk reduction of smoking-related diseases on its own when switching from cigarette smoking to THS. The strength of the evidence available to date for THS lies in the coherence of change across the spectrum of multiple studies and endpoints, including clinical risk endpoints (CREs), how they reflect the changes that would be induced by smoking cessation, and to what extent they provide mutual evidentiary support for each other (coherence and consistency). Taken together, all data form a system that facilitates the risk assessment of a candidate MRTP, such as THS. In other words, assessing the risk of diseases that take decades to develop, and to come to sound scientific conclusions on the risk reduction potential of a candidate MRTP, requires the totality of the evidence to be considered, and not just isolated studies or endpoints.

In summary, the level of emissions of harmful and potentially harmful constituents (HPHCs) generated by THS are on average 90% lower than found in cigarette smoke. Furthermore, our untargeted screening of the THS aerosol demonstrated that the THS aerosol is significantly less complex than

cigarette smoke, and that the exposures to the four compounds of potential toxicological concern elevated in the THS aerosol (compared with cigarette smoke) are actually below the level of toxicological concern. Moreover, and in contrast to cigarette smoke, THS aerosol does not contain carbon-based nanoparticles, which are known to cause cardiovascular and lung disease. Furthermore, our numerous non-clinical studies, which have consistently demonstrated a 90% reduction in toxicity for the THS aerosol compared with cigarette smoke across a wide range of *in vitro* and *in vivo* test systems. More importantly, studies in animal models of smoking-related diseases have clearly demonstrated the potential of THS to reduce the adverse effects of smoking.

To investigate how the reduction in emissions of HPHCs would translate into a reduction in exposure in humans, PMI conducted two 3-Month Reduced Exposure Studies in Japan and in the U.S. These two studies were primarily designed to assess the extent of exposure reduction to HPHCs in smokers who switched to THS in comparison with those who continued to smoke cigarettes. Furthermore, the studies compared the effects of switching to THS with those of smoking abstinence. This allows a comparison of the exposure reduction achievable when switching to THS with the maximum exposure reduction achieved by smoking cessation.

In these studies, we also monitored multiple CREs (or biomarkers of potential harm) to gain early indications as to whether the reduction in exposure leads to favorable changes in risk indicators. To select the CREs to assess, PMI conducted an extensive literature review and applied the following criteria:

1. The CRE must be linked to smoking-related diseases (e.g., through epidemiology).
2. The CRE must be responsive to smoking (smoking causes negative changes).
3. The CRE must reverse upon smoking cessation (cessation causes positive changes).

We focused on CREs that cover several smoking-related disease areas and mechanisms known to underlie the development of these diseases, such as cardiovascular and respiratory disease, inflammation, and oxidative stress. All of the CREs included in the Reduced Exposure Studies were linked to smoking-related disease and responsive to smoking. However, data for several CREs were sparse or inconclusive with regards to the effect of smoking cessation, as reported in the literature. Furthermore, several of the CREs were included in the study to monitor the respective CRE but were not expected to change over the duration of these studies. This was clearly outlined in the study protocols (see section 7.3.1 07 REXA07 JP and 7.3.1 08 REXA08 US of PMI's MRTPA for *IQOS*).

The CREs we have focused our reporting on were the CREs that have *a priori* fulfilled all three criteria stated above and were reported in the literature to change upon smoking cessation and within the time frame of the study.

It is also important to consider that the Reduced Exposure Studies were NOT DESIGNED to serve as the sole pivotal evidence with regards to changes in CREs and to show statistically significant changes in the CREs (i.e., in terms of sample size – see PMI's MRTPA for *IQOS*, section 7.3.1 07 REXA07 JP and 7.3.1 08 REXA08 US Appendices 16.1.8 to the clinical study reports).

Therefore, drawing confirmative conclusions on CREs from the Reduced Exposure Studies alone is invalid. However, the results observed for CREs in these studies confirmed that the reduction in exposure to HPHCs and the reduction in toxicity starts to translate into favorable biological and functional changes (i.e., the changes observed upon switching to THS move in the same direction and are of similar magnitude as those observed upon smoking cessation).

Our latest results from the 6-Month Exposure Response Study clearly demonstrate significant favorable changes in CREs in smokers switching to THS, even under conditions of up to 30% concomitant cigarette use. This study also demonstrated that the degree of exposure reduction and favorable changes in CREs is maximized following complete switching (i.e., abandoning cigarettes completely).

In summary, the statements made by the authors are incorrect, selective and misleading. The totality of evidence available on THS clearly demonstrates that THS presents less risk of harm, can reduced the risk of smoking-related diseases compared to continued smoking and is therefore different in risk profile. Although not risk free switching completely to THS is a much better choice for current adult smokers compared to continued smoking.

1 INTRODUCTION

The Department of Medicine, University of California, San Francisco, California, USA has recently published an article in Tobacco Control [reference] raising concerns that "*PMI's own in vivo clinical data on biomarkers of potential harm in Americans show that IQOS is not detectably different from conventional cigarettes*" [1]. The statements and conclusions made by the author are based on the results reported in the context of Philip Morris International's (PMI) Modified Risk Tobacco Product (MRTP) Application (MRTPA) for *IQOS*.

The main conclusion reported by the author is that "*the application [PMI's MRTPA for IQOS] includes comparisons of the levels of 24 biomarkers of potential harm in human smokers, including comparisons with people who smoke conventional cigarettes…[…]…and that in people who actually use IQOS, the levels of these biomarkers of potential harm are not detectably different from conventional cigarettes*."

This is considered to be "*consistent with the data PMI reported on the levels of toxicants in IQOS mainstream aerosol compared with mainstream smoke of 3R4F reference cigarettes. While many toxicants were lower in IQOS aerosol, 56 others were higher in IQOS emissions and 22 were more than twice as high, and 7 were more than an order of magnitude higher*."

Furthermore, the author states that "*IQOS uses an aerosol of ultrafine particles to deliver the nicotine. These ultrafine particles cause heart and lung disease*."

This report aims to clarify these findings and conclusions and to provide context by summarizing PMI's scientific approach to the assessment of THS as a candidate MRTP.

2 SUMMARY OF DATA ON AEROSOL CHEMISTRY, TOXOCITY, AND ANIMAL MODELS OF DISEASE

PMI has previously demonstrated that that the level of emissions of harmful and potentially harmful constituents (HPHCs) generated by the Tobacco Heating System (THS; marketed in several countries under the brand name IQOS) are on average 90% lower than found in cigarette smoke. Our full analysis of THS aerosol compared with cigarette smoke showed that only 750 compounds were present in THS aerosol, whereas we identified 4,330 compounds in smoke from the 3R4F reference cigarette developed by the University of Kentucky. This further confirmed the reduced complexity of the THS aerosol. Among these compounds, we identified that 53, 57, and 60 aerosol constituents were higher in concentration in *IQOS Regular*, *IQOS Smooth Menthol*, and *IQOS Fresh Menthol*, respectively, compared with 3R4F smoke. An analysis of this list of compounds, which are essentially tobacco blend- and flavor-related, highlighted only four compounds of potential toxicological concern. Our

evaluation, based upon published inhalation toxicology literature, indicates that the level of exposure to these compounds through the use of THS is below the level of toxicological concern. This is consistent with the *in vitro* and *in vivo* toxicological investigations of the THS aerosol, which systematically demonstrated an overall decrease in toxicity compared with cigarette smoke. The compounds referred to by the author as being one order of magnitude higher in THS vs. 3R4F are menthol and menthol-related flavors, not toxicants. Therefore, the statement "While many toxicants were lower in THS aerosol, 56 others were higher in THS emissions and 22 were more than twice as high, and 7 were more than an order of magnitude higher," is incorrect (Amendment to PMI's MRTPA for IQOS – published Dec 08th 2017).

Furthermore, the author stated that "*IQOS uses an aerosol of ultrafine particles to deliver the nicotine. These ultrafine particles cause heart and lung disease*." When looking at the possible impact of ultrafine particles, it is important to consider their origin and chemical composition and not merely their presence and size. THS aerosol consists exclusively of liquid droplets, mainly composed of water and glycerin and contains significantly lower levels of HPHCs compared to cigarette smoke. In contrast, cigarette smoke contains, besides HPHCs, a large number of solid carbon-based nanoparticles (cbNP). These cbNPs are produced during combustion and are well known to be associated with heart and lung disease. While a single cigarette delivers in the order of 0.5×10^{12} cbNPs, THS delivers no cbNPs [2].

3 SUMMARY OF CLINICAL DATA ON CLINICAL RISK ENDPOINTS AND HOW TO CONSIDER THEM IN THE CONTEXT OF THE TOTALITY OF EVIDENCE

The disorders induced by smoking are complex, and the diseases develop over a period of many years. No single endpoint or biomarker can, on its own, be considered as a surrogate measure for all of the adverse health effects associated with smoking.

In the PMI clinical studies, submitted as part of PMI's MRTPA for *IQOS*, clinical risk endpoints (CREs) (or biomarkers of potential harm) are used to provide collective evidence about the modification of the risk profile of THS in support of the available totality of evidence (non-clinical, clinical, and perception and behavioral studies) demonstrating the potential of THS to reduce the risk of smoking-related diseases.

The CREs included in the PMI clinical studies were assessed against a set of evidentiary prerequisites, namely [3]:

- Epidemiological evidence suggesting a robust relationship between each CRE and at least one smoking-related disease
- Clinical evidence linking cigarette smoking to the CRE consistent with the epidemiological evidence (smoking causes negative changes)
- Clinical evidence linking smoking cessation to the CRE, and evidence indicating that the CRE is reversible following smoking cessation consistent with the epidemiological evidence (smoking cessation causes positive changes).

We focused on CREs that cover several smoking-related disease areas and mechanisms known to underlie the development of these diseases, such as cardiovascular and respiratory disease, inflammation, and oxidative stress.

3.1 The 3-Month Reduced Exposure Studies

Two of the eight clinical studies, part of PMI's original MRTPA for *IQOS* (December 2016), were the 3-month, *ad libitum* use Reduced Exposure Studies in a confined and ambulatory setting (see PMI's MRTPA for *IQOS*, section 6.1.4.1.2 - Table 3), conducted in Japan (ZRHM-REXA-07-JP) [3] and in the U.S. (ZRHM-REXA-08-US). These two studies were primarily designed to assess the extent of exposure reduction to HPHCs in smokers who switched to THS in comparison with those who continued to smoke cigarettes [4]. The studies furthermore compared the effects of switching to THS with those of smoking abstinence. This provides an estimate of the maximum possible exposure reduction under the study conditions achievable by smoking cessation [4,5]. The Reduced Exposure Studies were not designed to show statistically significant changes in the CREs (i.e., in terms of sample size - see PMI's MRTPA for *IQOS*, section 7.3.1 07 REXA07 JP and 7.3.1 08 REXA08 US, appendices 16.1.8 to the clinical study reports). A longer and larger study would be needed for this purpose.

Furthermore, it is important to consider that all of the 24 CREs included in the Reduced Exposure Studies were linked to smoking-related disease and responsive to smoking, following the selection criteria outlined above. However, data as reported in the literature for several of the CREs included in these studies was sparse or inconclusive with regards to the effect of smoking cessation. Therefore, several of the CREs included in the study were included for the purpose of monitoring these CREs and were not necessarily expected to change over the duration of these studies. This was clearly outlined in the study protocols (see PMI's MRTPA for *IQOS*, section 7.3.1 07 REXA07 JP and 7.3.1 08 REXA08 US).

The CREs we have focused our reporting on were the CREs that have *a priori* fulfilled all three criteria stated above and were reported in the literature to change upon smoking cessation and within the time frame of the study.

This approach allowed an initial assessment of the effect of THS on CREs linked to smoking-related diseases and made it possible to gain early indications as to whether the reduction in exposure to HPHCs would lead to favorable changes in CREs and if the changes observed upon switching to THS would move in the same direction and would be of similar magnitude as those observed upon smoking cessation.

First, the magnitude of change in these CREs in smokers who abstained for the duration of the studies were small, which is expected in a healthy study population, yet their direction of change was consistent with the literature upon smoking cessation. Because these changes occurred upon smoking abstinence, which is known to reduce the risk of smoking-related disease, these changes are clinically relevant. They are indicative of the positive effects of cessation across a broad range of mechanisms, such as inflammation and oxidative stress, which are linked to multiple smoking-related diseases.

Second, apart from the white blood cell (WBC) count in the U.S. study, all markers changed in the direction of cessation upon switching to THS. The magnitudes of change were also not very different from those observed in the smoking abstinence groups. This is a strong indication that the reduction in HPHC exposure induced by switching to THS leads to positive changes in CREs. This is entirely coherent with the causal chain of events linking smoking to disease [3, 5].

Table 1 provides an overview on the changes observed for THS compared with those observed for continued smoking and smoking abstinence based on the data reported in section 6.1.4.4 of PMI's MRTPA for *IQOS* (see also PMI's MRTPA for *IQOS,* section 7.3.1.7 07 REXA07 JP and 7.3.1.8 08 REXA08 US, csr-app-15_2-tables, Table 15.2.4.25.1, Table 15.2.4.25.1.2, and Table 15.2.4.71) as well as the time frame when we expect changes in CREs to occur as reported in the literature.

3.2 The 6-Month Exposure Response Study

The clinical Exposure Response Study conducted in the U.S. (ZRHR-ERS-09-US) was designed to demonstrate favorable changes in CREs (or biomarkers of potential harm) in healthy smokers who switched from cigarette smoking to THS use in comparison with those who continued to smoke cigarettes. Therefore, the study design was different from the two 3-Month Reduced Exposure studies reported above in several aspects: (1) the duration of the exposure was longer (6 months versus 3 months), (2) it was conducted in a more real-life setting, without a confinement period at the beginning of the study, and (3) the number of study participants was much larger, which allowed a more accurate description of product use patterns in a more diverse study population. This data adds substantial clinical information about the U.S. adult smoker population and THS use.

Furthermore, the International Conference on Harmonization (ICH) E-9 "Statistical Principles for Clinical Trials" recommends that confirmatory clinical trials have a single primary endpoint with additional supporting endpoints [6]. In order for a single primary endpoint approach to be appropriate in the context of assessing a candidate MRTP, such as THS, the endpoint would need to provide sufficient information to adequately capture the multifaceted disease process and the range of clinically relevant changes required to demonstrate a "modification of the risk" of smoking-related diseases. To date no single marker has been identified which would fulfill such criteria. Therefore to demonstrate the risk reduction potential of a candidate MRTP, the Exposure Response Study considered multiple co-primary endpoints tested individually. However, the interpretation is based on the results across all of them (e.g., at least one endpoint is significant, a subset of the endpoints are significant, or all of the endpoints are significant). The approach PMI has taken for this study, i.e., to test each component and across the eight co-primary endpoints, is consistent with the reality of a range of organ and physiological systems affected by smoking. When assessing a set of co-primary endpoints the probability of finding one or more significant results due to chance alone needs to be considered and can be calculated. Using a Bernoulli process, the probability of finding five significant tests ($p<0.05$) by chance alone is extremely low (0.006%), which illustrates two important points related to the analysis strategy taken in this study:

1. The more individual tests that are required to simultaneously fall below the set α-level, the lower the probability they are all spurious. [7]
2. Several relatively high p-values (closer to 0.05) can be a stronger indication of a significant result than one relatively low p-value (less than 0.001).[8]

Based on the aforementioned, it is reasonable to assume that if a product is ineffective, the probability of finding favorable changes in most or all of the CREs that are part of the primary objective of this study is small. Therefore, it should not be necessary to require all of the co-primary endpoints to be statistically significant (p-value < 0.05) in order to control the error rate of wrongly approving an ineffective product [9].

Therefore, PMI has defined the success criteria for this study as:

(1) Having statistically significant improvements in the majority of the co-primary CREs (i.e., five out of eight co-primary CREs) using a one-sided test with adjusted type I error (α=1.5625%), and

(2) With all endpoints changing in the direction observed upon smoking cessation in the literature.

Another important aspect when using co-primary endpoints is to address multiplicity. For this purpose the Hailperin-Rüger method [10, 11] was used for this study which preserves the study-wise α-level by requiring that a subset of endpoints is found to be statistically significant. It tests each of the co-primary endpoints at an adjusted test-wise α-level and success is declared on the overall null hypothesis if a predefined subset of endpoints is found to be statistically significant.

In this study, the Hailperin-Rüger method was used to protect the overall study-wise two-sided α-level of 5% which allows to determine a one-sided testwise type I error level of 1.5625%. This was required for each of the eight tested co-primary CREs with at least five of them required to be statistically significantly modified in the direction expected upon smoking cessation and without the need for prior specification of which ones. Furthermore all co-primary CREs were required to shift in the same direction as reported in the literature for smoking cessation. The scientific justification for the design, sample size and analysis approach was submitted to the US Food and Drug Administration (FDA) on June 8, 2018, as part of the clinical study report together with the results of this study.

Given the ambulatory nature and duration of the study, it was assumed that some subjects randomized to THS would concomitantly use THS and cigarettes. This assumption was based on: (1) that this study was a clinical study with forced switching to a new product with different characteristics than the study subject's own brand of cigarettes; (2) that communication on potential benefits of the product, which may encourage switching, is not possible in a clinical study setting; and (3) that the data on the earlier heated tobacco product prototype "electrically heated cigarette smoking system" showed that concomitant cigarette use was reported in 30% of the users [12]. This is also in line with our experience regarding product use patterns in markets where THS is commercialized, where we observed that 70%–90% of THS users actually use THS more than 70% of the time, with 5%–15% of initial THS users switching back to cigarettes [13]. Therefore, the primary analysis in this study focuses on THS "as actually used," allowing up to 30% of concomitant cigarette use in the primary analysis population. This is another important difference compared with the 3-Month Reduced Exposure Studies, where the primary analysis population used THS for more than 95% of all product use experiences and not more than two cigarettes per study day. Product use assessment in the Exposure Response Study was based on self-reported tobacco product use by study participants, as recorded in their diaries over the 6-month post-randomization period.

Of the 984 randomized participants, 488 were randomized to THS, and 496 were randomized to continued cigarette (CC) smoking. In the THS group, 245 study participants (51.4%) were categorized as THS users, 142 study participants (29.8%) were categorized as dual-users, 3 study participants (0.6%) were categorized as CC users (analyzed together with subjects randomized to CC), and 24 study participants (4.9%) were categorized as users of other tobacco or nicotine-containing products. In the

CC group, 425 study participants (85.6%) were categorized as CC smokers, and 18 study participants (4.2 %) were categorized as users of other tobacco or nicotine-containing products. One hundred and twenty seven (127) study participants (74 study participants in the THS group and 53 study participants in the CC group) were excluded from the study[3]. In total, 803 randomized subjects completed the 6-month study.

The baseline smoking intensity (prior to the run-in period) across the study population was, on average, about 19 cigarettes per day (CPD), with an average smoking history of about 26 years (~24 pack years). Post-randomization, the 428 participants in the CC use category smoked, on average, 16.8±6.8 CPD. In the dual use category, the average daily consumption was 7.6±5.2 *HeatSticks*/day and 10.0±5.9 CPD, while in the THS use category, the average daily consumption was 16.5±8.9 *HeatSticks*/day and 2.0±2.4 CPD.

In short, the results observed in this larger and longer-term Exposure Response Study confirmed the initial trends of favorable changes in CREs observed in the 3-Month Reduced Exposure Studies.

First, the primary statistical objective of the 6-Month Exposure Response Study was met and demonstrated favorable changes in the eight co-primary CREs in smokers who switched from cigarette smoking to THS use. The eight co-primary CREs assessed as part of the primary objective were selected *a priori* based on the same criteria as described above. By using a one-sided test with the Hailperin-Rüger-adjusted α-level for multiple testing (1.5625%), five out of the eight predefined endpoints for the hypothesis test showed a statistically significant change. At a nominal testwise α-level of 5%, seven out of eight endpoints would have been significant.

Second, all co-primary endpoints shifted in the same direction as in smokers who quit, as reported in the literature.

Furthermore, multiple CREs assessed as secondary endpoints showed favorable change in the direction observed upon smoking cessation. The CREs assessed in this study as part of the secondary objectives included all CREs also assessed in the Reduced Exposure Studies.

Error! Reference source not found. provides an overview on the endpoints assessed in this study as well as the timeframe when we expected changes in CREs to occur as reported in the literature. The results of this study were reported on June 8, 2018, as an amendment to PMI's MRTPA for *IQOS* to the U.S. FDA.

[3] Reasons for exclusion from the study: no valid baseline value, no post randomization data for at least one primary endpoint, absence of at least one post-randomization product use record, or subjects excluded due to site termination.

PMI is currently finalizing a smoking cessation study (NCT02432729) that will provide further perspective to the results obtained in the Exposure Response Study.

4 DISCUSSION

As there is no single endpoint or study that is sufficient, on its own, to demonstrate the risk reduction potential of a candidate MRTP, such as THS, PMI's approach to the assessment of THS is based on the totality of evidence generated through a very broad range of studies [5]. The strength of the evidence available for THS lies in the consistent changes of a broad spectrum of endpoints, including CREs, across multiple studies and test systems, how these changes reflect those that would be induced by smoking cessation, and the extent that these changes provide mutual evidentiary support (coherence). Taken together, all data form a coherent system that facilitates the risk assessment of a candidate MRTP, such as THS.

Smoking-related cardiovascular diseases (CVD) develop because of chronic exposure to HPHCs, which cause oxidative stress and inflammation. These mechanisms, in turn, cause perturbations of biological networks linked to endothelial dysfunction, lipid metabolism, and platelet activation. These changes lead to atherosclerotic plaque formation and increased cardiovascular risk.

In PMI's MRTPA for *IQOS*, we have presented multiple lines of evidence that switching from cigarette smoking to THS use would be accompanied by a lower risk of CVD (summarized in see PMI's MRTPA for *IQOS,* section 2.7.6).

First, the level of emissions of HPHCs generated by THS are on average more than 90% lower than found in 3R4F cigarette smoke (see PMI's MRTPA for *IQOS*, section 6.1.1) [14-17]. The Reduced Exposure Studies have demonstrated that the reduced emission of HPHCs results in a significant reduction in exposure to HPHCs, including cardiovascular toxicants [4, 18-19]. Furthermore, the results of the 6-Month Exposure Response Study confirm these observations and show that these favorable changes are achieved even under conditions of concomitant cigarette use (up to 30% concomitant cigarette use in the THS group).

Second, this reduction in exposure to HPHCs has been shown across multiple *in vitro* and *in vivo* studies to result in a significantly reduced biological impact compared with cigarette smoke. This reduced impact is evidenced by the reduced perturbations of biological networks associated with the causation of CVD (e.g., oxidative stress, inflammation, monocyte-endothelial cell interaction) and the reduced monocyte adhesion to endothelial cells *in vitro* [20]. The results of the clinical Reduced Exposure Studies conducted in Japan (ZRHM-REXA-07-JP) [3] and the U.S. (ZRHM-REXA-08-US) showed that switching from cigarette smoking to THS use leads to a trend of favorable changes in the CREs of

oxidative stress, inflammation, endothelial function, lipid metabolism, and platelet activation, similar to those seen following smoking abstinence.

Third, the ApoE$^{-/-}$ mouse switching study demonstrated that animals that were initially exposed to cigarette smoke and subsequently switched to either THS aerosol or fresh air exposure showed very similar reductions in atherosclerotic plaque growth rates [21].

Fourth, the results of the 6-Month Exposure Response Study confirmed the previous clinical observation that the CREs associated with CVD all change in the direction of smoking cessation after switching from cigarette smoking to THS use, and this finding was maintained even under conditions of concomitant cigarette smoking (up to 30% of all product uses in the THS group) (Error! Reference source not found.).

Overall, the scientific data is remarkably consistent across all biological systems that were studied. Compared with cigarette smoke, THS aerosol had significantly reduced effects on mechanisms causally linked to atherosclerotic plaque formation in human-derived *in vitro* systems. Switching from cigarette smoke to THS aerosol exposure caused positive changes in CREs associated with cardiovascular risk and reduced atherosclerotic plaque growth in an animal model of disease. THS aerosol exposure performs in a manner similar to smoking cessation/abstinence when examined in both animal and human switching studies. Furthermore, the magnitude of the biological effects across all systems are coherent with a, on average, more than 90% reduction of HPHC emission by THS compared with cigarettes. The congruence of scientific findings (i.e., the totality of the evidence) indicates that smokers who switch to THS would have a lower risk of CVD development and progression compared with continued smoking

Chronic obstructive pulmonary disease (COPD) in smokers is triggered by exposure to cigarette smoke constituents, resulting in oxidative stress and inflammation. Oxidative stress and chronic inflammation, in turn, cause perturbations of biological networks and changes in alveolar and airway tissues. These changes in alveolar/airway cell functioning have an adverse impact on overall pulmonary function, leading to COPD.

In PMI's MRTPA, we have presented multiple lines of evidence that switching from cigarette smoking to THS use would be accompanied by a lower risk of COPD (summarized in PMI's MRTPA for *IQOS*, section 2.7.6).

First, THS significantly reduces the emission of HPHCs compared with cigarettes. Reduced Exposure clinical studies have demonstrated that this reduced HPHC emission results in a reduced exposure to HPHCs, including respiratory toxicants.

Second, this reduced exposure to HPHCs has been shown across multiple *in vitro* [22] and *in vivo* studies to result in a significantly reduced biological impact compared with cigarette smoke [21, 23-24]. This reduction in impact is evidenced by the reduced perturbations of biological networks associated with the causation of COPD (including inflammation, oxidative stress, apoptosis), less severe adaptive histopathological changes, the lack of alveolar destruction (emphysema), and reduced pulmonary dysfunction in animal models of emphysema [21] (summarized in PMI's MRTPA for *IQOS,* section 2.7.6). The results of the clinical Reduced Exposure Studies conducted in Japan (ZRHM-REXA-07-JP) [3] and the U.S. (ZRHM-REXA-08-US) showed that switching from cigarette smoking to THS use leads to a trend of positive changes in CREs of oxidative stress and inflammation, similar to those seen following smoking abstinence. Furthermore, measurements of forced expiratory volume in one second (FEV_1), although only studied over 3 months, indicated that lung function in smokers who switched to THS improved in the same manner as was seen in smokers who abstained for the duration of the study.

Third, the $ApoE^{-/-}$ mouse switching study demonstrated that animals that were initially exposed to cigarette smoke and subsequently switched to either THS aerosol or fresh air exposure showed very similar reductions in pulmonary inflammation and a stabilization of emphysema progression [21].

Fourth, the results of the 6-Month Exposure Response Study confirmed the previous clinical observation that the WBC count and FEV_1, the CREs associated with inflammation and COPD, changed in the direction of smoking cessation upon switching from cigarette smoking to THS use, even under conditions of concomitant cigarette use (up to 30%) (Error! Reference source not found.).

Overall, the scientific data a remarkably consistent across all biological systems that were studied. Compared with cigarette smoke, THS aerosol had significantly reduced effects on mechanisms causally linked to lung inflammation and COPD in human-derived *in vitro* systems. Switching from smoke to THS aerosol exposure caused positive changes in markers associated with COPD and reduced emphysema progression as well as lung function loss in an animal model of disease. This is now further corroborated by the results of the 6-Month Exposure Response Study, where switching from cigarette smoking to THS use, even under conditions of concomitant cigarette use (up to 30% of all product use in the THS group), led to a reduced decline in FEV_1, which is the expected direction of change upon smoking cessation. THS aerosol exposure thus performs in a manner similar to smoking cessation/abstinence when examined in both animal and human switching studies. Furthermore, the magnitude of the biological effects across all systems are coherent with an, on average, more than 90% reduction of HPHC emission by THS compared with cigarettes. The congruence of scientific findings (i.e., the totality of the evidence) indicates that smokers who switch to THS would have a lower risk of COPD development and progression compared with continued smoking.

The latency of smoking-related lung cancer appearance does not allow for clinical demonstrations of reduced risk with candidate MRTPs. However, there are multiple factors that make it likely that switching to THS aerosol from cigarette smoke would be accompanied by a lower risk of lung cancer than continued smoking. The rationale for this claim is based on the Adverse Outcome Pathway (AOP), which outlines the sequence of causally linked events leading from smoke/HPHC exposure to disease [5]. In the case of lung cancer, chronic exposure to high levels of carcinogenic HPHCs and cbNPs causes the perturbations in biological networks (genetic damage, inflammation, and oxidative stress), cellular dysfunction/death, tissue injury, and finally, disease. Cessation is known to reduce the risk of tobacco-related disease. This corresponds to removing the first causative step in the AOP (i.e., eliminating the exposure to HPHCs and cbNPs from cigarette smoke). This leads to a reduced perturbation of biological networks, reduced cell death and dysfunction, reduced tissue injury, and reduced organ damage. It is therefore expected that a candidate MRTP capable of reducing the exposure to carcinogenic HPHCs and cbNPs in a way similar to cessation will also show a biological outcome similar to cessation (i.e., a reduced risk of lung cancer).

One of the most recognized and highly carcinogenic compounds in cigarette smoke are the tobacco-specific nitrosamines (TSNA). TSNAs' unique source is tobacco, with no other source known to date. Studies such as the Shanghai Cohort Study [25] reported a significant relationship between the TSNAs 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and its biomarker of exposure, Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (Total NNAL), and lung cancer, and N-nitrosonornicotine (NNN) and its biomarker of exposure Total N-nitrosonornicotine (Total NNN) and esophageal cancer [25]. Hecht and colleagues reported odds ratios (OR) of 1.89 to 2.6 for lung cancer depending on the levels of Total NNAL (biomarker of exposure to NNK) as well as ORs of 3.99 to 17 for esophageal cancer, again, depending on the levels of NNN. In the PMI Reduced Exposure clinical studies conducted in an Asian population, the absolute levels of Total NNAL and NNN observed after switching to THS (22.48 pg/mg creatinine [95% CI: 18.82, 26.84] for Total NNAL; 0.90 pg/mg creatinine [95% CI: 0.70, 1.14] for NNN) are comparable with the levels reported by Hecht and colleagues in the control group (<29.29 for Total NNAL and <5.17 pg/mg creatinine for NNN). This provides clinical relevance to the observed levels of reduction.

The PMI studies reported in the PMI's MRTPA for *IQOS* have provided several demonstrations that switching from cigarette smoke to THS aerosol would significantly reduce the risk of lung cancer.

First, THS aerosol contains significantly reduced levels of carcinogenic HPHCs compared with cigarette smoke (on average by more than 93%) and no cbNPs.

Second, switching from cigarette smoking to THS use reduced the exposure to carcinogenic HPHCs to a level approaching the reductions induced by smoking cessation (all clinical Reduced Exposure

Studies). In fact, switching to THS achieved more than 95% of the effects of cessation in the 90-day clinical Reduced Exposure ambulatory studies.

Third, THS aerosol is significantly less genotoxic than cigarette smoke. Furthermore, THS aerosol induces significantly less DNA damage than cigarette smoke in multiple non-clinical studies conducted both *in vitro* and *in vivo* (summarized in PMI's MRTPA for *IQOS*, section 2.7.6). Moreover, advanced systems toxicology studies conducted in multiple *in vitro* and *in vivo* models have demonstrated that THS aerosol is significantly less toxic and induces significantly fewer perturbations of all studied biological networks (including inflammation, DNA damage-response, xenobiotic metabolism response, and oxidative stress response) than cigarette smoke.

Fourth, the results of the 6-Month Exposure Response Study and post-hoc analyses confirmed the previous clinical observation that exposure to carcinogens, including NNN and NNK, is significantly reduced upon switching from cigarette smoking to THS use (Total NNAL Relative Reduction = 43.5% [96.875% CI: 33.7, 51.9]; $p<0.001$), even under conditions of concomitant cigarette use (up to 30% of all product use in the THS group) (Error! Reference source not found.).

Taken together, these demonstrations offer evidence that smokers who switch from cigarette smoking to THS use would experience a significant reduction in exposure, biological impact, and ultimately, risk of lung cancer compared with continued smoking.

5 CONCLUSIONS

Considering the available evidence to date on THS use compared with continued smoking, we can conclude that:

- THS reduces the emissions of HPHCs by 90%–95% compared to cigarette smoke.
- Our untargeted screening of the THS aerosol demonstrated that the THS aerosol is significantly less complex compared with cigarette smoke.
- The level of exposure to four compounds that were elevated in THS aerosol and of potential toxicological concern are below the level of toxicological concern through the use of THS.
- In contrast to cigarette smoke, THS aerosol does not contain cbNPs, which are known to cause CVD and lung disease.
- Our non-clinical studies have demonstrated a 90% reduction in toxicity for THS compared with cigarette smoking.
- Animal models of smoking-related diseases have clearly demonstrated the potential of THS to reduce the adverse effects of smoking.

- In PMI clinical studies, CREs are used to provide collective evidence about the modification of the risk profile of THS in support of the totality of evidence available (non-clinical, clinical, and perception and behavioral studies) demonstrating the potential of THS to reduce the risk of smoking-related diseases.
- The primary objective of the 3-Month Reduced Exposure Studies was to demonstrate reduced exposure to HPHCs and not to serve as the sole pivotal evidence with regards to changes in CREs. Hence, the study was powered to assess changes in levels of biomarkers of exposure in a confirmatory manner and not CREs. Therefore, drawing confirmative conclusions on CREs from this study alone is invalid.
- CREs were included in these 3-Month Reduced Exposure Studies to investigate if a reduction in exposure to HPHCs starts to translate into favorable biological and functional changes (i.e., the changes observed upon switching to THS move in the same direction and are of similar magnitude as smoking cessation). The results of these studies confirmed these initial favorable changes, which were in line what was observed upon smoking abstinence.
- Our latest results from the 6-Month Exposure Response Study have clearly demonstrated significant favorable changes in CREs achieved by smokers when they switch to THS, even under up to 30% concomitant use of cigarettes.
- The 6-Month Exposure Response Study also demonstrated that the degree of exposure reduction and favorable changes in CREs is maximized with complete switching (i.e., abandoning cigarettes completely).

In summary, the statements made by the authors are incorrect, selective and misleading. The totality of evidence available on THS clearly demonstrates that THS presents less risk of harm, can reduced the risk of smoking-related diseases compared to continued smoking and is therefore different in risk profile. Although not risk free, switching completely to THS is a much better choice for current adult smokers compared to continued smoking.

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7 ABBREVIATIONS

3R4F	Reference cigarette from the University of Kentucky, USA
AOP	Adverse Outcome Pathway
cbNP	Carbon-Based-Nanoparticle
CC	Cigarette(s)
COPD	Chronic Obstructive Pulmonary Disease
CPD	Cigarettes Per Day
CRE	Clinical Risk Endpoint
CTP	Center of Tobacco Products
CVD	Cardiovascular Disease
DNA	Deoxyribonucleic Acid
FDA	U.S. Food and Drug Administration
FEV_1	Forced Expiratory Volume in One Second
HPHC	Harmful and Potentially Harmful Constituent
MRTP	Modified Risk Tobacco Product
MRTPA	Modified Risk Tobacco Product Application
Total NNAL	Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
(Total) NNN	(Total) N-nitrosonornicotine
NNK	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
OR	Odds Ratio
PMI, R&D	Philip Morris International, Research and Development
THS	Tobacco Heating System
TSNA	Tobacco Specific Nitrosamines
WBC	White Blood Cell Count

PMI SCIENCE
PHILIP MORRIS INTERNATIONAL

8 APPENDIX 1 – RESULTS OF CLINICAL RISK ENDPOINTS ASSESSED IN THE 3-MONTH REDUCED EXPOSURE STUDIES

Table 1 - Summary of Philip Morris Studies of Changes in CREs in IQOS users compared to Conventional Cigarette Smokers (95% confidence intervals in parenthesis) after 3 months

	3 months Study in Japan		**3 months Study in the US**		**Timeframe of change upon Smoking Cessation**
	THS (n=71) vs. CC (n=41)	**THS (n=71) vs. SA (n=37)**	**THS (n=47) vs. CC (n=32)**	**THS (n=47) vs. SA (n=9)**	
Inflammation (6.1.4.4.2*)					
White Blood Cell Count (WBC)	-0.57 GI/L (-1.04, -0.10)	-0.16 GI/L (-0.65, 0,33)	0.17 GI/L (-0.47, 0.81)	1.11 GI/L (0.07, 2.15)	6–12 months [1-4]
C reactive protein (CRP)	6.41% ↓ (-40.75, 37.77)	10.74%↑ (-27.33, 68.76)	16.23% ↓ (-21.69, 42.33)	2.61% ↓ (-46.17, 76.19)	> 12 months [5-7]
Soluble ICAM (sICAM-1)	8.72% ↓ (2.05, 14.94)	2.41%↑ (-4.76, 10.12)	**10.59%** ↓ (4.03, 16.71)	0.76% ↓ (-11.35, 11.09)	3 months [8-12]
Fibrinogen	5.42% ↓ (-1.80, 12.13)	0.61%↓ (-8.02, 7.40)	1.63% ↓ (-6.42, 9.08)	3.48% ↓ (-14.82, 9.38)	Hours – weeks [13-17]
Oxidative stress (6.1.4.4.3)					
Prostaglandin F2 alpha (8-epi-PGF2α)	12.71% ↓ (2.55, 21.81)	7.22%↓ (-17.2, 3.96)	13.46% ↓ (-1.95, 23.61)	5.41% ↓ (-22.26, 15.10)	2-4 weeks [19-22]
11-dehydro-thromboxane B2 (11-DTX-B2)	8.98% ↓ (-19.52, 2.94)	12.89%↑ (-0.53, 28.12)	3.56% ↓ (-23.31, 24.57)	3.88%↑ (-29.58, 53.23)	3 days [23, 24]

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Cholesterol and Triglycerides (6.1.4.4.4)					
High density lipoprotein-cholesterol (HDL-C)	4.53 mg/dL (1.17, 7.88)	-1.83 mg/dL (-5.28, 1.61)	1.4 mg/dL (-2.3, 5.0)	1.3 mg/dL (-4.4, 7.1)	3 months [25-28]
Low density lipoprotein-cholesterol (LDL-C)	0.87 mg/dL (-6.55, 8.30)	-4.74 mg/dL (-12.46, 2.99)	-3.3 mg/dL (-12.0, 5.4)	-5.1 mg/dL (-18.9, 8.6)	3 months [27-29]
Total cholesterol	2.00 mg/dL (-6.68, 10.67)	-8.30 mg/dL (-17.35, 0.75)	-4.0 mg/dL (-13.3, 5.2)	-1.4 mg/dL (-16.1, 13.2)	2-6 weeks [30][28]
Triglycerides	-6.25 mg/dL (-21.20, 8.69)	-18.69 mg/dL (-34.39, -2.99)	0.9 mg/dL (-12.8, 14.6)	11.6 mg/dL (-13.3, 5.2)	2-8 weeks [31-36][28]
Apolipoprotein A1 (Apo 1)	N/A	N/A	3.1 mg/dL (-4.6, 10. 7)	3.7 mg/dL (-8.3, 15.7)	2-6 weeks [30, 37-39]
Apolipoprotein B (Apo B)	N/A	N/A	-1.6 mg/dL (-7.24, 4.03)	-3.17 mg/dL (-12.14, 5.79)	
Physiological measures					
Systolic blood pressure	-0.59 mmHg (-3.80, 2.62)	-0.76 mmHg (-4.16, 2.65)	-0.7 mmHg (-4.5, 3.1)	1.7 mmHg (-4.3, 7.7)	Long-term
Diastolic blood pressure	-0.68 mmHg (-3.04, 1.69)	-1.68 mmHg (-4.16,0.79)	0.2 mmHg (-3.7, 4.0)	2.4 mmHg (-3.7, 8.4)	Long-term

Table 1 - Summary of Philip Morris Studies of Changes in CREs in IQOS users compared to Conventional Cigarette Smokers (95% confidence intervals in parenthesis) after 3 months

	3 months Study in Japan		3 months Study in the US		Timeframe of change upon Smoking Cessation
	THS (n=71) vs. CC (n=41)	**THS (n=71) vs. SA (n=37)**	**THS (n=47) vs. CC (n=32)**	**THS (n=47) vs. SA (n=9)**	
Lung Function (6.1.4.4.5)					
Forced expiratory volume in 1 second (FEV1)	1.91 %Pred (-0.14, 3.97)	-0.2%Pred (-2.15, 2.11)	0.53 % Pred (-2.09, 3.00) 0.05 L (-0.06, 0.15)	-1.46 % Pred (-6.63, 3.71) 0.02 L (-0.14, 0.15)	6-12 months [40-44]
FEV1/FVC (FVC=forced vital capacity)	N/A	N/A	0.00 (-0.02, 0.02)	-0.01 (-0.04, 0.02)	> 6 months
Mid expiratory flow (MEF 25-75) (L/s)	N/A	N/A	-0.67 (-6.33, 4.99)	1.23 (-7.62, 10.07)	> 6 months
Diffusion capacity for lung CO (DLCO) (mL/min/mmHg)	N/A	N/A	0.31 (-1.09, 1.72)	1.95 (-0.33, 4.22)	1 week [45, 46]
Rate constant of CO (KCO) (mmol/min/kPa/L)	N/A	N/A	0.05 (-0.02, 0.12)	0.04 (-0.09, 0.16)	1 – 2 weeks
Total lung capacity (TLC) (L)	N/A	N/A	0.09 (-0.25, 0.43)	0.39 (-0.13, 0.92)	> 6 months
Functional residual volume	N/A	N/A	-0.09 (-0.31, 0.13)	-0.42 (-0.76, -0.07)	> 6 months

Table 1 - Summary of Philip Morris Studies of Changes in CREs in IQOS users compared to Conventional Cigarette Smokers (95% confidence intervals in parenthesis) after 3 months

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	THS (n=71) vs. CC (n=41)	**THS (n=71) vs. SA (n=37)**	**THS (n=47) vs. CC (n=32)**	**THS (n=47) vs. SA (n=9)**	
(FRV) (L)					
Inspiratory capacity (IC) L)	N/A	N/A	0.21 (-0.08, 0.51)	0.88 (0.43, 1.33)	> 6 months
Vital capacity (VC) (L)	N/A	N/A	0.10 (0.00, 0.21)	0.05 (-0.10, 0.21)	> 6 months

9 APPENDIX 2 – RESULTS OF CO-PRIMARY CLINICAL RISK ENDPOINTS ASSESSED IN THE 6-MONTH EXPOSURE RESPONSE STUDIES

Table 2 - Summary of Philip Morris Studies of Changes in CREs in IQOS users compared to Conventional Cigarette Smokers (96.875% Confidence Intervals in parenthesis) after 6 months

Clinical Risk Endpoint	THS (n=245) vs. CC (n=428)	1-sided p-value (0.0156)	Expected Time to Change
Inflammation			
White Blood Cell Count (WBC)	-0.420 GI/L (-0.717, -0.123)*	0.001	6–12 months
Soluble ICAM (sICAM-1)	2.86% ↓ (-0.426, 6.04)+	0.030	3 months
Oxidative stress			
Prostaglandin F2 alpha (8-epi-PGF2α)	6.80% ↓ (-0.216, 13.3)+	0.018	2-4 weeks
11-dehydro-thromboxane B2 (11-DTX-B2)	4.74% ↓ (-7.50, 15.6])+	0.193	3 months
Cholesterol and Triglycerides			
High density lipoprotein-cholesterol (HDL-C)	3.09 mg/dL (1.10, 5.09)*	<0.001	3 months
Lung Function			
Forced expiratory volume in 1 second (FEV1)	1.28 % Pred. (0.145, 2.42)*	0.008	6-12 months
Oxygen Transport			
Carboxyhemoglobin (COHb)	32.2% ↓ (24.5, 39.0)+	<0.001	Hours
Genotoxicity			

Table 2 - Summary of Philip Morris Studies of Changes in CREs in IQOS users compared to Conventional Cigarette Smokers (96.875% Confidence Intervals in parenthesis) after 6 months

Clinical Risk Endpoint	THS (n=245) vs. CC (n=428)	1-sided p-value (0.0156)	Expected Time to Change
Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol Total NNAL	43.5% ↓ (33.7, 51.9) [+]	<0.001	Steady state after 3 months

NOTE: [+]: %↓ = Observed change presented as % relative reduction (relative to CC), *: Observed change presented as LS Mean Difference

Results of CREs assessed as part of the secondary endpoints, namely C reactive protein (CRP), Albumin in Urine, Homocysteine, Fibrinogen, Myeloperoxidase (MPO), Platelet Count, Low density lipoprotein-cholesterol (LDL-C), Total cholesterol, Triglycerides, Apolipoprotein A1 (Apo A1), Apolipoprotein B (Apo B), Apo B / Apo A1 ratio, HbA1C, Systolic blood pressure, Diastolic blood pressure, FEV1/FVC (FVC=forced vital capacity), Forced expiratory flow (FEF 25-75) (L/s), Total lung capacity (TLC) (%pred), Functional residual capacity (FRC) (%pred), Inspiratory capacity (IC) (%pred), Vital capacity (VC) (%pred), will be published upon release of the results of this study by the FDA in the context of PMIs MRTPA for THS (submitted June 08th 2018).

PMI left a lot of important things out of its toxicology studies of IQOS submitted to the FDA

tobacco.ucsf.edu/pmi-left-lot-important-things-out-its-toxicology-studies-iqos-submitted-fda

My colleagues at the UCSF TCOS just put this public comment in on Phlilip Morris' MRTP application for IQOS. The tracking number is 1k1-902j-m8kv. A PDF of the comment is available here.

Because PMI application did not report the full range of HPHCs in IQOS aerosol, characterize HPHCs in sidestream emissions, include a non-targeted analysis of chemicals in emissions, or conduct clinical studies to describe exposure to toxicants during dual use with other tobacco products, FDA must deny PMI's application

Gideon St.Helen, PhD1,2; Peyton Jacob III, PhD1,2; Natalie Nardone, PhD1,2;
Neal L. Benowitz, MD1,2,3
1Division of Clinical Pharmacology, Department of Medicine, University of California San Francisco; 2UCSF Tobacco Center of Regulatory Science; 3Department of Bioengineering and Therapeutic Sciences, University of California San Francisco
Docket Number: FDA-2017-D-3001
November 29, 2017

Philip Morris Products SA, a subsidiary of Philip Morris International (collectively referred to as PMI hereafter), has recently submitted a "modified risk tobacco product" (MRTP) application to the FDA for review and approval of IQOS. (We refer to the product as IQOS in this comment in place of tobacco heating system, THS 2.2.) According to FDA's draft guidance, an MRTP is "any tobacco product that is sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products."[1] FDA may issue an order allowing a product to be marketed as a modified risk product if it is demonstrated that the product: (1) significantly reduces harm and the risk of tobacco-related disease to individual tobacco users; and, (2) benefits the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products.

We recognize the possible benefit to individuals and public health of marketing tobacco products with substantially reduced risks profiles compared to currently marketed products such as combustible cigarettes, cigars, and some smokeless tobacco products. Given FDA's mission to protect Americans from tobacco-related diseases and death by regulating tobacco, it is critically important that FDA undergo a thorough science-based review of PMI's application to market IQOS as an MRTP. ***The PMI MRTP application lacks important information needed for the FDA to determine that IQOS should be marketed as an MRTP, so should deny the application until PMI presents the information necessary to demonstrate that any product permitted to be marketed as an MRTP actually reduces risk.***

1. **Aerosol Chemistry (Module 6.1.1.):**

1. ***PMI should report emission levels of all 93 HPHCs in IQOS aerosol .*** According to the FDA, harmful and potentially harmful constituents (HPHCs) are "chemicals or chemical compounds in tobacco products or tobacco smoke that cause or could cause harm to smokers or nonsmokers."[2] The FDA has an established list of 93 HPHCs.[3] Quantifying levels of HPHCs in aerosol/smoke of tobacco products that deliver nicotine through the pulmonary route is critical to understanding the potential health risks associated with these products. PMI measured the levels of 58 HPHCs, which they referred to as PMI-58, in mainstream IQOS aerosol. PMI claims that this list contains "chemical constituent representatives of all major toxicologically relevant chemical classes of compounds present in both the particulate-phase and gas/vapor-phase of cigarette smoke," (Module 6.1.1 Aerosol Chemistry p. 6). They also claim that it contains the 18 HPHCs subject to reporting on FDA's abbreviated list. No rationale for leaving out the other 35 HPHCs on the FDA's established list was given. The public (and the FDA) cannot assume that these 35 HPHCs are not important or that they are at much lower levels in IQOS emissions compared to other tobacco products. Since PMI is attempting to market IQOS as a reduced risk product, a more extensive rather than limited analysis of HPHCs is needed.
2. ***PMI should report levels of HPHCs in IQOS sidestream emissions .*** PMI's analysis of the PMI-58 HPHCs was done in mainstream IQOS aerosol. The implicit assumption is that IQOS has no sidestream emissions. However, research on IQOS by Imperial Tobacco Ltd. found "a large number of different VOC [volatile organic compound] species across a range of masses were released into the airspace" when IQOS was activated but not puffed on.[4] In order to protect non-users of tobacco products, FDA must insist that PMI fully characterizes HPHC levels in sidestream emissions from IQOS.
3. ***PMI should report results of non-targeted analyses of constituents in mainstream and sidestream IQOS emissions, in addition to their current targeted analysis.***

The MRTP application reports the results of analyses comparing the emissions of HPHCs from IQOS and a reference cigarette (Module 6.1.1 pp 13-19). The analyses reported by PMI show significant reductions in most of the HPHCs that were measured compared to emissions from a reference 3R4F cigarette.

Significantly, the reported studies fail to address the important question "does the aerosol generation process for IQOS produce substances not found in the smoke of conventional cigarettes, and if so, are any of these substances harmful or potentially harmful?" The main rationale for the development of IQOS and other heat-not-burn products is that combustion, meaning incomplete combustion of many organic materials, including tobacco, produces highly toxic substances such as some on the HPHC lists. The heat-not-burn products generate an inhalable aerosol without combustion, thereby purportedly eliminating or reducing the levels of substances that are generally formed as combustion by-products. ***Nevertheless, the heat required to generate the aerosol in IQOS will likely produce substances not detected in cigarette smoke. Substances in the IQOS (from tobacco or the numerous additives) could undergo heat-induced reactions to form new substances that***

might not survive in the higher temperature and strong oxidizing conditions in a combusted tobacco product.

There are reasons to suspect that the temperatures produced in IQOS are sufficient to cause chemical reactions to occur, as have been demonstrated with e-cigarettes. [5] In other words, substances in the aerosol may not be limited to those present in the tobacco prior to aerosol generation. E-cigarettes use heat to generate an inhalable aerosol without combustion, in a fashion similar to aerosol generation in a heat-not-burn product, and it is well known that numerous chemical reactions occur during the "vaping" process. For example, formation of toxic aldehydes, including formaldehyde, acetaldehyde, and acrolein, via dehydration and oxidation of the vehicles propylene glycol and glycerin is of particular concern.[6],[7] In addition, flavoring chemicals in e-cigarettes undergo thermal degradation and contribute significantly to levels of toxic aldehydes emitted in e-cigarette aerosol.[8]

Similarly, one would expect chemical reactions to occur during aerosol generation in IQOS, and ***there is no reason to expect that all of the substances formed, or that survive during aerosol generation, would be the same as those found in cigarette smoke.*** In fact, even among combusted tobacco products, the composition of the aerosols may differ. A recent study by Klupinski and colleagues reported that unique substances, such as ambrox, 3-methylbutanenitrile, and 4-methylimidazole, were found in little cigar smoke that were not found in cigarette smoke.[9] The study describes methodology for "non-targeted" analysis of tobacco smoke aerosol, and the authors suggest that "the same approach could also be applied to other samples to characterize constituents associated with tobacco product classes or specific tobacco products of interest. Such analyses are critical in identifying tobacco-related exposures that may affect public health." ***PMI should undertake such studies and report the full results.***

In addition to the "targeted" analyses for specific HPHCs that were carried out, PMI should carry out "non-targeted" analyses comparing IQOS aerosol with smoke from combustible tobacco products in an attempt to identify potentially toxic chemicals in IQOS aerosol that may not be present in tobacco smoke. The aforementioned study by Klupinski et al. constitutes "proof of concept" for the feasibility of such chemical analyses.

4. ***PMI should compare aerosol constituents of IQOS to that of other combustible tobacco products and e-cigarettes.*** While PMI's application focuses primarily on comparisons between IQOS emissions and combustible cigarette smoke, it is unlikely that IQOS will only be used by combustible cigarette smokers. Instead, the likely scenario is that at least some users of other combustible and non-combustible tobacco products will switch to IQOS. Unless PMI can guarantee that their product be marketed and sold to current combustible cigarette smokers only, it makes no sense that their comparison is limited to cigarettes. FDA should at least insist that PMI reports comparisons of HPHC emissions between IQOS and all combustible products and electronic nicotine delivery products. This set of data is critical for an accurate assessment of the relative safety/risks of IQOS ***as actually used*** compared to and in conjunction with (i.e., dual use) other tobacco products.
5. ***PMI should characterize free radical emissions in IQOS aerosol.*** Free radicals are

associated with oxidative stress, an underlying mechanism of many disease outcomes, including cardiovascular disease and cancer. Previous research has demonstrated high free radical emissions from e-cigarettes.[10] FDA should insist that PMI compares free radical emissions from IQOS with combustible tobacco products and e-cigarettes.

2. **Justification of selection of biomarkers of exposure (Module 6.1.3.1):**

1. ***PMI should expand the list of HPHCs for which systemic exposure was assessed.***

PMI used 1-hydroxypyrene, a metabolite of pyrene (a polycyclic aromatic hydrocarbon, PAH) as a biomarker of PAHs. We have previously demonstrated that 1-hydroxypyrene is not a selective measure of tobacco-related PAH exposure and is not highly related to nicotine intake and tobacco-specific nitrosamine exposure.[11] Instead, we found that monohydroxylated metabolites of fluorene (particularly 1-hydroxyfluorene) and 2-naphthol (a naphthalene metabolite) were more selective of tobacco smoke exposure. Given the link between PAH exposure and cancer, it is important that PMI reports PAH biomarkers that are more selective of tobacco smoke than 1-hydroxypyrene.

Further, PMI's list of 17 HPHCs, for which systemic exposure were assessed, do not include any inorganic compounds, phenols, and metals. Systemic exposure to these chemicals, especially metals, should be included in PMI's MRTP. One risk assessment model estimated that metals, such as cadmium, chromium (hexavalent), and arsenic, accounted for a significant fraction of the cancer and non-cancer disease risk indices of tobacco smoking.[12] For this reason, FDA should insist that PMI report exposure to metals from IQOS use.

3. **Summary of biomarkers of exposure assessments (Module 6.1.3.2.):**

PMI conducted four clinical studies to "demonstrate that the level of exposure to harmful substances has been statistically significantly reduced," based on FDA MRTP draft guidance. Two of the studies were 5-day studies in confinement, where smokers of combustible tobacco cigarettes were randomly assigned to either switch to IQOS, continue their own brand of cigarettes, or abstain from using tobacco products. The two other studies were 3-month studies consisting of 5 days of confinement followed by up to 3 months in their naturalistic environments (Module 6.1.3.2. p. 9). The first two studies were done in Poland and Japan and the latter two in Japan and the U.S. All studies contained 160 subjects, each. All four studies are of acceptable design, and included biomarker analysis in 24-hour urine (a strength).
However, there are some concerns:

1. ***PMI should present results of statistical tests.*** In figures such as Figure 1, 3, and 5 (Module 6.1.3.2. pp. 15, 20, and 25) comparisons of reduction in biomarkers of exposure to HPHCs are given for smokers who switch to IQOS and those who were in the abstinence arm. Simply stating the percentage reduction in exposure when a smoker moves from cigarettes to IQOS or from cigarettes to abstinence is not

sufficient. Important to our understanding of the relative safety/risks of IQOS is information on the magnitude of the exposure to toxicants when using IQOS compared to during abstinence. FDA should insist that results of statistical tests be presented for comparisons of reductions with IQOS compared to abstinence.

2. ***Clinical studies lacked racial diversity. PMI should investigate the effect of race on use patterns and biomarkers of exposure.*** The studies were conducted with either Japanese or Caucasians. As such, these studies are most likely not representative of the U.S. population, which is diverse racially. Metabolism of and reaction to the absorbed constituents of tobacco products,[13],[14] as well as attitudes, perceptions, preferences, and tobacco use patterns may differ across racial/ethnic groups. For example, we have observed racial differences in the manner in which combustible tobacco cigarettes are smoked and how cigarettes per day related to exposure biomarkers.[15] African Americans tend to smoke each cigarette much more intensely than Caucasian smokers do. African Americans and Native Indians have been shown to be more susceptible to lung cancer than Caucasians.[16] These previous observations underscore the need to include a racially diverse sample in assessing tobacco use patterns and toxicant exposures, and to conduct clinical studies with a sample that is representative of the U.S. population.
3. ***Noncompliance during outpatient (ambulatory) product use reduces the validity of conclusions made regarding reduced toxicant exposure from IQOS.*** The two 3-month studies included 5 days in a controlled setting and 85 or 86 days in their naturalistic environment. They compared the use of IQOS with combustible cigarette smoking and smoking abstinence. PMI implied that both studies showed significant reductions in HPHC biomarkers with use of IQOS, but did not present any associated P values to compare reductions in HPHC biomarkers during IQOS use and smoking abstinence. The results are presented together in Figure 5 (Module 6.1.3.2. p. 25) and Figure 8 (Module 6.1.3.2. p. 32), and are most likely meant to convey the message that IQOS use results in reductions in HPHCs comparable to smoking abstinence. To be a valid comparison, it is important that study participants complied with the assigned product/regime allocation, particularly those of the smoking abstinence arm. If participants in the abstinence arm smoked cigarettes (going against the study regime), percentage reductions in biomarkers of HPHCs would be lower, and most likely be comparable to that of reductions among participants in the IQOS arm, i.e. the study would show comparable reductions in HPHC exposure with IQOS and abstinence. It is not clear from the application how compliance was determined. Compliance was said to be “particularly high” for the first study. This is a relative term and needs to be quantified in the application. For the second study, PMI reports “good” compliance of subjects in the IQOS arm but “poor” compliance in the abstinence arm. With only 7-9 out of 41 subjects from the smoking abstinence arm being included in the “PP set” (it was not clear what PP set meant), comparisons of HPHC exposure reduction between IQOS use and smoking abstinence are not valid. PMI noted that “in light of the limited number of subjects in the [smoking abstinence] arm and the increased variability, the results obtained using the [smoking abstinence] arm should be interpreted with caution.” ***FDA has to ensure that PMI follows its own advice in interpreting the findings with caution. Until it does, FDA cannot rely on the data presented in the application.***

4. ***PMI should describe exposure biomarkers among dual use groups.*** Most e-cigarette users also smoke combustible cigarettes.[17] The most likely scenario if IQOS is allowed into the U.S. market is high prevalence of dual use of IQOS and tobacco cigarettes or other tobacco products. It is unknown if dual use would result in decreased exposure to tobacco smoke toxicants in the context of nicotine titration (harm reduction), or additive exposure to toxicants from cigarettes and IQOS. It is therefore imperative that FDA insist that PMI conducts studies to assess exposure to toxicants during periods of dual IQOS-tobacco cigarette use.

Conclusion

In summary, to ensure that IQOS is truly a modified risk tobacco product with net benefits to individual users and the population as a whole, before acting favorably on an MRTP application for ICOS, FDA should require that: (1) PMI expands the list of reported HPHCs tested in IQOS emissions and those included in biomarker analysis; (2) characterize HPHC emissions in sidestream aerosol from IQOS; (3) conduct non-targeted analysis to identify other potentially toxic constituents of IQOS emissions that may be unique to IQOS (in addition to reported targeted analysis); (4) compare aerosol constituents from IQOS with that of other combustible tobacco products such as cigars in addition to cigarettes; (5) characterize free radical emissions in IQOS aerosol; (6) conduct clinical studies with samples that are representative of the U.S. population (e.g. racial diversity); and, (7) conduct studies to describe exposure biomarkers during periods of dual use. Section 911(g) of the Family Smoking Prevention and Tobacco Control Act is clear and unambiguous: **FDA may issue an MRTP order *only if* PMI has demonstrated that IQOS, *as actually used by consumers*, will "(A) significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and (B) benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products." Since PMI has failed to make this required showing, FDA is not authorized to issue an MRTP order.**

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IQOS: examination of Philip Morris International's claim of reduced exposure

Gideon St.Helen,[1,2] Peyton Jacob III,[1,2] Natalie Nardone,[1] Neal L Benowitz[1,2,3]

[1]Division of Clinical Pharmacology, Department of Medicine, University of California San Francisco, San Francisco, California, USA
[2]Center for Tobacco Control Research and Education, University of California, San Francisco, California, USA
[3]Department of Bioengineering and Therapeutic Sciences, University of California San Francisco, San Francisco, California, USA

Correspondence to
Dr Gideon St.Helen, Division of Clinical Pharmacology and Experimental Therapeutics, University of California San Francisco, San Francisco, CA 94143-1220, USA;
Gideon.StHelen@ucsf.edu

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ABSTRACT

Background New electronic heated tobacco products are being introduced in the global market and are gaining popularity. In 2016, Philip Morris International, Inc. (PMI) submitted a modified risk tobacco product (MRTP) application to the Food and Drug Administration (FDA) to market IQOS in the USA with claims of reduced exposure and reduced risk.

Methods We examined PMI's MRTP application, specifically sections on aerosol chemistry and human exposure assessment, to assess the validity of PMI's claims of reduced exposure and risk.

Findings PMI reported levels for only 40 of 93 harmful and potentially harmful constituents (HPHCs) on FDA's HPHC list in IQOS mainstream aerosol. All substances in PMI's list of 58 constituents (PMI-58) were lower in IQOS emissions compared with mainstream smoke of 3R4F reference cigarettes. However, levels of 56 other constituents, which are not included in the PMI-58 list or FDA's list of HPHCs, were higher in IQOS emissions; 22 were >200% higher and seven were >1000% higher than in 3R4F reference cigarette smoke. PMI's studies also show significantly lower systemic exposure to some HPHCs from use of IQOS compared with smoking combustible cigarettes.

Conclusion PMI's data appear to support PMI's claim that IQOS reduces exposure to HPHCs. However, PMI's data also show significantly higher levels of several substances that are not recognised as HPHCs by the FDA in IQOS emissions compared with combustible cigarette smoke. The impact of these substances on the overall toxicity or harm of IQOS is not known.

INTRODUCTION

Many alternative tobacco products have entered the USA market in the last three decades. These include electronic cigarettes that heat a nicotine solution[1] as well as products that heat tobacco without combustion called heated tobacco products (HTPs) or heat-not-burn (HNB) products. A 2000 internal R J Reynolds document gave the rationale for the pursuit of an acceptable HTP:

> Given that no particular agent or group of agents can be definitely assigned the carcinogenic risk associated with cigarettes, the most effective strategy for reducing lung cancer risk in the smoking population is an overall reduction in both the number and concentration of particulate and vapor phase components. This strategy can be achieved by primarily heating, rather than burning, tobacco to form cigarette smoke aerosol.[2]

R J Reynolds first released Premier in 1988,[3] which was followed by Eclipse, a paper-encased tobacco plug heated by a carbon element.[4] Independent studies showed that use of Eclipse decreased tobacco cigarette consumption without causing withdrawal symptoms, maintained blood nicotine concentrations and decreased exposure to the carcinogenic tobacco-specific nitrosamine, 4-(methylnitrosamino)−1-(3-pyridyl)−1-butanone, but increased exposure to carbon monoxide (CO).[5–7] Other HTPs included Philip Morris' Accord, which was a combination of a handheld device that heated specially constructed cigarettes. One independent study showed that use of Accord suppressed withdrawal symptoms and reduced CO exposure.[8] Each iteration of HTPs was commercially unsuccessful, and most products were discontinued shortly after their introduction.[9]

Despite repeated failures at producing a commercially viable HTP, tobacco companies continue to research and develop these products. R J Reynolds launched a revamped Eclipse, rebranded as 'Revo', in November 2014. Revo was briefly test marketed in Wisconsin but pulled off the market.[10] Other current HTPs include British American Tobacco's Glo iFuse, a hybrid of HTP and e-cigarettes. It consists of a heating element, a liquid tank (like e-cigarettes) and a tobacco cavity through which the e-cigarette-like aerosol passes and is infused with tobacco flavour.[11] Japan Tobacco's Ploom Tech, which entered the Japanese market in 2016,[12] consists of a liquid cartridge and a capsule of granulated tobacco leaves that the vapour passes through.

Philip Morris Products S.A., a subsidiary of Philip Morris International, Inc. (PMI), developed IQOS ('I Quit Ordinary Smoking') as an HTP.[9 10] IQOS consists of a tobacco stick (HeatStick) and a battery-powered tobacco heating device.[13] As of May 2018, IQOS is currently sold in over 37 countries, including Japan, the UK and Canada.[14] Philip Morris Products S.A. filed a modified risk tobacco product (MRTP) application with the US Food and Drug Administration (FDA) in December 2016[15 16] to market IQOS in the USA with reduced exposure and reduced risk claims. The FDA's Tobacco Products Scientific Advisory Committee (TPSAC) reviewed the MRTP application in January 2018. The TPSAC committee approved, in an 8 to 1 vote, PMI's statement '*Scientific studies have shown that switching completely from cigarettes to the IQOS system significantly reduces your body's exposure to harmful or potentially harmful chemicals[HPHCs]*' was true.[17] Of the eight committee members who agreed with PMI's claim that IQOS significantly reduced exposure to HPHCs, a majority (five of eight) voted that PMI has not '*demonstrated that the reductions in exposure are reasonably likely to translate to a measurable and substantial reduction in morbidity and/or mortality*'.[17]

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Examination of PMI's studies, results and interpretation of data to support claims of reduced exposure and risk is critically important before FDA approval in order to protect public health, particularly as PMI's MRTP application and approval may set the precedent for other MRTP applications of similar products. This paper examines PMI's reported studies on IQOS aerosol chemistry and human exposure assessment, and we assessed whether they support PMI's claims of reduced exposure.

METHODS

We examined studies presented in PMI's MRTP application,[16] namely those in Module 6.1.1: *Aerosol Chemistry*; Module 6.1.3.1: *Justification of Selection of Biomarkers of Exposure*; and Module 6.1.3.2: *Summary of Biomarkers of Exposure Assessments*. We also reviewed data presented in the document, *Addendum to FDA Briefing Document: January 24–25, 2018*,[18] which was prepared by FDA's Center for Tobacco Products for the TPSAC meeting on IQOS held on 24 and 25 January 2018.

To examine the aerosol chemistry of IQOS, mainstream aerosol from IQOS HeatSticks (regular and menthol) and smoke from 3R4F reference cigarettes were generated according to the Health Canada Intense machine-smoking regimen on a Borgwaldt linear smoking machine type LM20X (Borgwaldt KC GmbH, Hamburg, Germany) for most analytes and Burghart rotary smoking machine type RMB 20 (Burghart Tabaktechnik GmbH, Wedel, Germany) for elements.[19] Methods for chemical analyses have been described previously.[19]

PMI conducted four clinical studies to examine whether human exposure to harmful substances are statistically significantly reduced with IQOS (Module 6.1.3.2).[16] All studies were randomised, controlled, open-label, three-arm, parallel group, single-centre studies. Studies ZRHR-REXC-03-EU (conducted in Poland) and ZRHR-REXC-04-JP (conducted in Japan) were conducted over 5 days in confinement. Each study included 160 combustible cigarette smokers who were randomly assigned to one of three arms, namely, IQOS with regular HeatSticks, commercially available combustible cigarettes or smoking abstinence. Use of IQOS or combustible cigarettes was from 06:30 to 23:00 and was ad libitum. Studies ZRHM-REXA-07-JP (conducted in Japan) and ZRHM-REXA-08-US (conducted in the USA) were conducted over 3 months, during which 160 participants were randomised to one of three arms in each study, namely, IQOS with menthol HeatSticks, commercially available menthol combustible cigarettes or smoking abstinence. These two studies included 5 days in confinement followed by 85 or 86 days, respectively, in an ambulatory setting. Participants in the IQOS or combustible cigarettes arms used each product ad libitum in confinement (06:30–23:00) and in the ambulatory setting. Compliance with study protocol could not be enforced during the ambulatory phase.

For the two 5-day confinement studies, it was evaluated whether reductions of 50% or more in 24 hours urine concentrations of mercapturic acid metabolites of 1,3-butadiene, acrolein and benzene and carboxyhaemoglobin in blood were observed in smokers assigned to IQOS compared with smokers who continued smoking combustible cigarettes. Levels of selected biomarkers of exposure over the 5-day exposure period were also compared between smokers who switched to IQOS and those who continued smoking and the maximum reduction in biomarker levels in abstinent smokers was assessed. For the two 3-month studies, they examined whether the geometric mean levels of biomarkers of exposure for IQOS (menthol) were lower relative to combustible cigarette (menthol) use. Differences in mercapturic acid metabolites of 1,3-butadiene, acrolein and benzene and carboxyhaemoglobin in blood were tested on day 5 and total 4-(methylnitrosamino)−1-(3-pyridyl)−1-butanol on day 90.

RESULTS

PMI reported the levels of 58 constituents (which PMI refers to as 'PMI-58') in mainstream aerosol generated from IQOS and 3R4F reference cigarettes (Module 6.1.1).[16] The PMI-58 list includes 40 (43%) out of the 93 harmful or potentially harmful constituents (HPHCs) on FDA's list of HPHCs.[20] The PMI-58 list included 18 additional constituents that do not appear on FDA's list of HPHCs, including water, total particulate matter, pyrene and nitrogen oxides. PMI concluded that the levels of HPHCs on the PMI-58 list were reduced by >92% on a stick basis and >89% on a normalised for nicotine basis for the regular tobacco stick, and >93% on a stick basis and >88% on a normalised for nicotine basis for the mentholated tobacco stick compared to 3R4F reference cigarette (Module 6.1.1, p. 45).[16]

Importantly, the addendum to the briefing document for the 24 and 25 January 2018 TPSAC meeting, prepared by FDA's Center for Tobacco Products,[18] presented additional data from PMI studies that showed higher levels of many substances in IQOS emissions compared with 3R4F cigarette smoke (table 1). The addendum consisted of data from Module 3.3.2 and section 6.1.1.3.4 of the MRTP application and appendix A of an amendment to the MRTP application. The addendum reported levels of 113 constituents, including 56 of the 58 constituents on the PMI-58 list (total particulate matter and nicotine-free dry particulate matter were the two exclusions) and 57 constituents that do not appear on the PMI-58 list. Fifty-six of the 57 non-PMI-58 constituents were higher in IQOS emission than in 3R4F smoke (median, 154% higher; range, undefined to 13 650% higher in IQOS aerosol vs 3R4F mainstream smoke); tar was the exception. Twenty-two of the non-PMI-58 constituents were at least 200% higher while seven were at least 1000% higher in IQOS emission compared with 3R4F mainstream smoke (table 1).

PMI characterised the droplet size distribution of IQOS aerosol by measuring the mass median aerodynamic diameter (MMAD) (the diameter at which 50% of the particles by mass are larger and 50% are smaller) and geometric standard deviation (presented in Module 6.1.1).[16] The MMAD for the various IQOS products tested (regular and menthol) ranged between 0.54 µm to 0.75 µm and fell within the respirability region, based on the respirability upper threshold defined at 2.5 µm. The range of MMAD for IQOS appears slightly larger than those of e-cigarettes and conventional tobacco cigarettes, which one report showed were about 0.15 µm and 0.17 µm, respectively.[21]

Regarding the human exposure studies, 11 of the 17 HPHCs measured are included in a list of 18 HPHCs that FDA recommends to be measured and reported in users of tobacco products.[20] PMI assessed systemic exposure to pyrene, which is not included in FDA's list of HPHCs, as a proxy for exposure to polycyclic aromatic hydrocarbons (PAHs) using 1-hydroxypyrene. PMI did not assess systemic exposure to inorganic compounds, phenols and metals.

Biomarkers of HPHCs measured were statistically significantly lower with IQOS use compared with combustible cigarette use (Module 6.1.3.2).[16] Reductions of at least 50% in levels of biomarkers of exposure to HPHCs were reported when smokers switched from combustible cigarettes to IQOS during 5 days of confinement; these reductions were sustained during the 85/86 days in ambulatory settings (Module 6.1.3.2, p. 145).

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Table 1 Compounds in mainstream aerosol of Marlboro HeatSticks compared with 3R4F reference cigarette

PMI product	Unit	PMI-58	IQOS HeatStick	3R4F	Change (%) with 3R4F on stick basis
1,2,3-Propanetriol, diacetate (diacetin)	µg/stick	No	1.23	0.381	↑ 223
1,2-Propanediol, 3-chloro	µg/stick	No	9.94	5.93	↑ 68
1,4-Dioxane, 2-ethyl-5-methyl-	µg/stick	No	0.055	0.0004	↑ 13 650
12,14-Labdadiene-7,8-diol, (8a,12E)	µg/stick	No	1.43	0.064	↑ 2134
1 hour-Indene, 2,3-dihydro-1,1,5,6-tetramethyl-	µg/stick	No	0.026	0.014	↑ 86
1-Hydroxy-2-butanone	µg/stick	No	0.947	0.465	↑ 104
1-Hydroxy-2-propanone(1,2-Propenediol)	µg/stick	No	162	96.8	↑ 67
2 (5H)-Furanone	µg/stick	No	5.32	1.99	↑ 167
2,3-Dihydro-5-hydroxy-6-methyl-4 hour-pyran-4-one	µg/stick	No	0.231	0.135	↑ 71
2,4-Dimethylcyclopent-4-ene-1,3-dione	µg/stick	No	0.333	0.193	↑ 73
2-Cyclopentene-1,4-dione	µg/stick	No	3.8	0.764	↑ 397
2-Formyl-1-methylpyrrole	µg/stick	No	0.128	0.064	↑ 100
2-Furancarboxaldehyde,5-methyl-	µg/stick	No	11.1	2.94	↑ 278
2-Furanmethanol	µg/stick	No	39.2	7	↑ 460
2-Furanmethanol, 5-methyl-	µg/stick	No	0.123	0.029	↑ 324
2 hour-Pyran-2-one,tetrahydro-5-hydroxy	µg/stick	No	4.45	3.11	↑ 43
2-Methylcyclobutane-1,3-dione	µg/stick	No	2.78	0.71	↑ 292
2-Propanone, 1-(acetyloxy)-	µg/stick	No	16.9	8.01	↑ 111
3 (2H)-Furanone, dihydro-2-methyl-	µg/stick	No	0.326	0.119	↑ 174
3-Methylvaleric acid	µg/stick	No	5.1	3.63	↑ 40
4(H)-Pyridine, N-acetyl-	µg/stick	No	0.296	0.112	↑ 164
5-Methylfurfural	µg/stick	No	0.995	0.632	↑ 57
Anhydro linalool oxide	µg/stick	No	0.457	0.291	↑ 57
Benzene, 1,2,3,4-tetramethyl-4-(1-methylethenyl)-	µg/stick	No	0.006	0.005	↑ 20
Benzenemethanol, 4-hydroxy-	µg/stick	No	0.011	0	↑
Benzoic acid, 2,5-dihydroxy-methyl	µg/stick	No	4.55	2.18	↑ 109
Butylated hydroxytoluene	µg/stick	No	0.132	0.007	↑ 1786
Butyrolactone	µg/stick	No	4.08	0.728	↑ 460
Cis-sesquisabinene hydrate	µg/stick	No	0.061	0	↑
Cyclohexane, 1,2-dioxo-	µg/stick	No	0.083	0.046	↑ 80
Cyclohexane-1,2-dione, 3-methyl-	µg/stick	No	0.101	0.073	↑ 38
Eicosane, 2-methyl-	µg/stick	No	0.05	0.014	↑ 257
Ergosterol	µg/stick	No	3.18	1.58	↑ 101
Ethyl 2,4-dioxohexanoate	µg/stick	No	6.73	3.57	↑ 89
Ethyl dodecanoate (ethyl laurate)	µg/stick	No	0.023	0	↑
Ethyl linoleate	µg/stick	No	0.135	0.008	↑ 1588
Ethyl linolenate	µg/stick	No	0.614	0.153	↑ 301
Furfural	µg/stick	No	31.1	25.9	↑ 20
Glycerol	mg/stick	No	5.02	2.08	↑ 141
Glycidol	µg/stick	No	5.71	1.76	↑ 224
Heneicosane, 2-methyl-	µg/stick	No	0.063	0.021	↑ 200
Hexadecanoic acid, ethyl ester	µg/stick	No	0.491	0.008	↑ 6038
Isolinderanolide	µg/stick	No	4.99	1.85	↑ 170
Isoquinoline, 3-methyl	µg/stick	No	6.29	4.99	↑ 26
Labdane-8,15-diol, (13S)	µg/stick	No	0.143	0.015	↑ 853
Lanost-8-en-3-ol, 24-methylene-, (3beta)	µg/stick	No	6.3	1.61	↑ 291
Maltoxazine	µg/stick	No	0.077	0.038	↑ 103
Methyl furoate	µg/stick	No	0.147	0.029	↑ 407
Phenylacetaldehyde	µg/stick	No	1.41	0.529	↑ 167
p-Menthan-3-ol	µg/stick	No	0.786	0.322	↑ 144
Propylene glycol	µg/stick	No	175	23.7	↑ 638
Pyranone	µg/stick	No	6.54	5.07	↑ 29
Pyranone	µg/stick	No	9.26	5.84	↑ 59
Pyridoxin	µg/stick	No	0.699	0.526	↑ 33
Stearate, ethyl-	µg/stick	No	0.074	0.003	↑ 2367

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Table 1 Continued

PMI product	Unit	PMI-58	IQOS HeatStick	3R4F	Change (%) with 3R4F on stick basis
Tar	mg/stick	No	19.4	25	↓ 22
Trans-4-hydroxymethyl-2-methyl-1,3-dioxolane	µg/stick	No	2.09	0.044	↑ 4650
1,3-Butadiene	µg/stick	Yes	0.21	89.2	↓ 99.8
1-Aminonaphthalene	ng/stick	Yes	0.043	20.9	↓ 99.8
2-Aminonaphthalene	ng/stick	Yes	0.022	17.5	↓ 99.9
3-Aminobiphenyl	ng/stick	Yes	0.007	4.6	↓ 99.8
4-Aminobiphenyl	ng/stick	Yes	0.009	3.21	↓ 99.7
Acetaldehyde	µg/stick	Yes	192	1602	↓ 88
Acetamide	µg/stick	Yes	2.96	13	↓ 77
Acetone	µg/stick	Yes	30.7	653	↓ 95
Acrolein	µg/stick	Yes	8.32	158	↓ 95
Acrylamide	µg/stick	Yes	1.58	4.5	↓ 65
Acrylonitrile	µg/stick	Yes	0.145	21.2	↓ 99.3
Ammonia	µg/stick	Yes	12.2	33.2	↓ 63
Arsenic	ng/stick	Yes	<0.36	<7.49	NA
Benz[a]anthracene	ng/stick	Yes	2.65	28.4	↓ 91
Benzene	µg/stick	Yes	0.45	77.3	↓ 99.4
Benzo[a]pyrene	ng/stick	Yes	0.736	13.3	↓ 94
Butyraldehyde	µg/stick	Yes	20.7	81.3	↓ 74
Cadmium	ng/stick	Yes	<0.28	89.2	↓ >99.7
Carbon monoxide	mg/stick	Yes	0.35	29.4	↓ 99
Catechol	µg/stick	Yes	14	84.1	↓ 83
Chromium	ng/stick	Yes	<11.0	<11.9	NA
Crotonaldehyde	µg/stick	Yes	<3.29	49.3	↓ >93
Dibenz[a,h] anthracene	ng/stick	Yes	<0.124	<0.689	NA
Ethylene oxide	µg/stick	Yes	<0.119	16	↓ >99.3
Formaldehyde	µg/stick	Yes	14.1	79.4	↓ 82
Hydrogen cyanide	µg/stick	Yes	<1.75	329	↓ >99.5
Hydroquinone	µg/stick	Yes	6.55	94.5	↓ 93
Isoprene	µg/stick	Yes	1.51	891	↓ 99.8
Lead	ng/stick	Yes	2.23	31.2	↓ 93
m-Cresol	µg/stick	Yes	0.042	4.24	↓ 99
Mercury	ng/stick	Yes	1.38	3.68	↓ 63
Methyl-ethyl-ketone	µg/stick	Yes	10.1	183	↓ 94
Nickel	ng/stick	Yes	<15.9	<12.9	NA
Nicotine	mg/stick	Yes	1.29	1.74	↓ 26
Nitric oxide	µg/stick	Yes	12.6	484	↓ 97
Nitro benzene	µg/stick	Yes	<0.011	<0.038	NA
Nitrogen oxides	µg/stick	Yes	14.2	538	↓ 97
N-nitrosoanabasine	ng/stick	Yes	2.35	29	↓ 92
N-nitrosoanatabine	ng/stick	Yes	14.7	254	↓ 94
NNK	ng/stick	Yes	7.8	244.7	↓ 97
NNN	ng/stick	Yes	10.1	271	↓ 96
o-Cresol	µg/stick	Yes	0.078	4.81	↓ 98
o-Toluidine	ng/stick	Yes	1.1	96.2	↓ 99
p-Cresol	µg/stick	Yes	0.071	9.6	↓ 99
Phenol	µg/stick	Yes	1.47	15.6	↓ 91
Propionaldehyde	µg/stick	Yes	10.8	109	↓ 90
Propylene oxide	ng/stick	Yes	142.3	896	↓ 84
Pyrene	ng/stick	Yes	8.2	79.2	↓ 90
Pyridine	µg/stick	Yes	6.58	30.9	↓ 79
Quinoline	µg/stick	Yes	<0.011	0.43	↓ >98
Resorcinol	µg/stick	Yes	<0.055	1.72	↓ >97
Selenium	ng/stick	Yes	1.27	<4.42	NA
Styrene	µg/stick	Yes	0.58	13.9	↓ 96

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Table 1 Continued

PMI product	Unit	PMI-58	IQOS HeatStick	3R4F	Change (%) with 3R4F on stick basis
Toluene	µg/stick	Yes	1.42	129	↓ 99
Vinyl chloride	ng/stick	Yes	<0.657	93.4	↓ >99
Water	mg/stick	Yes	30.2	14.7	↑ 105

Notes: presented in table 1 of *Addendum to FDA Briefing Document, January 24-25, 2018*, Meeting of the Tobacco Products Scientific Advisory Committee; sata source: section 3.3.2 and section 6.1.1.3.4 of the Modified Risk Tobacco Product application (MRTPAs) and appendix A of an amendment to the MRTPAs submitted on 8 December 2017. Total particulate matter and nicotine-free dry particulate matter, two constituents on the PMI-58 list were not reported by PMI in this table.
↑, higher in IQOS; ↓, lower in IQOS.
PMI, Philip Morris International; PMI-58, PMI's list of 58 constituents.

DISCUSSION

According to FDA's draft guidance, an MRTP is 'any tobacco product that is sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products'.[22] FDA may issue an order allowing a product to be marketed as a modified risk product if it is demonstrated that the product: (A) significantly reduces harm and the risk of tobacco-related disease to individual tobacco users; and (B) benefits the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products. PMI's data show that IQOS significantly reduces emissions and exposure to several HPHCs compared with combustible cigarettes. However, PMI's data also show that IQOS emissions contain higher levels of many other substances compared with combustible cigarettes. The impact of these substances on IQOS toxicity and harm are not known.

Over 7000 distinct substances have been identified in tobacco smoke, many of which are toxic or carcinogenic.[23] HPHCs in tobacco or tobacco smoke have been proposed by several public health authorities, such as the FDA,[20] as possible causes of tobacco-related morbidity and mortality. Elimination or reduction of exposure to these HPHCs may potentially reduce health risks, which is the premise of HTP technology. Schaller and colleagues[19] described five criteria used by PMI to select HPHCs to measure in IQOS aerosol for comparison with 3R4F reference cigarette. Criterion 1 includes smoke constituents determined by International Organization for Standardization (ISO) methods, such as total particulate matter, nicotine and CO. Criterion 2 includes priority toxicants in tobacco smoke selected from the lists issued by regulatory bodies or proposed by cognizant authorities, such as volatile organic compounds like acrylonitrile, 1,3-butadiene and benzene. Criterion 3 includes toxicants for which there is an established biomarker of exposure. Criterion 4 includes toxicants that are predominantly formed below 400°C and that are not included under 'Criterion 2', such as acrylamide and acetamide. Criterion 5 includes toxicants that are predominantly formed above 400°C and that are not included under 'Criterion 1' and 'Criterion 2', such as dibenz[a,h]anthracene and benz[a]anthracene.

PMI's conclusion that IQOS reduces exposure to HPHCs, which TPSAC agreed with,[17] is based, in part, on evidence of lower levels of PMI-58 substances in IQOS emissions compared with 3R4F reference cigarette smoke. However, the PMI-58 list is selective (based on PMI's criteria described before); PMI did not report levels of 53 HPHCs on FDA's list of 93 HPHCs. Of the 53 FDA HPHCs not measured, 50 are carcinogenic (eg, 2,6-dimethylaniline, benz[j]aceanthrylene, ethylbenzene and furan).[20] In addition to the PMI-58 substances, PMI measured levels of 57 other substances in IQOS emissions (non-PMI-58 substances). Importantly, 56 of these 57 non-PMI-58 substances were higher in IQOS aerosol compared with 3R4F mainstream cigarette smoke. It appears that IQOS reduces exposure to some toxicants but elevates exposure to other substances.

Given the elevated levels of the non-PMI-58 substances in IQOS aerosol compared with reference cigarette smoke, their inherent toxicities could play a role in the overall harm of IQOS. A number of these substances, including several that were more than 50% higher in IQOS aerosol, belong to chemical classes that are known to have significant toxicity, such as α,β-unsaturated carbonyl compounds (eg, 2-cyclopentene-1,4-dione),[24] 1,2-dicarbonyl compounds (eg, cyclohexane, 1,2-dioxo-),[25] furans (eg, 2 (5H)-furanone)[26] and epoxides (eg, anhydro linalool oxide).[27] There is limited information on the toxicity of many of the non-PMI-58 substances. We speculate that some of these substances are components of flavour additives in IQOS or thermal degradation compounds. For example, anhydro linalool oxide is listed among flavouring ingredients that are generally regarded as safe (for oral ingestion) by the Flavor and Extract Manufacturers' Association.[28]2 (5H)-Furanone is a food additive that suppresses appetite and/or food intake and has been shown to induce cellular DNA damage in vitro.[29 30] 2-Furanmethanol is a flavouring agent with a flavour profile of burnt, caramel or cooked.[31] 2-Furanmethanol also causes eye, nose, throat and skin irritation and has central nervous system effects.[31] 2-Cyclopentene-1,4-dione is likely generated from thermal breakdown of sugars.[32] 1-Hydroxy-2-butanone, a flavouring ingredient found in coffee and coffee products, is also a degradation product of polysaccharides.[33] Some compounds appear to be contaminants. 3-Chloro-1,2-propanediol (or 1,2-propanediol, 3-chloro), a food contaminant,[34] has not been shown to be genotoxic in vivo,[35] but mutagenic effects were observed at high concentrations in vitro experiments.[36] A 2-year study found increased incidence for the development of tumours in kidney and testis in male rats exposed to 3-chloro-1,2-propanediol.[37] 1,2,3-Propanetriol, diacetate (diacetin) is a solvent used for decaffeinating coffee.

PMI's MRTP application fails to address the important question of whether the aerosol generation process for IQOS produces toxic substances not found in the smoke of combustible cigarettes, which could have been answered through non-targeted chemical analysis. Combustible tobacco cigarettes reach about 900°C during a puff and smoulder at about 400°C between puffs.[23] The burning process, substances emitted and their levels vary at different temperatures.[38] Distillation, the process during which nicotine and aromas are transferred from tobacco to smoke, occurs below 300°C; pyrolysis occurs at about 300°C–700°C, entails the decomposition of biopolymers, proteins, and other organic materials and generates the majority of substances emitted in smoke; and combustion occurs above 750°C and results in the generation of carbon dioxide, CO and water.[38] HeatSticks are heated to a maximum of 350°C,[19] a temperature sufficient to enable pyrolytic decomposition of some organic materials. Formation of toxic volatile organic

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compounds, including formaldehyde, acetaldehyde and acrolein, via dehydration and oxidation of the humectants, propylene glycol and glycerin, have been reported in e-cigarette aerosols at similar temperatures as IQOS.[39–42] In addition, flavouring chemicals in e-cigarettes undergo thermal degradation and contribute significantly to levels of toxic aldehydes emitted in e-cigarette aerosol.[43] Since the constituents of HeatSticks may be different from that of combustible cigarettes, including flavourants and additives, it is plausible that the IQOS aerosol may contain substances not present in tobacco smoke.

A study by Klupinski and colleagues[44] reported that unique substances, such as ambrox, 3-methylbutanenitrile and 4-methylimidazole, were found in little cigar smoke that were not found in cigarette smoke, indicating that different tobacco products can have different chemical fingerprints and lead to different exposure and toxicological profiles. The study by Klupinski and colleagues describes methodology for 'non-targeted' analysis of tobacco smoke aerosol, and the authors suggest that 'the same approach could also be applied to other samples to characterize constituents associated with tobacco product classes or specific tobacco products of interest'. FDA should recommend that manufacturers of HTPs undertake 'non-targeted' analyses (along with targeted analysis), comparing HTP aerosol with smoke from combustible tobacco products to identify potentially toxic chemicals in HTP emissions that may not be present in tobacco smoke.

Although smoking machine studies are appropriate for examining the relative differences in emissions between products, they do not predict use patterns and systemic exposure to toxicants. PMI reported systemic exposure to 17 HPHCs in its human exposure studies. PMI did not assess systemic exposure to any inorganic compounds, phenols and metals, possibly due to the fact that there are no valid biomarkers for some substances or that the time course of the biomarkers may not be optimal for studies of the duration used by PMI. PMI used 1-hydroxypyrene, a metabolite of pyrene (a PAH) as a biomarker of PAHs. Pyrene is not included as an HPHC on FDA's list. We have previously demonstrated that 1-hydroxypyrene is not a selective measure of tobacco-related PAH exposure and is weakly related to nicotine intake and tobacco-specific nitrosamine exposure.[45] Instead, we found that monohydroxylated metabolites of fluorene (particularly 1-hydroxyfluorene) and 2-naphthol (a naphthalene metabolite) were more selective of tobacco smoke exposure. In characterising PAH exposure from HNB products, manufacturers should include biomarkers with relatively high selectivity for tobacco.

In conclusion, PMI's data show that IQOS emissions have significantly lower levels of several HPHCs compared with combustible cigarettes. Furthermore, PMI's data from human studies show that use of IQOS is associated with significantly lower systemic exposure to some HPHCs compared with smoking combustible cigarettes. These data appear to support PMI's claim that IQOS is a reduced exposure product. However, PMI's data also show significantly higher levels of other substances in IQOS emissions compared with combustible cigarette smoke. The impact of these substances on the overall toxicity or harm of IQOS is not known.

Contributors All authors were involved in interpretation of data and writing and revising the manuscript. All authors approve this version of the manuscript for publication.

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What this paper adds

- Studies conducted by Philip Morris International, Inc. (PMI) show that IQOS emissions contain lower levels of many harmful or potentially harmful constituents (HPHCs) compared with combustible tobacco smoke.
- PMI's studies show that use of IQOS results in significantly lower systemic exposure to several HPHCs compared with combustible cigarette smoking.
- PMI's own data also show that IQOS emissions contain many other substances, some of which are potentially toxic, at higher levels than in combustible cigarette smoke.

Disclaimer The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health, the Food and Drug Administration or TRDRP. The funding agencies played no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript.

Competing interests NLB has served on smoking cessation advisory boards for Pfizer and has been an occasional consultant to McNeil and Achieve Life Sciences and has served as a paid expert witness in litigation against tobacco companies.

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Possible hepatotoxicity of IQOS

On 25 January 2018, the Food and Drug Administration (FDA) Tobacco Scientific Advisory Committee unanimously voted (with one abstention) that Phillip Morris International (PMI) could not claim their heated tobacco product (HTP) IQOS (I-Quit-Ordinary-Smoking) would reduce the risk of tobacco-related diseases. Regardless, IQOS is already available in over 30 countries, and thus merits scrutiny from the scientific and medical communities. The preclinical and clinical data PMI submitted to FDA indicate that IQOS exposure may be associated with unexpected liver toxicity. We reviewed preclinical studies conducted by PMI scientists[1] and clinical studies of 5 and 90 days of exposure to IQOS and IQOS menthol[2–5] included in PMI's Modified Risk Tobacco Product application submitted to the US FDA.

Wong and colleagues[1] exposed 92 male and 92 female Sprague Dawley rats to up to 90 days of mainstream aerosol from IQOS, mainstream smoke from 3R4F research cigarettes, or room air (sham). After 90 days of exposure, liver weights and blood levels of alanine aminotransferase (ALT) were measured. ALT is an enzyme released into the blood by hepatocytes during hepatocellular injury[6] and liver weight is a sensitive measure of hepatocellular hypertrophy.[7] After 90 days, ALT levels and liver weights were significantly higher with IQOS than with conventional cigarettes in female animals (table 1). Hepatocellular vacuolisation, a sign of acute liver injury,[7] was significantly increased in IQOS-exposed female rats, an effect not seen in cigarette-exposed animals (table 1).

The human clinical data PMI submitted to FDA provide further cause for concern. Increased plasma bilirubin may signify cholestatic liver injury with impaired hepatic bile flow, accelerated red blood cell destruction, or decreased bilirubin metabolism.[7] Following 5 days of exposure to IQOS, conventional cigarettes or smoking abstinence, plasma bilirubin was elevated in 8.8% of IQOS subjects compared with 0% of cigarette smokers and 2.6% in abstainers.[2] In another 5-day study, the mean increase in ALT was higher with IQOS than with conventional cigarettes or smoking abstinence (4.5, 2.9 and 1.6 IU/L, respectively).[3] In a 90-day study of exposure to mentholated IQOS, mentholated cigarettes or smoking abstinence, the only subject experiencing a grade 2 (moderate) increase in ALT was in the IQOS group.[4] In another study, the rate of grade 1 (mild) increases in ALT after 60 days of exposure was highest with IQOS at 6.3% compared with 0% for conventional cigarettes and 2.6% with smoking abstinence.[5]

Hepatotoxicity constitutes a broad spectrum of injuries to the liver, with consequences ranging from asymptomatic lab abnormalities to hepatic failure and death.[6 7] Notably, there is some evidence that smoking cessation may be associated with a small increase in the unconjugated fraction of bilirubin over the next 1–4 weeks, averaging 0.06 mg/dL.[8] However, in the 5-day exposure study cited above, the rate of elevated bilirubin (>1.0 mg/dL) in IQOS users was over three times higher than that observed with smoking abstinence (8.8% vs 2.6%), and the mean increase above baseline was 0.05 mg/dL with IQOS compared with −0.07 mg/dL with smoking abstinence.[2] We can find no evidence in the literature that smoking cessation is associated with an increase in ALT.

Taken together, PMI's preclinical and clinical data constitute a concerning pattern of possible hepatotoxicity, especially considering the short period of exposure. These findings indicate IQOS may have unexpected organ toxicity that has not been associated with cigarettes. Although IQOS exposes users to lower levels of many toxins than conventional cigarettes, it exposes users to higher levels of other toxins (St Helen *et al*, submitted manuscript). Given the potential for synergistic hepatotoxicity with other medications (eg, acetaminophen), alcohol[9 10] and herbal supplements, the public health community should focus intense scrutiny on possible liver injury in users of IQOS and other HTPs. A broader implication of this finding is that health assessments of IQOS and other non-cigarette tobacco products should consider possible toxicities not associated with conventional cigarettes.

Table 1 Liver parameters in Sprague Dawley rats after 90 days of exposure

	Female			Male		
	Sham	IQOS	3R4F	Sham	IQOS	3R4F
ALT levels (IU/L)	51.0±4.4	73.0±3.2**,****	54.0±2.6	57.0±6.5	75.0±6.7*	68.0±5.8
Liver weight†	339.6±6.6	442.6±10.2***,****	386.7±15.1*	329.3±5.1	381.7±13.2**	373.0±7.9***
Hepatocellular vacuolisation	0.7±0.4	1.5±0.2*	1.2±0.3	1.4±0.3	0.8±0.4	1.8±0.8

Data are from Wong *et al*[1] and are presented as mean±SEM.
*P<0.05 relative to sham; **P<0.01 relative to sham; ***P<0.001 relative to sham; ****P<0.01 relative to 3R4F.
†Normalised to body weight and reported as $\times 10^{-4}$.
ALT, alanine aminotransferase.

Lauren Chun,[1] **Farzad Moazed,**[1] **Michael Matthay,**[1,2,3] **Carolyn Calfee,**[1,2,3] **Jeffrey Gotts**[1]

[1]Department of Medicine, University of California, San Francisco, San Francisco, California, USA
[2]Cardiovascular Research Institute, University of California, San Francisco, San Francisco, California, USA
[3]Department of Anesthesia, University of California, San Francisco, San Francisco, California, USA

Correspondence to Dr Jeffrey Gotts, Department of Medicine, University of California, San Francisco, San Francisco, CA 94143, USA; jeffrey.gotts@ucsf.edu

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Heat-not-burn tobacco products: a systematic literature review

Erikas Simonavicius,[1] Ann McNeill,[1,2] Lion Shahab,[3] Leonie S Brose[1,2]

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[1]Department of Addictions, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London, UK
[2]UK Centre for Tobacco and Alcohol Studies, UK
[3]Department of Behavioural Science and Health, University College London, London, UK

Correspondence to
Erikas Simonavicius, Department of Addictions, Institute of Psychiatry, Psychology and Neuroscience, King's College London, London SE5 8BB, UK; erikas.simonavicius@kcl.ac.uk

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ABSTRACT

Objective To review peer-reviewed evidence on heat-not-burn tobacco products (HnB), their secondhand emissions and use by humans; to identify differences between independent and industry-funded studies.

Data sources Medline, Embase, PsycINFO, ProQuest, Scopus and Web of Science databases were searched up to 6 November 2017 for studies on HnB published after December 2009; reference lists were screened and other researchers contacted, yielding 637 records.

Study selection Thirty-one publications on HnB secondhand emissions (n=16) or use by humans (n=15) were selected by two reviewers with excellent agreement (k=0.75).

Data extraction Data on authors' affiliations, HnB products, secondhand emissions and human exposure were extracted by one reviewer. Two reviewers assessed the quality of experimental HnB studies using the Effective Public Health Practice Project tool.

Data synthesis Twenty out of 31 studies were affiliated with tobacco industry. Studies on secondhand emissions varied by methodology, products and comparators. Compared with cigarettes, HnB delivered up to 83% of nicotine and reduced levels of harmful and potentially harmful toxicants by at least 62% and particulate matter by at least 75%. Experimental HnB use studies were limited to one product, reductions of human exposure to toxicants varied between 42% and 96%. HnB use suppressed urges to smoke, but participants rated HnB less satisfying than cigarettes. While limited by methodological heterogeneity, findings were largely similar for independent and industry-funded studies.

Conclusions Studies on HnB secondhand emissions and human use were heterogeneous and largely affiliated with the manufacturers. HnB exposed users and bystanders to toxicants, although at substantially lower levels than cigarettes.

INTRODUCTION

'Heat-not-burn' tobacco products (HnB) are electronic devices that heat processed tobacco instead of combusting it to supposedly deliver an aerosol with fewer toxicants than in cigarette smoke. Commercially available HnB systems like glo (produced by British American Tobacco (BAT)) or IQOS (Philip Morris International (PMI)) include a charger, a holder and tobacco sticks, plugs or capsules. Inserted into the holder, tobacco sticks are heated with an electronically controlled heating element. Other products, like iFuse from BAT or Ploom Tech from Japan Tobacco (JT), produce vapour from a non-tobacco source and pass it through a tobacco plug to absorb flavour and nicotine.[1] HnB products aim for a niche between combustible tobacco smoking and electronic cigarettes (e-cigarettes) that vaporise nicotine suspended in humectants.

'Safer' heated tobacco products that deliver nicotine but limit emissions of tar or carbon monoxide (CO) is a half-century old idea,[2] which had been unsuccessfully market-tested since 1988, first as 'Premier' by the RJ Reynolds Tobacco Company (RJR) and later as 'Eclipse' (RJR) and 'Accord' (PMI).[3] Of the current HnB products, IQOS was launched in several cities in Japan, Italy and Switzerland in 2014, iFuse was released in Romania in 2015 and glo and Ploom Tech were introduced to Japanese cities in 2016. Due to regulations restricting the sale of nicotine-containing e-cigarettes,[4] Japan was a fertile market for HnB producers,[5] suggesting that the products have potential 'for explosive global growth'.[6] By 2017, IQOS was available in 30 countries and was being considered by United States Food and Drug Administration for a reduced-risk product approval,[5] and the UK was one of the first countries to assign a separate taxation category for HnB products.[1 7]

Committees advising the UK government carried out a systematic review of HnB studies but excluded research funded by HnB manufacturers, which comprise the majority of evidence published to date.[8 9] Because of the paucity of evidence from independent sources, it is important to look at evidence from tobacco companies[10] and to validate their findings.[11] A recent Public Health England report reviewed evidence related to HnB products, including data from manufacturers.[12] However, expeditiously published new findings call for an update. This review aimed to systematically identify and synthesise evidence from peer-reviewed studies on HnB tobacco products and to answer the following questions:

1. How do the currently researched and marketed HnB products compare with other tobacco and nicotine products:
   a. in exposure to toxicants and health risks to humans through primary use and secondhand exposure?
   b. in key performance characteristics (eg, nicotine delivery, use profile and user satisfaction)?
2. What is the population-level uptake of HnB products?
3. Are there any differences between independent and manufacturer-funded studies?

METHODS

Search strategy and selection of studies

Medline, Embase, PsycINFO, ProQuest, Scopus and Web of Science databases were searched up to 13 July 2017 and the search was rerun on 6 November 2017. The full search strategy and search outcomes are

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Table 1 Studies included in the review

	Authors, year of publication	Funder, country	Study design	Heat-not-burn and reference products	Main aim
Studies on HnB mainstream emissions					
1	Auer *et al*,[21] 2017	Independent, Switzerland	Laboratory comparison study using smoking machines	IQOS Cigarette	To compare levels of HPHC in mainstream IQOS emissions with those in mainstream cigarette smoke.
2	Farsalinos *et al*,[22]2018	Independent, Greece	Laboratory comparison study using smoking machines	IQOS Cigarette E-cigarettes: (i) Ciga-like (ii) eGo-style, second generation (pen-style tank) (iii) Variable wattage (tank model)	To compare levels of nicotine in mainstream IQOS emissions from regular and menthol tobacco sticks with nicotine in different type of e-cigarettes aerosol and in mainstream cigarette smoke.
3	Bekki *et al*,[23] 2017	Independent, Japan	Laboratory comparison study using smoking machines	IQOS Cigarette	To compare levels of nicotine and HPHC in mainstream IQOS emissions from regular and menthol tobacco sticks with those in mainstream cigarette smoke.
4	Schaller *et al*,[24] 2016	PMI, Switzerland	Laboratory comparison study using smoking machines	THS 2.2/IQOS Cigarette	To compare levels of HPHC in mainstream IQOS emissions with those in mainstream cigarette smoke.
5	Schaller *et al*,[25] 2016	PMI, Switzerland	Laboratory comparison study using smoking machines	THS 2.2/IQOS Cigarette	To compare levels of HPHC in mainstream IQOS emissions from regular and menthol tobacco sticks with those in mainstream cigarette smoke.
6	Jaccard *et al*,[26] 2017	PMI, Switzerland	Laboratory comparison study using smoking machines	THS 2.2/IQOS Cigarette	To compare levels of HPHC in mainstream IQOS emissions with those in mainstream cigarette smoke.
7	Pratte *et al*,[27] 2017	PMI, Switzerland	Laboratory comparison study using smoking machines	THS 2.2/IQOS Cigarette	To compare numbers of solid particles in mainstream IQOS emissions with those in mainstream cigarette smoke.
8	Eaton *et al*,[28] 2018	BAT, UK	Laboratory comparison study using smoking machines	THP 1.0/glo Cigarette	To compare levels of HPHC in mainstream glo emissions with those in mainstream cigarette smoke.
9	Forster *et al*,[29] 2018	BAT, UK	Laboratory comparison study using smoking machines	THP 1.0/glo IQOS Cigarette	To compare levels of HPHC in mainstream glo emissions with those in mainstream IQOS emissions and cigarette smoke.
10	Poynton *et al*,[30] 2017	BAT, UK	Laboratory comparison study using smoking machines	iFuse Pen-style e-cigarette	To compare levels of HPHC in mainstream iFuse emissions with those in mainstream Vype ePen emissions and cigarette smoke.
Studies on HnB secondhand emissions					
11	Protano *et al*,[31] 2016	Independent, Italy	Laboratory comparison study using smoking volunteers	THS 2.2/IQOS Cigarette Hand-rolled cigarette E-cigarette (pen-style tank)	To compare levels of secondhand emissions.
12	Protano *et al*,[32] 2017	Independent, Italy	Laboratory comparison study using smoking volunteers	THS 2.2/IQOS Cigarette Hand-rolled cigarette Cigar Pipe E-cigarette (pen-style)	To compare levels of secondhand emissions.
13	Ruprecht *et al*,[33] 2017	Independent, not reported	Laboratory comparison study using smoking volunteers	THS 2.2/IQOS Cigarette E-cigarette (cartridge)	To compare levels of secondhand emissions.
14	Mitova *et al*,[34] 2016	PMI, Switzerland	Laboratory comparison study using smoking volunteers	THS 2.2/IQOS Cigarette	To compare levels of secondhand emissions.
15	O'Connell *et al*,[35] 2015	IT, UK	Laboratory comparison study using smoking volunteers.	THS 2.2/IQOS Nicorette inhalator E-cigarette (cigalike)	To compare levels of sidestream emissions.
16	Forster *et al*,[36] 2018	BAT, UK	Laboratory comparison study using smoking machines	THP 1.0/glo Cigarette	To compare levels of secondhand emissions.
Studies on human use of HnB					
17	Kamada *et al*,[39] 2016	Independent, Japan	Case report	IQOS	To report a case of acute eosinophilic pneumonia following use.

Continued

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Table 1 Continued

	Authors, year of publication	Funder, country	Study design	Heat-not-burn and reference products	Main aim
18	Lopez *et al*,[40] 2016	Independent, USA	Randomised crossover experimental trial	Pax LLTV Cigarette eGo e-cigarette (pen-style tank)	To compare nicotine delivery, expired air CO concentration and abstinence symptom suppression.
19	Brossard *et al*,[43] 2017	PMI, Japan	Randomised crossover experimental trial	THS 2.2/IQOS Cigarette Nicotine gum	To compare nicotine delivery and effects on urge to smoke.
20	Haziza *et al*,[44] 2016	PMI, Japan	RCT	THS 2.2/IQOS Cigarette	To compare exposure to HPHC during 5 days of use.
21	Haziza *et al*,[45] 2016	PMI, Poland	RCT	THS 2.2/IQOS Cigarette	To compare exposure to HPHC during 5 days of use.
22	Lüdicke *et al*,[46] 2017	PMI, Poland	RCT	THS 2.1 Cigarette	To compare exposure to HPHC during 5 days of use.
23	Lüdicke *et al*,[47] 2016	PMI, Poland	RCT	CHTP Cigarettes	To compare exposure to HPHC during 5 days of use.
24	Lüdicke *et al*,[48] 2018	PMI, Japan	RCT	THS 2.2/IQOS Cigarette	To compare exposure to HPHC during 5 days of use in confinement and further 85 days of use in an ambulatory setting.
25	Lüdicke *et al*,[49] 2017	PMI, Japan	RCT	THS 2.2/IQOS Cigarette	To compare effect on biologically and clinically relevant risk markers during 90 days of use.
26	Picavet *et al*,[50] 2016	PMI, UK	Randomised crossover experimental trial	THS 2.1 Cigarette	To compare nicotine delivery and effects on urge to smoke.
27	Gee *et al*,[51] 2017	BAT, Japan	Randomised crossover experimental trial	THP 1.0/glo IQOS Cigarette	To compare the puffing topography, mouth level exposure and average daily consumption.
28	Yuki *et al*,[52] 2017	JT, Japan	Randomised crossover experimental trial	PNTV/Ploom Tech Cigarette	To compare the pharmacokinetics of nicotine delivery.
Studies on HnB epidemiology					
29	Tabuchi *et al*,[41] 2016	Independent, Japan	Epidemiological study	IQOS Ploom Tech Glo	To report awareness and use of HnB products in a nationally representative sample.
30	Tabuchi *et al*,[5] 2017	Independent, Japan	Epidemiological study	IQOS Ploom Tech Glo	To assess population interest, rate of use, predictors of use and perceived effects of secondhand HnB aerosol.
31	Brose *et al*,[42] 2017	Independent, UK	Epidemiological study	IQOS Ploom Tech	To assess awareness and use of HnB products in a nationally representative sample.

BAT, British American Tobacco; CHTP, carbon-heated tobacco product; HPHC, harmful and potentially harmful compounds; IT, Imperial Tobacco; JTI, Japan Tobacco International; LLTV, loose-leave tobacco vaporiser; PMI, Philip Morris International; PNTV, Prototype novel tobacco vapour product; RCT, randomised controlled trial; THP, tobacco heating product; THS, tobacco heating system.

reported in supplementary appendices table A1 in Supplementary file 1. The searches included terms relating to HnB in general ('heat-not-burn', 'tobacco heating system') and brand names ('IQOS', 'Ploom', 'Heets', 'glo'), and were limited to studies published from 2010, to exclude papers on obsolete HnB devices. Additionally, reference lists were screened and other researchers contacted. Endnote X7 was used to record publications at all stages of the review. One reviewer (ES) screened titles and abstracts of initially included studies, and two reviewers (ES and LSB) independently screened full-text papers; Cohen's *kappa* was calculated as a measure of agreement.

Inclusion criteria

The review included peer-reviewed studies that focused on HnB use by humans and the products' health risks associated with use and secondhand exposure to HnB emissions.

Exclusion criteria

- Publication was not peer-reviewed or was a conference abstract.
- Published before 2010 or focus was a HnB device that is no longer available (eg, Premier, Eclipse, Accord).
- Focus was not a HnB device (ie, a device did not use tobacco to produce or flavour vapour).
- Publication was not in English, French, German, Lithuanian or Russian (languages known to authors).
- Animal or in vitro study (not directly related to human use).
- Publication presented the same data as earlier publication.
- Study assessed research methodology.

Data extraction and categorisation of included studies

The included studies were reviewed regardless of funding source. However, manufacturers that fund and report findings on their own products are inherently bound by conflict of interests. Throughout the review, funding sources of included studies were reported (table 1), and study outcomes were compared between independent and manufacturer-funded studies where the comparison was possible.

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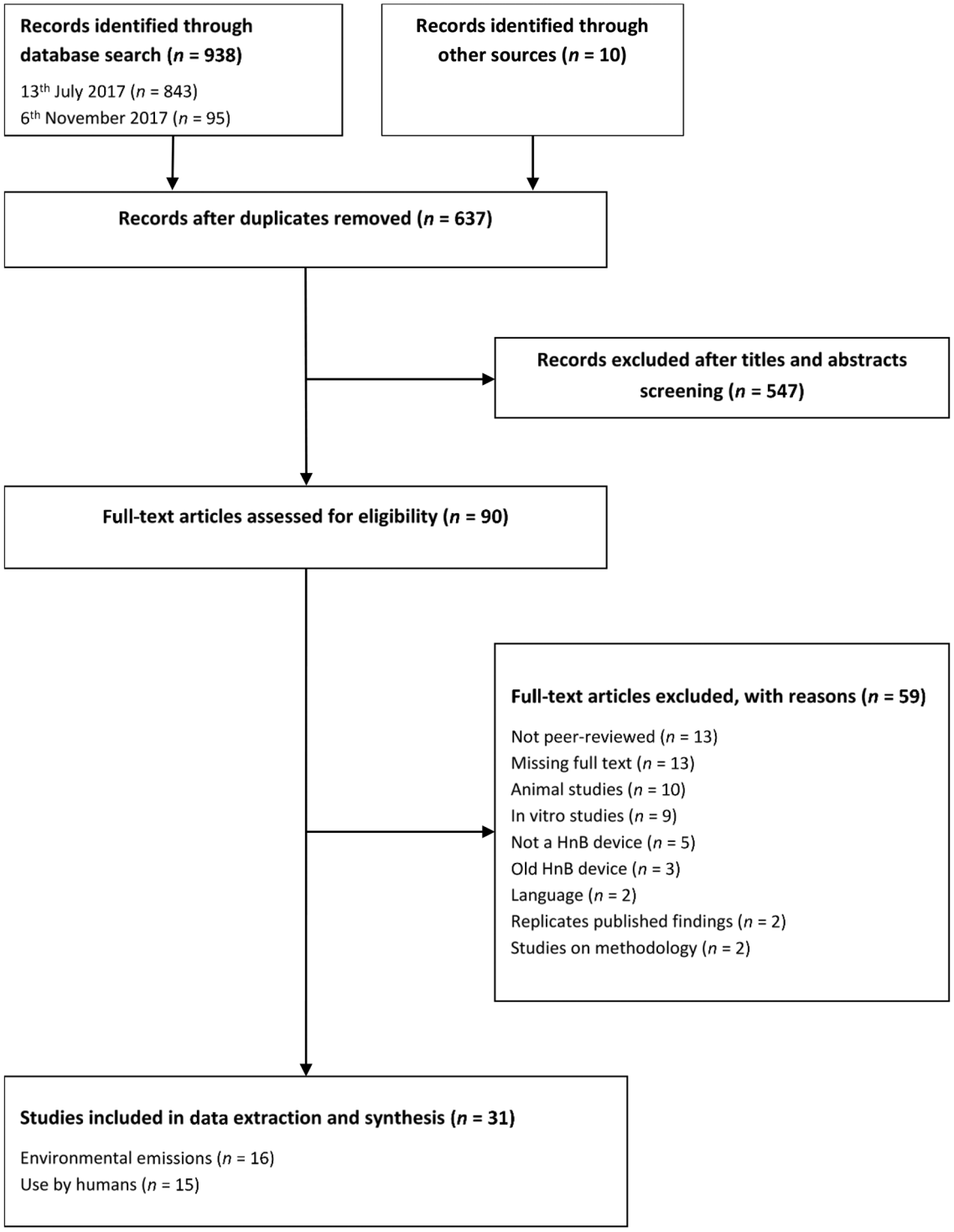


Figure 1 Systematic review PRISMA flow diagram.

Data on authors' affiliations, tested HnB products, methodology, HnB sidestream, mainstream and secondhand emissions and HnB use effects on humans were extracted to a predefined table by one reviewer (ES) and checked by a second reviewer (LSB).

Tobacco products' emissions are categorised into mainstream, sidestream and secondhand smoke. Mainstream smoke is the smoke that a user draws in,[13] and is measured in laboratory using standardised machine smoking regimens to replicate human smoking. Sidestream smoke is emitted from the lit end of a burning tobacco product[13] and is measured in standardised indoor and outdoor environments by recruiting smokers or using machine smoking to test the products. Secondhand smoke is the combination of exhaled mainstream and sidestream smoke.[13] The same categorisation is used throughout the paper for emissions from e-cigarettes and HnB products. Studies were categorised to:

i. Nicotine delivery and mainstream, sidestream and secondhand emissions of HnB products.
ii. HnB use by humans (experimental, epidemiological and case studies).

Assessment of risk of bias

Quality of experimental studies on HnB use by humans was assessed independently by two authors (ES and LSB) using the Effective Public Health Practice Project tool.[14] The tool evaluates

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Table 2 HnB products assessed in the included studies

HnB product and manufacturer	Release date, place	Description	Studies
Pax by Ploom (now PAX Labs)	2012, USA	Loose-leaf tobacco and cannabis vaporiser. Loose tobacco is placed into a chamber and heated by an electrically powered element.[40] A predecessor of Ploom Tech by JTI.	40
IQOS/THS 2.2 by PMI	2014, Japan, Italy and Switzerland	IQOS includes a holder, a charger and tobacco sticks (Heets). A tobacco stick (about 320 mg) is inserted into the holder and the tobacco is heated with an electronically controlled heating blade which is inserted into tobacco plug. Operating heating temperature<350°C. A single use lasts 6 min or up to 14 puffs.[61] Under ISO conditions, 12 puffs of the THS 2.2 yield 0.5 mg nicotine and 4.9 mg glycerol.[44]	5 21–27 29 31–35 39 41–45 48 49
iFuse by BAT	2015, Romania	iFuse includes an electronic vapour device with a rechargeable Li-ion battery and an integrated circuit power controller, onto which a cartomiser (Neopod) is attached. The disposable neopod comprises an atomiser, a liquid tank with 1.15 mL of non-flavoured nicotine liquid and a chamber containing a 130 mg tobacco plug. When the user presses a button, nicotine-containing vapour is produced, which is then drawn through the tobacco plug to absorb flavours. Before reaching the tobacco plug, the aerosol reaches an average maximum of <35°C.[30]	30
Glo/THP 1.0 by BAT	2016, Japan	Glo includes an electronic device with a rechargeable Li-ion battery and a heating chamber and tobacco sticks. A tobacco stick (about 260 mg) is heated in the heating chamber from the periphery. Operating heating temperature <250°C. Reaches operating temperature after 30–40 s and a single use lasts for another 3 min.[28]	5 28 29 36 41 51
Ploom Tech/PNTV by JTI	2016, Japan	PNTV includes a power supply unit, a cartridge with a heater and liquid and a capsule with tobacco blend. Generates a nicotine-free vapour by heating the unflavoured liquid; the vapour then passes through the tobacco capsule to absorb flavours and nicotine. Under HCI conditions, 50 puffs yield 1.10 mg nicotine.[52]	5 41 42 52
Carbon-heated tobacco product (CHTP) by PMI	Not released	A specifically designed electric lighter lights the carbon heating source which then heats a tobacco plug. Under ISO conditions, 12 puffs of the CHTP yield 0.4 mg nicotine and 2 mg glycerol, 3 mg tar and 1 mg CO.[47] A predecessor of TEEPS by PMI.	47
IQOS/THS 2.1 by PMI	Not released	THS 2.1 includes a holder, a charger and tobacco sticks. A tobacco stick is inserted into the holder and the tobacco is heated with an electronically controlled heating blade. Operating heating temperature<400°C. A single use lasts 6 min or up to 14 puffs. Under ISO conditions, 12 puffs of the THS 2.1 yield 0.3 mg nicotine and 5 mg glycerol.[46] A predecessor of commercially available IQOS/THS 2.2.	46 50

BAT, British American Tobacco; HnB, heat-not-burn tobacco product; ISO, International Organisation for Standardisation; PMI, Philip Morris International; PNTV, Prototype novel tobacco vapour product; JTI, Japan Tobacco International; LLTV, loose-leave tobacco vaporiser; PMI, Philip Morris International; THP, tobacco heating product; THS , tobacco heating system.

quality of quantitative studies by rating study selection bias, design, confounders, blinding, data collection method and withdrawals and dropouts as weak, moderate or strong. A study is considered of strong quality if no aspect has been rated weak, moderate if one aspect has been rated weak and weak if two or more aspects have been rated weak.[14]

Data synthesis

Findings were summarised in a narrative synthesis and quantitative results compared between studies where possible.

Studies on HnB emissions used either the International Organisation for Standardisation machine smoking regimen (ISO; 35 mL puff volume, 2 s puff duration, 30 s intervals between puffs, 14 puffs) or the Health Canada Intense regimen (HCI; 55 mL puff volume, 2 s puff duration, 30 s intervals between puffs, 14 puffs). The HCI regimen yields higher levels of harmful and potentially harmful compounds (HPHC),[15] but no machine smoking regimen corresponds to human smoking and exposure,[16 17] and their relevance to HnB use is not tested either. Reference products also differed between studies: the majority used 3R4F tobacco cigarettes (a reference product developed for research[18]), others used commercially available cigarettes (nicotine and CO yields provided where known) and e-cigarettes (cigalike, pen-style and tank-style).

Levels of nicotine and HPHC[19] delivered per single HnB use to aerosol were calculated and presented as percentage of the levels in smoke from a single reference cigarette. Where data on HnB emissions were provided per puff, a single HnB use was calculated as 14 puffs with reference to ISO and HCI regimens. If independent and manufacturer-funded studies used the same puffing regimen and HnB device, nicotine and HPHC levels were compared post hoc using independent samples t-test. For studies on pharmacokinetic nicotine delivery of HnB, key pharmacokinetic characteristics were compared between HnB products where possible.

Studies on HnB use by humans were grouped by the HnB product (table 1), and findings on levels of exposure to biomarkers of HPHC (see table S1 in Supplementary file 1), nicotine delivery characteristics, human puffing topography, effect on urges to smoke and subjective satisfaction with the products were reported and compared between studies if possible.

Randomised controlled trials (RCT) used a confinement procedure: after randomisation, participants stayed at a trial site for 5 days and were restricted to only using cigarettes or HnB products, or abstained from smoking.

RESULTS

Included studies

Out of 948 initially identified records, 31 publications were included (figure 1, table 1). Reviewers' agreement on study inclusion was excellent (k=0.75[20]). Sixteen included studies were on HnB emissions; 15 on human use of HnB products (n=21 965): of these, 11 were RCT and cross-over studies (n=1028), 3 were

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Table 3 Relative nicotine delivery in mainstream HnB or e-cigarette aerosol in comparison to nicotine delivered to mainstream cigarette smoke

	Auer *et al*[21] 2017*	Farsalinos *et al*[22] 2018†	Bekki *et al*[23] 2017	Schaller *et al*[24] 2016	Schaller *et al*[25] 2016	Jaccard *et al*[26] 2017	Forster *et al*[36] 2018	Poynton *et al*[30] 2017‡
Affiliation	University of Bern, Switzerland	University of Patras, Greece	National Institute of Public Health, Japan	PMI	PMI	PMI	BAT	BAT
Reference cigarette used	Lucky Strike Blue Lights	Marlboro Regular	3R4F	3R4F	3R4F	3R4F	3R4F	3R4F
Product	Nicotine levels, % (mg)							
Reference cigarette (set as 100%)	0.361	1.99	1.70	1.89	1.88	1.86	2.02	1.84
IQOS	83% (0.30)	71% (1.41)	65% (1.10)	70% (1.32)	73% (1.38)	61% (1.14)	57% (1.16)	–
Glo	–	–	–	–	–	–	23% (0.462)	–
iFuse	–	–	–	–	–	–	–	19% (2.56/0.358)
Cigalike e-cigarette	–	43% (0.86)	–	–	–	–	–	–
Second-generation pen-style e-cigarette	–	87% (1.73)	–	–	–	–	–	27% (3.57/0.500)
Third-generation tank-style e-cigarette	–	92% (1.84)	–	–	–	–	–	–

*Provided nicotine values under ISO machine puffing regimen.
† Nicotine levels for HnB and e-cigarettes provided under 4 s puffing regimen.
‡ Nicotine levels were provided for 100 puff blocks under 3 s puffing regimen; nicotine level for 14 puffs was calculated by multiplying the nicotine level for 100 puffs by 0.14.
–, Not measured; BAT, British American Tobacco; PMI, Philip Morris International.

epidemiological studies (n=20 936) and 1 a case report (n=1). Studies reviewed seven HnB tobacco products (table 2).

Studies on HnB nicotine levels and emissions

The included studies[21–36] compared HnB emissions with smoke from factory-made[21–34 36] or hand-rolled[31 32] cigarettes, emissions of e-cigarettes[22 30–33 35] and nicotine inhalator[35] (table 1). Six independent (not affiliated with manufacturers) studies[21–23 31–33] were conducted in Switzerland,[21] Greece,[22] Italy[31–33] and Japan.[23] Ten studies funded by manufacturers of tobacco products were conducted in Switzerland[24–27 34] and the UK.[28–30 35 36]

Nicotine levels in HnB tobacco sticks

Two independent studies[22 23] reported the amount of nicotine per gram of tobacco in a regular IQOS tobacco stick (15.2±1.1 and 15.7±0.2 mg/g) and in a menthol tobacco stick (15.6±1.7 and 17.1±0.6 mg/g), respectively.

Nicotine levels in mainstream HnB emissions

Three independent[21–23] and five manufacturer-funded studies[24–26 30 36] reported on nicotine levels in mainstream HnB aerosol (table 3). One independent study[21] used the ISO machine smoking regimen and seven used the HCI regimen.

Under the ISO regimen, the regular IQOS tobacco stick on average yielded 0.30 mg of nicotine,[21] while under the HCI regimen[22–26 29 30] nicotine levels in mainstream aerosol were 1.10–1.41 mg for IQOS, 0.46 mg for glo,[29] and 2.56 mg per 100 puffs or 0.36 mg per single use/14 puffs for iFuse[30] (table 3).

Compared with nicotine in smoke of reference cigarettes, nicotine in mainstream IQOS aerosol ranged from 57% to 83% across studies (table 3). One independent study[22] reported that IQOS delivered more nicotine than a cigalike e-cigarette but less than a pen-style or a tank-style e-cigarette (table 3). A study from glo manufacturers[36] reported that glo delivered 40% of nicotine compared with IQOS and 23% compared with reference cigarette, and a study from the manufacturer of iFuse[30] reported that iFuse per 14 puffs delivered less nicotine than a pen-style e-cigarette (72%) and a reference cigarette (19%) (table 3).

Levels of nicotine in mainstream IQOS aerosol did not differ between independent[22 23] and manufacturer-funded studies[24–26] that used the HCI machine puffing regimen (1.30 vs 1.28 mg of nicotine per tobacco stick, t(17) = 0.34, p=0.74).

One independent study compared nicotine transfer rates (in this case defined as the ratio of nicotine in mainstream emissions to nicotine in a tobacco stick or a cigarette): nicotine transfer rates were higher for IQOS regular (23.4%) and menthol (23.5%) tobacco sticks than for the 3R4F reference cigarette (11.3%).[23]

HPHC in mainstream HnB emissions

Two independent[21 23] and six manufacturer-funded studies[24–26 28–30] reported levels of HPHC in mainstream HnB aerosol compared with cigarette smoke (table 4).

One independent study[21] used data of 50 US cigarette brands[15] to compare levels of polycyclic aromatic hydrocarbons but, as a critique by PMI noted,[37] the authors had inadvertently used reference values obtained under HCI instead of ISO regimen. We provide both the originally published and recalculated ratios (table 4).

The study assessing iFuse[30] calculated HPHC yield per 100 3 s puffs on iFuse but followed an HCI regimen for the reference cigarette, creating discrepancies in comparison with other studies (table 4).

Compared with cigarettes, under HCI regimen machine-derived mainstream HnB emissions contained lower levels of nicotine (18%–73% of those in cigarette smoke), CO (reduction ≥98%), HPHC (reduction ≥62%) and tar (reduction ≥21%) (table 4).

One independent[23] and three manufacturer-funded studies[24–26] used the HCI machine-puffing regimen and reported findings

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Table 4 Relative levels of HPHC in mainstream HnB aerosol compared with reference cigarette

	Schaller *et al*[25] 2016	Schaller *et al*[24] 2016		Jaccard *et al*[26] 2017	Auer *et al*[21] 2017	Bekki *et al*[23] 2017		Eaton *et al*[28] 2018	Forster *et al*[36] 2018			Poynton *et al*[30] 2017
Affiliation	**PMI**	**PMI**		**PMI**	**University of Bern, Switzerland**	**National Institute of Public Health, Japan**		**BAT**	**BAT**			**BAT**
Tobacco stick	R. IQOS	R. IQOS	M. IQOS	R. IQOS	R. IQOS	R. IQOS	M. IQOS	R. glo	R. IQOS	R. glo	M. glo	R. iFuse
Reference cigarette	3R4F	3R4F	3R4F	3R4F	Lucky Strike Blue	3R4F	3R4F	3R4F	3R4F	3R4F	3R4F	3R4F
Puffing regimen	HCI	HCI	HCI	HCI	ISO	HCI	HCI	HCI	HCI	HCI	HCI	HCI*
1,3-Butadiene	<1%	<1%	<1%	<1%	–	–	–	<1%	<1%	<1%	<1%	<1%
1-Aminonaphthalene	<1%	<1%	<1%	<1%	–	–	–	–	<1%	<1%	<1%	<1%
2-Aminonaphthalene	<1%	<1%	<1%	<1%	–	–	–	–	<1%	<1%	<1%	3%
4-Aminobiphenyl	<1%	<2%	<2%	<1%	–	–	–	–	<1%	<1%	<1%	3%
Acetaldehyde	12%	14%	13%	13%	22%	–	–	5%	15%	5%	5%	<1%
Acrolein	7%	7%	6%	6%	82%	–	–	1%	6%	1%	2%	5%
Acrylonitrile	1%	<1%	<1%	<1%	–	–	–	–	<1%	<1%	<1%	<1%
Ammonia	38%	36%	35%	36%	–	–	–	–	33%	12%	15%	<50%
Benzene	<1%	<1%	<1%	<1%	–	–	–	<1%	<1%	<1%	<1%	<1%
Benzo[a]pyrene	7%	9%	8%	6%	4%†/8%‡	–	–	<3%	5%	2%	3%	<7%
Carbon monoxide	1%	2%	2%	1%	–	1%	1%	<1%	1%	<1%	<1%	21%
Crotonaldehyde	<6%	6%	5%	<6%	4%	–	–		5%	1%	2%	<3%
Formaldehyde	11%	10%	8%	9%	74%	–	–	6%	11%	6%	7%	13%
Isoprene	<1%	<1%	<1%	<1%	–	–	–	–	<1%	<1%	<1%	<1%
NNN	5%	6%	4%	4%	–	6%	8%	9%	4%	9%	7%	<1%
NNK	3%	3%	2%	3%	–	5%	5%	2%	4%	2%	2%	<1%
Toluene	2%	1%	1%	1%	–	–	–	–	1%	<1%	<1%	2%
Nicotine	73%	70%	64%	61%	84%	65%	71%	–	57%	23%	18%	139%
Water	203%	231%	188%	–	–	328%	350%	–	168%	80%	71%	–
Glycerol	203%	191%	163%	–	–	–	–	–	182%	129%	101%	–
Total particulate matter	122%	98%	89%	–	–	119%	135%	–	104%	56%	54%	–
Tar/nicotine-free dry particulate matter	79%	33%	40%	–	–	39%	53%	–	75%	46%	48%	–

*Puffing duration increased to 3 s, levels of HPHC for HnB product measured for 100 puffs.
†Originally reported proportions of HnB relative to polycyclic aromatic hydrocarbons in mainstream smoke of 50 commercial US cigarettes.
‡Proportions recalculated using mean values of polycyclic aromatic hydrocarbons in mainstream smoke of 50 commercial US cigarettes measured by ISO smoking regimen.[15]
BAT, British American Tobacco; HnB, heat-not-burn tobacco product; HPHC, harmful and potentially harmful compounds; ISO, International Organisation for Standardisation; M, menthol; NNK, nicotine-derived nitrosamine ketone; NNN, N-nitrosonornicotine; PMI, Philip Morris International; R, regular; –, not measured.

on the same HPHC in mainstream IQOS emissions. Levels of CO ($t(11)=1.28$, $p=0.23$), water ($t(8)=0.43$, $p=0.68$) and total particulate matter ($t(8)=1.77$, $p=0.11$) did not differ statistically significantly between independent and manufacturer-funded studies. Compared with manufacturer-funded studies, the independent study reported less tar (9.8 vs 15.0 mg, $t(8)=4.8$, $p=0.001$) and more tobacco-specific nitrosamines (19.2 vs 14.2 ng of N-nitrosonornicotine (NNN), $t(11)=7.7$, $p<0.001$; 12.3 vs 6.8 ng of nicotine-derived nitrosamine ketone (NNK), $t(11)=11.8$, $p<0.001$; 4.5 vs 3.0 ng of N-nitrosoanabasine (NAB), $t(4)=5.1$, $p=0.007$; 34.0 vs 19.2 ng of N-nitrosoanatabine (NAT), $t(8)=13.2$, $p<0.001$) in mainstream IQOS aerosol from a single tobacco stick.

Particulate matter and HPHC in sidestream and secondhand HnB emissions

Seven studies, three independent[31–33] and four funded by tobacco manufacturers,[27 34–36] compared HnB sidestream or secondhand emissions with smoke of factory-made[27 31–34 36] or hand-rolled[31 32] cigarettes, pipes and cigars,[32] aerosol from a nicotine inhalator[35] or e-cigarettes.[31–33 35]

A single study[35] funded by Imperial Tobacco company that does not manufacture HnB products[38] explicitly focused on sidestream emissions of a competitor's HnB product (IQOS). The study concluded that in contrast to a cigalike e-cigarette and a nicotine inhalator, IQOS produced sidestream emissions. Similarly, an independent study[32] concluded that higher particulate matter emissions from IQOS than from a pen-style e-cigarette could be explained by sidestream emissions.

Six studies, three independent[31–33] and three manufacturer-funded,[27 34 36] reported on particulate matter in HnB secondhand emissions. One study[31] reported that a pen-style e-cigarette and IQOS emitted 25% of the total particulate matter detected in smoke from a cigarette. Use of the e-cigarette produced higher peak concentration of particles in the air than use of IQOS, but the total amount and time for particles to disperse after use were longer for IQOS and composition of particles was not considered.[32] Most particles emitted by IQOS were <1000 nm,[33] and particles emitted by glo were in the same size range (150–250 nm diameter) as particles in cigarette smoke[36] (table 5). Compared with reference

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Table 5 Relative levels of HPHC and particulate matter in secondhand emissions from HnB products (ratio HnB:reference cigarette)

	Ruprecht *et al*[33] 2017	Mitova *et al*[34] 2016	Forster *et al*[36] 2018b
Affiliation	National Cancer Institute, Milan, Italy	PMI	BAT
HnB	IQOS	IQOS	Glo
Reference cigarette	Conventional cigarette	Marlboro Gold	Lucky Strike Regular
Setting	'A sitting room' (ACH=1.5)	'Residential' (ACH=1.2)	'Home' (ACH=1.2)
Secondhand emissions' markers			
370 nm UV BC (µg/m^3)	0.7%–0.8%	–	–
PM>0.3 (particles/cm^3)	2.8%–7.3%	–	–
PM$_{nm}$ (particles/cm^3)	22.0%–24.0%	–	–
PM 1 (µg/m^3)	0.9%–1.0%	–	HnB < background
PM 2.5 (µg/m^3)	1.3%–1.5%	Non-detectable	HnB < background
PM 10 (µg/m^3)	1.5%–1.7%	–	HnB < background
Ultraviolet particulate matter	–	Non-detectable	–
Fluorescent particulate matter	–	Non-detectable	–
Solanesol	–	Non-detectable	–
3-Ethenylpyridine	–	Non-detectable	Non-detectable
HPHC			
1,3-Butadiene	–	Non-detectable	Non-detectable
Acetaldehyde (µg/m^3)	5.0%–5.9%	6.0%	2.2%
Acrolein (µg/m^3)	1.8%–2.3%	Non-detectable	Non-detectable
Acrylonitrile	–	Non-detectable	Non-detectable
Benzene	–	1.7%	HnB = background
Carbon monoxide	–	3.8%	Non-detectable
Crotonaldehyde	–	Non-detectable	Non-detectable
Formaldehyde (µg/m^3)	6.9%–7.1%	7.6%	10.2%
Isoprene	–	HnB < background	HnB < background
Toluene	–	HnB < background	3.7%
Nicotine	–	6.2%	HnB < background
Nitrogen oxides	–	HnB < background	HnB < background
Nitrogen oxide	–	HnB < background	HnB < background

ACH, air changes per hour (ventilation rate of an indoor space defined as air volume added/removed from the space in 1 hour divided by the space volume); BAT, British American Tobacco; HnB, heat-not-burn tobacco product; HPHC, harmful and potentially harmful compounds; –, not measured; PM > 0.3, particulate matter larger than 0.3 µm; PM $_{nm}$, particulate matter in size range of 10–1000 nm; PMI, Philip Morris International; UV BC, ultraviolet black carbon.

cigarettes, particle mass in emissions from an e-cigarette and IQOS were <2%[33] and from glo was <1%.[36] Two studies by the manufacturer of IQOS[27 34] did not detect particulate matter in IQOS mainstream and secondhand emissions which was at odds with findings from independent studies.[27 34]

Three studies, one independent[33] and two manufacturer-funded,[34 36] also reported on HPHC in secondhand emissions (table 5). All studies detected HPHC in air after HnB use; HPHC levels in HnB secondhand emissions were lower than in cigarette smoke, but reported content of the emissions varied (table 5). Methods of the independent and manufacturer-funded studies were heterogeneous to make direct comparisons. However, the independent study[33] detected particulate matter and acrolein in IQOS secondhand emissions when the manufacturer-funded study[34] did not detect these.

Studies on HnB use by human participants

The 15 studies on HnB use by humans (5 independent[5 39–42] and 10 manufacturer-funded[43–52] (table 1) included 5 RCTs (one published in two parts),[44–49] 5 cross-over studies[38 39 47 48 50], 1 case report[39] and 3 epidemiological studies.[5 41 42]

Loose-leaf tobacco vaporiser (Pax)

An independent study[40] compared Pax, a cigarette and a pen-style e-cigarette on nicotine delivery to blood plasma, expired air CO, suppression of nicotine abstinence symptoms and satisfaction. Based on the research quality rating tool, the study was rated weak (see table S3 in Supplementary file 1). Plasma nicotine levels were 24.4 ng/mL after cigarette use, 14.3 ng/mL after use of Pax and 9.5 ng/mL after use of the e-cigarette. Expired air CO increased up to 16.9 parts per million (ppm) after smoking a cigarette but decreased after HnB and e-cigarette use to 4.5 ppm. Nicotine abstinence symptoms were most effectively suppressed after smoking a cigarette, use of Pax was less effective and e-cigarette use was least effective; no differences were observed between conditions. Study participants found the HnB and the e-cigarette significantly less satisfying than cigarettes.[40]

Carbon-heated tobacco product

One manufacturer-funded 5-day confinement RCT of moderate quality[47] compared levels of exposure with HPHC between smokers who were randomised to using carbon-heated tobacco product (CHTP) only, continued smoking or abstinence (see table S3 in Supplementary file 1; table 6).

Compared with participants who continued smoking, on day 5, CHTP users demonstrated less exposure to HPHC, took more frequent and longer puffs that were of higher average and total volume. Differences in CHTP and cigarette use frequency (19.7 vs 18.8 on day 5, respectively, p=0.57), total nicotine equivalents (19.1 vs 17.2 ng/mL) and plasma cotinine for the past 24 hours (319.8 vs 289.8 mg) were not statistically significant.

Tobacco heating system 2.1

Two manufacturer-funded studies of moderate[46] and weak quality[50] assessed tobacco heating system 2.1 (THS 2.1) (table 6, table S3 in Supplementary file 1).

Nicotine delivery

One manufacturer-funded study[50] compared the nicotine delivery of THS 2.1 use and cigarette smoking (table S2 in Supplementary file 1); after single use, they were similar in how fast plasma nicotine levels peaked (8 min median for both), reducing urges to smoke based on Questionnaire of Smoking Urges scores (THS 2.1 reduced by 19.4±22.4, cigarette by 19.5±23.1) and in the nicotine half-life length (2.6 vs 2.5 hours). Compared with cigarettes, THS 2.1 delivered lower peak levels of nicotine after single (8.4 vs 11.9 ng/mL) and ad libitum use (14.9 vs 24 ng/mL).

THS 2.1 users also consumed fewer tobacco sticks per day than smokers smoked cigarettes (10.9 vs 16.7, p<0.001) and perceived THS 2.1 less satisfying than cigarettes: rated it lower on four out of five modified cigarette evaluation scores (mCEQ)[53] subscales (smoking satisfaction, psychological rewards, enjoyment of respiratory tract sensation and craving reduction).

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Table 6 Product use and ratio of levels of exposure to HPHC in HnB users compared with cigarette smokers on the fifth day of confinement

	Lüdicke *et al*[47] 2016	Lüdicke *et al*[46] 2017	Haziza *et al*[44] 2016	Haziza *et al*[45] 2016	Lüdicke *et al*[48 49] 2018
Affiliation	PMI	PMI	PMI	PMI	PMI
HnB product	CHTP	THS 2.1	Regular IQOS	Regular IQOS	Menthol IQOS
Reference product	Regular cigarette	Regular cigarette	Regular cigarette	Regular cigarette	Menthol cigarette
Mean (SD) HnB vs cigarettes use on day 5	19.7 (7.8) vs 18.8 (4.4)	27.2 (9.1) vs 20.1 (3.2)	9.9 (3.9) vs 12.5 (3.5)	20.7 (8.1) vs 16.6 (3.8)	13.9 (4.3) vs 13.6 (4.7)
Exposure to HPHC % (95% CI) HnB:cigarettes ratio					
1,3-Butadiene	10%	12% (9% to 16%)	23% (18% to 29%)	8% (7% to 10%)	13%
1-Aminonaphthalene	–	–	4% (4% to 5%)	4% (3% to 5%)	6%
2-Aminonaphthalene	19%	11% (8% to 14%)	18% (15% to 21%)	12% (10% to 13%)	14%
4-Aminobiphenyl	16%	41% (31% to *53%)	18% (15% to 22%)	15% (13% to 17%)	21%
Acetaldehyde*	–	–	–	–	–
Acrolein	26%	28% (23% to 33%)	53% (46% to 61%)	42% (38% to 46%)	52%
Acrylonitrile	–	15% (12% to 18%)	21% (18% to 25%)	13% (12% to 15%)	18%
Ammonia*	–	–	–	–	–
Benzene	16%	7% (5% to 10%)	16% (13% to 19%)	6% (5% to 7%)	11%
Benzo[a]pyrene	–	–	30% (25% to 36%)	28% (23% to 33%)	28%
Carbon monoxide	39%	23% (21% to 26%)	47% (44% to 50%)	24% (22% to 25%)	45%
Crotonaldehyde	–	–	38% (32% to 45%)	23% (20% to 25%)	43%
Formaldehyde*	–	–	–	–	–
Isoprene*	–	–	–	–	–
N-nitrosonornicotine		12% (9% to 16%)	30% (24% to 38%)	24% (18% to 33%)	29%
Nicotine-derived nitrosamine ketone	52%	33% (25% to 44%)	49% (42% to 57%)	44% (39% to 48%)	44%
Toluene*	–	–	–	–	–
Nicotine	–	85% (62% to 115%)	113% (91% to 140%)‡/89.6%§	113% (91% to 140%)	–
Nicotine equivalents	111%	87% (76% to 100%)	105% (92% to 120%)‡/98.6%§	105% (92% to 120%)	118%
Cotinine	110%	88% (75% to 103%)	96% (71% to 131%)	111% (91% to 136%)	–
Ethylene oxide	–	–	47% (40% to 55%)	32% (27% to 38%)	51%
Pyrene	57%	43% (36% to 51%)	46% (41% to 52%)	44% (40% to 49%)	38%
o-Toluidine	49%	58% (48% to 71%)	51% (42% to 60%)	42% (36% to 48%)	41%

*Exposure to acetaldehyde, ammonia, formaldehyde, isoprene and toluene was not measured due to absence of valid biomarkers.
†Originally reported proportions.
‡Proportions calculated based on raw study figures.
HnB, heat-not-burn tobacco product; HPHC, harmful and potentially harmful compounds; –, not measured; PMI , Philip Morris International.

Exposure to HPHC

A manufacturer-funded 5-day confinement RCT[46] compared exposure levels to HPHC in smokers who were randomised to using only THS 2.1 or continued smoking. Exposure to HPHC was lower in the THS 2.1 group (table 6).

The THS 2.1 group used up to 35% more tobacco sticks than the smoking group smoked cigarettes (27.2 and 20.1, respectively, p=0.002) and demonstrated compensatory puffing (increased puff frequency, duration and volume). On day 5, the THS 2.1 group achieved 85% of nicotine and 88% of cotinine levels of the smoking group. Satisfaction with THS 2.1 was again significantly lower on the same four mCEQ subscales.

Tobacco heating system 2.2 (IQOS)

Five studies funded by the manufacturer of IQOS (PMI)[43–45 48 49] assessed IQOS (table 1).

Nicotine delivery

A study[43] of weak quality (see table S3 in Supplementary file 1) compared nicotine delivery between regular IQOS and regular cigarettes, menthol IQOS and menthol cigarettes and IQOS tobacco sticks and 2 mg nicotine gum. Peak plasma concentrations for both IQOS tobacco sticks and cigarettes were reached in 6 min, actual exposure to nicotine was comparable (IQOS:cigarettes ratio was 96.3% for regular and 98.1% for menthol), as was nicotine half-life (93.1% and 102.3%). Peak nicotine concentration ratio for regular IQOS versus cigarettes was 103.5% and for menthol IQOS versus menthol cigarettes, 88.5%. Compared with nicotine gum, the results were less clear: regular IQOS outperformed menthol IQOS for exposure to nicotine (127.2% and 55.9%) and peak nicotine concentration (240.2% and 101.6%). Relative to the gum, nicotine half-life was 87.3% for regular and 92.1% for menthol IQOS tobacco sticks.

Exposure to HPHC

Two 5-day confinement RCTs[44 45] (one strong, one moderate quality; table S3 in Supplementary file 1) assessed exposure to HPHC in smokers randomised to using IQOS, continuing smoking or abstaining from smoking for study period (table 6).

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Two publications[48 49] (moderate quality, table S3 in Supplementary file 1) reported on the same 5-day confinement RCT followed by 85 days in an unconfined setting. Exposure to HPHC and change in health risk markers were compared between smokers randomised to using menthol IQOS, continuing smoking or abstaining from smoking for study period (table 6).

Across the three studies, exposure to biomarkers of HPHC in the IQOS groups was lower than for smoking groups and approached exposure levels observed in abstinent groups.

Daily product use differed across studies: on day 5 the IQOS group in one study[44] used 20% fewer tobacco sticks than the smokers' group smoked cigarettes (p<0.001); in another study,[45] they used 25% more tobacco sticks than the smoking group smoked cigarettes (p<0.001) and in the third study,[48] consumption did not differ between groups (p=0.63). During an unconfined study period, participants in the IQOS group demonstrated high compliance (89.7%), and dual use of cigarettes and IQOS was low (<0.1 cigarette on average in the IQOS group).[48]

Throughout all three studies, IQOS users increased their puffing frequency, duration and number of puffs. IQOS use suppressed urges to smoke similarly to smoking cigarettes but was consistently rated lower on sensory and psychological satisfaction than cigarettes: in two studies, IQOS scored lower on four out of five mCEQ subscales[45 48] and in one study IQOS scored lower on the smoking satisfaction subscale.[44]

Over the 85 days following the 5-day confinement period, participants randomised to IQOS use demonstrated reductions in risk markers[54] associated with endothelial dysfunction, oxidative stress, inflammation and high-density lipoprotein cholesterol counts compared with participants randomised to continued smoking.[49]

Tobacco heating product 1.0 (glo)

A manufacturer-funded randomised cross-over trial[51] (weak quality, table S3 in Supplementary file 1) compared puffing topography, mouth level exposure and daily consumption of glo among cigarette smokers and smokers who dually used IQOS but were naïve to glo. In comparison to cigarette smoking, glo and IQOS users demonstrated significantly higher mean puff volumes (66.7 and 63.5 mL, respectively vs 48.9 mL for a cigarette), shorter puffing intervals (7.4 s and 8.3 s vs 9.7 s), and used glo and IQOS less frequently than cigarettes (12.1 and 13.7 tobacco sticks, respectively vs 16.3 cigarettes). Users of glo and IQOS differed in mean puff volume and average daily consumption: new glo users demonstrated higher mean puff volume (60.9±24.8 vs 55.1±23.9 mL) and used fewer tobacco sticks than the IQOS users (11.2±6.2 vs 13.4±7.8).

Prototype novel tobacco vapour product (Ploom Tech)

A manufacturer-funded randomised cross-over trial[52] (weak quality, table S3 in Supplementary file 1) compared the pharmacokinetic profiles of Ploom (table S2 in Supplementary file 1) and a reference cigarette. They did not differ in the time to reach peak plasma nicotine concentration (median for both 3.8 min) or in nicotine half-life after single use (1.66 for Ploom vs 1.86 hour for a cigarette). However, Ploom delivered significantly lower peak plasma nicotine concentration (45.7% of cigarette) and total exposure to nicotine after single use (68.3%, p=0.002).

Epidemiological studies on HnB use

The literature search identified three independently funded surveys on awareness and use of HnB products: two from Japan[5 41] and one from the UK.[42]

The studies from Japan reported findings from a nationally representative sample of 8240 respondents aged 15–69 years first surveyed in 2015[41] and followed up in 2016 (follow-up rate 65.6%) and 2017 (52.2%).[5] The data suggest growth in IQOS use: in 2015 0.3% reported using IQOS in the last 30 days, in 2016 this rose to 0.6%, and in 2017 to 3.6%.[5] The use of other HnB products (not mutually exclusive) in 2017 was lower: 1.2% had used Ploom in the last 30 days (a rise from 0.3% in 2015) and 0.8% had used glo in the last 30 days (no data for previous years).[5] The same study reported that among 11.9% of the sample that had been exposed to HnB secondhand emissions, more than a third (37%) experienced at least one symptom (eg, sore throat, eye pain, feeling ill, etc) related to this exposure.

Data from a nationally representative sample of 12 696 adults on awareness and use of HnB products in Great Britain (GB) were collected in March–April 2017[42]; 9.3% of the adult GB population were aware of HnB and 1.7% had tried or were using the products. Among those who had ever tried HnB, 39% had tried it once or twice and 13% had been using it daily. It should be noted, however, that participants were asked about HnB products prior to answering about e-cigarettes, which could have led to overestimating awareness and use of HnB products.

Case report on HnB use

A single case report[39] of acute eosinophilic pneumonia (AEP) following the use of HnB was identified. The study summarised the case of a Japanese man aged 20 years who used 20 HnB tobacco sticks per day for 6 months and increased to using 40 tobacco sticks 2 weeks before hospitalisation. Based on the relationship between cigarette smoking and AEP, the authors presumed that in this case the rapid increase in the daily use of tobacco sticks caused the onset of AEP. The case report concludes that despite HnB users being exposed to lower levels of HPHC compared with cigarette smokers, they are still susceptible to health risks in general and to acute eosinophilic pneumonia in particular.

DISCUSSION

The systematic search identified 31 peer-reviewed studies on seven HnB products. Eleven independent studies focused on awareness and use and secondhand emissions of HnB products, while 20 manufacturer-funded studies explored nicotine delivery and mainstream emissions and conducted RCTs assessing exposure to HPHC in HnB users.

By late 2017, awareness and use of HnB products were rising in Japan while in GB HnB use was rare.

Five RCTs demonstrated that switching from smoking cigarettes to using HnB significantly reduces but does not eliminate exposure to HPHC. The evidence, however, was limited to one currently available HnB product and came from a single tobacco manufacturer.

Single use of HnB delivered nicotine as quickly as smoking a cigarette but with lower peak concentration and total exposure to nicotine. When used ad libitum, HnB delivered comparable levels of nicotine and weakened urges to smoke similarly to cigarettes, nevertheless, HnB users reported compensatory puffing and consistently rated HnB less rewarding and satisfying than cigarettes.

Studies on machine-generated mainstream HnB emissions generally reported higher proportional reductions in exposure to HPHC than were observed in the RCTs on HnB use by humans. This suggests that machine smoking does not reliably replicate

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human use; this has been demonstrated for cigarettes[16] and it is likely even less reliable for HnB products.

The tested HnB products were heterogeneous in the way they worked and in the levels of nicotine and HPHC they delivered to mainstream aerosol. Compared with cigarettes, aerosol of IQOS (heating tobacco up to 350°C) contained the highest proportional levels of nicotine and HPHC, followed by glo (250°C) and iFuse (35°C), which produced the least toxicants and delivered the lowest levels of nicotine of the three. Compared with e-cigarettes, IQOS delivered less nicotine than a tank-style but more than a cigalike e-cigarette.

Evidence on HnB secondhand emissions suggested that HnB exposes users and bystanders to substantially lower but measurable levels of particulate matter and HPHC.

Comparisons between findings of independent and manufacturer-funded studies were limited due to heterogeneity in methods measuring mainstream and sidestream emissions or lack of independent evidence on HnB use by humans. Where the comparisons were possible, sample sizes were low and assumptions for t-tests could not be verified. Independent and manufacturer-funded studies reported similar levels of nicotine, CO, water and total particulate matter in mainstream IQOS aerosol, but diverged when reporting on tar (an independent study reported less) and tobacco-specific nitrosamines (manufacturer-funded studies reported less). Inferences from these comparisons are limited, as only two independent studies provided data on a limited number of HPHC. Conclusions on secondhand emissions from HnB devices were at odds between independent and manufacturer-funded studies, with PMI-funded studies reporting no particulate matter in IQOS secondhand emissions.

Limitations of the present evidence

Out of 11 trials on HnB use by humans, only 1 was not affiliated with a tobacco manufacturer[40]; the lack of independent evidence that could validate manufacturer data remains a major limitation.

Other limitations include that none of the trials on HnB use by humans registered a protocol before the enrolment of the first participant as recommended by the International Committee of Medical Journal Editors.[55] Other concerns that were raised in relation to studies funded by the manufacturer of IQOS pertained to the quality of their trials,[56] possible tobacco industry ties of the journal that published most studies on IQOS characteristics[57 58] and non-reporting levels of all 93 HPHC and other potentially harmful constituents in mainstream and sidestream emissions.[59]

Some manufacturer-funded publications appeared to overstate conclusions. For instance, studies concluded that IQOS was comparable in satisfaction to smoking[44 48] when it was repeatedly rated lower on four out of five mCEQ subscales.[53] Studies that reported similar findings on HnB secondhand emissions differed in their conclusions: manufacturer-funded studies concluded that HnB use impact on indoor air quality was negligible[34] or that HnB emissions were less harmful than cigarette smoke,[36] while an independent study concluded that despite lower emissions, HnB still pose evident risks through secondhand emissions.[33] Only one trial assessed health effects of long-term HnB (IQOS) use relative to abstinence and continued smoking.[49] However, the validity of the study follow-up results and conclusions are reduced by a lack of validation of self-reported abstinence and adherence to study condition.

Limitations of the systematic review

The review included data from manufacturer-funded studies but excluded reports or papers that were not peer-reviewed. As HnB manufacturers not always publish in peer-reviewed journals, this might have limited scope of our study. Nevertheless, this review provides the first comprehensive summary of up-to-date evidence on HnB tobacco products.

Future research

Machine smoking regimens were tailored for testing and comparing emissions from different tobacco cigarettes, and the validity of this method to measure emissions from HnB products is unclear. Future research should clarify whether the existing regimens reliably estimate HnB emissions or need adjusting. Until then, to promote reproducibility and comparisons between studies, research on HnB emissions would benefit from employing standardised protocols: by using the same machine smoking regimen (eg, HCI or other, adjusted for HnB), same reference products (eg, 3R4F tobacco cigarette) and screen for the same list of HPHC.

Current evidence on HnB sidestream emissions comes from a single manufacturer-funded study that is subject to conflict of interests; independent research could disentangle the preliminary disagreement.

Although research on mainstream and sidestream HnB emissions provides valuable preliminary data on HnB characteristics, it is unclear how well these findings represent the actual health risks of HnB use. The discrepancies in exposure to HPHC between machine puffing and human use studies suggest that findings on HnB mainstream emissions underestimate the actual exposure to toxicants. Instead of measuring HPHC levels in mainstream HnB emissions, independent research should prioritise validating manufacturers' findings on exposure to toxicants in HnB use by humans and comparing actual long-term health effects of HnB use with health outcomes of smoking, vaping or using nicotine replacement therapy.

Recently, HnB tobacco products have been introduced to multiple tobacco markets around the world, but only three independent studies from Japan and GB reported on awareness and use. There is a need for future surveillance on the uptake of HnB products and comparisons between countries with different regulatory frameworks for tobacco and nicotine products.

As more HnB products appear on the market, more manufacturer-funded studies are expected. This challenges independent researchers to critically evaluate and validate industry findings.[11] All researchers, whether affiliated with tobacco manufacturers or not, should aim for professional and transparent ways to preregister, conduct and report their findings.[60]

CONCLUSION

Peer-reviewed evidence on heated tobacco products indicates that HnB are effective nicotine delivery devices that expose users and bystanders to substantially fewer harmful and potentially harmful compounds than smoking cigarettes. The evidence is primarily drawn from tobacco industry data and lacks research on long-term HnB use effects on health. The HnB harm profile needs to be confirmed by independent research and compared with other alternative nicotine products that have reduced health risk exposure profiles.

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Contributors LSB conceived of the study idea, ES and LSB designed and implemented the searches and rated the quality of the included studies. ES extracted

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and synthesised the data and wrote the first and final version of the manuscript. All authors revised the manuscript and have approved its final version.

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Competing interests ES is a NIHR Maudsley Biomedical Research Centre PhD student in the Nicotine Research Group at the Institute of Psychiatry, Psychology & Neuroscience (IoPPN), King's College London. He has no links with any tobacco or e-cigarette manufacturers. AMcN is a Professor of Tobacco Addiction and leads the Nicotine Research Group at the IoPPN, King's College London. She is a Deputy Director of the UKCTAS. She receives funding for projects from a variety of funders such as CRUK and the National Institute for Health Research (NIHR) and has no links with any tobacco or e-cigarette manufacturers. LS is Senior Lecturer (Associate Professor) in Health Psychology at the Department of Behavioural Science and Health, University College London. He has received grants, personal fees and non-financial support (ie, research grants, consultancy, travel and hospitality) from Pfizer, Johnson & Johnson, the National Centre for Smoking Cessation and Training and Atlantis Health Care outside the submitted work. He has no links with any tobacco or e-cigarette manufacturers. LSB is a Senior Lecturer in the Nicotine Research Group at the IoPPN, King's College London and a member of the UKCTAS. She is a CRUK/BUPA Foundation Cancer Prevention Fellow. She has no links with any tobacco or e-cigarette manufacturers.

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Heat-not-burn tobacco products: concerns from the Italian experience

INTRODUCTION

Heat-not-burn (HNB) tobacco products are disposable tobacco sticks heated, rather than combusted, by an electronic device to generate an aerosol containing nicotine.[1] IQOS is the brand name of such a product by Philip Morris International, launched in 2014 in Italy as a pilot country for the European market. IQOS is now in commerce in 30 countries, including 19 European ones, and applications have been submitted to market it as a modified risk tobacco product in the USA.

Most safety data on this new tobacco product come from research conducted by the tobacco industry.[2] The few independent toxicological studies confirm that HNBs release harmful and potentially harmful substances, although at reduced levels as compared with conventional cigarettes.[1 3 4] To our knowledge, the only available studies on the use of HNBs are two repeated online surveys on Japanese adult population, showing a prevalence of IQOS users of 0.3% in 2015, 0.9% in 2016 and 3.6% in 2017.[5 6] We investigated HNB awareness and use in Italy, where IQOS is the only available HNB.

METHODS

In 2017, we conducted a face-to-face survey of 3086 subjects selected through multistage sampling to be representative of the general Italian population aged ≥15 years (52.4 million inhabitants).[7] Besides information on general sociodemographics, smoking and e-cigarette use, participants were asked about their awareness and use of IQOS.

RESULTS

One in five (19.5%) respondents were aware of IQOS, 1.4% have tried it and 2.3% intended to try it (table 1). Overall, 1.0% of never smokers, 0.8% of ex-smokers and 3.1% of current cigarette smokers have tried IQOS. Correspondingly, 1.2% of never e-cigarette users, 2.9% of ex-e-cigarette users and 7.7% of current e-cigarette users have tried IQOS.

DISCUSSION

Almost 3 years after having been launched, use of IQOS is still limited in the Italian population. However, our data indicate that 739 000 Italians have already tried IQOS, including 329 000 never smokers.

Table 1 Awareness and use* of IQOS, overall and according to selected characteristics. Italy, 2017

				Awareness of IQOS (%)†		
	N	Never heard about IQOS (%)†	Heard about IQOS, but don't know what it is (%)†	Never tried, without intention to try	Never tried, with intention to try	Already tried
Total	3086	69.9	10.6	15.8	2.3	1.4
Sex						
Men	1484	67.5	9.8	18.8	2.8	1.2
Women	1602	72.0	11.5	13.1	1.8	1.6
Age group (years)						
15–24	350	73.8	9.3	14.1	1.9	0.9
25–44	940	64.7	11.7	19.8	2.9	1.0
45–64	1018	65.0	12.3	17.8	2.5	2.4
≥65	778	80.6	7.8	9.2	1.5	1.0
Level of education‡						
Low	1098	76.7	9.0	11.5	1.8	1.0
Intermediate	1496	66.4	11.7	17.2	3.0	1.6
High	492	64.9	11.1	21.1	1.1	1.8
Geographical area						
Northern Italy	1426	68.3	10.3	17.0	2.7	1.8
Central Italy	623	71.2	11.4	14.2	2.3	0.9
Southern Italy and islands	1037	71.2	10.7	15.2	1.8	1.2
Cigarette smoking status§						
Never smoker	2009	70.9	11.6	14.8	1.7	1.0
Current smoker	688	63.4	10.2	18.3	5.0	3.1
Ex-smoker	389	75.9	6.4	16.4	0.5	0.8
E-cigarette use¶						
Never user	2924	71.2	10.2	15.7	1.7	1.2
Ex-user	86	55.1	10.6	19.3	12.1	2.9
Current user	76	35.6	27.2	15.5	14.0	7.7

*Awareness and use of IQOS was assessed using the following question 'Have you ever heard about 'IQOS', a device which heats (but does not burn) tobacco, have you ever tried it or do you have the intention to try it? Please, do not confuse IQOS with e-cigarettes or other vaping devices'. Participants were admitted to answer only one of the following options: (a) I have never heard about it; (b) I have heard about it, but I don't know what it is; (c) I have heard about it, I have never tried it, and I have no intention to try it; (d) I heard about it, I have never tried it but I have the intention to try it; (e) I have heard about it and I tried it.

†Row percentages.

‡Level of education: Low=middle school or below; Intermediate=high school; High=attending university or above.

§Ever cigarette smokers (current and ex-smokers) were participants who had smoked 100 or more cigarettes in their lifetime. Ex-smokers were participants who had quit smoking for at least 1 year, and current smokers were individuals continuing smoking or having stopped for less than 1 year.

¶Current e-cigarette users were individuals who occasionally or regularly used e-cigarettes at the time of interview. Ex-e-cigarette users were those who had quit e-cigarette use before the time of interview.

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Moreover, another 1 205 000 Italian adults, including 619 000 non-smokers (ie, never or ex-smokers) expressed their intention to try IQOS in the future.

In Italy, HNBs enjoy the same tax reduction of e-cigarettes (ie, 50% lower as compared with conventional cigarettes).[8] Moreover, they bypass the most important tobacco control policies: health warnings cover 30% of the HNB packaging without pictorial images, and the comprehensive smoking ban and the tobacco advertising bans are not applicable to HNBs.[8 9] These fiscal and regulatory benefits are due to the alleged belief in HNB harm reduction.[8 9] However, there is no evidence indicating that those products are effective for cessation from conventional cigarettes, and independent toxicological studies confirm that these products release measurable levels of carcinogenic compounds.[1 3 4] Thus, HNBs likely carry less risk than cigarettes, but are not risk-free. Moreover, their nicotine levels are similar to (ie, around 80%) those of conventional cigarettes.[1 3]

Limitations include the relatively small sample size that does not allow us to obtain stable prevalence estimates in subgroups. Moreover, the self-reported data may carry some misclassification of information, although we specifically reminded survey participants not to confuse IQOS with e-cigarettes.

We found that the absolute number of never smokers who have already tried IQOS in Italy is comparable to that of current smokers. Among Italian adults with an intention to try IQOS, the number of non-smokers even exceeds that of current smokers. Therefore, these findings suggest that IQOS may create new nicotine addicted generations.

Xiaoqiu Liu,[1] Alessandra Lugo,[1] Lorenzo Spizzichino,[2] Takahiro Tabuchi,[3] Roberta Pacifici,[4] Silvano Gallus[1]

[1]Department of Environmental Health Sciences, IRCCS - Istituto di Ricerche Farmacologiche "Mario Negri", Milan, Italy
[2]Prevention Department, Ministry of Health, Rome, Italy
[3]Cancer Control Center, Osaka International Cancer Institute, Osaka, Japan
[4]National Centre on Addiction and Doping, Istituto Superiore di Sanità, Rome, Italy

Correspondence to Dr Silvano Gallus, Department of Environmental Health Sciences, IRCCS - Istituto di Ricerche Farmacologiche "Mario Negri", Milan 20156, Italy; silvano.gallus@marionegri.it

Contributors SG and RP had the original idea for the study; XL and SG drafted the research letter; AL and XL conducted the data analysis; XL, AL, TT and SG gave substantial contribution to conception, design and interpretation of data; RP and LS gave contributions to conception and design of the study and provided data from the survey; all authors critically revised the manuscript and approved its final version.

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Heat-not-burn tobacco products: concerns from the Italian experience

Xiaoqiu Liu, Alessandra Lugo, Lorenzo Spizzichino, Takahiro Tabuchi, Roberta Pacifici and Silvano Gallus

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Electronic cigarettes in Italy: a tool for harm reduction or a gateway to smoking tobacco?

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1. Xiaoqiu Liu[1],
2. Alessandra Lugo[1],
3. Enrico Davoli[1],
4. Giuseppe Gorini[2],
5. Roberta Pacifici[3],
6. Esteve Fernández[4],
7. Silvano Gallus[1]

1. [1]Department of Environmental Health Sciences, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milano, Italy
2. [2]Oncological Network, Prevention and Research Institute (ISPRO), Florence, Italy
3. [3]National Centre on Addiction and Doping, Istituto Superiore di Sanità, Rome, Italy
4. [4]Institut Català d'Oncologia (ICO)-Institut d'Investigació Biomèdica de Bellvitge (IDIBELL), School of Medicine, Universitat de Barcelona, L'Hospitalet de Llobregat, Barcelona, Spain

1. Correspondence to Dr Silvano Gallus, Department of Environmental Health Sciences, Istituto di Ricerche Farmacologiche Mario Negri IRCCS , Milano 20156, Italy; silvano.gallus{at}marionegri.it

Abstract

Introduction More than a decade after electronic cigarettes (e-cigarette) hit the European market, we are still debating whether they may help or hinder tobacco control. It is therefore useful to explore the potential net effect of e-cigarette use in the general population.

Methods We annually conduct a face-to-face survey on smoking in Italy on a representative sample of the general population aged 15 years or over (52.4 million). A total of 15 406 subjects were interviewed in 2014–2018. We investigated the consequences of using e-cigarettes on tobacco smoking behaviour among ever and regular e-cigarette users.

Results In all, 5.7% of our sample reported ever e-cigarette use. Multivariate analyses showed more use by men, ex-smokers and current smokers. E-cigarette use decreased with age and increased with education and calendar year. Only 1.1% of subjects were regular e-cigarette users. This prevalence rose from 0.4% in 2014–2015 to 1.8% in 2016–2017 and was 1.3% in 2018. Among 522 ever users, 13.2% stopped

smoking after trying e-cigarettes and 22.2% started smoking or relapsed after using e-cigarettes. The corresponding estimates among regular users were 24.7% and 28.0%, respectively.

Conclusions Among Italian e-cigarette users, those (re)starting smoking after using e-cigarettes outnumber those who stop smoking after using e-cigarettes. From a public health point of view, e-cigarettes may have an unfavourable net effect. Consequently, if we are not able to prevent sales of e-cigarettes to non-smokers, this product will more likely stimulate smoking tobacco than reduce harm.

- cessation
- electronic nicotine delivery devices
- harm reduction
- denormalization

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- Contributors SG had the original idea for the study; RP provided the survey data; XL, AL, SG and RP gave substantial contribution to conception and design of data; AL and XL conducted the data analysis; XL and SG drafted the manuscript; all authors provided substantial contribution to the interpretation of data and critically revised the manuscript; all authors approved the final version of the manuscript.
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- Provenance and peer review Not commissioned; externally peer reviewed.

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Electronic cigarettes in Italy: a tool for harm reduction or a gateway to smoking tobacco?

Xiaoqiu Liu,[1] Alessandra Lugo,[1] Enrico Davoli,[1] Giuseppe Gorini,[2] Roberta Pacifici,[3] Esteve Fernández,[4] Silvano Gallus[1]

[1]Department of Environmental Health Sciences, Istituto di Ricerche Farmacologiche Mario Negri IRCCS, Milano, Italy
[2]Oncological Network, Prevention and Research Institute (ISPRO), Florence, Italy
[3]National Centre on Addiction and Doping, Istituto Superiore di Sanità, Rome, Italy
[4]Institut Català d'Oncologia (ICO)-Institut d'Investigació Biomèdica de Bellvitge (IDIBELL), School of Medicine, Universitat de Barcelona, L'Hospitalet de Llobregat, Barcelona, Spain

Correspondence to
Dr Silvano Gallus, Department of Environmental Health Sciences, Istituto di Ricerche Farmacologiche Mario Negri IRCCS , Milano 20156, Italy; silvano.gallus@marionegri.it

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INTRODUCTION

The electronic cigarette (e-cigarette) is a battery-powered device that heats a liquid containing propylene glycol, glycerin and/or water with flavours, to generate an inhalable aerosol containing nicotine or not. E-cigarettes were marketed in most high-income countries around 2010, and its popularity and use soon spread widely.[1] Some public and private organisations, including Public Health England, have endorsed e-cigarette use, on the basis of the widely accepted standpoint that they could be beneficial for heavy smokers who are not able to quit with standard support.[2 3] This endorsement, conflicting with the conclusions of the WHO[4] and the US National Academies of Sciences, Engineering, and Medicine,[5] has provoked much debate and concern over the spread and use of e-cigarettes.[6–8]

The debate is mainly due to uncertainty about the harmful effects of e-cigarettes and their effectiveness as a smoking cessation tool.[8] Indeed, the safety of e-cigarette use, particularly its long-term effects, remains unclear[9 10]: while these e-cigarettes emit less toxicants and carcinogens than conventional cigarettes, they are still measurable and vary widely with individual puffing topography and puff duration,[11] and from study to study.[12 13] Although some studies showed that e-cigarettes may help smokers cut down or stop smoking conventional cigarettes,[14–16] others found e-cigarettes even stop cessation or give low cessation rates, similar to those of smokers who have tried to quit with no aid.[10 17–19] There is also concern that e-cigarettes may undermine efforts to 'denormalise' smoking.[20] Finally, non-smokers trying e-cigarettes can succumb to nicotine addiction, particularly young people.[1 21 22]

To get a better picture of the potential net benefit of e-cigarette use in reducing tobacco consumption at a population level, we analysed data from our annual population-based surveys conducted in Italy from 2014 to 2018, where a specific section was devoted to e-cigarette use.

METHODS

Surveys were conducted by DOXA, the Italian branch of the Worldwide Independent Network/Gallup International Association, in collaboration with the Italian National Institute of Health and the Mario Negri Institute for Pharmacological Research. Each year, the survey is based on around 3000 subjects, representative of the general Italian population aged 15 years and over (52.4 million inhabitants in 2018), in terms of sex, age, area of residence and socioeconomic characteristics.[23] For the present analysis, the sample comprised 15 406 individuals aged 15 years or more (7393 men and 8013 women), enrolled in the survey conducted in 2014–2018.

Participants were selected by a representative multistage sampling. The first stage involved the selection of municipalities in all the 20 Italian regions, based on the region and the size of the municipality. We selected 116 municipalities in 2014, 110 in 2015, 2016 and 2017 and 119 in 2018 as representative of the regions sampled. In the second stage, an adequate number of electoral wards was randomly extracted in each municipality, so that the more or less affluent areas of the municipality were represented in the right proportions. In the third stage, individuals were randomly sampled from electoral rolls, within strata defined by sex and age. Adolescents aged 15–17 years, who were not included in the electoral lists, were randomly selected by a 'quota' method based on the sex and

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age proportions among them. A statistical weight was generated for each subject to ensure the representativeness of the Italian population aged 15 years or more.

Ad hoc trained interviewers conducted the survey using a structured questionnaire in a computer-assisted personal interview. Besides general information on sociodemographic characteristics, smoking status (never smoker, ex-smoker and current smoker) and other tobacco-related data were collected. Ever smokers (current smokers and ex-smokers) were participants who had smoked 100 or more cigarettes in their lifetime. Ex-smokers were participants who had quit smoking for at least 1 year, and current smokers were individuals smoking at the time of the interview or having stopped for less than 1 year. Participants were asked about their use of e-cigarettes, using the question: 'Do you use electronic cigarettes or other electronic devices for vaping (disposable or prefilled or refillable cartridges with liquid), even only occasionally?' (1) Yes, occasionally; (2) Yes, usually; (3) I used it in the past; (4) No. We define herewith as occasional e-cigarette users reporting the first answer, regular users the second answer, past users the third answer, current users first and second answers combined, and ever users first, second and third answers combined. Occasional and regular e-cigarette users (and past e-cigarette users in 2017 and 2018) were further investigated about the consequences of e-cigarette use on their tobacco smoking habits with the following question: 'Which of the following best describes the consequence of using electronic cigarettes on your current cigarette smoking consumption? (1) I started smoking conventional cigarettes (I did not smoke before, and now I smoke); (2) I re-started smoking conventional cigarettes (I was an ex-smoker, and now I relapsed); (3) I haven't changed my smoking habits (I smoke the same amount of conventional cigarettes as before); (4) I slightly reduced the number of conventional cigarettes per day; (5) I substantially reduced the number of conventional cigarettes per day; (6) I increased the number of conventional cigarettes per day; (7) I quit smoking; (8) I did not smoke conventional cigarettes before and I do not smoke now'. Almost all e-cigarette users (97%) provided a valid response to this question. In 2017–2018, a single-choice question to current e-cigarette users only investigated the type of e-cigarette used (with or without nicotine).

Descriptive statistics were used for the main results, including prevalence and the corresponding 95% confidence interval (CI) by categorical variables. In view of the small numbers, we grouped the survey year as 2014–2015, 2016–2017 and 2018. Statistical weights were used to reassure the representativeness of our sample in terms of age, sex, area of residence and socioeconomic characteristics. Odds ratios (OR) and the 95% CIs for ever—and regular—e-cigarette use were calculated using multivariate logistic regression models, adjusting for sex, age, level of education, smoking status, area of residence and survey year. A sensitivity analysis limited to data from 2017 and 2018 was done to explore whether the answers on the consequence of e-cigarette use differed between current and past users. Another sensitivity analysis was done on nicotine-containing e-cigarette users, that is, current users in 2014–2015, 2017–2018, to assess the consequence of their use of e-cigarettes on tobacco smoking. All analyses were done with SAS V.9.4 statistical package.

RESULTS

The distribution of 15 406 Italians aged 15 years or more according to their use of e-cigarettes is shown in table 1. Only 1.1% of Italian adults (95% CI: 1.0% to 1.3%) reported regular e-cigarette use, 1.1% (95% CI: 0.9% to 1.2%) occasional use and 3.5% (95% CI: 3.2% to 3.8%) past use (table 1). Among regular and occasional users, 62% were dual users (ie, current smokers and e-cigarette users): 81% in 2014–2015, 53% in 2016–2017 and 66% in 2018. Ever (ie, occasional, regular or

Table 1 Prevalence (per cent) of occasional, regular and past use of electronic cigarettes in a total sample of 15 406 Italians aged at least 15 years, overall and according to selected characteristics (Italy, 2014–2018)

		Electronic cigarette use (%)			
	n	Never use	Past use	Occasional use	Regular use
Total (number)	100.0 (15 406)	94.3 (14 528)	3.5 (533)	1.1 (165)	1.1 (178)
Sex					
Men	7393	92.9	4.3	1.2	1.5
Women	8013	95.6	2.7	1.0	0.8
Age (years)					
15–24	1751	93.7	3.8	1.7	0.8
25–44	4786	92.6	4.4	1.4	1.6
45–64	5034	93.4	4.2	1.1	1.4
≥65	3835	97.9	1.2	0.4	0.4
Level of education					
Low	5569	96.1	2.6	0.7	0.6
Intermediate	7370	92.6	4.5	1.4	1.5
High	2467	95.1	2.6	1.2	1.0
Smoking status					
Never smoker	10 046	98.6	0.6	0.3	0.4
Current smoker	3395	82.2	12.0	3.5	2.4
Ex-smoker	1965	93.2	3.2	0.8	2.8
Survey year					
2014–2015	6098	95.3	3.4	0.9	0.4
2016–2017	6086	93.1	3.8	1.3	1.8
2018	3222	94.9	3.0	0.8	1.3

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Table 2 Self-reported consequences of electronic cigarette use on the consumption of combustible cigarettes among 522 ever users and 182 regular users of electronic cigarettes (Italy, 2014–2018)

	Ever users		Regular users	
	n*	% (95% CI)	n*	% (95% CI)
Total	522	100.0	182	100.0
Detrimental change				
Started smoking (from never to current smoker)	54	10.3 (7.7 to 13.0)	32	17.6 (12.1 to 23.1)
Restarted smoking (from ex-smoker to current smoker) †	62	11.9 (9.1 to 14.7)	19	10.4 (6.0 to 14.9)
No change in smoking status				
Increased smoking intensity	6	1.2 (0.0 to 2.1)	3	1.7 (0.0 to 3.5)
Did not change smoking intensity	163	31.2 (27.3 to 35.2)	18	9.9 (5.6 to 14.2)
Did not smoke before and do not smoke now	29	5.6 (3.6 to 7.5)	8	4.4 (1.4 to 7.4)
Slightly reduced daily smoking intensity	97	18.6 (15.3 to 21.9)	25	13.7 (8.7 to 18.7)
Substantially reduced daily smoking intensity	42	8.1 (5.7 to 10.4)	32	17.6 (12.1 to 23.1)
Beneficial change				
Quit smoking (from current to ex-smoker)	69	13.2 (10.3 to 16.1)	45	24.7 (18.5 to 31.0)

*Number of e-cigarette users who provided information on consequences of e-cigarette use on their smoking behaviours (unweighted numbers). This study includes 891 ever users (143 in 2014, 164 in 2015, 262 in 2016, 174 in 2017 and 148 in 2018). The question on the consequence of e-cigarette use was not put to ex-users in 2014–2016 (n=355), while in 2017–2018 it was asked also to ex-users. There are nine occasional users and five regular users who did not answer this question. Numbers do not match those in table 1 because statistical weight was not considered in the table.
†This option was available only in the 2016–2018 surveys.

past) e-cigarette users were 5.7% with fewer women (4.4%) than men (7.1%; multivariate OR: 0.80; 95% CI: 0.68 to 0.91), inversely related to age (p for trend <0.001) and directly related to education (p for trend 0.021). Compared with never cigarette smokers (1.4%), ever e-cigarette use was more frequent among current smokers (17.8%; multivariate OR: 14.3; 95% CI: 11.8 to 17.3) and ex-smokers (6.8%; OR: 5.80; 95% CI: 4.51 to 7.45). The prevalence of ever e-cigarette use rose from 4.7% in 2014–2015, to 6.9% in 2016–2017 (OR: 1.52; 95% CI: 1.29 to 1.78) and was 5.2% in 2018 (OR: 1.01; 95% CI: 0.82 to 1.23). Fewer women than men were regular e-cigarette users (OR: 0.66; 95% CI: 0.49 to 0.91) and the rate decreased with increasing age (p for trend 0.008). No specific pattern was found for level of education (p for trend 0.121). Compared with never smokers, regular e-cigarette users were more frequent among current smokers (OR: 4.87; 95% CI: 3.33 to 7.12) and ex-smokers (OR: 7.23; 95% CI: 4.75 to 11.00). Compared with 2014–2015 (0.4%), Italians were more frequently regular e-cigarette users in 2016–2017 (1.8%; OR: 4.70; 95% CI: 3.01 to 7.33) and in 2018 (1.3%; OR: 3.10; 95% CI: 1.87 to 5.15; p for trend <0.001).

Among the 522 ever users (including 182 regular users), 13.2% (95% CI: 10.3% to 16.1%; n=69) reported having stopped smoking, therefore changing their smoking status from current to ex-smoker; 64.6% (95% CI: 60.5% to 68.7%; n=337) did not substantially change their smoking behaviour (including 139 who cut down the numbers of cigarettes smoked per day); and 22.2% (95% CI: 18.7% to 25.8%; n=116) reported they had started smoking or relapsed as a consequence of e-cigarette use, therefore changing their smoking status from non-smoker (ie, never or ex-smokers) to current smoker (table 2). The corresponding proportions among regular users were 24.7% (95% CI: 18.5% to 31.0%; n=45) who stopped smoking, 47.3% (95% CI: 40.0% to 54.5%; n=86) who did not substantially change their smoking behaviour and 28.0% (95% CI: 21.5% to 34.5%; n=51) who started smoking or relapsed. Sensitivity analysis using data from 2017 and 2018 showed that the rates of e-cigarette users (re)starting smoking were similar among current (22.0%) and past users (21.4%), while those quitting smoking were more frequent among regular/occasional e-cigarette users (20.0%) than past users (8.9%, only).

Among younger subjects (under 35 years), 7.1% were ever e-cigarette users. Among these, 5.5% reported having stopped smoking and 16.4% had (re)started smoking as a consequence of their e-cigarette experience. Among the 86 current users reporting in 2017 and 2018 that they used nicotine-containing e-cigarettes, 24 (27.9%) started/restarted smoking and 14 (16.3%) quit smoking (data not shown).

DISCUSSION

The prevalence of regular e-cigarette use in Italy is still relatively low, but it rose significantly from 0.4% in 2014–2015 to 1.3% in 2018. We explicitly asked ever users about the consequence of e-cigarette use on their smoking status. Among ever, regular, young e-cigarette users and subjects vaping nicotine-containing e-cigarettes, the number of those (re)starting smoking due to e-cigarette use systematically exceeded those quitting smoking with e-cigarette use. This indicates that only a small proportion of ever e-cigarette users in Italy potentially benefit from these e-cigarettes (only 13% quit smoking), and e-cigarette use seems to act as a gateway to smoking tobacco in a larger proportion (22%).

Our findings are in broad agreement with those by Soneji and colleagues,[24] who, using a Monte Carlo simulation model applied to data from different national surveys from the USA, concluded that e-cigarette use causes more population-level harm than benefit.[24]

A large proportion of e-cigarette users (27%) reported having (slightly or substantially) reduced their smoking intensity. This, however, cannot be considered an achievement from a public health perspective, given the growing evidence that (1) dual users are more likely to transition to exclusive combustible use than to remain in their dual-use category[25] and (2) there is no safe level of smoking for cardiovascular disease and overall mortality.[26]

Among participants who were current smokers at the time of starting e-cigarette use, only 17% stopped smoking. This hardly supports e-cigarette as an effective tool for stopping smoking, in agreement with other evidence.[10 27–29] In a previous

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meta-analysis, success in quitting smoking was 28% less in those who used e-cigarettes than in those who did not use them.[10] The most recent and comprehensive review gave conflicting results. The only two randomised controlled trials suggested a possible increase in smoking cessation using e-cigarettes with nicotine compared with e-cigarettes with no nicotine, but cohort studies suggested possibly lower rates of quitting using e-cigarettes than with other smoking cessation methods.[29]

We can confirm that most of the smokers who had started e-cigarette use (more than 80%) continued to smoke tobacco.[1 19] Several studies showed that many smokers transition to dual use, vaping in order to have nicotine intake in places where they cannot smoke combustible cigarettes, or so as to bother other people less.[30–33]

Pharmacological support for smoking cessation in Italy includes nicotine patches, chewing gums and nasal/oral sprays, approved by the Italian Medicines Agency after proof of safety and efficacy through the publication of clinical trials. These products can only be purchased in pharmacies and are promoted only to smokers. In contrast, e-cigarettes were marketed without any official approval and are available to anyone, including never smokers. Indeed, we found that 1.3% of never smokers had tried e-cigarettes, and 0.4% were regular e-cigarette users. Findings have been similar in the USA, where 4.1% of adult never smokers had tried e-cigarettes.[34] In agreement with the USA results,[35] we also found that 16% of ever (and 22% of regular) e-cigarette users had never smoked before using e-cigarettes. The potential risk of nicotine addiction among never smokers cannot be overlooked, since the majority of never smokers trying e-cigarettes started smoking afterwards.

The tobacco control environment is hard put to explain these transitions. In fact, in Italy over the period there was only a marginal improvement in selective tobacco regulations,[36] mainly aimed at children and which did not affect tobacco prices, adopted in 2016.[23] In the meantime, e-cigarettes enjoy 50% lower tax than conventional cigarettes. Although in 2017, excise taxes were introduced for e-cigarettes, the fiscal benefit for this product results in a substantially lower price as compared with cigarette tobacco. There are no national regulations against e-cigarette use in public places, except in schools,[37] and the social desirability of e-cigarette is neutral.

A large prospective study conducted in the UK recently confirmed findings from a meta-analysis on adolescents and young adults,[38] showing that baseline ever use of e-cigarettes was strongly associated with subsequent starting and escalation of conventional cigarette use among teenagers.[39] Our data too show 16% of young e-cigarette users started smoking as a consequence of their e-cigarette use.

In the current tobacco market, there are also heated tobacco products (HTPs) that heat disposable tobacco sticks, without reaching combustion, to generate a sort of 'cold smoke' containing nicotine.[40] Independent toxicological studies showed that these HTPs release relatively high nicotine levels—similar to those released by conventional cigarettes—and non-negligible amounts of harmful substances, including various carcinogens.[41–43] However, given the belief that they are less harmful, hence the fiscal and regulatory favours, HTP rapidly spread after 2016 in the Italian tobacco market.[40 44] This growth may be responsible, at least partially, for the lower number of Italian e-cigarette consumers in 2018 compared with 2016–2017.

Our study is limited by its cross-sectional design, which meant we could not observe the time sequence of the causal effects of e-cigarette use on smoking cessation. Therefore, the findings need to be confirmed by large longitudinal studies. In addition, the survey collected self-reported data, which is likely to suffer recall bias and imprecise responses. To reduce these limitations as far as possible, we explicitly explained the purpose of the questions, clearly asking ever e-cigarette users how their use had affected their smoking habits and providing all the mutually exclusive responses.

Another limitation is that the question on the consequences of e-cigarette use on their smoking habits was not put to past e-cigarette users in 2014–2016. However, this may, if anything, have led to underestimation of quitting smoking as the consequence of e-cigarette use. In a sensitivity analysis limited to data from 2017 and 2018, the number of e-cigarette users (re)starting smoking were similar among current and past users (around 22%), while those quitting smoking were more frequent among regular/occasional e-cigarette users (20%) than past users (only 9%). Thus, including past users in 2014–2016 may well have lowered the percentage of subjects quitting smoking with e-cigarette use.

Our classification of e-cigarette users as never, past, occasional and regular did not allow us to record the intensity of use (eg, daily use, number of puffs per day), so we could not identify intensive e-cigarette use, which has been shown to be directly related to quitting smoking.[45] Our study is also limited by the sample size, focusing on e-cigarette users only. For this reason, we merged data from the annual surveys conducted over the last 5 years.

In conclusion, the number of regular e-cigarette users increased in Italy from 2014 to 2018. Our data indicate that around 680 000 Italians regularly use e-cigarettes today. Among them, 170 000 stopped smoking after using e-cigarettes, while 190 000 (re)started smoking conventional cigarettes with e-cigarette use.

Given the limitations inherent to the cross-sectional study design and the fact that recall and social desirability biases could not be ruled out in self-reported data, our main findings need to be confirmed by longitudinal studies. Nevertheless, they do suggest that, from a public health point of view, e-cigarette commerce in Italy has had an unfavourable net effect. Consequently, if we are not able to regulate the sales, taxation, advertising and places of use, this product is more likely to act as an incentive for smoking rather than a strategy for reducing harm.

What this paper adds

- The popularity and use of electronic cigarettes (e-cigarette) worldwide has substantially spread in recent years.
- The scientific community is still debating whether e-cigarettes help or hinder tobacco control. The debate is mainly caused by the uncertainty on their effectiveness as a tool for smoking cessation.
- We found that in Italy the number of e-cigarette users (re) starting smoking after using e-cigarettes exceeded that of users quitting smoking by using these e-cigarettes.
- The spread of e-cigarettes may have an unfavourable net effect from the public health point of view.

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E-cigarettes linked to higher risk of stroke, heart attack, diseased arteries

eurekalert.org/pub_releases/2019-01/aha-elt012519.php

Public Release: 30-Jan-2019

American Stroke Association News Release - Abstract 9, Session A2

American Heart Association

DALLAS, Jan. 30, 2019 -- Using e-cigarettes increases your odds of having a stroke, heart attack and coronary heart disease, according to preliminary research to be presented in Honolulu at the American Stroke Association's International Stroke Conference 2019, a world premier meeting for researchers and clinicians dedicated to the science and treatment of cerebrovascular disease.

In 2016, 3.2 percent of U.S. adults and 11.3 percent of high school students reported using e-cigarettes in the preceding 30 days. Its use among young people increased by 900 percent between 2011 and 2015.

In the largest study to date examining e-cigarettes and stroke, researchers tapped a database of 400,000 respondents. That database, the 2016 behavioral risk factor surveillance system (BRFSS) survey, collected data from residents in all 50 states about their health-related risk behaviors, chronic health conditions and use of preventive services.

"Compared with non-users, e-cigarette users were younger, had a lower body mass index and a lower rate of diabetes," said Paul M. Ndunda, M.D., the study's author and an assistant professor in the School of Medicine at the University of Kansas in Wichita.

Some 66,795 respondents reported ever regularly using e-cigarettes. The control group was the 343,856 respondents who reported having never used e-cigarettes. Odds ratios were calculated using logistic regression analysis. Researchers found compared with non-users, e-cigarette users had:

- 71 percent higher risk of stroke;
- 59 percent higher risk of heart attack or angina;
- 40 percent higher risk of coronary heart disease; and
- Double the rate of cigarette smoking.

They also found 4.2 percent of e-cigarette users reported having suffered a stroke. However, the study data did not show deaths attributable to e-cigarette use.

The American Heart Association cautions against the use of e-cigarettes, stating that e-cigarettes containing nicotine are tobacco products that should be subject to all laws that apply to these products. The Association also calls for strong new regulations to prevent access, sales and marketing of e-cigarettes to youth and for more research into the product's health impact.

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Coauthor is Tabitha Muutu, M.D. Researchers reported no funding for this study.

Note: Scientific presentation is 7:12 a.m. HT/12:12 p.m. ET, Wednesday, Feb. 6, 2019.

Additional Resources:

* Downloadable multimedia related to this news release are on the right column of the release link https://newsroom.heart.org/news/e-cigarettes-linked-to-higher-risk-of-stroke-heart-attack-diseased-arteries?preview=1217dd515a48f12e78a2d0fa3b1ad741

* For more news from AHA International Stroke Conference 2019, follow us on Twitter @HeartNews #ISC19.

Statements and conclusions of study authors that are presented at American Heart Association scientific meetings are solely those of the study authors and do not necessarily reflect association policy or position. The association makes no representation or warranty as to their accuracy or reliability. The association receives funding primarily from individuals; foundations and corporations (including pharmaceutical, device manufacturers and other companies) also make donations and fund specific association programs and events. The association has strict policies to prevent these relationships from influencing the science content. Revenues from pharmaceutical and device corporations are available at https://www.heart.org/en/about-us/aha-financial-information.

About the American Stroke Association

The American Stroke Association is devoted to saving people from stroke -- the No. 2 cause of death in the world and a leading cause of serious disability. We team with millions of volunteers to fund innovative research, fight for stronger public health policies and provide lifesaving tools and information to prevent and treat stroke. The Dallas-based association officially launched in 1998 as a division of the American Heart Association. To learn more or to get involved, call 1-888-4STROKE or visit StrokeAssociation.org. Follow us on Facebook and Twitter.

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E-cigs ARE dangerous: Vaping raises risks of stroke, heart disease and attacks

dailymail.co.uk/health/article-6646161/E-cigs-dangerous-Vaping-raises-risks-stroke-heart-disease-attacks.html

January 30, 2019

Vaping e-cigarettes raises the risks of having a heart attack, stroke, or heart disease, a new study finds.

About one in 20 US adults use e-cigarettes and many of them claim to do so because they are 'healthier' than combustible cigarettes.

But the devices are still relatively new and poorly understood.

As more and more research on them comes out, it becomes increasingly clear that 'safer' doesn't mean safe.

The latest study, conducted by the American Heart Association, found that heart attacks are nearly 60 percent more common among vapers, who are at a 71 percent higher risk of stroke.

+1
Originally marketed as a 'safer' alternative to smoking combustible tobacco, e-cigarettes raise risks of heart attack and disease as well as stroke, new research suggests

When e-cigarettes started appearing on the shelves of smoke shops and convenience stores, they were often advertised as a cessation aid for smokers.

But now, it's become clear they are more likely to be an addition to, rather than substitute for, combustible cigarettes.

The American Heart Association (AHA) study found that people who vape are twice as likely to also smoke traditional cigarettes as are those who don't vape.

In all likelihood, the high rates of dual usage contribute to a number of poorer health effects seen in e-cig users.

Smoking is the number one cause of lung cancer because inhaling smoke from burned plant matter is highly carcinogenic, so vapor from e-liquids so far seems somewhat safer for the longs.

But a growing body of research suggests that e-cigarettes are just as bad for the heart and cardiovascular system as traditional cigarettes.

Teen vaping is an 'epidemic' FDA declares, blaming Juul and... Over half of vaping teenagers have never smoked a real... You DO have time for the gym: Exercising for 15 minutes... British mothers are being let down: Almost a QUARTER are...

Last year, the American Heart Association found that both combustible and e-cigarettes corrupt the lining of the blood vessels, preventing them from dilating and inhibiting the flow of blood.

This narrowing of blood's passageways makes the heart have to work harder and damages it over time.

Now, Association's largest study on e-cigs and stroke confirms the link between vaping and potentially fatal blood clots.

In its survey of 400,000 people, the AHA found that nearly 66,795 respondents who vaped had a 71 percent higher risk of stroke.

The same group was at a 59 percent higher risk of having a heart attack or angina.

And they were at 40 percent greater risk of developing heart disease.

Although the rate of stroke among e-cig users was notable - 4.2 percent had suffered one - the researchers could not conclude that vaping kills.

Worryingly, rates of e-cig use are highest among the young people. Just 4.2 percent of adults vape, as compared to 11.3 percent of high school students.

That may mean that that generation will face more heart disease, stroke and heart attack than those that came before them.

'It's obviously quite concerning,' said Dr Larry Goldstein, chairman of the department of neurology and co-director of the Kentucky Neuroscience Institute.

'This is a potential chip of the spear, of a wave of cardio-vascular disease, that may be coming in the future, especially since this has been so attractive to young users.'

He advised the public health officials must continue to push for a ban on sweet flavored e-liquids that are so enticing to younger users.

'This is the first real data that we're seeing associating e-cigarette use with hard cardiovascular events,' he added.

'But it's quite a concern, especially since nationwide now we've seen a leveling off in, and in many instances an increase in the risk of stroke-related mortality in the country. It's hard to know what contribution this has to that, but it doesn't appear to be safer, or safe right now from the data that's available.'

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Survey Finds Higher Risk Of Stroke Among E-Cigarette Users

npr.org/sections/health-shots/2019/01/30/689905296/survey-finds-higher-risk-of-stroke-among-e-cigarette-users

Shots

Health News From NPR

Public Health

January 30, 201912:17 PM ET

Jonathan Lambert



"There's a certain notion that e-cigarettes are harmless," says Dr. Paul Ndunda, an assistant professor at the School of Medicine at the University of Kansas in Wichita. "But ... while they're less harmful than normal cigarettes, their use still comes with risks."

RyanJLane/Getty Images

The use of e-cigarettes is associated with an increased risk of heart attack, heart disease and stroke, according to research that is scheduled to be presented Feb. 6 at the American Stroke Association's International Stroke Conference in Honolulu.

Concern around the health effects of e-cigarette use has grown in recent years, fueled by a surge in their popularity and a belief that they're safe alternatives to normal cigarettes.

E-cigarette use among high school students increased by 900 percent between 2011 and 2015. In 2018, more than 3.6 million young people in the U.S., including 1 in 5 high school students, were users of e-cigarettes, according to the Centers for Disease Control and

Prevention.

"There's a certain notion that e-cigarettes are harmless," says Dr. Paul Ndunda, the study's author and an assistant professor at the School of Medicine at the University of Kansas in Wichita. "But this study and previous other studies show that while they're less harmful than normal cigarettes, their use still comes with risks."

The researchers used data collected by the 2016 Behavioral Risk Factor Surveillance System, a phone survey sponsored by several federal agencies, including the CDC. The survey includes people in all 50 states, asking about risky health-related behaviors, like smoking, and whether respondents have been diagnosed with any health problems.

Of the more than 400,000 respondents in 2016, 66,795 reported having used e-cigarettes at least once, and compared with nonusers, e-cigarette users had a 71 percent higher risk of stroke, 59 percent higher risk of heart attack and 40 percent higher risk of heart disease.

Ndunda says that the nature of the analysis prevented the research team from accurately calculating the absolute risk of heart attack and stroke from the database.

The findings haven't been published in a peer-reviewed scientific journal, but Ndunda says the researchers plan on submitting their results soon.

"These results are important as they qualitatively and quantitatively agree with previous studies," says Stanton Glantz, a tobacco and e-cigarette researcher at University of California, San Francisco, who wasn't involved in this work but did publish another study that linked e-cigarette use to higher risk of heart attack. "The fact that the stroke and heart attack risk factors are not that different is also the same pattern you see with cigarette smoking, which adds extra weight to this study too."

However, many e-cigarette users also smoke conventional cigarettes.

In fact, Ndunda found e-cigarette users are twice as likely to also smoke conventional cigarettes, compared with people who don't use e-cigarettes.

To see the health effects 0f e-cigarette use alone, Ndunda and his colleague Dr. Tabitha Muutu compared people who had only used e-cigarettes — not conventional cigarettes — to nonsmokers.

"Even in that group there was a 29 percent higher risk of stroke and a 25 percent higher risk of heart attack," Ndunda says. Taken together, these two analyses point to an additive effect of e-cigarette and conventional cigarette use.

"So if you're a dual user, which many e-cig users are, you're actually worse off," says Glantz, who found a similar additive effect in his study.

Scientists aren't quite sure how e-cigarettes lead to this higher risk.

E-cigarette smoking may contribute to the gradual buildup of fatty deposits in arteries, Glantz says. But he thinks researchers may be detecting a link between increased risk for heart attacks and strokes and e-cigarette use because of a more immediate effect on the cardiovascular system.

You could have this pre-existing buildup, Glantz says, "and then you use the e-cigarette and that triggers a bunch of inflammatory processes, the release of oxidizing agents and things which then interfere with normal functioning of the blood and blood vessels, and that triggers a heart attack or stroke."

"This study certainly has limitations," Ndunda says. For one, this study couldn't distinguish between occasional e-cigarette use and those who vape more frequently. "It likely matters how much you're using, and we couldn't evaluate that here," Ndunda says.

E-cigarettes can deliver a range of nicotine concentrations and a wide variety of chemical flavorings, adding further complications to the analysis. The study's design also means it can only show an association between e-cigarette use and risk, not cause and effect.

Ndunda added that a study that identifies e-cigarette users early and then tracks their health over time would yield a clearer picture of the consequences of vaping.

Dr. Chitra Dinakar, a clinical professor of pulmonary and critical care medicine at the Stanford University School of Medicine who has studied the health effects of e-cigarettes, says this work, which only surveys adults 18 and older, "does not reflect the risk of stroke in younger users." Still, she says, "this is an important topic that merits ongoing scrutiny."

Jonathan Lambert is an intern on NPR's Science Desk. You can follow him on Twitter: @evolambert.

About

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Vaping Health Risks: Study Links E-cigs to Heart Attack and Stroke—but There's More to It

newsweek.com/vaping-health-risks-e-cigs-heart-attack-stroke-study-links-theres-more-it-1309203

By Kashmira Gander January 30, 2019

People who smoke e-cigarettes are more likely to suffer from conditions including heart disease and stroke, research has suggested.

A preliminary study presented at the American Stroke Association's International Stroke Conference 2019, Honolulu, which has not yet been peer reviewed, linked vaping to cardiovascular disease. However, experts not involved in the work explained the association may come down to the past habits of vape users.

Between 2011 and 2015, the use of e-cigarettes in the U.S. has spiked by 900 percent, the authors of the research pointed out. The team at the University of Kansas wanted to provide an insight into the potential health implications of this habit, and specifically the potential risk of stroke.

The researchers studied 2016 data from the Behavioral Risk Factor Surveillance System survey, carried out each year by the Centers for Disease Control and Prevention. 66,795 respondents used e-cigarettes regularly, while 343,856 had never used the devices. They also took into account information on the age and sex of participants, whether they smoked, had diabetes, how much they exercised and their BMI.

The fifth of respondents who used e-cigarettes were younger on average compared with non-users, at 44 years old compared with 57 years old; had a lower BMI score; and were less likely to have diabetes.

But vape users were also more likely to smoke cigarettes, and had higher chance of suffering from a stroke, angina and coronary heart disease, according to the study.

Dr. Paul Ndunda, study author and assistant professor in the School of Medicine at the University of Kansas in Wichita, told *Newsweek* this study is the first to show an association between e-cigarette use and stroke. It is also one of the largest studies to show an association between e-cigarette use and heart disease, he said.

However, he acknowledged his study was limited in several ways. It was cross-sectional, meaning it does not prove causation but only association between disease and vaping. And e-cigarette and smoking were not quantified in the data, only if the participants were smokers or non-smokers.

“This research calls for well designed, large, long-term population studies to assess whether e-cigarettes cause stroke and cardiovascular disease,” he said.

Dr. Aaron Scott of the Institute of Inflammation and Ageing at the University of Birmingham, U.K., who was not involved in the study, explained to *Newsweek*: “This abstract doesn't tell us much more than what is already known.

"Most of the people using e-cigarettes are going to be ex-smokers and, as such, they will have a history of tobacco use and a higher risk of heart disease. The effects of nicotine on atherosclerosis [where plaque builds up inside your arteries] are also already well investigated.

“In terms of cardiovascular damage, the nicotine in e-cigarettes may, in the long run, prove to have similar effects to smoking traditional cigarettes but until long term sequential data is obtained it remains speculation."

His colleague, Professor David Thickett, also of the Institute of Inflammation and Ageing, agreed that observational studies such as this need to be “backed up by cohort studies that are followed over time.”

Addressing the potential harms of vaping more generally, Ndunda said there is still a lot that we don’t know about health effects of e-cigarettes.

“In addition to other known risks of e-cigarettes, there may be risks to brain and heart health. Therefore; those who haven’t started vaping and don’t smoke combustible cigarettes are probably better off not starting vaping. Those that are vaping, for purposes other than quitting smoking are probably better off stopping. Those that vape as a smoking cessation aid need to have a discussion with their doctors. There may be other effective methods suitable for them.”

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He pointed out the FDA has not approved e-cigarettes in the U.S. for smoking cessation.

However, Ndunda stressed research suggests regular cigarettes “present more health risks than e-cigarettes and e-cigarettes may have a role in quitting for some smokers but there is need for more research in this area and the public health implications of recommending e-cigarettes for smoking cessation is complicated."

Researchers believe e-cigarettes could be linked to cardiovascular problems. Getty Images

Survey Finds Higher Risk Of Stroke Among E-Cigarette Users

npr.org/sections/health-shots/2019/01/30/689905296/survey-finds-higher-risk-of-stroke-among-e-cigarette-users

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Jonathan Lambert



"There's a certain notion that e-cigarettes are harmless," says Dr. Paul Ndunda, an assistant professor at the School of Medicine at the University of Kansas in Wichita. "But ... while they're less harmful than normal cigarettes, their use still comes with risks."

RyanJLane/Getty Images

The use of e-cigarettes is associated with an increased risk of heart attack, heart disease and stroke, according to research that is scheduled to be presented Feb. 6 at the American Stroke Association's International Stroke Conference in Honolulu.

Concern around the health effects of e-cigarette use has grown in recent years, fueled by a surge in their popularity and a belief that they're safe alternatives to normal cigarettes.

E-cigarette use among high school students increased by 900 percent between 2011 and 2015. In 2018, more than 3.6 million young people in the U.S., including 1 in 5 high school students, were users of e-cigarettes, according to the Centers for Disease Control and

Prevention.

"There's a certain notion that e-cigarettes are harmless," says Dr. Paul Ndunda, the study's author and an assistant professor at the School of Medicine at the University of Kansas in Wichita. "But this study and previous other studies show that while they're less harmful than normal cigarettes, their use still comes with risks."

The researchers used data collected by the 2016 Behavioral Risk Factor Surveillance System, a phone survey sponsored by several federal agencies, including the CDC. The survey includes people in all 50 states, asking about risky health-related behaviors, like smoking, and whether respondents have been diagnosed with any health problems.

Of the more than 400,000 respondents in 2016, 66,795 reported having used e-cigarettes at least once, and compared with nonusers, e-cigarette users had a 71 percent higher risk of stroke, 59 percent higher risk of heart attack and 40 percent higher risk of heart disease.

Ndunda says that the nature of the analysis prevented the research team from accurately calculating the absolute risk of heart attack and stroke from the database.

The findings haven't been published in a peer-reviewed scientific journal, but Ndunda says the researchers plan on submitting their results soon.

"These results are important as they qualitatively and quantitatively agree with previous studies," says Stanton Glantz, a tobacco and e-cigarette researcher at University of California, San Francisco, who wasn't involved in this work but did publish another study that linked e-cigarette use to higher risk of heart attack. "The fact that the stroke and heart attack risk factors are not that different is also the same pattern you see with cigarette smoking, which adds extra weight to this study too."

However, many e-cigarette users also smoke conventional cigarettes.

In fact, Ndunda found e-cigarette users are twice as likely to also smoke conventional cigarettes, compared with people who don't use e-cigarettes.

To see the health effects 0f e-cigarette use alone, Ndunda and his colleague Dr. Tabitha Muutu compared people who had only used e-cigarettes — not conventional cigarettes — to nonsmokers.

"Even in that group there was a 29 percent higher risk of stroke and a 25 percent higher risk of heart attack," Ndunda says. Taken together, these two analyses point to an additive effect of e-cigarette and conventional cigarette use.

"So if you're a dual user, which many e-cig users are, you're actually worse off," says Glantz, who found a similar additive effect in his study.

Scientists aren't quite sure how e-cigarettes lead to this higher risk.

E-cigarette smoking may contribute to the gradual buildup of fatty deposits in arteries, Glantz says. But he thinks researchers may be detecting a link between increased risk for heart attacks and strokes and e-cigarette use because of a more immediate effect on the cardiovascular system.

You could have this pre-existing buildup, Glantz says, "and then you use the e-cigarette and that triggers a bunch of inflammatory processes, the release of oxidizing agents and things which then interfere with normal functioning of the blood and blood vessels, and that triggers a heart attack or stroke."

"This study certainly has limitations," Ndunda says. For one, this study couldn't distinguish between occasional e-cigarette use and those who vape more frequently. "It likely matters how much you're using, and we couldn't evaluate that here," Ndunda says.

E-cigarettes can deliver a range of nicotine concentrations and a wide variety of chemical flavorings, adding further complications to the analysis. The study's design also means it can only show an association between e-cigarette use and risk, not cause and effect.

Ndunda added that a study that identifies e-cigarette users early and then tracks their health over time would yield a clearer picture of the consequences of vaping.

Dr. Chitra Dinakar, a clinical professor of pulmonary and critical care medicine at the Stanford University School of Medicine who has studied the health effects of e-cigarettes, says this work, which only surveys adults 18 and older, "does not reflect the risk of stroke in younger users." Still, she says, "this is an important topic that merits ongoing scrutiny."

Jonathan Lambert is an intern on NPR's Science Desk. You can follow him on Twitter: @evolambert.

About

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Vaping Health Risks: Study Links E-cigs to Heart Attack and Stroke—but There's More to It

newsweek.com/vaping-health-risks-e-cigs-heart-attack-stroke-study-links-theres-more-it-1309203

By Kashmira Gander January 30, 2019

People who smoke e-cigarettes are more likely to suffer from conditions including heart disease and stroke, research has suggested.

A preliminary study presented at the American Stroke Association's International Stroke Conference 2019, Honolulu, which has not yet been peer reviewed, linked vaping to cardiovascular disease. However, experts not involved in the work explained the association may come down to the past habits of vape users.

Between 2011 and 2015, the use of e-cigarettes in the U.S. has spiked by 900 percent, the authors of the research pointed out. The team at the University of Kansas wanted to provide an insight into the potential health implications of this habit, and specifically the potential risk of stroke.

The researchers studied 2016 data from the Behavioral Risk Factor Surveillance System survey, carried out each year by the Centers for Disease Control and Prevention. 66,795 respondents used e-cigarettes regularly, while 343,856 had never used the devices. They also took into account information on the age and sex of participants, whether they smoked, had diabetes, how much they exercised and their BMI.

The fifth of respondents who used e-cigarettes were younger on average compared with non-users, at 44 years old compared with 57 years old; had a lower BMI score; and were less likely to have diabetes.

But vape users were also more likely to smoke cigarettes, and had higher chance of suffering from a stroke, angina and coronary heart disease, according to the study.

Dr. Paul Ndunda, study author and assistant professor in the School of Medicine at the University of Kansas in Wichita, told *Newsweek* this study is the first to show an association between e-cigarette use and stroke. It is also one of the largest studies to show an association between e-cigarette use and heart disease, he said.

However, he acknowledged his study was limited in several ways. It was cross-sectional, meaning it does not prove causation but only association between disease and vaping. And e-cigarette and smoking were not quantified in the data, only if the participants were smokers or non-smokers.

“This research calls for well designed, large, long-term population studies to assess whether e-cigarettes cause stroke and cardiovascular disease,” he said.

Dr. Aaron Scott of the Institute of Inflammation and Ageing at the University of Birmingham, U.K., who was not involved in the study, explained to *Newsweek*: “This abstract doesn't tell us much more than what is already known.

"Most of the people using e-cigarettes are going to be ex-smokers and, as such, they will have a history of tobacco use and a higher risk of heart disease. The effects of nicotine on atherosclerosis [where plaque builds up inside your arteries] are also already well investigated.

“In terms of cardiovascular damage, the nicotine in e-cigarettes may, in the long run, prove to have similar effects to smoking traditional cigarettes but until long term sequential data is obtained it remains speculation."

His colleague, Professor David Thickett, also of the Institute of Inflammation and Ageing, agreed that observational studies such as this need to be “backed up by cohort studies that are followed over time.”

Addressing the potential harms of vaping more generally, Ndunda said there is still a lot that we don’t know about health effects of e-cigarettes.

“In addition to other known risks of e-cigarettes, there may be risks to brain and heart health. Therefore; those who haven’t started vaping and don’t smoke combustible cigarettes are probably better off not starting vaping. Those that are vaping, for purposes other than quitting smoking are probably better off stopping. Those that vape as a smoking cessation aid need to have a discussion with their doctors. There may be other effective methods suitable for them.”

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He pointed out the FDA has not approved e-cigarettes in the U.S. for smoking cessation.

However, Ndunda stressed research suggests regular cigarettes “present more health risks than e-cigarettes and e-cigarettes may have a role in quitting for some smokers but there is need for more research in this area and the public health implications of recommending e-cigarettes for smoking cessation is complicated."

Researchers believe e-cigarettes could be linked to cardiovascular problems. Getty Images

E-cigarettes linked to higher risk of stroke, heart attack, diseased arteries

eurekalert.org/pub_releases/2019-01/aha-elt012519.php

Public Release: 30-Jan-2019

American Stroke Association News Release - Abstract 9, Session A2

American Heart Association

DALLAS, Jan. 30, 2019 -- Using e-cigarettes increases your odds of having a stroke, heart attack and coronary heart disease, according to preliminary research to be presented in Honolulu at the American Stroke Association's International Stroke Conference 2019, a world premier meeting for researchers and clinicians dedicated to the science and treatment of cerebrovascular disease.

In 2016, 3.2 percent of U.S. adults and 11.3 percent of high school students reported using e-cigarettes in the preceding 30 days. Its use among young people increased by 900 percent between 2011 and 2015.

In the largest study to date examining e-cigarettes and stroke, researchers tapped a database of 400,000 respondents. That database, the 2016 behavioral risk factor surveillance system (BRFSS) survey, collected data from residents in all 50 states about their health-related risk behaviors, chronic health conditions and use of preventive services.

"Compared with non-users, e-cigarette users were younger, had a lower body mass index and a lower rate of diabetes," said Paul M. Ndunda, M.D., the study's author and an assistant professor in the School of Medicine at the University of Kansas in Wichita.

Some 66,795 respondents reported ever regularly using e-cigarettes. The control group was the 343,856 respondents who reported having never used e-cigarettes. Odds ratios were calculated using logistic regression analysis. Researchers found compared with non-users, e-cigarette users had:

- 71 percent higher risk of stroke;
- 59 percent higher risk of heart attack or angina;
- 40 percent higher risk of coronary heart disease; and
- Double the rate of cigarette smoking.

They also found 4.2 percent of e-cigarette users reported having suffered a stroke. However, the study data did not show deaths attributable to e-cigarette use.

The American Heart Association cautions against the use of e-cigarettes, stating that e-cigarettes containing nicotine are tobacco products that should be subject to all laws that apply to these products. The Association also calls for strong new regulations to prevent access, sales and marketing of e-cigarettes to youth and for more research into the product's health impact.

###

Coauthor is Tabitha Muutu, M.D. Researchers reported no funding for this study.

Note: Scientific presentation is 7:12 a.m. HT/12:12 p.m. ET, Wednesday, Feb. 6, 2019.

Additional Resources:

* Downloadable multimedia related to this news release are on the right column of the release link https://newsroom.heart.org/news/e-cigarettes-linked-to-higher-risk-of-stroke-heart-attack-diseased-arteries?preview=1217dd515a48f12e78a2d0fa3b1ad741

* For more news from AHA International Stroke Conference 2019, follow us on Twitter @HeartNews #ISC19.

Statements and conclusions of study authors that are presented at American Heart Association scientific meetings are solely those of the study authors and do not necessarily reflect association policy or position. The association makes no representation or warranty as to their accuracy or reliability. The association receives funding primarily from individuals; foundations and corporations (including pharmaceutical, device manufacturers and other companies) also make donations and fund specific association programs and events. The association has strict policies to prevent these relationships from influencing the science content. Revenues from pharmaceutical and device corporations are available at https://www.heart.org/en/about-us/aha-financial-information.

About the American Stroke Association

The American Stroke Association is devoted to saving people from stroke -- the No. 2 cause of death in the world and a leading cause of serious disability. We team with millions of volunteers to fund innovative research, fight for stronger public health policies and provide lifesaving tools and information to prevent and treat stroke. The Dallas-based association officially launched in 1998 as a division of the American Heart Association. To learn more or to get involved, call 1-888-4STROKE or visit StrokeAssociation.org. Follow us on Facebook and Twitter.

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Safe smoking alternative e-cigarette revealed as dangerous and addictive

thelantern.com/2019/01/safe-smoking-alternative-e-cigarette-revealed-as-dangerous-and-addictive/

Katie Hamilton



JUUL Labs announced changes to its marketing and products fol;lowing a public warning by the FDA. Credit: Courtesy TNS

It doesn't take much searching to find someone using an e-cigarette on campus, but the devices that came on to the scene as a safe smoking alternative might actually be a fruity problem.

According to Dr. Robert Jackler, professor and chair of the Department of Otolaryngology Head and Neck Surgery at Stanford University School of Medicine, e-cigarettes have helped create a "nicotine arms race." Instead of lowering the use of nicotine, e-cigarettes have seen an alarming increase of use among America's youth, which can largely be connected to JUUL Labs that came on the market in 2015.

"JUUL is absolutely a gateway to nicotine and young people all over America are getting addicted to nicotine using JUUL," Jackler said. "Once you're addicted to nicotine as a young person, there's some evidence that it rewires your brain and makes you more susceptible to further addictions."

JUUL Labs, which is now worth $15 billion, beat out Facebook as the fastest company ever to reach a valuation of $10 billion, Jackler said. Also, JUUL Labs holds a 76 percent share of the e-cigarette market, meaning 1-in-3 e-cigarette sales will be a JUUL product.

The 2018 National Youth Tobacco Survey found that around 21 percent of high schoolers use e-cigarettes, a 78 percent increase from 2017.

The Federal Drug Administration released a statement in September regarding the JUUL epidemic among teens, pressuring the company to change its marketing techniques that allowed minors to easily obtain its products.

JUUL announced in November that it would stop selling its mango, fruit, creme and cucumber flavored pods in all retail stores, but will still sell them on its website, which requires buyers to be 21 and older.

Smoke Zone, a local vape store on High Street, discontinued its supply of JUUL products in October after the FDA statement was released, according to Smoke Zone employee Alan Bischoff.

Bischoff said that Smoke Zone originally started carrying JUUL products in June due to the high demand on campus. In the time they sold JUUL products, the fruity flavors sold much quicker than the tobacco flavors, he said.

“All the ones you sell are mango, mint and crème brulee; it doesn’t taste like nicotine, you don’t feel like your smoking,” Bischoff said. “The last ones you sell will be tobacco.”

Jackler believes the flavors are what hook young people in to trying the product. He said he believes JUUL markets its sweet and fruity flavors to teens the same way super markets organize their fruity flavored cereal on the bottom shelves in a kid’s sightline while the bland, corn cereal flavors are at the top for adults.

In addition to the FDA statement, Bischoff said the store stopped selling JUUL products because Smoke Zone employees didn’t like them, didn’t want to risk selling to minors and felt they weren’t feasible for students. He pointed to a sign in the store that said that 42 JUUL pod ($168 worth) is equivalent to one $20 bottle of vape juice, encouraging e-cigarette users to choose the long-term cheaper option.

“It’s not good for you and it’s not cost effective, so we’re not going to rip people off,” Bischoff said.

Jackler estimated JUUL users spend roughly $1,000 to $2,000 a year just to feed their nicotine addiction.

Other “copycat” companies are creating products like JUUL at cheaper prices to make creating a nicotine addiction more feasible, according to Jackler, which is what he feels is a huge part of the nicotine arms race.

Jackler said that nicotine itself isn’t hugely problematic but rather the vehicle that brings the nicotine. He said that breathing in the vapor and flavoring chemicals can harm the lungs.

E-cigarettes are almost certainly safer than regular combustible cigarettes, Jackler said, but that doesn’t mean that smoking e-cigarettes is safe. He said research on the long-term effects of using e-cigarettes is in the works and might be ready within the next two years,

which will hopefully combat the idea of e-cigarettes being harmless devices.

“We know that if you start smoking [cigarettes] as a teenager, you don’t get lung cancer right away but rather when you’re forty or fifty,” Jackler said. “We are very concerned that people who are starting with JUUL today if they use it for ten or 20 years they’re likely to get serious lung disease.”

Bischoff said JUUL is not promoted as a product that contains high levels of nicotine, but rather as something that tastes good and is popular. He said he doesn’t believe anyone needs the amount of nicotine provided in JUUL pods that people would desire to get their hands on.

JUUL pods contain around five percent of nicotine per pod, one of the highest levels of nicotine on the market, which is equivalent to a pack of cigarettes. Jackler said that the level of nicotine in JUUL pods are intended for heavily addicted adult smokers, which can be dangerous in the hands of a naïve young person trying nicotine for the first time.

Jackler said that most users are unaware of the amount or the presence of nicotine in JUUL pods making them prone to unwittingly developing an addiction.

“It doesn’t take too much JUUL before you become hooked and before first thing in the morning you’re looking for your JUUL to take a hit and you’re going out between classes or even in the back of a classroom and blowing the vapor down your shirt or into a backpack cause you really crave it and you need it,” Jackler said. “Once that’s happening, you are addicted and it’s going to be very hard to stop.”

E-cigarettes were introduced originally to help wean off addicted cigarette smokers. With the misuse of products by young people, Jackler suggests that e-cigarette users trying to quit can either switch to lower nicotine leveled products gradually, meet with a doctor who helps with tobacco cessation or quit cold turkey.

Disclaimer: The contents of this publication are solely the responsibility of the authors and do not necessarily represent the official views of the US Department of Health and Human Services or any of its agencies.

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Heat-Not-Burn Tobacco Cigarettes: Smoke by Any Other Name

The tobacco industry's most recent response to the documented harms of cigarette smoking was to launch new heat-not-burn (HNB) tobacco cigarettes.[1] Philip Morris International (PMI) created IQOS (I-Quit-Ordinary-Smoking): disposable tobacco sticks soaked in propylene glycol, which are inserted in a holder in the HNB cigarette. The tobacco is heated with an electric blade at 350°C. The cigarettes are marketed by PMI as a "revolutionary technology that heats tobacco without burning it, giving you the true taste of tobacco, with no smoke, no ash and less smell."[2] In many countries, laws that protect people from passive smoke only apply to smoked tobacco products. Philip Morris International claims that IQOS releases no smoke because the tobacco does not combust and the tobacco leaves are only heated not burned. However, there can be smoke without fire. The harmful components of tobacco cigarette smoke are products of incomplete combustion (pyrolysis) and the degradation of tobacco cigarettes through heat (thermogenic degradation). Complete combustion occurs at a high temperature (>1300°C), higher than the heat generated by smoking a tobacco cigarette (<800°C). Typical markers of pyrolysis and thermogenic degradation of tobacco cigarettes are acetaldehyde, an irritant carcinogenic volatile organic compound, benzo[a]pyrene, a carcinogenic polycyclic aromatic hydrocarbon, and carbon monoxide.

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Pilot programs for IQOS began in 2014 in Japan and in 2015 in Switzerland and Italy. An internet survey in Japan published in 2015 suggested that younger individuals (15 to 39 years of age) were more likely to use IQOS, as were former smokers and current smokers.[3] Since 2016, a total of 19 countries have allowed the sale of IQOS cigarettes. In June 2016, data from PMI revealed that IQOS had captured 2.2% of the cigarette market in Japan. IQOS is not yet sold in the United States, but in December 2016, PMI submitted a modified risk tobacco product application to the US Food and Drug Administration. If successful, PMI will be less restricted in its marketing for the IQOS than for conventional tobacco cigarettes. Smokers and nonsmokers need accurate information about toxic compounds released in IQOS smoke. This information should come from sources independent of the tobacco industry, but the only analyses we found were from PMI and PMI competitors.[1]

Methods | We compared the contents of IQOS (IQOS Holder, IQOS Pocket Charger, Marlboro HeatSticks [regular], and Heets, Philipp Morris SA) smoke with the contents of conventional cigarettes (Lucky Strike Blue Lights). We used a smoking device designed and tested in our facility to capture the mainstream aerosol and developed to meet standards for common cigarettes and e-cigarettes.[4] We followed the International Organization for Standardization standards for puff volume (35 mL) at 2 puffs per minute, based on observation of IQOS smokers, who took a mean of 14 puffs during 5 to 6 minutes. We analyzed volatile organic compounds and nicotine by gas chromatography coupled to a flame ionization detector and polycyclic aromatic hydrocarbons using high-performance liquid chromatography coupled to a fluorescence detector, as previously described.[4] We trapped polycyclic aromatic hydrocarbons from IQOS cigarette smoke in a glass filter (Whatman 37 mm Ø GF/B) mounted in line with an XAD2 cartridge. For each sampling, 10 IQOS cigarettes were smoked. Each sampling support was desorbed in 10 mL of acetonitrile and sonicated for 1 hour. The eluate was evaporated in a vacuum concentrator (Speed Vac SC-200, ThermoFisher Scientific) set with 30 millibars and 27*g* until the residue was almost dry to prevent evaporation of the most volatile polycyclic aromatic hydrocarbons. The residue was filtered with polytetrafluoroethylene membrane (Acrodisc CR 13 mm, 0.45 µm, Pall Life Sciences) before it was analyzed with a high-performance liquid chromatography device (Ultimate 3000, ThermoFisher Scientific) equipped with a fluorescence detector (FLD-3000RS), UV detector (VWD-3000), and a separation column Nucleodur EC 150 × 3 mm C18 3 µm (Macherey-Nagel) under isocratic conditions (1.2 mL · min^{-1}). We injected 2 µL into the high-performance liquid chromatography chain; methanol/water (70/30) with acetonitrile was the eluent solvent at an initial ratio of 100% to 0% (4 minutes) and a linear gradient up to 100% acetonitrile (12 minutes). We did not analyze polycyclic aromatic hydrocarbons generated by conventional cigarettes and present the mean values in the 35 best-selling cigarettes brands in the United States, as reported by Vu et al.[5] We monitored the temperature near the heater blade inside the IQOS holder and the core of the conventional cigarette at a sampling rate of 3 Hz with a type k thermocouple.

Results | Volatile organic compounds, polycyclic aromatic hydrocarbons, and carbon monoxide were present in IQOS smoke (**Table**). The temperature of the IQOS was lower (330°C) than the conventional cigarette (684°C).[5] The IQOS smoke had 84% of the nicotine found in conventional cigarette smoke.

Discussion | The smoke released by IQOS contains elements from pyrolysis and thermogenic degradation that are the same harmful constituents of conventional tobacco cigarette smoke. International experts were invited by PMI to describe the IQOS aerosol; one expert claims that "less than 2% by weight of the aerosol components may derive from the pyrolysis of the tobacco substrate which would not be sufficient to characterize the aerosol as 'smoke.'"[6(p 2)] In contrast, our analyses reveal that advertising slogans such as "heat-not-burn" are

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Table. Concentrations of 8 Volatile Organic Compounds, 16 Polycyclic Aromatic Hydrocarbons, 3 Inorganic Compounds, and Nicotine in Mainstream Aerosol and Temperature of the HNB IQOS Cigarette and Conventional Cigarettes

Analyzed Compound	HNB Cigarette		Conventional Cigarette		Proportion of the Chemical in HNB and Conventional Cigarettes, %
	Amount, Mean (SD)	No. of Replications for Each Assay	Amount, Mean (SD)	No. of Replications for Each Assay	
Volatile organic compounds, µg per cigarette[a]					
Acetaldehyde	133 (35)	5	610[b]	1	22
Acetone	12.0 (12.9)	5	95.5 (13.5)	2	13
Acroleine	0.9 (0.6)	2	1.1	1	82
Benzaldehyde	1.2 (1.4)	5	2.4 (2.6)	2	50
Crotonaldehyde	0.7 (0.9)	5	17.4	1	4
Formaldehyde	3.2 (2.7)	5	4.3 (0.4)	2	74
Isovaleraldehyde	3.5 (3.1)	5	8.5 (10.8)	2	41
Propionaldehyde	7.8 (4.3)	5	29.6 (36.6)	2	26
Polycyclic aromatic hydrocarbons, ng per cigarette[c]					
Naphthalene	1.6 (0.5)	4	1105 (269)	7	0.1
Acenaphthylene	1.9 (0.6)	4	235 (39)	7	0.8
Acenaphthene	145 (54)	4	49 (9)	7	295
Fluorene	1.5 (0.6)	4	371 (56)	7	0.4
Anthracene	0.3 (0.1)	4	130 (18)	7	0.2
Phenanthrene	2.0 (0.2)	4	292 (44)	7	0.7
Fluoranthene	7.3 (1.1)	4	123 (18)	7	6
Pyrene	6.4 (1.1)	4	89 (15)	7	7
Benz[a]anthracene	1.8 (0.4)	4	33 (4.2)	7	6
Chrysene	1.5 (0.3)	4	48 (6.2)	7	3
Benzo[b]fluoranthene	0.5 (0.2)	4	24 (2.9)	7	2
Benzo[k]fluoranthene	0.4 (0.2)	4	4.3 (2.8)	7	9
Benzo[a]pyrene	0.8 (0.1)	4	20 (2.9)	7	4
Indeno[1,2,3-cd]pyrene	ND	4	NA	NA	NA
Benzo[ghi]perylene	ND	4	NA	NA	NA
Dibenzo[a,h]anthracene	ND	4	NA	NA	NA
Inorganics, ppm in the mainstream smoke[d]					
Carbon dioxide	3057 (532)	5	>9000	3	NA
Carbon monoxide	328 (76)	5	>2000	3	NA
Nitric oxide	5.5 (1.5)	5	89.4 (71.6)	3	6
Other measures					
Nicotine, µg per cigarette[a]	301 (213)	4	361	1	84
Temperature, °C	330 (10)	2	684 (197)	1	NA
Puff total count	12.6 (2.4)	32	13.3 (3.1)	6	NA

Abbreviations: HNB, heat-not-burn; NA, not analyzed; ND, not detected.

[a] We applied the methods described previously in Varlet et al[4] to analyze volatile organic compounds and nicotine.

[b] Because there was only 1 replication, no SD can be computed.

[c] We present values reported from Vu et al[5] for the ISO smoking regimen and for a mean of the 35 top-selling US cigarette brands.

[d] Carbon dioxide was measured with a Testo 535 (Testo), and carbon monoxide and nitric oxide were measured with a Pac 7000 that detected carbon monoxide (Draeger). The apparatus measured the smoke when it was released from the syringe pump.

no substitute for science. Dancing around the definition of smoke to avoid indoor-smoking bans is unethical. Principle 1 for implementing article 8 of the World Health Organization convention on tobacco control highlights that we should reject ideas that there is a threshold value for toxic effects from second-hand smoke. Independent studies should further evaluate the health effects of the IQOS. In the meantime, heated tobacco products such as IQOS should fall under the same indoor-smoking bans as for conventional tobacco cigarettes.

Reto Auer, MD, MAS
Nicolas Concha-Lozano, PhD
Isabelle Jacot-Sadowski, MD
Jacques Cornuz, MD, MPH
Aurélie Berthet, PhD

Author Affiliations: Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland (Auer); Department of Ambulatory Care and Community Medicine, University of Lausanne, Lausanne, Switzerland (Auer, Jacot-Sadowski, Cornuz); Institute for Work and Health, University of Lausanne and Geneva, Lausanne, Switzerland (Concha-Lozano, Berthet).

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Corresponding Author: Reto Auer, MD, MAS, Institute of Primary Health Care (BIHAM), University of Bern, Gesellschaftsstrasse 49, 3012 Bern, Switzerland (reto.auer@biham.unibe.ch).

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Editor's Note

No Smoke—Just Cancer-Causing Chemicals

Heat-not-burn tobacco products are for sale around the world. Although they are not yet on the market in the United States, Phillip Morris International has applied to the US Food and Drug Administration (FDA) to sell these products. These products threaten the progress that has been made on decreasing the harms of second-hand smoke because existing bans may not apply to these heat-not-burn products. However, as convincingly reported by Auer and colleagues,[1] although these products may or may not produce smoke, they release cancer-causing chemicals. As shown in their table, heat-not-burn cigarettes release similar levels of many volatile organic compounds and nicotine as conventional cigarettes and higher levels of the polycyclic aromatic hydrocarbon acenaphthene than conventional cigarettes. They are bad for health because they release cancer-causing chemicals, and I hope the FDA will not approve them for that important reason. If the FDA does approve the sale of these products, existing smoking bans should be amended to include these products.

Mitchell H. Katz, MD

Author Affiliations: Los Angeles County Department of Health Services, Los Angeles, California; Deputy Editor, *JAMA Internal Medicine*.

Corresponding Author: Mitchell H. Katz, MD, Los Angeles County Department of Health Services, 313 N Figueroa St, Rm 912, Los Angeles, CA 90012 (mkatz@dhs.lacounty.gov).

Conflict of Interest Disclosures: None reported.

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COMMENT & RESPONSE

Neuroleptics for Delirium: More Research Is Needed

To the Editor We read with interest the Original Investigation in a recent issue of *JAMA Internal Medicine* by Agar et al[1] on the management of delirium in the palliative care setting. Delirium is one of the most common and disturbing syndromes at the end of life,[2] and there are few well-designed studies to inform practice.[3] Because data from geriatrics and other populations cannot be extrapolated to the palliative care setting, this important study[1] provides unique insights into the role of haloperidol and risperidone compared with placebo; however, several issues regarding the study design complicate its interpretation.

We wonder if the composite subscore of the Nursing Delirium Screening Scale (NuDesc) is an appropriate primary outcome. Although NuDesc has been validated, this subscore has not been studied before, and the minimal clinical important difference has not been defined. While haloperidol and risperidone arms were associated with statistically significant worse NuDesc subscores, the magnitude of change may not be clinically meaningful based on the investigator-defined cutoff (<1 point).

If haloperidol and risperidone were indeed ineffective, could the low medication doses explain it? In our acute palliative care unit, daily haloperidol doses of more than 8 mg were often needed for patients who were agitated.[4,5] We are also curious that despite the low dose and short duration of neuroleptic use, Agar et al[1] reported shortened survival with risperidone. Given the large number of secondary outcomes, these findings should be considered as hypothesis-generating, and further studies are needed.

These are confusing times. Clinicians caring for patients with agitated delirium have to grapple with the dilemma of uncertain benefits and potential risks with neuroleptics for a distressing condition for which few other proven interventions are available. While identification of reversible causes and nonpharmacological measures seem intuitive, these interventions need to be standardized and tested formally in the palliative care setting in which delirium is often severe, progressive, and irreversible. For the large portion of patients who do not respond to these measures, neuroleptics may still have a role for refractory agitation. This study also reopens the debate on whether benzodiazepines alone should be considered for delirium. Given this is a single study enrolling predominantly patients with mild delirium (median Memorial Delirium Assessment Scale score, 13-15), it is premature to close the chapter on neuroleptics in palliative care as suggested by the authors and the accompanying editorial.[1] Instead, this study highlights the tremendous opportunities

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PART 3

Scientists describe problems in Philip Morris e-cigarette experiments



HOT PRODUCT: A man demonstrates the iQOS smoking device of Philip Morris International. The device is now sold in more than two dozen countries. REUTERS/Jaime Saldarriaga

Part 3: Former employees and contractors have detailed irregularities in the clinical experiments that underpin Philip Morris International's application to the FDA for approval of its iQOS smoking device. The agency is expected to decide by next year on whether the tobacco giant can sell its new product in the U.S.

By TOM LASSETER, PARITOSH BANSAL, THOMAS WILSON, AMI MIYAZAKI, DUFF WILSON and ADITYA KALRA | Filed Dec. 20, 2017, noon GMT

TOKYO/NEUCHATEL, Switzerland – The U.S. Food and Drug Administration is weighing whether to approve a potentially path-breaking smoking device by Philip

giant's application to the agency.

By heating tobacco instead of burning it, the company says the device, known as iQOS, avoids subjecting smokers to the same levels of carcinogens and other toxic substances found in a regular cigarette. The company has spent more than $3 billion developing new smoking platforms like iQOS. As part of that initiative, Philip Morris has published extensive scientific findings, based in part on clinical studies.

Tamara Koval, who worked at the company from 2012 to 2014 and helped coordinate clinical trials for the device, questioned the quality of some of the researchers and sites contracted to carry out those experiments. Koval was a co-author of the company's protocol used to run the studies globally. When she highlighted an irregularity in one of the studies, Koval said, Philip Morris excluded her from meetings.

Reuters also found irregularities during interviews with some of the principal investigators contracted to conduct the trials for the company. One principal investigator said he knew nothing about tobacco. Philip Morris had to jettison the experiment that investigator performed after it emerged he hadn't followed a basic procedure for obtaining informed consent from participants during clinical trials.

A second investigator submitted urine samples that exceeded what a human being is capable of, according to two former company employees, and then initially refused to acknowledge there was a problem. A third said he doesn't hold such company-sponsored clinical trials in high regard, describing them as "dirty" because their purpose is more commercial than scientific.

After reviewing Reuters' findings, Philip Morris said in a statement that "all studies were conducted by suitably qualified and trained Principal Investigators." The company said it understands that "FDA inspectors have already audited some facilities" involved in the trials. Philip Morris also said it had taken steps to address "any reported irregularity in our studies."

"Our policies encourage speaking up about suspected violations of law or our policies and we do not tolerate retaliation against those who speak up," the company said.

In addition to former Philip Morris employees involved with the iQOS program, Reuters interviewed six of the 11 principal investigators who were responsible for five of eight clinical trials the company submitted to the FDA. Reuters also reviewed hundreds of pages of publicly available Philip Morris study reports and FDA filings.

That reporting identified shortcomings in the training and professionalism of some of the lead investigators, as well as their knowledge of the study results.

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Graphic: Philip Morris' iQOS


Sidebar: No more harmful than coffee



CRITICAL VOICE: Former Philip Morris employee Tamara Koval, who helped coordinate clinical trials for the iQOS device, questioned the quality of the researchers contracted to conduct the experiments. REUTERS/Denis Balibouse

"Taken as a whole, it's clear they do not have the sophistication to carry out adequate and well-controlled clinical trials."

David Kessler, FDA commissioner from 1990 to 1997, on Philip Morris.

A group of tobacco research and policy experts reviewed detailed summaries of Reuters' reporting and Philip Morris' response. The experts, including a former head of the FDA and two former scientific advisers for the agency, said those findings raise concerns about Philip Morris' clinical trial program.

"Taken as a whole, it's clear they do not have the sophistication to carry out adequate and well-controlled clinical trials," said David Kessler, the FDA's commissioner from 1990 to 1997, referring to the company. "I am not inferring any malicious intent here, just that they lack sophistication, because this is not their bread and butter."

If the FDA has already audited some of the trial sites used by Philip Morris, the agency "should carefully review its audits and possibly expand them," said Kessler, a former dean of the medical school at Yale University.

Tom Eissenberg, who served on the FDA's tobacco products scientific advisory committee until earlier this year, said: "The FDA should audit."

Reuters did not find any evidence that the outcome of the experiments presented by the company to the FDA was manipulated or falsified.

The new insights into the company's clinical trial program for iQOS come at a crucial time for Philip Morris. The world's largest publicly traded tobacco company by market value and maker of Marlboro cigarettes has applied to the U.S. FDA to be able to sell iQOS in America, and also for permission to market it as a modified-risk tobacco product. That designation could mean that Philip Morris is allowed to market iQOS as presenting less harm or risk of disease to users than traditional tobacco.

application.

Philip Morris says the device, which heats small tobacco inserts, is meant for smokers who would not otherwise quit. Its chief executive officer, Andre Calantzopoulos, has told investors and media alike that he intends to one day replace cigarettes with products like iQOS. So far, iQOS makes up a fraction of the company's $75 billion revenues and Philip Morris continues to market conventional cigarettes across the globe.



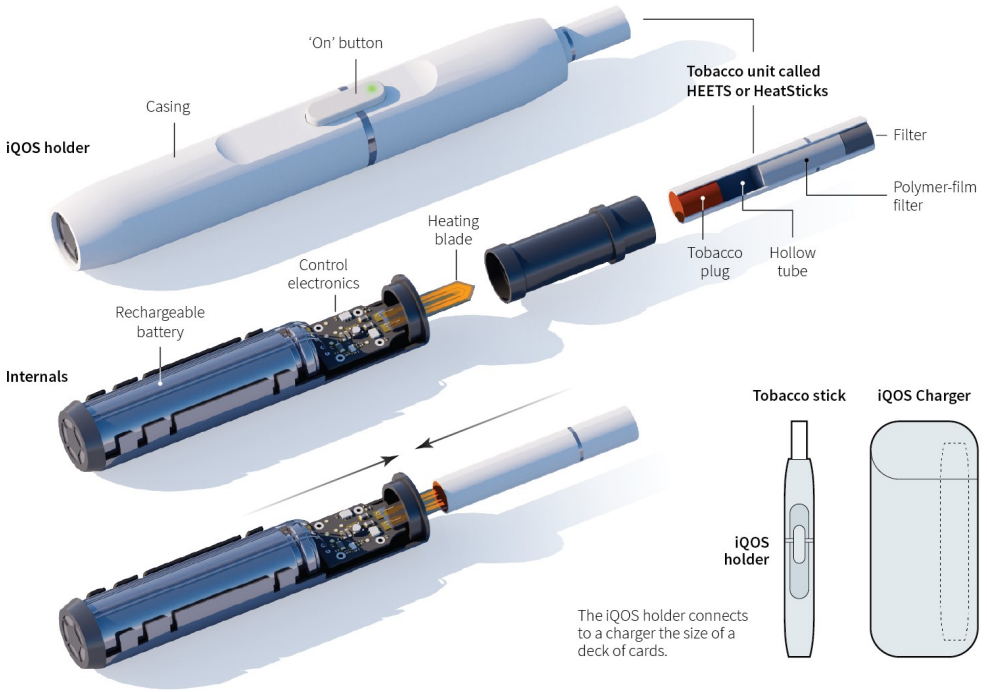
FUTURE VISION: Andre Calantzopoulos, Philip Morris International's chief executive, has said he plans to ultimately replace cigarettes with products like iQOS. REUTERS/Tony Gentile

Internal Philip Morris documents reviewed by Reuters show the significance of iQOS goes beyond its profit potential. The device is now sold in more than two dozen nations after it was first launched in Japan and Italy during late 2014.

The company has a 10-year plan for what it calls "normalization" of the tobacco industry, according to a 2014 strategy document. The industry has been shunned over the past two decades for producing and marketing products that kill people and previously lying about it. Under a section on "strategies and actions" to achieve that goal, the document lists, among other things, new smoking devices such as iQOS and the scientific research involved in developing them.

Philip Morris' iQOS

Philip Morris International's iQOS heats tobacco instead of burning it, releasing nicotine-laced vapor. The company says that means the device avoids subjecting smokers to the same levels of carcinogens and other toxic substances found in a regular cigarette.



Sources: Philip Morris International; TechInsights Inc

Told about that document, Philip Morris said: "The suggestion that the purpose of our development of IQOS and our scientific research program is to 'normalize' the tobacco industry is false."

showed the device significantly reduced the level of certain harmful substances that users were exposed to compared with cigarettes, and satisfied their nicotine cravings. “In fact the level of reduction is so considerable, it approaches 95% of the levels measured in smokers who quit altogether,” the company said in a statement to Reuters.

Taken along with the company’s laboratory studies, Philip Morris said, the research program “in its entirety demonstrates that IQOS is likely to reduce the risk of smoking related diseases.”

Philip Morris is responsible for the majority of the science that has been published about iQOS. “Those who criticize us should probably look at our science,” said Tommaso Di Giovanni, a company spokesman, during a tour of Philip Morris’ research and development headquarters in March.



RESEARCH CENTER: Known as the Cube, Philip Morris developed the iQOS device at its R&D facility in Switzerland. REUTERS/Denis Balibouse

“All studies were conducted by suitably qualified and trained Principal Investigators.”

Philip Morris International in a statement to Reuters.

The eight clinical experiments that Philip Morris submitted to the FDA were conducted between 2013 and 2015. For one study, scientists in Texas and Florida did not respond

such as Good Clinical Practice. That best-practices document says investigators "should be qualified by training and experience and should have adequate resources" to properly conduct a trial.

Masayuki Sugimoto, the principal investigator who oversaw testing at one facility used by Philip Morris to conduct a trial, said his Tokyo clinic is "heavily in the red."

Sugimoto said he generally has little confidence that all the participants in experiments like the one he ran for Philip Morris on nicotine tell the truth about their smoking history – that is, whether they smoke.

Speaking about the final study report from the Philip Morris trial, Sugimoto said in an interview that he generally doesn't have time to read such things in detail. He said he probably signed a document indicating he had received the final report. Sugimoto gestured with his thumb and forefinger to indicate a thick document: "I just don't read them."

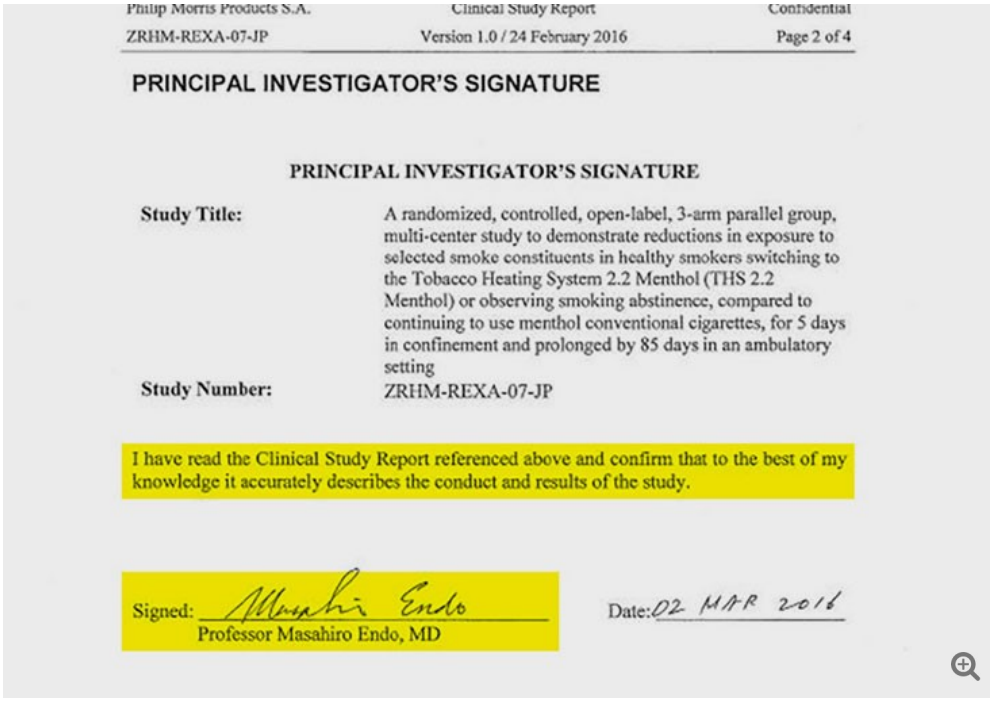
Philip Morris said that it "did not receive any such comments or statements from the PI," or principal investigator. Sugimoto's study, it said, was completed "without any issues." The company said the study data was reviewed and discussed with the investigator throughout the trial.

The Japanese company hired to monitor studies in the country, CMIC Holdings Co Ltd, said in a statement that researchers confirmed that trial participants were smokers by using urine tests.

Asked about the tests, Sugimoto said he thought they would prevent non-smokers from joining the trial but added, "I don't know whether they were done that rigorously."

Told of Sugimoto's doubts about the honesty of study participants, Eissenberg, who served on the FDA's tobacco products scientific advisory committee from 2011 to 2017, said "it raises a great deal of concern."

A principal investigator "is required to make sure that the participants meet the inclusion-exclusion criteria that are in the protocol," said Eissenberg. He was referring to the fact that clinical trial subjects' backgrounds – such as whether they are smokers – should meet the parameters of the experiment for the data to be valid. "And a PI should have confidence in that," he said.



Philip Morris Products S.A. Clinical Study Report Confidential
ZRHM-REXA-07-JP Version 1.0 / 24 February 2016 Page 2 of 4

PRINCIPAL INVESTIGATOR'S SIGNATURE

PRINCIPAL INVESTIGATOR'S SIGNATURE

Study Title: A randomized, controlled, open-label, 3-arm parallel group, multi-center study to demonstrate reductions in exposure to selected smoke constituents in healthy smokers switching to the Tobacco Heating System 2.2 Menthol (THS 2.2 Menthol) or observing smoking abstinence, compared to continuing to use menthol conventional cigarettes, for 5 days in confinement and prolonged by 85 days in an ambulatory setting

Study Number: ZRHM-REXA-07-JP

I have read the Clinical Study Report referenced above and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

Signed: Masahiro Endo
Professor Masahiro Endo, MD

Date: 02 MAR 2016

SIGNED DOCUMENT: Masahiro Endo, one of the principal investigators on the iQOS clinical trials, signed off on the study report for the experiments he conducted. In an interview with Reuters, he initially said he was not aware of the results of the trials.

At another laboratory in Japan, issues with how the study was carried out were so acute that data from 56 participants was thrown out, raising questions about the competence of the principal investigator. Philip Morris halted the study at that location.

In the company's study documentation released by the FDA, Philip Morris recorded the reason for discarding the data as non-compliance with good clinical practices, specifically "failure of the site to meet sample collection procedures and data recording procedures."

Kishor Lad, who was Philip Morris' data manager on the study, said the site crossed a line of what's allowed during such trials: It collected samples before getting informed consent forms signed by the volunteers. "Completely a no-no in the GCP world," Lad said, using the acronym for good clinical practice.

Philip Morris confirmed to Reuters that "informed consent was not obtained prior to execution of a study procedure" – specifically, the collection of urine samples. The problem was identified by CMIC, the contract research group, during a routine monitoring visit, Philip Morris said. A subsequent round of audits, it added, "led to prompt discontinuation of the study at the Seishukai Clinic." The incident, the company said, was properly logged in the study report and the submission to the FDA.

"It suggests the investigator had no idea, did not understand or just didn't care what his responsibilities were in conducting the study," said Greg Koski, a former director of the U.S. federal Office for Human Research Protections, which advocates for research subjects. "This is such a flagrant violation, that investigator shouldn't be doing clinical studies."

Mamoru Oki was the principal investigator at the time at the facility, the Seishukai Clinic in Tokyo. Reached by phone, Oki said: "My specialty is urology and I don't know anything about tobacco, so I cannot talk."

committee from 2010 to 2013, said a principal investigator's professed lack of knowledge about tobacco is not ideal.

"For any tobacco-related clinical trial, an investigator with a background in tobacco product research would have better qualifications to evaluate the study results than a novice," she said.

The study continued at a parallel site, the Tokyo Heart Center.

During an interview at the center, principal investigator Masahiro Endo said repeatedly that he had no idea what the results were from his study.

"We did medically safe and accurate blood samples, but were not told the results. So even if we are asked questions, we won't be able to answer," he said. "We were paid, it ended there."

But in a statement signed last year and submitted by Philip Morris to the FDA, Endo said he had read the clinical study report from the company and confirmed "that to the best of my knowledge it accurately describes the conduct and results of the study." Principal investigators in all of the Philip Morris clinical trials signed the same statement.

A day after speaking with Reuters, Endo sent an email clarifying that after checking his records he saw that he'd signed a receipt saying he received a report on the results and acknowledging that he'd be listed as the principal investigator. He had spoken during the interview "with a fuzzy memory," Endo said.

Clinical trial experts interviewed by Reuters said it's not uncommon for principal investigators to be unaware of test results sent to a third party specialty laboratory for analysis. But they also emphasized that if companies want better science, they need the investigators to be more involved with all aspects of a study.

"It seems like the investigator here is in the role of a technician, not as a principal investigator," said Kessler, the former FDA commissioner.

Kessler said it's hard to understand how such investigators could have signed off on the clinical study report "when they clearly were not versed in the study results."

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Other principal investigators described their work differently.

Fumimasa Nobuoka, a principal investigator on one of the trials in Japan, said he read the Philip Morris study report: "I thought it was well done, well written."

James Borders, who was the principal investigator for a study held in Lexington, Kentucky, said the experiments in his trial were done ethically and followed sound scientific practice.

Borders, who became chief medical officer at the Baptist Health Lexington hospital, said such studies help consumers make an informed decision. His decision to be involved with the study, he said, hinged on the proposition that a device like iQOS could be the "lesser of two evils."



SHOP DISPLAY: An iQOS store in the upmarket Tokyo shopping district of Ginza. The device was first launched in Japan in 2014. REUTERS/Kim Kyung-Hoon

Philip Morris said that while it sponsored the clinical trials, the experiments were "performed by reputable research facilities" and monitored by contract research organizations – companies used to oversee such studies. It hired U.S.-based Covance Inc to serve as its global contract research organization, according to an internal Philip Morris 2013 assessment plan. Covance, a unit of Laboratory Corporation of America Holdings, declined to comment.

CMIC, the company hired to monitor the Japan studies, said in a statement: "All the clinical trials you referred to were conducted in accordance with GCP guidelines" – good clinical practices – "and we believe that the results of the trials are scientifically trustworthy."

As part of her job coordinating between Philip Morris and those contracted to run its clinical trials, Koval, the former company scientist, conducted medical safety training across the world for principal investigators and others involved with the iQOS studies.

During one study training session in Tokyo, Koval said, she realized some of the researchers could not speak English well and she was unable to communicate with them. Koval said she does not speak Japanese and there was no interpreter present.

"I was like, Jesus, what are we doing here?" she said. At dinner later, Koval said, she saw two of the men, and they were unable to describe in English what their jobs were.

When asked about Koval's session, Philip Morris said it was a meeting with its contract research organization and others. It added that "all PIs and team members with active roles in the study were fluent in English."

But Sugimoto, one of the Japanese principal investigators, told Reuters in an interview, "I can't speak English."

And Endo, another of the lead researchers, said that when Philip Morris executives visited his site someone was present who helped translate "questions like whether to cut the crusts off bread" when giving food to study subjects.

exceeded the limits of what a human being is capable of producing in a single day, according to Koval and Lad, the former clinical data manager.

Lad, who worked at Philip Morris from 2012 to 2015, said he didn't think anything "malicious" had happened. Maybe urine samples were swapped or there was a mistake with the containers used to collect the urine, he said.

But when the principal investigator for the Polish site was asked about the results, she would not admit there was a problem, Lad and Koval said. Instead, they said, the scientist explained that the test subjects were large Polish men.

Philip Morris said that "a few participants" in an early stage of the trial "produced unusually large volumes of urine." Because medical tests showed no problems with the subjects, the company said, the investigator did not initially consider the samples to be "adverse events."

After discussion with the medical monitors of the study as well as Philip Morris, the investigator "ultimately decided to mark these incidences as adverse events," the company said. An investigation at the site confirmed that researchers had followed study protocol and good clinical practices, the company said.

The principal investigator running the study in Poland for Philip Morris, Katarzyna Jarus-Dziedzic, declined to discuss what happened with the urine case at her site, citing confidentiality.

Koval said that after she raised concerns about the Polish study with Philip Morris executives in Switzerland she was excluded from meetings.

Philip Morris said in a statement that Koval was "part of the team" that followed up on the urine samples. In fact, the company said, she was "an active member" of the group that finalized the data set from the studies for further analysis.

Koval confirmed that she was part of the team and involved with the data set. But she stood by her account that she was shut out of conversations and meetings about the urine samples.

In 2014, Philip Morris terminated her contract, Koval said. She said she returned to the pharmaceutical industry a few months later and now works for Swiss drugs giant Novartis AG.

After leaving Philip Morris, Koval was given a certificate of service that said, "Tamara drove clinical program development activities." It said she had demonstrated "professionalism" and "unwavering commitment" in her work.

Additional reporting by Ari Rabinovitch in Jerusalem, Joe Brock in Johannesburg, Anna Koper in Warsaw, Amanda Ferguson in Belfast, Hyunjoo Jin in Seoul and Kate Kelland in London.

No more harmful than coffee

By PARITOSH BANSAL, TOM LASSETER, DUFF WILSON and ADITYA KALRA

About a decade later that quest culminated in the iQOS, a device that heats tobacco but does not burn it. Philip Morris says the lack of combustion means smokers are exposed to far lower levels of toxic emissions than with regular cigarettes. “The ultimate result of this is reduced tobacco related harm and diseases,” the company said in a statement.

The world’s largest publicly traded tobacco company by market value has applied to the U.S. Food and Drug Administration to market iQOS as less harmful than cigarettes.

But four scientists and researchers who worked for the company on the iQOS program told Reuters that while Philip Morris was able to prove the lower amounts of exposure to harmful substances, that doesn’t necessarily mean that using the device is less likely to result in disease than regular cigarettes.

“Exposure is not directly linked to the risk of having a disease,” said Urban, a scientist who worked at Philip Morris until 2010 analyzing data from clinical and laboratory experiments. “The diseases are much too complicated.”



EXPOSURE AND RISK: Hans-Joerg Urban, who worked as a scientist at Philip Morris, said that proving iQOS users are less exposed to harmful substances than cigarette smokers, doesn’t mean they are less at risk of getting tobacco-related diseases. REUTERS/Arnd Wiegmann

Dorothy Hatsukami, a former member of the FDA’s tobacco products scientific advisory committee, agrees. “At this point, research is still too nascent to say with certainty that reduced exposure translates into reduced risk,” she said.

Philip Morris is seeking FDA approval to market iQOS under two different standards. It has applied for approval as a device that reduces exposure to harmful substances. It has also applied on a second track with a higher bar – to get approval to market it as carrying reduced risk of tobacco-related disease. The first option, a special provision for companies that are unable to meet the threshold of reduced risk, comes with a restriction. Consumers cannot be “misled into believing” the product is less harmful than other tobacco products, FDA regulations say.

If the FDA approves the application, that would raise the possibility of Philip Morris International’s former parent company and U.S. partner, Altria Group Inc, capturing market share in a nation where overall cigarette sales plummeted more than 30 percent between 2005 and 2016.

Kishor Lad, a clinical data manager at the company between 2012 and 2015, said to prove the product presents less risk of tobacco-related disease, the company would need to conduct large clinical trials over several years to show that people who used iQOS lived longer than people who smoked cigarettes.

Philip Morris said it disagrees. Under U.S. regulations, the company said, the FDA “does not require premarket epidemiological data as a condition of marketing authorization.”

Lad added that it’s not correct to say that “if you’re less exposed to these harmful substances then, sort of, it’s less harmful for you.”

The Philip Morris Files

By Tom Lasseter, Paritosh Bansal, Thomas Wilson, Ami Miyazaki, Duff Wilson and Aditya Kalra
Picture Editor: Thomas White

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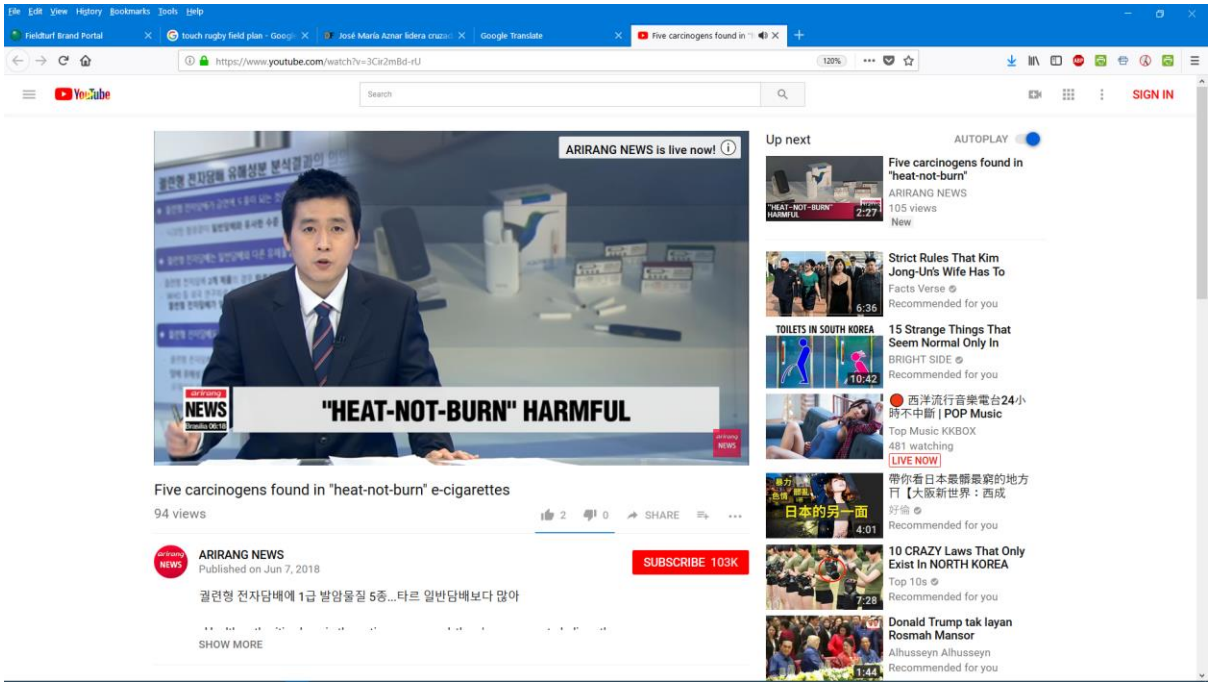
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Vaping Swiss lab finds toxic substances in Philip Morris e-cigarette

swissinfo.ch/eng/vaping_swiss-lab-finds-toxic-substances-in-philip-morris-e-cigarette/44878990



Experts warn inhaling even very small amounts of isocyanates can cause serious health damage.

(Keystone)

Highly toxic substances escape from the filters of IQOS electronic cigarettes produced by Swiss-based tobacco manufacturer Philip Morris International.

The finding, reported by the SonntagsZeitungexternal link, was made by a laboratory commissioned by the Blue Cross of Bern, Solothurn and Fribourg.

These dangerous toxins, called isocyanates, are released when polymer filters are heated to 100 degrees Celsius.

However, the laboratory did not check whether the substance is inhaled by the smoker.

"If isocyanates are inhaled during the use of IQOS, it is very problematic," warns Rainer Kaelin, a pulmonologist and former vice-president of the Swiss Lung League.

Even inhaling very small amounts, he notes, can cause serious health damage.

Voluntary ban

Isocyanates can cause illness even three months after exposure. In some extreme cases, the inhalation of isocyanates into the air has "led to fatal diseases after one year", Kaelin said.

Philip Morris acknowledges the problem, but a spokesman for the tobacco company assured the newspaper that the toxin is not inhaled when using an IQOS cigarette.

Last year Swiss producers of electronic cigarettes, and several retail outlets that sell such products agreed to a voluntary ban on the sale to minors until a Swiss law change comes into effect.



Working at a multinational Inside Philip Morris International: On a mission to convince the skeptics

What is it like to work inside the world's largest tobacco company as it tries to radically reinvent itself?

By Jessica Davis Plüss

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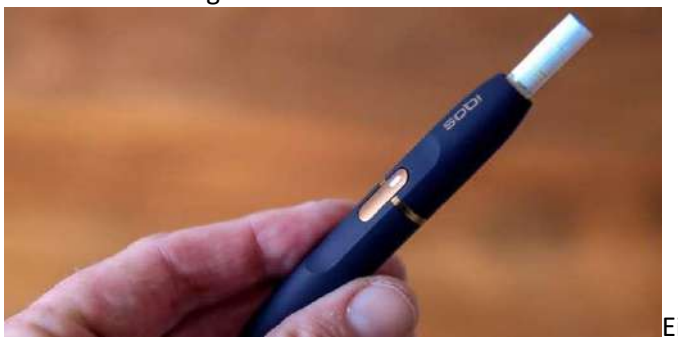
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https://www.nau.ch/news/schweiz/elektrische-zigarette-giftige-stoffe-in-produkten-von-philip-morris-65505208

Elektrische Zigarette: Giftige Stoffe in Produkten von Philip Morris

Die elektrische Zigarette von Philip Morris enthält giftige Stoffe. Der Hersteller beteuert aber, diese würden nicht eingeatmet.



Ein Mann hält eine E-Zigarette des Typs iqos der Firma Philip Morris in einem Tabakgeschäft in der Hand. - dpa

Das Wichtigste in Kürze

- Bei den Filtern der E-Zigaretten Iqos lösen sich gifte Stoffe.
- Doch der Hersteller Philip Morris beteuert, dass diese nicht eingeatmet werden.

Die boomende elektrische Zigarette soll gefährdend sein. Aus den Filtern der Marke Iqos von Philip Morris entweichen bei Erwärmung hochgiftige Stoffe. Das hat ein Labor im Auftrag des Blauen Kreuzes Bern-Solothurn-Freiburg entdeckt, wie die «SonntagsZeitung» berichtet.

Bei der Untersuchung wurden die Polymerfilter auf 100 Grad erhitzt. Das Labor stellte dabei fest, dass sich gefährliche Giftstoffe – sogenannte Isocyanate – vom Filter lösen. Ob der Stoff beim Konsum inhaliert wird, wurde nicht getestet.



Das Logo von Philip Morris. Die Elektrische Zigarette von Iqos stehtin der Kritik. - Keystone

Rainer Kaelin, Waadtländer Lungenspezialist und früherer Vizepräsident der Lungenliga Schweiz, warnte gegenüber der Zeitung. «Wenn sich erhärtet, dass beim Konsum von Iqos Isocyanate eingeatmet werden, ist das hoch problematisch». Bereits das Einatmen sehr kleiner Mengen könne die Gesundheit stark schädigen und bereits nach drei Monaten krank machen. Im Extremfall habe das Einatmen von Isocyanaten in der Luft «bereits nach einem Jahr zu Krankheiten mit tödlichem Verlauf geführt».

Philip Morris sieht Problematik nicht ganz

Philip Morris räumt dem Bericht zufolge die Existenz des Gifts in der elektrische Zigarette ein. Im Alltagsgebrauch von Iqos werde der Stoff aber nicht inhaliert, versicherte ein Konzernsprecher mit Verweis auf eigene detaillierte Untersuchungen.

Das Blaue Kreuz widerspricht den Aussagen des Konzerns. Philip Morris will künftig gegen 40 Prozent des Umsatzes mit «risikoreduzierten Produkten» erwirtschaften. Der Konzern preist Iqos als eine «potenziell weniger schädliche Alternative zu herkömmlichen Zigaretten» an

Translated

Electric Cigarette: Toxic substances in products of Philip Morris

The electric cigarette by Philip Morris contains toxic substances. The manufacturer claims that they would not be inhaled.

E-cigarettes A man holds an iqos e-cigarette from Philip Morris in a tobacco shop in his hand. - dpa
the essentials in brief

The filters of e-cigarettes Iqos release poisonous substances.
But the manufacturer Philip Morris assures that these are not inhaled.

The booming electric cigarette should be dangerous. Philip Morris Iqos filters release highly toxic substances when heated. This has been discovered by a laboratory commissioned by the Blue Cross Bern-Solothurn-Freiburg, as reported by "SonntagsZeitung".

In the study, the polymer filters were heated to 100 degrees. The laboratory found that dangerous toxins - so-called isocyanates - are released from the filter. Whether the substance is inhaled during consumption has not been tested.

E-cigarettes
The logo of Philip Morris. The Electric Cigarette from Iqos is in the criticism. - Keystone

Rainer Kaelin, Vaud lung specialist and former vice president of the Swiss Lung League, warned the newspaper. "**If it is confirmed that isocyanates are inhaled when Iqos is consumed, this is highly problematic**". Inhaling even very small amounts can severely damage your health and make you sick after just three months. In extreme cases, the inhalation of isocyanates in the air "has led to fatal diseases already after one year".

Philip Morris does not quite see the problem

According to the report, Philip Morris admits the existence of the poison in the electric cigarette. In the everyday use of Iqos the substance is not inhaled, assured a company spokesman with reference to their own detailed investigations.

The Blue Cross contradicts the statements of the group. In the future, Philip Morris wants to generate around 40 percent of its sales with "risk-reduced products". The group praises Iqos as a "potentially less harmful alternative to traditional cigarettes"

Gift in Filtern der E-Zigaretten von Philip Morris

tagesanzeiger.ch/wirtschaft/unternehmen-und-konjunktur/Gift-im-Filter-von-E-Zigaretten-von-Philip-Morris/story/12776821

Das Blaue Kreuz weist gefährliche Stoffe in den Filtern der E-Zigaretten von Philip Morris nach. Der Konzern beteuert, diese würden nicht eingeatmet.



Im Labor lösten sich Giftstoffe vom Filter: Iqos wird als risikoarmes Produkt beworben. Foto: R. Gaillard/REA/laif

Mischa Aebi
Redaktor Politik
@sonntagszeitung ABO+ 07.04.2019

Feedback

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Fehler.

Bereits zwei Jahre nach ihrer Markteinführung sind die E-Zigaretten Iqos von Philip Morris ein Renner. Es sei «die mit Abstand erfolgreichste Neueinführung einer Industrie-Markenfamilie im deutschen Zigarettenmarkt seit Jahrzehnten», sagte jüngst Markus Essing, Chef von Philip Morris Deutschland. Der Konzern will künftig 40 Prozent des Umsatzes mit «risikoreduzierten Produkten» wie Iqos erwirtschaften. Iqos seien eine «potenziell weniger schädliche Alternative zu herkömmlichen Zigaretten».

Nun lässt ein Befund des Blauen Kreuzes Bern-Solothurn-Freiburg aufhorchen. Die Suchtpräventions-Fachstelle liess Filter von Iqos bei einem anerkannten Labor auf Giftstoffe untersuchen. Dazu wurden die Polymerfilter auf 100 Grad erhitzt. Dabei hat das Labor festgestellt, dass sich gefährliche Giftstoffe – sogenannte Isocyanate – vom Filter lösen. Ob beim Konsumieren von E-Zigaretten diese Giftstoffe eingeatmet werden, wurde nicht getestet. Der Zuständige beim Blauen Kreuz, Markus Wildermuth, ist besorgt: «Beim Gebrauch werden die Filter noch stärker erhitzt als im Labor.» Es bestehe deshalb das Risiko, dass sich die gefundenen Giftstoffe beim Inhalieren von Iqos lösen.

Arzt: «Hochproblematisch, wenn sich das erhärtet»

Der renommierte Lungenarzt Rainer Kaelin teilt die Sorgen des Blauen Kreuzes: «Bereits das Einatmen sehr kleiner Mengen Isocyanate kann die Gesundheit stark schädigen.» Isocyanate müsse man aus gesundheitlicher Sicht einer anderen Kategorie zuordnen als die Schadstoffe im Tabakrauch. Stoffe, die bei der Tabakverbrennung entstehen, schaden der Gesundheit laut Kaelin in der Regel nur, wenn man sie über einen längeren Zeitraum einatmet. «Isocyanate können hingegen bereits nach drei Monaten krank machen.» Im Extremfall habe das Einatmen von Isocyanaten in der Luft «bereits nach einem Jahr zu Krankheiten mit tödlichem Verlauf geführt».

Isocyanate können Lungenkrankheiten auslösen, vergleichbar mit der obstruktiven chronischen Lungenerkrankung COPD. Kaelin war acht Jahre Vizepräsident der Lungenliga. Für Arbeitsplätze, an welchen mit Isocyanat-haltigen Stoffen gearbeitet wird, gibt es strenge Vorschriften. Die Konzentration darf nicht höher als 0,02 Milligramm pro Kubikmeter Luft sein. Kaelin warnt: «Wenn sich erhärtet, dass beim Konsum von Iqos Isocyanate eingeatmet werden, ist das aus meiner Sicht hochproblematisch». Isocyanate in Iqos können laut Kaelin selbst dann gesundheitsschädigend sein, wenn sie unter den Grenzwerten der Suva liegen.

Studien zeigen das Gegenteil

Philip Morris räumt auf Anfrage ein, man habe die giftigen Stoffe in den Filtern der Iqos unter ähnlichen Bedingungen ebenfalls identifiziert. Es sei «jedoch wichtig zu bemerken, dass der Filter nicht so verwendet wurde, wie dies ein Iqos-Benutzer unter Alltagsbedingungen tun würde», hält Philip-Morris-Sprecher Julian Pidoux in der Stellungnahme fest. Um zu verstehen, welche Bestandteile von einem Iqos-Benutzer unter Alltagsbedingungen tatsächlich inhaliert werden, habe «Philip Morris das Aerosol von Iqos mit Nachweisgrenzen bis in den Millionstelgrammbereich pro Stick vollständig analysiert», so Pidoux. Im von einem Iqos-

Benutzer inhalierten Aerosol habe man kein Isocyanate identifiziert. «Wir können daher bestätigen, dass Benutzer von Iqos diesen Verbindungen bei der Verwendung des Produkts nicht ausgesetzt sind.»

Für Wildermuth vom Blauen Kreuz ist das wenig beruhigend: «Wir konnten belegen, dass die Filter beim gewöhnlichen Gebrauch partiell schmelzen und dabei auf eine Temperatur erhitzt werden, bei welcher sich Isocyanate tatsächlich ablösen.» Philip Morris bestreite dagegen bis heute, dass der Filter beim Iqos-Konsum partiell schmilzt, obwohl auch eine US-Studie sowie zahlreiche Rückmeldungen von Iqos-Konsumenten das Gegenteil zeigten, sagt Wildermuth. Zudem sei es per se problematisch, wenn solche Konsumwaren Giftstoffe enthielten. «Solange nicht unabhängige Forscher der möglichen Gefährdung durch Isocyanate nachgehen, bleiben die Iqos-Benutzer einem potenziellen Risiko ausgesetzt.»

(SonntagsZeitung)

Erstellt: 07.04.2019, 12:15 Uhr

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JaNein

Artikel zum Thema

Schon 15-Jährige stehen auf E-Zigaretten



Suchtexperten sind alarmiert: Mehr als die Hälfte der Buben hat schon an einer E-Zigarette gezogen.
Mehr...

30.03.2019

Kommt jetzt das Werbeverbot für E-Zigaretten?

Bereits 15-Jährige dampfen, wie Zahlen von Sucht Schweiz zeigen. Nun steigt der Druck auf die Politik.
Mehr...

Gregor Poletti. 29.03.2019

Wie E-Zigaretten das Herzinfarktrisiko beeinflussen

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Das Neuste Wirtschaft

SICK IN 3 MONTHS -POISON IN PHILIP MORRIS E-CIGS

«In drei Monaten krank» – Gift in E-Zigaretten von Philip Morris

bluewin.ch/de/news/vermischtes/hochgiftige-stoffe-in-den-filtern-von-e-zigaretten-von-philip-morris-entdeckt-235685.html



E-Zigaretten sind eine immer beliebter werdene Alternative zu herkömmlichen Kippen. Gesünder sind sie aber nicht: In den Filtern der Marke Iqos haben Wissenschaftler nun hochgiftige Stoffe nachgewiesen.
DPA / Symbolbild

Dampfen statt qualmen: E-Zigaretten werden immer beliebter. In den Filtern einer bekannten Marke hat das Blaue Kreuz nun hochgiftige Stoffe nachgewiesen. Der Hersteller beteuert, dass diese Dämpfe nicht eingeatmet würden.

In den Filtern der boomenden E-Zigaretten Iqos von Philip Morris entweichen bei Erwärmung hochgiftige Stoffe. Das hat ein Labor im Auftrag des Blauen Kreuzes Bern-Solothurn-Freiburg entdeckt, wie die «SonntagsZeitung» (kostenpflichtiger Artikel) berichtet.

Bei der Untersuchung wurden die Polymerfilter auf 100 Grad erhitzt. Das Labor stellte dabei fest, dass sich gefährliche Giftstoffe – sogenannte Isocyanate – vom Filter lösen. «Beim Gebrauch werden die Filter noch stärker erhitzt als im Labor», zitiert die «SonntagsZeitung» Markus Wildermuth, beim Blauen Kreuz zuständig für den Test.

Ob der Stoff beim Konsum inhaliert wird, wurde nicht getestet. Rainer Kaelin, Waadtländer Lungenspezialist und früherer Vizepräsident der Lungenliga Schweiz, warnte gegenüber der Zeitung dennoch: «Wenn sich erhärtet, dass beim Konsum von Iqos Isocyanate eingeatmet werden, ist das hoch problematisch.»

Suchtstudie

Schweizer Jugendliche dampfen gerne



Isocyanate sind ein gefährliches Gift. Sie schädigen die Membranen menschlicher Zellen. Sie kommen unter anderem in Lösungsmitteln, Beschichtungen, Lacken oder Industrieschäumen vor. Für Arbeitsplätze gelten strenge Vorschriften.

Die Schadstoffe können zu Augenverletzungen wie Hornhautschäden und Atemwegsreizungen bis hin zu Asthma oder der obstruktiven chronischen Lungenerkrankung COPD führen. Daneben können sie allergische Reaktionen hervorrufen. Das Einatmen aus der Umgebungsluft kann bereits nach einem Jahr zu tödlichen Krankheiten führen.

1984 entwichen im indischen Tank einer Pestizidfabrik des US-Chemiekonzerns Union Carbide im indischen Bhopal rund 40 Tonnen eines Isocyanats. Das führte zur Katastrophe von Bophal, die über 2800 Menschen das Leben kostete. Mehrere Hunderttausende trugen schwere Verletzungen wie Augen- und Schleimhautschäden davon.

Bereits das Einatmen sehr kleiner Mengen könne die Gesundheit stark schädigen und bereits nach drei Monaten krank machen. Im Extremfall habe das Einatmen von Isocyanaten in der Luft «bereits nach einem Jahr zu Krankheiten mit tödlichem Verlauf geführt».

Genussmittel

Viel Rauch um E-Zigaretten im 2018



Philip Morris räumt dem Bericht zufolge die Existenz des Gifts ein. Im Alltagsgebrauch von Iqos werde der Stoff aber nicht inhaliert, versicherte ein Konzernsprecher mit Verweis auf eigene detaillierte Untersuchungen.

Das Blaue Kreuz widerspricht den Aussagen des Konzerns. «Wir konnten belegen, dass die Filter beim gewöhnlichen Gebrauch partiell schmelzen und dabei auf eine Temperatur erhitzt werden, bei welcher sich Isocyanate tatsächlich ablösen», sagt Markus Wildermuth im «Tages-Anzeiger».

Philip Morris will künftig gegen 40 Prozent des Umsatzes mit «risikoreduzierten Produkten» erwirtschaften. Der Konzern preist Iqos als eine «potenziell weniger schädliche Alternative zu herkömmlichen Zigaretten» an.



1:18

Wie süchtig ist die Schweizer Jugend?

Während der Konsum von Alkohol, Zigaretten und Cannabis seit 2014 gleich bleiben, sind Jugendliche zunehmend offen für E-Zigaretten. In der Studie 2018 für das Bundesamt für Gesundheit präsentiert Sucht Schweiz dieses und weitere Ergebnisse zum Gesundheitsverhalten und dem Substanzkonsum der Jugendlichen in der Schweiz.

28.03.2019

Zurück zur Startseite

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iQOS: evidence of pyrolysis and release of a toxicant from plastic

Barbara Davis, Monique Williams, Prue Talbot

Department of Molecular, Cell and Systems Biology, University of California, Riverside, California, USA

Correspondence to
Dr Prue Talbot, Department of Molecular, Cell and Systems Biology, University of California, Riverside, CA 92521, USA; talbot@ucr.edu

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ABSTRACT

Objective To evaluate performance of the I quit original smoking (iQOS) heat-not-burn system as a function of cleaning and puffing topography, investigate the validity of manufacturer's claims that this device does not burn tobacco and determine if the polymer-film filter is potentially harmful.

Methods iQOS performance was evaluated using five running conditions incorporating two different cleaning protocols. Heatsticks were visually and stereomicroscopically inspected preuse and postuse to determine the extent of tobacco plug charring (from pyrolysis) and polymer-film filter melting, and to elucidate the effects of cleaning on charring. Gas chromatography–mass spectrometry headspace analysis was conducted on unused polymer-film filters to determine if potentially toxic chemicals are emitted from the filter during heating.

Results For all testing protocols, pressure drop decreased as puff number increased. Changes in testing protocols did not affect aerosol density. Charring due to pyrolysis (a form of organic matter thermochemical decomposition) was observed in the tobacco plug after use. When the manufacturer's cleaning instructions were followed, both charring of the tobacco plug and melting of the polymer-film filter increased. Headspace analysis of the polymer-film filter revealed the release of formaldehyde cyanohydrin at 90°C, which is well below the maximum temperature reached during normal usage.

Discussion Device usage limitations may contribute to decreases in interpuff intervals, potentially increasing user's intake of nicotine and other harmful chemicals. This study found that the tobacco plug does char and that charring increases when the device is not cleaned between heatsticks. Release of formaldehyde cyanohydrin is a concern as it is highly toxic at very low concentrations.

INTRODUCTION

With the rise of smoking alternatives, the electronic nicotine delivery systems market has boomed, with electronic cigarettes (EC) being among the most popular worldwide.[1 2] However, there are still a number of conventional (combustible) cigarette smokers who would welcome a cigarette-like tobacco-containing/nicotine-containing product that is devoid of or has a significantly reduced toxicity compared with conventional cigarettes.[1] To appeal to this demographic, Philip Morris International (PMI) has released a new product called the iQOS (I quit original smoking), which is a 'heat-not-burn' system,[3] as an alternative to conventional cigarettes and EC. The iQOS system uses a flange, called the 'heater', which is composed of a silver, gold, platinum, ceramic coating,[4] to heat a rolled, cast-leaf sheet of tobacco impregnated with glycerin, thereby creating an aerosol without combustion.[3] This aerosolisation process is proposed to reduce the user's exposure to toxic and carcinogenic chemicals produced by the combustion of tobacco.[5 6] Thus, the consumer gets the 'harm reduction' component of EC along with the mouth/throat feel of a conventional cigarette. The iQOS system has been well received in Japan and Italy. The iQOS is currently sold in 26 markets by PMI with plans to expand to over 30 countries, including the USA.[7]

Although this product has been extensively evaluated by the manufacturer,[3 5 6 8–13] these studies appeared in a journal that may have a deficient review process,[14] emphasising the need for independent evaluation of the iQOS. As our initial study, we have evaluated the performance of the iQOS system under various conditions, tested the effects of cleaning on performance and pyrolysis and determined the composition of and potential health risk from the polymer-film filter.

MATERIALS AND METHODS

iQOS product acquisition and storage

Four iQOS tobacco heating system kits, manufactured by Philip Morris Products S.A. (Switzerland), were purchased online at eBay (https://www.ebay.com/) from sellers with a 98% or higher satisfaction rating. Kits arrived sealed and in excellent condition. Kits were inventoried, and the components of each kit were placed into individual plastic containers and stored in a dry area at 22°C when not in use.

Cartons of Marlboro (blue box) heatsticks, manufactured by Philip Morris Brands Sàrl (Italy), were purchased in Japan and shipped to us via a personal shopper. Each carton was individually sealed and in excellent condition. Heatsticks were stored, unopened, in a dry, dark area at 22°C in their cartons until used. Unused heatsticks from opened packs were stored in an airtight bag in their carton.

Cleaning the iQOS

iQOS holders were tested using two cleaning regimens: (1) the 'per-use' cleaning protocol in which the device was thoroughly cleaned after each heatstick using the cleaning sticks to remove residual fluid and tobacco plug debris from the heater and surrounding base and to clean out the cap and (2) the manufacturer's recommended cleaning instructions in which the cleaning cycle was used after every 20 heatsticks before using the brush cleaners. When heatstick fragments were left behind, the cleaning hook was used to remove these pieces, as

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necessary, and the holder cap was cleaned by a 5 min warm water immersion. The instructions clearly state that the holder itself is not to be wetted.

Performance evaluation

Pressure drop, which measures the draw resistance of the heatstick, aerosol absorbance (density), a measure of particulate matter trapped within the aerosol, and puff number were evaluated for iQOS products using equipment and protocols described previously.[15–17] Pressure drop across heatsticks was evaluated using a Cole-Parmer Masterflex L/S peristaltic pump (Vernon Hills, Illinois, USA) connected to a U-tube water manometer to detect the change in differential pressure for each puff. Airflow rates were precalculated/precalibrated to the appropriate pump speed using a conversion factor provided by the pump head manufacturer, and flow rate was verified using a Brooks Instruments Sho-Rate flow meter (Hatfield, Pennsylvania, USA). Aerosol density was evaluated by capturing aerosols in a tubular cuvette, and absorbance was measured immediately at 420 nm using a Bausch & Lomb spectrophotometer (120 V, 0.9 A, Rochester, New York, USA).

iQOS devices were evaluated with five operating conditions; four (conditions 1–4) used the per-use cleaning protocol and one (condition 5) used the manufacturer's recommended cleaning instructions. The pump head, tubing set-up and running conditions were as follows: (1) low airflow rate 2 s protocol—the peristaltic pump was outfitted with a Cole-Parmer Masterflex Model 7015-21 pump head (standard pump head) using Masterflex Tygon E-LFL (tubing size 15) tubing to generate a flow rate of 7 mL/s with a 2 s puff duration for a total puff volume of 14 mL, 14 puffs were taken at 25 s intervals; (2) low airflow rate 4 s protocol—the same pump set-up and running conditions as for condition 1 with a 4 s puff duration generating a 28 mL puff volume; (3) International Organization for Standardization (ISO)—the pump was outfitted with a Cole-Parmer Masterflex L/S Easy-Load II Model 77200-52 high-performance pump head with Masterflex Tygon E-LFL (tubing size 15) producing a 17.5 mL/s flow rate with a 2 s puff duration, generating a total puff volume of 35 mL, with a total of six puffs taken, one puff every minute; (4) the Health Canada standard (HCI)—a Cole-Parmer Masterflex L/S Easy-Load II Model 77200-52 high-performance pump head was used with Masterflex Tygon E3603 (tubing size 36) tubing for a flow rate of 27.5 mL/s, with a 2 s puff for a total puff volume of 55 mL, 12 puffs were taken at 30 s intervals; (5) manufacturer's recommended cleaning (HCI), the same pump set-up and running conditions as described for condition 4 but in the absence of per-use cleaning; for this protocol the manufacturer's recommended cleaning instructions were followed (table 1). For conditions 1–4, three different iQOS devices were evaluated with each device being tested in triplicate, that is, a new heatstick was used for each experiment; condition 5 employed a single device in which 10 heatsticks were tested without cleaning between each stick.

Effect of use on the tobacco plug and polymer-film filter

The condition of the tobacco plugs was evaluated by visual and microscopic inspection and imaged using a Nikon C-LEDS stereomicroscope equipped with a Nikon Digital Sight DS-Vi1 camera head (Nikon, Minato, Tokyo, Japan) before and after use. Some heatsticks were dissected before and after use to further evaluate residual char (referred to as 'char' only) of the tobacco plugs and the condition of the polymer-film filter.

Gas chromatography–mass spectrometry analysis of iQOS heatstick polymer-film filters

Gas chromatography–mass spectrometry (GC–MS) using a qualitative wide-scope screening method was performed using an Agilent 7890B GC coupled with a 5977A MSD equipped with a

Table 1 Performance of iQOS heat-not-burn holders

Holder	Puff duration	Puff interval	Airflow rate (mL/s)	Puff volume (mL)	Total number of puffs	Average pressure drop (mm H_2O)	Average absorbance
Low airflow rate 2 s protocol*							
A	2	25	7	14	14	13±5	0.42±0.08
B	2	25	7	14	14	13±4	0.45±0.08
C	2	25	7	14	14	18±7	0.46±0.06
Low airflow rate 4 s protocol†							
A	4	25	7	28	14	9±4	0.41±0.05
B	4	25	7	28	14	11±4	0.46±0.09
C	4	25	7	28	14	10±4	0.49±0.04
ISO standard‡							
A	2	60	17.5	35	6	62±5	0.49±0.10
B	2	60	17.5	35	6	65±8	0.54±0.09
C	2	60	17.5	35	6	57±5	0.49±0.04
HCI standard§							
A	2	30	27.5	55	12	103±9	0.26±0.03
B	2	30	27.5	55	12	100±9	0.41±0.05
C	2	30	27.5	55	12	105±13	0.42±0.05
Manufacturer's recommended cleaning (HCI)¶							
E	2	30	27.5	55	12	103±12	0.46±0.06

*Per-use cleaning protocol, standard pump head with Tygon 15 tubing.
†Per-use cleaning protocol, standard pump head with Tygon 15 tubing.
‡Per-use cleaning protocol, high-performance pump head with Tygon 15 tubing.
§Per-use cleaning protocol, high-performance pump head with Tygon 36 tubing.
¶Manufacturer's recommended cleaning, HCI, high-performance pump head with Tygon 36 tubing.
HCI, Health Canada Standard ; ISO, International Organization for Standardization; iQOS, I quit original smoking.

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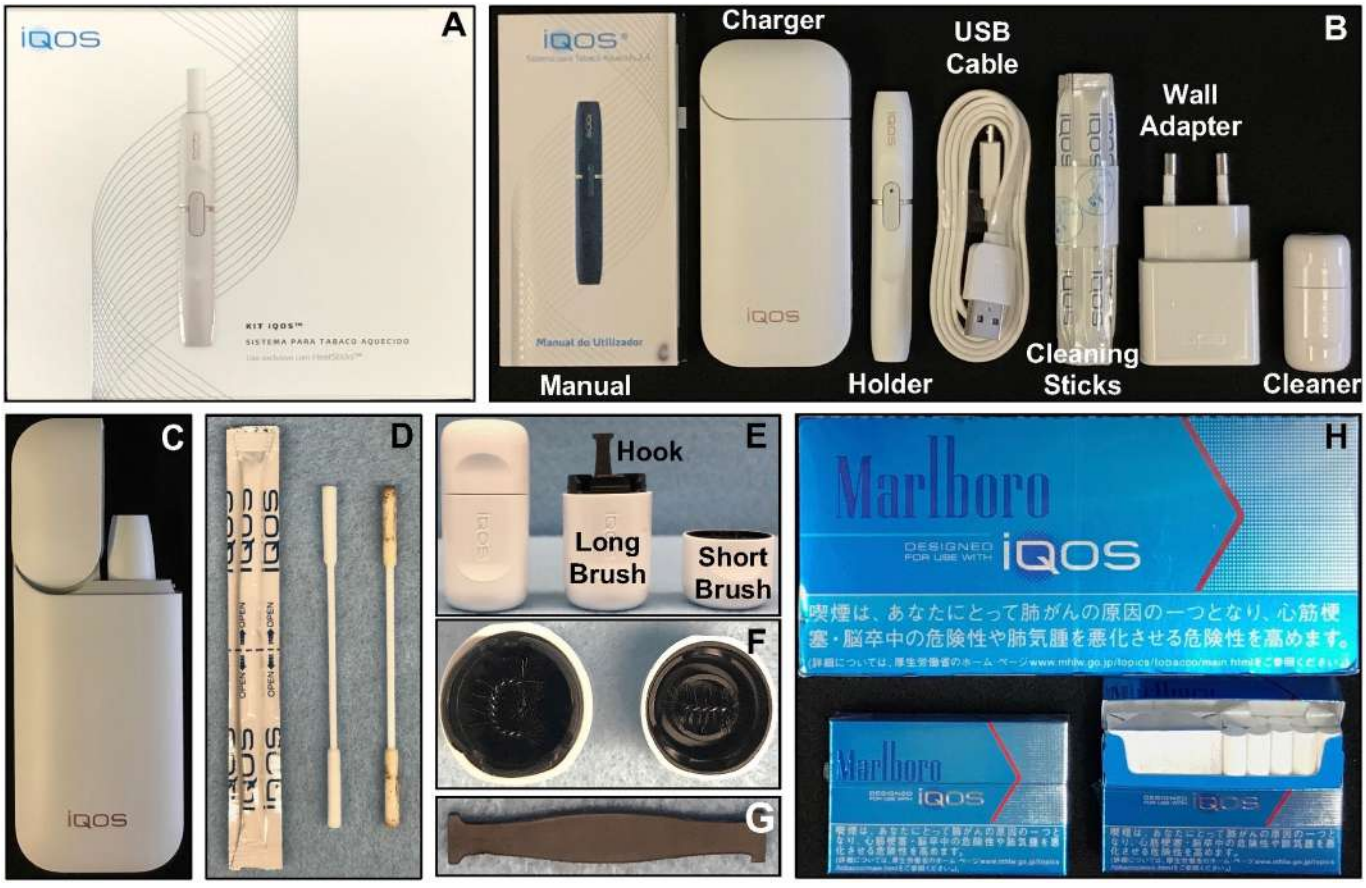


Figure 1 The I quit original smoking (iQOS) heat-not-burn system. (A) An iQOS starter kit. (B) The kit consists of an instruction manual, iQOS pocket charger, iQOS holder, USB cable, iQOS cleaning sticks, wall charging adapter and iQOS cleaner. (C) Profile view of iQOS holder inside a pocket charger. (D) Individual pack of iQOS cleaning sticks with an example of an unused stick and a stick after a single use per end. (E) A closed and opened iQOS cleaner; the larger end contains the long brush and protruding cleaning hook, and the shorter end contains the short brush. (F) Internal view of the iQOS cleaner showing the two brushes (long brush on the left, short brush on the right). (G) The cleaning hook removed from the iQOS cleaner. (H) Marlboro iQOS Heat Stick carton (containing 10 individual packs), sealed individual pack and opened pack exposing heatsticks.

7698A Headspace Sampler (Santa Clara, California, USA). Evaluation of iQOS aerosols was performed using headspace analysis. Chromatographic separation was accomplished using an Agilent J&W HP-5ms Ultra Inert GC Column (30 mx0.25 mmx0.25 µm) and ultra-pure helium (>99.999% purity) as the carrier gas at a flow rate of 1.5 mL/min. For headspace analysis, three unused heatsticks were dissected, polymer-film filters were removed, and a 3 mm portion (16.7%) closest to the tobacco plug were excised and placed into 20 mL headspace vials. All samples were analysed with a split ratio of 50:1, a solvent delay of 2 min, with blank analysis between each sample. GC ramp conditions were as follows: 40°C for 5 min, 45°C for 5 min, 90°C for 5 min, 130°C for 5 min, 135°C for 5 min, 165°C for 5 min, 190°C for 2 min, all temperature ramps were at 10°C/min. Ionisation of compounds was performed using electron impact ionisation at 70 eV in positive mode, the ion source maintained at 250°C and chemicals were identified using the National Institue of Standards and Technology mass spectral library (Gaithersburg, Maryland, USA), only chemicals with an 85% or higher probably match were listed as identifiable.

RESULTS

Components in the iQOS heat-not-burn system

The iQOS kit (figure 1A–G) consists of an instruction manual written in German, English, Portuguese and Italian, a pocket charger, the holder (device), a Universal Serial Bus (USB) cable and a European wall adapter plug for charging, moist cleaning sticks to clean the holder and cap, and the cleaner, which contains a long brush for cleaning the inside of the holder, where the heater is housed, a short brush for cleaning the cap and a hook for removing pieces of tobacco plug left in the holder/cap. A universal power adapter was purchased from Amazon (https://www.amazon.com/) and used to charge the pocket charger unit. Each carton of iQOS heatsticks contained 10 individually wrapped packs, and each pack had 20 heatsticks (figure 1H).

The iQOS kit components had an overall feel of good craftsmanship. The fabrication of the tobacco plug cast-leaf demonstrates a waste not want not strategy in that the plug is fabricated from pulverised tobacco remnants/waste materials, including tobacco stems, torn leaf material and leaf dust.[18] These items are reconstituted with natural adhesives and glycerin (a solvent that is used in EC fluids to produce aerosol) and processed into sheets forming cast-leaf, which is rolled and used as the tobacco plug.[3]

Cleaning of iQOS device

The interior chamber of the holder contained a heating element, referred to in the iQOS instruction manual as the silver, gold, platinum, ceramic-coated heater (figure 2). Unused holders were clean and debris-free with a white base and white heater with a metallic coil in its centre (figure 2A–C). Used holders

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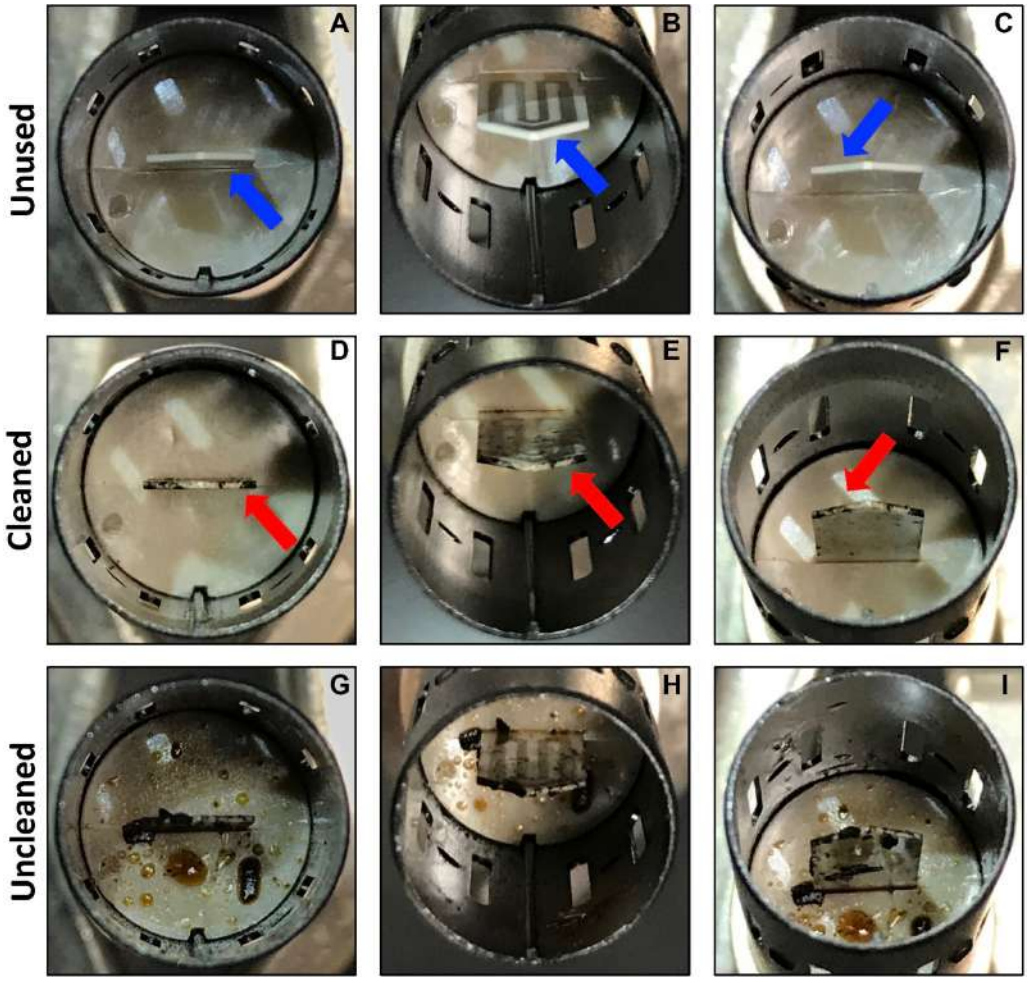


Figure 2 Internal view of the I quit original smoking holder. (A–C) Clean, unused holder showing heater (blue arrows). (D–F) Used holder that was cleaned after every use; black residue remains on heater (red arrows). (G–I) Used holder that was not cleaned between uses (10 uses).

that were thoroughly cleaned with the cleaning sticks between each heatstick were generally similar to the unused holder, except that the heating element had deposits of hardened dark debris that was not removed by the cleaning stick, cleaning cycle of the pocket charger or long brush (figure 2D–F). In the used holder that was not cleaned between heatsticks (manufacturer's recommended cleaning), brown liquid and particulates covered the base, walls and heater (figure 2G–I). With continued use in the absence of cleaning, the volume of liquid and debris increased, and the pieces of debris became darker and appeared more charred (figure 2D–I were taken after the 10th heatstick was used).

iQOS performance

The iQOS gives users a maximum of 14 puffs during a 6 min window per heatstick, after which it must be recharged before it can be used again. Performance of the iQOS was evaluated using five puffing protocols (figure 3, table 1). For protocols 1–4, three different iQOS devices (holders A, B and C) were tested in triplicate, that is, a new heatstick was used for each experiment, and each device underwent an intensive cleaning between each heatstick. For protocol 5, a single device (holder E) was used, and it was not cleaned between 10 heatsticks (average of the first three heatsticks is shown in figure 3I,J). For all testing protocols, pressure drop decreased as puff number increased. Aerosol density readings increased with use, peaking around puffs 7–9 and then begin to decrease. Although pump set-up affected pressure drop, it did not affect aerosol absorbance which remained similar under all running conditions, However, differences in testing conditions may lead to alterations in the chemical constituents present within the aerosol without altering aerosol density. Not cleaning did not affect performance except that pressure drop was more variable during the first four puffs in the uncleaned trials.

Tobacco plug charring

Dissection of unused and used heatsticks showed tobacco plug charring (figure 4A). Stereomicroscopic comparison of unused (figure 4B) and used (figure 4C) tobacco plugs confirmed charring or blackening of the cast-leaf. Visual and stereomicroscopic inspection of used heatsticks show the effects cleaning had on device heat production. Comparison of the first and 10th used heatstick from holder A (per-use cleaning) shows that with regular cleaning the charred area surrounding the heater, referred to as the zone of charring, does not increase with use (figure 4D,E). The effects of cleaning on heating were most evident during the course of the manufacturer's recommended cleaning (HCI) testing. Comparison of these heatsticks to unused and per-use cleaned heatsticks showed that in the absence of regular cleaning, the zone of charring increased as the number of heatsticks tested increased (figure 4H–L).

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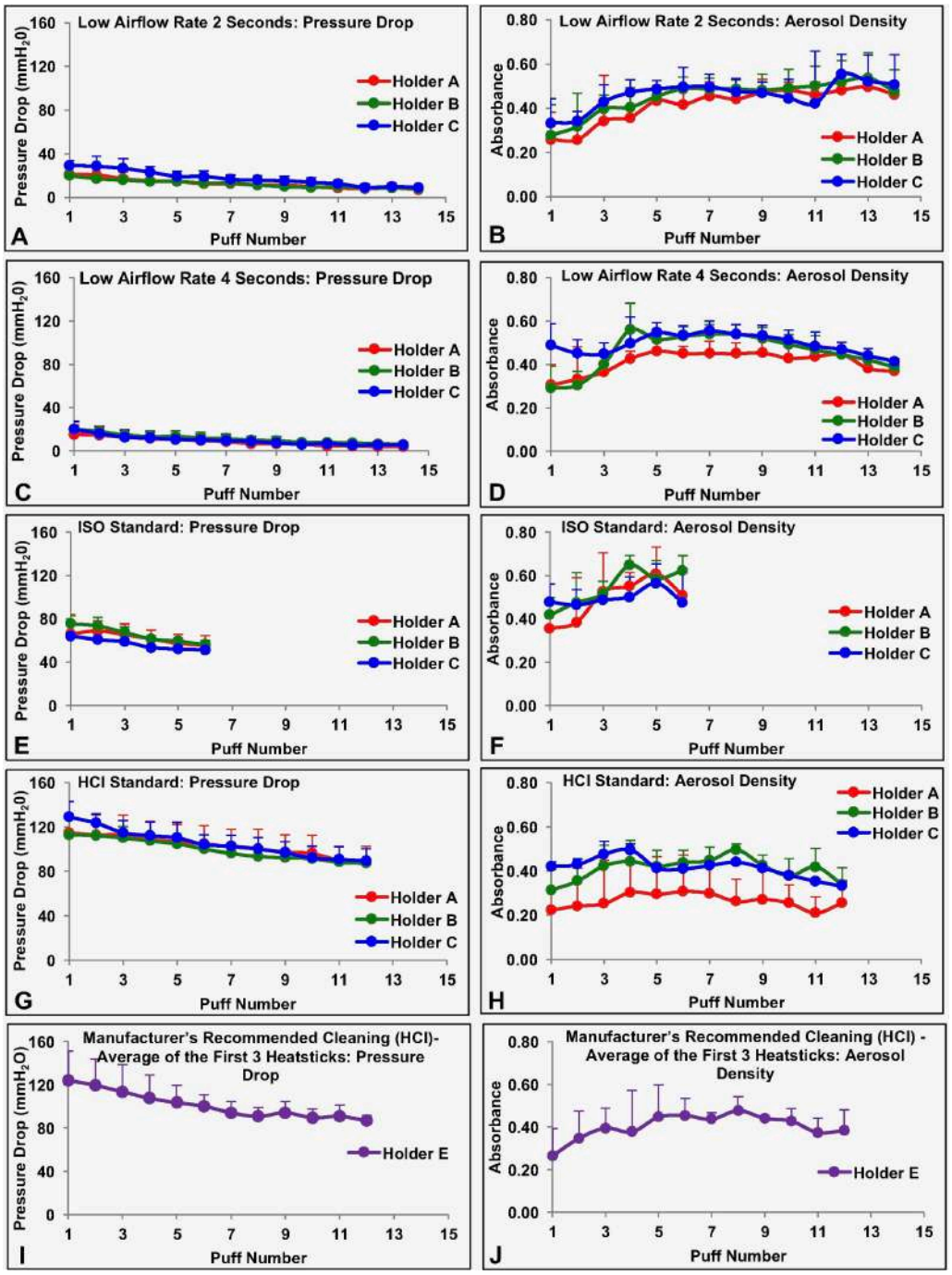


Figure 3 Performance characteristics of the I quit original smoking heat-not-burn system. (A, C, E, G and I) Pressure drop is plotted versus the puff number for five puffing protocols. (B, D, F, H and J) Absorbance is plotted versus puff number for the five puffing protocols. Each line of the graph represents the average of three heatsticks for an individual holder (holder A=red, holder B=green, holder C=blue and holder E=purple). HCI, Health Canada Standard ; ISO, International Organization for Standardization.

Polymer-film melting

Effects of cleaning on heating were not exclusive to the tobacco plug; figure 4A shows that the polymer-film filter (labeled 2), which is separated from the tobacco plug (condition 4) by the hollow acetate filter (condition 3), was adversely effected. The aerosol produced by the iQOS was hot enough to melt the polymer-film filter, which could allow release of potentially hazardous chemicals. Melting of the polymer-film filter was evident by slight yellowing of the filter, as well as by narrowing of the end closest to the tobacco plug (figure 4A indicated by black arrow). This melting and subsequent cooling of the filter caused it to harden, preventing it from being longitudinally dissected. Comparison of unused and used polymer-film filters from both per-use and manufacturer's recommended cleaning experiments showed the relationship between cleaning and increased heat generation. First (figure 4F) and 10th (figure 4G) filters from cleaned devices showed similar discoloration and melting to that of the first filter from the uncleaned device (figure 4N). Comparison of these heatsticks to subsequent manufacturer's recommended cleaning used heatsticks showed discoloration and melting of the polymer-film filter increased with increased use (figure 4M–Q).

Headspace analysis of unused polymer-film filters

GC–MS headspace analysis of unused polymer-film filters showed the presence of ε-caprolactone and lactide, common

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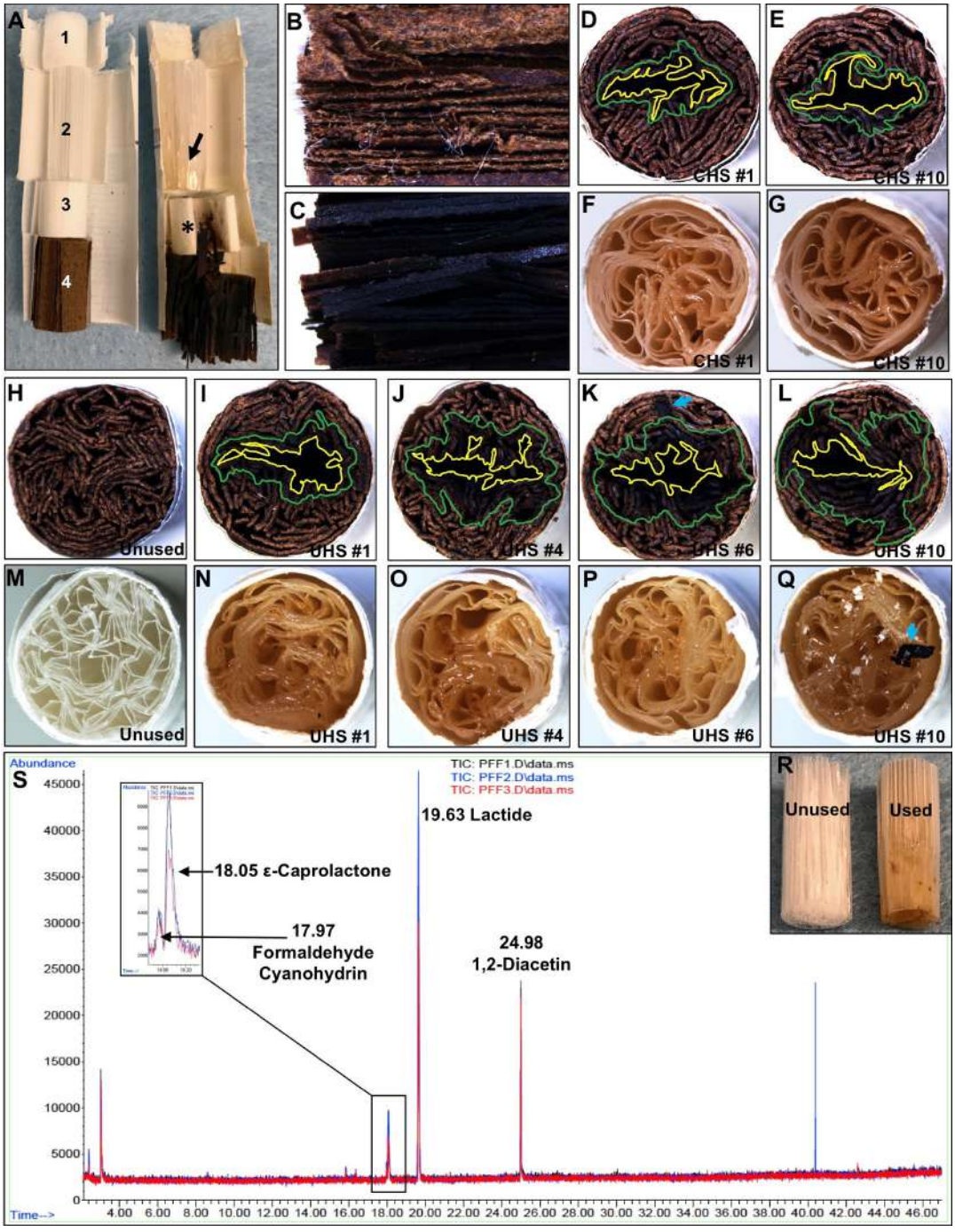


Figure 4 Charring of tobacco plug and melting of polymer-film filter. (A) Dissected heatsticks, each heatstick is composed of: (1) the low-density cellulose mouthpiece filter, (2) polymer-film filter, (3) hollow acetate tube and (4) tobacco plug. Heatsticks from left to right are unused stick with the paper overwrap peeled away, and used stick with the paper overwrap removed with the mouthpiece filter and hollow acetate tube sliced open; black arrow indicates melted region of the polymer-film filter, black asterisk denotes tobacco plug fragments that have been drawn into the hollow acetate tube. (B) An unused tobacco plug. (C) Used tobacco plug showing charring/darkening with use. (D,E) Cross sections of tobacco plugs from the first (D) and 10th (E) heatstick of holder A of the cleaned experiment. Yellow outlined area indicates a void in the cast-leaf left by the heater, the area between the yellow and green outlines are the charred portions of the tobacco plug. (F,G) Cross sections of polymer-film filter from the first (F) and 10th (G) heat stick. Polymer-film filter images shown coincide with tobacco plug images (D) and (E). (For D–G, CHS=cleaned device heatstick.) (H–L) Cross sections of tobacco plugs before use (H) and after use from the first, fourth, sixth and 10th heatstick of the uncleaned experiment (I–L). Yellow outlined area indicates a void in the cast-leaf left by the heater, area between the yellow and green outlines are the charred portions of the tobacco plug. (M–Q) Cross sections of polymer-film filter before (M) and after use (N–Q). Polymer-film filter images shown coincide with tobacco plug images (H–L). Blue arrowheads show charred pieces of cast-leaf that are affixed to the tobacco plug (K) and polymer-film filter (Q). (For (I–L) and (N–Q), UHS=uncleaned device heatstick). (R) Unused and used whole polymer-film filters showing discoloration and film melting, as demonstrated by the narrowing of the used filter. (S) Gas chromatography–mass spectrometry headspace analysis of unused polymer-film filter. Chromatogram shows an overlay of three runs, relative abundance was plotted versus retention time in minutes, unidentifiable peaks were unlabelled. Inset shows a magnified view of peaks with close retention times.

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components in plastics, as well as 1,2-diacetin, a plasticiser (figure 4S). However, of most concern was the presence of formaldehyde cyanohydrin (glycolonitrile), an acute toxicant often used in the production of synthetic resins and used as a solvent.[19] Formaldehyde cyanohydrin was eluted at 17.97 min, when the column reached 90°C.

DISCUSSION

Unlike some EC, which often show significant variation in craftsmanship and performance within and between brands,[15 20] the iQOS appearance, design and performance data are consistent with a product that is well manufactured. However, some design features of the iQOS, such the limited time allowed per heatstick and the need to consume the entire heatstick within this time or alternatively waste part of it, will affect user's topography and may lead to unwanted exposure to potentially toxic chemicals emitted from melting plastic and from pyrolysis of tobacco.

In contrast to tobacco and EC, which usually have no constraints on puffing, the iQOS only operates for 6 min, at which time it automatically shuts off and requires charging before it can be used again. Since a maximum of 14 puffs can be taken from each iQOS heatstick, puffing needs to be done at about 25 s intervals to take full advantage of each heatstick; used heatsticks that have not been fully exhausted cannot be used again as reinsertion would cause the delicate cast-leaf tobacco plug to crumble. This may not appeal to all users, and users who puff less frequently would have a lower number of puffs/heatstick. For users wishing to maximise each heatstick, this limitation will force them to alter their smoking topography by decreasing the interpuff interval and/or accelerating the rate at which they puff, leading to larger volumes of aerosol inhalation.

The manufacturer's cleaning instructions were not fully developed in the instruction manual. The cleaning protocol recommended using the cleaning function of the charger followed by cleaning with the brushes after 20 heatsticks and removing any large fragments of tobacco plug with the hook if necessary. The iQOS kit was equipped with cleaning sticks (figure 1B,D), yet their use was not mentioned in the instruction manual. Our data show that use of one heatstick left a significant amount of debris, fluid and fragments of cast-leaf in the holder (figure 2).

While iQOS heatsticks do not produce a flame, they were always charred after use, which we interpret to be a result of pyrolysis. The zone of charring was greater when cleaning was not performed between heatsticks, suggesting that build-up of fluid and debris in the holder increases pyrolytic temperatures. These data are consistent with the idea that despite similarities in performance characteristics, the cleanliness of the device plays a critical role in thermal regulation. Pyrolysis of tobacco is an endothermic reaction which occurs at temperatures between 200°C and 600°C, during which the majority of volatile and semivolatile components of cigarette smoke are formed.[21 22] Although the Philip Morris study indicated that the aerosol produced by iQOS devices reduce the amount of chemicals found on the Food and Drug Administration's Harmful and Potentially Harmful Constituents list by limiting tobacco pyrolysis,[5] our study, showing charring, in conjunction with a study by Auer *et al*, which confirmed the presence of volatile organic compounds, polycyclic aromatic hydrocarbons, carbon dioxide and nitric oxide,[23] contradict the claim that tobacco pyrolysis is minimised in iQOS. Although iQOS operates at temperatures less than 350°C, this does not negate the formation of volatile and semivolatile harmful constituents of tobacco smoke, which tend to have boiling points that range from 70°C to 300°C.[21 22]

Heatsticks used in this experiment were dissected and the severity of polymer-film filter melting was examined. The function of the polymer-film filter is to cool the aerosol,[3] thus, it would seem that the polymer composing the film should be heat resistant, although, ε-caprolactone, also known as polycaprolactone, tends to have a low-melting point which is thickness dependent.[24] The intensity of the heat produced by the iQOS, under both cleaned and uncleaned conditions, was sufficient to melt the polymer-film filter, even though it was not in direct contact with the heater. The amount of damage to the film (increase in melt and alteration of coloration) increased with each heatstick when cleaning was done per the manufacturer's recommended procedure (after 20 heatsticks). Discoloration may be a product of heating and/or staining from the brown fluid that is expelled from the tobacco plug during use.

Our GC–MS data indicate that components of the polymer-film filter are aerosolised at relatively low temperatures. GC–MS headspace analysis of unused filters suggests the polymer-film filter is a combination of ε-caprolactone, lactide, 1,2-diacetin and other unidentified chemicals. The chemicals released from the film filter during heating may not be suitable for inhalation. Thus, it is unknown if the film filter material is safe for use in products where it would undergo intense cycles of heating and cooling. Of greatest concern was the release from the polymer filter of formaldehyde cyanohydrin, a highly toxic chemical that is metabolised in the liver and broken down into formaldehyde and cyanide.[19] Formaldehyde cyanohydrin can be fatal to humans,[19 25 26] with studies showing mouse inhalation LD_{Lo}, the lowest dose of a toxicant that causes the death of an animal,[27] values as 27 ppm/8 hour.[28 29] iQOS holders operate at temperatures between 330°C and 349°C,[3 23] and as a safety feature, the device shuts off when temperatures reach 350°C. The release of formaldehyde cyanohydrin from unused filters during GC–MS analysis occurred at 90°C, a temperature that all users will exceed.

In conclusion, the iQOS appears to be well manufactured, and performance data were consistent between heatsticks. However, the product has limitations that will affect user topography and the application of standard smoking protocols, such as the ISO 3308, which could not be used for more than six puffs with this product. Users may be forced to smoke at a rapid pace in order to fully maximise heatsticks. Decreasing the interpuff interval could lead to an increase in intake of nicotine[30] and carbonyls.[31] This study also showed that the iQOS is not strictly a

What this paper adds

- Performance characteristics were generally uniform between devices and heatsticks.
- I quit original smoking (iQOS) device usage limitations make modifications to some current smoking standards necessary for proper evaluation of products.
- Device limitations may decrease users' interpuff intervals, increasing possible toxic exposures.
- iQOS holders heat hot enough to cause charring of the tobacco plug via pyrolysis and melting of the polymer-film filter.
- iQOS holder cleanliness affects and contributes to increased charring of the tobacco plug and melting of the polymer-film filter.
- Formaldehyde cyanohydrin, a toxicant, was released from the polymer-film filter at 90°C.

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'heat-not-burn' tobacco product. The iQOS tobacco appeared to char without ignition, and charring increased when cleaning was not done after each use. This study also showed the potential dangers that the polymer-film filter poses. This thin plastic sheet, readily melts during iQOS use and releases formaldehyde cyanohydrin, a dangerous toxicant. This study has shown that the iQOS system may not be as harm-free as claimed and also emphasises the urgent need for further safety testing as the popularity and user base of this product is growing rapidly.

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iQOS: evidence of pyrolysis and release of a toxicant from plastic

Barbara Davis, Monique Williams and Prue Talbot

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Philip Morris shifts focus to 'smoke free' nicotine products

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9 April 2019

Tobacco

Flagship IQOS e-cigarette brand not yet approved in US and researchers have questioned its benefits





Philip Morris has taken a big gamble on IQOS (pictured), which stands for 'I Quit Ordinary Smoking' © Reuters

Alice Hancock in London

yesterday

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Philip Morris International, one of the world's biggest tobacco companies, has said it wants to focus on "smoke free" nicotine products while acknowledging this will cannibalise sales of conventional cigarettes.

But while the US-based group touts the decision as a historic switch that will reduce consumer risks, its flagship IQOS e-cigarette brand has not yet been approved in the US and experts maintain Philip Morris has yet to satisfy them on health issues.

Jacek Olczak, Philip Morris's chief operating officer, said the company's strategy of becoming "smoke-free" could happen "much faster" than planned. "You know that the problem is cannibalising, or can put a lot of risk on the existing business, but you still think it is the right thing to do," he said.

Philip Morris has taken a big gamble on IQOS, directing almost all of its research and marketing budgets at the product. It aims for so-called "reduced-risk" products to account for 30 per cent of its shipment volumes by 2025, up from just over five per cent last year. In its annual report, it said that 92 per cent of its $383m research and development expense went on the new devices.

On Monday, it launched a publicity campaign, "Year of UnSmoke", to draw attention to its efforts to phase out cigarettes in favour of other products.

However, scientists have cast serious doubt over the health claims for IQOS. Dr Stanton Glantz, a tobacco specialist at the University of California San Francisco, said that he and his team had gone through the "several thousand" pages of Philip Morris's submission to the US Food and Drug Administration for IQOS.

"The most fundamental observation about IQOS is that if you take [Philip Morris's] data, it doesn't support their claims that IQOS is better than cigarettes," he said.

The IQOS device works by heating up tobacco to a lower level than conventional cigarettes. Traditional tobacco products when lit reach temperatures of about 600C. IQOS heats the tobacco to 350C which, according to Philip Morris's website, means "the levels of harmful chemicals are significantly reduced compared to cigarette smoke".

However, Dr Glantz said research shows that heated tobacco products still release ultrafine particles that transmit nicotine into the lungs.

He also pointed out that his team had found that, of 24 medical tests of metrics such as blood pressure and lung function undertaken by Philip Morris on IQOS users, none showed a detectable difference between IQOS and normal cigarettes.

Other researchers have said there may be higher liver toxicity in IQOS users and the same deterioration in users' arteries as for smokers.

Philip Morris has rejected the findings of the UCSF researchers. "The totality of the evidence across our aerosol chemistry, non-clinical and clinical studies, clearly demonstrates that switching completely to IQOS presents less risk of harm than continuing to smoke cigarettes," said Dr Moira Gilchrist, the company's vice-president of scientific communications.

She said no solid particles were delivered to a user's lungs, and she disputed the claims about liver damage and cardiovascular disease.

The product has not yet received FDA approval.

Mr Olczak, who has used IQOS since the prototype came out in 2012, said the company's science "has to be impeccable". The product is already selling well in Japan, where nicotine vaping liquid is banned.

In its fourth-quarter results for 2018, Philip Morris said shipments of its heated tobacco products were up 14.2 per cent to 41.4bn units. Cigarette shipment volumes were down 2.8 per cent to 740.3bn units.

Analysts at UBS said in a report published last month that "the most important catalyst for investor perception [of heated tobacco products] will be the launch of IQOS in the US", which they said they expected in the second half of this year.

This story has been changed to reflect the fact that IQOS does not stand for "I Quit Ordinary Smoking"

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'Heat-not-burn' cigarettes still damage lungs

reuters.com/article/us-health-iqos/heat-not-burn-cigarettes-still-damage-lungs-idUSKCN1M12CB

(Reuters Health) - A new type of “heat-not-burn” cigarette may lead to just as much lung damage as traditional cigarettes, a recent study suggests.

So-called “heat-not-burn” devices are designed to heat disposable tobacco sticks and give users the taste of tobacco without the smoke or ash.

For the study, researchers analyzed data submitted by Philip Morris International to the U.S. Food and Drug Administration when the company was trying to win regulatory approval to market its I-Quit-Ordinary Smoking (IQOS) product as a safer alternative to traditional cigarettes.

The FDA has yet to weigh in on whether Philip Morris can sell its IQOS device as a lower-risk cigarette alternative. But an expert scientific panel convened by the FDA recommended against such a move earlier this year, and the new study offers fresh evidence of health risks associated with IQOS.

When smokers switched from traditional cigarettes to “heat-not-burn” devices, researchers didn’t find any evidence of improvements in lung function or reductions in inflammation that can signal tobacco-related blood vessel damage.

“Even if a patient could switch completely from regular cigarettes to heat-not-burn products, Philip Morris International’s own data shows that there will continue to be significant health risks associated with these products,” said lead study author Dr. Farzad Moazed of the University of California, San Francisco.

“Although quitting smoking is challenging, there are many other options for smoking cessation that are more effective and safer than the use of these products,” Moazed said by email.

There is evidence that IQOS may reduce exposure to certain harmful chemicals, Moazed said, a point Philip Morris emphasized in a statement released after the FDA advisory panel decision. (bit.ly/2O0S42z)

Philip Morris also disputed the study authors’ conclusions.

"The totality of evidence available on IQOS supports that it is likely to present less risk of harm compared to continued smoking,” Philip Morris said in an emailed statement to Reuters Health. "This includes a significant reduction in inflammatory response and favorable changes in lung function." (bit.ly/2QPuiVF)

“Heated tobacco products, also known as heat-not-burn products, generate a nicotine aerosol by heating sticks made up of tobacco and other chemicals without lighting them on fire,” Moazed said. “While this reduces the amount of some of the harmful chemicals associated with

smoking, it increases the levels of other chemicals, and the evidence to date shows that these products continue to result in harm."

While there's limited data on the safety of IQOS relative to traditional cigarettes, and no long-term studies, the available evidence suggests that the devices are just as harmful to the lungs and immune system as traditional cigarettes, Moazed's team concludes in Tobacco Control.

It's also unclear from research to date whether IQOS might help smokers quit, a factor that might influence how scientists think about the safety of these devices and other tobacco products sold as alternatives to traditional cigarettes.

The human studies Philip Morris submitted to the FDA excluded people who were "dual users" of both traditional cigarettes and IQOS devices, the study authors note.

Any safety advantage relative to traditional cigarettes might be diminished if people continue to smoke traditional cigarettes once they start using IQOS devices, said Bonnie Halpern-Felsher, a tobacco prevention researcher at Stanford University School of Medicine in Palo Alto, California, who wasn't involved in the study.

"We have no studies outside of Philip Morris on whether these IQOS will actually help people quit or on their relative safety," Halpern-Felsher added. "People are unlikely to understand what "switching completely" means and that therefore they are likely to be misled," by any safety claims that are contingent on smoking cessation.

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Assessment of industry data on pulmonary and immunosuppressive effects of IQOS

Farzad Moazed,[1] Lauren Chun,[2] Michael A Matthay,[3] Carolyn S Calfee,[3] Jeffrey Gotts[1]

[1]Department of Medicine, University of California San Francisco, San Francisco, California, USA
[2]Cardiovascular Research Institute, University of California San Francisco, San Francisco, California, USA
[3]Department of Anesthesia, University of California San Francisco, San Francisco, California, USA

Correspondence to
Dr Farzad Moazed, Department of Medicine, University of California San Francisco, San Francisco, CA 94143, USA; farzad.moazed@ucsf.edu

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ABSTRACT

Introduction Heated tobacco products are being touted as novel reduced-harm tobacco products by tobacco companies. In the USA, Philip Morris International submitted a modified risk tobacco product (MRTP) application to the US Food and Drug Administration in 2016 in which it purports that its heated tobacco product, I-Quit-Ordinary-Smoking (IQOS), is associated with reduced harm compared with conventional cigarettes.

Methods We reviewed Philip Morris International's MRTP application to assess the pulmonary and immune toxicities associated with IQOS use in both animal and human studies.

Results Among rats exposed to IQOS, there was evidence of pulmonary inflammation and immunomodulation. In human users, there was no evidence of improvement in pulmonary inflammation or pulmonary function in cigarette smokers who were switched to IQOS.

Conclusion IQOS is associated with significant pulmonary and immunomodulatory toxicities with no detectable differences between conventional cigarette smokers and those who were switched to IQOS in Philip Morris International's studies. Philip Morris International also failed to consider how dual use and secondhand aerosol exposure may further impact, and likely increase, the harms associated with these products.

INTRODUCTION

Conventional cigarettes have long been known to have numerous pulmonary toxicities. Cigarettes generate inflammation in the lung; over time, chronic inflammation contributes directly to the development of significant respiratory diseases including chronic obstructive pulmonary disease (COPD) and lung cancer.[1–3] In addition, cigarette smoke directly impacts immunity in the lung[4] and smoking is associated with an increased risk of respiratory infection,[5–7] a leading cause of mortality worldwide.[8 9] Driven by decades of data indicating the harms of cigarettes, public health campaigns have decreased the prevalence of cigarette smoking worldwide.[10]

In the setting of public awareness of the dangers of cigarettes and declining cigarette smoking in many parts of the world, tobacco companies have repeatedly attempted to develop 'safer cigarettes', including 'low-tar' cigarettes, electronic cigarettes and heated tobacco products (HTPs). HTPs heat tobacco to temperatures (~600°F) below the temperatures observed in conventional cigarettes (>900°F) to avoid combustion and produce a nicotine aerosol that is inhaled by the user. Given these lower temperatures and the subsequent lack of combustion generated by these products, tobacco companies have argued that these products are healthier than conventional cigarettes and represent a harm reduction tool that could aid conventional cigarette smokers. However, to date, there has been little data that support HTPs as less harmful compared with conventional cigarettes.

On 5 December 2016, Philip Morris International (PMI) submitted an application to the US Food and Drug Administration (FDA) to market its HTP, I-Quit-Ordinary-Smoking (IQOS), as a 'modified risk tobacco product' (MRTP) in the USA. Section 911 of the Family Smoking Prevention and Tobacco Control Act requires the FDA to enforce rigorous standards that tobacco companies must meet before marketing a product as an MRTP. Section 911(g) mandates that the FDA may issue an MRTP order only if the applicant has demonstrated by substantial and objective scientific evidence that its product, as it is actually used by consumers, will '(A) significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and (B) benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products'. These standards place the burden on the applicant to demonstrate that their product results in decreased harm, rather than merely equivalence. Such standards may often require a variety of studies, including invasive and/or longitudinal testing, in both animal and human models to provide evidence of reduced harm. This paper uses information and data from the publicly available PMI MRTP application to compare IQOS and conventional cigarettes in animal and human studies of pulmonary health and evaluate PMI's claim of harm reduction related to pulmonary health.

METHODS

In order to conduct this study, we searched PMI's publicly available MRTP application for data relevant to the pulmonary and immune toxicity of IQOS. In addition, when identified, publicly available raw data were downloaded from the FDA MRTP application to conduct independent statistical analyses.

Preclinical studies

Our analysis of PMI's preclinical studies focuses on data presented by Wong and colleagues,[11] which was published in Regulatory Toxicology and Pharmacology in 2016, and included in Module 7.2: Preclinical Studies of PMI's MRTP application. In order to compare the effects of IQOS emissions to

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conventional cigarette smoke, PMI conducted a 90-day inhalation study in 10-week-old male and female Sprague-Dawley rats. Outcomes included markers of inflammation, histopathology, transcriptomics and standard toxicological endpoints, with comparisons of sham-exposed rats and rats exposed to the aerosol of IQOS and 3R4F research cigarettes. The IQOS product tested in these studies was the Tobacco Heated Systems (THS) V.2.2 tobacco stick which uses the FR1 tobacco blend. Rats were nose-exposed in flow-pass inhalation chambers for 6 hours per day to aerosols that were diluted with filtered air to obtain targeted nicotine concentrations ranging from 15 to 50 µg per litre aerosol. Unless otherwise stated, we focused on the highest level of aerosol nicotine for each product. Toxicants were measured at the breathing zone of the rats in the inhalation chambers and reported in ppm (carbon monoxide) or µg/litre (acetaldehyde, acrolein, formaldehyde).

Human studies

Our analyses of human clinical studies are based on the data presented in PMI's MRTP application's Executive Summary, Module 6: Summaries of all research findings, and Module 7.3.1: Scientific Studies and analyses (Studies in Adult Human Studies: Clinical Studies). The human data within these sections draw from two primary studies: ZRHR-REXA-07-JP, performed in Japan and ZRHM-REXA-08-US, performed in the USA. Briefly, both studies enrolled otherwise healthy adults who smoked at least 10 conventional cigarettes per day for the prior 3 years and randomised them into one of three groups: (1) those who smoked menthol conventional cigarettes, (2) those who quit completely and (3) those who switched to IQOS with menthol heatsticks. Participants were initially followed in confinement for 5 days of usage and then in the ambulatory setting for a total of 90 days. The goal of the 90-day ambulatory study period was to examine changes in biomarkers of exposure and clinical harm related to IQOS in near-real-world conditions. During the ambulatory study period, participants were discouraged from dual use. All participants kept a usage diary that documented their tobacco product usage. At the day 90-study visit, several clinical risk points were assessed including plasma white blood cell count (WBC), C reactive protein (CRP) and pulmonary function testing (PFT). Clinical risk endpoints were then compared between participants who continued smoking conventional cigarettes and those that were switched to HTPs.

Statistical analyses

PMI's main analyses included analysis of variance testing with baseline value, product exposure, sex and baseline cigarette consumption as fixed effect factors. We conducted independent analysis of publicly available raw data from PMI's MRTP application. We used Student's t test, analysis of variance testing and Pearson's χ^2 test to compare normally distributed variables. Non-normally distributed variables were compared using the Mann-Whitney Wilcoxon U-test or Kruskal-Wallis test. A p value ≤ 0.05 was considered statistically significant. Statistical analyses were performed with STATA V.15.0 (StataCorp).

RESULTS

Preclinical studies

A comparison of the toxicant profiles of IQOS, 3R4F cigarettes and sham exposure conditions revealed that, while containing generally lower toxicant levels than 3R4F smoke, IQOS emissions contain significant levels of volatile organic compounds, including known toxicants such as acrolein, acetaldehyde and formaldehyde. IQOS-exposed rats had impaired weight gain during the 90-day exposure compared with sham, but greater weight gain compared with animals exposed to 3R4F smoke. Similarly, IQOS-exposed rats had a trend towards increased numbers of inflammatory cells in bronchoalveolar lavage (BAL), but significantly less BAL cellularity than 3R4F-exposed rats (table 1). Respiratory histopathology demonstrated that IQOS caused significant epithelial hyperplasia and metaplasia compared with sham, though to a lesser extent than was observed following 3R4F exposure. Taken together, these data suggest that IQOS induces a significant inflammatory injury, but less severe than that observed with intense cigarette smoke exposure.

Table 1 Summary of preclinical pulmonary findings for I-Quit-Ordinary-Smoking (IQOS) compared with sham and 3R4F research cigarette groups

Parameter	Sham (n=10)	IQOS (n=8–10)	3R4F (n=9)
Lung weight (normalised to body weight)	35.8 (1.4)	40.3 (1.0)*	50.6 (1.4)*†
BAL cell count‡ (×10^5/lung)	22.9 (3.4)	42.5 (7.1)*	116.4 (13.4)*†
BAL inflammatory markers MIP-1β, MCP-3, MPO, PAI-1		↑*	↑*†
Respiratory epithelial hyperplasia and metaplasia		↑*	↑*†

Unless otherwise specified, results signify those from male rats at the highest nicotine exposure levels for each group.
*Significantly increased compared with sham.
†Significantly increased compared with IQOS.
‡Female rats at targeted nicotine 23 µg/L.
BAL, bronchoalveolar lavage; MCP, monocyte chemoattractant protein; MIP, macrophage inflammatory protein; MPO, myeloperoxidase; PAI, plasminogen activator inhibitor.

PMI's data indicate that IQOS exposure may be associated with substantial immunomodulatory effects (table 2). Animals exposed to IQOS developed systemic neutrophilia that trended nearly 75% higher than that observed in rats exposed to 3R4F smoke. Notably, blood neutrophil counts in female rats remained elevated compared with both sham and 3R4F exposed animals following a 6-week recovery period. Furthermore, IQOS-exposed animals had higher levels of thymic atrophy (by gross organ weight and histology) than both sham and 3R4F-exposed groups. Although functional immunological assays were not reported, thymic atrophy has previously been associated with decreases in host memory T cell populations[12] and reductions in the speed and sensitivity of host immune function.[13]

Table 2 Summary of preclinical systemic immune effects of I-Quit-Ordinary-Smoking (IQOS) compared with sham and 3R4F research cigarettes

Parameter	Sham (n=8–10)	IQOS (n=7–9)	3R4F (n=9–10)
Blood neutrophil count (10^9/L)	1.3 (0.3)	4.8 (2.1)*	2.7 (0.4)*
Thymus weight	4.0 (0.4)	2.6 (0.6)*	2.5 (0.3)*
Histological thymic atrophy score	0.1 (0.1)	1.8 (0.4)*	1.1 (0.4)*

Unless otherwise specified, results signify those from male rats at the highest nicotine exposure levels for each group.
*Significantly different compared with sham; statistical comparisons between IQOS and 3R4F were not reported for blood neutrophil count or thymic atrophy score.

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Table 3 Participant demographics and baseline data for Japan-based (ZRHR-REXA-07-JP) and US-based (ZRHM-REXA-08-US) studies

Japan-based study ZRHR-REXA-07-JP				
Measurement	Conventional cigarettes (n=41)	Abstinence (n=37)	IQOS (n=70)	P values
Age	38±11	38±10	38±11	0.99
Male (%)	24 (59%)	22 (59%)	39 (56%)	0.92
Smoking history				
10 – 19 cig/day	23 (56%)	20 (54%)	36 (51%)	0.92
>19 cig/day	18 (44%)	17 (46%)	34 (49%)	
FEV1 (% predicted)	94±9	93±10	94±8	0.69
FEV1/FVC	0.81±0.05	0.81±0.06	0.82±0.07	0.73
WBC (GI/L)	5.8±1.4	6.4±1.9	5.9±1.2	0.12
CRP (mg/L)	0.1 (0.1–0.26)	0.1 (0.1–0.45)	0.1 (0.1–0.45)	0.81
US-based study ZRHM-REXA-08-US				
Measurement	Conventional cigarettes (n=32)	Smoking abstinence (n=9)	IQOS (n=47)	P values
Age (years)	34±10	41±11	37±13	0.27
Male	20 (63%)	7 (78%)	28 (60%)	0.59
Smoking history				
10–19 cig/day	19 (59%)	6 (67%)	21 (45%)	0.29
>19 cig/day	13 (41%)	3 (33%)	26 (55%)	
FEV1 (% predicted)	97±14	96±11	93±13	0.46
FEV1/FVC	0.79±0.07	0.78±0.04	0.80±0.05	0.74
WBC (GI/L)	8.3±1.8	6.9±2.2	8.3±1.7	0.08
CRP (mg/L)	0.1 (0.1–0.2)	0.1 (0.03–0.2)	0.1 (0.1–0.3)	0.11

IQOS, I-Quit-Ordinary-Smoking; CRP, C reactive protein; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; WBC, white blood cell count.

Table 4 Difference (95% CI) in 90-day pulmonary function testing between I-Quit-Ordinary-Smoking users and conventional cigarette smokers as presented by Philip Morris International

Clinical endpoint	US-based study ZRHM-REXA-08-US* (n=77)	Japan-based study ZRHR-REXA-07-JP† (n=111)
FEV1 (% predicted)	0.53 (–2.09 to 3.00)	1.91 (–0.14 to 3.97)
FEV1/FVC	0.00 (–0.02 to 0.02)	N/A
MEF 25–75 (L/s)	–0.67 (–6.33 to 4.99)	N/A
DLCO (mL/min/mm Hg)	0.31 (–1.09 to 1.72)	N/A
KCO (mmol/min/kPa/L)	0.05 (–0.02 to 0.12)	N/A
TLC (L)	0.09 (–0.25 to 0.43)	N/A
FRV (L)	–0.09 (–0.31 to 0.13)	N/A
IC (L)	0.21 (–0.08 to 0.51)	N/A
VC (L)	0.10 (0.00 to 0.21)	N/A

*Without bronchodilator.
†With bronchodilator.
DLCO, diffusion capacity of lung for carbon monoxide; IC, inspiratory capacity; FEV1, forced expiratory volume in 1 s; FRV, functional residual volume; FVC, forced vital capacity; KCO, rate constant of carbon monoxide; MEF, mid expiratory flow; N/A, not conducted or reported by PMI; TLC, total lung capacity; VC, vital capacity.

Human studies

Japan-based study

The Japan-based study randomised 231 participants between two study sites. However, only one of these sites collected participant data at 90 days. After limiting the sample to participants who had samples drawn at 90 days (n=160), and excluding those who were lost to follow-up (n=12), 148 participants remained. At the day 0 baseline visit, we found no difference in age or sex between groups (table 3). We did not detect a difference between groups in baseline pulmonary function, CRP or WBC, although there was a trend towards increased levels of WBC in the smoking abstinence group.

At the 90-day study visit, PMI reported decreased plasma WBC in IQOS users compared with conventional cigarette smokers (6.14 GI/L vs 5.57 GI/L, difference: –0.57 GI/L, 95% CI: −1.04 to −0.10). Given that WBC had also been measured at the day 0 baseline visit, we compared the change in WBC from baseline to 90 days between groups, rather than only comparing the level at 90 days. We found that compared with cigarette smokers, participants using IQOS had a decrease in plasma WBC (difference: −0.63 GI/L, 95% CI: −1.1 to −0.2, p=0.006). There was no significant difference in the change in WBC between the IQOS and smoking abstinence group. PMI did not detect a difference in CRP levels at 90 days between cigarette smokers and IQOS users (95% CI for difference between groups: –40.75 to 37.77). In our analyses, we did not detect a significant difference in the change in CRP from baseline to 90 days between IQOS users (median: 0 mg/L) and either cigarette smokers (median: 0 mg/L, p=1.0) or the smoking abstinence group (median: 0 mg/L, p=0.74).

PMI also reported on forced expiratory volume in 1 s (FEV1) without bronchodilator administration and found no difference in FEV1 at 90 days between cigarette smokers and IQOS users (table 4). We independently studied the change in FEV1 from day 0 baseline to 90 days. We found no difference between the three groups in the change in FEV1 (cigarette smoking group: −0.3 % predicted, 95% CI: −2.3 to −1.7; smoking abstinence group: 1.5 % predicted, 95% CI: −0.3 to 3.3; IQOS group: 1.5 % predicted, 95% CI: 0.3 to 2.6, p=0.2).

US-based study

In the US-based study, 88 participants underwent testing at 90 days. At the day 0 baseline visit, we did not detect a difference between the three arms in age, sex, pulmonary function, WBC or CRP, although there was a trend towards increased CRP in the IQOS group and decreased WBC in the smoking abstinence group (table 3).

In the US-based study, PMI reported no difference in plasma WBC at 90 days between participants who continued to smoke conventional cigarettes and those who were randomised to IQOS (7.09 GI/L vs 7.26 GI/L, difference: 0.17 GI/L, 95% CI: - 0.47 to 0.81). Similarly, PMI reported no difference in CRP levels between conventional cigarette smokers and IQOS users (95% CI for difference between groups: −21.69 to 42.33). In our independent analyses, we did not detect a difference in the change in WBC from baseline to 90-day visit between the IQOS arm and either the conventional cigarette arm (difference: - 0.06 mg/L, 95% CI: −0.8 to 0.7, p=0.87) or the smoking abstinence arm (difference: - 0.5 mg/L, 95% CI: −1.6 to 0.7, p=0.43). Similarly, we did not detect a difference in change in CRP from baseline to day 90 visit between the IQOS group and either the conventional cigarette group (p=0.30) or the smoking abstinence group (p=0.50).

The US-based study conducted more extensive PFTs than the Japan-based study and notably these tests were performed following bronchodilator administration, which differed from the Japan-based study. At 90 days, PMI did not report a significant difference between the IQOS and conventional cigarette

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Table 5 Changes in pulmonary function testing from day 0 to day 90 in the US-based study (ZRHM-REXA-08-US)

Clinical endpoint	Conventional cigarettes (n=30)	IQOS (n=47)	Smoking abstinence (n=9)	P values
FEV1 (% predicted)	−3.1 (−5.6 to −1.7)	−2.3 (−4.6 to −0.04)	−2.9 (−11.3 to 5.6)	0.72
FVC (% predicted)	−2.6 (−4.4 to 0.9)	−1.8 (−3.4 to −0.05)	−0.6 (−4.5 to 3.4)	0.57
FEV1/FVC	0.01 (−0.004 to 0.02)	−0.004 (−0.02 to 0.01)	0.04 (0.002 to 0.08)	0.01
MEF 25–75 (L/s)	−0.1 (−0.3 to 0.2)	−0.1 (−0.3 to 0.05)	0.2 (−0.8 to 1.1)	0.57
DLCO (mL/min/mm Hg)	0.2 (−1.0 to 1.3)	0.2 (−0.8 to 1.2)	−1.5 (−5.1 to 2.2)	0.40
TLC (L)	−0.3 (−0.6 to 0.1)	−0.02 (−0.3 to 0.2)	−0.6 (2.0 to 0.7)	0.15

DLCO, diffusion capacity of lung for carbon monoxide; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; MEF, mid expiratory flow; TLC, total lung capacity.

group for any of the pulmonary function tests that were assessed. We conducted independent analyses of the change in pulmonary function from baseline day 0 to 90-day visits between groups. We did not detect a difference in changes in pulmonary function over time between the three groups except for FEV1/FVC, which increased slightly in the smoking abstinence group relative to both the conventional cigarette group and the IQOS group (table 5). There were no other differences detected between the IQOS group and either the conventional cigarette or smoking abstinence groups.

DISCUSSION

The FDA requires that MRTP applicants demonstrate that their products, as actually used by consumers, will reduce harm in individuals and benefit the health of the public overall. PMI's data are incomplete as they lack adequate endpoints to specifically assess subclinical pulmonary toxicity in humans and do not incorporate enough longitudinal measures for the tests they do include. Additionally, PMI fails to account for real-world usage patterns and secondhand aerosol exposures that may negatively impact both individual and public health. However, even the data that are presented by PMI suggest that IQOS has significant potential to induce adverse pulmonary health effects in humans.

Data from PMI's MRTP application indicate that compared with conventional cigarettes, emissions from IQOS have lower levels of volatile organic compounds and are associated with decreased levels of pulmonary inflammation in rats after 90 days of exposure. However, compared with sham controls, IQOS induces significant changes in the respiratory epithelium and airspaces that are consistent with inflammatory injury. Furthermore, the two clinical studies of real-world usage cited by PMI do not definitively show evidence of reduced inflammation in IQOS users compared with conventional cigarette smokers. Although a very small reduction in plasma WBC was observed in IQOS users in the Japan-based study, there was no difference in plasma WBC in the US-based study. In addition, there was no difference in CRP levels between conventional smokers and IQOS users in either study.

While inflammation is an important toxic mediator in a number of respiratory diseases that have been linked to cigarette smoking, plasma WBC and CRP are not direct measures of pulmonary inflammation but rather non-specific measures of systemic inflammation. There was no difference in levels of these biomarkers at 90 days between conventional cigarette smokers and those who quit smoking, suggesting that these are poorly sensitive markers, particularly when measured over such a short period of time. There are several more specific measures that can assess pulmonary inflammation in humans, including studies of inflammatory biomarkers in sputum, airway tissue or BAL fluid.[14 15] Such tests directly sample lung tissue and thus more accurately reflect processes in the lung. However, despite presenting no human data directly from the lung, PMI concludes that 'human clinical studies have confirmed that clinical markers of … inflammation show positive changes, similar to those seen following smoking abstinence' (PMI MRTP Application, Section 2.7, Executive Summary, p. 106) and that these changes indicate that 'smokers who switch to [IQOS] would have a lower risk of COPD compared with continued smoking' (PMI MRTP Application, Section 2.7, Executive Summary, p. 107). Thus, PMI not only fails to accurately assess pulmonary inflammation in their human studies, but also misleadingly concludes that their IQOS product reduces inflammation and the risk of COPD in humans, a claim that is simply not supported by their data.

Neither PMI's Japanese nor American ambulatory human clinical study shows any statistically significant improvement in any measure of PFT. In fact, after 3 months of usage, smokers who have transitioned to IQOS use have the same pulmonary function as those who continued to smoke conventional cigarettes. Notably, PMI reports several cases of worsening pulmonary function in IQOS users in their adverse event reports (Appendix A6.1.5.4 in the PMI MRTP application). However, PMI concludes that 'in the Japanese study (ZRHM-REXA-07-JP), smokers who switched to THS had an increase of 1.91 percent of predicted value (%Pred) in their FEV1 as compared with smokers who continued to smoke cigarettes' (PMI MRTP Application, Section 2.7, Executive Summary, p. 92) and that 'in the US study (ZRHM-REXA-08-US), the difference in FEV1 values between smokers who switched to THS and those who continued to smoke was smaller in magnitude as compared with in the Japanese study. Nonetheless, the results were consistent and trended in the expected direction following smoking abstinence' (PMI MRTP Application, Section 2.7, Executive Summary, p. 93). These conclusions are simply not supported by PMI's own actual data, which shows no statistically significant difference in pulmonary function between IQOS users and conventional smokers. Furthermore, the relatively short period of follow-up fails to address longer term effects of IQOS on pulmonary function. While prior studies have shown that there are small improvements in pulmonary function in the first year of smoking cessation,[16] a significant benefit arises from a slowing in the decline of lung function over many years.[16 17] A 90-day study period is simply not long enough to detect any meaningful changes in lung function, as evidenced by the lack of difference detected in pulmonary function between the smoking abstinence group and the conventional cigarette or IQOS groups for almost all tests of pulmonary function measured. Thus, the short follow-up period in PMI's studies is unable to assess the important clinical question of the long-term effects on IQOS on pulmonary health compared with both conventional cigarettes and complete smoking cessation.

Conventional cigarettes are known to directly impact immunity and are associated with increased rates of respiratory infection.[5–7] PMI's animal data suggest that IQOS may impact immunity, inducing thymic atrophy in exposed rats. Given that respiratory

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infection represents a leading cause of morbidity and mortality worldwide,[8 9] this finding raises alarm that IQOS could increase the risk of infection in users and indicates that further studies of the immunomodulatory effects of IQOS are needed, including animal models of respiratory infection. Notably, PMI reports several cases of infection associated with human IQOS use in their adverse data reports (Appendix A6.1.5.4), which adds to the concern that these products may adversely affect immunity and predispose users to developing infection. The omission of additional studies on the immune effects of IQOS from PMI's MRTP application is significant and further clouds the picture on the true health risks of IQOS.

PMI's analyses focus on studying the harms associated with exclusive IQOS use. However, there is significant data that dual or poly use, the use of two or more tobacco products, will be a significant usage pattern among IQOS users. In PMI's US-based study, nearly one in four participants was still using conventional cigarettes after being switched to IQOS. Internationally, per PMI's own reports, it is estimated that up to 30% of IQOS users also use an additional tobacco product, including conventional cigarettes.[18] However, despite significant evidence of the potential for dual use among IQOS users,[19] PMI has failed to simulate dual use in their animal studies. Furthermore, in their human studies, PMI strictly prevented dual use during confinement study periods and strongly discouraged, although somewhat unsuccessfully, dual use in the ambulatory setting, resulting in less validity to their claims that it mimicked a 'real world' setting. In addition, no analyses are performed on the effects of dual use that was known to occur. Given that dual use is likely to impact any potential for harm reduction for individual users, its omission from PMI's study design and analyses on harm reduction potential is a glaring one.

Finally, PMI studies fail to account for the pulmonary health effects of secondhand aerosol exposure. A prior study of HTPs found that they do generate sidestream aerosol, the primary component of secondhand smoke exposure,[20] which comprises a large number of volatile organic compounds, polycyclic aromatic hydrocarbons and ultrafine particles.[21 22] Furthermore, a recent study found that people exposed to secondhand IQOS emissions experienced symptoms, including sore throat (20.6%), eye pain (22.3%) and feeling ill (25.1%).[19] Given that a number of public health organisations, including WHO, have deemed that no level of sidestream exposure is safe or acceptable,[23] these findings are clearly concerning and merit further study, which PMI has either failed to conduct or present.

In conclusion, PMI's IQOS MRTP application raises significant concerns about the pulmonary safety of IQOS. PMI ignores the effect of dual use and secondhand aerosol exposure in both study design and analyses; furthermore, no measurements of inflammation specific to the lung were made in any of the human studies presented, and the duration of follow-up does not allow for any meaningful study of pulmonary function. Any future studies of these products must include measurements specific to the lung, such as in sputum or BAL fluid, as well as additional longitudinal follow-up to more accurately assess the acute and chronic toxicities of these products. In addition, given that dual use is expected to be the predominant usage pattern, it is critical that future studies take into account dual use when assessing the public health impact of these products. However, even if these significant gaps were ignored, PMI's own data show that IQOS is associated with significant pulmonary and immune toxicity that does not appear to be significantly different from cigarette smoking in real-world human users.

What this paper adds

- Heated tobacco products are being touted as reduced harm tobacco products by tobacco companies across the world despite limited scientific evidence supporting this claim.
- Philip Morris's modified risk tobacco product (MRTP) application for I-Quit-Ordinary-Smoking (IQOS) shows that IQOS generates significant pulmonary and immunomodulatory harm, most notably in human studies.
- With regards to pulmonary and immunomodulatory harm, based on the limited available data to date, IQOS use does not appear to significantly differ from conventional cigarettes.

Contributors All authors contributed to the study design/concept, interpretation of the data and drafting/revisions of the manuscript. All authors give final approval and agree to be accountable for all aspects of the work.

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Short Communication Open Access

Heated Tobacco Products Create Side-Stream Emissions: Implications for Regulation

Grant O'Connell[1], Peter Wilkinson[1], Kerstin MM Burseg[2], Stephen J Stotesbury[1], John D Pritchard[1]*

[1]*Imperial Tobacco Ltd, 121 Winterstoke Road, Bristol, BS3 2LL, UK*
[2]*Reemtsma Cigarettenfabriken GmbH - Imperial Tobacco Group, Albert-Einstein-Ring 7, D-22761, Hamburg, Germany*

Abstract

A number of tobacco manufacturers are promoting products where the tobacco is reportedly "heated" rather than burned. It has been claimed that certain heated tobacco products produce only mainstream and no side-stream emissions. In this study we investigated these claims for a commercially available heated tobacco product and, by using a simple experimental design, investigated whether the high temperature heating of the tobacco matrix during product activation and use results in the generation of side-stream emissions. By way of comparison, the Nicorette® inhalator and a leading e-cigarette brand were also investigated. Our findings indicated that a large number of different chemical compounds were released into the airspace around the heated tobacco product when switched on and during consumer use indicating the generation of side-stream emissions. As the public health community has concluded there is no safe level of exposure to tobacco-containing product emissions, this would be of concern and warrants further investigation. Based on our data showing side-stream emissions from the tobacco matrix, the use of heated tobacco products in indoor public places should fall under the same regulations as cigarettes.

Keywords: Heated tobacco; Heat-not-burn; E-cigarette; Nicorette; Side-stream emissions; Second-hand smoke; Nicotine; Tobacco

Introduction

It is well known that when tobacco burns, many thousands of chemicals are released from the tobacco matrix and are inhaled by consumers and bystanders [1,2]. It has been stated that the majority of smoking-related diseases are caused not by nicotine but by the generation of harmful or potentially harmful smoke constituents (HPHCs) from the burning of tobacco [3,4]. In response, a number of tobacco manufacturers are promoting products where the tobacco is reportedly "heated" rather than burned in an attempt to reduce HPHC emissions [5-7]. This is not a new concept, as cigarette-based heated tobacco products were first marketed in the USA in the 1980s and proved to be commercially unsuccessful. Heated tobacco products are now being revived and repositioned as an alternative for smokers who may not wish to replace conventional cigarettes with non-tobacco products such as electronic cigarettes (e-cigarettes). While some manufacturers claim heated tobacco products do not produce side-stream emissions, the major component of 'second-hand smoke', this has yet to be independently verified [8-12]. Since the World Health Organisation has stated "*there is no safe level of exposure to second-hand tobacco smoke*" [13] and the British Medical Association (BMA) has stated that "*almost 85 per cent of second-hand smoke is in the form of invisible, odourless gases*" [14], claims of an absence of side-stream emissions from heated tobacco products warrants investigation. To that end, we sought to investigate whether or not side-stream emissions were generated by a commercially available heated tobacco product. For comparative purposes, we also investigated the Nicorette® inhalator and a leading e-cigarette.

Experimental Section

The analytical technique Proton Transfer Reaction-Mass Spectrometry (PTR-MS) was used to sample and analyze for any side-stream emissions released to the airspace around an iQOS heated tobacco product with regular Marlboro *HeatSticks* (manufacturer, Philip Morris International) when activated by the user (but not puffed) and also during product use. Additionally, sampling was conducted for a Nicorette® inhalator (15 mg nicotine replacement aid; manufacturer, McNeil Consumer Healthcare Ltd) and Blu™ closed system e-cigarette (18 mg nicotine; manufacturer, Fontem Ventures B.V.) All products used in this study were used in accordance with manufacturer's instructions and consumed *ad libitum* i.e., there was no pre-defined consumption requirement. For each of the different products, a number of replicate puffs were made and representative data from a single puff is shown. In short, the PTR-MS instrument ionizes volatile organic compounds (VOCs) in the gas phase through their reaction with H_3O^+ to form protonated VOCs ($VOCH^+$) which can then be detected by a mass spectrometer [15]. This process can be run on air samples with or without dilution as normal air gases (e.g., N_2, O_2, CO_2) have a proton affinity less than water and thus are not ionized. Most VOCs have a proton affinity greater than water and therefore are readily ionized and detected [15]. Analyses with PTR-MS can be conducted in real-time and continuously without the need for sample preparation [15]. Airspace analysis was conducted by connecting the PTR-MS inlet to the test chamber and sampling directly. PTR-MS operating conditions were as follows: drift tube voltage, 500 V; drift tube pressure, 2.3 mbar; drift tube temperature, 120°C; drift tube length, 9.3 cm; *E/N* ratio, 130 Td (Townsends; where *E* is electric field and *N* is the number density of the gas in the drift tube; 1 Td=10^{-17} cm^2 V $molecule^{-1}$); inlet temperature, 120°C. The experimental set-up is outlined in Figure 1.

Results and Discussion

Qualitative characterization of side-stream emissions

Following activation of the iQOS heated tobacco product, as per the manufacturer's instructions, a large number of different VOC species across a range of masses were released into the airspace (Figure 2A). This clearly indicates the generation of side-stream emissions when the device is activated but not puffed by the consumer, which

***Corresponding author:** John D Pritchard, Imperial Tobacco Ltd, 121 Winterstoke Road, Bristol, BS3 2LL, UK, Tel: 440117-933-7556; E-mail: john.pritchard@uk.imptob.com

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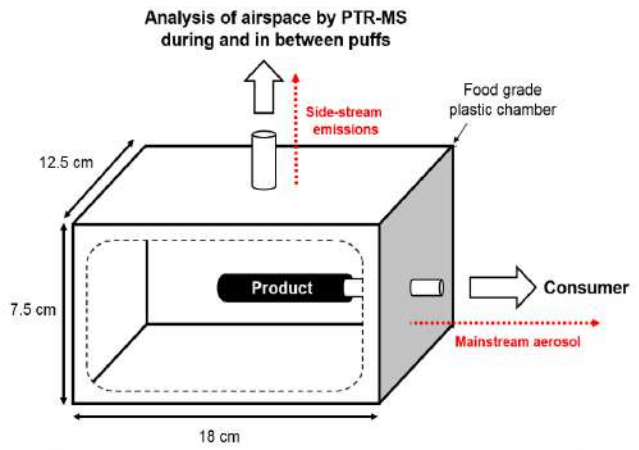


Figure 1: Schematic representation showing experimental set-up and the side-stream emissions capture chamber.

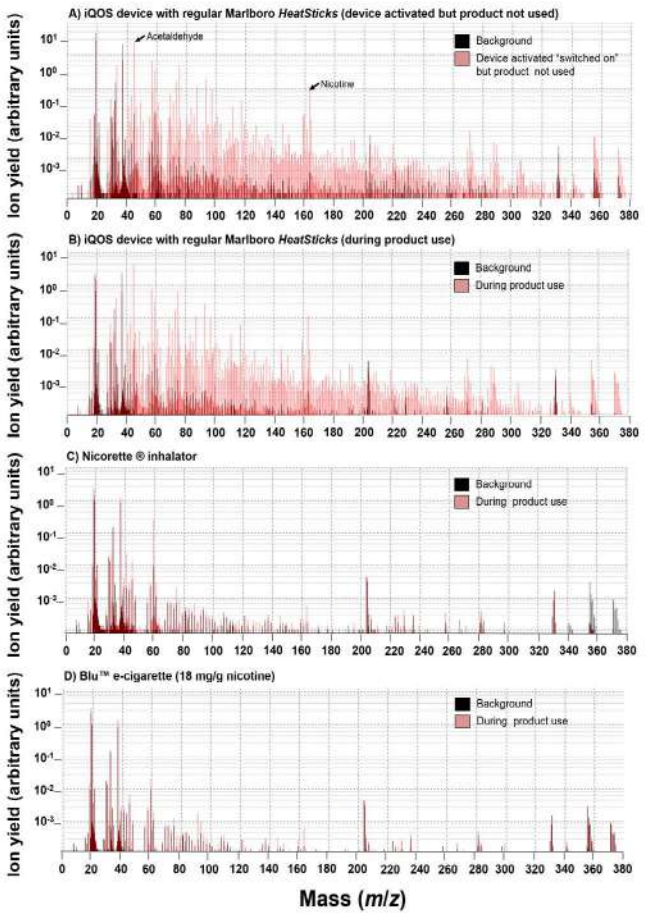


Figure 2: Representative PTR-MS mass spectra of the VOCs released to the airspace for (**A**) iQOS with regular Marlboro *HeatStick* when activated "switched on" but product not actively puffed and (**B**) during consumer use of the iQOS device with regular Marlboro *HeatSticks*; (**C**) during consumer use of the Nicorette® inhalator; and (**D**) during consumer use of the Blu™ e-cigarette. Specific compound (peaks) at *m/z* 45 is protonated acetaldehyde and *m/z* 163 is protonated nicotine and is labelled with arrowheads in (**A**).

would be released into the ambient air, raising potential concerns for bystanders. Furthermore, during active puffing on the heated tobacco product, side-stream emissions are also released (Figure 2B). These chemicals are being released from the high temperature heating of the tobacco matrix in the *HeatSticks*. Given the similarities of the Marlboro branded *HeatStick* used in the iQOS device to a conventional cigarette, the detection of side-stream emissions is perhaps not surprising even though it has been stated that such products produce no side-stream aerosol/smoke [8-12]. Given the findings presented in this pilot study, this requires further investigation.

The PTR-MS mass spectra of the VOCs in the airspace around the Nicorette® inhalator (Figure 2C) and the e-cigarette (Figure 2D) during product use are virtually indistinguishable. Moreover, the Nicorette® inhalator and the e-cigarette profiles are entirely distinct from that of the heated tobacco product, as may be anticipated given these products do not contain tobacco. The Nicorette® inhalator was selected as an appropriate comparator in this study as the UK Medicines and Healthcare products Regulatory Agency (MHRA) has indicated this should be used as a reference product, if manufacturers intend to license e-cigarettes as medicinal products [16].

Future investigations

PTR-MS is a one dimensional technique that characterizes VOCs via their mass; to enable identification of the chemicals in the side-stream emissions from the heated tobacco product it is necessary to further calibrate the machine for identification and quantification of compounds of regulatory interest e.g., HPHCs in tobacco products and tobacco smoke as developed by the US Food and Drug Administration (FDA) [17]. We will therefore determine the identities of the many different VOCs released to the airspace, and by extension to the bystander's breathing space, from the heated tobacco product when activated and used by the consumer. Moreover, it is also conceivable that differences in side-stream emissions may be observed under varying user consumption topographies. Further research in these areas will be informative.

Conclusions

The release of side-stream emissions from heated tobacco products has been observed by PTR-MS using the simple method presented here. These emissions are generated by the high temperature heating of the *HeatSticks* tobacco matrix inserted within the iQOS device.

The public health community has stated that there is no safe level of exposure to tobacco-containing product emissions [13,18], and so the side-stream constituents including nicotine, released during activation and use of the iQOS heated tobacco product can lead to exposure to bystanders; this would be of concern to public health authorities and warrants further investigation.

It is conceivable that based on these findings and the conclusions of public health community regarding tobacco product emissions, the use of heated tobacco products should be included in smoke-free legislation.

Conflicts of Interest

The work in this short communication was supported by Imperial Tobacco Group. Imperial Tobacco Group is the parent company of Fontem Ventures B.V., the manufacturer of the e-cigarette used in this study.

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PMI's own in vivo clinical data on biomarkers of potential harm in Americans show that IQOS is not detectably different from conventional cigarettes

Stanton A Glantz[1,2]

[1]Department of Medicine/Division of Cardiology, University of California San Francisco, San Francisco, CA 94143-1390, USA
[2]Center for Tobacco Control Research and Education, University of California San Francisco, San Francisco, CA 94143-1390, USA

Correspondence to
Professor Stanton A Glantz, Department of Medicine/Cardiology, University of California San Francisco, San Francisco, CA 94143-1390, USA; glantz@medicine.ucsf.edu

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ABSTRACT

Introduction New 'heated tobacco products' are being marketed in several countries with claims that they expose users to lower levels of toxins than conventional cigarettes which could be read as being less likely to cause health problems than conventional cigarettes. In the USA, Philip Morris International (PMI) has submitted an application to the Food and Drug Administration for permission to market its heated tobacco product, IQOS, with reduced exposure and reduced risk claims.

Methods Analysis of detailed results on 24 biomarkers of potential harm in PMI studies of humans using IQOS compared with humans using conventional cigarettes.

Results Among American adults, there is no statistically detectable difference between IQOS and conventional cigarette users for 23 of the 24 biomarkers of potential harm in PMI's studies. In Japan, there were no significant differences between people using IQOS and conventional cigarettes in 10 of 13 biomarkers of potential harm. It is likely that some of the significant differences are false positives.

Conclusion Despite delivering lower levels of some toxins than conventional cigarettes, PMI's own data fail to show consistently lower risks of harm in humans using its heated tobacco product, IQOS, than conventional cigarettes.

INTRODUCTION

Nicotine is the addictive drug in tobacco. Burning the tobacco generates an aerosol of ultrafine particles that carries nicotine deep into smokers' lungs, where it is absorbed and rapidly reaches the brain. That burning yields toxic chemicals that cause disease. Ever since people started understanding in the 1950s that smoking kills, millions have struggled to stop smoking. The tobacco companies, desperate to keep and expand their customers, have been trying to make 'safer cigarettes' since the 1960s.[1] They have also developed products that avoided burning, including e-cigarettes,[2] nicotine replacement therapy,[3] and products that heat the tobacco without setting it on fire. As of January 2018 all the major multinational tobacco companies had developed, or were in the process of developing, so-called 'heated tobacco products' (HTP; also called 'heat-not-burn' tobacco products). Because these devices generate their nicotine aerosols by heating a stick of ground tobacco and chemicals without setting the tobacco on fire, they generally produce fewer toxic chemicals than a conventional cigarette, which is promoted as meaning or implying that these products are not as dangerous as conventional cigarettes.

In 2015, Philip Morris International (PMI) started test marketing its IQOS HTP outside the USA on the grounds that it is not as bad as a cigarette because 'the tobacco is heated and not burned, the levels of harmful chemicals are significantly reduced compared to cigarette smoke.'[4]

Because IQOS is a new tobacco product, PMI needs to obtain premarket authorisation from the US Food and Drug Administration (FDA) to sell it in the USA. In particular, PMI wants to market IQOS with reduced risk claims, what US law calls a 'modified risk tobacco product' (MRTP). To obtain authorisation to market IQOS with reduced risk claims, PMI submitted an application to the FDA in December 2016.[5] As required by law, FDA has made most of the application available for the public to review. The application includes comparisons of the levels of 24 biomarkers of potential harm in human smokers, including comparisons with people who smoke conventional cigarettes. These biomarkers include measures of inflammation, oxidative stress, cholesterol and triglycerides, blood pressure and lung function. This paper uses information in the PMI application to evaluate this comparison and concludes that in people who actually use IQOS, the levels of these biomarkers of potential harm are not detectably different from conventional cigarettes.

METHODS

The results analysed in this paper are from PMI's 'Three-month Reduced Exposure in a confined and ambulatory setting' studies (ZRHR-REXA-07-JP in Japan and ZRHM-REXA-08-US in the USA) that present human clinical studies of non-cancer biomarkers of potential harm presented in PMI's MRTP application's[5] Executive Summary, Module 6: Summaries of All Research Findings, and Module 7.3.1: Scientific Studies and Analyses (Studies in Adult Human Studies: Clinical Studies), specifically the data on 24 biomarkers of potential harm *in human users* derived from two of their 'Reduced Exposure' studies: ZRHR-REXA-07-JP in Japan and ZRHM-REXA-08-US in the USA.

As described in Section 6.1.4.3.2 of the application, cigarette smokers were randomised, controlled, open-label, three-arm parallel group studies in which smokers were randomised to IQOS (menthol), continued smoking their current brand of cigarettes or smoking abstinence. Baseline data were collected on day 0 immediately before randomisation, people were held during a 5-day confinement period then released to the ambulatory setting and observed at 90 (±3 (range)) days

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after randomisation. (Some variables were measured during confinement and before 90 days, but are not considered in this analysis.) During the confinement period, product use was directed and monitored by the study staff and participating smokers were controlled for product compliance. Subjects assigned to conventional cigarettes or IQOS used the products without restriction (ad libitum) during an extended daily time window (16 hours); dual use of conventional cigarettes and IQOS was not permitted. The 3-month ambulatory phase was designed to reflect a near real-world environment where dual use of IQOS and conventional cigarettes or other tobacco products could occur. PMI selected a 3-month extended ambulatory follow-up period so that the study would be long enough to assess the initial changes in some of the clinical risk endpoints that have been shown to be reversible within 2 weeks to 3 months.

The final sample (table 1) consisted of people who were adherent with their assigned study product and without major protocol deviations that impacted the validity of the evaluation of the study results. This sample was designed to assess the maximum exposure reduction achievable (what PMI characterised as the 'optimal effect') in subjects who were using IQOS ad libitum and exclusively or at least predominantly, rather than the effect in the full population representing a heterogeneous exposure (eg, as mixed product use, or non-use of the assigned product).

The point estimates and 95% confident intervals (CIs) at day 90 were computed using least squares means from an analysis of covariance with study arm as a factor adjusting for baseline value, sex and average daily conventional cigarette consumption over the last 4 weeks as reported during screening. (Thus, the width of the CIs for the differences between IQOS and conventional cigarette use in table 1 benefits from the information in the smoking abstinence group even though those subjects are not directly involved in the point estimates being compared.) Endpoints that were not normally distributed were log-transformed (base e) prior to analysis, then back-transformed to calculate least squares means ratios to compare IQOS with conventional cigarettes.

Both trials were registered with ClinTrials.gov.

Specific results are based on measures of inflammation in Section 6.1.4.4.2; cholesterol, triglycerides and physiological measures related to heart disease in Section 6.1.4.4.4; and lung function in Section 6.1.4.4.5.

RESULTS

Among American adults, there is no statistically detectable difference between IQOS and conventional cigarettes for 23 of the 24 biomarkers of potential harm in PMI's studies (table 1). This is indicated by the fact that 23 of the 95% CIs include zero (ie, no statistically significant difference). Moreover, when using the conventional 95% confidence standard for statistical hypothesis testing, one would expect 5% of the tests to yield false positives. Five per cent of 24 tests is 1.2 tests, which means that one would expect one false positive result. PMI had one positive result (soluble intercellular adhesion molecule (ICAM)), which is what one would expect by chance.

PMI also reported the results on 13 biomarkers of potential harm among Japanese people (table 1). There were significant improvements in 4/13 of these biomarkers, 3 markers of inflammation (white cell count, prostaglandin F2 alpha and soluble ICAM) and 1 measure of cholesterol (high-density lipoprotein cholesterol). When using the conventional 95% confidence standard one would expect 0.65 positive tests, which means one would expect one false positive test.

Table 1 Summary of Philip Morris studies of changes in biomarkers in IQOS users compared with conventional cigarette smokers after 90 days of product use (95% CIs in parenthesis)

	Japan	USA
Inflammation (6.1.4.4.2**)		
White cell count	**−0.57 GI/L (−1.04 to −0.10)**	0.17 GI/L (−0.47 to 0.81)
C-reactive protein (CRP)	6.41% ↓ (−40.75 to 37.77)	16.23% ↓ (−21.69 to 42.33)
Soluble ICAM (sICAM-1)	**8.72% ↓ (2.05 to 14.94)**	**10.59% ↓ (4.03 to 16.71)**
Fibrinogen	5.42% ↓ (−1.80 to 12.13)	1.63% ↓ (−6.42 to 9.08)
Oxidative stress (6.1.4.4.3)		
Prostaglandin F2 alpha (8-epi-PGF2α)	**12.71% ↓ (2.55 to 21.81)**	13.46% ↓ (−1.95 to 23.61)
11-dehydrothromboxane B2 (11DTXB2)	5.42% ↓ (−1.80 to 12.13)	3.56% ↓ (−23.31 to 24.57)
Cholesterol and triglycerides (6.1.4.4.4)		
High-density lipoprotein cholesterol (HDL-C)	**4.53** mg/dL **(1.17 to 7.88)**	1.4 mg/dL (−2.3 to 5.0)
Low-density lipoprotein cholesterol (LDL-C)	0.87 mg/dL (−6.55 to 8.30)	−3.3 mg/dL (−12.0 to 5.4)
Total cholesterol	2.00 mg/dL (−6.68 to 10.67)	−4.0 mg/dL (−13.3 to 5.2)
Triglycerides	−6.25 mg/dL (−21.20 to 8.69)	0.9 mg/dL (−12.8 to 14.6)
Apolipoprotein A1 (apoA1)	NA	3.1 mg/dL (−4.6 to 10. 7)
Apolipoprotein B (apoB)	NA	−1.6 mg/dL (−7.24 to 4.03)
Physiological measures		
Systolic blood pressure	−0.59 mm Hg (−3.80 to 2.62)	−0.7 mm Hg (−4.5 to 3.1)
Diastolic blood pressure	−0.68 mm Hg (−3.04 to 1.69)	0.2 mm Hg (−3.7 to 4.0)
Lung function (6.1.4.4.5)		
Forced expiratory volume in 1 s (FEV_1)	1.91 %Pred (−0.14 to 3.97)	0.53 %Pred (−2.09 to 3.00) 0.05 L (−0.06 to 0.15)
FEV_1/FVC (forced vital capacity)	NA	0.00 (−0.02 to 0.02)
Mid-expiratory flow (MEF 25–75) (L/s)	NA	−0.67 (−6.33 to 4.99)
Diffusion capacity for lung CO (DLCO) (mL/min/mm Hg)	NA	0.31 (−1.09 to 1.72)
Rate constant of CO (KCO) (mmol/min/kPa/L)	NA	0.05 (−0.02 to 0.12)
Total lung capacity (TLC) (L)	NA	0.09 (−0.25 to 0.43)
Functional residual volume (FRV) (L)	NA	−0.09 (−0.31 to 0.13)
Inspiratory capacity (IC) (L)	NA	0.21 (−0.08 to 0.51)
Vital capacity (VC) (L)	NA	0.10 (0.00 to 0.21)
Summary		
Number of biomarkers tested	13	24
Number significantly improved	3	1
Number expected by chance	1	1

Continued

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Table 1 Continued

	Japan	USA
Sample sizes		
IQOS	70	47†
Conventional cigarettes	41	32‡
Smoking abstinence	37	9§

The results are either IQOS:CC or IQOS-CC (conventional cigarettes).
Bold results are statistically significant differences (p<05).
*Section of Philip Morris International's Modified Risk Tobacco Product application.
†n=45 for fibrinogen, 8-epi-PGF2α, 11DTXB2, systolic blood pressure, diastolic blood pressure, DCLO and KCO.
‡n=30 for FEV_1, FEV_1/FVC, MEF 25–75, DLCO, KCO, TLC, FRV, IC and VC.
§n=8 for DLCO and 7 for KCO.
ICAM, intercellular adhesion molecule; NA, not applicable.

DISCUSSION

These human data are important information because they represent direct evidence on how IQOS affects people who use the product. They show that, despite the evidence that PMI submitted that the levels of some toxins in IQOS aerosol are lower than in conventional cigarettes,[5] fewer toxic chemicals, however, do not necessarily translate into lower harm when people use the product.

In its MRTP application, PMI did not discuss the results of the conventional statistical tests described in the Results section, which are routine for such scientific analysis. Rather, they simply emphasise the direction of changes while ignoring the fact that these differences are within what would be expected based on simple randomness. No tobacco company would tolerate such assertions made by the FDA or other public health authorities.

The results reported in PMI's application (and in a published paper[6]) for Japan are slightly more positive for IQOS, with 4 of 13 biomarkers showing differences from conventional cigarettes (where one would expect one false positive by chance). These results are not strong enough to warrant drawing a conclusion of reduced risk. The conclusion of no significant difference on biomarkers of potential harm is based on taking PMI's results at face value despite the tobacco companies' (including Philip Morris) long record of manipulating the design, analysis and presentation of their published scientific studies <<ED: Citation should be "7-12" no "7-13".>>.[7–13]

Like cigarettes (and e-cigarettes), IQOS uses an aerosol of ultrafine particles to deliver the nicotine. These ultrafine particles cause heart and lung disease. The adverse health effects of these particles and many of the other toxins do not drop in proportion to reducing the dose, so even low levels of exposure can be dangerous.[13] This effect is why smoke-free environment laws are followed by big drops in heart attacks and other diseases despite the fact that secondhand smokers breathe in much less smoke that the smokers.[14] In addition, while the IQOS does not set the tobacco stick on fire, it heats it to 350°C (660°F), which is still hot enough to cause pyrolysis. There is already independent evidence that IQOS compromises functioning of arteries,[15] a key risk factor for heart disease and heart attacks, as badly as a cigarette.

The clinical studies that PMI reported appropriately did not include cancer because carcinogenic effects take much longer to be manifest than cardiovascular and pulmonary effects. Even if the levels of carcinogens delivered by IQOS are lower than conventional cigarettes on a per-puff basis, these lower exposure levels may not yield proportionately lower cancer risks because both the intensity and duration of exposure impact cancer risk.[16–18]

The purpose of this paper is to assess the data on biomarkers of potential harm of the Philip Morris IQOS HTP system in people who were actually using the system compared with people who smoke conventional cigarettes based on the information submitted to the US FDA in PMI's MRTP application for IQOS. On 31 March 2018, the author conducted a PubMed search using the search term '(IQOS or 'heat not burn' or 'heated tobacco product') and (health or harm) and (human or clinical)'. This search returned 33 papers, none of which reported on comparisons of in vivo biomarkers of potential harm in people using IQOS (or any other HTP system) compared with conventional cigarettes. Thus, as of 9 July 2018, the data in the PMI MRTP application remained the only publicly available evidence on the in vivo human clinical effects of IQOS compared with conventional cigarettes.

While this analysis is limited to the data presented in PMI's IQOS MRTP application to the FDA, it is likely that the effects of other HTPs being developed by other tobacco companies will have similar effects because the fundamental principles behind all these products are the same.

On 15 June 2018, PMI issued a press release, 'Philip Morris (PM) Announces Positive Results from New Clinical Study on IQOS,'[19] that said, 'all eight of the primary clinical risk endpoints moved in the same direction as observed for smoking cessation in the group who switched to IQOS, with statistically significant changes in five of the eight endpoints compared with on-going smoking.' While PMI did not release any detailed results, examining the protocol (on ClinicalTrials.gov) revealed that this new study only examined six clinical measures, compared with the 24 in MRTP application (table 1). (The other two were biomarkers of exposure.) PMI did not say which of the changes were statistically significant, raising the possibility that the protocol and analysis were manipulated to achieve positive results.[8 9] PMI increased the sample size from 88 in the original US study to 984. While bigger studies are better, the fact is that making the sample size big enough will increase the power to the point that almost any difference will reach statistical significance regardless of whether it is clinically significant or not. The true measure of reduced risk would be statistically significant changes that were large enough to be clinically significant in enough biomarkers of potential harm to be meaningful.

PMI's failure to show significant improvements in these biomarkers of potential harm is consistent with the data PMI reported on the levels of toxicants in IQOS mainstream aerosol compared with mainstream smoke of 3R4F reference cigarettes.[20] While many toxicants were lower in IQOS aerosol, 56 others were higher in IQOS emissions and 22 were more than twice as high, and 7 were more than an order of magnitude higher.

In short, PMI's results in humans failed to meet the legal requirement that IQOS 'as it is actually used by consumers, will significantly reduce harm and the risk of tobacco-related disease to individual users' that US law requires before the FDA can approve a reduced risk claim. In the USA, PMI wants to sell IQOS with claims that 'Scientific studies have shown that switching completely from cigarettes to the IQOS system can reduce the risks of tobacco-related diseases' and 'Switching completely to IQOS presents less risk of harm than continuing to smoke cigarettes'[5]; these claims are not substantiated by PMI's own data.

On 25 January 2018, based in part on the information in this paper (which had been submitted to FDA as a public comment) showing gaps in PMI's scientific evidence, the FDA's Tobacco Products Scientific Advisory Committee voted that PMI had failed to demonstrate that its proposed modified (reduced) risk labelling and advertising claims for IQOS were demonstrated by scientific evidence.[21]

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What this paper adds

- Heated tobacco products are being marketed in several countries with claims of reduced exposure to toxins compared with conventional cigarettes.
- Studies conducted in people using Philip Morris International's IQOS heated tobacco product did not reveal detectably better measures of biomarkers of potential harm than conventional cigarettes in human tests.
- These products should not be permitted to be marketed with claims that state or imply reduced risks compared with conventional cigarettes.

Based on the data in the PMI MRTP application for IQOS, neither the US FDA nor comparable authorities elsewhere in the world should permit such claims to be made. All companies wishing to market HTPs with reduced risk claims should be held to the same standard, and their claims independently verified.

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Data sharing statement All data are available in the PMI MRTP application on the FDA website.

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IQOS: examination of Philip Morris International's claim of reduced exposure

Gideon St.Helen,[1,2] Peyton Jacob III,[1,2] Natalie Nardone,[1] Neal L Benowitz[1,2,3]

[1]Division of Clinical Pharmacology, Department of Medicine, University of California San Francisco, San Francisco, California, USA
[2]Center for Tobacco Control Research and Education, University of California, San Francisco, California, USA
[3]Department of Bioengineering and Therapeutic Sciences, University of California San Francisco, San Francisco, California, USA

Correspondence to
Dr Gideon St.Helen, Division of Clinical Pharmacology and Experimental Therapeutics, University of California San Francisco, San Francisco, CA 94143-1220, USA;
Gideon.StHelen@ucsf.edu

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ABSTRACT

Background New electronic heated tobacco products are being introduced in the global market and are gaining popularity. In 2016, Philip Morris International, Inc. (PMI) submitted a modified risk tobacco product (MRTP) application to the Food and Drug Administration (FDA) to market IQOS in the USA with claims of reduced exposure and reduced risk.

Methods We examined PMI's MRTP application, specifically sections on aerosol chemistry and human exposure assessment, to assess the validity of PMI's claims of reduced exposure and risk.

Findings PMI reported levels for only 40 of 93 harmful and potentially harmful constituents (HPHCs) on FDA's HPHC list in IQOS mainstream aerosol. All substances in PMI's list of 58 constituents (PMI-58) were lower in IQOS emissions compared with mainstream smoke of 3R4F reference cigarettes. However, levels of 56 other constituents, which are not included in the PMI-58 list or FDA's list of HPHCs, were higher in IQOS emissions; 22 were >200% higher and seven were >1000% higher than in 3R4F reference cigarette smoke. PMI's studies also show significantly lower systemic exposure to some HPHCs from use of IQOS compared with smoking combustible cigarettes.

Conclusion PMI's data appear to support PMI's claim that IQOS reduces exposure to HPHCs. However, PMI's data also show significantly higher levels of several substances that are not recognised as HPHCs by the FDA in IQOS emissions compared with combustible cigarette smoke. The impact of these substances on the overall toxicity or harm of IQOS is not known.

INTRODUCTION

Many alternative tobacco products have entered the USA market in the last three decades. These include electronic cigarettes that heat a nicotine solution[1] as well as products that heat tobacco without combustion called heated tobacco products (HTPs) or heat-not-burn (HNB) products. A 2000 internal R J Reynolds document gave the rationale for the pursuit of an acceptable HTP:

> Given that no particular agent or group of agents can be definitely assigned the carcinogenic risk associated with cigarettes, the most effective strategy for reducing lung cancer risk in the smoking population is an overall reduction in both the number and concentration of particulate and vapor phase components. This strategy can be achieved by primarily heating, rather than burning, tobacco to form cigarette smoke aerosol.[2]

R J Reynolds first released Premier in 1988,[3] which was followed by Eclipse, a paper-encased tobacco plug heated by a carbon element.[4] Independent studies showed that use of Eclipse decreased tobacco cigarette consumption without causing withdrawal symptoms, maintained blood nicotine concentrations and decreased exposure to the carcinogenic tobacco-specific nitrosamine, 4-(methylnitrosamino)−1-(3-pyridyl)−1-butanone, but increased exposure to carbon monoxide (CO).[5–7] Other HTPs included Philip Morris' Accord, which was a combination of a handheld device that heated specially constructed cigarettes. One independent study showed that use of Accord suppressed withdrawal symptoms and reduced CO exposure.[8] Each iteration of HTPs was commercially unsuccessful, and most products were discontinued shortly after their introduction.[9]

Despite repeated failures at producing a commercially viable HTP, tobacco companies continue to research and develop these products. R J Reynolds launched a revamped Eclipse, rebranded as 'Revo', in November 2014. Revo was briefly test marketed in Wisconsin but pulled off the market.[10] Other current HTPs include British American Tobacco's Glo iFuse, a hybrid of HTP and e-cigarettes. It consists of a heating element, a liquid tank (like e-cigarettes) and a tobacco cavity through which the e-cigarette-like aerosol passes and is infused with tobacco flavour.[11] Japan Tobacco's Ploom Tech, which entered the Japanese market in 2016,[12] consists of a liquid cartridge and a capsule of granulated tobacco leaves that the vapour passes through.

Philip Morris Products S.A., a subsidiary of Philip Morris International, Inc. (PMI), developed IQOS ('I Quit Ordinary Smoking') as an HTP.[9 10] IQOS consists of a tobacco stick (HeatStick) and a battery-powered tobacco heating device.[13] As of May 2018, IQOS is currently sold in over 37 countries, including Japan, the UK and Canada.[14] Philip Morris Products S.A. filed a modified risk tobacco product (MRTP) application with the US Food and Drug Administration (FDA) in December 2016[15 16] to market IQOS in the USA with reduced exposure and reduced risk claims. The FDA's Tobacco Products Scientific Advisory Committee (TPSAC) reviewed the MRTP application in January 2018. The TPSAC committee approved, in an 8 to 1 vote, PMI's statement '*Scientific studies have shown that switching completely from cigarettes to the IQOS system significantly reduces your body's exposure to harmful or potentially harmful chemicals [HPHCs]*' was true.[17] Of the eight committee members who agreed with PMI's claim that IQOS significantly reduced exposure to HPHCs, a majority (five of eight) voted that PMI has not '*demonstrated that the reductions in exposure are reasonably likely to translate to a measurable and substantial reduction in morbidity and/or mortality*'.[17]

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Examination of PMI's studies, results and interpretation of data to support claims of reduced exposure and risk is critically important before FDA approval in order to protect public health, particularly as PMI's MRTP application and approval may set the precedent for other MRTP applications of similar products. This paper examines PMI's reported studies on IQOS aerosol chemistry and human exposure assessment, and we assessed whether they support PMI's claims of reduced exposure.

METHODS

We examined studies presented in PMI's MRTP application,[16] namely those in Module 6.1.1: *Aerosol Chemistry*; Module 6.1.3.1: *Justification of Selection of Biomarkers of Exposure*; and Module 6.1.3.2: *Summary of Biomarkers of Exposure Assessments*. We also reviewed data presented in the document, *Addendum to FDA Briefing Document: January 24–25, 2018*,[18] which was prepared by FDA's Center for Tobacco Products for the TPSAC meeting on IQOS held on 24 and 25 January 2018.

To examine the aerosol chemistry of IQOS, mainstream aerosol from IQOS HeatSticks (regular and menthol) and smoke from 3R4F reference cigarettes were generated according to the Health Canada Intense machine-smoking regimen on a Borgwaldt linear smoking machine type LM20X (Borgwaldt KC GmbH, Hamburg, Germany) for most analytes and Burghart rotary smoking machine type RMB 20 (Burghart Tabaktechnik GmbH, Wedel, Germany) for elements.[19] Methods for chemical analyses have been described previously.[19]

PMI conducted four clinical studies to examine whether human exposure to harmful substances are statistically significantly reduced with IQOS (Module 6.1.3.2).[16] All studies were randomised, controlled, open-label, three-arm, parallel group, single-centre studies. Studies ZRHR-REXC-03-EU (conducted in Poland) and ZRHR-REXC-04-JP (conducted in Japan) were conducted over 5 days in confinement. Each study included 160 combustible cigarette smokers who were randomly assigned to one of three arms, namely, IQOS with regular HeatSticks, commercially available combustible cigarettes or smoking abstinence. Use of IQOS or combustible cigarettes was from 06:30 to 23:00 and was ad libitum. Studies ZRHM-REXA-07-JP (conducted in Japan) and ZRHM-REXA-08-US (conducted in the USA) were conducted over 3 months, during which 160 participants were randomised to one of three arms in each study, namely, IQOS with menthol HeatSticks, commercially available menthol combustible cigarettes or smoking abstinence. These two studies included 5 days in confinement followed by 85 or 86 days, respectively, in an ambulatory setting. Participants in the IQOS or combustible cigarettes arms used each product ad libitum in confinement (06:30–23:00) and in the ambulatory setting. Compliance with study protocol could not be enforced during the ambulatory phase.

For the two 5-day confinement studies, it was evaluated whether reductions of 50% or more in 24 hours urine concentrations of mercapturic acid metabolites of 1,3-butadiene, acrolein and benzene and carboxyhaemoglobin in blood were observed in smokers assigned to IQOS compared with smokers who continued smoking combustible cigarettes. Levels of selected biomarkers of exposure over the 5-day exposure period were also compared between smokers who switched to IQOS and those who continued smoking and the maximum reduction in biomarker levels in abstinent smokers was assessed. For the two 3-month studies, they examined whether the geometric mean levels of biomarkers of exposure for IQOS (menthol) were lower relative to combustible cigarette (menthol) use. Differences in mercapturic acid metabolites of 1,3-butadiene, acrolein and benzene and carboxyhaemoglobin in blood were tested on day 5 and total 4-(methylnitrosamino)−1-(3-pyridyl)−1-butanol on day 90.

RESULTS

PMI reported the levels of 58 constituents (which PMI refers to as 'PMI-58') in mainstream aerosol generated from IQOS and 3R4F reference cigarettes (Module 6.1.1).[16] The PMI-58 list includes 40 (43%) out of the 93 harmful or potentially harmful constituents (HPHCs) on FDA's list of HPHCs.[20] The PMI-58 list included 18 additional constituents that do not appear on FDA's list of HPHCs, including water, total particulate matter, pyrene and nitrogen oxides. PMI concluded that the levels of HPHCs on the PMI-58 list were reduced by >92% on a stick basis and >89% on a normalised for nicotine basis for the regular tobacco stick, and >93% on a stick basis and >88% on a normalised for nicotine basis for the mentholated tobacco stick compared to 3R4F reference cigarette (Module 6.1.1, p. 45).[16]

Importantly, the addendum to the briefing document for the 24 and 25 January 2018 TPSAC meeting, prepared by FDA's Center for Tobacco Products,[18] presented additional data from PMI studies that showed higher levels of many substances in IQOS emissions compared with 3R4F cigarette smoke (table 1). The addendum consisted of data from Module 3.3.2 and section 6.1.1.3.4 of the MRTP application and appendix A of an amendment to the MRTP application. The addendum reported levels of 113 constituents, including 56 of the 58 constituents on the PMI-58 list (total particulate matter and nicotine-free dry particulate matter were the two exclusions) and 57 constituents that do not appear on the PMI-58 list. Fifty-six of the 57 non-PMI-58 constituents were higher in IQOS emission than in 3R4F smoke (median, 154% higher; range, undefined to 13 650% higher in IQOS aerosol vs 3R4F mainstream smoke); tar was the exception. Twenty-two of the non-PMI-58 constituents were at least 200% higher while seven were at least 1000% higher in IQOS emission compared with 3R4F mainstream smoke (table 1).

PMI characterised the droplet size distribution of IQOS aerosol by measuring the mass median aerodynamic diameter (MMAD) (the diameter at which 50% of the particles by mass are larger and 50% are smaller) and geometric standard deviation (presented in Module 6.1.1).[16] The MMAD for the various IQOS products tested (regular and menthol) ranged between 0.54 µm to 0.75 µm and fell within the respirability region, based on the respirability upper threshold defined at 2.5 µm. The range of MMAD for IQOS appears slightly larger than those of e-cigarettes and conventional tobacco cigarettes, which one report showed were about 0.15 µm and 0.17 µm, respectively.[21]

Regarding the human exposure studies, 11 of the 17 HPHCs measured are included in a list of 18 HPHCs that FDA recommends to be measured and reported in users of tobacco products.[20] PMI assessed systemic exposure to pyrene, which is not included in FDA's list of HPHCs, as a proxy for exposure to polycyclic aromatic hydrocarbons (PAHs) using 1-hydroxypyrene. PMI did not assess systemic exposure to inorganic compounds, phenols and metals.

Biomarkers of HPHCs measured were statistically significantly lower with IQOS use compared with combustible cigarette use (Module 6.1.3.2).[16] Reductions of at least 50% in levels of biomarkers of exposure to HPHCs were reported when smokers switched from combustible cigarettes to IQOS during 5 days of confinement; these reductions were sustained during the 85/86 days in ambulatory settings (Module 6.1.3.2, p. 145).

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Table 1 Compounds in mainstream aerosol of Marlboro HeatSticks compared with 3R4F reference cigarette

PMI product	Unit	PMI-58	IQOS HeatStick	3R4F	Change (%) with 3R4F on stick basis
1,2,3-Propanetriol, diacetate (diacetin)	µg/stick	No	1.23	0.381	↑ 223
1,2-Propanediol, 3-chloro	µg/stick	No	9.94	5.93	↑ 68
1,4-Dioxane, 2-ethyl-5-methyl-	µg/stick	No	0.055	0.0004	↑ 13 650
12,14-Labdadiene-7,8-diol, (8a,12E)	µg/stick	No	1.43	0.064	↑ 2134
1 hour-Indene, 2,3-dihydro-1,1,5,6-tetramethyl-	µg/stick	No	0.026	0.014	↑ 86
1-Hydroxy-2-butanone	µg/stick	No	0.947	0.465	↑ 104
1-Hydroxy-2-propanone(1,2-Propenediol)	µg/stick	No	162	96.8	↑ 67
2 (5H)-Furanone	µg/stick	No	5.32	1.99	↑ 167
2,3-Dihydro-5-hydroxy-6-methyl-4 hour-pyran-4-one	µg/stick	No	0.231	0.135	↑ 71
2,4-Dimethylcyclopent-4-ene-1,3-dione	µg/stick	No	0.333	0.193	↑ 73
2-Cyclopentene-1,4-dione	µg/stick	No	3.8	0.764	↑ 397
2-Formyl-1-methylpyrrole	µg/stick	No	0.128	0.064	↑ 100
2-Furancarboxaldehyde,5-methyl-	µg/stick	No	11.1	2.94	↑ 278
2-Furanmethanol	µg/stick	No	39.2	7	↑ 460
2-Furanmethanol, 5-methyl-	µg/stick	No	0.123	0.029	↑ 324
2 hour-Pyran-2-one,tetrahydro-5-hydroxy	µg/stick	No	4.45	3.11	↑ 43
2-Methylcyclobutane-1,3-dione	µg/stick	No	2.78	0.71	↑ 292
2-Propanone, 1-(acetyloxy)-	µg/stick	No	16.9	8.01	↑ 111
3 (2H)-Furanone, dihydro-2-methyl-	µg/stick	No	0.326	0.119	↑ 174
3-Methylvaleric acid	µg/stick	No	5.1	3.63	↑ 40
4(H)-Pyridine, N-acetyl-	µg/stick	No	0.296	0.112	↑ 164
5-Methylfurfural	µg/stick	No	0.995	0.632	↑ 57
Anhydro linalool oxide	µg/stick	No	0.457	0.291	↑ 57
Benzene, 1,2,3,4-tetramethyl-4-(1-methylethenyl)-	µg/stick	No	0.006	0.005	↑ 20
Benzenemethanol, 4-hydroxy-	µg/stick	No	0.011	0	↑
Benzoic acid, 2,5-dihydroxy-methyl	µg/stick	No	4.55	2.18	↑ 109
Butylated hydroxytoluene	µg/stick	No	0.132	0.007	↑ 1786
Butyrolactone	µg/stick	No	4.08	0.728	↑ 460
Cis-sesquisabinene hydrate	µg/stick	No	0.061	0	↑
Cyclohexane, 1,2-dioxo-	µg/stick	No	0.083	0.046	↑ 80
Cyclohexane-1,2-dione, 3-methyl-	µg/stick	No	0.101	0.073	↑ 38
Eicosane, 2-methyl-	µg/stick	No	0.05	0.014	↑ 257
Ergosterol	µg/stick	No	3.18	1.58	↑ 101
Ethyl 2,4-dioxohexanoate	µg/stick	No	6.73	3.57	↑ 89
Ethyl dodecanoate (ethyl laurate)	µg/stick	No	0.023	0	↑
Ethyl linoleate	µg/stick	No	0.135	0.008	↑ 1588
Ethyl linolenate	µg/stick	No	0.614	0.153	↑ 301
Furfural	µg/stick	No	31.1	25.9	↑ 20
Glycerol	mg/stick	No	5.02	2.08	↑ 141
Glycidol	µg/stick	No	5.71	1.76	↑ 224
Heneicosane, 2-methyl-	µg/stick	No	0.063	0.021	↑ 200
Hexadecanoic acid, ethyl ester	µg/stick	No	0.491	0.008	↑ 6038
Isolinderanolide	µg/stick	No	4.99	1.85	↑ 170
Isoquinoline, 3-methyl	µg/stick	No	6.29	4.99	↑ 26
Labdane-8,15-diol, (13S)	µg/stick	No	0.143	0.015	↑ 853
Lanost-8-en-3-ol, 24-methylene-, (3beta)	µg/stick	No	6.3	1.61	↑ 291
Maltoxazine	µg/stick	No	0.077	0.038	↑ 103
Methyl furoate	µg/stick	No	0.147	0.029	↑ 407
Phenylacetaldehyde	µg/stick	No	1.41	0.529	↑ 167
p-Menthan-3-ol	µg/stick	No	0.786	0.322	↑ 144
Propylene glycol	µg/stick	No	175	23.7	↑ 638
Pyranone	µg/stick	No	6.54	5.07	↑ 29
Pyranone	µg/stick	No	9.26	5.84	↑ 59
Pyridoxin	µg/stick	No	0.699	0.526	↑ 33

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Table 1 Continued

PMI product	Unit	PMI-58	IQOS HeatStick	3R4F	Change (%) with 3R4F on stick basis
Stearate, ethyl-	µg/stick	No	0.074	0.003	↑ 2367
Tar	mg/stick	No	19.4	25	↓ 22
Trans-4-hydroxymethyl-2-methyl-1,3-dioxolane	µg/stick	No	2.09	0.044	↑ 4650
1,3-Butadiene	µg/stick	Yes	0.21	89.2	↓ 99.8
1-Aminonaphthalene	ng/stick	Yes	0.043	20.9	↓ 99.8
2-Aminonaphthalene	ng/stick	Yes	0.022	17.5	↓ 99.9
3-Aminobiphenyl	ng/stick	Yes	0.007	4.6	↓ 99.8
4-Aminobiphenyl	ng/stick	Yes	0.009	3.21	↓ 99.7
Acetaldehyde	µg/stick	Yes	192	1602	↓ 88
Acetamide	µg/stick	Yes	2.96	13	↓ 77
Acetone	µg/stick	Yes	30.7	653	↓ 95
Acrolein	µg/stick	Yes	8.32	158	↓ 95
Acrylamide	µg/stick	Yes	1.58	4.5	↓ 65
Acrylonitrile	µg/stick	Yes	0.145	21.2	↓ 99.3
Ammonia	µg/stick	Yes	12.2	33.2	↓ 63
Arsenic	ng/stick	Yes	<0.36	<7.49	NA
Benz[a]anthracene	ng/stick	Yes	2.65	28.4	↓ 91
Benzene	µg/stick	Yes	0.45	77.3	↓ 99.4
Benzo[a]pyrene	ng/stick	Yes	0.736	13.3	↓ 94
Butyraldehyde	µg/stick	Yes	20.7	81.3	↓ 74
Cadmium	ng/stick	Yes	<0.28	89.2	↓ >99.7
Carbon monoxide	mg/stick	Yes	0.35	29.4	↓ 99
Catechol	µg/stick	Yes	14	84.1	↓ 83
Chromium	ng/stick	Yes	<11.0	<11.9	NA
Crotonaldehyde	µg/stick	Yes	<3.29	49.3	↓ >93
Dibenz[a,h] anthracene	ng/stick	Yes	<0.124	<0.689	NA
Ethylene oxide	µg/stick	Yes	<0.119	16	↓ >99.3
Formaldehyde	µg/stick	Yes	14.1	79.4	↓ 82
Hydrogen cyanide	µg/stick	Yes	<1.75	329	↓ >99.5
Hydroquinone	µg/stick	Yes	6.55	94.5	↓ 93
Isoprene	µg/stick	Yes	1.51	891	↓ 99.8
Lead	ng/stick	Yes	2.23	31.2	↓ 93
m-Cresol	µg/stick	Yes	0.042	4.24	↓ 99
Mercury	ng/stick	Yes	1.38	3.68	↓ 63
Methyl-ethyl-ketone	µg/stick	Yes	10.1	183	↓ 94
Nickel	ng/stick	Yes	<15.9	<12.9	NA
Nicotine	mg/stick	Yes	1.29	1.74	↓ 26
Nitric oxide	µg/stick	Yes	12.6	484	↓ 97
Nitro benzene	µg/stick	Yes	<0.011	<0.038	NA
Nitrogen oxides	µg/stick	Yes	14.2	538	↓ 97
N-nitrosoanabasine	ng/stick	Yes	2.35	29	↓ 92
N-nitrosoanatabine	ng/stick	Yes	14.7	254	↓ 94
NNK	ng/stick	Yes	7.8	244.7	↓ 97
NNN	ng/stick	Yes	10.1	271	↓ 96
o-Cresol	µg/stick	Yes	0.078	4.81	↓ 98
o-Toluidine	ng/stick	Yes	1.1	96.2	↓ 99
p-Cresol	µg/stick	Yes	0.071	9.6	↓ 99
Phenol	µg/stick	Yes	1.47	15.6	↓ 91
Propionaldehyde	µg/stick	Yes	10.8	109	↓ 90
Propylene oxide	ng/stick	Yes	142.3	896	↓ 84
Pyrene	ng/stick	Yes	8.2	79.2	↓ 90
Pyridine	µg/stick	Yes	6.58	30.9	↓ 79
Quinoline	µg/stick	Yes	<0.011	0.43	↓ >98
Resorcinol	µg/stick	Yes	<0.055	1.72	↓ >97

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Table 1 Continued

PMI product	Unit	PMI-58	IQOS HeatStick	3R4F	Change (%) with 3R4F on stick basis
Selenium	ng/stick	Yes	1.27	<4.42	NA
Styrene	µg/stick	Yes	0.58	13.9	↓ 96
Toluene	µg/stick	Yes	1.42	129	↓ 99
Vinyl chloride	ng/stick	Yes	<0.657	93.4	↓ >99
Water	mg/stick	Yes	30.2	14.7	↑ 105

Notes: presented in table 1 of *Addendum to FDA Briefing Document, January 24-25, 2018*, Meeting of the Tobacco Products Scientific Advisory Committee; sata source: section 3.3.2 and section 6.1.1.3.4 of the Modified Risk Tobacco Product application (MRTPAs) and appendix A of an amendment to the MRTPAs submitted on 8 December 2017. Total particulate matter and nicotine-free dry particulate matter, two constituents on the PMI-58 list were not reported by PMI in this table.
↑, higher in IQOS; ↓, lower in IQOS.
PMI, Philip Morris International; PMI-58, PMI's list of 58 constituents.

DISCUSSION

According to FDA's draft guidance, an MRTP is 'any tobacco product that is sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products'.[22] FDA may issue an order allowing a product to be marketed as a modified risk product if it is demonstrated that the product: (A) significantly reduces harm and the risk of tobacco-related disease to individual tobacco users; and (B) benefits the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products. PMI's data show that IQOS significantly reduces emissions and exposure to several HPHCs compared with combustible cigarettes. However, PMI's data also show that IQOS emissions contain higher levels of many other substances compared with combustible cigarettes. The impact of these substances on IQOS toxicity and harm are not known.

Over 7000 distinct substances have been identified in tobacco smoke, many of which are toxic or carcinogenic.[23] HPHCs in tobacco or tobacco smoke have been proposed by several public health authorities, such as the FDA,[20] as possible causes of tobacco-related morbidity and mortality. Elimination or reduction of exposure to these HPHCs may potentially reduce health risks, which is the premise of HTP technology. Schaller and colleagues[19] described five criteria used by PMI to select HPHCs to measure in IQOS aerosol for comparison with 3R4F reference cigarette. Criterion 1 includes smoke constituents determined by International Organization for Standardization (ISO) methods, such as total particulate matter, nicotine and CO. Criterion 2 includes priority toxicants in tobacco smoke selected from the lists issued by regulatory bodies or proposed by cognizant authorities, such as volatile organic compounds like acrylonitrile, 1,3-butadiene and benzene. Criterion 3 includes toxicants for which there is an established biomarker of exposure. Criterion 4 includes toxicants that are predominantly formed below 400°C and that are not included under 'Criterion 2', such as acrylamide and acetamide. Criterion 5 includes toxicants that are predominantly formed above 400°C and that are not included under 'Criterion 1' and 'Criterion 2', such as dibenz[a,h]anthracene and benz[a]anthracene.

PMI's conclusion that IQOS reduces exposure to HPHCs, which TPSAC agreed with,[17] is based, in part, on evidence of lower levels of PMI-58 substances in IQOS emissions compared with 3R4F reference cigarette smoke. However, the PMI-58 list is selective (based on PMI's criteria described before); PMI did not report levels of 53 HPHCs on FDA's list of 93 HPHCs. Of the 53 FDA HPHCs not measured, 50 are carcinogenic (eg, 2,6-dimethylaniline, benz[j]aceanthrylene, ethylbenzene and furan).[20] In addition to the PMI-58 substances, PMI measured levels of 57 other substances in IQOS emissions (non-PMI-58 substances). Importantly, 56 of these 57 non-PMI-58 substances were higher in IQOS aerosol compared with 3R4F mainstream cigarette smoke. It appears that IQOS reduces exposure to some toxicants but elevates exposure to other substances.

Given the elevated levels of the non-PMI-58 substances in IQOS aerosol compared with reference cigarette smoke, their inherent toxicities could play a role in the overall harm of IQOS. A number of these substances, including several that were more than 50% higher in IQOS aerosol, belong to chemical classes that are known to have significant toxicity, such as α,β-unsaturated carbonyl compounds (eg, 2-cyclopentene-1,4-dione),[24] 1,2-dicarbonyl compounds (eg, cyclohexane, 1,2-dioxo-),[25] furans (eg, 2 (5H)-furanone)[26] and epoxides (eg, anhydro linalool oxide).[27] There is limited information on the toxicity of many of the non-PMI-58 substances. We speculate that some of these substances are components of flavour additives in IQOS or thermal degradation compounds. For example, anhydro linalool oxide is listed among flavouring ingredients that are generally regarded as safe (for oral ingestion) by the Flavor and Extract Manufacturers' Association.[28]2 (5H)-Furanone is a food additive that suppresses appetite and/or food intake and has been shown to induce cellular DNA damage in vitro.[29 30] 2-Furanmethanol is a flavouring agent with a flavour profile of burnt, caramel or cooked.[31] 2-Furanmethanol also causes eye, nose, throat and skin irritation and has central nervous system effects.[31] 2-Cyclopentene-1,4-dione is likely generated from thermal breakdown of sugars.[32] 1-Hydroxy-2-butanone, a flavouring ingredient found in coffee and coffee products, is also a degradation product of polysaccharides.[33] Some compounds appear to be contaminants. 3-Chloro-1,2-propanediol (or 1,2-propanediol, 3-chloro), a food contaminant,[34] has not been shown to be genotoxic in vivo,[35] but mutagenic effects were observed at high concentrations in vitro experiments.[36] A 2-year study found increased incidence for the development of tumours in kidney and testis in male rats exposed to 3-chloro-1,2-propanediol.[37] 1,2,3-Propanetriol, diacetate (diacetin) is a solvent used for decaffeinating coffee.

PMI's MRTP application fails to address the important question of whether the aerosol generation process for IQOS produces toxic substances not found in the smoke of combustible cigarettes, which could have been answered through non-targeted chemical analysis. Combustible tobacco cigarettes reach about 900°C during a puff and smoulder at about 400°C between puffs.[23] The burning process, substances emitted and their levels vary at different temperatures.[38] Distillation, the process during which

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nicotine and aromas are transferred from tobacco to smoke, occurs below 300°C; pyrolysis occurs at about 300°C–700°C, entails the decomposition of biopolymers, proteins, and other organic materials and generates the majority of substances emitted in smoke; and combustion occurs above 750°C and results in the generation of carbon dioxide, CO and water.[38] HeatSticks are heated to a maximum of 350°C,[19] a temperature sufficient to enable pyrolytic decomposition of some organic materials. Formation of toxic volatile organic compounds, including formaldehyde, acetaldehyde and acrolein, via dehydration and oxidation of the humectants, propylene glycol and glycerin, have been reported in e-cigarette aerosols at similar temperatures as IQOS.[39–42] In addition, flavouring chemicals in e-cigarettes undergo thermal degradation and contribute significantly to levels of toxic aldehydes emitted in e-cigarette aerosol.[43] Since the constituents of HeatSticks may be different from that of combustible cigarettes, including flavourants and additives, it is plausible that the IQOS aerosol may contain substances not present in tobacco smoke.

A study by Klupinski and colleagues[44] reported that unique substances, such as ambrox, 3-methylbutanenitrile and 4-methylimidazole, were found in little cigar smoke that were not found in cigarette smoke, indicating that different tobacco products can have different chemical fingerprints and lead to different exposure and toxicological profiles. The study by Klupinski and colleagues describes methodology for 'non-targeted' analysis of tobacco smoke aerosol, and the authors suggest that 'the same approach could also be applied to other samples to characterize constituents associated with tobacco product classes or specific tobacco products of interest'. FDA should recommend that manufacturers of HTPs undertake 'non-targeted' analyses (along with targeted analysis), comparing HTP aerosol with smoke from combustible tobacco products to identify potentially toxic chemicals in HTP emissions that may not be present in tobacco smoke.

Although smoking machine studies are appropriate for examining the relative differences in emissions between products, they do not predict use patterns and systemic exposure to toxicants. PMI reported systemic exposure to 17 HPHCs in its human exposure studies. PMI did not assess systemic exposure to any inorganic compounds, phenols and metals, possibly due to the fact that there are no valid biomarkers for some substances or that the time course of the biomarkers may not be optimal for studies of the duration used by PMI. PMI used 1-hydroxypyrene, a metabolite of pyrene (a PAH) as a biomarker of PAHs. Pyrene is not included as an HPHC on FDA's list. We have previously demonstrated that 1-hydroxypyrene is not a selective measure of tobacco-related PAH exposure and is weakly related to nicotine intake and tobacco-specific nitrosamine exposure.[45] Instead, we found that monohydroxylated metabolites of fluorene (particularly 1-hydroxyfluorene) and 2-naphthol (a naphthalene metabolite) were more selective of tobacco smoke exposure. In characterising PAH exposure from HNB products, manufacturers should include biomarkers with relatively high selectivity for tobacco.

In conclusion, PMI's data show that IQOS emissions have significantly lower levels of several HPHCs compared with combustible cigarettes. Furthermore, PMI's data from human studies show that use of IQOS is associated with significantly lower systemic exposure to some HPHCs compared with smoking combustible cigarettes. These data appear to support PMI's claim that IQOS is a reduced exposure product. However, PMI's data also show significantly higher levels of other substances in IQOS emissions compared with combustible cigarette smoke. The impact of these substances on the overall toxicity or harm of IQOS is not known.

What this paper adds

- Studies conducted by Philip Morris International, Inc. (PMI) show that IQOS emissions contain lower levels of many harmful or potentially harmful constituents (HPHCs) compared with combustible tobacco smoke.
- PMI's studies show that use of IQOS results in significantly lower systemic exposure to several HPHCs compared with combustible cigarette smoking.
- PMI's own data also show that IQOS emissions contain many other substances, some of which are potentially toxic, at higher levels than in combustible cigarette smoke.

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Competing interests NLB has served on smoking cessation advisory boards for Pfizer and has been an occasional consultant to McNeil and Achieve Life Sciences and has served as a paid expert witness in litigation against tobacco companies.

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Light and mild redux: heated tobacco products' reduced exposure claims are likely to be misunderstood as reduced risk claims

Lucy Popova,[1] Lauren Kass Lempert,[2] Stanton A Glantz[2,3]

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[1]School of Public Health, Georgia State University, Atlanta, Georgia, USA
[2]Center for Tobacco Control Research & Education, University of California, San Francisco, California, USA
[3]Department of Medicine, Cardiovascular Research Institute, Philip R. Lee Institute for Health Policy Studies, Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, San Francisco, California, USA

Correspondence to
Dr Lucy Popova, School of Public Health, Georgia State University, Atlanta, GA 30302, USA; lpopova1@gsu.edu

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ABSTRACT

Introduction Heated tobacco products (HTPs) are being marketed in several countries around the world with claims that they are less harmful than combusted cigarettes, based on assertions that they expose users to lower levels of toxicants. In the USA, Philip Morris International (PMI) has submitted an application to the Food and Drug Administration (FDA) in 2016 seeking authorisation to market its HTPs, IQOS, with reduced risk and reduced exposure claims.

Methods We examined the PMI's Perception and Behavior Assessment Studies evaluating perceptions of reduced risk claims that were submitted to the FDA and made publicly available.

Results Qualitative and quantitative studies conducted by PMI demonstrate that adult consumers in the USA perceive reduced exposure claims as reduced risk claims.

Conclusion The data in the PMI modified risk tobacco product IQOS application do not support reduced risk claims and the reduced exposure claims are perceived as reduced risk claims, which is explicitly prohibited by the FDA. Allowing PMI to promote IQOS as reduced exposure would amount to a legally sanctioned repeat of the 'light' and 'mild' fraud which, for conventional cigarettes, is prohibited by the US law and the WHO Framework Convention on Tobacco Control.

INTRODUCTION

Heated tobacco products (HTPs), also called heat-not-burn products, are tobacco products that heat tobacco to temperatures that avoid combustion and produce a nicotine aerosol that is inhaled by smokers and may also generate side-stream emissions.[1] As of February 2018, HTP entrants into the global market included Philip Morris International's (PMI)'s 'IQOS', British American Tobacco's 'Glo', Japan Tobacco's 'Ploom Tech' and RJ Reynolds' revamped 'Eclipse'. Because of the growing evidence of severe negative health effects of smoking and smokers' concerns about their health, tobacco companies have been motivated to create 'safer cigarettes' since the 1960s, and in 1988 they first introduced HTPs, marketing them as less harmful than combusted cigarettes. While HTPs produce different toxic chemicals than combusted cigarettes,[2] the human health effects of HTPs are not completely understood and the evidence that PMI submitted to the US Food and Drug Administration (FDA) revealed that, in terms of the clinical biomarkers of disease[3] or pulmonary and immune toxicity,[4] IQOS was not significantly different from cigarettes.

As of February 2018, the new HTPs, like PMI's IQOS, were being sold in multiple countries around the world in minimalist high-tech looking stores that resemble Apple stores.[5–7] Advertisements and marketing materials for IQOS emphasise both its superiority over combustible cigarettes (in terms of cleanliness and customisability) and similarity to them (in terms of product's taste, size and providing similar behavioural experience).[6] Claims about health benefits or lower risks of IQOS are not emphasised in the marketing materials and some of the materials carry minimal health warnings, such as 'This tobacco product can harm your health and is addictive'[6] or it is 'not risk-free or a safe alternative to cigarettes but it is a much better choice than smoking.'[7] Before IQOS is introduced into the US market, PMI needs the FDA's permission. The 2009 Family Smoking Prevention and Tobacco Control Act[8] (FSPTCA) assigns the FDA authority to regulate the manufacturing, marketing and distribution of tobacco products in the USA. Tobacco manufacturers may seek authorisation from FDA to market products with claims that they reduce risks of tobacco-related diseases compared with other tobacco products currently on the market.

To obtain FDA authorisation to market a product as a 'modified risk tobacco product' (MRTP), a company must submit an MRTP application to FDA. FDA may issue one of two types of orders permitting such marketing: (1) a 'risk modification order' or (2) an 'exposure modification order'.[9 10] For a *risk modification* order, a company must provide scientific evidence that the product 'as actually used by consumers will (1) significantly reduce harm and the risk of tobacco-related disease to individual users and (2) benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products.'[10] When such scientific evidence is not available and cannot be obtained without long-term epidemiological studies, an *exposure modification* order can be issued if the company demonstrates that such an order would be appropriate for promoting public health (once again taking into account both users and non-users) and that lower levels of harmful chemicals in the product will likely result in reduced death and disease among individual tobacco users. Under the exposure modification order, the marketing claim can only state that the product has lower levels of or is free of a certain substance. Furthermore, a company needs to demonstrate that "consumers will not be misled into believing that the product is […] less harmful or presents […] less of a risk of disease than

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one or more other commercially marketed tobacco products."[9] The FSPTCA puts the burden on the MRTP applicant, not the FDA, to demonstrate that the product presents reduced risk or reduced exposure and to demonstrate that consumers do not perceive reduced exposure claims as reduced risk claims.

Long before the MRTP process was enacted in 2009, tobacco companies had been misleading the public with reduced exposure claims since the 1950s, asserting that filtered and low-tar cigarettes[11] gave smokers 'less tar and nicotine',[12] a reduced exposure claim. 'Light' and 'mild' cigarettes have been marketed to smokers concerned about their health and positioned as an alternative to quitting smoking.[13–15] Even though advertisements for light and mild cigarettes almost never explicitly stated that they would reduce risk of tobacco-related disease, people who saw these advertisements with reduced exposure claims perceived these cigarettes to have lower health risks than regular cigarettes.[16 17]

Furthermore, these cigarettes did not result in lower levels of exposure to harmful chemicals for users. Tobacco companies created them with microscopic ventilation holes in the filters to draw in air and reduce machine-measured tar and nicotine, which gave the appearance that these products delivered lower emissions to the user.[18 19] However, the cigarette companies designed these products so that smokers would compensate for dilution of the smoke by blocking ventilation holes with their lips, taking larger puffs or taking more frequent puffs.[20–23]

This inherently deceptive nature of reduced exposure and reduced risk ('light' and 'mild') marketing claims was at the core of the US Department of Justice's Racketeer Influenced and Corrupt Organization (RICO) Act lawsuit against the major cigarette companies for defrauding the public about the dangers of smoking and which essentially became the basis of the FSPTCA's MRTP provisions. In August 2006, Federal Judge Gladys Kessler held[24] that the tobacco companies, including Philip Morris, violated RICO by fraudulently covering up the health risks associated with smoking and for marketing their products to children. Judge Kessler found that the companies "have engaged in and executed – and *continue to engage in and execute* -- a massive 50 year scheme to defraud the public, including consumers of cigarettes, in violation of RICO [emphasis added]." In her 1683-page opinion with extensive Findings of Fact, Judge Kessler found, among other fraudulent acts, that Philip Morris and other tobacco companies deceptively marketed cigarettes characterised as 'light' or 'low tar', while knowing that those cigarettes were at least as hazardous as 'full flavoured' cigarettes; misled smokers, former smokers and non-smokers to believe that these cigarettes were safer and deliberately targeted the youth market (see table 1 for examples of relevant findings). Importantly, the court found that there was a reasonable likelihood that defendants would continue to violate RICO in future.

Following the 2006 RICO decision, in 2009, Congress recognised and described the tobacco companies' use of reduced exposure claims to mislead the public and Judge Kessler's findings in 14 of the 49 Findings for the FSPTCA.[10] Of particular relevance, Congressional Finding 40 states: "The dangers of products sold or distributed as modified risk tobacco products that do not in fact reduce risk are so high that there is a compelling governmental interest in ensuring that statements about modified risk tobacco products are complete, accurate, and relate to the overall disease risk of the product."

Given the long history of the tobacco industry using reduced exposure claims to mislead consumers into believing that the products in question have reduced risk, most notably through the use of 'light' and 'mild' cigarette claims, it is important to evaluate to what extent the modified risk claims for the new HTP products are based on scientific evidence and whether reduced exposure claims are perceived by consumers as reduced risk claims. This paper uses the materials in the PMI MRTP application made public by the FDA to evaluate these claims.

Table 1 Relevant findings from Racketeer Influenced and Corrupt Organization case

"According to [Brand Manager of Marlboro from 1969 to 1972, James] Morgan, Philip Morris made a calculated decision to use the phrase 'lower tar and nicotine' even though its own marketing research indicated that consumers interpreted that phrase as meaning that the cigarettes not only contained comparatively less tar and nicotine, but also that they were a healthier option."	[24] Para 2402, p. 888
"Morgan, who later became CEO of Philip Morris, further explained in 2002 that rather than relying on the tar and nicotine numbers from the FTC Method, 'the major influence in people's perceptions in the tar of a cigarette would have come from the marketing positioning of a brand as opposed to people literally reading the FTC [tar and nicotine figures]."	[24] Para 2403, p. 888
Philip Morris and the other tobacco companies knew that "many smokers who were concerned and anxious about the health risks from smoking would rely on the health claims made for low tar cigarettes as a reason, or excuse, for not quitting smoking"	[24] Para 2627, p. 971

METHODS

We examined the materials in the PMI MRTP applications to FDA[25] for its HTP IQOS system and Heatstick products (PMI also refers to IQOS as Tobacco Heating System (THS) 2.2 in these materials). On 5 December 2016, PMI submitted its MRTP applications asking the FDA to authorise marketing of IQOS with reduced risk and reduced exposure claims. Our analysis is based on the Executive Summary[26] and Module 7: Scientific Studies and Analyses,[27] specifically Section 7.3 Studies in Adult Human Subject (7.3.2 Perception and Behavior Assessment (PBA) Studies), studies THS-PBA-02-US, THS-PBA-03-US, THS-PBA-04-US and THS-PBA-05-REC-US. We report PMI's findings on the consumer perceptions of reduced exposure claims.

RESULTS

To develop and evaluate marketing messages and materials with reduced risks and reduced exposure claims, PMI conducted Consumer PBA Studies (table 2). Participants were recruited by phone from proprietary databases maintained by local research agencies, which include people interested in participating in market research. Participants' smoking status was based on self-report.

Qualitative studies

PMI's qualitative studies (THS-PBA-02-US and THS-PBA-04-US) were conducted by TNS Qualitative. Focus groups and individual interviews were conducted in person, in facilities with one-way mirrors with PMI representatives observing the studies. They followed discussion guides and employed 'visual aids' to position products on relative risk and interest to use scales. Focus groups lasted 2.5 hours, while individual interviews took 1.5 hours. Participants evaluated various messages containing either reduced exposure or reduced risk claims. In THS-PBA-02-US, they evaluated 13 messages in focus groups in Phase 1 (Online Supplementary 1), which were subsequently modified

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Table 2 Philip Morris International's (PMI)'s Consumer Perception and Behavior Assessment (PBA) Studies in the USA

Study name	Methodology	Location	Study year	Participants	Age	Materials
THS-PBA-02-US	Qualitative 20 focus groups (n=113) 37 individual interviews	Boston, MA Chicago, IL Charlotte, NC Phoenix, AZ	Oct–Dec 2013	S-NITQ, S-ITQ, FS, NS*	21+	Nine potential 'plain text'† messages‡
THS-PBA-03-US	Quantitative (n=1713)	Chicago, IL Marlton, NJ Phoenix, AZ Atlanta, GA	Oct–Dec 2014	S-NITQ, S-ITQ, FS, NS	LA+	Three potential 'plain text'† messages selected from THS-PBA-02-US
THS-PBA-04-US	Qualitative 28 individual interviews	Chicago, IL Phoenix, AZ	Dec 2014	AS, FS, NS	18+	Five potential branded§ communication materials with claims selected from THS-PBA-02-US
THS-PBA-05-RRC-US	Quantitative (n=2255)	Paramus, NJ Dallas, TX St Louis, MO Los Angeles, CA	Jul 2015	S-NITQ, S-ITQ, FS, NS	LA+	Three branded§ communication materials with claim #1 'Reduced risks of tobacco-related diseases'
THS-PBA-05-RRC2-US	Quantitative (n=2247)	Marlton, NJ Chicago, IL Tampa, FL Denver, CO	Sep 2015	S-NITQ, S-ITQ, FS, NS	LA+	Three branded§ communication materials with the claim #2—'Reduced risk of harm'
THS-PBA-05-REC-US	Quantitative (n=2272)	Framingham, MA San Diego, CA St Louis, MO Baltimore, MD	Dec 2015	S-NITQ, S-ITQ, FS, NS	LA+	Three branded§ communication materials with the claim #3 'Reduced body's exposure to harmful and potentially harmful chemicals'

*Never smokers participated only in Phase 2 of THS-PBA-02-US.
†'Plain text' message describes the information communicated on the product.
‡The table in the PMI document says nine messages, but the file (Online Supplementary 1) for Phase 1 shows 13 messages because there are two versions of some (A1, A2, B, C1, C2, D and so on). Phase 2 tested seven messages (Online Supplementary 2).
§The branded communication materials were brochure, pack and direct mail piece with iQOS commercial name and the Tobacco Sticks as HeatSticks with the Marlboro Brand.
AS, adult smokers; FS, adult former smokers; LA, legal smoking age; NS, adult never smokers; S-ITQ, adult smokers with the Intention to quit; S-NITQ, adult smokers with no intention to quit.
Source: adapted from table 1 Overview of the Studies from PMI Research and Development[51] (p. 7).

into seven messages for testing with individual interviews in Phase 2 (Online Supplementary 2).

Participants frequently equated reduced exposure claims with reduced risk, conflating the reduction in chemicals with lower chances of developing tobacco-related health issues. For example, female smoker (21–34 years old, Phoenix) stated: "It reduces your body's exposure to the chemicals… that would be my biggest take-away… it suggests that it is better for you than a traditional cigarette." When asked to clarify: (Better—In what way?), she specified: "It's the lesser of two evils; it's a better bad choice… It reduces harmful chemicals which is likely to reduce your chances of getting a tobacco-related disease."

While the PMI's claims that reduced exposure does not mean reduced harm tried to address this issue, some people found this juxtaposition of a claim of reduced exposure and no reduced harm confusing and hard to believe, which reduced credibility of the message source. Female smoker (21–35 years old, Boston) explained: "It says to me that if you smoke this or if you use this thing, you're still at risk of getting all those diseases that they claim it reduces your exposure to… The way it's worded… I'm not buying into it. It's kind of doubletalk… […] It's flip flopping, saying it will reduce but you still might get it, or … It's just weird, it doesn't make me want to use it at all, now that I'm reading this… This makes me less likely to use it, because I'm… almost mad that it tries to claim that it… has benefits, but it really doesn't."

The THS-PBA-02-US Study report concludes that all messages (both reduced risk and reduced exposure claims) were perceived by participants as statements about lower harm. In Phase 2, three out of seven messages were reduced exposure claims. For all three reduced exposure messages, the PMI's report stated that participants perceived IQOS to be a lower risk than conventional cigarettes because the tobacco is heated, not burned, which results in reduced 'exposure to harmful chemicals' (pp. 31, 34) and 'the absence of smoke and second-hand smoke' (p. 37).[28] For the four reduced risk messages, the report similarly concluded that the product was 'perceived to be a lower risk than conventional cigarettes' (pp. 40, 42, 44, 46) by 'reducing the production of harmful chemicals found in cigarette smoke and providing a possible chance of reducing the risk of tobacco-related diseases' (pp. 44, 46).[28]

The fact that PMI's report does not distinguish perception of reduced risk and reduced exposure provides additional evidence that reduced exposure claims are viewed as reduced risk claims.

The findings from the second qualitative study (THS-PBA-04-US) that assessed reduced risk and reduced exposure claims in the context of marketing materials (brochure, pack and direct mail) portray a similar picture. The study report concludes that "There is a clear recognition that this is an innovative product that heats, rather than burns, the tobacco using electronic technology combining the tobacco taste satisfaction of CC's [conventional cigarettes] with hygiene benefits (less odor, no ash, less mess) and the potential to reduce the risk to health compared to smoking conventional cigarettes."[29] Also, "Understanding is generally consistent across all label, labeling and marketing material and subject groups."[29]

In this second qualitative study, reduced exposure claims in combination with the information that IQOS does not reduce risk of tobacco-related disease (presented as 'Important Warning') were also perceived as confusing and contradictory, but still made participants rate the risk as moderate, below the

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risk of conventional cigarettes. Some participants were able to articulate that reduced exposure does not mean reduced risk:

> "It's still as risky as smoking a cigarette. It does not mean a reduction in the risk of developing tobacco related diseases… Tobacco related diseases are what you get from smoking cigarettes. It's telling me that even though it scientifically reduces my body's exposure to these chemicals, I have the exact same risk of developing a tobacco-related disease." (female adult smoker, 26–35 years old, Chicago).

Yet others were still very optimistic about the product that offers reduced risk, particularly appreciating the implications of reduced exposure as the ability to use HTPs in smoke-free places:

> "There's still a risk, so we all know we can't get anywhere besides-you can't get anywhere, you can't even hide from that, so there's going to be risk. But it's just a better way of smoking a cigarette. It gives you a better option. 'Real tobacco, no fire, tobacco heating system', so obviously trying to make it a better way of smoking, make it better for you to smoke at your workplace, school, anywhere. So yeah, that's what I get from it. Well, they give you the less odor, no fire. It even tells you-it gives you a little hint that it will be better for the people that's around you worrying about affecting them, so that's good." (male adult smoker, 18–25 years old, Phoenix).

In summary, PMI's qualitative studies demonstrate that US adults understand reduced exposure claim to mean that the lower levels of harmful chemicals in the product means reduced risk of health harms.

Quantitative studies

PMI reports results of two quantitative studies (THS-PBA-03-US and THS-PBA-05-REC-US, see table 2 for details) that were conducted by Covance Market Access Service. Quantitative studies were five-arm parallel group experiments, where each arm corresponded to the different message condition tested in the study. Studies used computer-assisted self-interviews (with computer-assisted personal interviews for more in-depth questions in THS-PBA-03-US) and lasted 45 min on average. The outcome measures used in these studies are presented in table 3. For the purpose of our study, we focus on the measures PMI used to assess global comprehension and risk perceptions because they indicate to what extent reduced exposure claims are perceived as reduced risk claims.

In THS-PBA-03-US, five different text-based messages were evaluated: four contained reduced exposure claims and one had a reduced risk claim (figure 1). Participants were randomised into five groups, where each group saw one of the messages. For the measure of global comprehension, the proportion selecting the answer 'Reduces the risk of tobacco-related diseases' was 18% for reduced exposure Message 3, 28% (Message 2), 32% (Message 1) and 35% (Message 4). For all perceived risk measures (health risk to self (figure 3), addiction risk and risk to others), participants rated IQOS lower in risk than cigarettes for all messages, whether it was a reduced exposure message or a reduced risk message.

In THS-PBA-05-REC-US, participants evaluated marketing materials with a reduced exposure warning: a brochure, a pack

Table 3 Outcome measures in quantitative studies

Construct	Instrument	Example question
Intent to Use	The Intent to Use Questionnaire ► Intention to Try (ie, to sample at least once; two items) ► Intention to Use (ie, for continued usage; two items) (Answers on 6-point scale from 'Definitely Not' to 'Definitely').	Based on what you know about IQOS, how likely or unlikely are you to try IQOS? If you try IQOS and like it, and taking into consideration the prices that are shown on the material, how likely or unlikely are you to use IQOS regularly?
Change in Intention to Quit Smoking	Yes/No questions based on Prochaska and DiClemente's Stages of Change model (Prochaska and DiClemente 1982) measured before and after exposure to THS 2.2 message to determine change in Intention to Quit Smoking (four items).	Are you seriously considering quitting smoking within the next 6 months?
Comprehension	1. 'Global comprehension': overall comprehension of the THS 2.2 message on exposure to harmful chemicals and risk of tobacco-related diseases of using THS 2.2. 2. 'Specific comprehension': comprehension of three specific parts of the THS 2.2 message: the Intended Users Statement, Evidence Statement and Warning Statement. Both types of comprehension were assessed with multiple choice questions; five response options were presented, with one correct option, three incorrect options and an option for 'don't know'.	1. Thinking about all of the information on the card, would you say that compared with cigarettes, using THS 2.2: a. Has a greater risk of tobacco-related diseases b. Reduces the risk of tobacco-related diseases c. Has not been demonstrated to reduce the risk of tobacco-related diseases (correct) d. Eliminates the risk of tobacco-related diseases e. Don't know 2. What happens to tobacco when IQOS is used? a. It is burned b. It remains at room temperature c. It is cooled d. It is heated but not burned (correct) e. Don't know
Risk Perception	The Perceived Risk Instrument-Personal Risk comprised of two domains, each measured by a unidimensional scale: 1. Perceived Health Risk 18-item scale 2. Perceived Addiction Risk 7-item scale 3. Perceived Harm to Others (two separate questions) Answers were no risk, low risk, moderate risk, high risk, very high risk and don't know and were later converted into a 0–100 scale (0=no risk and 100=very high risk).	1. If you were to start using IQOS, what do you think would be the risk, if any, to you personally of getting the following (sometime during your lifetime) because you use IQOS… losing some sense of taste, having heart disease, an earlier death, having sores of the mouth or throat and so on. 2. If you were to start using IQOS, what do you think would be the risk, if any, to you personally of experiencing the following because you use IQOS… being unable to quit cigarettes, feeling like you have to smoke cigarettes and so on. 3. If you were to start using IQOS, what do you think would be the risk, if any, to others because you use IQOS… harming others through your secondhand smoke, harming unborn baby.

Source: adapted from table 17 in the Executive Summary, p. 121.[26]

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Message 1	Message 2	Message 3	Message 4	Message 5
Evidence Statement 1 (reduced exposure)	Evidence Statement 1 (reduced exposure)	Evidence Statement 2 (reduced exposure)	Evidence Statement 2 (reduced exposure)	Evidence Statement 3 (reduced risk)
• When tobacco is burned, it produces many harmful or potentially harmful chemicals. • THS 2.2 heats tobacco but does not burn it • With the except ion of nicotine, with THS 2.2 there is a significant reduction in the production of harmful or potentially harmful chemicals	• When tobacco is burned, it produces many harmful or potentially harmful chemicals. • THS 2.2 heats tobacco but does not burn it • With the except ion of nicotine, with THS 2.2 there is a significant reduction in the production of harmful or potentially harmful chemicals	• THS 2.2 heats tobacco but does not burn it • This significantly reduces the production of harmful or potentially harmful chemicals • Scientific studies have shown that switching completely from cigarettes to THS 2.2 significantly reduces your body's exposure to harmful or potentially harmful chemicals	• THS 2.2 heats tobacco but does not burn it • This significantly reduces the production of harmful or potentially harmful chemicals • Scientific studies have shown that switching completely from cigarettes to THS 2.2 significantly reduces your body's exposure to harmful or potentially harmful chemicals	• THS 2.2 heats tobacco but does not burn it • This significantly reduces the production of harmful or potentially harmful chemicals • Scientific studies have shown that switching completely from cigarettes to THS 2.2 can reduce the risks of tobacco-related diseases
WARNING A	Warning B1	WARNING A	Warning B2	Warning C
• **It has not been demonstrated** that switching to THS 2.2 reduces the risk of developing tobacco-related diseases compared to smoking cigarettes • THS 2.2 tobacco sticks contain nicotine which is addictive • Using THS 2.2 can harm your health	• A significant reduction in the production of harmful chemicals, compared to cigarettes, **does not mean a reduction in the risk of tobacco-related diseases** • THS 2.2 tobacco sticks contain nicotine which is addictive • Using THS 2.2 can harm your health	• **It has not been demonstrated** that switching to THS 2.2 reduces the risk of • developing tobacco-related diseases compared to smoking cigarettes • THS 2.2 tobacco sticks contain nicotine which is addictive • Using THS 2.2 can harm your health	• A significant reduction in the your body's exposure to harmful chemicals compared to cigarettes, **does not mean a reduction in the risk of tobacco-related diseases** • THS 2.2 tobacco sticks contain nicotine which is addictive • Using THS 2.2 can harm your health	• Reduced risk **does not mean no risk**. The best way to reduce your risk of tobacco-related diseases is to completely quit tobacco use • THS 2.2 tobacco sticks contain nicotine which is addictive • Using THS 2.2 can harm your health

Figure 1 Reduced exposure and reduced risk messages used in study THS-PBA-03-US. Note: same messages are indicated by the same colour. PBA, Perception and Behavior Assessment.

and a direct mail piece (figure 2). In this study, all materials had a reduced exposure claim, but it was paired with either a Surgeon General (SG) warning for cigarettes or a PMI-developed warning for IQOS communicating that reduced exposure does not mean reduced risk, that IQOS contains addictive nicotine and that IQOS can be harmful ('PMI Important Warning' in figure 2). Participants were randomised into five groups: (1) brochure with SG warning, (2) brochure with PMI warning, (3) pack with the SG warning, (4) pack with PMI warning and (5) direct mail piece with PMI warning.

Between 26% of participants (brochure with a PMI warning) and 58% (pack with SG warning) selected an answer that using IQOS reduces the risk of tobacco-related diseases for the global comprehension measure. An additional 0.8–2.6% answered that it 'eliminates the risk of tobacco-related diseases.' The proportion of participants who answered 'don't know' was 3.1–12.3%. In sum, a large proportion of participants who saw the reduced exposure messages selected answers indicating that tobacco-related disease risk is reduced by switching from cigarettes to IQOS.

For the measures of perceived risk to self, IQOS was rated lower than cigarettes. IQOS was rated similar in perceived risks to e-cigarettes for all measures of perceived risk (figure 3).

Participants also consistently rated IQOS as lower in perceived risk of addiction than combusted cigarettes, even though the marketing brochure did not contain any information on how IQOS compared with cigarettes in terms of addiction risk. PMI's report speculated that participants might be inferring lower perceived addiction risk for IQOS based on the information about reduced exposure to harmful chemicals.[30]

PMI's study report[31] concluded, "In general, reduced exposure messages may present a greater challenge than reduced risk messages on comprehension of disease risk" (p. 74). "It appears likely that consumers will typically infer a degree of reduced disease risk, even where such inferences are explicitly contradicted by warning statements" (p. 76).[31] The report suggested that reduced exposure claims for IQOS "may present an apparent contradiction between (1) reductions in HPHCs [harmful or potentially harmful chemicals identified by the FDA in conventional cigarettes] and (2) a lack of reduced risk for disease" where participants have a hard time reconciling these claims. The report referred the FDA MRTP Draft Guidance, which also acknowledged that "there may be challenges to constructing appropriate claim language that conveys the potential benefits of the product to tobacco users and does not convey that the product is less harmful than other tobacco products.[9] In summary, PMI's quantitative studies corroborated the findings from qualitative studies that US adults perceive reduced exposure claims as reduced risk claims.

DISCUSSION

PMI proposed to market IQOS with reduced exposure and reduced risk claims in the USA. PMI's own qualitative and quantitative studies consistently show that reduced exposure claims are likely to be perceived as reduced risk claims and will,

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Reduced Exposure Claim (REC) and associated Warnings (Tested in study THS-PBA-05-REC-US)

AVAILABLE EVIDENCE TO DATE:

- The *iQOS* system heats tobacco but does not burn it.
- This significantly reduces the production of harmful and potentially harmful chemicals.
- Scientific studies have shown that switching completely from cigarettes to the *iQOS* system significantly reduces your body's exposure to harmful or potentially harmful chemicals.

SURGEON GENERAL'S WARNINGS:

- Smoking Causes Lung Cancer, Heart Disease, Emphysema, And May Complicate Pregnancy.
- Quitting Smoking Now Greatly Reduces Serious Risks to Your Health.
- Smoking By Pregnant Women May Result in Fetal Injury, Premature Birth, And Low Birth Weight.
- Cigarette Smoke Contains Carbon Monoxide.

PMI IMPORTANT WARNING:

- It has not been demonstrated that switching to the *iQOS* system reduces the risk of developing tobacco-related diseases compared to smoking cigarettes.
- *HeatSticks* contain nicotine, which is addictive.
- Using the *iQOS* system can harm your health.



Figure 2 Reduced exposure message and an example of marketing materials from study THS-PBA-05-REC-US. In study THS-PBA-05-REC-US, all marketing materials carried a reduced exposure claim. PBA, Perception and Behavior Assessment; PMI, Philip Morris International.

therefore, mislead the public. While few studies outside the tobacco industry evaluated consumer perceptions of reduced risk or reduced exposure claims for non-cigarette tobacco products,[32–34] the results were similar. El-Toukhy *et al*[34] found that modified exposure claims reduced perceived risks of snus and e-cigarette products among adults and adolescents. These results indicate that perceptions of exposure and risk are highly correlated and communication about one— either lower risk or lower exposure—reduces perceptions of both risk and chemical exposure.

The conclusion that consumers interpret reduced exposure information as reduced harm seems to hold across different contexts and tobacco products. The tobacco industry's 'reduced exposure' claims are perceived as indicators of lower harm, as demonstrated by the PMI's studies reviewed here and by research on 'light' and 'mild' descriptors.[16 17] Furthermore, studies on different ways to communicate amounts of harmful chemicals in cigarettes consistently show that consumers misinterpret quantities of harmful chemicals as indicators of health risks.[35 36] This misperception holds regardless of the way the information on reduced exposure is presented: graphically, numbers only, or numbers with additional information, such as common use of these chemicals.[37]

The tobacco industry has a long history of using reduced exposure claims to mislead consumers into believing that the products in question have reduced risk, most notably through the use of 'light' and 'mild' cigarette claims.[24] Therefore, it is particularly important that the FDA and comparable authorities elsewhere in the world take care not to give legal sanction for PMI or other tobacco companies to market their IQOS or other similar products to mislead the public in the same way that it and other tobacco companies have done with earlier products. In particular, IQOS and other HTPs should not be permitted to be marketed with labelling or advertising that claims or implies modified exposure because the PMI's own studies demonstrate that consumers perceive reduced exposure claims as reduced risk claims. Both US law (FSPTCA, 911(g) and 903)[10] and the Framework Convention on Tobacco Control[38] (FCTC) and FCTC's

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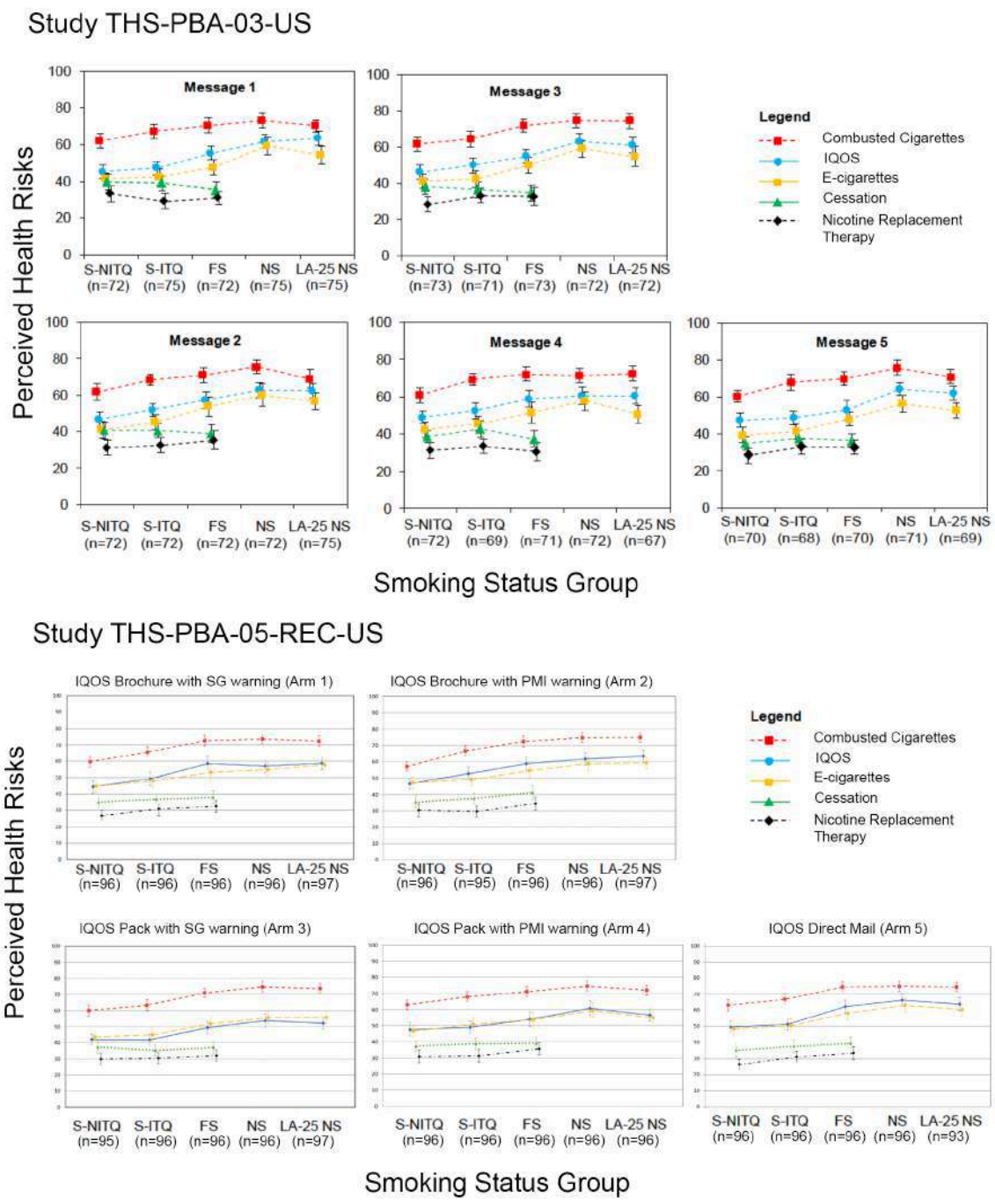


Figure 3 Participants in a quantitative study (THS-PBA-03-US, top panel) perceived health risk of IQOS to be significantly lower than health risks of combusted cigarettes, regardless of whether they saw a reduced exposure claim (Messages 1–4) or a reduced risk claim (Message 5)[31] (p. 68). Similarly, participants in THS-PBA-05-REC-US (bottom panel) rated perceived health risks of IQOS lower than combusted cigarettes for all marketing materials with reduced exposure claim[30] (pp. 56, 72, 86). Note: answers were no risk, low risk, moderate risk, high risk, very high risk and don't know and were later converted into a 0–100 scale (0=no risk and 100=very high risk). Error bars represent 95% CIs from the mean. Connecting lines are only to highlight clustering of outcomes for each comparator along the y-axis across IQOS messages. Abbreviations for Smoking Status Group: FS , adult former smokers; LA-25 NS , adult never smokers aged between their state legal smoking age (18 or 21) to 25 years; NS , adult never smokers; PBA, Perception and Behavior Assessment; PMI, Philip Morris International; SG, Surgeon General; S-ITQ, adult smokers with the intention to quit combusted cigarettes; S-NITQ, adult smokers with no intention to quit combusted cigarettes.

Guidelines for Implementation[39] prohibit tobacco product labelling that is false or misleading, especially labelling that would mislead consumers to believe that the product is less harmful than other products.[40]

Even though tobacco companies almost never marketed light and mild cigarettes with explicit claims of reduced health risks, promotions focused on reduced exposure (lower tar and nicotine) made smokers believe they were reducing their health risks

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by switching to light cigarettes.[13–17] Later, tobacco companies went further to promote light and mild cigarettes with aspirational messages, linking light cigarettes to highly desirable places and situations, such as style, relaxation and sophistication.[41] PMI is using the same playbook in marketing IQOS around the world by promoting IQOS as sophisticated and aspirational,[7]emphasising the themes of cleanliness, customisation and sociability.[6] Based on what we have learnt from marketing of light cigarettes and natural tobacco,[42–44] as well as the results of PMI's own research, it is likely that these claims will also be understood by consumers as reduced risk claims.[34]

Limitations and directions for future research

We report findings from PMI's qualitative and quantitative studies, relying primarily on the summary reports for each study rather than re-analysing the raw data. Our study is limited by the shortcomings of the original studies. For example, it is possible that participants in the qualitative studies perceived reduced exposure claims as reduced risk claims in part because they were exposed to all claims during their focus groups or interviews. These studies focused on more intensive message processing under conditions of participants paying attention to the messages. In the real world, these claims might be processed differently, and the resultant perceptions might be different. Future research should investigate how understanding of reduced exposure and reduced risk claims varies under situations of limited attention and unmotivated processing. Combining reduced risk/exposure claims with warning information that comes from a different source (such as the government) might result in differential processing by various people and more studies need to be done with warnings attributed to various sources to evaluate whether the findings were the artefacts of these specific claims.

Another area worth examining is the role of the source of modified risk information. The PMI's studies do not report on who the consumers attributed the claims to; however, given what we know, understanding whether consumers think this information comes from FDA or from tobacco companies would play an important role. Past research found that consumers (including tobacco users) generally trust FDA and generally distrust tobacco companies.[45] Furthermore, attributing reduced risk claims to FDA might make consumers mistakenly believe that the government endorsed these products and further reduce their risk perceptions, resulting in less informed decision making in the marketplace.[33]

CONCLUSION

PMI's MRTP application for IQOS makes reduced risk claims about IQOS that, like its earlier 'light' and 'mild' claims that were deemed fraudulent in the RICO case, are not substantiated by PMI's own internal research reported in its application.[2–4] Several of the other papers in this supplement indicate that IQOS is not significantly less harmful than combusted cigarettes[2–4 46 47] and that while IQOS had lower levels of pulmonary cytotoxicity[48] and carcinogens[49] than combusted cigarettes, they were higher than those of e-cigarettes. Therefore, the limited evidence on the health risks of HTPs does not support the much lower levels of perceived harm that PMI's consumer studies found. Even the evidence for the reduced exposure claim is questionable because PMI's data show *higher* levels of exposure than conventional cigarettes to some toxins.[2]

In the MRPT application, PMI makes an argument that the 'reduction in exposure to toxicants provides the foundation for the reduced harm rationale for this product as an MRTP', which further indicates that they do not currently have evidence aside from the data on reduced emissions to demonstrate effects on health. However, this is exactly what FDA says is not sufficient to show reduced risk, that is, to demonstrate that IQOS 'significantly reduce[s] harm and the risk of tobacco-related disease to individual users.' On 25 January 2018, the FDA Tobacco Products Scientific Advisory Committee (TPSAC) voted not to accept Philip Morris' claims that IQOS is less harmful than cigarettes (with 8 'No's and 1 'Abstain'). The TPSAC found (on an 8 to 1 vote) that the evidence presented by PMI demonstrated its reduced exposure claim, but unanimously rejected the idea that PMI demonstrated that consumers accurately understand the risks of IQOS. The important point is that the evidence from consumer studies clearly indicates that even a reduced exposure claim does not meet the regulatory criteria because consumers will understand such a claim as a reduced risk claim.

PMI's reduced exposure claims in its labelling and marketing for IQOS and similar claims for HTPs made by other companies are likely to be misunderstood as reduced risk claims. Therefore, FDA and other regulatory agencies in other countries should not permit PMI or any other tobacco company to market IQOS with reduced exposure claims. If PMI and other tobacco companies are allowed to make confusing (if not deliberately deceptive) claims in its labelling and/or advertising, it is likely to result in consumers being misled into believing HTPs are endorsed by regulatory agencies or into misunderstanding HTP's harmfulness.[50] In short, despite PMI's contradictory statements,[26] the actual reports, transcripts and data submitted by PMI to FDA provide substantial evidence that consumers perceive reduced exposure claims as reduced risk claims. Allowing PMI to promote IQOS as reduced exposure would amount to a legally sanctioned repeat of the 'light' and 'mild' fraud which, for conventional cigarettes, is prohibited by the US law and the FCTC.

What this paper adds

- The US Food and Drug Administration can authorise marketing of tobacco products as causing less exposure to harmful chemicals or lowering health risks. The law requires that claims of lower exposure do not mislead the public into believing the product presents reduced risk of health harm.
- The evidence in Philip Morris International's qualitative and quantitative studies submitted as part of its modified risk tobacco product application reveals that adult consumers in the USA perceive reduced exposure claims as reduced risk claims.
- Without evidence of reduced risk, claims of lower exposure are inherently misleading because they will be interpreted as reduced risk claims even if they do not explicitly make reduced risk claims.

Contributors All authors conceptualised the study, contributed to the writing and revision and approved the final version of the manuscript. LP and LKL analysed the data.

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Short Communication Open Access

Heated Tobacco Products Create Side-Stream Emissions: Implications for Regulation

Grant O'Connell[1], Peter Wilkinson[1], Kerstin MM Burseg[2], Stephen J Stotesbury[1], John D Pritchard[1]*

[1]*Imperial Tobacco Ltd, 121 Winterstoke Road, Bristol, BS3 2LL, UK*
[2]*Reemtsma Cigarettenfabriken GmbH - Imperial Tobacco Group, Albert-Einstein-Ring 7, D-22761, Hamburg, Germany*

Abstract

A number of tobacco manufacturers are promoting products where the tobacco is reportedly "heated" rather than burned. It has been claimed that certain heated tobacco products produce only mainstream and no side-stream emissions. In this study we investigated these claims for a commercially available heated tobacco product and, by using a simple experimental design, investigated whether the high temperature heating of the tobacco matrix during product activation and use results in the generation of side-stream emissions. By way of comparison, the Nicorette® inhalator and a leading e-cigarette brand were also investigated. Our findings indicated that a large number of different chemical compounds were released into the airspace around the heated tobacco product when switched on and during consumer use indicating the generation of side-stream emissions. As the public health community has concluded there is no safe level of exposure to tobacco-containing product emissions, this would be of concern and warrants further investigation. Based on our data showing side-stream emissions from the tobacco matrix, the use of heated tobacco products in indoor public places should fall under the same regulations as cigarettes.

Keywords: Heated tobacco; Heat-not-burn; E-cigarette; Nicorette; Side-stream emissions; Second-hand smoke; Nicotine; Tobacco

Introduction

It is well known that when tobacco burns, many thousands of chemicals are released from the tobacco matrix and are inhaled by consumers and bystanders [1,2]. It has been stated that the majority of smoking-related diseases are caused not by nicotine but by the generation of harmful or potentially harmful smoke constituents (HPHCs) from the burning of tobacco [3,4]. In response, a number of tobacco manufacturers are promoting products where the tobacco is reportedly "heated" rather than burned in an attempt to reduce HPHC emissions [5-7]. This is not a new concept, as cigarette-based heated tobacco products were first marketed in the USA in the 1980s and proved to be commercially unsuccessful. Heated tobacco products are now being revived and repositioned as an alternative for smokers who may not wish to replace conventional cigarettes with non-tobacco products such as electronic cigarettes (e-cigarettes). While some manufacturers claim heated tobacco products do not produce side-stream emissions, the major component of 'second-hand smoke', this has yet to be independently verified [8-12]. Since the World Health Organisation has stated "*there is no safe level of exposure to second-hand tobacco smoke*" [13] and the British Medical Association (BMA) has stated that "*almost 85 per cent of second-hand smoke is in the form of invisible, odourless gases*" [14], claims of an absence of side-stream emissions from heated tobacco products warrants investigation. To that end, we sought to investigate whether or not side-stream emissions were generated by a commercially available heated tobacco product. For comparative purposes, we also investigated the Nicorette® inhalator and a leading e-cigarette.

Experimental Section

The analytical technique Proton Transfer Reaction-Mass Spectrometry (PTR-MS) was used to sample and analyze for any side-stream emissions released to the airspace around an iQOS heated tobacco product with regular Marlboro *HeatSticks* (manufacturer, Philip Morris International) when activated by the user (but not puffed) and also during product use. Additionally, sampling was conducted for a Nicorette® inhalator (15 mg nicotine replacement aid; manufacturer, McNeil Consumer Healthcare Ltd) and Blu™ closed system e-cigarette (18 mg nicotine; manufacturer, Fontem Ventures B.V.) All products used in this study were used in accordance with manufacturer's instructions and consumed *ad libitum* i.e., there was no pre-defined consumption requirement. For each of the different products, a number of replicate puffs were made and representative data from a single puff is shown. In short, the PTR-MS instrument ionizes volatile organic compounds (VOCs) in the gas phase through their reaction with H_3O^+ to form protonated VOCs ($VOCH^+$) which can then be detected by a mass spectrometer [15]. This process can be run on air samples with or without dilution as normal air gases (e.g., N_2, O_2, CO_2) have a proton affinity less than water and thus are not ionized. Most VOCs have a proton affinity greater than water and therefore are readily ionized and detected [15]. Analyses with PTR-MS can be conducted in real-time and continuously without the need for sample preparation [15]. Airspace analysis was conducted by connecting the PTR-MS inlet to the test chamber and sampling directly. PTR-MS operating conditions were as follows: drift tube voltage, 500 V; drift tube pressure, 2.3 mbar; drift tube temperature, 120°C; drift tube length, 9.3 cm; *E/N* ratio, 130 Td (Townsends; where *E* is electric field and *N* is the number density of the gas in the drift tube; 1 Td=10^{-17} cm^2 V $molecule^{-1}$); inlet temperature, 120°C. The experimental set-up is outlined in Figure 1.

Results and Discussion

Qualitative characterization of side-stream emissions

Following activation of the iQOS heated tobacco product, as per the manufacturer's instructions, a large number of different VOC species across a range of masses were released into the airspace (Figure 2A). This clearly indicates the generation of side-stream emissions when the device is activated but not puffed by the consumer, which

***Corresponding author:** John D Pritchard, Imperial Tobacco Ltd, 121 Winterstoke Road, Bristol, BS3 2LL, UK, Tel: 440117-933-7556; E-mail: john.pritchard@uk.imptob.com

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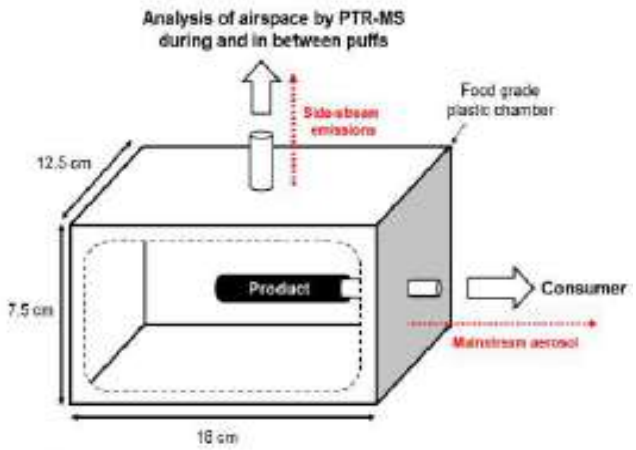


Figure 1: Schematic representation showing experimental set-up and the side-stream emissions capture chamber.

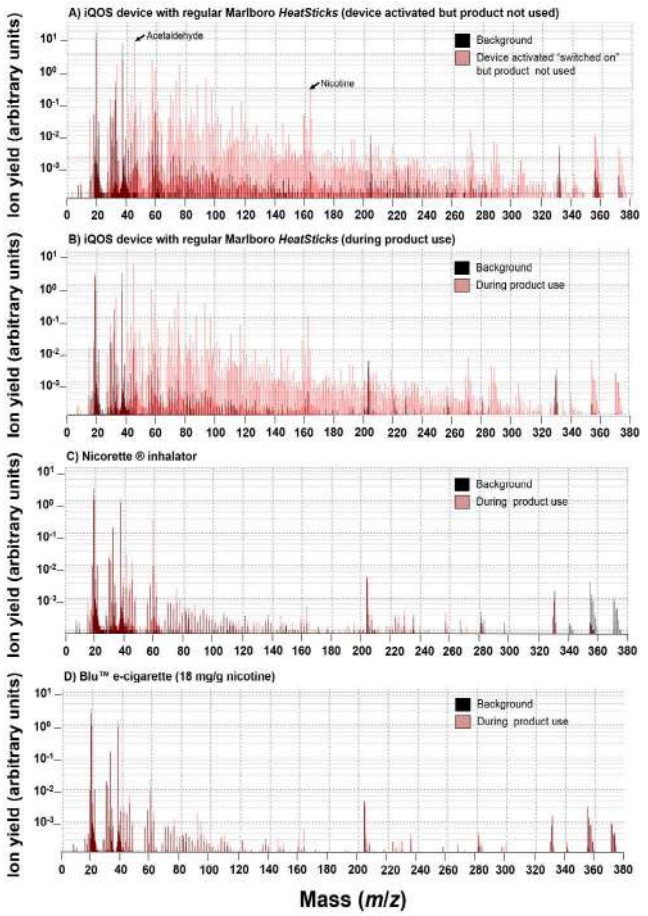


Figure 2: Representative PTR-MS mass spectra of the VOCs released to the airspace for (**A**) iQOS with regular Marlboro *HeatStick* when activated "switched on" but product not actively puffed and (**B**) during consumer use of the iQOS device with regular Marlboro *HeatSticks*; (**C**) during consumer use of the Nicorette® inhalator; and (**D**) during consumer use of the Blu™ e-cigarette. Specific compound (peaks) at *m/z* 45 is protonated acetaldehyde and *m/z* 163 is protonated nicotine and is labelled with arrowheads in (**A**).

would be released into the ambient air, raising potential concerns for bystanders. Furthermore, during active puffing on the heated tobacco product, side-stream emissions are also released (Figure 2B). These chemicals are being released from the high temperature heating of the tobacco matrix in the *HeatSticks*. Given the similarities of the Marlboro branded *HeatStick* used in the iQOS device to a conventional cigarette, the detection of side-stream emissions is perhaps not surprising even though it has been stated that such products produce no side-stream aerosol/smoke [8-12]. Given the findings presented in this pilot study, this requires further investigation.

The PTR-MS mass spectra of the VOCs in the airspace around the Nicorette® inhalator (Figure 2C) and the e-cigarette (Figure 2D) during product use are virtually indistinguishable. Moreover, the Nicorette® inhalator and the e-cigarette profiles are entirely distinct from that of the heated tobacco product, as may be anticipated given these products do not contain tobacco. The Nicorette® inhalator was selected as an appropriate comparator in this study as the UK Medicines and Healthcare products Regulatory Agency (MHRA) has indicated this should be used as a reference product, if manufacturers intend to license e-cigarettes as medicinal products [16].

Future investigations

PTR-MS is a one dimensional technique that characterizes VOCs via their mass; to enable identification of the chemicals in the side-stream emissions from the heated tobacco product it is necessary to further calibrate the machine for identification and quantification of compounds of regulatory interest e.g., HPHCs in tobacco products and tobacco smoke as developed by the US Food and Drug Administration (FDA) [17]. We will therefore determine the identities of the many different VOCs released to the airspace, and by extension to the bystander's breathing space, from the heated tobacco product when activated and used by the consumer. Moreover, it is also conceivable that differences in side-stream emissions may be observed under varying user consumption topographies. Further research in these areas will be informative.

Conclusions

The release of side-stream emissions from heated tobacco products has been observed by PTR-MS using the simple method presented here. These emissions are generated by the high temperature heating of the *HeatSticks* tobacco matrix inserted within the iQOS device.

The public health community has stated that there is no safe level of exposure to tobacco-containing product emissions [13,18], and so the side-stream constituents including nicotine, released during activation and use of the iQOS heated tobacco product can lead to exposure to bystanders; this would be of concern to public health authorities and warrants further investigation.

It is conceivable that based on these findings and the conclusions of public health community regarding tobacco product emissions, the use of heated tobacco products should be included in smoke-free legislation.

Conflicts of Interest

The work in this short communication was supported by Imperial Tobacco Group. Imperial Tobacco Group is the parent company of Fontem Ventures B.V., the manufacturer of the e-cigarette used in this study.

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PMI left a lot of important things out of its toxicology studies of IQOS submitted to the FDA

tobacco.ucsf.edu/pmi-left-lot-important-things-out-its-toxicology-studies-iqos-submitted-fda

My colleagues at the UCSF TCOS just put this public comment in on Phlilip Morris' MRTP application for IQOS. The tracking number is 1k1-902j-m8kv. A PDF of the comment is available here.

Because PMI application did not report the full range of HPHCs in IQOS aerosol, characterize HPHCs in sidestream emissions, include a non-targeted analysis of chemicals in emissions, or conduct clinical studies to describe exposure to toxicants during dual use with other tobacco products, FDA must deny PMI's application

Gideon St.Helen, PhD1,2; Peyton Jacob III, PhD1,2; Natalie Nardone, PhD1,2;
Neal L. Benowitz, MD1,2,3
1Division of Clinical Pharmacology, Department of Medicine, University of California San Francisco; 2UCSF Tobacco Center of Regulatory Science; 3Department of Bioengineering and Therapeutic Sciences, University of California San Francisco
Docket Number: FDA-2017-D-3001
November 29, 2017

Philip Morris Products SA, a subsidiary of Philip Morris International (collectively referred to as PMI hereafter), has recently submitted a "modified risk tobacco product" (MRTP) application to the FDA for review and approval of IQOS. (We refer to the product as IQOS in this comment in place of tobacco heating system, THS 2.2.) According to FDA's draft guidance, an MRTP is "any tobacco product that is sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products."[1] FDA may issue an order allowing a product to be marketed as a modified risk product if it is demonstrated that the product: (1) significantly reduces harm and the risk of tobacco-related disease to individual tobacco users; and, (2) benefits the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products.

We recognize the possible benefit to individuals and public health of marketing tobacco products with substantially reduced risks profiles compared to currently marketed products such as combustible cigarettes, cigars, and some smokeless tobacco products. Given FDA's mission to protect Americans from tobacco-related diseases and death by regulating tobacco, it is critically important that FDA undergo a thorough science-based review of PMI's application to market IQOS as an MRTP. ***The PMI MRTP application lacks important information needed for the FDA to determine that IQOS should be marketed as an MRTP, so should deny the application until PMI presents the information necessary to demonstrate that any product permitted to be marketed as an MRTP actually reduces risk.***

1. **Aerosol Chemistry (Module 6.1.1.):**

1. ***PMI should report emission levels of all 93 HPHCs in IQOS aerosol .*** According to the FDA, harmful and potentially harmful constituents (HPHCs) are "chemicals or chemical compounds in tobacco products or tobacco smoke that cause or could cause harm to smokers or nonsmokers."[2] The FDA has an established list of 93 HPHCs.[3] Quantifying levels of HPHCs in aerosol/smoke of tobacco products that deliver nicotine through the pulmonary route is critical to understanding the potential health risks associated with these products. PMI measured the levels of 58 HPHCs, which they referred to as PMI-58, in mainstream IQOS aerosol. PMI claims that this list contains "chemical constituent representatives of all major toxicologically relevant chemical classes of compounds present in both the particulate-phase and gas/vapor-phase of cigarette smoke," (Module 6.1.1 Aerosol Chemistry p. 6). They also claim that it contains the 18 HPHCs subject to reporting on FDA's abbreviated list. No rationale for leaving out the other 35 HPHCs on the FDA's established list was given. The public (and the FDA) cannot assume that these 35 HPHCs are not important or that they are at much lower levels in IQOS emissions compared to other tobacco products. Since PMI is attempting to market IQOS as a reduced risk product, a more extensive rather than limited analysis of HPHCs is needed.
2. ***PMI should report levels of HPHCs in IQOS sidestream emissions .*** PMI's analysis of the PMI-58 HPHCs was done in mainstream IQOS aerosol. The implicit assumption is that IQOS has no sidestream emissions. However, research on IQOS by Imperial Tobacco Ltd. found "a large number of different VOC [volatile organic compound] species across a range of masses were released into the airspace" when IQOS was activated but not puffed on.[4] In order to protect non-users of tobacco products, FDA must insist that PMI fully characterizes HPHC levels in sidestream emissions from IQOS.
3. ***PMI should report results of non-targeted analyses of constituents in mainstream and sidestream IQOS emissions, in addition to their current targeted analysis.***

The MRTP application reports the results of analyses comparing the emissions of HPHCs from IQOS and a reference cigarette (Module 6.1.1 pp 13-19). The analyses reported by PMI show significant reductions in most of the HPHCs that were measured compared to emissions from a reference 3R4F cigarette.

Significantly, the reported studies fail to address the important question "does the aerosol generation process for IQOS produce substances not found in the smoke of conventional cigarettes, and if so, are any of these substances harmful or potentially harmful?" The main rationale for the development of IQOS and other heat-not-burn products is that combustion, meaning incomplete combustion of many organic materials, including tobacco, produces highly toxic substances such as some on the HPHC lists. The heat-not-burn products generate an inhalable aerosol without combustion, thereby purportedly eliminating or reducing the levels of substances that are generally formed as combustion by-products. ***Nevertheless, the heat required to generate the aerosol in IQOS will likely produce substances not detected in cigarette smoke. Substances in the IQOS (from tobacco or the numerous additives) could undergo heat-induced reactions to form new substances that***

might not survive in the higher temperature and strong oxidizing conditions in a combusted tobacco product.

There are reasons to suspect that the temperatures produced in IQOS are sufficient to cause chemical reactions to occur, as have been demonstrated with e-cigarettes. [5] In other words, substances in the aerosol may not be limited to those present in the tobacco prior to aerosol generation. E-cigarettes use heat to generate an inhalable aerosol without combustion, in a fashion similar to aerosol generation in a heat-not-burn product, and it is well known that numerous chemical reactions occur during the "vaping" process. For example, formation of toxic aldehydes, including formaldehyde, acetaldehyde, and acrolein, via dehydration and oxidation of the vehicles propylene glycol and glycerin is of particular concern.[6],[7] In addition, flavoring chemicals in e-cigarettes undergo thermal degradation and contribute significantly to levels of toxic aldehydes emitted in e-cigarette aerosol.[8]

Similarly, one would expect chemical reactions to occur during aerosol generation in IQOS, and ***there is no reason to expect that all of the substances formed, or that survive during aerosol generation, would be the same as those found in cigarette smoke.*** In fact, even among combusted tobacco products, the composition of the aerosols may differ. A recent study by Klupinski and colleagues reported that unique substances, such as ambrox, 3-methylbutanenitrile, and 4-methylimidazole, were found in little cigar smoke that were not found in cigarette smoke.[9] The study describes methodology for "non-targeted" analysis of tobacco smoke aerosol, and the authors suggest that "the same approach could also be applied to other samples to characterize constituents associated with tobacco product classes or specific tobacco products of interest. Such analyses are critical in identifying tobacco-related exposures that may affect public health." ***PMI should undertake such studies and report the full results.***

In addition to the "targeted" analyses for specific HPHCs that were carried out, PMI should carry out "non-targeted" analyses comparing IQOS aerosol with smoke from combustible tobacco products in an attempt to identify potentially toxic chemicals in IQOS aerosol that may not be present in tobacco smoke. The aforementioned study by Klupinski et al. constitutes "proof of concept" for the feasibility of such chemical analyses.

4. ***PMI should compare aerosol constituents of IQOS to that of other combustible tobacco products and e-cigarettes.*** While PMI's application focuses primarily on comparisons between IQOS emissions and combustible cigarette smoke, it is unlikely that IQOS will only be used by combustible cigarette smokers. Instead, the likely scenario is that at least some users of other combustible and non-combustible tobacco products will switch to IQOS. Unless PMI can guarantee that their product be marketed and sold to current combustible cigarette smokers only, it makes no sense that their comparison is limited to cigarettes. FDA should at least insist that PMI reports comparisons of HPHC emissions between IQOS and all combustible products and electronic nicotine delivery products. This set of data is critical for an accurate assessment of the relative safety/risks of IQOS ***as actually used*** compared to and in conjunction with (i.e., dual use) other tobacco products.
5. ***PMI should characterize free radical emissions in IQOS aerosol.*** Free radicals are

associated with oxidative stress, an underlying mechanism of many disease outcomes, including cardiovascular disease and cancer. Previous research has demonstrated high free radical emissions from e-cigarettes.[10] FDA should insist that PMI compares free radical emissions from IQOS with combustible tobacco products and e-cigarettes.

2. **Justification of selection of biomarkers of exposure (Module 6.1.3.1):**

1. ***PMI should expand the list of HPHCs for which systemic exposure was assessed.***

PMI used 1-hydroxypyrene, a metabolite of pyrene (a polycyclic aromatic hydrocarbon, PAH) as a biomarker of PAHs. We have previously demonstrated that 1-hydroxypyrene is not a selective measure of tobacco-related PAH exposure and is not highly related to nicotine intake and tobacco-specific nitrosamine exposure.[11] Instead, we found that monohydroxylated metabolites of fluorene (particularly 1-hydroxyfluorene) and 2-naphthol (a naphthalene metabolite) were more selective of tobacco smoke exposure. Given the link between PAH exposure and cancer, it is important that PMI reports PAH biomarkers that are more selective of tobacco smoke than 1-hydroxypyrene.

Further, PMI's list of 17 HPHCs, for which systemic exposure were assessed, do not include any inorganic compounds, phenols, and metals. Systemic exposure to these chemicals, especially metals, should be included in PMI's MRTP. One risk assessment model estimated that metals, such as cadmium, chromium (hexavalent), and arsenic, accounted for a significant fraction of the cancer and non-cancer disease risk indices of tobacco smoking.[12] For this reason, FDA should insist that PMI report exposure to metals from IQOS use.

3. **Summary of biomarkers of exposure assessments (Module 6.1.3.2.):**

PMI conducted four clinical studies to "demonstrate that the level of exposure to harmful substances has been statistically significantly reduced," based on FDA MRTP draft guidance. Two of the studies were 5-day studies in confinement, where smokers of combustible tobacco cigarettes were randomly assigned to either switch to IQOS, continue their own brand of cigarettes, or abstain from using tobacco products. The two other studies were 3-month studies consisting of 5 days of confinement followed by up to 3 months in their naturalistic environments (Module 6.1.3.2. p. 9). The first two studies were done in Poland and Japan and the latter two in Japan and the U.S. All studies contained 160 subjects, each. All four studies are of acceptable design, and included biomarker analysis in 24-hour urine (a strength).
However, there are some concerns:

1. ***PMI should present results of statistical tests.*** In figures such as Figure 1, 3, and 5 (Module 6.1.3.2. pp. 15, 20, and 25) comparisons of reduction in biomarkers of exposure to HPHCs are given for smokers who switch to IQOS and those who were in the abstinence arm. Simply stating the percentage reduction in exposure when a smoker moves from cigarettes to IQOS or from cigarettes to abstinence is not

sufficient. Important to our understanding of the relative safety/risks of IQOS is information on the magnitude of the exposure to toxicants when using IQOS compared to during abstinence. FDA should insist that results of statistical tests be presented for comparisons of reductions with IQOS compared to abstinence.

2. ***Clinical studies lacked racial diversity. PMI should investigate the effect of race on use patterns and biomarkers of exposure.*** The studies were conducted with either Japanese or Caucasians. As such, these studies are most likely not representative of the U.S. population, which is diverse racially. Metabolism of and reaction to the absorbed constituents of tobacco products,[13],[14] as well as attitudes, perceptions, preferences, and tobacco use patterns may differ across racial/ethnic groups. For example, we have observed racial differences in the manner in which combustible tobacco cigarettes are smoked and how cigarettes per day related to exposure biomarkers.[15] African Americans tend to smoke each cigarette much more intensely than Caucasian smokers do. African Americans and Native Indians have been shown to be more susceptible to lung cancer than Caucasians.[16] These previous observations underscore the need to include a racially diverse sample in assessing tobacco use patterns and toxicant exposures, and to conduct clinical studies with a sample that is representative of the U.S. population.
3. ***Noncompliance during outpatient (ambulatory) product use reduces the validity of conclusions made regarding reduced toxicant exposure from IQOS.*** The two 3-month studies included 5 days in a controlled setting and 85 or 86 days in their naturalistic environment. They compared the use of IQOS with combustible cigarette smoking and smoking abstinence. PMI implied that both studies showed significant reductions in HPHC biomarkers with use of IQOS, but did not present any associated P values to compare reductions in HPHC biomarkers during IQOS use and smoking abstinence. The results are presented together in Figure 5 (Module 6.1.3.2. p. 25) and Figure 8 (Module 6.1.3.2. p. 32), and are most likely meant to convey the message that IQOS use results in reductions in HPHCs comparable to smoking abstinence. To be a valid comparison, it is important that study participants complied with the assigned product/regime allocation, particularly those of the smoking abstinence arm. If participants in the abstinence arm smoked cigarettes (going against the study regime), percentage reductions in biomarkers of HPHCs would be lower, and most likely be comparable to that of reductions among participants in the IQOS arm, i.e. the study would show comparable reductions in HPHC exposure with IQOS and abstinence. It is not clear from the application how compliance was determined. Compliance was said to be “particularly high” for the first study. This is a relative term and needs to be quantified in the application. For the second study, PMI reports “good” compliance of subjects in the IQOS arm but “poor” compliance in the abstinence arm. With only 7-9 out of 41 subjects from the smoking abstinence arm being included in the “PP set” (it was not clear what PP set meant), comparisons of HPHC exposure reduction between IQOS use and smoking abstinence are not valid. PMI noted that “in light of the limited number of subjects in the [smoking abstinence] arm and the increased variability, the results obtained using the [smoking abstinence] arm should be interpreted with caution.” ***FDA has to ensure that PMI follows its own advice in interpreting the findings with caution. Until it does, FDA cannot rely on the data presented in the application.***

4. ***PMI should describe exposure biomarkers among dual use groups.*** Most e-cigarette users also smoke combustible cigarettes.[17] The most likely scenario if IQOS is allowed into the U.S. market is high prevalence of dual use of IQOS and tobacco cigarettes or other tobacco products. It is unknown if dual use would result in decreased exposure to tobacco smoke toxicants in the context of nicotine titration (harm reduction), or additive exposure to toxicants from cigarettes and IQOS. It is therefore imperative that FDA insist that PMI conducts studies to assess exposure to toxicants during periods of dual IQOS-tobacco cigarette use.

Conclusion

In summary, to ensure that IQOS is truly a modified risk tobacco product with net benefits to individual users and the population as a whole, before acting favorably on an MRTP application for ICOS, FDA should require that: (1) PMI expands the list of reported HPHCs tested in IQOS emissions and those included in biomarker analysis; (2) characterize HPHC emissions in sidestream aerosol from IQOS; (3) conduct non-targeted analysis to identify other potentially toxic constituents of IQOS emissions that may be unique to IQOS (in addition to reported targeted analysis); (4) compare aerosol constituents from IQOS with that of other combustible tobacco products such as cigars in addition to cigarettes; (5) characterize free radical emissions in IQOS aerosol; (6) conduct clinical studies with samples that are representative of the U.S. population (e.g. racial diversity); and, (7) conduct studies to describe exposure biomarkers during periods of dual use. Section 911(g) of the Family Smoking Prevention and Tobacco Control Act is clear and unambiguous: **FDA may issue an MRTP order *only if* PMI has demonstrated that IQOS, *as actually used by consumers*, will "(A) significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and (B) benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products." Since PMI has failed to make this required showing, FDA is not authorized to issue an MRTP order.**

[1] Guidance for Industry. Modified Risk Tobacco Product Applications. Draft Guidance.

[2] https://www.fda.gov/TobaccoProducts/Labeling/ProductsIngredientsComponen...

[3] https://www.fda.gov/TobaccoProducts/Labeling/RulesRegulationsGuidance/uc...

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Comparative assessment of the side-stream aerosols emitted from heat-not-burn tobacco devices, e-cigarettes and traditional cigarettes

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Abstract

Consumption of e-cigarettes has increased significantly in recent years, necessitating further research on the potential health risks/benefits of these devices. Recently, Philip Morris International entered the e-cigarette market with the launch of “iQOS”, a “heat-not-burn” cigarette that has been described as a hybrid between traditional and electronic cigarettes. In a recent study (Saffari et al. 2014, Environ. Sci. Process Impacts, 2259-2267), we presented exposure to particulate metals and organic compounds from e-cigarettes. In this study, we have used a similar approach to further expand our previous analyses by characterizing the iQOS. Black carbon (BC) in addition to particle mass and number concentration were measured using continuous monitors, inside of an office environment during e-cigarette and iQOS consumption sessions. Additionally, particle-bound metals and organic compounds as well as gas-phase aldehydes were quantified using time-integrated chemical analysis methods. Moreover, indoor emission rate of these chemical species were quantified by conducting parallel outdoor measurements followed by development of an indoor mass balance model. Our results indicated a substantial decrease in the emission of metals (with the exception of Ni and Cr), BC and organic compounds in e-cigarettes compared to traditional cigarettes. Analysis of the same species in the iQOS

side-stream smoke, however, indicated that while PAHs were mostly non-detected in the iQOS smoke, certain n-alkanes, organic acids were still emitted in substantial levels from iQOS.

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1. Second-hand e-cigarette smoke compared to regular cigarette smoke
   MedicalXpress
2. 'Increased levels of toxic metals' in e-cigarette secondhand smoke
   Marie Ellis, Medical News Today
3. US panel rejects marketing plan for heated tobacco device
   MedicalXpress
4. Study identifies two additional carcinogens not previously reported in e-cigarette vapor
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iQOS: evidence of pyrolysis and release of a toxicant from plastic

Barbara Davis, Monique Williams, Prue Talbot

Department of Molecular, Cell and Systems Biology, University of California, Riverside, California, USA

Correspondence to
Dr Prue Talbot, Department of Molecular, Cell and Systems Biology, University of California, Riverside, CA 92521, USA; talbot@ucr.edu

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ABSTRACT

Objective To evaluate performance of the I quit original smoking (iQOS) heat-not-burn system as a function of cleaning and puffing topography, investigate the validity of manufacturer's claims that this device does not burn tobacco and determine if the polymer-film filter is potentially harmful.

Methods iQOS performance was evaluated using five running conditions incorporating two different cleaning protocols. Heatsticks were visually and stereomicroscopically inspected preuse and postuse to determine the extent of tobacco plug charring (from pyrolysis) and polymer-film filter melting, and to elucidate the effects of cleaning on charring. Gas chromatography–mass spectrometry headspace analysis was conducted on unused polymer-film filters to determine if potentially toxic chemicals are emitted from the filter during heating.

Results For all testing protocols, pressure drop decreased as puff number increased. Changes in testing protocols did not affect aerosol density. Charring due to pyrolysis (a form of organic matter thermochemical decomposition) was observed in the tobacco plug after use. When the manufacturer's cleaning instructions were followed, both charring of the tobacco plug and melting of the polymer-film filter increased. Headspace analysis of the polymer-film filter revealed the release of formaldehyde cyanohydrin at 90°C, which is well below the maximum temperature reached during normal usage.

Discussion Device usage limitations may contribute to decreases in interpuff intervals, potentially increasing user's intake of nicotine and other harmful chemicals. This study found that the tobacco plug does char and that charring increases when the device is not cleaned between heatsticks. Release of formaldehyde cyanohydrin is a concern as it is highly toxic at very low concentrations.

INTRODUCTION

With the rise of smoking alternatives, the electronic nicotine delivery systems market has boomed, with electronic cigarettes (EC) being among the most popular worldwide.[1 2] However, there are still a number of conventional (combustible) cigarette smokers who would welcome a cigarette-like tobacco-containing/nicotine-containing product that is devoid of or has a significantly reduced toxicity compared with conventional cigarettes.[1] To appeal to this demographic, Philip Morris International (PMI) has released a new product called the iQOS (I quit original smoking), which is a 'heat-not-burn' system,[3] as an alternative to conventional cigarettes and EC. The iQOS system uses a flange, called the 'heater', which is composed of a silver, gold, platinum, ceramic coating,[4] to heat a rolled, cast-leaf sheet of tobacco impregnated with glycerin, thereby creating an aerosol without combustion.[3] This aerosolisation process is proposed to reduce the user's exposure to toxic and carcinogenic chemicals produced by the combustion of tobacco.[5 6] Thus, the consumer gets the 'harm reduction' component of EC along with the mouth/throat feel of a conventional cigarette. The iQOS system has been well received in Japan and Italy. The iQOS is currently sold in 26 markets by PMI with plans to expand to over 30 countries, including the USA.[7]

Although this product has been extensively evaluated by the manufacturer,[3 5 6 8–13] these studies appeared in a journal that may have a deficient review process,[14] emphasising the need for independent evaluation of the iQOS. As our initial study, we have evaluated the performance of the iQOS system under various conditions, tested the effects of cleaning on performance and pyrolysis and determined the composition of and potential health risk from the polymer-film filter.

MATERIALS AND METHODS

iQOS product acquisition and storage

Four iQOS tobacco heating system kits, manufactured by Philip Morris Products S.A. (Switzerland), were purchased online at eBay (https://www.ebay.com/) from sellers with a 98% or higher satisfaction rating. Kits arrived sealed and in excellent condition. Kits were inventoried, and the components of each kit were placed into individual plastic containers and stored in a dry area at 22°C when not in use.

Cartons of Marlboro (blue box) heatsticks, manufactured by Philip Morris Brands Sàrl (Italy), were purchased in Japan and shipped to us via a personal shopper. Each carton was individually sealed and in excellent condition. Heatsticks were stored, unopened, in a dry, dark area at 22°C in their cartons until used. Unused heatsticks from opened packs were stored in an airtight bag in their carton.

Cleaning the iQOS

iQOS holders were tested using two cleaning regimens: (1) the 'per-use' cleaning protocol in which the device was thoroughly cleaned after each heatstick using the cleaning sticks to remove residual fluid and tobacco plug debris from the heater and surrounding base and to clean out the cap and (2) the manufacturer's recommended cleaning instructions in which the cleaning cycle was used after every 20 heatsticks before using the brush cleaners. When heatstick fragments were left behind, the cleaning hook was used to remove these pieces, as

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necessary, and the holder cap was cleaned by a 5 min warm water immersion. The instructions clearly state that the holder itself is not to be wetted.

Performance evaluation

Pressure drop, which measures the draw resistance of the heatstick, aerosol absorbance (density), a measure of particulate matter trapped within the aerosol, and puff number were evaluated for iQOS products using equipment and protocols described previously.[15–17] Pressure drop across heatsticks was evaluated using a Cole-Parmer Masterflex L/S peristaltic pump (Vernon Hills, Illinois, USA) connected to a U-tube water manometer to detect the change in differential pressure for each puff. Airflow rates were precalculated/precalibrated to the appropriate pump speed using a conversion factor provided by the pump head manufacturer, and flow rate was verified using a Brooks Instruments Sho-Rate flow meter (Hatfield, Pennsylvania, USA). Aerosol density was evaluated by capturing aerosols in a tubular cuvette, and absorbance was measured immediately at 420 nm using a Bausch & Lomb spectrophotometer (120 V, 0.9 A, Rochester, New York, USA).

iQOS devices were evaluated with five operating conditions; four (conditions 1–4) used the per-use cleaning protocol and one (condition 5) used the manufacturer's recommended cleaning instructions. The pump head, tubing set-up and running conditions were as follows: (1) low airflow rate 2 s protocol—the peristaltic pump was outfitted with a Cole-Parmer Masterflex Model 7015-21 pump head (standard pump head) using Masterflex Tygon E-LFL (tubing size 15) tubing to generate a flow rate of 7 mL/s with a 2 s puff duration for a total puff volume of 14 mL, 14 puffs were taken at 25 s intervals; (2) low airflow rate 4 s protocol—the same pump set-up and running conditions as for condition 1 with a 4 s puff duration generating a 28 mL puff volume; (3) International Organization for Standardization (ISO)—the pump was outfitted with a Cole-Parmer Masterflex L/S Easy-Load II Model 77200-52 high-performance pump head with Masterflex Tygon E-LFL (tubing size 15) producing a 17.5 mL/s flow rate with a 2 s puff duration, generating a total puff volume of 35 mL, with a total of six puffs taken, one puff every minute; (4) the Health Canada standard (HCI)—a Cole-Parmer Masterflex L/S Easy-Load II Model 77200-52 high-performance pump head was used with Masterflex Tygon E3603 (tubing size 36) tubing for a flow rate of 27.5 mL/s, with a 2 s puff for a total puff volume of 55 mL, 12 puffs were taken at 30 s intervals; (5) manufacturer's recommended cleaning (HCI), the same pump set-up and running conditions as described for condition 4 but in the absence of per-use cleaning; for this protocol the manufacturer's recommended cleaning instructions were followed (table 1). For conditions 1–4, three different iQOS devices were evaluated with each device being tested in triplicate, that is, a new heatstick was used for each experiment; condition 5 employed a single device in which 10 heatsticks were tested without cleaning between each stick.

Effect of use on the tobacco plug and polymer-film filter

The condition of the tobacco plugs was evaluated by visual and microscopic inspection and imaged using a Nikon C-LEDS stereomicroscope equipped with a Nikon Digital Sight DS-Vi1 camera head (Nikon, Minato, Tokyo, Japan) before and after use. Some heatsticks were dissected before and after use to further evaluate residual char (referred to as 'char' only) of the tobacco plugs and the condition of the polymer-film filter.

Gas chromatography–mass spectrometry analysis of iQOS heatstick polymer-film filters

Gas chromatography–mass spectrometry (GC–MS) using a qualitative wide-scope screening method was performed using an Agilent 7890B GC coupled with a 5977A MSD equipped with a

Table 1 Performance of iQOS heat-not-burn holders

Holder	Puff duration	Puff interval	Airflow rate (mL/s)	Puff volume (mL)	Total number of puffs	Average pressure drop (mm H_2O)	Average absorbance
Low airflow rate 2 s protocol*							
A	2	25	7	14	14	13±5	0.42±0.08
B	2	25	7	14	14	13±4	0.45±0.08
C	2	25	7	14	14	18±7	0.46±0.06
Low airflow rate 4 s protocol†							
A	4	25	7	28	14	9±4	0.41±0.05
B	4	25	7	28	14	11±4	0.46±0.09
C	4	25	7	28	14	10±4	0.49±0.04
ISO standard‡							
A	2	60	17.5	35	6	62±5	0.49±0.10
B	2	60	17.5	35	6	65±8	0.54±0.09
C	2	60	17.5	35	6	57±5	0.49±0.04
HCI standard§							
A	2	30	27.5	55	12	103±9	0.26±0.03
B	2	30	27.5	55	12	100±9	0.41±0.05
C	2	30	27.5	55	12	105±13	0.42±0.05
Manufacturer's recommended cleaning (HCI)¶							
E	2	30	27.5	55	12	103±12	0.46±0.06

*Per-use cleaning protocol, standard pump head with Tygon 15 tubing.
†Per-use cleaning protocol, standard pump head with Tygon 15 tubing.
‡Per-use cleaning protocol, high-performance pump head with Tygon 15 tubing.
§Per-use cleaning protocol, high-performance pump head with Tygon 36 tubing.
¶Manufacturer's recommended cleaning, HCI, high-performance pump head with Tygon 36 tubing.
HCI, Health Canada Standard ; ISO, International Organization for Standardization; iQOS, I quit original smoking.

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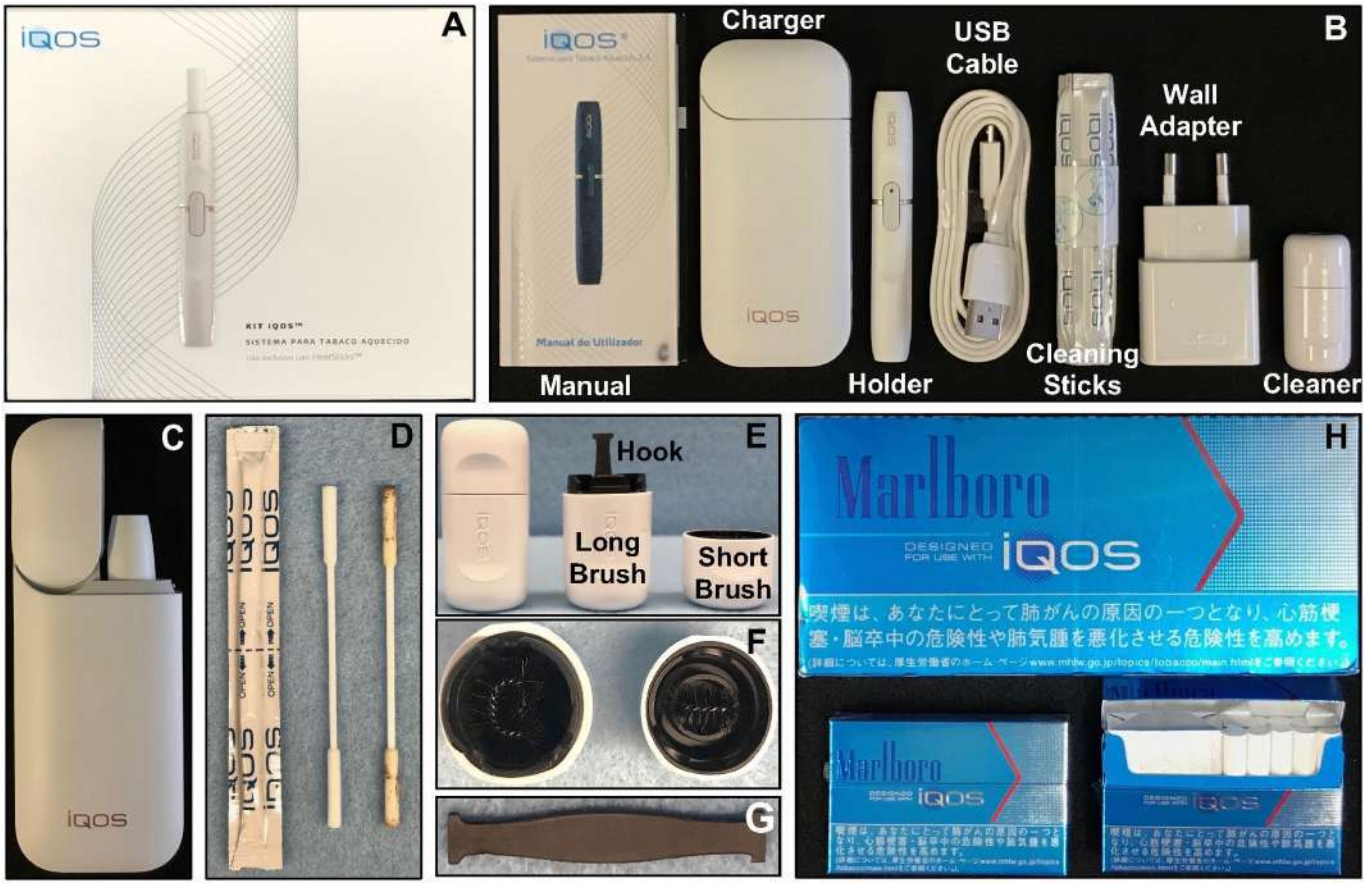


Figure 1 The I quit original smoking (iQOS) heat-not-burn system. (A) An iQOS starter kit. (B) The kit consists of an instruction manual, iQOS pocket charger, iQOS holder, USB cable, iQOS cleaning sticks, wall charging adapter and iQOS cleaner. (C) Profile view of iQOS holder inside a pocket charger. (D) Individual pack of iQOS cleaning sticks with an example of an unused stick and a stick after a single use per end. (E) A closed and opened iQOS cleaner; the larger end contains the long brush and protruding cleaning hook, and the shorter end contains the short brush. (F) Internal view of the iQOS cleaner showing the two brushes (long brush on the left, short brush on the right). (G) The cleaning hook removed from the iQOS cleaner. (H) Marlboro iQOS Heat Stick carton (containing 10 individual packs), sealed individual pack and opened pack exposing heatsticks.

7698A Headspace Sampler (Santa Clara, California, USA). Evaluation of iQOS aerosols was performed using headspace analysis. Chromatographic separation was accomplished using an Agilent J&W HP-5ms Ultra Inert GC Column (30 mx0.25 mmx0.25 µm) and ultra-pure helium (>99.999% purity) as the carrier gas at a flow rate of 1.5 mL/min. For headspace analysis, three unused heatsticks were dissected, polymer-film filters were removed, and a 3 mm portion (16.7%) closest to the tobacco plug were excised and placed into 20 mL headspace vials. All samples were analysed with a split ratio of 50:1, a solvent delay of 2 min, with blank analysis between each sample. GC ramp conditions were as follows: 40°C for 5 min, 45°C for 5 min, 90°C for 5 min, 130°C for 5 min, 135°C for 5 min, 165°C for 5 min, 190°C for 2 min, all temperature ramps were at 10°C/min. Ionisation of compounds was performed using electron impact ionisation at 70 eV in positive mode, the ion source maintained at 250°C and chemicals were identified using the National Institue of Standards and Technology mass spectral library (Gaithersburg, Maryland, USA), only chemicals with an 85% or higher probably match were listed as identifiable.

RESULTS

Components in the iQOS heat-not-burn system

The iQOS kit (figure 1A–G) consists of an instruction manual written in German, English, Portuguese and Italian, a pocket charger, the holder (device), a Universal Serial Bus (USB) cable and a European wall adapter plug for charging, moist cleaning sticks to clean the holder and cap, and the cleaner, which contains a long brush for cleaning the inside of the holder, where the heater is housed, a short brush for cleaning the cap and a hook for removing pieces of tobacco plug left in the holder/cap. A universal power adapter was purchased from Amazon (https://www.amazon.com/) and used to charge the pocket charger unit. Each carton of iQOS heatsticks contained 10 individually wrapped packs, and each pack had 20 heatsticks (figure 1H).

The iQOS kit components had an overall feel of good craftsmanship. The fabrication of the tobacco plug cast-leaf demonstrates a waste not want not strategy in that the plug is fabricated from pulverised tobacco remnants/waste materials, including tobacco stems, torn leaf material and leaf dust.[18] These items are reconstituted with natural adhesives and glycerin (a solvent that is used in EC fluids to produce aerosol) and processed into sheets forming cast-leaf, which is rolled and used as the tobacco plug.[3]

Cleaning of iQOS device

The interior chamber of the holder contained a heating element, referred to in the iQOS instruction manual as the silver, gold, platinum, ceramic-coated heater (figure 2). Unused holders were clean and debris-free with a white base and white heater with a metallic coil in its centre (figure 2A–C). Used holders

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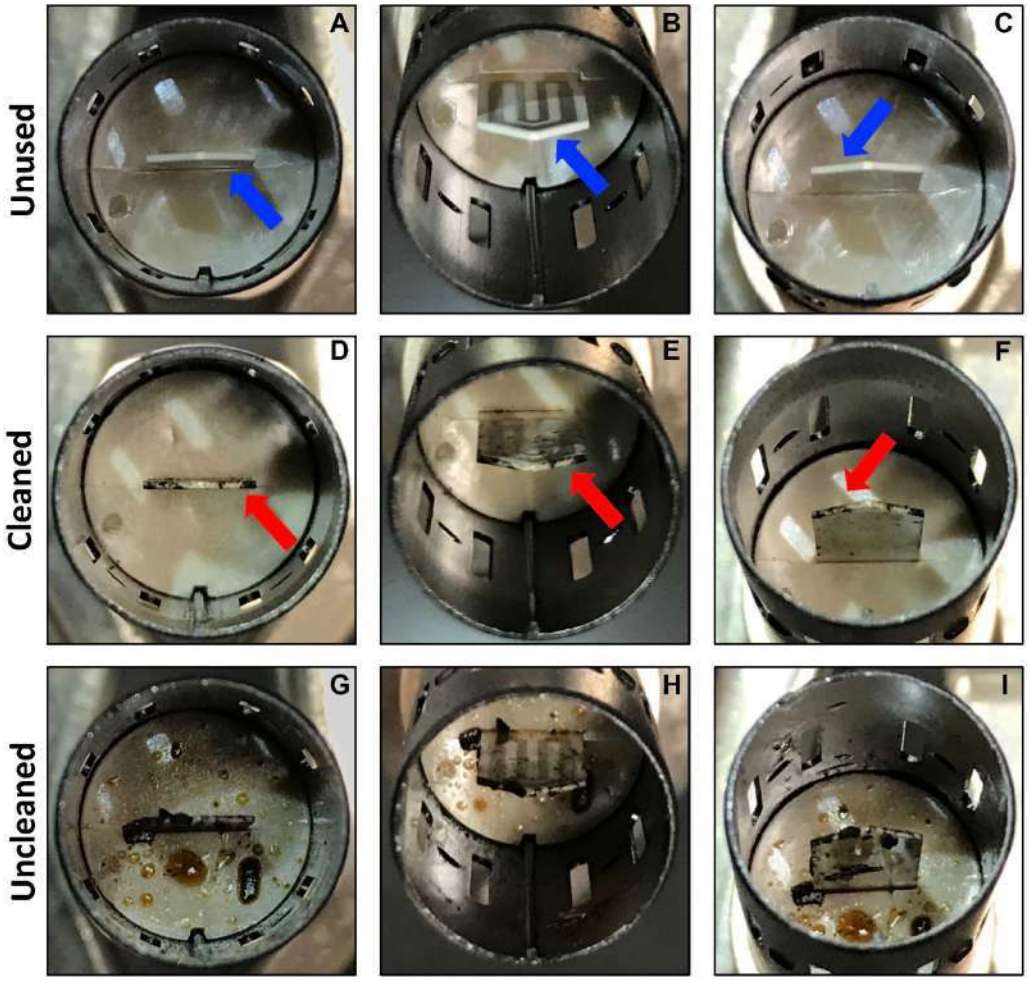


Figure 2 Internal view of the I quit original smoking holder. (A–C) Clean, unused holder showing heater (blue arrows). (D–F) Used holder that was cleaned after every use; black residue remains on heater (red arrows). (G–I) Used holder that was not cleaned between uses (10 uses).

that were thoroughly cleaned with the cleaning sticks between each heatstick were generally similar to the unused holder, except that the heating element had deposits of hardened dark debris that was not removed by the cleaning stick, cleaning cycle of the pocket charger or long brush (figure 2D–F). In the used holder that was not cleaned between heatsticks (manufacturer's recommended cleaning), brown liquid and particulates covered the base, walls and heater (figure 2G–I). With continued use in the absence of cleaning, the volume of liquid and debris increased, and the pieces of debris became darker and appeared more charred (figure 2D–I were taken after the 10th heatstick was used).

iQOS performance

The iQOS gives users a maximum of 14 puffs during a 6 min window per heatstick, after which it must be recharged before it can be used again. Performance of the iQOS was evaluated using five puffing protocols (figure 3, table 1). For protocols 1–4, three different iQOS devices (holders A, B and C) were tested in triplicate, that is, a new heatstick was used for each experiment, and each device underwent an intensive cleaning between each heatstick. For protocol 5, a single device (holder E) was used, and it was not cleaned between 10 heatsticks (average of the first three heatsticks is shown in figure 3I,J). For all testing protocols, pressure drop decreased as puff number increased. Aerosol density readings increased with use, peaking around puffs 7–9 and then begin to decrease. Although pump set-up affected pressure drop, it did not affect aerosol absorbance which remained similar under all running conditions, However, differences in testing conditions may lead to alterations in the chemical constituents present within the aerosol without altering aerosol density. Not cleaning did not affect performance except that pressure drop was more variable during the first four puffs in the uncleaned trials.

Tobacco plug charring

Dissection of unused and used heatsticks showed tobacco plug charring (figure 4A). Stereomicroscopic comparison of unused (figure 4B) and used (figure 4C) tobacco plugs confirmed charring or blackening of the cast-leaf. Visual and stereomicroscopic inspection of used heatsticks show the effects cleaning had on device heat production. Comparison of the first and 10th used heatstick from holder A (per-use cleaning) shows that with regular cleaning the charred area surrounding the heater, referred to as the zone of charring, does not increase with use (figure 4D,E). The effects of cleaning on heating were most evident during the course of the manufacturer's recommended cleaning (HCI) testing. Comparison of these heatsticks to unused and per-use cleaned heatsticks showed that in the absence of regular cleaning, the zone of charring increased as the number of heatsticks tested increased (figure 4H–L).

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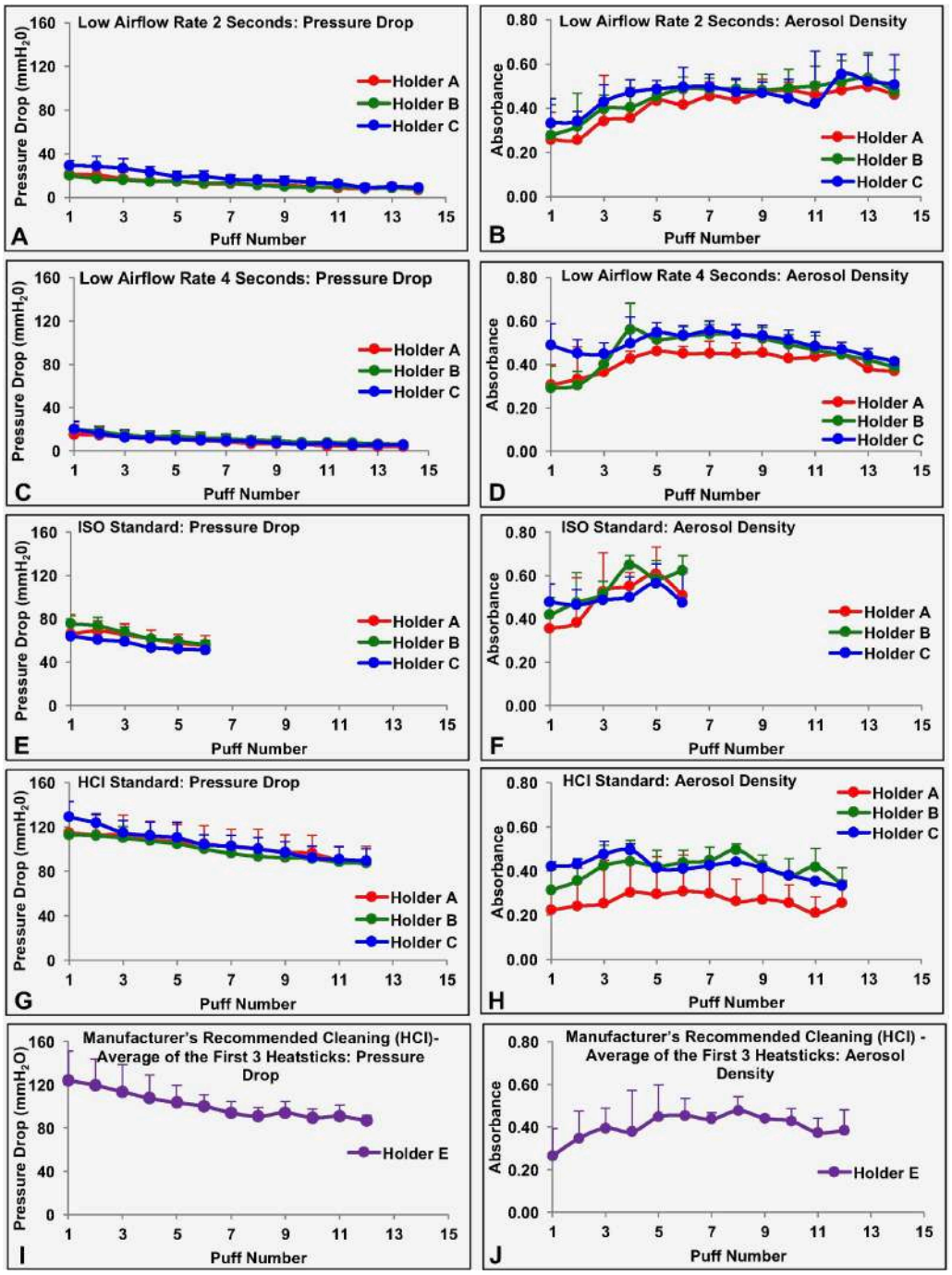


Figure 3 Performance characteristics of the I quit original smoking heat-not-burn system. (A, C, E, G and I) Pressure drop is plotted versus the puff number for five puffing protocols. (B, D, F, H and J) Absorbance is plotted versus puff number for the five puffing protocols. Each line of the graph represents the average of three heatsticks for an individual holder (holder A=red, holder B=green, holder C=blue and holder E=purple). HCI, Health Canada Standard ; ISO, International Organization for Standardization.

Polymer-film melting

Effects of cleaning on heating were not exclusive to the tobacco plug; figure 4A shows that the polymer-film filter (labeled 2), which is separated from the tobacco plug (condition 4) by the hollow acetate filter (condition 3), was adversely effected. The aerosol produced by the iQOS was hot enough to melt the polymer-film filter, which could allow release of potentially hazardous chemicals. Melting of the polymer-film filter was evident by slight yellowing of the filter, as well as by narrowing of the end closest to the tobacco plug (figure 4A indicated by black arrow). This melting and subsequent cooling of the filter caused it to harden, preventing it from being longitudinally dissected. Comparison of unused and used polymer-film filters from both per-use and manufacturer's recommended cleaning experiments showed the relationship between cleaning and increased heat generation. First (figure 4F) and 10th (figure 4G) filters from cleaned devices showed similar discoloration and melting to that of the first filter from the uncleaned device (figure 4N). Comparison of these heatsticks to subsequent manufacturer's recommended cleaning used heatsticks showed discoloration and melting of the polymer-film filter increased with increased use (figure 4M–Q).

Headspace analysis of unused polymer-film filters

GC–MS headspace analysis of unused polymer-film filters showed the presence of ε-caprolactone and lactide, common

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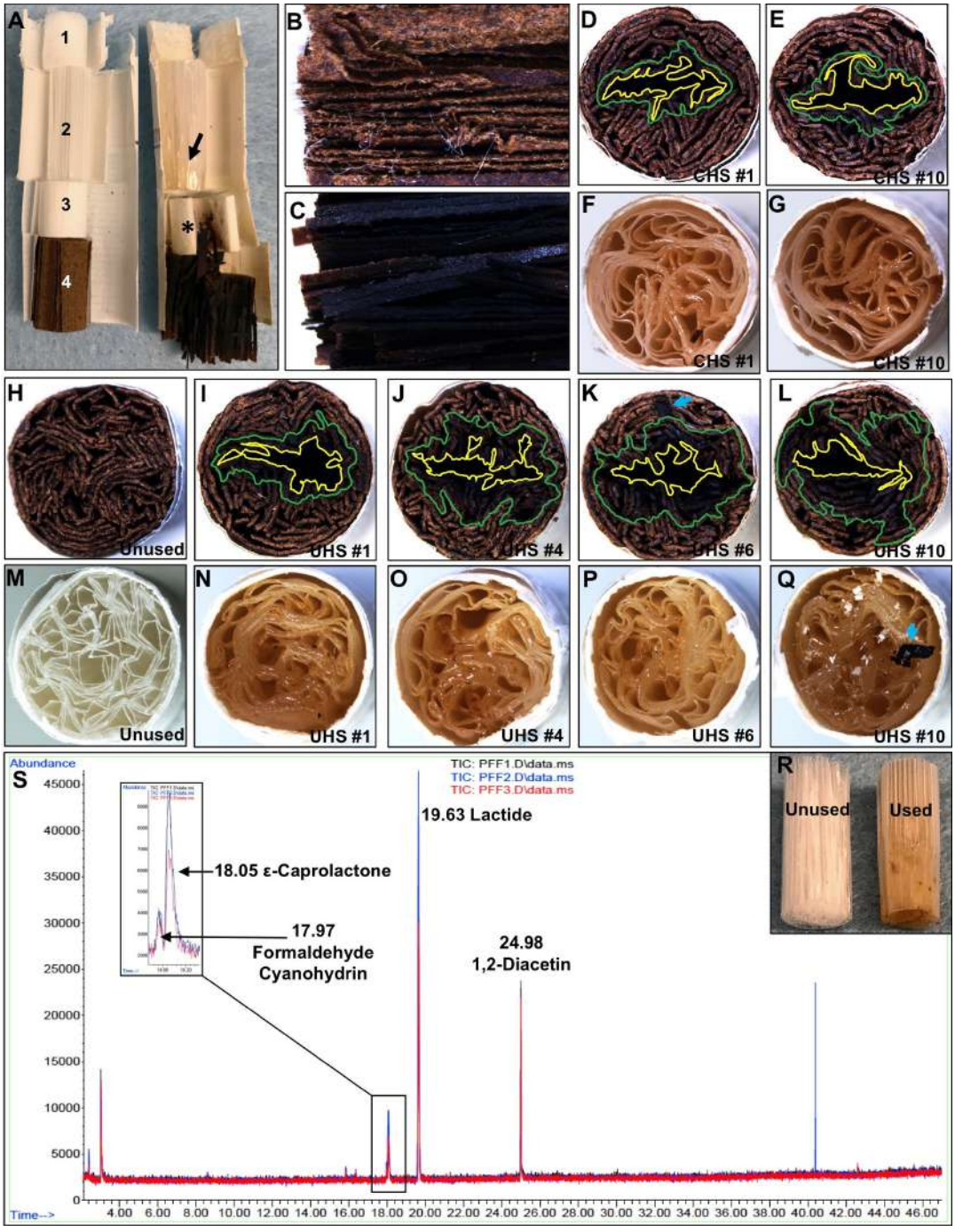


Figure 4 Charring of tobacco plug and melting of polymer-film filter. (A) Dissected heatsticks, each heatstick is composed of: (1) the low-density cellulose mouthpiece filter, (2) polymer-film filter, (3) hollow acetate tube and (4) tobacco plug. Heatsticks from left to right are unused stick with the paper overwrap peeled away, and used stick with the paper overwrap removed with the mouthpiece filter and hollow acetate tube sliced open; black arrow indicates melted region of the polymer-film filter, black asterisk denotes tobacco plug fragments that have been drawn into the hollow acetate tube. (B) An unused tobacco plug. (C) Used tobacco plug showing charring/darkening with use. (D,E) Cross sections of tobacco plugs from the first (D) and 10th (E) heatstick of holder A of the cleaned experiment. Yellow outlined area indicates a void in the cast-leaf left by the heater, the area between the yellow and green outlines are the charred portions of the tobacco plug. (F,G) Cross sections of polymer-film filter from the first (F) and 10th (G) heat stick. Polymer-film filter images shown coincide with tobacco plug images (D) and (E). (For D–G, CHS=cleaned device heatstick.) (H–L) Cross sections of tobacco plugs before use (H) and after use from the first, fourth, sixth and 10th heatstick of the uncleaned experiment (I–L). Yellow outlined area indicates a void in the cast-leaf left by the heater, area between the yellow and green outlines are the charred portions of the tobacco plug. (M–Q) Cross sections of polymer-film filter before (M) and after use (N–Q). Polymer-film filter images shown coincide with tobacco plug images (H–L). Blue arrowheads show charred pieces of cast-leaf that are affixed to the tobacco plug (K) and polymer-film filter (Q). (For (I–L) and (N–Q), UHS=uncleaned device heatstick). (R) Unused and used whole polymer-film filters showing discoloration and film melting, as demonstrated by the narrowing of the used filter. (S) Gas chromatography–mass spectrometry headspace analysis of unused polymer-film filter. Chromatogram shows an overlay of three runs, relative abundance was plotted versus retention time in minutes, unidentifiable peaks were unlabelled. Inset shows a magnified view of peaks with close retention times.

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components in plastics, as well as 1,2-diacetin, a plasticiser (figure 4S). However, of most concern was the presence of formaldehyde cyanohydrin (glycolonitrile), an acute toxicant often used in the production of synthetic resins and used as a solvent.[19] Formaldehyde cyanohydrin was eluted at 17.97 min, when the column reached 90°C.

DISCUSSION

Unlike some EC, which often show significant variation in craftsmanship and performance within and between brands,[15 20] the iQOS appearance, design and performance data are consistent with a product that is well manufactured. However, some design features of the iQOS, such the limited time allowed per heatstick and the need to consume the entire heatstick within this time or alternatively waste part of it, will affect user's topography and may lead to unwanted exposure to potentially toxic chemicals emitted from melting plastic and from pyrolysis of tobacco.

In contrast to tobacco and EC, which usually have no constraints on puffing, the iQOS only operates for 6 min, at which time it automatically shuts off and requires charging before it can be used again. Since a maximum of 14 puffs can be taken from each iQOS heatstick, puffing needs to be done at about 25 s intervals to take full advantage of each heatstick; used heatsticks that have not been fully exhausted cannot be used again as reinsertion would cause the delicate cast-leaf tobacco plug to crumble. This may not appeal to all users, and users who puff less frequently would have a lower number of puffs/heatstick. For users wishing to maximise each heatstick, this limitation will force them to alter their smoking topography by decreasing the interpuff interval and/or accelerating the rate at which they puff, leading to larger volumes of aerosol inhalation.

The manufacturer's cleaning instructions were not fully developed in the instruction manual. The cleaning protocol recommended using the cleaning function of the charger followed by cleaning with the brushes after 20 heatsticks and removing any large fragments of tobacco plug with the hook if necessary. The iQOS kit was equipped with cleaning sticks (figure 1B,D), yet their use was not mentioned in the instruction manual. Our data show that use of one heatstick left a significant amount of debris, fluid and fragments of cast-leaf in the holder (figure 2).

While iQOS heatsticks do not produce a flame, they were always charred after use, which we interpret to be a result of pyrolysis. The zone of charring was greater when cleaning was not performed between heatsticks, suggesting that build-up of fluid and debris in the holder increases pyrolytic temperatures. These data are consistent with the idea that despite similarities in performance characteristics, the cleanliness of the device plays a critical role in thermal regulation. Pyrolysis of tobacco is an endothermic reaction which occurs at temperatures between 200°C and 600°C, during which the majority of volatile and semivolatile components of cigarette smoke are formed.[21 22] Although the Philip Morris study indicated that the aerosol produced by iQOS devices reduce the amount of chemicals found on the Food and Drug Administration's Harmful and Potentially Harmful Constituents list by limiting tobacco pyrolysis,[5] our study, showing charring, in conjunction with a study by Auer *et al*, which confirmed the presence of volatile organic compounds, polycyclic aromatic hydrocarbons, carbon dioxide and nitric oxide,[23] contradict the claim that tobacco pyrolysis is minimised in iQOS. Although iQOS operates at temperatures less than 350°C, this does not negate the formation of volatile and semivolatile harmful constituents of tobacco smoke, which tend to have boiling points that range from 70°C to 300°C.[21 22]

Heatsticks used in this experiment were dissected and the severity of polymer-film filter melting was examined. The function of the polymer-film filter is to cool the aerosol,[3] thus, it would seem that the polymer composing the film should be heat resistant, although, ε-caprolactone, also known as polycaprolactone, tends to have a low-melting point which is thickness dependent.[24] The intensity of the heat produced by the iQOS, under both cleaned and uncleaned conditions, was sufficient to melt the polymer-film filter, even though it was not in direct contact with the heater. The amount of damage to the film (increase in melt and alteration of coloration) increased with each heatstick when cleaning was done per the manufacturer's recommended procedure (after 20 heatsticks). Discoloration may be a product of heating and/or staining from the brown fluid that is expelled from the tobacco plug during use.

Our GC–MS data indicate that components of the polymer-film filter are aerosolised at relatively low temperatures. GC–MS headspace analysis of unused filters suggests the polymer-film filter is a combination of ε-caprolactone, lactide, 1,2-diacetin and other unidentified chemicals. The chemicals released from the film filter during heating may not be suitable for inhalation. Thus, it is unknown if the film filter material is safe for use in products where it would undergo intense cycles of heating and cooling. Of greatest concern was the release from the polymer filter of formaldehyde cyanohydrin, a highly toxic chemical that is metabolised in the liver and broken down into formaldehyde and cyanide.[19] Formaldehyde cyanohydrin can be fatal to humans,[19 25 26] with studies showing mouse inhalation LD_{Lo}, the lowest dose of a toxicant that causes the death of an animal,[27] values as 27 ppm/8 hour.[28 29] iQOS holders operate at temperatures between 330°C and 349°C,[3 23] and as a safety feature, the device shuts off when temperatures reach 350°C. The release of formaldehyde cyanohydrin from unused filters during GC–MS analysis occurred at 90°C, a temperature that all users will exceed.

In conclusion, the iQOS appears to be well manufactured, and performance data were consistent between heatsticks. However, the product has limitations that will affect user topography and the application of standard smoking protocols, such as the ISO 3308, which could not be used for more than six puffs with this product. Users may be forced to smoke at a rapid pace in order to fully maximise heatsticks. Decreasing the interpuff interval could lead to an increase in intake of nicotine[30] and carbonyls.[31] This study also showed that the iQOS is not strictly a

What this paper adds

- Performance characteristics were generally uniform between devices and heatsticks.
- I quit original smoking (iQOS) device usage limitations make modifications to some current smoking standards necessary for proper evaluation of products.
- Device limitations may decrease users' interpuff intervals, increasing possible toxic exposures.
- iQOS holders heat hot enough to cause charring of the tobacco plug via pyrolysis and melting of the polymer-film filter.
- iQOS holder cleanliness affects and contributes to increased charring of the tobacco plug and melting of the polymer-film filter.
- Formaldehyde cyanohydrin, a toxicant, was released from the polymer-film filter at 90°C.

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'heat-not-burn' tobacco product. The iQOS tobacco appeared to char without ignition, and charring increased when cleaning was not done after each use. This study also showed the potential dangers that the polymer-film filter poses. This thin plastic sheet, readily melts during iQOS use and releases formaldehyde cyanohydrin, a dangerous toxicant. This study has shown that the iQOS system may not be as harm-free as claimed and also emphasises the urgent need for further safety testing as the popularity and user base of this product is growing rapidly.

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iQOS: evidence of pyrolysis and release of a toxicant from plastic

Barbara Davis, Monique Williams and Prue Talbot

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Heat-Not-Burn Tobacco Cigarettes: Smoke by Any Other Name

The tobacco industry's most recent response to the documented harms of cigarette smoking was to launch new heat-not-burn (HNB) tobacco cigarettes.[1] Philip Morris International (PMI) created IQOS (I-Quit-Ordinary-Smoking): disposable tobacco sticks soaked in propylene glycol, which are inserted in a holder in the HNB cigarette. The tobacco is heated with an electric blade at 350°C. The cigarettes are marketed by PMI as a "revolutionary technology that heats tobacco without burning it, giving you the true taste of tobacco, with no smoke, no ash and less smell."[2] In many countries, laws that protect people from passive smoke only apply to smoked tobacco products. Philip Morris International claims that IQOS releases no smoke because the tobacco does not combust and the tobacco leaves are only heated not burned. However, there can be smoke without fire. The harmful components of tobacco cigarette smoke are products of incomplete combustion (pyrolysis) and the degradation of tobacco cigarettes through heat (thermogenic degradation). Complete combustion occurs at a high temperature (>1300°C), higher than the heat generated by smoking a tobacco cigarette (<800°C). Typical markers of pyrolysis and thermogenic degradation of tobacco cigarettes are acetaldehyde, an irritant carcinogenic volatile organic compound, benzo[a]pyrene, a carcinogenic polycyclic aromatic hydrocarbon, and carbon monoxide.

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Pilot programs for IQOS began in 2014 in Japan and in 2015 in Switzerland and Italy. An internet survey in Japan published in 2015 suggested that younger individuals (15 to 39 years of age) were more likely to use IQOS, as were former smokers and current smokers.[3] Since 2016, a total of 19 countries have allowed the sale of IQOS cigarettes. In June 2016, data from PMI revealed that IQOS had captured 2.2% of the cigarette market in Japan. IQOS is not yet sold in the United States, but in December 2016, PMI submitted a modified risk tobacco product application to the US Food and Drug Administration. If successful, PMI will be less restricted in its marketing for the IQOS than for conventional tobacco cigarettes. Smokers and nonsmokers need accurate information about toxic compounds released in IQOS smoke. This information should come from sources independent of the tobacco industry, but the only analyses we found were from PMI and PMI competitors.[1]

Methods | We compared the contents of IQOS (IQOS Holder, IQOS Pocket Charger, Marlboro HeatSticks [regular], and Heets, Philipp Morris SA) smoke with the contents of conventional cigarettes (Lucky Strike Blue Lights). We used a smoking device designed and tested in our facility to capture the mainstream aerosol and developed to meet standards for common cigarettes and e-cigarettes.[4] We followed the International Organization for Standardization standards for puff volume (35 mL) at 2 puffs per minute, based on observation of IQOS smokers, who took a mean of 14 puffs during 5 to 6 minutes. We analyzed volatile organic compounds and nicotine by gas chromatography coupled to a flame ionization detector and polycyclic aromatic hydrocarbons using high-performance liquid chromatography coupled to a fluorescence detector, as previously described.[4] We trapped polycyclic aromatic hydrocarbons from IQOS cigarette smoke in a glass filter (Whatman 37 mm Ø GF/B) mounted in line with an XAD2 cartridge. For each sampling, 10 IQOS cigarettes were smoked. Each sampling support was desorbed in 10 mL of acetonitrile and sonicated for 1 hour. The eluate was evaporated in a vacuum concentrator (Speed Vac SC-200, ThermoFisher Scientific) set with 30 millibars and 27*g* until the residue was almost dry to prevent evaporation of the most volatile polycyclic aromatic hydrocarbons. The residue was filtered with polytetrafluoroethylene membrane (Acrodisc CR 13 mm, 0.45 µm, Pall Life Sciences) before it was analyzed with a high-performance liquid chromatography device (Ultimate 3000, ThermoFisher Scientific) equipped with a fluorescence detector (FLD-3000RS), UV detector (VWD-3000), and a separation column Nucleodur EC 150 × 3 mm C18 3 µm (Macherey-Nagel) under isocratic conditions (1.2 mL · min^{-1}). We injected 2 µL into the high-performance liquid chromatography chain; methanol/water (70/30) with acetonitrile was the eluent solvent at an initial ratio of 100% to 0% (4 minutes) and a linear gradient up to 100% acetonitrile (12 minutes). We did not analyze polycyclic aromatic hydrocarbons generated by conventional cigarettes and present the mean values in the 35 best-selling cigarettes brands in the United States, as reported by Vu et al.[5] We monitored the temperature near the heater blade inside the IQOS holder and the core of the conventional cigarette at a sampling rate of 3 Hz with a type k thermocouple.

Results | Volatile organic compounds, polycyclic aromatic hydrocarbons, and carbon monoxide were present in IQOS smoke (**Table**). The temperature of the IQOS was lower (330°C) than the conventional cigarette (684°C).[5] The IQOS smoke had 84% of the nicotine found in conventional cigarette smoke.

Discussion | The smoke released by IQOS contains elements from pyrolysis and thermogenic degradation that are the same harmful constituents of conventional tobacco cigarette smoke. International experts were invited by PMI to describe the IQOS aerosol; one expert claims that "less than 2% by weight of the aerosol components may derive from the pyrolysis of the tobacco substrate which would not be sufficient to characterize the aerosol as 'smoke.'"[6(p 2)] In contrast, our analyses reveal that advertising slogans such as "heat-not-burn" are

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Table. Concentrations of 8 Volatile Organic Compounds, 16 Polycyclic Aromatic Hydrocarbons, 3 Inorganic Compounds, and Nicotine in Mainstream Aerosol and Temperature of the HNB IQOS Cigarette and Conventional Cigarettes

Analyzed Compound	HNB Cigarette		Conventional Cigarette		Proportion of the Chemical in HNB and Conventional Cigarettes, %
	Amount, Mean (SD)	No. of Replications for Each Assay	Amount, Mean (SD)	No. of Replications for Each Assay	
Volatile organic compounds, µg per cigarette[a]					
Acetaldehyde	133 (35)	5	610[b]	1	22
Acetone	12.0 (12.9)	5	95.5 (13.5)	2	13
Acroleine	0.9 (0.6)	2	1.1	1	82
Benzaldehyde	1.2 (1.4)	5	2.4 (2.6)	2	50
Crotonaldehyde	0.7 (0.9)	5	17.4	1	4
Formaldehyde	3.2 (2.7)	5	4.3 (0.4)	2	74
Isovaleraldehyde	3.5 (3.1)	5	8.5 (10.8)	2	41
Propionaldehyde	7.8 (4.3)	5	29.6 (36.6)	2	26
Polycyclic aromatic hydrocarbons, ng per cigarette[c]					
Naphthalene	1.6 (0.5)	4	1105 (269)	7	0.1
Acenaphthylene	1.9 (0.6)	4	235 (39)	7	0.8
Acenaphthene	145 (54)	4	49 (9)	7	295
Fluorene	1.5 (0.6)	4	371 (56)	7	0.4
Anthracene	0.3 (0.1)	4	130 (18)	7	0.2
Phenanthrene	2.0 (0.2)	4	292 (44)	7	0.7
Fluoranthene	7.3 (1.1)	4	123 (18)	7	6
Pyrene	6.4 (1.1)	4	89 (15)	7	7
Benz[a]anthracene	1.8 (0.4)	4	33 (4.2)	7	6
Chrysene	1.5 (0.3)	4	48 (6.2)	7	3
Benzo[b]fluoranthene	0.5 (0.2)	4	24 (2.9)	7	2
Benzo[k]fluoranthene	0.4 (0.2)	4	4.3 (2.8)	7	9
Benzo[a]pyrene	0.8 (0.1)	4	20 (2.9)	7	4
Indeno[1,2,3-cd]pyrene	ND	4	NA	NA	NA
Benzo[ghi]perylene	ND	4	NA	NA	NA
Dibenzo[a,h]anthracene	ND	4	NA	NA	NA
Inorganics, ppm in the mainstream smoke[d]					
Carbon dioxide	3057 (532)	5	>9000	3	NA
Carbon monoxide	328 (76)	5	>2000	3	NA
Nitric oxide	5.5 (1.5)	5	89.4 (71.6)	3	6
Other measures					
Nicotine, µg per cigarette[a]	301 (213)	4	361	1	84
Temperature, °C	330 (10)	2	684 (197)	1	NA
Puff total count	12.6 (2.4)	32	13.3 (3.1)	6	NA

Abbreviations: HNB, heat-not-burn; NA, not analyzed; ND, not detected.

[a] We applied the methods described previously in Varlet et al[4] to analyze volatile organic compounds and nicotine.

[b] Because there was only 1 replication, no SD can be computed.

[c] We present values reported from Vu et al[5] for the ISO smoking regimen and for a mean of the 35 top-selling US cigarette brands.

[d] Carbon dioxide was measured with a Testo 535 (Testo), and carbon monoxide and nitric oxide were measured with a Pac 7000 that detected carbon monoxide (Draeger). The apparatus measured the smoke when it was released from the syringe pump.

no substitute for science. Dancing around the definition of smoke to avoid indoor-smoking bans is unethical. Principle 1 for implementing article 8 of the World Health Organization convention on tobacco control highlights that we should reject ideas that there is a threshold value for toxic effects from second-hand smoke. Independent studies should further evaluate the health effects of the IQOS. In the meantime, heated tobacco products such as IQOS should fall under the same indoor-smoking bans as for conventional tobacco cigarettes.

Reto Auer, MD, MAS
Nicolas Concha-Lozano, PhD
Isabelle Jacot-Sadowski, MD
Jacques Cornuz, MD, MPH
Aurélie Berthet, PhD

Author Affiliations: Institute of Primary Health Care (BIHAM), University of Bern, Bern, Switzerland (Auer); Department of Ambulatory Care and Community Medicine, University of Lausanne, Lausanne, Switzerland (Auer, Jacot-Sadowski, Cornuz); Institute for Work and Health, University of Lausanne and Geneva, Lausanne, Switzerland (Concha-Lozano, Berthet).

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Corresponding Author: Reto Auer, MD, MAS, Institute of Primary Health Care (BIHAM), University of Bern, Gesellschaftsstrasse 49, 3012 Bern, Switzerland (reto.auer@biham.unibe.ch).

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Study concept and design: Auer, Concha-Lozano, Jacot-Sadowski, Berthet.
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Drafting of the manuscript: Auer, Concha-Lozano, Berthet.
Critical revision of the manuscript for important intellectual content: Concha-Lozano, Jacot-Sadowski, Cornuz.
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Editor's Note

No Smoke—Just Cancer-Causing Chemicals

Heat-not-burn tobacco products are for sale around the world. Although they are not yet on the market in the United States, Phillip Morris International has applied to the US Food and Drug Administration (FDA) to sell these products. These products threaten the progress that has been made on decreasing the harms of second-hand smoke because existing bans may not apply to these heat-not-burn products. However, as convincingly reported by Auer and colleagues,[1] although these products may or may not produce smoke, they release cancer-causing chemicals. As shown in their table, heat-not-burn cigarettes release similar levels of many volatile organic compounds and nicotine as conventional cigarettes and higher levels of the polycyclic aromatic hydrocarbon acenaphthene than conventional cigarettes. They are bad for health because they release cancer-causing chemicals, and I hope the FDA will not approve them for that important reason. If the FDA does approve the sale of these products, existing smoking bans should be amended to include these products.

Mitchell H. Katz, MD

Author Affiliations: Los Angeles County Department of Health Services, Los Angeles, California; Deputy Editor, *JAMA Internal Medicine*.

Corresponding Author: Mitchell H. Katz, MD, Los Angeles County Department of Health Services, 313 N Figueroa St, Rm 912, Los Angeles, CA 90012 (mkatz@dhs.lacounty.gov).

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COMMENT & RESPONSE

Neuroleptics for Delirium: More Research Is Needed

To the Editor We read with interest the Original Investigation in a recent issue of *JAMA Internal Medicine* by Agar et al[1] on the management of delirium in the palliative care setting. Delirium is one of the most common and disturbing syndromes at the end of life,[2] and there are few well-designed studies to inform practice.[3] Because data from geriatrics and other populations cannot be extrapolated to the palliative care setting, this important study[1] provides unique insights into the role of haloperidol and risperidone compared with placebo; however, several issues regarding the study design complicate its interpretation.

We wonder if the composite subscore of the Nursing Delirium Screening Scale (NuDesc) is an appropriate primary outcome. Although NuDesc has been validated, this subscore has not been studied before, and the minimal clinical important difference has not been defined. While haloperidol and risperidone arms were associated with statistically significant worse NuDesc subscores, the magnitude of change may not be clinically meaningful based on the investigator-defined cutoff (<1 point).

If haloperidol and risperidone were indeed ineffective, could the low medication doses explain it? In our acute palliative care unit, daily haloperidol doses of more than 8 mg were often needed for patients who were agitated.[4,5] We are also curious that despite the low dose and short duration of neuroleptic use, Agar et al[1] reported shortened survival with risperidone. Given the large number of secondary outcomes, these findings should be considered as hypothesis-generating, and further studies are needed.

These are confusing times. Clinicians caring for patients with agitated delirium have to grapple with the dilemma of uncertain benefits and potential risks with neuroleptics for a distressing condition for which few other proven interventions are available. While identification of reversible causes and nonpharmacological measures seem intuitive, these interventions need to be standardized and tested formally in the palliative care setting in which delirium is often severe, progressive, and irreversible. For the large portion of patients who do not respond to these measures, neuroleptics may still have a role for refractory agitation. This study also reopens the debate on whether benzodiazepines alone should be considered for delirium. Given this is a single study enrolling predominantly patients with mild delirium (median Memorial Delirium Assessment Scale score, 13-15), it is premature to close the chapter on neuroleptics in palliative care as suggested by the authors and the accompanying editorial.[1] Instead, this study highlights the tremendous opportunities

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iQOS: evidence of pyrolysis and release of a toxicant from plastic

Barbara Davis, Monique Williams, Prue Talbot

Department of Molecular, Cell and Systems Biology, University of California, Riverside, California, USA

Correspondence to
Dr Prue Talbot, Department of Molecular, Cell and Systems Biology, University of California, Riverside, CA 92521, USA; talbot@ucr.edu

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ABSTRACT

Objective To evaluate performance of the I quit original smoking (iQOS) heat-not-burn system as a function of cleaning and puffing topography, investigate the validity of manufacturer's claims that this device does not burn tobacco and determine if the polymer-film filter is potentially harmful.

Methods iQOS performance was evaluated using five running conditions incorporating two different cleaning protocols. Heatsticks were visually and stereomicroscopically inspected preuse and postuse to determine the extent of tobacco plug charring (from pyrolysis) and polymer-film filter melting, and to elucidate the effects of cleaning on charring. Gas chromatography–mass spectrometry headspace analysis was conducted on unused polymer-film filters to determine if potentially toxic chemicals are emitted from the filter during heating.

Results For all testing protocols, pressure drop decreased as puff number increased. Changes in testing protocols did not affect aerosol density. Charring due to pyrolysis (a form of organic matter thermochemical decomposition) was observed in the tobacco plug after use. When the manufacturer's cleaning instructions were followed, both charring of the tobacco plug and melting of the polymer-film filter increased. Headspace analysis of the polymer-film filter revealed the release of formaldehyde cyanohydrin at 90°C, which is well below the maximum temperature reached during normal usage.

Discussion Device usage limitations may contribute to decreases in interpuff intervals, potentially increasing user's intake of nicotine and other harmful chemicals. This study found that the tobacco plug does char and that charring increases when the device is not cleaned between heatsticks. Release of formaldehyde cyanohydrin is a concern as it is highly toxic at very low concentrations.

INTRODUCTION

With the rise of smoking alternatives, the electronic nicotine delivery systems market has boomed, with electronic cigarettes (EC) being among the most popular worldwide.[1 2] However, there are still a number of conventional (combustible) cigarette smokers who would welcome a cigarette-like tobacco-containing/nicotine-containing product that is devoid of or has a significantly reduced toxicity compared with conventional cigarettes.[1] To appeal to this demographic, Philip Morris International (PMI) has released a new product called the iQOS (I quit original smoking), which is a 'heat-not-burn' system,[3] as an alternative to conventional cigarettes and EC. The iQOS system uses a flange, called the 'heater', which is composed of a silver, gold, platinum, ceramic coating,[4] to heat a rolled, cast-leaf sheet of tobacco impregnated with glycerin, thereby creating an aerosol without combustion.[3] This aerosolisation process is proposed to reduce the user's exposure to toxic and carcinogenic chemicals produced by the combustion of tobacco.[5 6] Thus, the consumer gets the 'harm reduction' component of EC along with the mouth/throat feel of a conventional cigarette. The iQOS system has been well received in Japan and Italy. The iQOS is currently sold in 26 markets by PMI with plans to expand to over 30 countries, including the USA.[7]

Although this product has been extensively evaluated by the manufacturer,[3 5 6 8–13] these studies appeared in a journal that may have a deficient review process,[14] emphasising the need for independent evaluation of the iQOS. As our initial study, we have evaluated the performance of the iQOS system under various conditions, tested the effects of cleaning on performance and pyrolysis and determined the composition of and potential health risk from the polymer-film filter.

MATERIALS AND METHODS

iQOS product acquisition and storage

Four iQOS tobacco heating system kits, manufactured by Philip Morris Products S.A. (Switzerland), were purchased online at eBay (https://www.ebay.com/) from sellers with a 98% or higher satisfaction rating. Kits arrived sealed and in excellent condition. Kits were inventoried, and the components of each kit were placed into individual plastic containers and stored in a dry area at 22°C when not in use.

Cartons of Marlboro (blue box) heatsticks, manufactured by Philip Morris Brands Sàrl (Italy), were purchased in Japan and shipped to us via a personal shopper. Each carton was individually sealed and in excellent condition. Heatsticks were stored, unopened, in a dry, dark area at 22°C in their cartons until used. Unused heatsticks from opened packs were stored in an airtight bag in their carton.

Cleaning the iQOS

iQOS holders were tested using two cleaning regimens: (1) the 'per-use' cleaning protocol in which the device was thoroughly cleaned after each heatstick using the cleaning sticks to remove residual fluid and tobacco plug debris from the heater and surrounding base and to clean out the cap and (2) the manufacturer's recommended cleaning instructions in which the cleaning cycle was used after every 20 heatsticks before using the brush cleaners. When heatstick fragments were left behind, the cleaning hook was used to remove these pieces, as

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necessary, and the holder cap was cleaned by a 5 min warm water immersion. The instructions clearly state that the holder itself is not to be wetted.

Performance evaluation

Pressure drop, which measures the draw resistance of the heatstick, aerosol absorbance (density), a measure of particulate matter trapped within the aerosol, and puff number were evaluated for iQOS products using equipment and protocols described previously.[15–17] Pressure drop across heatsticks was evaluated using a Cole-Parmer Masterflex L/S peristaltic pump (Vernon Hills, Illinois, USA) connected to a U-tube water manometer to detect the change in differential pressure for each puff. Airflow rates were precalculated/precalibrated to the appropriate pump speed using a conversion factor provided by the pump head manufacturer, and flow rate was verified using a Brooks Instruments Sho-Rate flow meter (Hatfield, Pennsylvania, USA). Aerosol density was evaluated by capturing aerosols in a tubular cuvette, and absorbance was measured immediately at 420 nm using a Bausch & Lomb spectrophotometer (120 V, 0.9 A, Rochester, New York, USA).

iQOS devices were evaluated with five operating conditions; four (conditions 1–4) used the per-use cleaning protocol and one (condition 5) used the manufacturer's recommended cleaning instructions. The pump head, tubing set-up and running conditions were as follows: (1) low airflow rate 2 s protocol—the peristaltic pump was outfitted with a Cole-Parmer Masterflex Model 7015-21 pump head (standard pump head) using Masterflex Tygon E-LFL (tubing size 15) tubing to generate a flow rate of 7 mL/s with a 2 s puff duration for a total puff volume of 14 mL, 14 puffs were taken at 25 s intervals; (2) low airflow rate 4 s protocol—the same pump set-up and running conditions as for condition 1 with a 4 s puff duration generating a 28 mL puff volume; (3) International Organization for Standardization (ISO)—the pump was outfitted with a Cole-Parmer Masterflex L/S Easy-Load II Model 77200-52 high-performance pump head with Masterflex Tygon E-LFL (tubing size 15) producing a 17.5 mL/s flow rate with a 2 s puff duration, generating a total puff volume of 35 mL, with a total of six puffs taken, one puff every minute; (4) the Health Canada standard (HCI)—a Cole-Parmer Masterflex L/S Easy-Load II Model 77200-52 high-performance pump head was used with Masterflex Tygon E3603 (tubing size 36) tubing for a flow rate of 27.5 mL/s, with a 2 s puff for a total puff volume of 55 mL, 12 puffs were taken at 30 s intervals; (5) manufacturer's recommended cleaning (HCI), the same pump set-up and running conditions as described for condition 4 but in the absence of per-use cleaning; for this protocol the manufacturer's recommended cleaning instructions were followed (table 1). For conditions 1–4, three different iQOS devices were evaluated with each device being tested in triplicate, that is, a new heatstick was used for each experiment; condition 5 employed a single device in which 10 heatsticks were tested without cleaning between each stick.

Effect of use on the tobacco plug and polymer-film filter

The condition of the tobacco plugs was evaluated by visual and microscopic inspection and imaged using a Nikon C-LEDS stereomicroscope equipped with a Nikon Digital Sight DS-Vi1 camera head (Nikon, Minato, Tokyo, Japan) before and after use. Some heatsticks were dissected before and after use to further evaluate residual char (referred to as 'char' only) of the tobacco plugs and the condition of the polymer-film filter.

Gas chromatography–mass spectrometry analysis of iQOS heatstick polymer-film filters

Gas chromatography–mass spectrometry (GC–MS) using a qualitative wide-scope screening method was performed using an Agilent 7890B GC coupled with a 5977A MSD equipped with a

Table 1 Performance of iQOS heat-not-burn holders

Holder	Puff duration	Puff interval	Airflow rate (mL/s)	Puff volume (mL)	Total number of puffs	Average pressure drop (mm H_2O)	Average absorbance
Low airflow rate 2 s protocol*							
A	2	25	7	14	14	13±5	0.42±0.08
B	2	25	7	14	14	13±4	0.45±0.08
C	2	25	7	14	14	18±7	0.46±0.06
Low airflow rate 4 s protocol†							
A	4	25	7	28	14	9±4	0.41±0.05
B	4	25	7	28	14	11±4	0.46±0.09
C	4	25	7	28	14	10±4	0.49±0.04
ISO standard‡							
A	2	60	17.5	35	6	62±5	0.49±0.10
B	2	60	17.5	35	6	65±8	0.54±0.09
C	2	60	17.5	35	6	57±5	0.49±0.04
HCI standard§							
A	2	30	27.5	55	12	103±9	0.26±0.03
B	2	30	27.5	55	12	100±9	0.41±0.05
C	2	30	27.5	55	12	105±13	0.42±0.05
Manufacturer's recommended cleaning (HCI)¶							
E	2	30	27.5	55	12	103±12	0.46±0.06

*Per-use cleaning protocol, standard pump head with Tygon 15 tubing.
†Per-use cleaning protocol, standard pump head with Tygon 15 tubing.
‡Per-use cleaning protocol, high-performance pump head with Tygon 15 tubing.
§Per-use cleaning protocol, high-performance pump head with Tygon 36 tubing.
¶Manufacturer's recommended cleaning, HCI, high-performance pump head with Tygon 36 tubing.
HCI, Health Canada Standard ; ISO, International Organization for Standardization; iQOS, I quit original smoking.

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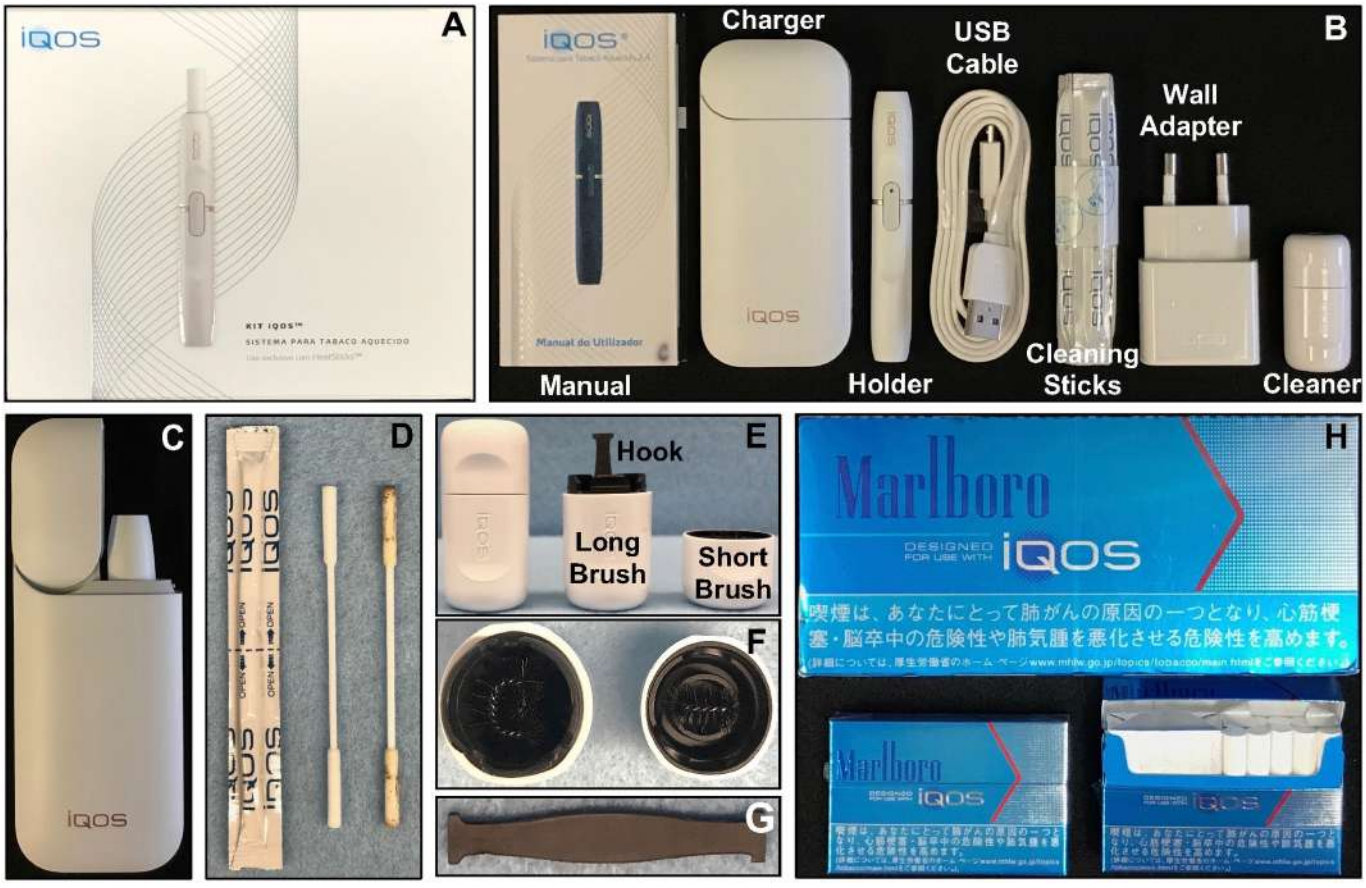


Figure 1 The I quit original smoking (iQOS) heat-not-burn system. (A) An iQOS starter kit. (B) The kit consists of an instruction manual, iQOS pocket charger, iQOS holder, USB cable, iQOS cleaning sticks, wall charging adapter and iQOS cleaner. (C) Profile view of iQOS holder inside a pocket charger. (D) Individual pack of iQOS cleaning sticks with an example of an unused stick and a stick after a single use per end. (E) A closed and opened iQOS cleaner; the larger end contains the long brush and protruding cleaning hook, and the shorter end contains the short brush. (F) Internal view of the iQOS cleaner showing the two brushes (long brush on the left, short brush on the right). (G) The cleaning hook removed from the iQOS cleaner. (H) Marlboro iQOS Heat Stick carton (containing 10 individual packs), sealed individual pack and opened pack exposing heatsticks.

7698A Headspace Sampler (Santa Clara, California, USA). Evaluation of iQOS aerosols was performed using headspace analysis. Chromatographic separation was accomplished using an Agilent J&W HP-5ms Ultra Inert GC Column (30 mx0.25 mmx0.25 µm) and ultra-pure helium (>99.999% purity) as the carrier gas at a flow rate of 1.5 mL/min. For headspace analysis, three unused heatsticks were dissected, polymer-film filters were removed, and a 3 mm portion (16.7%) closest to the tobacco plug were excised and placed into 20 mL headspace vials. All samples were analysed with a split ratio of 50:1, a solvent delay of 2 min, with blank analysis between each sample. GC ramp conditions were as follows: 40°C for 5 min, 45°C for 5 min, 90°C for 5 min, 130°C for 5 min, 135°C for 5 min, 165°C for 5 min, 190°C for 2 min, all temperature ramps were at 10°C/min. Ionisation of compounds was performed using electron impact ionisation at 70 eV in positive mode, the ion source maintained at 250°C and chemicals were identified using the National Institue of Standards and Technology mass spectral library (Gaithersburg, Maryland, USA), only chemicals with an 85% or higher probably match were listed as identifiable.

RESULTS

Components in the iQOS heat-not-burn system

The iQOS kit (figure 1A–G) consists of an instruction manual written in German, English, Portuguese and Italian, a pocket charger, the holder (device), a Universal Serial Bus (USB) cable and a European wall adapter plug for charging, moist cleaning sticks to clean the holder and cap, and the cleaner, which contains a long brush for cleaning the inside of the holder, where the heater is housed, a short brush for cleaning the cap and a hook for removing pieces of tobacco plug left in the holder/cap. A universal power adapter was purchased from Amazon (https://www.amazon.com/) and used to charge the pocket charger unit. Each carton of iQOS heatsticks contained 10 individually wrapped packs, and each pack had 20 heatsticks (figure 1H).

The iQOS kit components had an overall feel of good craftsmanship. The fabrication of the tobacco plug cast-leaf demonstrates a waste not want not strategy in that the plug is fabricated from pulverised tobacco remnants/waste materials, including tobacco stems, torn leaf material and leaf dust.[18] These items are reconstituted with natural adhesives and glycerin (a solvent that is used in EC fluids to produce aerosol) and processed into sheets forming cast-leaf, which is rolled and used as the tobacco plug.[3]

Cleaning of iQOS device

The interior chamber of the holder contained a heating element, referred to in the iQOS instruction manual as the silver, gold, platinum, ceramic-coated heater (figure 2). Unused holders were clean and debris-free with a white base and white heater with a metallic coil in its centre (figure 2A–C). Used holders

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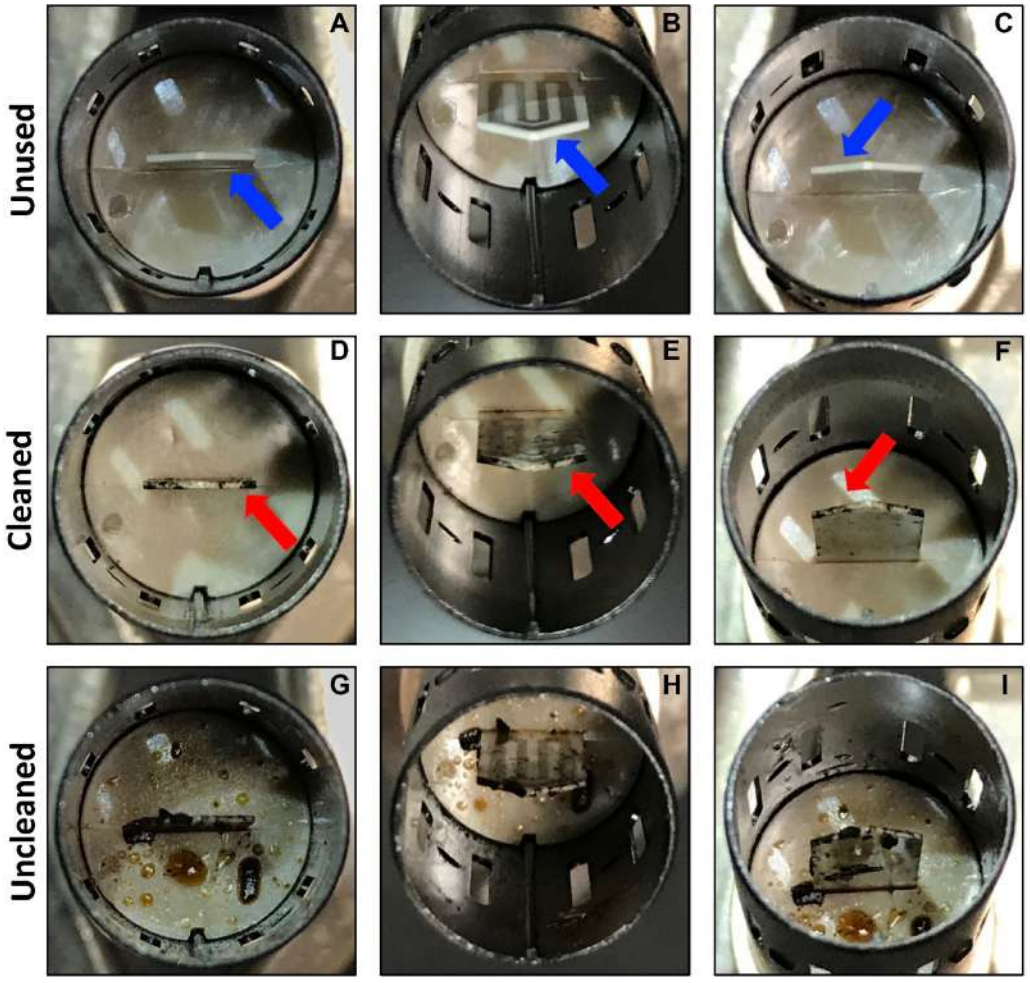


Figure 2 Internal view of the I quit original smoking holder. (A–C) Clean, unused holder showing heater (blue arrows). (D–F) Used holder that was cleaned after every use; black residue remains on heater (red arrows). (G–I) Used holder that was not cleaned between uses (10 uses).

that were thoroughly cleaned with the cleaning sticks between each heatstick were generally similar to the unused holder, except that the heating element had deposits of hardened dark debris that was not removed by the cleaning stick, cleaning cycle of the pocket charger or long brush (figure 2D–F). In the used holder that was not cleaned between heatsticks (manufacturer's recommended cleaning), brown liquid and particulates covered the base, walls and heater (figure 2G–I). With continued use in the absence of cleaning, the volume of liquid and debris increased, and the pieces of debris became darker and appeared more charred (figure 2D–I were taken after the 10th heatstick was used).

iQOS performance

The iQOS gives users a maximum of 14 puffs during a 6 min window per heatstick, after which it must be recharged before it can be used again. Performance of the iQOS was evaluated using five puffing protocols (figure 3, table 1). For protocols 1–4, three different iQOS devices (holders A, B and C) were tested in triplicate, that is, a new heatstick was used for each experiment, and each device underwent an intensive cleaning between each heatstick. For protocol 5, a single device (holder E) was used, and it was not cleaned between 10 heatsticks (average of the first three heatsticks is shown in figure 3I,J). For all testing protocols, pressure drop decreased as puff number increased. Aerosol density readings increased with use, peaking around puffs 7–9 and then begin to decrease. Although pump set-up affected pressure drop, it did not affect aerosol absorbance which remained similar under all running conditions, However, differences in testing conditions may lead to alterations in the chemical constituents present within the aerosol without altering aerosol density. Not cleaning did not affect performance except that pressure drop was more variable during the first four puffs in the uncleaned trials.

Tobacco plug charring

Dissection of unused and used heatsticks showed tobacco plug charring (figure 4A). Stereomicroscopic comparison of unused (figure 4B) and used (figure 4C) tobacco plugs confirmed charring or blackening of the cast-leaf. Visual and stereomicroscopic inspection of used heatsticks show the effects cleaning had on device heat production. Comparison of the first and 10th used heatstick from holder A (per-use cleaning) shows that with regular cleaning the charred area surrounding the heater, referred to as the zone of charring, does not increase with use (figure 4D,E). The effects of cleaning on heating were most evident during the course of the manufacturer's recommended cleaning (HCI) testing. Comparison of these heatsticks to unused and per-use cleaned heatsticks showed that in the absence of regular cleaning, the zone of charring increased as the number of heatsticks tested increased (figure 4H–L).

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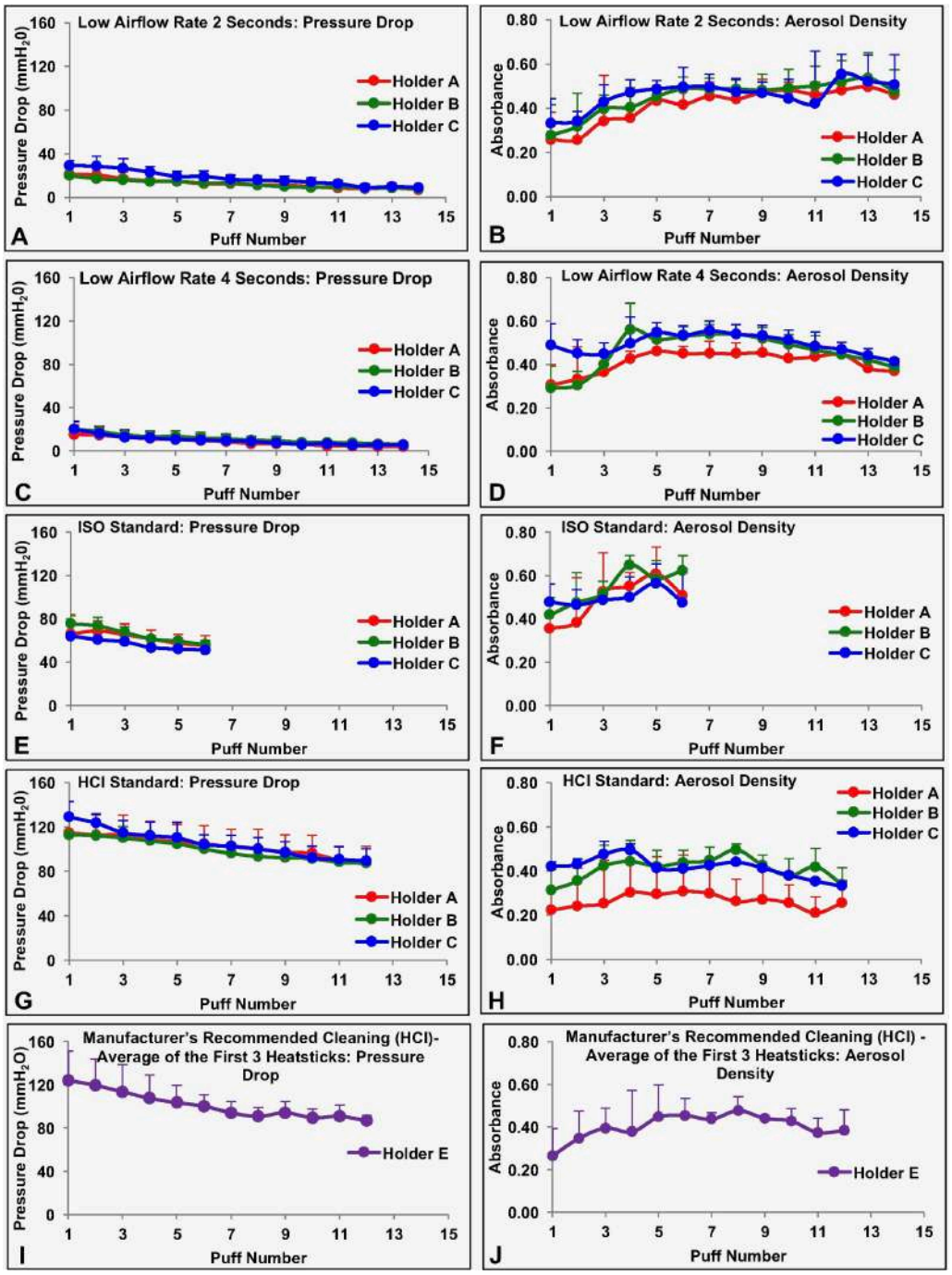


Figure 3 Performance characteristics of the I quit original smoking heat-not-burn system. (A, C, E, G and I) Pressure drop is plotted versus the puff number for five puffing protocols. (B, D, F, H and J) Absorbance is plotted versus puff number for the five puffing protocols. Each line of the graph represents the average of three heatsticks for an individual holder (holder A=red, holder B=green, holder C=blue and holder E=purple). HCI, Health Canada Standard ; ISO, International Organization for Standardization.

Polymer-film melting

Effects of cleaning on heating were not exclusive to the tobacco plug; figure 4A shows that the polymer-film filter (labeled 2), which is separated from the tobacco plug (condition 4) by the hollow acetate filter (condition 3), was adversely effected. The aerosol produced by the iQOS was hot enough to melt the polymer-film filter, which could allow release of potentially hazardous chemicals. Melting of the polymer-film filter was evident by slight yellowing of the filter, as well as by narrowing of the end closest to the tobacco plug (figure 4A indicated by black arrow). This melting and subsequent cooling of the filter caused it to harden, preventing it from being longitudinally dissected. Comparison of unused and used polymer-film filters from both per-use and manufacturer's recommended cleaning experiments showed the relationship between cleaning and increased heat generation. First (figure 4F) and 10th (figure 4G) filters from cleaned devices showed similar discoloration and melting to that of the first filter from the uncleaned device (figure 4N). Comparison of these heatsticks to subsequent manufacturer's recommended cleaning used heatsticks showed discoloration and melting of the polymer-film filter increased with increased use (figure 4M–Q).

Headspace analysis of unused polymer-film filters

GC–MS headspace analysis of unused polymer-film filters showed the presence of ε-caprolactone and lactide, common

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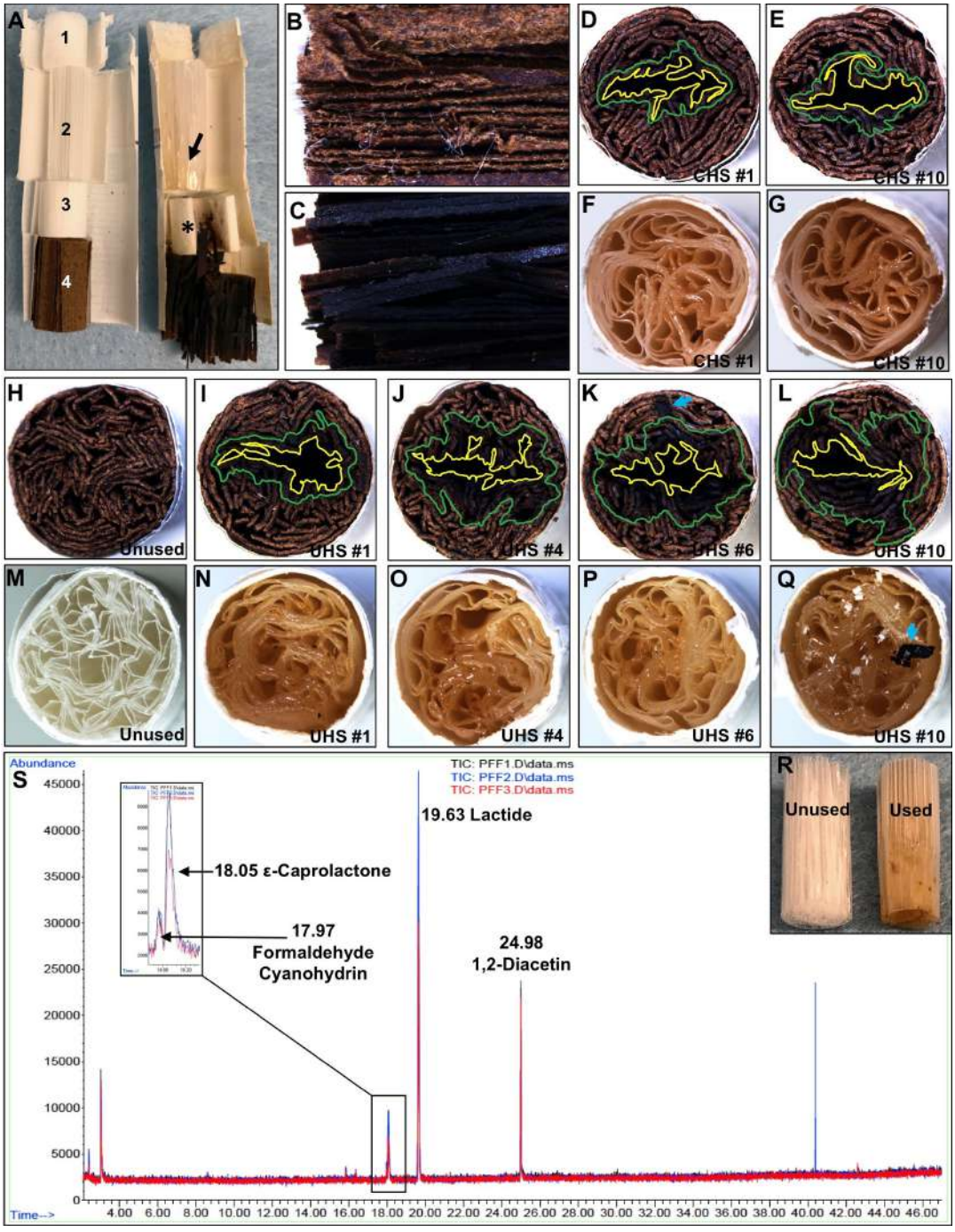


Figure 4 Charring of tobacco plug and melting of polymer-film filter. (A) Dissected heatsticks, each heatstick is composed of: (1) the low-density cellulose mouthpiece filter, (2) polymer-film filter, (3) hollow acetate tube and (4) tobacco plug. Heatsticks from left to right are unused stick with the paper overwrap peeled away, and used stick with the paper overwrap removed with the mouthpiece filter and hollow acetate tube sliced open; black arrow indicates melted region of the polymer-film filter, black asterisk denotes tobacco plug fragments that have been drawn into the hollow acetate tube. (B) An unused tobacco plug. (C) Used tobacco plug showing charring/darkening with use. (D,E) Cross sections of tobacco plugs from the first (D) and 10th (E) heatstick of holder A of the cleaned experiment. Yellow outlined area indicates a void in the cast-leaf left by the heater, the area between the yellow and green outlines are the charred portions of the tobacco plug. (F,G) Cross sections of polymer-film filter from the first (F) and 10th (G) heat stick. Polymer-film filter images shown coincide with tobacco plug images (D) and (E). (For D–G, CHS=cleaned device heatstick.) (H–L) Cross sections of tobacco plugs before use (H) and after use from the first, fourth, sixth and 10th heatstick of the uncleaned experiment (I–L). Yellow outlined area indicates a void in the cast-leaf left by the heater, area between the yellow and green outlines are the charred portions of the tobacco plug. (M–Q) Cross sections of polymer-film filter before (M) and after use (N–Q). Polymer-film filter images shown coincide with tobacco plug images (H–L). Blue arrowheads show charred pieces of cast-leaf that are affixed to the tobacco plug (K) and polymer-film filter (Q). (For (I–L) and (N–Q), UHS=uncleaned device heatstick). (R) Unused and used whole polymer-film filters showing discoloration and film melting, as demonstrated by the narrowing of the used filter. (S) Gas chromatography–mass spectrometry headspace analysis of unused polymer-film filter. Chromatogram shows an overlay of three runs, relative abundance was plotted versus retention time in minutes, unidentifiable peaks were unlabelled. Inset shows a magnified view of peaks with close retention times.

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components in plastics, as well as 1,2-diacetin, a plasticiser (figure 4S). However, of most concern was the presence of formaldehyde cyanohydrin (glycolonitrile), an acute toxicant often used in the production of synthetic resins and used as a solvent.[19] Formaldehyde cyanohydrin was eluted at 17.97 min, when the column reached 90°C.

DISCUSSION

Unlike some EC, which often show significant variation in craftsmanship and performance within and between brands,[15 20] the iQOS appearance, design and performance data are consistent with a product that is well manufactured. However, some design features of the iQOS, such the limited time allowed per heatstick and the need to consume the entire heatstick within this time or alternatively waste part of it, will affect user's topography and may lead to unwanted exposure to potentially toxic chemicals emitted from melting plastic and from pyrolysis of tobacco.

In contrast to tobacco and EC, which usually have no constraints on puffing, the iQOS only operates for 6 min, at which time it automatically shuts off and requires charging before it can be used again. Since a maximum of 14 puffs can be taken from each iQOS heatstick, puffing needs to be done at about 25 s intervals to take full advantage of each heatstick; used heatsticks that have not been fully exhausted cannot be used again as reinsertion would cause the delicate cast-leaf tobacco plug to crumble. This may not appeal to all users, and users who puff less frequently would have a lower number of puffs/heatstick. For users wishing to maximise each heatstick, this limitation will force them to alter their smoking topography by decreasing the interpuff interval and/or accelerating the rate at which they puff, leading to larger volumes of aerosol inhalation.

The manufacturer's cleaning instructions were not fully developed in the instruction manual. The cleaning protocol recommended using the cleaning function of the charger followed by cleaning with the brushes after 20 heatsticks and removing any large fragments of tobacco plug with the hook if necessary. The iQOS kit was equipped with cleaning sticks (figure 1B,D), yet their use was not mentioned in the instruction manual. Our data show that use of one heatstick left a significant amount of debris, fluid and fragments of cast-leaf in the holder (figure 2).

While iQOS heatsticks do not produce a flame, they were always charred after use, which we interpret to be a result of pyrolysis. The zone of charring was greater when cleaning was not performed between heatsticks, suggesting that build-up of fluid and debris in the holder increases pyrolytic temperatures. These data are consistent with the idea that despite similarities in performance characteristics, the cleanliness of the device plays a critical role in thermal regulation. Pyrolysis of tobacco is an endothermic reaction which occurs at temperatures between 200°C and 600°C, during which the majority of volatile and semivolatile components of cigarette smoke are formed.[21 22] Although the Philip Morris study indicated that the aerosol produced by iQOS devices reduce the amount of chemicals found on the Food and Drug Administration's Harmful and Potentially Harmful Constituents list by limiting tobacco pyrolysis,[5] our study, showing charring, in conjunction with a study by Auer *et al*, which confirmed the presence of volatile organic compounds, polycyclic aromatic hydrocarbons, carbon dioxide and nitric oxide,[23] contradict the claim that tobacco pyrolysis is minimised in iQOS. Although iQOS operates at temperatures less than 350°C, this does not negate the formation of volatile and semivolatile harmful constituents of tobacco smoke, which tend to have boiling points that range from 70°C to 300°C.[21 22]

Heatsticks used in this experiment were dissected and the severity of polymer-film filter melting was examined. The function of the polymer-film filter is to cool the aerosol,[3] thus, it would seem that the polymer composing the film should be heat resistant, although, ε-caprolactone, also known as polycaprolactone, tends to have a low-melting point which is thickness dependent.[24] The intensity of the heat produced by the iQOS, under both cleaned and uncleaned conditions, was sufficient to melt the polymer-film filter, even though it was not in direct contact with the heater. The amount of damage to the film (increase in melt and alteration of coloration) increased with each heatstick when cleaning was done per the manufacturer's recommended procedure (after 20 heatsticks). Discoloration may be a product of heating and/or staining from the brown fluid that is expelled from the tobacco plug during use.

Our GC–MS data indicate that components of the polymer-film filter are aerosolised at relatively low temperatures. GC–MS headspace analysis of unused filters suggests the polymer-film filter is a combination of ε-caprolactone, lactide, 1,2-diacetin and other unidentified chemicals. The chemicals released from the film filter during heating may not be suitable for inhalation. Thus, it is unknown if the film filter material is safe for use in products where it would undergo intense cycles of heating and cooling. Of greatest concern was the release from the polymer filter of formaldehyde cyanohydrin, a highly toxic chemical that is metabolised in the liver and broken down into formaldehyde and cyanide.[19] Formaldehyde cyanohydrin can be fatal to humans,[19 25 26] with studies showing mouse inhalation LD_{Lo}, the lowest dose of a toxicant that causes the death of an animal,[27] values as 27 ppm/8 hour.[28 29] iQOS holders operate at temperatures between 330°C and 349°C,[3 23] and as a safety feature, the device shuts off when temperatures reach 350°C. The release of formaldehyde cyanohydrin from unused filters during GC–MS analysis occurred at 90°C, a temperature that all users will exceed.

In conclusion, the iQOS appears to be well manufactured, and performance data were consistent between heatsticks. However, the product has limitations that will affect user topography and the application of standard smoking protocols, such as the ISO 3308, which could not be used for more than six puffs with this product. Users may be forced to smoke at a rapid pace in order to fully maximise heatsticks. Decreasing the interpuff interval could lead to an increase in intake of nicotine[30] and carbonyls.[31] This study also showed that the iQOS is not strictly a

What this paper adds

- Performance characteristics were generally uniform between devices and heatsticks.
- I quit original smoking (iQOS) device usage limitations make modifications to some current smoking standards necessary for proper evaluation of products.
- Device limitations may decrease users' interpuff intervals, increasing possible toxic exposures.
- iQOS holders heat hot enough to cause charring of the tobacco plug via pyrolysis and melting of the polymer-film filter.
- iQOS holder cleanliness affects and contributes to increased charring of the tobacco plug and melting of the polymer-film filter.
- Formaldehyde cyanohydrin, a toxicant, was released from the polymer-film filter at 90°C.

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'heat-not-burn' tobacco product. The iQOS tobacco appeared to char without ignition, and charring increased when cleaning was not done after each use. This study also showed the potential dangers that the polymer-film filter poses. This thin plastic sheet, readily melts during iQOS use and releases formaldehyde cyanohydrin, a dangerous toxicant. This study has shown that the iQOS system may not be as harm-free as claimed and also emphasises the urgent need for further safety testing as the popularity and user base of this product is growing rapidly.

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Contributors BD: conceiving and designing experiments, performing experiments, writing and editing manuscript. MW: performing performance experiments and writing part of the Materials and methods section. PT: conceiving and designing experiments, editing manuscript, obtaining funds and overseeing the project.

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Disclaimer The content is solely the responsibility of the authors and does not necessarily represent the official views of the TRDRP.

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iQOS: evidence of pyrolysis and release of a toxicant from plastic

Barbara Davis, Monique Williams and Prue Talbot

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PMI left a lot of important things out of its toxicology studies of IQOS submitted to the FDA

tobacco.ucsf.edu/pmi-left-lot-important-things-out-its-toxicology-studies-iqos-submitted-fda

My colleagues at the UCSF TCOS just put this public comment in on Phlilip Morris' MRTP application for IQOS. The tracking number is 1k1-902j-m8kv. A PDF of the comment is available here.

Because PMI application did not report the full range of HPHCs in IQOS aerosol, characterize HPHCs in sidestream emissions, include a non-targeted analysis of chemicals in emissions, or conduct clinical studies to describe exposure to toxicants during dual use with other tobacco products, FDA must deny PMI's application

Gideon St.Helen, PhD1,2; Peyton Jacob III, PhD1,2; Natalie Nardone, PhD1,2;
Neal L. Benowitz, MD1,2,3
1Division of Clinical Pharmacology, Department of Medicine, University of California San Francisco; 2UCSF Tobacco Center of Regulatory Science; 3Department of Bioengineering and Therapeutic Sciences, University of California San Francisco
Docket Number: FDA-2017-D-3001
November 29, 2017

Philip Morris Products SA, a subsidiary of Philip Morris International (collectively referred to as PMI hereafter), has recently submitted a "modified risk tobacco product" (MRTP) application to the FDA for review and approval of IQOS. (We refer to the product as IQOS in this comment in place of tobacco heating system, THS 2.2.) According to FDA's draft guidance, an MRTP is "any tobacco product that is sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products."[1] FDA may issue an order allowing a product to be marketed as a modified risk product if it is demonstrated that the product: (1) significantly reduces harm and the risk of tobacco-related disease to individual tobacco users; and, (2) benefits the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products.

We recognize the possible benefit to individuals and public health of marketing tobacco products with substantially reduced risks profiles compared to currently marketed products such as combustible cigarettes, cigars, and some smokeless tobacco products. Given FDA's mission to protect Americans from tobacco-related diseases and death by regulating tobacco, it is critically important that FDA undergo a thorough science-based review of PMI's application to market IQOS as an MRTP. ***The PMI MRTP application lacks important information needed for the FDA to determine that IQOS should be marketed as an MRTP, so should deny the application until PMI presents the information necessary to demonstrate that any product permitted to be marketed as an MRTP actually reduces risk.***

1. **Aerosol Chemistry (Module 6.1.1.):**

1. ***PMI should report emission levels of all 93 HPHCs in IQOS aerosol .*** According to the FDA, harmful and potentially harmful constituents (HPHCs) are "chemicals or chemical compounds in tobacco products or tobacco smoke that cause or could cause harm to smokers or nonsmokers."[2] The FDA has an established list of 93 HPHCs.[3] Quantifying levels of HPHCs in aerosol/smoke of tobacco products that deliver nicotine through the pulmonary route is critical to understanding the potential health risks associated with these products. PMI measured the levels of 58 HPHCs, which they referred to as PMI-58, in mainstream IQOS aerosol. PMI claims that this list contains "chemical constituent representatives of all major toxicologically relevant chemical classes of compounds present in both the particulate-phase and gas/vapor-phase of cigarette smoke," (Module 6.1.1 Aerosol Chemistry p. 6). They also claim that it contains the 18 HPHCs subject to reporting on FDA's abbreviated list. No rationale for leaving out the other 35 HPHCs on the FDA's established list was given. The public (and the FDA) cannot assume that these 35 HPHCs are not important or that they are at much lower levels in IQOS emissions compared to other tobacco products. Since PMI is attempting to market IQOS as a reduced risk product, a more extensive rather than limited analysis of HPHCs is needed.
2. ***PMI should report levels of HPHCs in IQOS sidestream emissions .*** PMI's analysis of the PMI-58 HPHCs was done in mainstream IQOS aerosol. The implicit assumption is that IQOS has no sidestream emissions. However, research on IQOS by Imperial Tobacco Ltd. found "a large number of different VOC [volatile organic compound] species across a range of masses were released into the airspace" when IQOS was activated but not puffed on.[4] In order to protect non-users of tobacco products, FDA must insist that PMI fully characterizes HPHC levels in sidestream emissions from IQOS.
3. ***PMI should report results of non-targeted analyses of constituents in mainstream and sidestream IQOS emissions, in addition to their current targeted analysis.***

The MRTP application reports the results of analyses comparing the emissions of HPHCs from IQOS and a reference cigarette (Module 6.1.1 pp 13-19). The analyses reported by PMI show significant reductions in most of the HPHCs that were measured compared to emissions from a reference 3R4F cigarette.

Significantly, the reported studies fail to address the important question "does the aerosol generation process for IQOS produce substances not found in the smoke of conventional cigarettes, and if so, are any of these substances harmful or potentially harmful?" The main rationale for the development of IQOS and other heat-not-burn products is that combustion, meaning incomplete combustion of many organic materials, including tobacco, produces highly toxic substances such as some on the HPHC lists. The heat-not-burn products generate an inhalable aerosol without combustion, thereby purportedly eliminating or reducing the levels of substances that are generally formed as combustion by-products. ***Nevertheless, the heat required to generate the aerosol in IQOS will likely produce substances not detected in cigarette smoke. Substances in the IQOS (from tobacco or the numerous additives) could undergo heat-induced reactions to form new substances that***

might not survive in the higher temperature and strong oxidizing conditions in a combusted tobacco product.

There are reasons to suspect that the temperatures produced in IQOS are sufficient to cause chemical reactions to occur, as have been demonstrated with e-cigarettes. [5] In other words, substances in the aerosol may not be limited to those present in the tobacco prior to aerosol generation. E-cigarettes use heat to generate an inhalable aerosol without combustion, in a fashion similar to aerosol generation in a heat-not-burn product, and it is well known that numerous chemical reactions occur during the "vaping" process. For example, formation of toxic aldehydes, including formaldehyde, acetaldehyde, and acrolein, via dehydration and oxidation of the vehicles propylene glycol and glycerin is of particular concern.[6],[7] In addition, flavoring chemicals in e-cigarettes undergo thermal degradation and contribute significantly to levels of toxic aldehydes emitted in e-cigarette aerosol.[8]

Similarly, one would expect chemical reactions to occur during aerosol generation in IQOS, and ***there is no reason to expect that all of the substances formed, or that survive during aerosol generation, would be the same as those found in cigarette smoke.*** In fact, even among combusted tobacco products, the composition of the aerosols may differ. A recent study by Klupinski and colleagues reported that unique substances, such as ambrox, 3-methylbutanenitrile, and 4-methylimidazole, were found in little cigar smoke that were not found in cigarette smoke.[9] The study describes methodology for "non-targeted" analysis of tobacco smoke aerosol, and the authors suggest that "the same approach could also be applied to other samples to characterize constituents associated with tobacco product classes or specific tobacco products of interest. Such analyses are critical in identifying tobacco-related exposures that may affect public health." ***PMI should undertake such studies and report the full results.***

In addition to the "targeted" analyses for specific HPHCs that were carried out, PMI should carry out "non-targeted" analyses comparing IQOS aerosol with smoke from combustible tobacco products in an attempt to identify potentially toxic chemicals in IQOS aerosol that may not be present in tobacco smoke. The aforementioned study by Klupinski et al. constitutes "proof of concept" for the feasibility of such chemical analyses.

4. ***PMI should compare aerosol constituents of IQOS to that of other combustible tobacco products and e-cigarettes.*** While PMI's application focuses primarily on comparisons between IQOS emissions and combustible cigarette smoke, it is unlikely that IQOS will only be used by combustible cigarette smokers. Instead, the likely scenario is that at least some users of other combustible and non-combustible tobacco products will switch to IQOS. Unless PMI can guarantee that their product be marketed and sold to current combustible cigarette smokers only, it makes no sense that their comparison is limited to cigarettes. FDA should at least insist that PMI reports comparisons of HPHC emissions between IQOS and all combustible products and electronic nicotine delivery products. This set of data is critical for an accurate assessment of the relative safety/risks of IQOS ***as actually used*** compared to and in conjunction with (i.e., dual use) other tobacco products.
5. ***PMI should characterize free radical emissions in IQOS aerosol.*** Free radicals are

associated with oxidative stress, an underlying mechanism of many disease outcomes, including cardiovascular disease and cancer. Previous research has demonstrated high free radical emissions from e-cigarettes.[10] FDA should insist that PMI compares free radical emissions from IQOS with combustible tobacco products and e-cigarettes.

2. **Justification of selection of biomarkers of exposure (Module 6.1.3.1):**

1. ***PMI should expand the list of HPHCs for which systemic exposure was assessed.***

PMI used 1-hydroxypyrene, a metabolite of pyrene (a polycyclic aromatic hydrocarbon, PAH) as a biomarker of PAHs. We have previously demonstrated that 1-hydroxypyrene is not a selective measure of tobacco-related PAH exposure and is not highly related to nicotine intake and tobacco-specific nitrosamine exposure.[11] Instead, we found that monohydroxylated metabolites of fluorene (particularly 1-hydroxyfluorene) and 2-naphthol (a naphthalene metabolite) were more selective of tobacco smoke exposure. Given the link between PAH exposure and cancer, it is important that PMI reports PAH biomarkers that are more selective of tobacco smoke than 1-hydroxypyrene.

Further, PMI's list of 17 HPHCs, for which systemic exposure were assessed, do not include any inorganic compounds, phenols, and metals. Systemic exposure to these chemicals, especially metals, should be included in PMI's MRTP. One risk assessment model estimated that metals, such as cadmium, chromium (hexavalent), and arsenic, accounted for a significant fraction of the cancer and non-cancer disease risk indices of tobacco smoking.[12] For this reason, FDA should insist that PMI report exposure to metals from IQOS use.

3. **Summary of biomarkers of exposure assessments (Module 6.1.3.2.):**

PMI conducted four clinical studies to "demonstrate that the level of exposure to harmful substances has been statistically significantly reduced," based on FDA MRTP draft guidance. Two of the studies were 5-day studies in confinement, where smokers of combustible tobacco cigarettes were randomly assigned to either switch to IQOS, continue their own brand of cigarettes, or abstain from using tobacco products. The two other studies were 3-month studies consisting of 5 days of confinement followed by up to 3 months in their naturalistic environments (Module 6.1.3.2. p. 9). The first two studies were done in Poland and Japan and the latter two in Japan and the U.S. All studies contained 160 subjects, each. All four studies are of acceptable design, and included biomarker analysis in 24-hour urine (a strength).
However, there are some concerns:

1. ***PMI should present results of statistical tests.*** In figures such as Figure 1, 3, and 5 (Module 6.1.3.2. pp. 15, 20, and 25) comparisons of reduction in biomarkers of exposure to HPHCs are given for smokers who switch to IQOS and those who were in the abstinence arm. Simply stating the percentage reduction in exposure when a smoker moves from cigarettes to IQOS or from cigarettes to abstinence is not

sufficient. Important to our understanding of the relative safety/risks of IQOS is information on the magnitude of the exposure to toxicants when using IQOS compared to during abstinence. FDA should insist that results of statistical tests be presented for comparisons of reductions with IQOS compared to abstinence.

2. ***Clinical studies lacked racial diversity. PMI should investigate the effect of race on use patterns and biomarkers of exposure.*** The studies were conducted with either Japanese or Caucasians. As such, these studies are most likely not representative of the U.S. population, which is diverse racially. Metabolism of and reaction to the absorbed constituents of tobacco products,[13],[14] as well as attitudes, perceptions, preferences, and tobacco use patterns may differ across racial/ethnic groups. For example, we have observed racial differences in the manner in which combustible tobacco cigarettes are smoked and how cigarettes per day related to exposure biomarkers.[15] African Americans tend to smoke each cigarette much more intensely than Caucasian smokers do. African Americans and Native Indians have been shown to be more susceptible to lung cancer than Caucasians.[16] These previous observations underscore the need to include a racially diverse sample in assessing tobacco use patterns and toxicant exposures, and to conduct clinical studies with a sample that is representative of the U.S. population.
3. ***Noncompliance during outpatient (ambulatory) product use reduces the validity of conclusions made regarding reduced toxicant exposure from IQOS.*** The two 3-month studies included 5 days in a controlled setting and 85 or 86 days in their naturalistic environment. They compared the use of IQOS with combustible cigarette smoking and smoking abstinence. PMI implied that both studies showed significant reductions in HPHC biomarkers with use of IQOS, but did not present any associated P values to compare reductions in HPHC biomarkers during IQOS use and smoking abstinence. The results are presented together in Figure 5 (Module 6.1.3.2. p. 25) and Figure 8 (Module 6.1.3.2. p. 32), and are most likely meant to convey the message that IQOS use results in reductions in HPHCs comparable to smoking abstinence. To be a valid comparison, it is important that study participants complied with the assigned product/regime allocation, particularly those of the smoking abstinence arm. If participants in the abstinence arm smoked cigarettes (going against the study regime), percentage reductions in biomarkers of HPHCs would be lower, and most likely be comparable to that of reductions among participants in the IQOS arm, i.e. the study would show comparable reductions in HPHC exposure with IQOS and abstinence. It is not clear from the application how compliance was determined. Compliance was said to be “particularly high” for the first study. This is a relative term and needs to be quantified in the application. For the second study, PMI reports “good” compliance of subjects in the IQOS arm but “poor” compliance in the abstinence arm. With only 7-9 out of 41 subjects from the smoking abstinence arm being included in the “PP set” (it was not clear what PP set meant), comparisons of HPHC exposure reduction between IQOS use and smoking abstinence are not valid. PMI noted that “in light of the limited number of subjects in the [smoking abstinence] arm and the increased variability, the results obtained using the [smoking abstinence] arm should be interpreted with caution.” ***FDA has to ensure that PMI follows its own advice in interpreting the findings with caution. Until it does, FDA cannot rely on the data presented in the application.***

4. ***PMI should describe exposure biomarkers among dual use groups.*** Most e-cigarette users also smoke combustible cigarettes.[17] The most likely scenario if IQOS is allowed into the U.S. market is high prevalence of dual use of IQOS and tobacco cigarettes or other tobacco products. It is unknown if dual use would result in decreased exposure to tobacco smoke toxicants in the context of nicotine titration (harm reduction), or additive exposure to toxicants from cigarettes and IQOS. It is therefore imperative that FDA insist that PMI conducts studies to assess exposure to toxicants during periods of dual IQOS-tobacco cigarette use.

Conclusion

In summary, to ensure that IQOS is truly a modified risk tobacco product with net benefits to individual users and the population as a whole, before acting favorably on an MRTP application for ICOS, FDA should require that: (1) PMI expands the list of reported HPHCs tested in IQOS emissions and those included in biomarker analysis; (2) characterize HPHC emissions in sidestream aerosol from IQOS; (3) conduct non-targeted analysis to identify other potentially toxic constituents of IQOS emissions that may be unique to IQOS (in addition to reported targeted analysis); (4) compare aerosol constituents from IQOS with that of other combustible tobacco products such as cigars in addition to cigarettes; (5) characterize free radical emissions in IQOS aerosol; (6) conduct clinical studies with samples that are representative of the U.S. population (e.g. racial diversity); and, (7) conduct studies to describe exposure biomarkers during periods of dual use. Section 911(g) of the Family Smoking Prevention and Tobacco Control Act is clear and unambiguous: **FDA may issue an MRTP order *only if* PMI has demonstrated that IQOS, *as actually used by consumers*, will "(A) significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and (B) benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products." Since PMI has failed to make this required showing, FDA is not authorized to issue an MRTP order.**

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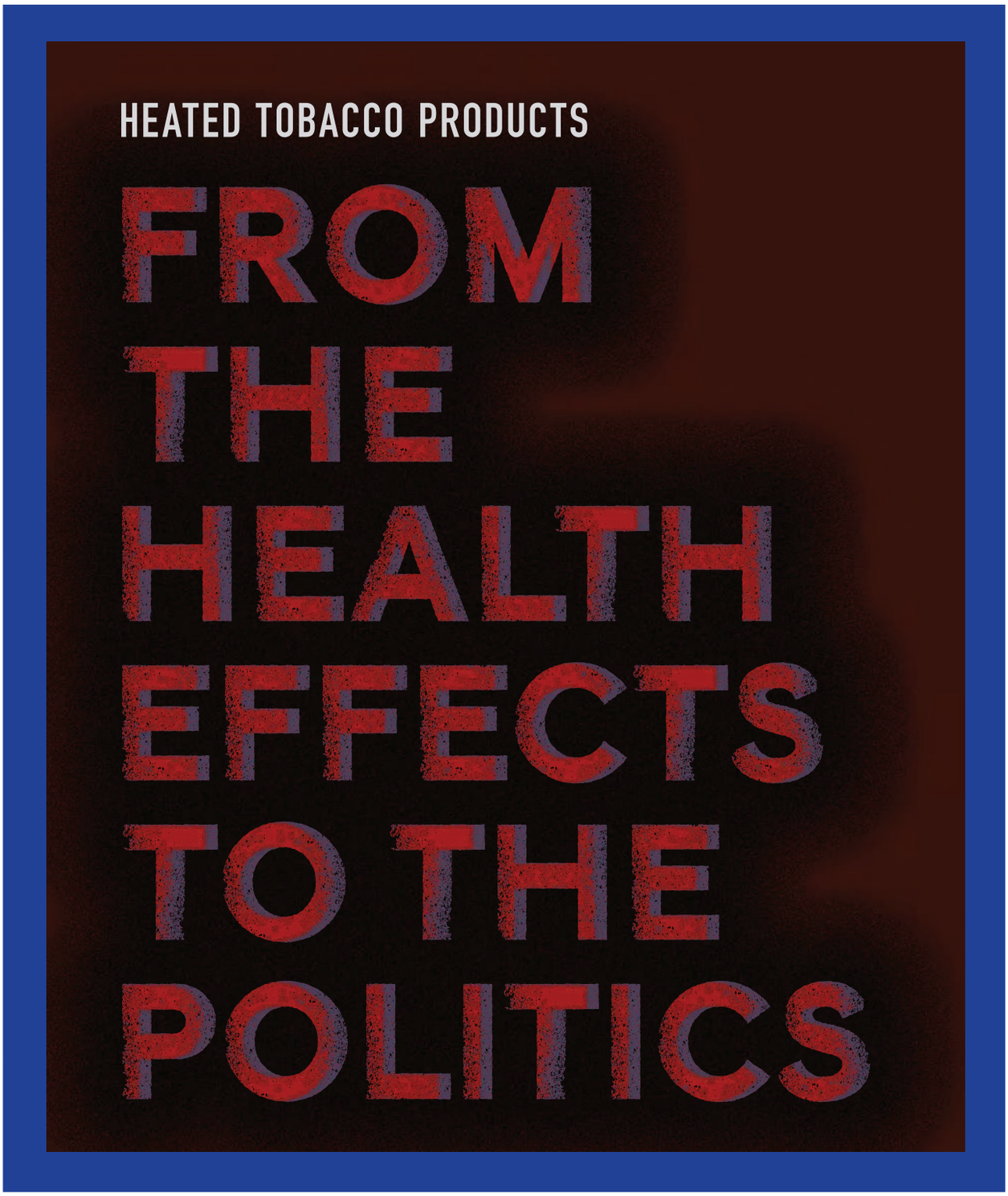
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Heated tobacco products: the example of IQOS

Stanton A Glantz

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Correspondence to
Professor Stanton A Glantz, Department of Medicine, Center for Tobacco Control Research and Education, Cardiovascular Research Institute, Philip R. Lee Institute for Health Policy Studies, Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, San Francisco, CA 94143-1390, USA; glantz@medicine.ucsf.edu

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Heated tobacco products (HTP) represent the latest in a long line of products tobacco companies have developed and marketed as less dangerous than conventional cigarettes, beginning with so-called 'safer cigarettes' in the 1960s.[1 2] HTP (figure 1) heat tobacco to generate an inhaled nicotine aerosol and are marketed using messages that explicitly or implicitly claim they are safer than cigarettes.[3–8]

In 2018, HTP were available in many countries (table 1). In the USA, before marketing new tobacco products, the Family Smoking Prevention and Tobacco Control Act[9] (FSPTCA) requires premarket review by the Food and Drug Administration (FDA) to demonstrate that marketing them would be 'appropriate for the protection of the public health' (FSPTCA sections 910 and 905(j)). Additionally, to market any new tobacco product in the USA with claims of reduced risk or reduced exposure to toxins compared to other tobacco products ('Modified Risk Tobacco Product'; MRTP), the company must first obtain an MRTP marketing order from the FDA. In December 2016, Philip Morris International (PMI) submitted an application to market IQOS, one of its HTP, with MRTP claims.[10] PMI's MRTP application included extensive details about the product, the chemistry of the aerosol it produces, related toxicology, effects on clinical measures in people, perceptions of the product and its packaging (including warning labels), and behavioural factors. This application sought FDA approval of PMI's claims that smokers who switched completely to IQOS would reduce their health risks or exposure to dangerous substances compared with smoking cigarettes.

As of November 2017, there were 31 studies of HTP published in the peer reviewed literature, 20 of which were affiliated with the tobacco industry.[11] The 11 independent studies focused on awareness, use, and secondhand emissions of HTP, while the industry affiliated papers examined nicotine delivery and mainstream emissions and exposures to selected toxicants. The fact that the literature has been dominated by industry is particularly concerning because tobacco companies have a record of publishing incomplete or manipulated information and presenting it to governments.[12–16] For example, PMI[17–20] and British American Tobacco[21–23] (BAT) conducted and published studies arguing that additives did not increase cigarettes' toxicities. However, internal PMI documents and analysis of PMI's data done by people independent of the tobacco industry revealed that many toxicants increased when additives—notably menthol—were present.[15]

PMI's IQOS MRTP application (the 'application') provides an opportunity to analyse PMI's data. This supplement to *Tobacco Control* includes eight papers that present analyses of PMI's application by researchers independent of the tobacco industry and 12 papers that provide independent assessments of HTP effects, including their political and policy implications. Together, these papers provide insights into IQOS (and, in broad terms, other HTP) and support the January 2018 vote by the FDA Tobacco Product Scientific Advisory Committee that PMI's application did not demonstrate it reduced risk claims for IQOS[24] (online supplementary table S1). These papers also put HTP in the overall context of the tobacco companies' plans to maintain and grow their markets in the future and outline regulatory responses.

HEALTH EFFECTS

The fundamental justification for introducing HTP is the claim that they are substantially less dangerous than conventional cigarettes. PMI's application includes PMI's 3-month study of 24 non-cancer biomarkers of potential harm (BOPH) in humans using IQOS compared with conventional cigarettes. These biomarkers include measures of inflammation, oxidative stress, cholesterol and triglycerides, blood pressure, and lung function. (PMI did separate studies of biomarkers of exposure, several of which are carcinogens.) While PMI's application emphasises that these biomarkers generally changed in positive directions, Glantz's[25] examination of the data revealed no statistically detectable difference between IQOS and conventional cigarettes for 23 of the 24 BOPH in Americans and 10 of 13 in Japanese. Moreover, it is likely that the few significant differences were false positives. Thus, despite delivering lower levels of some toxicants, PMI's own data fail to show consistently lower risks of harm in humans using IQOS compared with conventional cigarettes.

In June, 2018 PMI issued a press release[26] announcing that a 6-month human study comparing IQOS with conventional cigarettes found eight biomarkers improved in those who switched to IQOS. PMI did not provide specific results. In contrast to the application, PMI's new study only examined six BOPH (plus two biomarkers of exposure). Further, PMI did not report the full range of biomarkers used in the earlier study although they can be measured in a blood sample or simple physiological test. This additional study raises questions about PMI manipulating the experimental design or data analysis as it and other companies have a history of doing.[15]

While HTP are presented as 'new', they are simply the latest incarnation of a technology tobacco companies have been developing for decades. Elias *et al*[2]analysed previously secret PMI documents, public communications and the

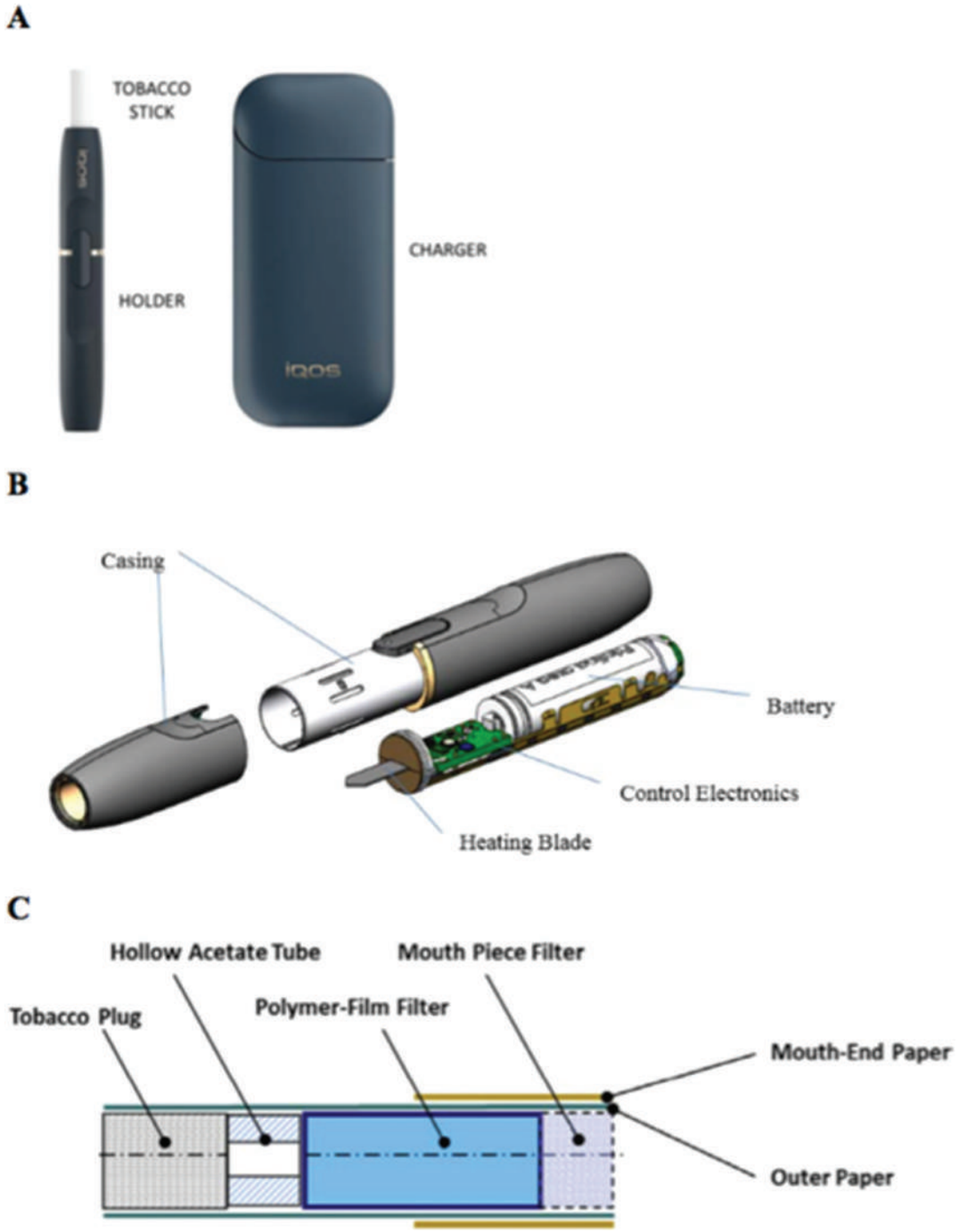


Figure 1 (A) The Philip Morris International IQOS charger, holder and HeetStick (tobacco stick). (B) Schematic drawing of holder. (C) Schematic of HeetStick tobacco stick.[10]

application to compare IQOS to Accord, an earlier HTP that PMI unsuccessfully marketed in the USA and Japan in 1998 and 2006, respectively. PMI's public statements seemed contradictory, claiming that Accord reduced exposure to harmful constituents while consistently emphasising that the reductions did not mean Accord was safer than conventional cigarettes. In terms of aerosol chemistry, Accord had lower levels than IQOS of some toxicants and higher levels of others. PMI appears to be capitalising on the MRTP process to make reduced exposure claims for IQOS despite the fact that overall toxicant exposures are not, on average, different than Accord.

Discussion of HTP (as well as e-cigarettes) has focused on cancer even though cardiovascular and metabolic disease kill about as many smokers as cancer.[27] Unlike cancer, the dose–response relationship for cardiovascular effects is highly non-linear, with large effects at low doses.[28] An important pathway through which tobacco use increases the risk of heart disease is by impairing the ability of arteries to enlarge when needed to accommodate increases in blood flow (flow mediated dilation, FMD). Nabavizadeh *et al*[29] tested whether exposure to IQOS aerosol impaired FMD in a well-established experimental model in which rats inhale IQOS aerosol from a single

Table 1 Availability of heated tobacco product by major cigarette company and country of availability (January 2018)

Company	Product	Year launched	Countries/comments
British American Tobacco	iFuse* glo	2015 2016	Romania, Japan, Switzerland, Canada, South Korea, Russia.
China National Tobacco Corporation/State Tobacco Monopoly Administration (STMA)	Not reported	Not launched	A few of the companies claim to have over 30 patents of HTP and continue to be engaged in research and development of these products. But none yet are in the market.
Imperial Brands	Not reported	Not launched	Focusing on e-cigarettes at the moment, claims to have options to launch when it deems that time is right.
Japan Tobacco International	Ploom TECH†	2016	Japan, Switzerland.
KT&G Corp	lil	2017	South Korea
Philip Morris International‡	IQOS TEEPS§	2014 Not yet launched	Canada, Guatemala, Colombia, Czech Republic, Denmark, France, Germany, Greece, Israel, Italy, Kazakhstan, Lithuania, Monaco, Netherlands, Poland, Portugal, Romania, Russia, Serbia, Slovak Republic, Slovenia, Spain, Switzerland, Ukraine, United Kingdom, South Africa, South Korea, Japan, New Zealand.

Source: Bialous and Glantz.[49]

*It is unclear that iFuse will remain in the market in Romania, where glo was introduced in 2018.

†Ploom TECH is described as a hybrid between an HTP and a vaporiser. It is to be used with Mevius capsules. Mevius is one of JTI's best-selling cigarette brands. The capsules contain tobacco that are then heated by vapour.

‡PMI website states that it is developing a new heated nicotine delivery product that has no tobacco, STEEM, among other 'reduced risk' products.

§We do not know what TEEPS stands for, it is not included in the product's description (https://www.pmi.com/smoke-free-products/teeps-carbon-heated-tobacco-product).

HTP, heated tobacco product; JTI, Japan Tobacco International;PMI, Philip Morris International.

HeetStick (the IQOS tobacco stick), mainstream smoke from a single Marlboro Red cigarette, or clean air. In contrast with PMI's application claiming that IQOS causes less impairment than conventional cigarettes, Nabavizadeh *et al*[29] showed IQOS aerosol's acute effects impaired vascular endothelial function (measured with FMD) comparably with cigarette smoke.

Moazed *et al*[30] found data in PMI's application raising significant concerns about IQOS' pulmonary effects. Rats exposed to IQOS suffered pulmonary inflammation and immunomodulation. Although PMI did not report any direct measures of pulmonary inflammation in humans, they measured pulmonary function and found no evidence of improvement in cigarette smokers who switched to IQOS. PMI's application also ignores the effect of dual use and secondhand aerosol exposure.

Independent research confirmed adverse effects of IQOS aerosol on lung cells. Leigh *et al*[31] exposed human bronchial epithelial cells in vitro to aerosols from three PMI products: IQOS (tobacco flavour), an e-cigarette (MarkTen, tobacco flavour) and a conventional cigarette (Marlboro Red) at comparable nicotine levels at the air–liquid interface. IQOS showed significantly higher cytotoxicity than e-cigarettes, but less than combustible cigarettes. These observations have important legal implications in the USA because to authorise marketing IQOS with reduced risk claims, the FDA would have to find that IQOS would benefit the public health and significantly reduce harm or reduce exposure to harmful substances 'compared to the similar types of tobacco products then on the market' (FSPTCA section 911(g)(2)(B)(ii)), and e-cigarettes were currently on the market at the time that PMI submitted its application.

Reinforcing the need to compare HTP to e-cigarettes rather than cigarettes, Leigh *et al*[32] compared the levels of carcinogenic tobacco specific nitrosamines (TSNA) in IQOS aerosols to MarkTen e-cigarettes and Marlboro Red 100 conventional cigarettes at comparable nicotine delivery levels. TSNA yields per puff in IQOS aerosol was an order of magnitude lower than in Marlboro cigarette smoke, but an order of magnitude higher than in MarkTen e-cigarettes. In short, IQOS does not reduce exposure to these important carcinogens nearly as much as e-cigarettes.

Most discussion of the toxicants in non-cigarette tobacco products compare them to cigarettes on the assumption that if the non-cigarette products deliver lower levels of toxicants than cigarettes, the products would be less dangerous. However, St Helen *et al*[33] found that PMI's data only support its claim that IQOS reduces exposure to some (40 of 93) harmful and potentially harmful constituents (HPHCs) identified by the FDA. PMI's data also show significantly higher levels of many toxicants not on the FDA HPHC list in IQOS aerosol compared with cigarette smoke, with 22 over twice as high and 7 over 10 times higher. Therefore, it is important to expand chemical assessment of emissions from HTP and other new tobacco products beyond those found in cigarette smoke.

It is possible that HTP could cause some diseases not caused by conventional cigarettes. Chun *et al*[34] identified animal and human studies in PMI's application suggesting that IQOS may cause liver toxicity not observed in cigarette users. PMI compared liver toxicity in rats exposed to IQOS or cigarette smoke, and found that several measures of liver toxicity (liver weights, blood levels of alanine aminotransferase and hepatocellular vacuolisation) increased more in female (but not male) rats exposed to IQOS than cigarettes. PMI's human clinical data also suggested the possibility of increased liver injury in one of their studies: following 5 days of using IQOS, conventional cigarettes, or smoking abstinence, plasma bilirubin was higher in IQOS users than conventional smokers or abstainers. PMI Science posted a response to this paper on its website stating that "based on an analysis of our toxicological studies and clinical studies performed according to international standards of good practice, there is *no evidence* that IQOS use leads to hepatotoxicity [emphasis added]."[35] In contrast to this unequivocal statement, the point that Chun et al make is not that the data PMI submitted to the FDA prove hepatotoxicity, but that the combination of animal data and some of the human data constitute a pattern worth careful consideration, especially in light of the short duration of the studies and lack of additional potential insults to the liver including alcohol use and other drug use that is common in smokers.

IQOS (and likely HTP generally) are simply *different* from conventional cigarettes and deliver less of some toxicants and more of others, so that IQOS may pose lower, the same or higher health risks than cigarettes depending on the disease. IQOS emits more of several important toxins with more adverse health effects than e-cigarettes.

PERCEPTIONS OF THE PRODUCT AND WARNING LABELS

Despite the evidence discussed above, in 2018 IQOS and other HTP were being marketed around the world with claims that they are less harmful than cigarettes because they expose users to lower levels of some toxicants. Popova *et al*[36] examined the qualitative and quantitative Perception and Behavior Assessment Studies in PMI's application which revealed that consumers perceive even reduced exposure claims as reduced risk claims. Allowing PMI to promote IQOS with reduced exposure claims would amount to permitting the kind of 'light' and 'mild' fraud that the FSPTCA and WHO Framework Convention on Tobacco Control (FCTC) expressly prohibit for other tobacco products.

This misunderstanding of reduced exposure as reduced risk bears directly on how IQOS should be labelled so as not to mislead consumers. McKelvey *et al*[37] examined PMI's application focusing on the statements that switching completely from cigarettes to IQOS reduces risk. PMI failed to demonstrate that current smokers will understand what 'switching completely' means, and therefore failed to demonstrate that their IQOS will not decrease smokers' intentions to quit smoking, or that IQOS users will 'switch completely' (PMI's other studies showed most people use IQOS and cigarettes concurrently, so-called dual users.) Additionally, PMI's study design and measurement instruments suffered design flaws, and their reporting of associated findings is misleading. Experience with other products such as e-cigarettes suggests consumers will not understand that they must completely quit smoking cigarettes to achieve the claimed health benefits of IQOS. Rather, consumers will likely misunderstand unsupported claims of reduced risks to mean IQOS are risk-free.

Independently confirming PMI's results, El-Toukhy *et al*[38] examined the impact of reduced exposure and reduced harm MRTP claims in a national sample of US adults and adolescents. They found that communicating lower risk in MRTP claims led to lower perceived risk among adults and adolescents and increased the likelihood that adults would use the product. Reduced exposure claims led to lower perceived chemical quantity and lower perceived risk, but had no effect on likelihood of product use. Adults and adolescents misinterpreted reduced exposure claims as communicating lower risk, even when no explicit reduced risk claims were made. Because reduced exposure MRTP claims are not permissible under US law if they mislead the public to believe the product presents less risk of harm, these studies demonstrate that reduced exposure claims for IQOS are impermissible.

These concerns are particularly acute for adolescents who are susceptible to using novel tobacco products. E-cigarettes provide a cautionary tale for any new tobacco product coming to market: e-cigarettes have attracted youth at low risk of initiating nicotine use with cigarettes,[39] many of whom then proceed to cigarettes.[40] McKelvey *et al*[41] found that PMI's application failed to provide any evidence regarding the effect IQOS and its marketing will have on the likelihood that adolescents who are not tobacco users or who are former tobacco users will start nicotine use with IQOS. Instead, PMI conducted studies of adults that relied on 'behavioural intention' as a proxy to predict IQOS use, ignoring evidence that these models do not accurately predict tobacco use. Of added concern, the IQOS name, packaging and retail shops resemble popular cell phones that attract youth.[42] PMI's data and independent scientific studies regarding novel tobacco products (including e-cigarettes) marketing suggest IQOS will attract adolescent and young adult non-users to initiate tobacco use with IQOS and could also increase polyuse of different tobacco products.

Hair *et al*[43] examined IQOS marketing in Japan and Switzerland and studied consumer perceptions, attitudes and behaviours. Expert interviews and IQOS packaging and marketing analyses revealed that IQOS was marketed as a clean, chic and pure product which resonated in cultures that value cleanliness, exclusivity and high-tech appearances. Japanese consumers used IQOS for socialising with non-smokers. Focus group participants in both Japan and Switzerland reported lower levels of satisfaction with IQOS than cigarettes, although many found the packaging appealing. Few participants reported potential health benefits compared with cigarettes.

PMI introduced IQOS to Korea in May 2017. Three months later, Kim *et al*[44] conducted an online survey of young adults including current, ever and non-users. Rather than switching from conventional cigarettes to IQOS, all current IQOS users continued to use cigarettes or e-cigarettes. There were no IQOS-only users. Current users believed IQOS less harmful or useful to stop smoking. The observation that all the current IQOS users were dual users of conventional cigarettes or e-cigarettes contradicts PMI's assumption that cigarette smokers would switch to HTP.

As of July 2018, the FDA had not authorised HTP for sale in the USA, but awareness and use were increasing. Nyman *et al*[45] assessed awareness and use of HTP in the USA. From 2016 to 2017, adult awareness of HTP increased from 9.3% to 12.4%, ever use increased from 1.4% to 2.2% and current use doubled from 0.5% to 1.1%. Non-white adults, cigarette smokers, and both current and former users of e-cigarettes were more likely to use HTP.

POLICY, POLITICS AND LAW

Tobacco companies have promoted 'harm reduction' for decades. Although tobacco harm reduction proponents take British psychologist Michael Russell's 1976 idea that 'people smoke for nicotine but they die from the tar'[46] as an article of faith, he simply presented it as a 'hypothesis'. Elias and Ling[47] examined tobacco industry documents and found that Russell collaborated with BAT on two 'safer cigarette' studies and received £55 000 (£300 850 or $398 000 in 2018) to study medium-nicotine low-tar cigarettes. The most prominent early HTP was RJ Reynolds' (RJR) Premier, introduced in the USA in 1988. Russell engaged extensively with RJR about Premier's 'positive aspects' and published an unsigned 1991 *Lancet* editorial[48] endorsing Premier as a 'near-perfect low tar cigarette' 2 years after RJR stopped marketing Premier without disclosing his conflict of interest. Although Premier failed, RJR saw future business opportunities for novel products if endorsed by health authorities, making conflicts of interest highly important considerations in assessing product endorsements, including those published by high-impact medical journals.

It is important to consider HTP in the context of multinational tobacco companies' product mix and response to the tightening regulatory environment promoted by FCTC. Bialous and Glantz[49] describe how HTP extend the industry's strategies to undermine government regulation by reframing tobacco companies from part of the problem to part of the solution. Under the 'harm reduction' moniker, companies are attempting

to rehabilitate their reputations to more effectively influence governments to roll back existing tobacco control policies or create exemptions for HTP. Where regulations are absent or loopholes exempt HTP from existing regulations, companies' market HTP to increase social acceptability for all their tobacco products. Governments must ensure that HTP are regulated or banned, and reject partnerships with tobacco companies to promote 'harm reduction'. Doing so requires governments in countries where HTP are not available to keep them out or, if allowed in the market, strictly regulate them under the FCTC.

Israel illustrates how PMI took advantage of regulatory ambiguity to implement an aggressive campaign promoting IQOS as safer than conventional cigarettes. Rosen and Kislev[50] describe how PMI promoted IQOS as part of its 'Smoke-Free Israel vision' after launching IQOS in December 2016. The campaign began with quiet pre-market meetings with government officials, followed by meetings in Israel's Parliament and an intense campaign in the printed press to promote harm reduction and PMI's 'Smoke-Free Israel vision'. The public campaign included digital and print marketing aimed at young people to promote PMI's 'Smoke-Free Israel vision' and harm reduction using the theme 'IQOS Changes Everything', that stressed IQOS was clean with less smell and no ash. PMI's campaign initially resulted in IQOS' exemption from tobacco regulations. These policies were later reversed after three petitions to the Supreme Court, pressure from health organisations and leading politicians, and wide press coverage of PMI's influence on Parliament's decision-making process. Israel's weak and poorly enforced advertising restrictions, however, have allowed PMI to continue its marketing claims.

In determining whether any new tobacco product may be sold, including HTP, the FDA must consider the product's overall population health impact. Importantly, in addition to any changes in specific toxicity for current smokers who switch from cigarettes to HTP, the availability of HTP affects nicotine and cigarette initiation and cessation. For products that have not been on the market to empirically answer these questions, modelling is an important element of the decision-making process. Max *et al*[51] evaluated PMI's Population Health Impact Model (PHIM), as used in its application, in comparison with other available models. Although similar to many published models, PHIM includes assumptions likely to lead to a positive assessment of IQOS' population health impact. PHIM does not consider impacts on morbidity, underestimates mortality, does not include impacts on non-users, ignores the impact of IQOS on nicotine product initiation among never smokers and does not use the latest US data to set the model's parameters. Because PHIM systematically underestimates the impact of IQOS on the population as a whole, it cannot adequately justify marketing IQOS as 'appropriate to protect public health'.

The most important change in the policy environment since the tobacco companies were last actively promoting HTP in the 1980s and 1990s is the advent of formal regulatory regimes for tobacco products through the FSPTCA in the USA and the FCTC globally. Lempert and Glantz[52] analysed laws and obligations that apply to the introduction, labelling and marketing of IQOS under FSPTCA and FCTC. PMI's premarket tobacco application and MRTP application for IQOS do not meet FSPTCA requirements on reduced harm or net public health benefit. The FDA can only authorise sale of new products through the new tobacco product pathway that are better for public health than products currently on the market, and e-cigarettes, currently sold in the USA, should probably be the comparator product. FCTC obligates parties to implement laws to reduce tobacco use and nicotine addiction, and the introduction of any new tobacco product must be assessed against this goal. PMI's aggressive marketing techniques for IQOS using targeted customer interventions and sophisticated technologies to capture data and monitor use directly from the IQOS device via the internet[53] should concern privacy and public health advocates. Moreover, nothing in the US law or FCTC prevents authorities from prohibiting HTP. If not banned, all HTP components should be regulated as stringently as tobacco products, including restrictions on labelling, advertising, sales to minors, price and taxation policies, and smoke-free measures, and these laws should be aggressively enforced.

CONCLUSION

HTP are the latest effort by tobacco companies to adapt to a changing regulatory landscape to maintain and expand their customer base amid declining social acceptability of tobacco use and declining cigarette consumption. IQOS and other HTP are the newest in a long string of products designed to retain customers and protect tobacco companies' reputations and political influence. Because US law required PMI to provide detailed results of their IQOS research for its MRTP application, it was possible to independently assess their research. PMI's own data do not support its claims that IQOS is less dangerous than cigarettes. While IQOS may expose users to lower levels of some toxicants than cigarettes, they also expose users to higher levels of other toxicants. Likewise, IQOS likely exposes users to lower risks of some diseases and higher risks of others. PMI's research, confirmed by independent research, also highlights the fact that reduced exposure claims are misunderstood as reduced harm claims. These facts raise serious concerns that HTP and their marketing will harm youth and young adults and undermine cessation among smokers without providing health benefits to smokers who use them.

Fortunately, regulatory tools are in place to make rational, evidence-based decisions about these products. The question is whether public health advocates will ensure that policy-makers prioritise protecting public health and prevent tobacco companies from again using their extensive public relations and political resources to avoid regulation and protect profits. Policy makers should give greater weight to the advice provided by public health scientists than to submissions from industry when it comes to regulating tobacco products such as HTP.

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Heated tobacco products: things we do and do not know

Irina Stepanov,[1] Alistair Woodward[2]

[1]Masonic Cancer Center and Division of Environmental Health Sciences, University of Minnesota, Minneapolis, Minnesota, USA
[2]Department of Epidemiology and Biostatistics, University of Auckland, Auckland, New Zealand

Correspondence to
Dr Irina Stepanov, Masonic Cancer Center and Division of Environmental Health Sciences, University of Minnesota, Minneapolis, MN 55455, USA; stepa011@umn.edu

This Special Issue is focused on IQOS, electronic devices that offer yet another nicotine delivery alternative to smoking regular tobacco cigarettes. IQOS are designed to heat rather than burn tobacco, and represent somewhat of a hybrid of a regular cigarette and an electronic cigarette. Little is known about the toxicity and the public health impact of these products, relative to both the combustible cigarettes and other nicotine delivery products. Nevertheless, IQOS and other heated tobacco products (HTPs) are gaining popularity in some countries, caused in large part by the manufacturer's aggressive advertising and assertions that these devices are safe.

Most in the public health world would agree that the best evidence-based approaches should be applied to reduce death and illness due to tobacco use. Such approaches may include supporting addicted tobacco users to move to alternatives that are less harmful and truly reduce the population burden of tobacco diseases. It is important to bear in mind these two goals – alternative tobacco delivery devices may be less risky than combustible cigarettes for the individual smoker, but if they do not lead to a reduction in the prevalence of smoking there is no gain for public health.

What do we know about the safety of IQOS and the effect that introduction of these devices may have on smoking rates and the population burden of disease and premature mortality? Unfortunately information about IQOS and similar products is, at present, largely limited to industry reports. These include observations from marketing and data from product toxicity and human exposure studies. The papers in this Special Issue take a close look at the industry material, as well as the limited emerging academic literature on HTPs. The findings in broad terms are not terribly surprising. Data are scarce, and in particular, there are no long-term studies in human populations of the consequences of use of IQOS. Nevertheless an addictive product is being promoted by over-emphasising (or in some cases exaggerating) the limited evidence for its capacity to reduce harm, while minimising evidence on its potential toxicity. A sceptical view, conditioned by history, would be that this may be part of strategic efforts by the industry to retain existing consumers of tobacco products and generate new lifelong nicotine-dependent users. We offer some suggestions about what we do not know at present about IQOS, but need to understand to best inform tobacco control policies.

Research independent of the industry is required to inform product users, public health professionals, and regulatory agencies about the potential public health impact of IQOS and other HTPs. In addition, if reports of research studies are submitted by the industry to regulatory agencies, there must be careful analysis of raw laboratory data to ensure the results are well tested and appropriately interpreted.

The chemical profile and toxicity of IQOS and other HTPs must be thoroughly investigated. It is critical to understand where these products are positioned along the continuum of risk relative not only to combustible cigarettes but also to other nicotine delivery devices that may have lower toxicity profile, such as e-cigarettes. Unlike e-cigarettes, HTPs do contain tobacco and therefore, even in the absence of combustion, are expected to deliver to their users thousands of chemicals that are present in the tobacco material. Moreover, some of the tobacco chemicals that would be partially or completely decomposed during the combustion process may be present in the emissions of HTPs. Thus, it is possible that HTPs deliver to their users a unique chemical mixture with a distinct toxicity profile. As the result, the benefits of reductions in exposure to some of the 'usual suspects', such as polycyclic aromatic hydrocarbons, may be attenuated by new health risks. Lastly, similar to e-cigarettes, IQOS and other HTPs contain substantial amounts of propylene glycol that is aerosolized when the device is in use. Oxidative stress and inflammation, some of which is most likely driven by exposures to the products of thermal decomposition of propylene glycol, are emerging as key concerns in assessing the long-term health consequences of e-cigarette use. It seems likely that users of HTPs will face similar risks, if these do indeed apply.

Characteristics of current and potential users of HTPs need to be taken into consideration while assessing the potential public health impact of these products. The concept of the continuum of harm often focuses on the toxicity profile of the product, as compared with cigarette smoke and isolated from the characteristics of the user. Similar to e-cigarettes, the relative harmfulness of HTPs may be greatly affected by whether or not a user is a former smoker, uses the product together with continued smoking of regular cigarettes, has significant co-morbidities (cardiovascular and lung diseases in particular), or a propensity to become a life-long nicotine-dependent user.

It is important to understand what HTPs will do to the prevalence of smoking. In the absence of substantial, reliable data, decisions about products such as IQOS are an exercise in risk management. On the one hand, there is the possibility of foregoing benefits (if there is a true, net reduction in harm), on the other the prospect of inflicting serious risks to health. How this balancing act is viewed will depend to some extent on context. Where the

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prevalence of smoking is already low and falling, a conservative approach to new tobacco products is understandable. Where prevalence is high, and in some population groups is hardly budging despite concerted effort, then there may a greater willingness to explore alternatives to the combustible cigarette.

Finally, we note that current smokers who are concerned about their health risks and can afford electronic tobacco or nicotine delivery devices represent only a fraction of the tobacco industry's total consumer base. Regular tobacco cigarettes are still being aggressively marketed to low-income markets worldwide, contributing to sustained tobacco consumption and the narrative of demand-driven cigarette manufacturing and sales. Once again, a history-conditioned sceptical view would be that marketing of products like IQOS is just a new way to appeal to a wider variety of nicotine consumers. Will the industry attempt to maintain their diverse consumer base by whatever means available? The most likely answer is yes, because this is what it takes to stay in the business of tobacco.

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PMI's own in vivo clinical data on biomarkers of potential harm in Americans show that IQOS is not detectably different from conventional cigarettes

Stanton A Glantz[1,2]

[1]Department of Medicine/Division of Cardiology, University of California San Francisco, San Francisco, CA 94143-1390, USA
[2]Center for Tobacco Control Research and Education, University of California San Francisco, San Francisco, CA 94143-1390, USA

Correspondence to
Professor Stanton A Glantz, Department of Medicine/Cardiology, University of California San Francisco, San Francisco, CA 94143-1390, USA; glantz@medicine.ucsf.edu

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ABSTRACT

Introduction New 'heated tobacco products' are being marketed in several countries with claims that they expose users to lower levels of toxins than conventional cigarettes which could be read as being less likely to cause health problems than conventional cigarettes. In the USA, Philip Morris International (PMI) has submitted an application to the Food and Drug Administration for permission to market its heated tobacco product, IQOS, with reduced exposure and reduced risk claims.

Methods Analysis of detailed results on 24 biomarkers of potential harm in PMI studies of humans using IQOS compared with humans using conventional cigarettes.

Results Among American adults, there is no statistically detectable difference between IQOS and conventional cigarette users for 23 of the 24 biomarkers of potential harm in PMI's studies. In Japan, there were no significant differences between people using IQOS and conventional cigarettes in 10 of 13 biomarkers of potential harm. It is likely that some of the significant differences are false positives.

Conclusion Despite delivering lower levels of some toxins than conventional cigarettes, PMI's own data fail to show consistently lower risks of harm in humans using its heated tobacco product, IQOS, than conventional cigarettes.

INTRODUCTION

Nicotine is the addictive drug in tobacco. Burning the tobacco generates an aerosol of ultrafine particles that carries nicotine deep into smokers' lungs, where it is absorbed and rapidly reaches the brain. That burning yields toxic chemicals that cause disease. Ever since people started understanding in the 1950s that smoking kills, millions have struggled to stop smoking. The tobacco companies, desperate to keep and expand their customers, have been trying to make 'safer cigarettes' since the 1960s.[1] They have also developed products that avoided burning, including e-cigarettes,[2] nicotine replacement therapy,[3] and products that heat the tobacco without setting it on fire. As of January 2018 all the major multinational tobacco companies had developed, or were in the process of developing, so-called 'heated tobacco products' (HTP; also called 'heat-not-burn' tobacco products). Because these devices generate their nicotine aerosols by heating a stick of ground tobacco and chemicals without setting the tobacco on fire, they generally produce fewer toxic chemicals than a conventional cigarette, which is promoted as meaning or implying that these products are not as dangerous as conventional cigarettes.

In 2015, Philip Morris International (PMI) started test marketing its IQOS HTP outside the USA on the grounds that it is not as bad as a cigarette because 'the tobacco is heated and not burned, the levels of harmful chemicals are significantly reduced compared to cigarette smoke.'[4]

Because IQOS is a new tobacco product, PMI needs to obtain premarket authorisation from the US Food and Drug Administration (FDA) to sell it in the USA. In particular, PMI wants to market IQOS with reduced risk claims, what US law calls a 'modified risk tobacco product' (MRTP). To obtain authorisation to market IQOS with reduced risk claims, PMI submitted an application to the FDA in December 2016.[5] As required by law, FDA has made most of the application available for the public to review. The application includes comparisons of the levels of 24 biomarkers of potential harm in human smokers, including comparisons with people who smoke conventional cigarettes. These biomarkers include measures of inflammation, oxidative stress, cholesterol and triglycerides, blood pressure and lung function. This paper uses information in the PMI application to evaluate this comparison and concludes that in people who actually use IQOS, the levels of these biomarkers of potential harm are not detectably different from conventional cigarettes.

METHODS

The results analysed in this paper are from PMI's 'Three-month Reduced Exposure in a confined and ambulatory setting' studies (ZRHR-REXA-07-JP in Japan and ZRHM-REXA-08-US in the USA) that present human clinical studies of non-cancer biomarkers of potential harm presented in PMI's MRTP application's[5] Executive Summary, Module 6: Summaries of All Research Findings, and Module 7.3.1: Scientific Studies and Analyses (Studies in Adult Human Studies: Clinical Studies), specifically the data on 24 biomarkers of potential harm *in human users* derived from two of their 'Reduced Exposure' studies: ZRHR-REXA-07-JP in Japan and ZRHM-REXA-08-US in the USA.

As described in Section 6.1.4.3.2 of the application, cigarette smokers were randomised, controlled, open-label, three-arm parallel group studies in which smokers were randomised to IQOS (menthol), continued smoking their current brand of cigarettes or smoking abstinence. Baseline data were collected on day 0 immediately before randomisation, people were held during a 5-day confinement period then released to the ambulatory setting and observed at 90 (±3 (range)) days

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after randomisation. (Some variables were measured during confinement and before 90 days, but are not considered in this analysis.) During the confinement period, product use was directed and monitored by the study staff and participating smokers were controlled for product compliance. Subjects assigned to conventional cigarettes or IQOS used the products without restriction (ad libitum) during an extended daily time window (16 hours); dual use of conventional cigarettes and IQOS was not permitted. The 3-month ambulatory phase was designed to reflect a near real-world environment where dual use of IQOS and conventional cigarettes or other tobacco products could occur. PMI selected a 3-month extended ambulatory follow-up period so that the study would be long enough to assess the initial changes in some of the clinical risk endpoints that have been shown to be reversible within 2 weeks to 3 months.

The final sample (table 1) consisted of people who were adherent with their assigned study product and without major protocol deviations that impacted the validity of the evaluation of the study results. This sample was designed to assess the maximum exposure reduction achievable (what PMI characterised as the 'optimal effect') in subjects who were using IQOS ad libitum and exclusively or at least predominantly, rather than the effect in the full population representing a heterogeneous exposure (eg, as mixed product use, or non-use of the assigned product).

The point estimates and 95% confident intervals (CIs) at day 90 were computed using least squares means from an analysis of covariance with study arm as a factor adjusting for baseline value, sex and average daily conventional cigarette consumption over the last 4 weeks as reported during screening. (Thus, the width of the CIs for the differences between IQOS and conventional cigarette use in table 1 benefits from the information in the smoking abstinence group even though those subjects are not directly involved in the point estimates being compared.) Endpoints that were not normally distributed were log-transformed (base e) prior to analysis, then back-transformed to calculate least squares means ratios to compare IQOS with conventional cigarettes.

Both trials were registered with ClinTrials.gov.

Specific results are based on measures of inflammation in Section 6.1.4.4.2; cholesterol, triglycerides and physiological measures related to heart disease in Section 6.1.4.4.4; and lung function in Section 6.1.4.4.5.

RESULTS

Among American adults, there is no statistically detectable difference between IQOS and conventional cigarettes for 23 of the 24 biomarkers of potential harm in PMI's studies (table 1). This is indicated by the fact that 23 of the 95% CIs include zero (ie, no statistically significant difference). Moreover, when using the conventional 95% confidence standard for statistical hypothesis testing, one would expect 5% of the tests to yield false positives. Five per cent of 24 tests is 1.2 tests, which means that one would expect one false positive result. PMI had one positive result (soluble intercellular adhesion molecule (ICAM)), which is what one would expect by chance.

PMI also reported the results on 13 biomarkers of potential harm among Japanese people (table 1). There were significant improvements in 4/13 of these biomarkers, 3 markers of inflammation (white cell count, prostaglandin F2 alpha and soluble ICAM) and 1 measure of cholesterol (high-density lipoprotein cholesterol). When using the conventional 95% confidence standard one would expect 0.65 positive tests, which means one would expect one false positive test.

Table 1 Summary of Philip Morris studies of changes in biomarkers in IQOS users compared with conventional cigarette smokers after 90 days of product use (95% CIs in parenthesis)

	Japan	USA
Inflammation (6.1.4.4.2**)		
White cell count	**−0.57 GI/L (−1.04 to −0.10)**	0.17 GI/L (−0.47 to 0.81)
C-reactive protein (CRP)	6.41% ↓ (−40.75 to 37.77)	16.23% ↓ (−21.69 to 42.33)
Soluble ICAM (sICAM-1)	**8.72% ↓ (2.05 to 14.94)**	**10.59% ↓ (4.03 to 16.71)**
Fibrinogen	5.42% ↓ (−1.80 to 12.13)	1.63% ↓ (−6.42 to 9.08)
Oxidative stress (6.1.4.4.3)		
Prostaglandin F2 alpha (8-epi-PGF2α)	**12.71% ↓ (2.55 to 21.81)**	13.46% ↓ (−1.95 to 23.61)
11-dehydrothromboxane B2 (11DTXB2)	5.42% ↓ (−1.80 to 12.13)	3.56% ↓ (−23.31 to 24.57)
Cholesterol and triglycerides (6.1.4.4.4)		
High-density lipoprotein cholesterol (HDL-C)	**4.53** mg/dL **(1.17 to 7.88)**	1.4 mg/dL (−2.3 to 5.0)
Low-density lipoprotein cholesterol (LDL-C)	0.87 mg/dL (−6.55 to 8.30)	−3.3 mg/dL (−12.0 to 5.4)
Total cholesterol	2.00 mg/dL (−6.68 to 10.67)	−4.0 mg/dL (−13.3 to 5.2)
Triglycerides	−6.25 mg/dL (−21.20 to 8.69)	0.9 mg/dL (−12.8 to 14.6)
Apolipoprotein A1 (apoA1)	NA	3.1 mg/dL (−4.6 to 10. 7)
Apolipoprotein B (apoB)	NA	−1.6 mg/dL (−7.24 to 4.03)
Physiological measures		
Systolic blood pressure	−0.59 mm Hg (−3.80 to 2.62)	−0.7 mm Hg (−4.5 to 3.1)
Diastolic blood pressure	−0.68 mm Hg (−3.04 to 1.69)	0.2 mm Hg (−3.7 to 4.0)
Lung function (6.1.4.4.5)		
Forced expiratory volume in 1 s (FEV_1)	1.91 %Pred (−0.14 to 3.97)	0.53 %Pred (−2.09 to 3.00) 0.05 L (−0.06 to 0.15)
FEV_1/FVC (forced vital capacity)	NA	0.00 (−0.02 to 0.02)
Mid-expiratory flow (MEF 25–75) (L/s)	NA	−0.67 (−6.33 to 4.99)
Diffusion capacity for lung CO (DLCO) (mL/min/mm Hg)	NA	0.31 (−1.09 to 1.72)
Rate constant of CO (KCO) (mmol/min/kPa/L)	NA	0.05 (−0.02 to 0.12)
Total lung capacity (TLC) (L)	NA	0.09 (−0.25 to 0.43)
Functional residual volume (FRV) (L)	NA	−0.09 (−0.31 to 0.13)
Inspiratory capacity (IC) (L)	NA	0.21 (−0.08 to 0.51)
Vital capacity (VC) (L)	NA	0.10 (0.00 to 0.21)
Summary		
Number of biomarkers tested	13	24
Number significantly improved	3	1
Number expected by chance	1	1

Continued

Table 1 Continued

	Japan	USA
Sample sizes		
IQOS	70	47†
Conventional cigarettes	41	32‡
Smoking abstinence	37	9§

The results are either IQOS:CC or IQOS-CC (conventional cigarettes).
Bold results are statistically significant differences (p<05).
*Section of Philip Morris International's Modified Risk Tobacco Product application.
†n=45 for fibrinogen, 8-epi-PGF2α, 11DTXB2, systolic blood pressure, diastolic blood pressure, DCLO and KCO.
‡n=30 for FEV_1, FEV_1/FVC, MEF 25–75, DLCO, KCO, TLC, FRV, IC and VC.
§n=8 for DLCO and 7 for KCO.
ICAM, intercellular adhesion molecule; NA, not applicable.

DISCUSSION

These human data are important information because they represent direct evidence on how IQOS affects people who use the product. They show that, despite the evidence that PMI submitted that the levels of some toxins in IQOS aerosol are lower than in conventional cigarettes,[5] fewer toxic chemicals, however, do not necessarily translate into lower harm when people use the product.

In its MRTP application, PMI did not discuss the results of the conventional statistical tests described in the Results section, which are routine for such scientific analysis. Rather, they simply emphasise the direction of changes while ignoring the fact that these differences are within what would be expected based on simple randomness. No tobacco company would tolerate such assertions made by the FDA or other public health authorities.

The results reported in PMI's application (and in a published paper[6]) for Japan are slightly more positive for IQOS, with 4 of 13 biomarkers showing differences from conventional cigarettes (where one would expect one false positive by chance). These results are not strong enough to warrant drawing a conclusion of reduced risk. The conclusion of no significant difference on biomarkers of potential harm is based on taking PMI's results at face value despite the tobacco companies' (including Philip Morris) long record of manipulating the design, analysis and presentation of their published scientific studies <<ED: Citation should be "7-12" no "7-13".>>.[7–13]

Like cigarettes (and e-cigarettes), IQOS uses an aerosol of ultrafine particles to deliver the nicotine. These ultrafine particles cause heart and lung disease. The adverse health effects of these particles and many of the other toxins do not drop in proportion to reducing the dose, so even low levels of exposure can be dangerous.[13] This effect is why smoke-free environment laws are followed by big drops in heart attacks and other diseases despite the fact that secondhand smokers breathe in much less smoke that the smokers.[14] In addition, while the IQOS does not set the tobacco stick on fire, it heats it to 350°C (660°F), which is still hot enough to cause pyrolysis. There is already independent evidence that IQOS compromises functioning of arteries,[15] a key risk factor for heart disease and heart attacks, as badly as a cigarette.

The clinical studies that PMI reported appropriately did not include cancer because carcinogenic effects take much longer to be manifest than cardiovascular and pulmonary effects. Even if the levels of carcinogens delivered by IQOS are lower than conventional cigarettes on a per-puff basis, these lower exposure levels may not yield proportionately lower cancer risks because both the intensity and duration of exposure impact cancer risk.[16–18]

The purpose of this paper is to assess the data on biomarkers of potential harm of the Philip Morris IQOS HTP system in people who were actually using the system compared with people who smoke conventional cigarettes based on the information submitted to the US FDA in PMI's MRTP application for IQOS. On 31 March 2018, the author conducted a PubMed search using the search term '(IQOS or 'heat not burn' or 'heated tobacco product') and (health or harm) and (human or clinical)'. This search returned 33 papers, none of which reported on comparisons of in vivo biomarkers of potential harm in people using IQOS (or any other HTP system) compared with conventional cigarettes. Thus, as of 9 July 2018, the data in the PMI MRTP application remained the only publicly available evidence on the in vivo human clinical effects of IQOS compared with conventional cigarettes.

While this analysis is limited to the data presented in PMI's IQOS MRTP application to the FDA, it is likely that the effects of other HTPs being developed by other tobacco companies will have similar effects because the fundamental principles behind all these products are the same.

On 15 June 2018, PMI issued a press release, 'Philip Morris (PM) Announces Positive Results from New Clinical Study on IQOS,'[19] that said, 'all eight of the primary clinical risk endpoints moved in the same direction as observed for smoking cessation in the group who switched to IQOS, with statistically significant changes in five of the eight endpoints compared with on-going smoking.' While PMI did not release any detailed results, examining the protocol (on ClinicalTrials.gov) revealed that this new study only examined six clinical measures, compared with the 24 in MRTP application (table 1). (The other two were biomarkers of exposure.) PMI did not say which of the changes were statistically significant, raising the possibility that the protocol and analysis were manipulated to achieve positive results.[8 9] PMI increased the sample size from 88 in the original US study to 984. While bigger studies are better, the fact is that making the sample size big enough will increase the power to the point that almost any difference will reach statistical significance regardless of whether it is clinically significant or not. The true measure of reduced risk would be statistically significant changes that were large enough to be clinically significant in enough biomarkers of potential harm to be meaningful.

PMI's failure to show significant improvements in these biomarkers of potential harm is consistent with the data PMI reported on the levels of toxicants in IQOS mainstream aerosol compared with mainstream smoke of 3R4F reference cigarettes.[20] While many toxicants were lower in IQOS aerosol, 56 others were higher in IQOS emissions and 22 were more than twice as high, and 7 were more than an order of magnitude higher.

In short, PMI's results in humans failed to meet the legal requirement that IQOS 'as it is actually used by consumers, will significantly reduce harm and the risk of tobacco-related disease to individual users' that US law requires before the FDA can approve a reduced risk claim. In the USA, PMI wants to sell IQOS with claims that 'Scientific studies have shown that switching completely from cigarettes to the IQOS system can reduce the risks of tobacco-related diseases' and 'Switching completely to IQOS presents less risk of harm than continuing to smoke cigarettes'[5]; these claims are not substantiated by PMI's own data.

On 25 January 2018, based in part on the information in this paper (which had been submitted to FDA as a public comment) showing gaps in PMI's scientific evidence, the FDA's Tobacco Products Scientific Advisory Committee voted that PMI had failed to demonstrate that its proposed modified (reduced) risk labelling and advertising claims for IQOS were demonstrated by scientific evidence.[21]

Based on the data in the PMI MRTP application for IQOS, neither the US FDA nor comparable authorities elsewhere in

What this paper adds

- Heated tobacco products are being marketed in several countries with claims of reduced exposure to toxins compared with conventional cigarettes.
- Studies conducted in people using Philip Morris International's IQOS heated tobacco product did not reveal detectably better measures of biomarkers of potential harm than conventional cigarettes in human tests.
- These products should not be permitted to be marketed with claims that state or imply reduced risks compared with conventional cigarettes.

the world should permit such claims to be made. All companies wishing to market HTPs with reduced risk claims should be held to the same standard, and their claims independently verified.

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Data sharing statement All data are available in the PMI MRTP application on the FDA website.

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Vascular endothelial function is impaired by aerosol from a single IQOS HeatStick to the same extent as by cigarette smoke

Pooneh Nabavizadeh,[1] Jiangtao Liu,[1] Christopher M Havel,[2] Sharina Ibrahim,[3] Ronak Derakhshandeh,[1] Peyton Jacob III,[2,4] Matthew L Springer[1,3,4]

[1]Cardiovascular Research Institute, University of California, San Francisco, San Francisco, California, USA
[2]Division of Clinical Pharmacology and Experimental Therapeutics, University of California, San Francisco, San Francisco, California, USA
[3]Division of Cardiology, University of California, San Francisco, San Francisco, California, USA
[4]Center for Tobacco Control Research and Education, University of California, San Francisco, San Francisco, California, USA

Correspondence to
Dr Matthew L Springer, Division of Cardiology, University of California, San Francisco, San Francisco, CA 94143, USA; matt.springer@ucsf.edu

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ABSTRACT

Background Heated tobacco products (also called 'heat-not-burn' products) heat tobacco at temperatures below that of combustion, causing nicotine and other compounds to aerosolise. One such product, IQOS from Philip Morris International, is being marketed internationally with claims of harm reduction. We sought to determine whether exposure to IQOS aerosol impairs arterial flow-mediated dilation (FMD), a measure of vascular endothelial function that is impaired by tobacco smoke.

Methods We exposed anaesthetised rats (n=8/group) via nose cone to IQOS aerosol from single HeatSticks, mainstream smoke from single Marlboro Red cigarettes or clean air for a series of consecutive 30 s cycles over 1.5–5 min. Each cycle consisted of 15 or 5 s of exposure followed by removal from the nose cone. We measured pre-exposure and postexposure FMD, and postexposure serum nicotine and cotinine.

Results FMD was impaired comparably by ten 15 s exposures and ten 5 s exposures to IQOS aerosol and to cigarette smoke, but not by clean air. Serum nicotine levels were similar to plasma levels after humans have smoked one cigarette, confirming that exposure conditions had real-world relevance. Postexposure nicotine levels were ~4.5-fold higher in rats exposed to IQOS than to cigarettes, despite nicotine being measured in the IQOS aerosol at ~63% the amount measured in smoke. When IQOS exposure was briefer, leading to comparable serum nicotine levels to the cigarette group, FMD was still comparably impaired.

Conclusions Acute exposures to IQOS aerosol impairs FMD in rats. IQOS use does not necessarily avoid the adverse cardiovascular effects of smoking cigarettes.

INTRODUCTION

Heated tobacco products (also called 'heat-not-burn' tobacco products) heat tobacco at temperatures that avoid combustion but cause the nicotine to aerosolise. Philip Morris International's (PMI's) heated tobacco product IQOS is now marketed in at least 30 non-US countries and has been considerably more successful than similar products introduced at various times over the last three decades.[1] In 2017, Philip Morris Products S.A. submitted modified-risk tobacco product (MRTP) applications to the FDA to market IQOS in the USA with reduced risk claims.[2]

IQOS is composed of three main parts: HeatStick, holder and pocket charger (figure 1). HeatSticks, which contain long strips of processed and reformed tobacco packed together (figure 1), are inserted in the holder for use. The holder contains an electronic heating blade that is activated by pressing a side button on the holder and heats the mixture of tobacco and other compounds in the HeatSticks to 350°C. Aerosol is generated as the user inhales through the HeatStick/holder combination.

Despite harm reduction claims by the tobacco industry and the clinical and basic research reported by PMI researchers,[3–23] the cardiovascular health effects of IQOS and similar products are incompletely understood. Notably, industry-supported studies of potential cardiovascular consequences of IQOS aerosol exposure published to date have not included some common measures of adverse effects of smoke exposure, such as vascular endothelial function tested in vivo. As IQOS has been marketed widely, it is important to study the health effects of this product so that regulatory agencies such as the FDA and consumers can make informed decisions.

Endothelial function assessed by arterial flow-mediated dilation (FMD) is a validated measure of cardiovascular health effects and is defined as the per cent by which the arteries vasodilate in response to an increase in blood flow.[24] Endothelial cells lining the vessel sense increases in flow and respond by producing nitric oxide, which triggers the artery to grow in diameter to accommodate the increased demand. In humans, FMD is determined by temporarily interrupting and restoring blood flow to the forearm, and using ultrasound to measure the increase in brachial artery diameter caused by the resulting sudden increase in flow. FMD is a clinical prognostic indicator of endothelial function and cardiovascular health.[25–27] Acute and chronic exposures to secondhand smoke and active smoking impair FMD in humans.[28–31] While such studies have typically focused on exposure to smoke, one group has reported that exposure to e-cigarette aerosol can impair FMD,[32] raising the possibility that this effect is not limited to smoke from combustion and suggesting that inhalation of other non-combustible tobacco products may also have similar consequences.

We previously developed and validated an in vivo rat model for FMD measurements using high-resolution ultrasound and microsurgical techniques.[33] We showed that exposure of rats to sidestream smoke (from the smouldering tip; an accepted approximation of secondhand smoke) of cigarettes, little cigars and marijuana impairs FMD in an endothelium-dependent manner (endothelium-independent

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Figure 1 IQOS. IQOS is composed of three main parts: HeatStick, holder and pocket charger. HeatSticks are inserted in the holder, which contains an electronic heating blade to heat tobacco and release aerosol. HeatSticks contain strips of processed and reformed tobacco. Photos by MLS and PN.

vasodilation induced by nitroglycerin is not impaired).[34–36] The consistent responses of humans and rats to smoke and non-combustion aerosols from multiple sources led us to hypothesise that IQOS aerosol can similarly cause endothelial dysfunction. We report here that exposure to IQOS aerosol impairs FMD to the same extent as mainstream cigarette smoke.

MATERIALS AND METHODS

Animals

We used male Sprague-Dawley rats (Charles River, MI) at 8–10 weeks of age with body weights of 200–250 g as has been the standard condition for our previous studies on smoke exposure. Rats were anaesthetised with intraperitoneal injection of ketamine (100 mg/kg)/xylazine (5 mg/kg) for these experiments. During all procedures, rats were kept on a heating pad to prevent hypothermia. Frequency and depth of respiration were closely monitored to ensure full anaesthesia and supplemental intraperitoneal (IP) anaesthetic was given if necessary.

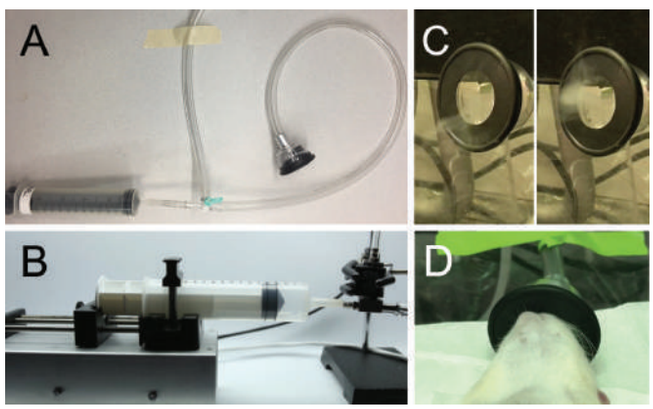


Figure 2 Aerosol generation and exposure systems. (A) Manual exposure system. (B) Analytical vaping machine made by Gram Research. (C) IQOS aerosol coming out of nose cone. (D) Rat's nose placed in the nose cone. Photos in A, C and D by PN; photo in B from Gram Research with permission.

Mainstream smoke/aerosol generation and exposure

Russian IQOS Parliament branded HeatSticks and an IQOS device from Ukraine were used for the first part of the project. Due to heating blade breaking incidences during cleaning, IQOS devices obtained from Japan and subsequently from South Korea were used for later exposures.

We exposed rats (n=8/group) via nose cone to IQOS aerosol, Marlboro cigarette mainstream smoke or clean air as control. The exposure regimen consisted of a series of consecutive 30 s cycles, each consisting of 15 or 5 s of exposure followed by removal of the nose cone for the rest of the 30 s interval. Each rat was exposed to either 10 cycles over 5 min or 3 cycles over 1.5 min, depending on the experiment, to approximate the consumption of a single IQOS HeatStick or less. To generate the aerosol and mainstream smoke, we used a manual syringe pump system for the initial experiment and then purchased a Gram Universal Vaping Machine version 5.0 (Gram Research, Oakland, California, USA) for the subsequent experiments (figure 2). The vaping machine contains an automatic syringe pump and has been shown to reproducibly generate aerosols from e-cigarettes under controlled conditions.[37] Both systems generated 35 mL of aerosol over 2 s and the vents on the side of the cigarette filters remained unoccluded. Separate sets of syringe pump, nose cone and connecting tubes and valves were used to avoid cross-contamination. The IQOS holder was fully cleaned and recharged after each use.

Endothelial function measurements

We used our previously established living rat model[33] to measure FMD before and after each exposure in individual animals.

We made a 1 cm incision on the rat's groin and surgically dissected around the common iliac artery. We then placed an arterial loop occluder consisting of a 5–0 Prolene filament under the artery and passed it through a 15 cm PE–90 tubing to enable transient occlusion of blood flow after suturing the skin. A series of diameter images of the femoral artery and accompanying Doppler blood flow images were recorded with a 35 MHz ultrasound transducer (Vevo660; VisualSonics, Toronto, Canada) before transient surgical occlusion at baseline. We induced a transient limb ischaemia for 5 min and obtained ultrasound imaging immediately after reperfusion, and then every 30 s for 5 min.

We used an automated program (Brachial Analyzer 5; Medical Imaging Applications, Coralville, Iowa, USA) to measure baseline artery diameter and peak postischaemia diameter during diastole. FMD was calculated as the per cent increase in the diameter of the artery after the transient ischaemia. FMD was measured before and after exposures to smoke or IQOS aerosol, as summarised schematically in figure 3A,B. The investigator was blinded to exposure conditions during FMD procedure, analysis of ultrasound images and subsequent calculations.

Serum nicotine and cotinine measurements

For measurement of nicotine and its metabolite cotinine, we collected blood immediately after exposure (from IQOS-exposed and cigarette-exposed rats not being used for FMD measurement; n=5/group) and 20 min later (from IQOS-exposed and cigarette-exposed rats after the final FMD measurement; n=8/group) via thoracotomy and cardiac puncture using a 23G blood collection set (BD Vacutainer) and untreated tubes. We centrifuged the blood samples at 800 rcf for 15 min and immediately

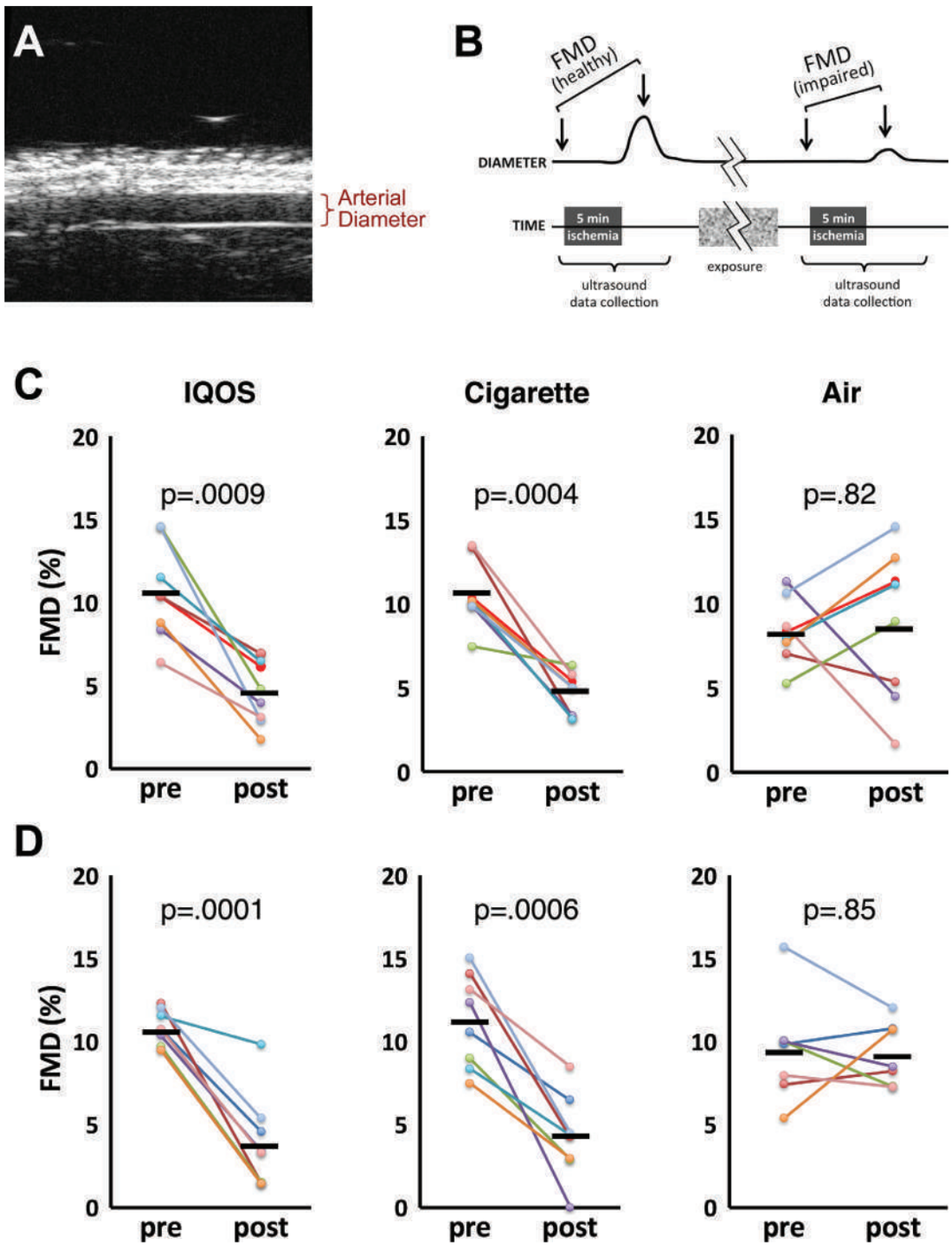


Figure 3 Arterial flow-mediated dilation was impaired by mainstream cigarette smoke and IQOS aerosol. (A) Ultrasound imaging of rat femoral artery. (B) FMD experimental design: FMD was measured pre-exposure and postexposure in each rat. (C) FMD after 10 cycles of 15 s exposure +15 s break. (D) FMD after 10 cycles of 5 s exposure +25 s break. Coloured lines denote individual rats pre-exposure and postexposure; bars denote group means; p values are derived from paired 2-tailed t-tests. FMD, flow-mediated dilation.

stored the serum samples at −80°C. Concentrations of nicotine and cotinine were determined by gas chromatography—tandem mass spectrometry.[38] The limits of quantitation were 1 ng/mL for nicotine and 10 ng/mL for cotinine.

Aerosol and mainstream smoke nicotine measurements

We measured nicotine in both gas and particle phases of the IQOS aerosol and mainstream smoke from Marlboro Red cigarettes and 1R6F research cigarettes using the method described above. Particle phase nicotine was captured in mainstream aerosol and smoke on Cambridge filter pads placed downstream of the cigarette/IQOS filter, using modified ISO conditions of one 35 mL puff every 30 s for a total of 10 puffs (n=3/group). The filtered aerosol went through an impinger filled with 0.036 N HCl to trap the gas phase nicotine. We also analysed the postuse residual material in the HeatSticks as well as unused HeatSticks for nicotine levels. The filters and the contents of the HeatStick were

extracted with 20 mL of an extraction buffer containing 25% by volume of t-butanol, 0.5 M citric acid and 20 mM ascorbic acid by sonicating for 60 min at 60°C. The tubes were centrifuged at 3000 *g* for 5 min and aliquots of the supernatant were analysed. Liquid chromatography-tandem mass spectrometry[37] was used to measure the nicotine levels in the samples.

Statistics

We used paired t-tests to compare the FMD values in each group before and after exposures. Errors are presented in this report as SD. A two-way repeated measures analysis of variance (ANOVA) was run to examine the effect of type and duration of exposure on per cent FMD reduction. P value of <0.05 was considered statistically significant. Calculations were done using Stata V.13.1.

RESULTS

Comparable impairment of FMD by exposure to IQOS aerosol and cigarette mainstream smoke

Exposure in the first experiment (figure 3C) consisted of 10 cycles of 15 s exposure +15 s break (out of the nose cone). A subsequent experiment (figure 3D) used the more realistic regimen of 10 cycles of 5 s exposure +25 s break.

FMD was reduced comparably by ten 15 s exposures to IQOS aerosol (10.6±2.9% pre-exposure vs 4.5±1.9% postexposure, p=0.0009) and cigarette smoke (10.6±2.0% pre-exposure vs 4.6±1.3% postexposure, p=0.0004). FMD was not affected in the clean air control group (8.3±1.9% vs 8.8±4.5%, p=0.82).

FMD was also impaired comparably by ten 5 s exposures to IQOS aerosol and cigarette smoke (10.8±1.0% pre-exposure vs 3.8±2.6% postexposure, p=0.0001; and 11.2±2.6% pre-exposure vs 4.2±2.3% postexposure, p=0.0006, respectively). FMD was not affected in the air control group (9.5±3.0% vs 8.1±1.8%, p=0.85).

A two-way repeated measures ANOVA revealed that there was not a significant interaction between type and duration of exposure on per cent FMD reduction, F (2, 41)=0.30, p=0.73. The per cent FMD impairment was not significantly different in groups exposed for 5 s compared with 15 s (p=0.27), which suggests that the endothelial response was saturated with a single HeatStick or cigarette.

Serum nicotine was comparable to that resulting from smoking by humans

To evaluate the accuracy of the exposure conditions in our rats and its relevance to real-world levels, we compared the post-cigarette exposure serum nicotine levels in rats to that reported for humans (figure 4). In rats subjected to the 10 x (5+25 s) regimen, mean nicotine levels in samples immediately after exposure were 70.3±26.3 and 15.0±7.7 ng/mL in the IQOS and cigarette groups, respectively. Average nicotine levels immediately after exposure in the cigarette group was similar to the levels in humans after smoking one cigarette (~10–50 ng/mL),[39 40] confirming that the exposure conditions were relevant to real-world smoking. In the serum samples taken 20 min after the exposure, mean nicotine levels were 39.7±18.9 and 5.6±2.5 ng/mL in IQOS and cigarette groups. Serum cotinine levels were 4.6±1.9 and 6.5±2.8 ng/mL in IQOS-exposed group immediately after exposure and 20 min later. In the cigarette-exposed group, cotinine was undetectable after exposure and 0.8±1.4 ng/mL after 20 min.

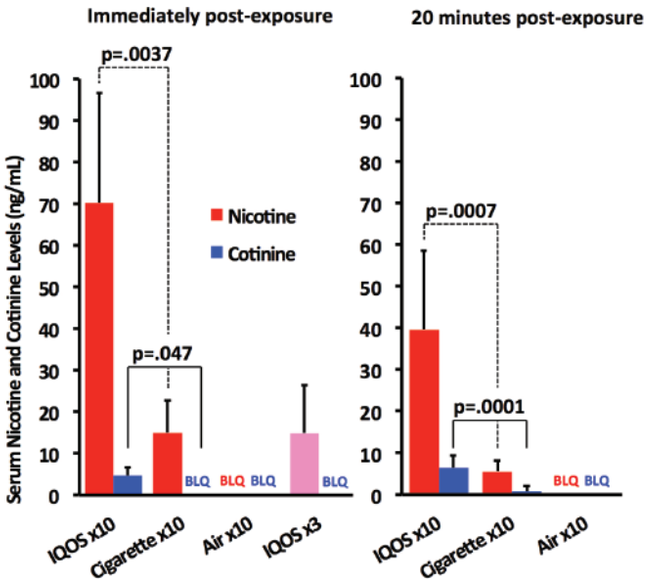


Figure 4 Serum nicotine and cotinine levels immediately and 20 min postexposure. Samples were taken after 10 cycles of 5 s exposure +25 s break. P values are derived from two-tailed Student's t-tests. IQOS x10, 10 IQOS exposure cycles; cigarette x10, 10 cigarette exposure cycles; air x10, 10 air exposure cycles; IQOS x3, three IQOS exposure cycles; BLQ, below level of quantification.

Serum nicotine and cotinine levels were significantly higher in the IQOS-exposed group compared with the cigarette-exposed group at all times. Nicotine and cotinine were not detected in the air groups.

Comparable FMD impairment from lower level IQOS exposure

Because the nicotine levels in IQOS group were substantially higher than that in the cigarette group, impairment of FMD in the IQOS group could potentially be attributed to excessive nicotine exposure. Therefore, we titrated the IQOS exposure timing down to conditions that led to serum nicotine comparable with the cigarette group (three 5+25 s cycles rather than 10 cycles led to 14.8±11.6 ng/mL serum nicotine initially). Average FMD in a group of rats exposed to three cycles of IQOS aerosol decreased significantly from 11.0±4.2 to 4.5±1.5 (p=0.0019). A group of four air-exposed rats that was included for blinding purposes showed no significant change in FMD (figure 5).

Higher nicotine in Marlboro Red smoke than IQOS aerosol

To determine if the higher serum nicotine levels resulting from IQOS exposure than smoke exposure reflected higher nicotine concentrations in IQOS aerosol, we measured nicotine in both kinds of emissions, using both Marlboro Red cigarettes and 1R6F research cigarettes for comparison. Total nicotine levels in smoke from the Marlboro cigarettes were significantly higher than that in IQOS aerosol (1.07±0.05 vs 0.67±0.02, p=0.0006). Nicotine levels in the 1R6F smoke were similar to IQOS aerosol levels (table 1).

Nicotine in the IQOS aerosol gas phase was below the detection limits. Analysis of HeatSticks before and after use also revealed that the nicotine in the aerosol is mainly in the particle phase.

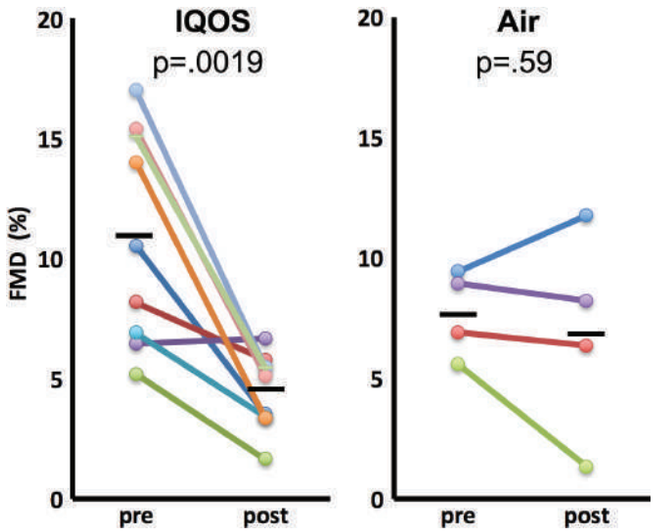


Figure 5 Reduced IQOS exposure to match nicotine absorption level of the cigarette group still impairs FMD to a comparable extent. Coloured lines denote individual rats pre-exposure and postexposure; bars denote group means; p values are derived from paired two-tailed t-tests. Exposure conditions were three cycles of 5 s exposure +25 s break. FMD, flow-mediated dilation.

DISCUSSION

Historically, the tobacco industry has made a major effort to introduce their so-called heat-not-burn tobacco products to consumers as reduced-risk products. Unlike earlier generation products such as R.J. Reynolds' Premier (1988), Eclipse (1996, 2003) and Revo (2015), and Philip Morris' Accord (1998) and Heatbar (2006), IQOS has been successfully marketed in at least 30 countries.[1 41 42] Although IQOS is currently not available in the USA, industry analysts are making optimistic predictions regarding successful future US marketing of IQOS.[41 43] Our aim was to study the vascular effects of exposure to IQOS aerosol before this product achieves more widespread use. To our knowledge, this is the first study of the effects of IQOS aerosol on vascular endothelial function in a physiological model.

PMI strongly implies in publications[21 23 44] and in their MRTP applications[45] that IQOS causes less endothelial dysfunction than conventional cigarettes. Their conclusions were based only on cultured cell behaviour[21] and circulating sICAM-1 protein[23] that indirectly reflect processes relevant to vascular function, but do not directly assess endothelial function physiologically.

Table 1 Nicotine concentration in IQOS aerosol, cigarette mainstream smoke and IQOS tobacco

Material	Total nicotine (mg) Mean±SD
IQOS aerosol (n=3)	
Particle phase	0.67±0.02*
Gas phase	BLQ
Marlboro Red MS (n=3)	
Particle phase	1.07±0.05*
1R6F MS (n=3)	
Particle phase	0.65±0.04
Used IQOS HeatStick (residual; n=3)	3.16±0.67
Unused IQOS HeatStick (n=4)	3.92±0.11

*P=0.0006 between starred values.
BLQ, below level of quantification; MS, mainstream smoke.

PMI's physiological cardiovascular studies were limited to the demonstration that long-term IQOS aerosol exposure led to less aortic plaque than cigarette smoke in transgenic mice predisposed to atherosclerosis.[44] In contrast, our direct evaluation of IQOS aerosol's acute effects showed that brief exposures to IQOS aerosol from a single HeatStick caused rapid impairment of vascular endothelial function in rats comparable with that caused by cigarette smoke. We assessed endothelial function with FMD, a validated measure of cardiovascular health effects[24–27] that has been used by numerous groups to evaluate cardiovascular effects of smoke exposure in humans and animals.[28–31 34–36] Therefore, our approach provides a robust readout of potential adverse effects of IQOS aerosol on endothelial function, and indicates that IQOS use is likely to have rapid adverse vascular effects comparable with those from cigarette smoking.

We chose to use a nose cone smoke/aerosol delivery system, rather than a whole-body exposure system, to prevent exposure via the ocular and oral routes and also to prevent subsequent oral exposure from licking fur and paws. Establishment of an exact relationship between our rat exposure conditions and human exposure is limited by differences in route of administration (rats are obligate nose breathers with complex nasal topography[46] while humans inhale cigarette smoke orally), differences between human intentional aerosol inhalation volume and anaesthetised rat tidal (inhalation) volumes,[47 48] and differences in airway clearance rates.[49] Sophisticated models have been developed to convert inhalation dosimetry between rats and humans,[49] but smoke does not present a straightforward situation due to the combination of gas and highly heterogeneous particles that behave differently in such models. Therefore, to assess whether our exposure conditions were relevant to real-world smoking, we measured serum nicotine levels and confirmed that nicotine in the rats that were exposed to cigarette smoke for ten 5+25 s cycles were similar to the levels found in humans immediately after smoking one cigarette, validating our exposure model for cigarettes.

However, the serum nicotine level in the IQOS-exposed group under identical conditions was more than four times higher than in the cigarette group. This was surprising; our results revealed that the nicotine content in the IQOS aerosol in our generation system was much lower than that in the Marlboro mainstream smoke (table 1). Moreover, nicotine content in the filler and aerosol is reported in the literature to be roughly comparable for HeatSticks and cigarettes.[50 51] The underlying reason for this remains unclear and deserves further investigation. One potential explanation for this difference could be particle size difference which determines to what extent the particles reach the respiratory zone. Nonetheless, reducing the number of IQOS exposure cycles from 10 to 3, to result in comparable serum nicotine concentrations to the cigarette group still led to impairment of FMD. Of note, the extents of FMD impairment in the three IQOS and cigarette groups were quite similar, indicating an extremely rapid saturation of the response to mainstream levels of smoke and IQOS aerosol.

A limitation of this study is that all functional measurements were obtained in anaesthetised rats which was necessary for the FMD procedure to be carried out. However, as in our previous reports using ketamine/xylazine,[34–36] as well as our prior study unrelated to smoke in which isoflurane was used,[52] negative control groups showed no significant alteration of FMD from preintervention to postintervention, and the relative responses of experimental and control groups have been consistent and reproducible. Moreover, prospective human exposure

experiments have shown similar impairment of FMD by smoke inhalation in conscious individuals.[30 31 53]

Regarding potential variability between experiments, we used a manual syringe-pump-driven system to generate smoke and IQOS aerosol for our initial experiment, and a commercially available automatic vaping system for our subsequent experiments. The manual system was modelled after the automatic system; that is, the relevant volumes and aerosol paths were the same in all experiments. The volume of air drawn through the cigarettes and HeatSticks, and the time over which the syringe pump plunger was moved, were the same in all experiments, although slightly more accurate with the automatic system. Similarly, due to broken heating blades as described in the Materials and methods section, we used IQOS holders from three different countries over the course of the project. The characteristics of these electronic devices are presumably highly controlled and would not be expected to vary greatly by country. We did not perform comparative analyses of aerosols generated from the three devices. When it was necessary to switch from a broken device to a new one, rats in both experimental and control groups were exposed to aerosol from the new device.

We conclude that mainstream IQOS aerosol from a single HeatStick can rapidly and substantially impair endothelial function in rats comparably to smoke from a cigarette. While these findings do not prove that inhalation of IQOS aerosol causes endothelial dysfunction in humans, the results underscore that integrative physiological assays of function can reveal adverse health effects not noted in PMI's biomarker and cell culture studies,[2] and suggest that at least some of the adverse health effects of cigarettes may not be avoided by using IQOS.

What this paper adds

- IQOS is a new heated tobacco product from Philip Morris International that has been marketed in 30 countries and has been portrayed to consumers and regulatory agencies as modified-risk tobacco product.
- Brief exposures to IQOS aerosol cause endothelial dysfunction, a well-established physiological measure of cardiovascular risk that is also caused by exposure to cigarette smoke, to the same extent as cigarette smoke in rats.
- Acute exposure to IQOS aerosol impairs flow-mediated dilation in rats.
- Use of IQOS does not necessarily avoid the adverse cardiovascular effects of cigarette smoking.

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Contributors PN, JL, CMH, SI and RD performed experiments and collected/analysed data. PN, CMH, PJ and MLS designed experiments, PN and MLS conceived of the project and wrote the paper.

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Competing interests None declared.

Patient consent Not required.

Ethics approval All animal procedures were approved by the University of California, San Francisco Institutional Animal Care and Use Committee.

Provenance and peer review Not commissioned; externally peer reviewed.

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Assessment of industry data on pulmonary and immunosuppressive effects of IQOS

Farzad Moazed,[1] Lauren Chun,[2] Michael A Matthay,[3] Carolyn S Calfee,[3] Jeffrey Gotts[1]

[1]Department of Medicine, University of California San Francisco, San Francisco, California, USA
[2]Cardiovascular Research Institute, University of California San Francisco, San Francisco, California, USA
[3]Department of Anesthesia, University of California San Francisco, San Francisco, California, USA

Correspondence to
Dr Farzad Moazed, Department of Medicine, University of California San Francisco, San Francisco, CA 94143, USA; farzad.moazed@ucsf.edu

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ABSTRACT

Introduction Heated tobacco products are being touted as novel reduced-harm tobacco products by tobacco companies. In the USA, Philip Morris International submitted a modified risk tobacco product (MRTP) application to the US Food and Drug Administration in 2016 in which it purports that its heated tobacco product, I-Quit-Ordinary-Smoking (IQOS), is associated with reduced harm compared with conventional cigarettes.

Methods We reviewed Philip Morris International's MRTP application to assess the pulmonary and immune toxicities associated with IQOS use in both animal and human studies.

Results Among rats exposed to IQOS, there was evidence of pulmonary inflammation and immunomodulation. In human users, there was no evidence of improvement in pulmonary inflammation or pulmonary function in cigarette smokers who were switched to IQOS.

Conclusion IQOS is associated with significant pulmonary and immunomodulatory toxicities with no detectable differences between conventional cigarette smokers and those who were switched to IQOS in Philip Morris International's studies. Philip Morris International also failed to consider how dual use and secondhand aerosol exposure may further impact, and likely increase, the harms associated with these products.

INTRODUCTION

Conventional cigarettes have long been known to have numerous pulmonary toxicities. Cigarettes generate inflammation in the lung; over time, chronic inflammation contributes directly to the development of significant respiratory diseases including chronic obstructive pulmonary disease (COPD) and lung cancer.[1–3] In addition, cigarette smoke directly impacts immunity in the lung[4] and smoking is associated with an increased risk of respiratory infection,[5–7] a leading cause of mortality worldwide.[8 9] Driven by decades of data indicating the harms of cigarettes, public health campaigns have decreased the prevalence of cigarette smoking worldwide.[10]

In the setting of public awareness of the dangers of cigarettes and declining cigarette smoking in many parts of the world, tobacco companies have repeatedly attempted to develop 'safer cigarettes', including 'low-tar' cigarettes, electronic cigarettes and heated tobacco products (HTPs). HTPs heat tobacco to temperatures (~600°F) below the temperatures observed in conventional cigarettes (>900°F) to avoid combustion and produce a nicotine aerosol that is inhaled by the user. Given these lower temperatures and the subsequent lack of combustion generated by these products, tobacco companies have argued that these products are healthier than conventional cigarettes and represent a harm reduction tool that could aid conventional cigarette smokers. However, to date, there has been little data that support HTPs as less harmful compared with conventional cigarettes.

On 5 December 2016, Philip Morris International (PMI) submitted an application to the US Food and Drug Administration (FDA) to market its HTP, I-Quit-Ordinary-Smoking (IQOS), as a 'modified risk tobacco product' (MRTP) in the USA. Section 911 of the Family Smoking Prevention and Tobacco Control Act requires the FDA to enforce rigorous standards that tobacco companies must meet before marketing a product as an MRTP. Section 911(g) mandates that the FDA may issue an MRTP order only if the applicant has demonstrated by substantial and objective scientific evidence that its product, as it is actually used by consumers, will '(A) significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and (B) benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products'. These standards place the burden on the applicant to demonstrate that their product results in decreased harm, rather than merely equivalence. Such standards may often require a variety of studies, including invasive and/or longitudinal testing, in both animal and human models to provide evidence of reduced harm. This paper uses information and data from the publicly available PMI MRTP application to compare IQOS and conventional cigarettes in animal and human studies of pulmonary health and evaluate PMI's claim of harm reduction related to pulmonary health.

METHODS

In order to conduct this study, we searched PMI's publicly available MRTP application for data relevant to the pulmonary and immune toxicity of IQOS. In addition, when identified, publicly available raw data were downloaded from the FDA MRTP application to conduct independent statistical analyses.

Preclinical studies

Our analysis of PMI's preclinical studies focuses on data presented by Wong and colleagues,[11] which was published in Regulatory Toxicology and Pharmacology in 2016, and included in Module 7.2: Preclinical Studies of PMI's MRTP application. In order to compare the effects of IQOS emissions to

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conventional cigarette smoke, PMI conducted a 90-day inhalation study in 10-week-old male and female Sprague-Dawley rats. Outcomes included markers of inflammation, histopathology, transcriptomics and standard toxicological endpoints, with comparisons of sham-exposed rats and rats exposed to the aerosol of IQOS and 3R4F research cigarettes. The IQOS product tested in these studies was the Tobacco Heated Systems (THS) V.2.2 tobacco stick which uses the FR1 tobacco blend. Rats were nose-exposed in flow-pass inhalation chambers for 6 hours per day to aerosols that were diluted with filtered air to obtain targeted nicotine concentrations ranging from 15 to 50 µg per litre aerosol. Unless otherwise stated, we focused on the highest level of aerosol nicotine for each product. Toxicants were measured at the breathing zone of the rats in the inhalation chambers and reported in ppm (carbon monoxide) or µg/litre (acetaldehyde, acrolein, formaldehyde).

Human studies

Our analyses of human clinical studies are based on the data presented in PMI's MRTP application's Executive Summary, Module 6: Summaries of all research findings, and Module 7.3.1: Scientific Studies and analyses (Studies in Adult Human Studies: Clinical Studies). The human data within these sections draw from two primary studies: ZRHR-REXA-07-JP, performed in Japan and ZRHM-REXA-08-US, performed in the USA. Briefly, both studies enrolled otherwise healthy adults who smoked at least 10 conventional cigarettes per day for the prior 3 years and randomised them into one of three groups: (1) those who smoked menthol conventional cigarettes, (2) those who quit completely and (3) those who switched to IQOS with menthol heatsticks. Participants were initially followed in confinement for 5 days of usage and then in the ambulatory setting for a total of 90 days. The goal of the 90-day ambulatory study period was to examine changes in biomarkers of exposure and clinical harm related to IQOS in near-real-world conditions. During the ambulatory study period, participants were discouraged from dual use. All participants kept a usage diary that documented their tobacco product usage. At the day 90-study visit, several clinical risk points were assessed including plasma white blood cell count (WBC), C reactive protein (CRP) and pulmonary function testing (PFT). Clinical risk endpoints were then compared between participants who continued smoking conventional cigarettes and those that were switched to HTPs.

Statistical analyses

PMI's main analyses included analysis of variance testing with baseline value, product exposure, sex and baseline cigarette consumption as fixed effect factors. We conducted independent analysis of publicly available raw data from PMI's MRTP application. We used Student's t test, analysis of variance testing and Pearson's χ^2 test to compare normally distributed variables. Non-normally distributed variables were compared using the Mann-Whitney Wilcoxon U-test or Kruskal-Wallis test. A p value ≤ 0.05 was considered statistically significant. Statistical analyses were performed with STATA V.15.0 (StataCorp).

RESULTS

Preclinical studies

A comparison of the toxicant profiles of IQOS, 3R4F cigarettes and sham exposure conditions revealed that, while containing generally lower toxicant levels than 3R4F smoke, IQOS emissions contain significant levels of volatile organic compounds, including known toxicants such as acrolein, acetaldehyde and formaldehyde. IQOS-exposed rats had impaired weight gain during the 90-day exposure compared with sham, but greater weight gain compared with animals exposed to 3R4F smoke. Similarly, IQOS-exposed rats had a trend towards increased numbers of inflammatory cells in bronchoalveolar lavage (BAL), but significantly less BAL cellularity than 3R4F-exposed rats (table 1). Respiratory histopathology demonstrated that IQOS caused significant epithelial hyperplasia and metaplasia compared with sham, though to a lesser extent than was observed following 3R4F exposure. Taken together, these data suggest that IQOS induces a significant inflammatory injury, but less severe than that observed with intense cigarette smoke exposure.

PMI's data indicate that IQOS exposure may be associated with substantial immunomodulatory effects (table 2). Animals exposed to IQOS developed systemic neutrophilia that trended nearly 75% higher than that observed in rats exposed to 3R4F smoke. Notably, blood neutrophil counts in female rats remained elevated compared with both sham and 3R4F exposed animals following a 6-week recovery period. Furthermore, IQOS-exposed animals had higher levels of thymic atrophy (by gross organ weight and histology) than both sham and 3R4F-exposed groups. Although functional immunological assays were not reported, thymic atrophy has previously been associated with decreases in host memory T cell populations[12] and reductions in the speed and sensitivity of host immune function.[13]

Table 1 Summary of preclinical pulmonary findings for I-Quit-Ordinary-Smoking (IQOS) compared with sham and 3R4F research cigarette groups

Parameter	Sham (n=10)	IQOS (n=8–10)	3R4F (n=9)
Lung weight (normalised to body weight)	35.8 (1.4)	40.3 (1.0)*	50.6 (1.4)*†
BAL cell count‡ ($\times 10^5$/lung)	22.9 (3.4)	42.5 (7.1)*	116.4 (13.4)*†
BAL inflammatory markers MIP-1β, MCP-3, MPO, PAI-1		↑*	↑*†
Respiratory epithelial hyperplasia and metaplasia		↑*	↑*†

Unless otherwise specified, results signify those from male rats at the highest nicotine exposure levels for each group.
*Significantly increased compared with sham.
†Significantly increased compared with IQOS.
‡Female rats at targeted nicotine 23 µg/L.
BAL, bronchoalveolar lavage; MCP, monocyte chemoattractant protein; MIP, macrophage inflammatory protein; MPO, myeloperoxidase; PAI, plasminogen activator inhibitor.

Table 2 Summary of preclinical systemic immune effects of I-Quit-Ordinary-Smoking (IQOS) compared with sham and 3R4F research cigarettes

Parameter	Sham (n=8–10)	IQOS (n=7–9)	3R4F (n=9–10)
Blood neutrophil count (10^9/L)	1.3 (0.3)	4.8 (2.1)*	2.7 (0.4)*
Thymus weight	4.0 (0.4)	2.6 (0.6)*	2.5 (0.3)*
Histological thymic atrophy score	0.1 (0.1)	1.8 (0.4)*	1.1 (0.4)*

Unless otherwise specified, results signify those from male rats at the highest nicotine exposure levels for each group.
*Significantly different compared with sham; statistical comparisons between IQOS and 3R4F were not reported for blood neutrophil count or thymic atrophy score.

Table 3 Participant demographics and baseline data for Japan-based (ZRHR-REXA-07-JP) and US-based (ZRHM-REXA-08-US) studies

Japan-based study ZRHR-REXA-07-JP				
Measurement	**Conventional cigarettes (n=41)**	**Abstinence (n=37)**	**IQOS (n=70)**	**P values**
Age	38±11	38±10	38±11	0.99
Male (%)	24 (59%)	22 (59%)	39 (56%)	0.92
Smoking history				
10 – 19 cig/day	23 (56%)	20 (54%)	36 (51%)	0.92
>19 cig/day	18 (44%)	17 (46%)	34 (49%)	
FEV1 (% predicted)	94±9	93±10	94±8	0.69
FEV1/FVC	0.81±0.05	0.81±0.06	0.82±0.07	0.73
WBC (GI/L)	5.8±1.4	6.4±1.9	5.9±1.2	0.12
CRP (mg/L)	0.1 (0.1–0.26)	0.1 (0.1–0.45)	0.1 (0.1–0.45)	0.81
US-based study ZRHM-REXA-08-US				
Measurement	**Conventional cigarettes (n=32)**	**Smoking abstinence (n=9)**	**IQOS (n=47)**	**P values**
Age (years)	34±10	41±11	37±13	0.27
Male	20 (63%)	7 (78%)	28 (60%)	0.59
Smoking history				
10–19 cig/day	19 (59%)	6 (67%)	21 (45%)	0.29
>19 cig/day	13 (41%)	3 (33%)	26 (55%)	
FEV1 (% predicted)	97±14	96±11	93±13	0.46
FEV1/FVC	0.79±0.07	0.78±0.04	0.80±0.05	0.74
WBC (GI/L)	8.3±1.8	6.9±2.2	8.3±1.7	0.08
CRP (mg/L)	0.1 (0.1–0.2)	0.1 (0.03–0.2)	0.1 (0.1–0.3)	0.11

IQOS, I-Quit-Ordinary-Smoking; CRP, C reactive protein; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; WBC, white blood cell count.

Table 4 Difference (95% CI) in 90-day pulmonary function testing between I-Quit-Ordinary-Smoking users and conventional cigarette smokers as presented by Philip Morris International

Clinical endpoint	US-based study ZRHM-REXA-08-US* (n=77)	Japan-based study ZRHR-REXA-07-JP† (n=111)
FEV1 (% predicted)	0.53 (–2.09 to 3.00)	1.91 (–0.14 to 3.97)
FEV1/FVC	0.00 (–0.02 to 0.02)	N/A
MEF 25–75 (L/s)	–0.67 (–6.33 to 4.99)	N/A
DLCO (mL/min/mm Hg)	0.31 (–1.09 to 1.72)	N/A
KCO (mmol/min/kPa/L)	0.05 (–0.02 to 0.12)	N/A
TLC (L)	0.09 (–0.25 to 0.43)	N/A
FRV (L)	–0.09 (–0.31 to 0.13)	N/A
IC (L)	0.21 (–0.08 to 0.51)	N/A
VC (L)	0.10 (0.00 to 0.21)	N/A

*Without bronchodilator.
†With bronchodilator.
DLCO, diffusion capacity of lung for carbon monoxide; IC, inspiratory capacity; FEV1, forced expiratory volume in 1 s; FRV, functional residual volume; FVC, forced vital capacity; KCO, rate constant of carbon monoxide; MEF, mid expiratory flow; N/A, not conducted or reported by PMI; TLC, total lung capacity; VC, vital capacity.

Human studies

Japan-based study

The Japan-based study randomised 231 participants between two study sites. However, only one of these sites collected participant data at 90 days. After limiting the sample to participants who had samples drawn at 90 days (n=160), and excluding those who were lost to follow-up (n=12), 148 participants remained. At the day 0 baseline visit, we found no difference in age or sex between groups (table 3). We did not detect a difference between groups in baseline pulmonary function, CRP or WBC, although there was a trend towards increased levels of WBC in the smoking abstinence group.

At the 90-day study visit, PMI reported decreased plasma WBC in IQOS users compared with conventional cigarette smokers (6.14 GI/L vs 5.57 GI/L, difference: –0.57 GI/L, 95% CI: −1.04 to −0.10). Given that WBC had also been measured at the day 0 baseline visit, we compared the change in WBC from baseline to 90 days between groups, rather than only comparing the level at 90 days. We found that compared with cigarette smokers, participants using IQOS had a decrease in plasma WBC (difference: −0.63 GI/L, 95% CI: −1.1 to −0.2, p=0.006). There was no significant difference in the change in WBC between the IQOS and smoking abstinence group. PMI did not detect a difference in CRP levels at 90 days between cigarette smokers and IQOS users (95% CI for difference between groups: –40.75 to 37.77). In our analyses, we did not detect a significant difference in the change in CRP from baseline to 90 days between IQOS users (median: 0 mg/L) and either cigarette smokers (median: 0 mg/L, p=1.0) or the smoking abstinence group (median: 0 mg/L, p=0.74).

PMI also reported on forced expiratory volume in 1 s (FEV1) without bronchodilator administration and found no difference in FEV1 at 90 days between cigarette smokers and IQOS users (table 4). We independently studied the change in FEV1 from day 0 baseline to 90 days. We found no difference between the three groups in the change in FEV1 (cigarette smoking group: −0.3 % predicted, 95% CI: −2.3 to −1.7; smoking abstinence group: 1.5 % predicted, 95% CI: −0.3 to 3.3; IQOS group: 1.5 % predicted, 95% CI: 0.3 to 2.6, p=0.2).

US-based study

In the US-based study, 88 participants underwent testing at 90 days. At the day 0 baseline visit, we did not detect a difference between the three arms in age, sex, pulmonary function, WBC or CRP, although there was a trend towards increased CRP in the IQOS group and decreased WBC in the smoking abstinence group (table 3).

In the US-based study, PMI reported no difference in plasma WBC at 90 days between participants who continued to smoke conventional cigarettes and those who were randomised to IQOS (7.09 GI/L vs 7.26 GI/L, difference: 0.17 GI/L, 95% CI: - 0.47 to 0.81). Similarly, PMI reported no difference in CRP levels between conventional cigarette smokers and IQOS users (95% CI for difference between groups: −21.69 to 42.33). In our independent analyses, we did not detect a difference in the change in WBC from baseline to 90-day visit between the IQOS arm and either the conventional cigarette arm (difference: - 0.06 mg/L, 95% CI: −0.8 to 0.7, p=0.87) or the smoking abstinence arm (difference: - 0.5 mg/L, 95% CI: −1.6 to 0.7, p=0.43). Similarly, we did not detect a difference in change in CRP from baseline to day 90 visit between the IQOS group and either the conventional cigarette group (p=0.30) or the smoking abstinence group (p=0.50).

The US-based study conducted more extensive PFTs than the Japan-based study and notably these tests were performed following bronchodilator administration, which differed from the Japan-based study. At 90 days, PMI did not report a significant difference between the IQOS and conventional cigarette

Table 5 Changes in pulmonary function testing from day 0 to day 90 in the US-based study (ZRHM-REXA-08-US)

Clinical endpoint	Conventional cigarettes (n=30)	IQOS (n=47)	Smoking abstinence (n=9)	P values
FEV1 (% predicted)	–3.1 (–5.6 to –1.7)	–2.3 (–4.6 to –0.04)	–2.9 (–11.3 to 5.6)	0.72
FVC (% predicted)	–2.6 (–4.4 to 0.9)	–1.8 (–3.4 to –0.05)	–0.6 (–4.5 to 3.4)	0.57
FEV1/FVC	0.01 (–0.004 to 0.02)	–0.004 (–0.02 to 0.01)	0.04 (0.002 to 0.08)	0.01
MEF 25–75 (L/s)	–0.1 (–0.3 to 0.2)	–0.1 (–0.3 to 0.05)	0.2 (–0.8 to 1.1)	0.57
DLCO (mL/min/mm Hg)	0.2 (–1.0 to 1.3)	0.2 (–0.8 to 1.2)	–1.5 (–5.1 to 2.2)	0.40
TLC (L)	–0.3 (–0.6 to 0.1)	–0.02 (–0.3 to 0.2)	–0.6 (2.0 to 0.7)	0.15

DLCO, diffusion capacity of lung for carbon monoxide; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; MEF, mid expiratory flow; TLC, total lung capacity.

group for any of the pulmonary function tests that were assessed. We conducted independent analyses of the change in pulmonary function from baseline day 0 to 90-day visits between groups. We did not detect a difference in changes in pulmonary function over time between the three groups except for FEV1/FVC, which increased slightly in the smoking abstinence group relative to both the conventional cigarette group and the IQOS group (table 5). There were no other differences detected between the IQOS group and either the conventional cigarette or smoking abstinence groups.

DISCUSSION

The FDA requires that MRTP applicants demonstrate that their products, as actually used by consumers, will reduce harm in individuals and benefit the health of the public overall. PMI's data are incomplete as they lack adequate endpoints to specifically assess subclinical pulmonary toxicity in humans and do not incorporate enough longitudinal measures for the tests they do include. Additionally, PMI fails to account for real-world usage patterns and secondhand aerosol exposures that may negatively impact both individual and public health. However, even the data that are presented by PMI suggest that IQOS has significant potential to induce adverse pulmonary health effects in humans.

Data from PMI's MRTP application indicate that compared with conventional cigarettes, emissions from IQOS have lower levels of volatile organic compounds and are associated with decreased levels of pulmonary inflammation in rats after 90 days of exposure. However, compared with sham controls, IQOS induces significant changes in the respiratory epithelium and airspaces that are consistent with inflammatory injury. Furthermore, the two clinical studies of real-world usage cited by PMI do not definitively show evidence of reduced inflammation in IQOS users compared with conventional cigarette smokers. Although a very small reduction in plasma WBC was observed in IQOS users in the Japan-based study, there was no difference in plasma WBC in the US-based study. In addition, there was no difference in CRP levels between conventional smokers and IQOS users in either study.

While inflammation is an important toxic mediator in a number of respiratory diseases that have been linked to cigarette smoking, plasma WBC and CRP are not direct measures of pulmonary inflammation but rather non-specific measures of systemic inflammation. There was no difference in levels of these biomarkers at 90 days between conventional cigarette smokers and those who quit smoking, suggesting that these are poorly sensitive markers, particularly when measured over such a short period of time. There are several more specific measures that can assess pulmonary inflammation in humans, including studies of inflammatory biomarkers in sputum, airway tissue or BAL fluid.[14 15] Such tests directly sample lung tissue and thus more accurately reflect processes in the lung. However, despite presenting no human data directly from the lung, PMI concludes that 'human clinical studies have confirmed that clinical markers of … inflammation show positive changes, similar to those seen following smoking abstinence' (PMI MRTP Application, Section 2.7, Executive Summary, p. 106) and that these changes indicate that 'smokers who switch to [IQOS] would have a lower risk of COPD compared with continued smoking' (PMI MRTP Application, Section 2.7, Executive Summary, p. 107). Thus, PMI not only fails to accurately assess pulmonary inflammation in their human studies, but also misleadingly concludes that their IQOS product reduces inflammation and the risk of COPD in humans, a claim that is simply not supported by their data.

Neither PMI's Japanese nor American ambulatory human clinical study shows any statistically significant improvement in any measure of PFT. In fact, after 3 months of usage, smokers who have transitioned to IQOS use have the same pulmonary function as those who continued to smoke conventional cigarettes. Notably, PMI reports several cases of worsening pulmonary function in IQOS users in their adverse event reports (Appendix A6.1.5.4 in the PMI MRTP application). However, PMI concludes that 'in the Japanese study (ZRHM-REXA-07-JP), smokers who switched to THS had an increase of 1.91 percent of predicted value (%Pred) in their FEV1 as compared with smokers who continued to smoke cigarettes' (PMI MRTP Application, Section 2.7, Executive Summary, p. 92) and that 'in the US study (ZRHM-REXA-08-US), the difference in FEV1 values between smokers who switched to THS and those who continued to smoke was smaller in magnitude as compared with in the Japanese study. Nonetheless, the results were consistent and trended in the expected direction following smoking abstinence' (PMI MRTP Application, Section 2.7, Executive Summary, p. 93). These conclusions are simply not supported by PMI's own actual data, which shows no statistically significant difference in pulmonary function between IQOS users and conventional smokers. Furthermore, the relatively short period of follow-up fails to address longer term effects of IQOS on pulmonary function. While prior studies have shown that there are small improvements in pulmonary function in the first year of smoking cessation,[16] a significant benefit arises from a slowing in the decline of lung function over many years.[16 17] A 90-day study period is simply not long enough to detect any meaningful changes in lung function, as evidenced by the lack of difference detected in pulmonary function between the smoking abstinence group and the conventional cigarette or IQOS groups for almost all tests of pulmonary function measured. Thus, the short follow-up period in PMI's studies is unable to assess the important clinical question of the long-term effects on IQOS on pulmonary health compared with both conventional cigarettes and complete smoking cessation.

Conventional cigarettes are known to directly impact immunity and are associated with increased rates of respiratory infection.[5–7] PMI's animal data suggest that IQOS may impact immunity, inducing thymic atrophy in exposed rats. Given that respiratory

infection represents a leading cause of morbidity and mortality worldwide,[8 9] this finding raises alarm that IQOS could increase the risk of infection in users and indicates that further studies of the immunomodulatory effects of IQOS are needed, including animal models of respiratory infection. Notably, PMI reports several cases of infection associated with human IQOS use in their adverse data reports (Appendix A6.1.5.4), which adds to the concern that these products may adversely affect immunity and predispose users to developing infection. The omission of additional studies on the immune effects of IQOS from PMI's MRTP application is significant and further clouds the picture on the true health risks of IQOS.

PMI's analyses focus on studying the harms associated with exclusive IQOS use. However, there is significant data that dual or poly use, the use of two or more tobacco products, will be a significant usage pattern among IQOS users. In PMI's US-based study, nearly one in four participants was still using conventional cigarettes after being switched to IQOS. Internationally, per PMI's own reports, it is estimated that up to 30% of IQOS users also use an additional tobacco product, including conventional cigarettes.[18] However, despite significant evidence of the potential for dual use among IQOS users,[19] PMI has failed to simulate dual use in their animal studies. Furthermore, in their human studies, PMI strictly prevented dual use during confinement study periods and strongly discouraged, although somewhat unsuccessfully, dual use in the ambulatory setting, resulting in less validity to their claims that it mimicked a 'real world' setting. In addition, no analyses are performed on the effects of dual use that was known to occur. Given that dual use is likely to impact any potential for harm reduction for individual users, its omission from PMI's study design and analyses on harm reduction potential is a glaring one.

Finally, PMI studies fail to account for the pulmonary health effects of secondhand aerosol exposure. A prior study of HTPs found that they do generate sidestream aerosol, the primary component of secondhand smoke exposure,[20] which comprises a large number of volatile organic compounds, polycyclic aromatic hydrocarbons and ultrafine particles.[21 22] Furthermore, a recent study found that people exposed to secondhand IQOS emissions experienced symptoms, including sore throat (20.6%), eye pain (22.3%) and feeling ill (25.1%).[19] Given that a number of public health organisations, including WHO, have deemed that no level of sidestream exposure is safe or acceptable,[23] these findings are clearly concerning and merit further study, which PMI has either failed to conduct or present.

In conclusion, PMI's IQOS MRTP application raises significant concerns about the pulmonary safety of IQOS. PMI ignores the effect of dual use and secondhand aerosol exposure in both study design and analyses; furthermore, no measurements of inflammation specific to the lung were made in any of the human studies presented, and the duration of follow-up does not allow for any meaningful study of pulmonary function. Any future studies of these products must include measurements specific to the lung, such as in sputum or BAL fluid, as well as additional longitudinal follow-up to more accurately assess the acute and chronic toxicities of these products. In addition, given that dual use is expected to be the predominant usage pattern, it is critical that future studies take into account dual use when assessing the public health impact of these products. However, even if these significant gaps were ignored, PMI's own data show that IQOS is associated with significant pulmonary and immune toxicity that does not appear to be significantly different from cigarette smoking in real-world human users.

What this paper adds

- Heated tobacco products are being touted as reduced harm tobacco products by tobacco companies across the world despite limited scientific evidence supporting this claim.
- Philip Morris's modified risk tobacco product (MRTP) application for I-Quit-Ordinary-Smoking (IQOS) shows that IQOS generates significant pulmonary and immunomodulatory harm, most notably in human studies.
- With regards to pulmonary and immunomodulatory harm, based on the limited available data to date, IQOS use does not appear to significantly differ from conventional cigarettes.

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Cytotoxic effects of heated tobacco products (HTP) on human bronchial epithelial cells

Noel J Leigh, Phillip L Tran, Richard J O'Connor, Maciej Lukasz Goniewicz

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Department of Health Behavior, Roswell Park Comprehensive Cancer Center, Buffalo, New York, USA

Correspondence to
Dr Maciej Lukasz Goniewicz, Department of Health Behavior, Division of Cancer Prevention and Population Sciences, Roswell Park Comprehensive Cancer, Buffalo, NY 14203, USA; maciej.goniewicz@roswellpark.org

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ABSTRACT

Background Heated tobacco product(s) (HTP), also called heat-not-burn products, are a re-emerging class of tobacco products that purport to reduce health risk compared with smoking combustible tobacco products. This study examined the potential toxic effects of inhaling emissions from an HTP in comparison with electronic and combustible tobacco cigarettes.

Methods Inhalation toxicity of HTP (IQOS; tobacco flavour), e-cigarette (MarkTen; tobacco flavour) and tobacco cigarette (Marlboro Red) was examined in vitro using an air–liquid interface with human bronchial epithelial cells (H292). Cells were exposed directly to 55 puffs from the e-cigarette, 12 puffs from the HTP and 8 puffs from the tobacco cigarette to equilibrate nicotine delivery to the cells across products. Cytotoxicity was measured using neutral red uptake and trypan blue assays. Cytotoxic effects of each tested product (HTP, e-cigarette and tobacco cigarette) were compared with an air control. Release of inflammatory markers (cytokines) was measured using ELISA.

Results The HTP showed higher cytotoxicity compared with the air controls using the neutral red assay. The HTP also showed higher cytotoxicity than the e-cigarette, but lower cytotoxicity than the combustible cigarettes using the same assay. A significant increase in cytokines levels, compared with air controls, was observed postexposure to tobacco smoke but not to emissions from HTP or e-cigarette aerosol.

Discussion Using limited cytotoxic measures, the HTP showed reduced cytotoxicity relative to a combustible cigarette but higher toxicity than an e-cigarette. More comprehensive testing is needed to determine long-term effects of inhaling emissions from HTP.

BACKGROUND

In conventional cigarettes, once tobacco is heated above 600°C, combustion occurs, and smoke containing harmful chemicals is released.[1] Heated tobacco product(s) (HTP) release nicotine-containing emissions without burning tobacco. These products heat rather than burn tobacco, using an electronically controlled heating element. Hypothetically, by reducing the formation temperature, HTP products may emit lower levels of tobacco combustion byproducts and show reduced toxicity compared with combustible tobacco cigarettes. Some early models of HTP products were developed in the late 1980s; however, they did not reach a significant number of consumers and were withdrawn from the market.[1] The HTP IQOS device was developed by Philip Morris International (PMI) and launched in international markets in mid-2014. According to manufacturer data, IQOS devices heat tobacco to temperatures up to 350°C, avoiding combustion.[2]

In December 2016, PMI submitted an application to the US Food and Drug Administration for their HTP IQOS to be authorised as a modified risk tobacco product. Claims of lowered risk of IQOS (non-combustible tobacco product) compared with conventional cigarettes (combustible cigarettes) are based almost exclusively on industry-funded research, and reliable independent research is not available to support these claims as of early 2018. A PMI-funded study reported a 90% reduction in cytotoxicity, determined by the neutral red uptake assay and the mutagenic potency in the mouse lymphoma assay, between HTP versus combustible tobacco cigarettes.[3] Results showed only minor histopathological alterations and minimal cytotoxicity on HTP emission exposure compared with combustible cigarette smoke (1% for HTP vs 30% for tobacco cigarette). Among the 14 proinflammatory mediators analysed, only five exhibited significant shifts with HTP exposure compared with 11 on combustible cigarette smoke exposure.[4] Transcriptomic and metabolomic analysis indicated a general reduction of the impact in HTP emission-exposed samples with respect to tobacco smoke-exposed controls (~79% lower biological impact compared with tobacco smoke).[4] In the 90-day inhalation exposure study, PMI examined microRNA (miRNA) levels in the bronchoalveolar lavage fluid from lungs of Sprague Dawley rats exposed to HTP compared with tobacco smoke.[5] Transcriptomic and metabolomics study performed on Sprague Dawley rats exposed to tobacco smoke or HTP emissions showed that only tobacco smoke caused global miRNA downregulation in nasal epithelium and lung parenchyma. Upregulation of specific miRNA species indicated that they were causal elements in the inflammatory response in tobacco smoke-exposed lungs, but they were reduced after HTP emission exposure.[6]

Although all of above-cited studies evaluated relative effects of IQOS to combustible cigarettes, none of the studies cited above compared toxicity of IQOS to e-cigarettes. Independent research is therefore urgently needed to provide a balanced view on absolute potential health impact of HTP and the relative effects compared with other potential reduced-risk products like e-cigarettes.

Since there is a critical knowledge gap in the potential impact of HTP emissions on respiratory health, this study examined the potential cytotoxic effects of inhaling emissions from an HTP in comparison with the electronic and combustible cigarettes using an in-vitro model.

MATERIALS AND METHODS

Products

Three nicotine-containing products made by PMI were used in this study: (1) HTP (IQOS; with the PMI Amber HeatSticks (HEETS), (2) e-cigarettes (MarkTen brand; 3.5% nicotine, tobacco flavoured) and (3) tobacco cigarette (Marlboro Red 85 mm). The HTP was purchased in Florence, Italy, and the electronic and tobacco cigarettes were purchased in Buffalo, USA.

Generation of emissions from tested products

Emissions from tested products were generated using a Borgwaldt LX-1 (Richmond, Virginia, USA) single-port, piston-operated smoking machine. The Health Canada Intense puffing protocol was used with the following conditions: 2 s puff duration, every 30 s, with a 55 mL puff volume. The number of puffs varied, depending on the product tested, to represent one smoking session. This was accomplished by using one tobacco cigarette and one HTP HEETS, and then matching nicotine delivery from one HTP HEETS to an e-cigarette. In our previous smoking-machine study using the Health Canada Intense puffing protocol,[7] we found that one tobacco cigarette delivered 2.1 mg/cigarette in 8 puffs, the HTP delivered 1.4 mg/HEETS in 12 puffs and the e-cigarette delivered a similar amount of nicotine as the HTP 1.3 mg/session with 55 puffs.[7] Air exposures (control), 55 puffs over a total of 30 min, were run during each experiment.

Cell exposure conditions

Cells were acutely exposed, on three separate days, to emissions (both gas phase and particulates), aerosol or smoke from tobacco products using an air–liquid interface (ALI) interface. The NCI-H292 human bronchial epithelial cell line (ATCC) was plated on 0.4 µm permeable supports (PS) 24 hours prior to experimentation under previously described conditions.[8] Immediately prior to exposure, the media were removed from the apical side of the PS, and cell-containing inserts (n=3) were placed in the ALI chamber. While the apical side of the cells were directly exposed to either: (1) an air control, (2) emissions from HTP, (3) aerosol from e-cigarettes or (4) smoke from tobacco cigarettes, fresh media were cycled over the basal side of the PS at a flow rate of 5 mL/min. After exposure, the apical side was resubmerged with complete or neutral red media until assay measurements 2.5 hours later. The ALI chamber was cleaned with methanol and distilled water between each of the four exposure conditions. A detailed description of this exposure system can be found in our previous study[8] and online supplementary materials.

Toxicity assays

After 2.5 hours, cytotoxicity of exposed H292 cells was measured using two assays: neutral red uptake and trypan blue assays. The neutral red uptake assay provides a quantitative estimation of the number of metabolically active cells attached to the PS, based on the ability of viable cells to incorporate and bind the supravital dye neutral red into lysosomes.[9] The trypan blue assay, a cell viability assay, is based on the principle that live cells possess intact cell membranes that exclude certain dyes, such as trypan blue, whereas dead cells do not.[10] This assay measured the number of live cells attached to the PS (removed by trypsin) and the number of dead cells in the fresh apical media. Cytokines released into the fresh apical media were measured as an indicator of cell inflammatory response. Six cytokines (interleukin (IL)-1β, IL-6, IL-10, CXCL1, CXCL2 and CXCL10) were measured using commercially available ELISA kits (Abcam and R&D System) following the manufacturers' protocols. These cytokines were chosen as a panel of inflammatory markers commonly used in in-vitro, in-vivo and clinical human studies. Changes in those markers have been shown to correlate with several clinically relevant outcomes and diseases.[11–15] A detailed description of these assays can be found in our previous study[8] and online supplementary materials.

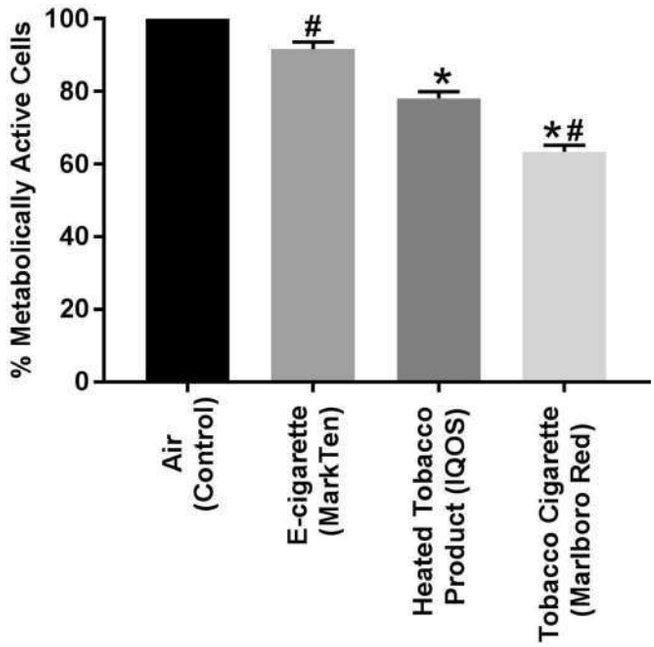


Figure 1 Metabolic activity (neutral red assay) from H292 bronchial epithelial cells directly exposed using an air–liquid interface to emissions from heated tobacco product (HTP), e-cigarette, combustible tobacco cigarette and air (controls). Emissions were generated from a MarkTen electronic cigarette (55 puffs), IQOS HTP (12 puffs/heetstick) and Marlboro Red combustible cigarette (eight puffs/cigarette). *Significant difference compared with the air control ($p<0.05$). #Significant difference compared with IQOS product ($p<0.05$).

Statistical analysis

Statistical analysis was performed using Prism V.6.07 (GraphPad). Kruskal-Wallis non-parametric tests and Dunn multiple comparison tests were performed for each study outcome to compare: (1) each product versus air controls, (2) combustible cigarettes versus HTP and (3) e-cigarettes versus HTP. All experiments were performed in triplicate, with each outcome measured three times per experiment (three wells per chamber).

RESULTS

Metabolic activity of H292 cells decreased significantly after exposure to HTP emissions compared with the air control ($p=0.002$, figure 1). Exposure to combustible tobacco smoke but not to e-cigarette aerosols also resulted in decreased cell viability ($p<0.001$, online supplementary figure 1) and metabolic activity ($p<0.001$, figure 1), compared with the air controls. The neutral red assay, but not the trypan blue assay, revealed that IQOS emissions were significantly more toxic compared with e-cigarette aerosol ($p=0.044$, figure 1 and online supplementary figure 1).

We were only able to detect IL-1β and IL-6 released to media after exposure to all tested products; all other cytokine levels were below the limit of quantitation. There was no statistically significant differences between cytokines levels released

postexposure to HTP emissions compared with air controls (IL-1β: 13.7±5.1 vs 13.5±6.4; IL-6: 6.9±2.1 vs 11.8±3.2 pg/10^7 cells; mean±SD; all $p>0.05$, online supplementary figures 2 and 3). HTP showed reduced release of cytokines compared with combustible cigarettes (IL-1β: 13.7±5.1 vs 133.6±41.9; IL-6: 6.9±2.1 vs 65.5±21.7 pg/10^7 cells; all $p<0.05$, online supplementary figures 2 and 3). Levels of cytokines measured postexposure to HTP did not differ statistically from levels detected postexposure e-cigarettes (IL-1β: 13.7±5.1 vs 12.9±4.7; IL-6: 6.9±2.1 vs 12.2±2.7 pg/10^7 cells; all $p<0.05$, online supplementary figures 2 and 3). Smoke generated from tobacco cigarettes increased cytokine levels compared with air controls, as well as the two other products ($p<0.05$).

DISCUSSION

This pilot study used an established ALI system to examine the cytotoxic and inflammatory effects of an HTP. Our results show that emissions from HTP caused damage to human bronchial epithelial cells relative to air controls. At the same time, HTP emissions showed lower toxicity compared with combustible cigarettes but higher toxicity compared with e-cigarettes. Our data suggest that use of IQOS products may lead to increased risk of respiratory health impairment, and although this risk may be reduced compared with smoking tobacco cigarettes, it is likely to be higher than risk from vaping e-cigarettes.[16] However, it is important to note that the data presented have shown the relative effects of acute exposure to three different tobacco products and that further research is needed to determine the long-term health effects of the HTP product use.

In addition to the cytotoxicity results, we measured two important markers of inflammatory response. Cytokine IL-1β is involved in a variety of cellular activities, including cell proliferation, differentiation and apoptosis. Cytokine IL-6 is primarily produced at sites of acute and chronic inflammation and has been implicated in a wide variety of inflammation-associated disease states. In summary, we found that bronchial epithelial cells exposed to HTP emissions released less IL-1β and IL-6 than cells exposed to cigarette smoke. Additionally, no differences in cytokine concentrations were found between the e-cigarette and the HTP. The rapid death of cells exposed to tobacco smoke may have resulted in low levels of cytokines measured in our study since the proinflammatory activity of dead cells decays over time, presumably as the active cell components are degraded. While it is possible that in some situations intracellular stores of proinflammatory cytokines might be released on cell disintegration and cause inflammation, most of these mediators have restricted expression in cells and therefore cannot account for how the cells induce inflammation on death.[17]

An important limitation of our study is that we have used a single type of immortalised cell line to examine cytotoxicity. Although the ALI exposure provides a novel and specific exposure approach for performing the biological study on health effects related to inhalation of emerging tobacco products, extrapolating data from in-vitro studies to human risks remains hypothetical.[18] This model may not recapitulate how these products affect tissues and do not aim to estimate any harmful effects in IQOS users. Future in-vitro studies with organotypic models as well as in-vivo animal studies are needed to confirm our findings. When real-life data on IQOS users' behaviours and puffing topography are available, future studies should adopt an appropriate exposure protocol that reflects real-life product use conditions.[19] Finally, since our study focused on the acute toxic effects of HTP, our observations require verification in chronic exposure models, more relevant to regular use of HTP.

What this paper adds

- The extent to which heated tobacco product(s) (HTP) impact respiratory health is currently not defined.
- We tested cytotoxicity of HTP using cell viability and metabolic activity assays and examined the release of inflammatory cytokines in bronchial epithelial cells. These cells were exposed in vitro directly to HTP emissions and the results were compared with the observed effects after exposure to air (controls), e-cigarette aerosols and smoke from combustible tobacco cigarettes.
- We found that emissions from HTP damaged bronchial epithelial cells, and their cytotoxic effect was higher compared with e-cigarettes but lower compared with combustible tobacco cigarettes.

Contributors MLG contributed to the conception of the work. MLG and NJL contributed to data analysis. MLG, NJL and RJO drafted the manuscript. NJL and PLT ran all experiments. All authors approved the final version of the manuscript. MLG has full access to all study data and takes responsibility for the integrity of the data and accuracy of the data analysis.

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IQOS: examination of Philip Morris International's claim of reduced exposure

Gideon St.Helen,[1,2] Peyton Jacob III,[1,2] Natalie Nardone,[1] Neal L Benowitz[1,2,3]

[1]Division of Clinical Pharmacology, Department of Medicine, University of California San Francisco, San Francisco, California, USA
[2]Center for Tobacco Control Research and Education, University of California, San Francisco, California, USA
[3]Department of Bioengineering and Therapeutic Sciences, University of California San Francisco, San Francisco, California, USA

Correspondence to
Dr Gideon St.Helen, Division of Clinical Pharmacology and Experimental Therapeutics, University of California San Francisco, San Francisco, CA 94143-1220, USA; Gideon.StHelen@ucsf.edu

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ABSTRACT

Background New electronic heated tobacco products are being introduced in the global market and are gaining popularity. In 2016, Philip Morris International, Inc. (PMI) submitted a modified risk tobacco product (MRTP) application to the Food and Drug Administration (FDA) to market IQOS in the USA with claims of reduced exposure and reduced risk.

Methods We examined PMI's MRTP application, specifically sections on aerosol chemistry and human exposure assessment, to assess the validity of PMI's claims of reduced exposure and risk.

Findings PMI reported levels for only 40 of 93 harmful and potentially harmful constituents (HPHCs) on FDA's HPHC list in IQOS mainstream aerosol. All substances in PMI's list of 58 constituents (PMI-58) were lower in IQOS emissions compared with mainstream smoke of 3R4F reference cigarettes. However, levels of 56 other constituents, which are not included in the PMI-58 list or FDA's list of HPHCs, were higher in IQOS emissions; 22 were >200% higher and seven were >1000% higher than in 3R4F reference cigarette smoke. PMI's studies also show significantly lower systemic exposure to some HPHCs from use of IQOS compared with smoking combustible cigarettes.

Conclusion PMI's data appear to support PMI's claim that IQOS reduces exposure to HPHCs. However, PMI's data also show significantly higher levels of several substances that are not recognised as HPHCs by the FDA in IQOS emissions compared with combustible cigarette smoke. The impact of these substances on the overall toxicity or harm of IQOS is not known.

INTRODUCTION

Many alternative tobacco products have entered the USA market in the last three decades. These include electronic cigarettes that heat a nicotine solution[1] as well as products that heat tobacco without combustion called heated tobacco products (HTPs) or heat-not-burn (HNB) products. A 2000 internal R J Reynolds document gave the rationale for the pursuit of an acceptable HTP:

> Given that no particular agent or group of agents can be definitely assigned the carcinogenic risk associated with cigarettes, the most effective strategy for reducing lung cancer risk in the smoking population is an overall reduction in both the number and concentration of particulate and vapor phase components. This strategy can be achieved by primarily heating, rather than burning, tobacco to form cigarette smoke aerosol.[2]

R J Reynolds first released Premier in 1988,[3] which was followed by Eclipse, a paper-encased tobacco plug heated by a carbon element.[4] Independent studies showed that use of Eclipse decreased tobacco cigarette consumption without causing withdrawal symptoms, maintained blood nicotine concentrations and decreased exposure to the carcinogenic tobacco-specific nitrosamine, 4-(methylnitrosamino)−1-(3-pyridyl)−1-butanone, but increased exposure to carbon monoxide (CO).[5–7] Other HTPs included Philip Morris' Accord, which was a combination of a handheld device that heated specially constructed cigarettes. One independent study showed that use of Accord suppressed withdrawal symptoms and reduced CO exposure.[8] Each iteration of HTPs was commercially unsuccessful, and most products were discontinued shortly after their introduction.[9]

Despite repeated failures at producing a commercially viable HTP, tobacco companies continue to research and develop these products. R J Reynolds launched a revamped Eclipse, rebranded as 'Revo', in November 2014. Revo was briefly test marketed in Wisconsin but pulled off the market.[10] Other current HTPs include British American Tobacco's Glo iFuse, a hybrid of HTP and e-cigarettes. It consists of a heating element, a liquid tank (like e-cigarettes) and a tobacco cavity through which the e-cigarette-like aerosol passes and is infused with tobacco flavour.[11] Japan Tobacco's Ploom Tech, which entered the Japanese market in 2016,[12] consists of a liquid cartridge and a capsule of granulated tobacco leaves that the vapour passes through.

Philip Morris Products S.A., a subsidiary of Philip Morris International, Inc. (PMI), developed IQOS ('I Quit Ordinary Smoking') as an HTP.[9 10] IQOS consists of a tobacco stick (HeatStick) and a battery-powered tobacco heating device.[13] As of May 2018, IQOS is currently sold in over 37 countries, including Japan, the UK and Canada.[14] Philip Morris Products S.A. filed a modified risk tobacco product (MRTP) application with the US Food and Drug Administration (FDA) in December 2016[15 16] to market IQOS in the USA with reduced exposure and reduced risk claims. The FDA's Tobacco Products Scientific Advisory Committee (TPSAC) reviewed the MRTP application in January 2018. The TPSAC committee approved, in an 8 to 1 vote, PMI's statement '*Scientific studies have shown that switching completely from cigarettes to the IQOS system significantly reduces your body's exposure to harmful or potentially harmful chemicals[HPHCs*]' was true.[17] Of the eight committee members who agreed with PMI's claim that IQOS significantly reduced exposure to HPHCs, a majority (five of eight) voted that PMI has not '*demonstrated that the reductions in exposure are reasonably likely to translate to a measurable and substantial reduction in morbidity and/or mortality*'.[17]

Examination of PMI's studies, results and interpretation of data to support claims of reduced exposure and risk is critically important before FDA approval in order to protect public health, particularly as PMI's MRTP application and approval may set the precedent for other MRTP applications of similar products. This paper examines PMI's reported studies on IQOS aerosol chemistry and human exposure assessment, and we assessed whether they support PMI's claims of reduced exposure.

METHODS

We examined studies presented in PMI's MRTP application,[16] namely those in Module 6.1.1: *Aerosol Chemistry*; Module 6.1.3.1: *Justification of Selection of Biomarkers of Exposure*; and Module 6.1.3.2: *Summary of Biomarkers of Exposure Assessments*. We also reviewed data presented in the document, *Addendum to FDA Briefing Document: January 24–25, 2018*,[18] which was prepared by FDA's Center for Tobacco Products for the TPSAC meeting on IQOS held on 24 and 25 January 2018.

To examine the aerosol chemistry of IQOS, mainstream aerosol from IQOS HeatSticks (regular and menthol) and smoke from 3R4F reference cigarettes were generated according to the Health Canada Intense machine-smoking regimen on a Borgwaldt linear smoking machine type LM20X (Borgwaldt KC GmbH, Hamburg, Germany) for most analytes and Burghart rotary smoking machine type RMB 20 (Burghart Tabaktechnik GmbH, Wedel, Germany) for elements.[19] Methods for chemical analyses have been described previously.[19]

PMI conducted four clinical studies to examine whether human exposure to harmful substances are statistically significantly reduced with IQOS (Module 6.1.3.2).[16] All studies were randomised, controlled, open-label, three-arm, parallel group, single-centre studies. Studies ZRHR-REXC-03-EU (conducted in Poland) and ZRHR-REXC-04-JP (conducted in Japan) were conducted over 5 days in confinement. Each study included 160 combustible cigarette smokers who were randomly assigned to one of three arms, namely, IQOS with regular HeatSticks, commercially available combustible cigarettes or smoking abstinence. Use of IQOS or combustible cigarettes was from 06:30 to 23:00 and was ad libitum. Studies ZRHM-REXA-07-JP (conducted in Japan) and ZRHM-REXA-08-US (conducted in the USA) were conducted over 3 months, during which 160 participants were randomised to one of three arms in each study, namely, IQOS with menthol HeatSticks, commercially available menthol combustible cigarettes or smoking abstinence. These two studies included 5 days in confinement followed by 85 or 86 days, respectively, in an ambulatory setting. Participants in the IQOS or combustible cigarettes arms used each product ad libitum in confinement (06:30–23:00) and in the ambulatory setting. Compliance with study protocol could not be enforced during the ambulatory phase.

For the two 5-day confinement studies, it was evaluated whether reductions of 50% or more in 24 hours urine concentrations of mercapturic acid metabolites of 1,3-butadiene, acrolein and benzene and carboxyhaemoglobin in blood were observed in smokers assigned to IQOS compared with smokers who continued smoking combustible cigarettes. Levels of selected biomarkers of exposure over the 5-day exposure period were also compared between smokers who switched to IQOS and those who continued smoking and the maximum reduction in biomarker levels in abstinent smokers was assessed. For the two 3-month studies, they examined whether the geometric mean levels of biomarkers of exposure for IQOS (menthol) were lower relative to combustible cigarette (menthol) use. Differences in mercapturic acid metabolites of 1,3-butadiene, acrolein and benzene and carboxyhaemoglobin in blood were tested on day 5 and total 4-(methylnitrosamino)−1-(3-pyridyl)−1-butanol on day 90.

RESULTS

PMI reported the levels of 58 constituents (which PMI refers to as 'PMI-58') in mainstream aerosol generated from IQOS and 3R4F reference cigarettes (Module 6.1.1).[16] The PMI-58 list includes 40 (43%) out of the 93 harmful or potentially harmful constituents (HPHCs) on FDA's list of HPHCs.[20] The PMI-58 list included 18 additional constituents that do not appear on FDA's list of HPHCs, including water, total particulate matter, pyrene and nitrogen oxides. PMI concluded that the levels of HPHCs on the PMI-58 list were reduced by >92% on a stick basis and >89% on a normalised for nicotine basis for the regular tobacco stick, and >93% on a stick basis and >88% on a normalised for nicotine basis for the mentholated tobacco stick compared to 3R4F reference cigarette (Module 6.1.1, p. 45).[16]

Importantly, the addendum to the briefing document for the 24 and 25 January 2018 TPSAC meeting, prepared by FDA's Center for Tobacco Products,[18] presented additional data from PMI studies that showed higher levels of many substances in IQOS emissions compared with 3R4F cigarette smoke (table 1). The addendum consisted of data from Module 3.3.2 and section 6.1.1.3.4 of the MRTP application and appendix A of an amendment to the MRTP application. The addendum reported levels of 113 constituents, including 56 of the 58 constituents on the PMI-58 list (total particulate matter and nicotine-free dry particulate matter were the two exclusions) and 57 constituents that do not appear on the PMI-58 list. Fifty-six of the 57 non-PMI-58 constituents were higher in IQOS emission than in 3R4F smoke (median, 154% higher; range, undefined to 13 650% higher in IQOS aerosol vs 3R4F mainstream smoke); tar was the exception. Twenty-two of the non-PMI-58 constituents were at least 200% higher while seven were at least 1000% higher in IQOS emission compared with 3R4F mainstream smoke (table 1).

PMI characterised the droplet size distribution of IQOS aerosol by measuring the mass median aerodynamic diameter (MMAD) (the diameter at which 50% of the particles by mass are larger and 50% are smaller) and geometric standard deviation (presented in Module 6.1.1).[16] The MMAD for the various IQOS products tested (regular and menthol) ranged between 0.54 µm to 0.75 µm and fell within the respirability region, based on the respirability upper threshold defined at 2.5 µm. The range of MMAD for IQOS appears slightly larger than those of e-cigarettes and conventional tobacco cigarettes, which one report showed were about 0.15 µm and 0.17 µm, respectively.[21]

Regarding the human exposure studies, 11 of the 17 HPHCs measured are included in a list of 18 HPHCs that FDA recommends to be measured and reported in users of tobacco products.[20] PMI assessed systemic exposure to pyrene, which is not included in FDA's list of HPHCs, as a proxy for exposure to polycyclic aromatic hydrocarbons (PAHs) using 1-hydroxypyrene. PMI did not assess systemic exposure to inorganic compounds, phenols and metals.

Biomarkers of HPHCs measured were statistically significantly lower with IQOS use compared with combustible cigarette use (Module 6.1.3.2).[16] Reductions of at least 50% in levels of biomarkers of exposure to HPHCs were reported when smokers switched from combustible cigarettes to IQOS during 5 days of confinement; these reductions were sustained during the 85/86 days in ambulatory settings (Module 6.1.3.2, p. 145).

Table 1 Compounds in mainstream aerosol of Marlboro HeatSticks compared with 3R4F reference cigarette

PMI product	Unit	PMI-58	IQOS HeatStick	3R4F	Change (%) with 3R4F on stick basis
1,2,3-Propanetriol, diacetate (diacetin)	µg/stick	No	1.23	0.381	↑ 223
1,2-Propanediol, 3-chloro	µg/stick	No	9.94	5.93	↑ 68
1,4-Dioxane, 2-ethyl-5-methyl-	µg/stick	No	0.055	0.0004	↑ 13 650
12,14-Labdadiene-7,8-diol, (8a,12E)	µg/stick	No	1.43	0.064	↑ 2134
1 hour-Indene, 2,3-dihydro-1,1,5,6-tetramethyl-	µg/stick	No	0.026	0.014	↑ 86
1-Hydroxy-2-butanone	µg/stick	No	0.947	0.465	↑ 104
1-Hydroxy-2-propanone(1,2-Propenediol)	µg/stick	No	162	96.8	↑ 67
2 (5H)-Furanone	µg/stick	No	5.32	1.99	↑ 167
2,3-Dihydro-5-hydroxy-6-methyl-4 hour-pyran-4-one	µg/stick	No	0.231	0.135	↑ 71
2,4-Dimethylcyclopent-4-ene-1,3-dione	µg/stick	No	0.333	0.193	↑ 73
2-Cyclopentene-1,4-dione	µg/stick	No	3.8	0.764	↑ 397
2-Formyl-1-methylpyrrole	µg/stick	No	0.128	0.064	↑ 100
2-Furancarboxaldehyde,5-methyl-	µg/stick	No	11.1	2.94	↑ 278
2-Furanmethanol	µg/stick	No	39.2	7	↑ 460
2-Furanmethanol, 5-methyl-	µg/stick	No	0.123	0.029	↑ 324
2 hour-Pyran-2-one,tetrahydro-5-hydroxy	µg/stick	No	4.45	3.11	↑ 43
2-Methylcyclobutane-1,3-dione	µg/stick	No	2.78	0.71	↑ 292
2-Propanone, 1-(acetyloxy)-	µg/stick	No	16.9	8.01	↑ 111
3 (2H)-Furanone, dihydro-2-methyl-	µg/stick	No	0.326	0.119	↑ 174
3-Methylvaleric acid	µg/stick	No	5.1	3.63	↑ 40
4(H)-Pyridine, N-acetyl-	µg/stick	No	0.296	0.112	↑ 164
5-Methylfurfural	µg/stick	No	0.995	0.632	↑ 57
Anhydro linalool oxide	µg/stick	No	0.457	0.291	↑ 57
Benzene, 1,2,3,4-tetramethyl-4-(1-methylethenyl)-	µg/stick	No	0.006	0.005	↑ 20
Benzenemethanol, 4-hydroxy-	µg/stick	No	0.011	0	↑
Benzoic acid, 2,5-dihydroxy-methyl	µg/stick	No	4.55	2.18	↑ 109
Butylated hydroxytoluene	µg/stick	No	0.132	0.007	↑ 1786
Butyrolactone	µg/stick	No	4.08	0.728	↑ 460
Cis-sesquisabinene hydrate	µg/stick	No	0.061	0	↑
Cyclohexane, 1,2-dioxo-	µg/stick	No	0.083	0.046	↑ 80
Cyclohexane-1,2-dione, 3-methyl-	µg/stick	No	0.101	0.073	↑ 38
Eicosane, 2-methyl-	µg/stick	No	0.05	0.014	↑ 257
Ergosterol	µg/stick	No	3.18	1.58	↑ 101
Ethyl 2,4-dioxohexanoate	µg/stick	No	6.73	3.57	↑ 89
Ethyl dodecanoate (ethyl laurate)	µg/stick	No	0.023	0	↑
Ethyl linoleate	µg/stick	No	0.135	0.008	↑ 1588
Ethyl linolenate	µg/stick	No	0.614	0.153	↑ 301
Furfural	µg/stick	No	31.1	25.9	↑ 20
Glycerol	mg/stick	No	5.02	2.08	↑ 141
Glycidol	µg/stick	No	5.71	1.76	↑ 224
Heneicosane, 2-methyl-	µg/stick	No	0.063	0.021	↑ 200
Hexadecanoic acid, ethyl ester	µg/stick	No	0.491	0.008	↑ 6038
Isolinderanolide	µg/stick	No	4.99	1.85	↑ 170
Isoquinoline, 3-methyl	µg/stick	No	6.29	4.99	↑ 26
Labdane-8,15-diol, (13S)	µg/stick	No	0.143	0.015	↑ 853
Lanost-8-en-3-ol, 24-methylene-, (3beta)	µg/stick	No	6.3	1.61	↑ 291
Maltoxazine	µg/stick	No	0.077	0.038	↑ 103
Methyl furoate	µg/stick	No	0.147	0.029	↑ 407
Phenylacetaldehyde	µg/stick	No	1.41	0.529	↑ 167
p-Menthan-3-ol	µg/stick	No	0.786	0.322	↑ 144
Propylene glycol	µg/stick	No	175	23.7	↑ 638
Pyranone	µg/stick	No	6.54	5.07	↑ 29
Pyranone	µg/stick	No	9.26	5.84	↑ 59
Pyridoxin	µg/stick	No	0.699	0.526	↑ 33
Stearate, ethyl-	µg/stick	No	0.074	0.003	↑ 2367

Continued

Table 1 Continued

PMI product	Unit	PMI-58	IQOS HeatStick	3R4F	Change (%) with 3R4F on stick basis
Tar	mg/stick	No	19.4	25	↓ 22
Trans-4-hydroxymethyl-2-methyl-1,3-dioxolane	µg/stick	No	2.09	0.044	↑ 4650
1,3-Butadiene	µg/stick	Yes	0.21	89.2	↓ 99.8
1-Aminonaphthalene	ng/stick	Yes	0.043	20.9	↓ 99.8
2-Aminonaphthalene	ng/stick	Yes	0.022	17.5	↓ 99.9
3-Aminobiphenyl	ng/stick	Yes	0.007	4.6	↓ 99.8
4-Aminobiphenyl	ng/stick	Yes	0.009	3.21	↓ 99.7
Acetaldehyde	µg/stick	Yes	192	1602	↓ 88
Acetamide	µg/stick	Yes	2.96	13	↓ 77
Acetone	µg/stick	Yes	30.7	653	↓ 95
Acrolein	µg/stick	Yes	8.32	158	↓ 95
Acrylamide	µg/stick	Yes	1.58	4.5	↓ 65
Acrylonitrile	µg/stick	Yes	0.145	21.2	↓ 99.3
Ammonia	µg/stick	Yes	12.2	33.2	↓ 63
Arsenic	ng/stick	Yes	<0.36	<7.49	NA
Benz[a]anthracene	ng/stick	Yes	2.65	28.4	↓ 91
Benzene	µg/stick	Yes	0.45	77.3	↓ 99.4
Benzo[a]pyrene	ng/stick	Yes	0.736	13.3	↓ 94
Butyraldehyde	µg/stick	Yes	20.7	81.3	↓ 74
Cadmium	ng/stick	Yes	<0.28	89.2	↓ >99.7
Carbon monoxide	mg/stick	Yes	0.35	29.4	↓ 99
Catechol	µg/stick	Yes	14	84.1	↓ 83
Chromium	ng/stick	Yes	<11.0	<11.9	NA
Crotonaldehyde	µg/stick	Yes	<3.29	49.3	↓ >93
Dibenz[a,h] anthracene	ng/stick	Yes	<0.124	<0.689	NA
Ethylene oxide	µg/stick	Yes	<0.119	16	↓ >99.3
Formaldehyde	µg/stick	Yes	14.1	79.4	↓ 82
Hydrogen cyanide	µg/stick	Yes	<1.75	329	↓ >99.5
Hydroquinone	µg/stick	Yes	6.55	94.5	↓ 93
Isoprene	µg/stick	Yes	1.51	891	↓ 99.8
Lead	ng/stick	Yes	2.23	31.2	↓ 93
m-Cresol	µg/stick	Yes	0.042	4.24	↓ 99
Mercury	ng/stick	Yes	1.38	3.68	↓ 63
Methyl-ethyl-ketone	µg/stick	Yes	10.1	183	↓ 94
Nickel	ng/stick	Yes	<15.9	<12.9	NA
Nicotine	mg/stick	Yes	1.29	1.74	↓ 26
Nitric oxide	µg/stick	Yes	12.6	484	↓ 97
Nitro benzene	µg/stick	Yes	<0.011	<0.038	NA
Nitrogen oxides	µg/stick	Yes	14.2	538	↓ 97
N-nitrosoanabasine	ng/stick	Yes	2.35	29	↓ 92
N-nitrosoanatabine	ng/stick	Yes	14.7	254	↓ 94
NNK	ng/stick	Yes	7.8	244.7	↓ 97
NNN	ng/stick	Yes	10.1	271	↓ 96
o-Cresol	µg/stick	Yes	0.078	4.81	↓ 98
o-Toluidine	ng/stick	Yes	1.1	96.2	↓ 99
p-Cresol	µg/stick	Yes	0.071	9.6	↓ 99
Phenol	µg/stick	Yes	1.47	15.6	↓ 91
Propionaldehyde	µg/stick	Yes	10.8	109	↓ 90
Propylene oxide	ng/stick	Yes	142.3	896	↓ 84
Pyrene	ng/stick	Yes	8.2	79.2	↓ 90
Pyridine	µg/stick	Yes	6.58	30.9	↓ 79
Quinoline	µg/stick	Yes	<0.011	0.43	↓ >98
Resorcinol	µg/stick	Yes	<0.055	1.72	↓ >97
Selenium	ng/stick	Yes	1.27	<4.42	NA
Styrene	µg/stick	Yes	0.58	13.9	↓ 96

Continued

Table 1 Continued

PMI product	Unit	PMI-58	IQOS HeatStick	3R4F	Change (%) with 3R4F on stick basis
Toluene	µg/stick	Yes	1.42	129	↓ 99
Vinyl chloride	ng/stick	Yes	<0.657	93.4	↓ >99
Water	mg/stick	Yes	30.2	14.7	↑ 105

Notes: presented in table 1 of *Addendum to FDA Briefing Document, January 24-25, 2018*, Meeting of the Tobacco Products Scientific Advisory Committee; sata source: section 3.3.2 and section 6.1.1.3.4 of the Modified Risk Tobacco Product application (MRTPAs) and appendix A of an amendment to the MRTPAs submitted on 8 December 2017. Total particulate matter and nicotine-free dry particulate matter, two constituents on the PMI-58 list were not reported by PMI in this table.
↑, higher in IQOS; ↓, lower in IQOS.
PMI, Philip Morris International; PMI-58, PMI's list of 58 constituents.

DISCUSSION

According to FDA's draft guidance, an MRTP is 'any tobacco product that is sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products'.[22] FDA may issue an order allowing a product to be marketed as a modified risk product if it is demonstrated that the product: (A) significantly reduces harm and the risk of tobacco-related disease to individual tobacco users; and (B) benefits the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products. PMI's data show that IQOS significantly reduces emissions and exposure to several HPHCs compared with combustible cigarettes. However, PMI's data also show that IQOS emissions contain higher levels of many other substances compared with combustible cigarettes. The impact of these substances on IQOS toxicity and harm are not known.

Over 7000 distinct substances have been identified in tobacco smoke, many of which are toxic or carcinogenic.[23] HPHCs in tobacco or tobacco smoke have been proposed by several public health authorities, such as the FDA,[20] as possible causes of tobacco-related morbidity and mortality. Elimination or reduction of exposure to these HPHCs may potentially reduce health risks, which is the premise of HTP technology. Schaller and colleagues[19] described five criteria used by PMI to select HPHCs to measure in IQOS aerosol for comparison with 3R4F reference cigarette. Criterion 1 includes smoke constituents determined by International Organization for Standardization (ISO) methods, such as total particulate matter, nicotine and CO. Criterion 2 includes priority toxicants in tobacco smoke selected from the lists issued by regulatory bodies or proposed by cognizant authorities, such as volatile organic compounds like acrylonitrile, 1,3-butadiene and benzene. Criterion 3 includes toxicants for which there is an established biomarker of exposure. Criterion 4 includes toxicants that are predominantly formed below 400°C and that are not included under 'Criterion 2', such as acrylamide and acetamide. Criterion 5 includes toxicants that are predominantly formed above 400°C and that are not included under 'Criterion 1' and 'Criterion 2', such as dibenz[a,h]anthracene and benz[a]anthracene.

PMI's conclusion that IQOS reduces exposure to HPHCs, which TPSAC agreed with,[17] is based, in part, on evidence of lower levels of PMI-58 substances in IQOS emissions compared with 3R4F reference cigarette smoke. However, the PMI-58 list is selective (based on PMI's criteria described before); PMI did not report levels of 53 HPHCs on FDA's list of 93 HPHCs. Of the 53 FDA HPHCs not measured, 50 are carcinogenic (eg, 2,6-dimethylaniline, benz[j]aceanthrylene, ethylbenzene and furan).[20] In addition to the PMI-58 substances, PMI measured levels of 57 other substances in IQOS emissions (non-PMI-58 substances). Importantly, 56 of these 57 non-PMI-58 substances were higher in IQOS aerosol compared with 3R4F mainstream cigarette smoke. It appears that IQOS reduces exposure to some toxicants but elevates exposure to other substances.

Given the elevated levels of the non-PMI-58 substances in IQOS aerosol compared with reference cigarette smoke, their inherent toxicities could play a role in the overall harm of IQOS. A number of these substances, including several that were more than 50% higher in IQOS aerosol, belong to chemical classes that are known to have significant toxicity, such as α,β-unsaturated carbonyl compounds (eg, 2-cyclopentene-1,4-dione),[24] 1,2-dicarbonyl compounds (eg, cyclohexane, 1,2-dioxo-),[25] furans (eg, 2 (5H)-furanone)[26] and epoxides (eg, anhydro linalool oxide).[27] There is limited information on the toxicity of many of the non-PMI-58 substances. We speculate that some of these substances are components of flavour additives in IQOS or thermal degradation compounds. For example, anhydro linalool oxide is listed among flavouring ingredients that are generally regarded as safe (for oral ingestion) by the Flavor and Extract Manufacturers' Association.[28]2 (5H)-Furanone is a food additive that suppresses appetite and/or food intake and has been shown to induce cellular DNA damage in vitro.[29 30] 2-Furanmethanol is a flavouring agent with a flavour profile of burnt, caramel or cooked.[31] 2-Furanmethanol also causes eye, nose, throat and skin irritation and has central nervous system effects.[31] 2-Cyclopentene-1,4-dione is likely generated from thermal breakdown of sugars.[32] 1-Hydroxy-2-butanone, a flavouring ingredient found in coffee and coffee products, is also a degradation product of polysaccharides.[33] Some compounds appear to be contaminants. 3-Chloro-1,2-propanediol (or 1,2-propanediol, 3-chloro), a food contaminant,[34] has not been shown to be genotoxic in vivo,[35] but mutagenic effects were observed at high concentrations in vitro experiments.[36] A 2-year study found increased incidence for the development of tumours in kidney and testis in male rats exposed to 3-chloro-1,2-propanediol.[37] 1,2,3-Propanetriol, diacetate (diacetin) is a solvent used for decaffeinating coffee.

PMI's MRTP application fails to address the important question of whether the aerosol generation process for IQOS produces toxic substances not found in the smoke of combustible cigarettes, which could have been answered through non-targeted chemical analysis. Combustible tobacco cigarettes reach about 900°C during a puff and smoulder at about 400°C between puffs.[23] The burning process, substances emitted and their levels vary at different temperatures.[38] Distillation, the process during which nicotine and aromas are transferred from tobacco to smoke, occurs below 300°C; pyrolysis occurs at about 300°C–700°C, entails the decomposition of biopolymers, proteins, and other organic materials and generates the majority of substances emitted in smoke; and combustion occurs above 750°C and results in the generation of carbon dioxide, CO and water.[38] HeatSticks are heated to a maximum of 350°C,[19] a temperature sufficient to enable pyrolytic decomposition of some organic materials. Formation of toxic volatile organic

compounds, including formaldehyde, acetaldehyde and acrolein, via dehydration and oxidation of the humectants, propylene glycol and glycerin, have been reported in e-cigarette aerosols at similar temperatures as IQOS.[39–42] In addition, flavouring chemicals in e-cigarettes undergo thermal degradation and contribute significantly to levels of toxic aldehydes emitted in e-cigarette aerosol.[43] Since the constituents of HeatSticks may be different from that of combustible cigarettes, including flavourants and additives, it is plausible that the IQOS aerosol may contain substances not present in tobacco smoke.

A study by Klupinski and colleagues[44] reported that unique substances, such as ambrox, 3-methylbutanenitrile and 4-methylimidazole, were found in little cigar smoke that were not found in cigarette smoke, indicating that different tobacco products can have different chemical fingerprints and lead to different exposure and toxicological profiles. The study by Klupinski and colleagues describes methodology for 'non-targeted' analysis of tobacco smoke aerosol, and the authors suggest that 'the same approach could also be applied to other samples to characterize constituents associated with tobacco product classes or specific tobacco products of interest'. FDA should recommend that manufacturers of HTPs undertake 'non-targeted' analyses (along with targeted analysis), comparing HTP aerosol with smoke from combustible tobacco products to identify potentially toxic chemicals in HTP emissions that may not be present in tobacco smoke.

Although smoking machine studies are appropriate for examining the relative differences in emissions between products, they do not predict use patterns and systemic exposure to toxicants. PMI reported systemic exposure to 17 HPHCs in its human exposure studies. PMI did not assess systemic exposure to any inorganic compounds, phenols and metals, possibly due to the fact that there are no valid biomarkers for some substances or that the time course of the biomarkers may not be optimal for studies of the duration used by PMI. PMI used 1-hydroxypyrene, a metabolite of pyrene (a PAH) as a biomarker of PAHs. Pyrene is not included as an HPHC on FDA's list. We have previously demonstrated that 1-hydroxypyrene is not a selective measure of tobacco-related PAH exposure and is weakly related to nicotine intake and tobacco-specific nitrosamine exposure.[45] Instead, we found that monohydroxylated metabolites of fluorene (particularly 1-hydroxyfluorene) and 2-naphthol (a naphthalene metabolite) were more selective of tobacco smoke exposure. In characterising PAH exposure from HNB products, manufacturers should include biomarkers with relatively high selectivity for tobacco.

In conclusion, PMI's data show that IQOS emissions have significantly lower levels of several HPHCs compared with combustible cigarettes. Furthermore, PMI's data from human studies show that use of IQOS is associated with significantly lower systemic exposure to some HPHCs compared with smoking combustible cigarettes. These data appear to support PMI's claim that IQOS is a reduced exposure product. However, PMI's data also show significantly higher levels of other substances in IQOS emissions compared with combustible cigarette smoke. The impact of these substances on the overall toxicity or harm of IQOS is not known.

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What this paper adds

- Studies conducted by Philip Morris International, Inc. (PMI) show that IQOS emissions contain lower levels of many harmful or potentially harmful constituents (HPHCs) compared with combustible tobacco smoke.
- PMI's studies show that use of IQOS results in significantly lower systemic exposure to several HPHCs compared with combustible cigarette smoking.
- PMI's own data also show that IQOS emissions contain many other substances, some of which are potentially toxic, at higher levels than in combustible cigarette smoke.

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Tobacco-specific nitrosamines (TSNA) in heated tobacco product IQOS

BACKGROUND

Heated tobacco products (HTP) have an electrical heating component, like e-cigarettes, that heats processed tobacco to 350°C releasing volatile components that often are not detectable in e-cigarettes.[1] Although many combustion by-products may be eliminated in HTP devices, nitrosamines are generated in the process of tobacco curing rather than during combustion, and may be transferred from the HTP into the aerosol that it generates.[2–4] We hypothesised that HTP may be a significant source of tobacco-specific nitrosamines (TSNA). This pilot study determined TSNA yields in aerosol emitted from HTP in comparison to the electronic and tobacco cigarettes.

METHODS

HTP (IQOS; Amber, tobacco flavour), e-cigarettes (MarkTen; 3.5% nicotine, tobacco flavoured) and tobacco cigarettes (Marlboro Red 100) were tested using a Borgwaldt LX-1 smoking machine following the Health Canada Intense protocol (55 mL puff volume, 2 s duration, 30 s interval). Using this puffing protocol, we generated aerosol from a single HTP HeatStick (12 puffs), single tobacco cigarette (8 puffs) and from e-cigarette (55 puffs). We used different number of puffs for each product to achieve a comparable nicotine delivery across all tested products. Cambridge filters (44 mm) were used to capture the total particulate matter from all tested products. The control samples (blanks) were generated by passing 55 puffs of air through the filter. Cambridge filters were spiked with deuterated internal standards and extracted using 20 mL 100 mM ammonium acetate. The following TSNAs were measured using liquid chromatography-tandem mass spectrometry: N'-nitrosoanabasine, N'-nitrosoanatabine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and N'-nitrosonornicotine (Toronto Research Chemicals; Canada).[5] A limit of quantitation for each compound was 0.5 ng/filter. Nicotine was measured using gas chromatography with nitrogen-phosphorous detector (GC-NPD) method as described previously.[6] Each product was tested in triplicate. The average TSNA yields for each product were calculated per single puff and per puffing session. We used analysis of variance to test for statistical differences between the three tested products and t-tests to compare TSNA yields from HTP with yields detected in e-cigarettes and combustible cigarettes.

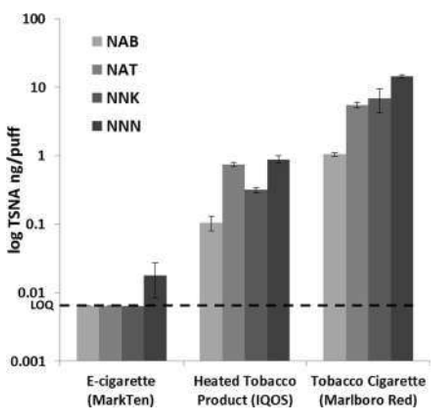


Figure 1 Yields of tobacco-specific nitrosamines (TSNA) (per puff) in aerosols generated from IQOS heated tobacco product (12 puffs/HeatStick), MarkTen e-cigarette (55 puffs) and smoke from Marlboro Red 100 combustible cigarettes (8 puffs/cigarette). The data presented are log transformed. LOQ, limit of quantitation; NAB, N'-nitrosoanabasine; NAT, N'-nitrosoanatabine; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNN, N'-nitrosonornicotine.

RESULTS

All four TSNA compounds analysed were detected in the HTP. The yields of individual TSNA per puff in the HTP aerosols were 8–22 times lower than in tobacco cigarette smoke (figure 1; all $p<0.05$). HTP delivered 1.4 ± 0.2 mg nicotine from a single HeatStick (12 puffs); e-cigarette 1.3 ± 0.2 mg per 55 puffs; and a single combustible cigarette 2.1 ± 0.1 mg (8 puffs). TSNA yields normalised per nicotine delivery were also significantly higher in the HTP than those found in e-cigarettes and significantly lower than those found in tobacco cigarettes, except for NNK ($p<0.05$). TSNA yields in a single tobacco cigarette were between 7 and 17 times higher than TSNA yields in a single HTP HeatStick. No TSNAs were detected in the air control samples.

CONCLUSIONS

Like combustible products, HTPs emit substantial levels of carcinogenic TSNA. Although HTP emits lower amounts of TSNA than combustible cigarettes, the amounts are significantly higher than from e-cigarettes. Our findings are consistent with prior reports.[3 4 7] One limitation of this study is that one puffing protocol was used for all devices. While this was helpful in comparing TSNA and nicotine delivery between devices, machine-based measurements are not represented of human smoking patterns or constitute intake.[8 9] The tested HTP does not reduce emissions of an important class of tobacco carcinogens to the same degree as other commercially available technologies.

Noel J Leigh, Mary N Palumbo, Anthony M Marino, Richard J O'Connor, Maciej Lukasz Goniewicz

Department of Health Behavior, Roswell Park Comprehensive Cancer Center, Buffalo, NY, USA

Correspondence to Dr Maciej Lukasz Goniewicz, Division of Cancer Prevention and Population Sciences, Department of Health Behavior, Roswell Park Comprehensive Cancer, Buffalo, NY 14263, USA; maciej.goniewicz@roswellpark.org

Contributors MLG contributed to the conception of the work. MLG and NJL contributed to data analysis. AMM, MNP, MLG, NJL and RJO drafted the manuscript. AMM, MNP and NJL ran all experiments. All authors approved the final version of the manuscript. MLG has full access to all study data and takes responsibility for the integrity of the data and accuracy of the data analysis.

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Possible hepatotoxicity of IQOS

On 25 January 2018, the Food and Drug Administration (FDA) Tobacco Scientific Advisory Committee unanimously voted (with one abstention) that Phillip Morris International (PMI) could not claim their heated tobacco product (HTP) IQOS (I-Quit-Ordinary-Smoking) would reduce the risk of tobacco-related diseases. Regardless, IQOS is already available in over 30 countries, and thus merits scrutiny from the scientific and medical communities. The preclinical and clinical data PMI submitted to FDA indicate that IQOS exposure may be associated with unexpected liver toxicity. We reviewed preclinical studies conducted by PMI scientists[1] and clinical studies of 5 and 90 days of exposure to IQOS and IQOS menthol[2–5] included in PMI's Modified Risk Tobacco Product application submitted to the US FDA.

Wong and colleagues[1] exposed 92 male and 92 female Sprague Dawley rats to up to 90 days of mainstream aerosol from IQOS, mainstream smoke from 3R4F research cigarettes, or room air (sham). After 90 days of exposure, liver weights and blood levels of alanine aminotransferase (ALT) were measured. ALT is an enzyme released into the blood by hepatocytes during hepatocellular injury[6] and liver weight is a sensitive measure of hepatocellular hypertrophy.[7] After 90 days, ALT levels and liver weights were significantly higher with IQOS than with conventional cigarettes in female animals (table 1). Hepatocellular vacuolisation, a sign of acute liver injury,[7] was significantly increased in IQOS-exposed female rats, an effect not seen in cigarette-exposed animals (table 1).

The human clinical data PMI submitted to FDA provide further cause for concern. Increased plasma bilirubin may signify cholestatic liver injury with impaired hepatic bile flow, accelerated red blood cell destruction, or decreased bilirubin metabolism.[7] Following 5 days of exposure to IQOS, conventional cigarettes or smoking abstinence, plasma bilirubin was elevated in 8.8% of IQOS subjects compared with 0% of cigarette smokers and 2.6% in abstainers.[2] In another 5-day study, the mean increase in ALT was higher with IQOS than with conventional cigarettes or smoking abstinence (4.5, 2.9 and 1.6 IU/L, respectively).[3] In a 90-day study of exposure to mentholated IQOS, mentholated cigarettes or smoking abstinence, the only subject experiencing a grade 2 (moderate) increase in ALT was in the IQOS group.[4] In another study, the rate of grade 1 (mild) increases in ALT after 60 days of exposure was highest with IQOS at 6.3% compared with 0% for conventional cigarettes and 2.6% with smoking abstinence.[5]

Hepatotoxicity constitutes a broad spectrum of injuries to the liver, with consequences ranging from asymptomatic lab abnormalities to hepatic failure and death.[6 7] Notably, there is some evidence that smoking cessation may be associated with a small increase in the unconjugated fraction of bilirubin over the next 1–4 weeks, averaging 0.06 mg/dL.[8] However, in the 5-day exposure study cited above, the rate of elevated bilirubin (>1.0 mg/dL) in IQOS users was over three times higher than that observed with smoking abstinence (8.8% vs 2.6%), and the mean increase above baseline was 0.05 mg/dL with IQOS compared with −0.07 mg/dL with smoking abstinence.[2] We can find no evidence in the literature that smoking cessation is associated with an increase in ALT.

Taken together, PMI's preclinical and clinical data constitute a concerning pattern of possible hepatotoxicity, especially considering the short period of exposure. These findings indicate IQOS may have unexpected organ toxicity that has not been associated with cigarettes. Although IQOS exposes users to lower levels of many toxins than conventional cigarettes, it exposes users to higher levels of other toxins (St Helen *et al*, submitted manuscript). Given the potential for synergistic hepatotoxicity with other medications (eg, acetaminophen), alcohol[9 10] and herbal supplements, the public health community should focus intense scrutiny on possible liver injury in users of IQOS and other HTPs. A broader implication of this finding is that health assessments of IQOS and other non-cigarette tobacco products should consider possible toxicities not associated with conventional cigarettes.

Table 1 Liver parameters in Sprague Dawley rats after 90 days of exposure

	Female			Male		
	Sham	IQOS	3R4F	Sham	IQOS	3R4F
ALT levels (IU/L)	51.0±4.4	73.0±3.2**,****	54.0±2.6	57.0±6.5	75.0±6.7*	68.0±5.8
Liver weight†	339.6±6.6	442.6±10.2***,****	386.7±15.1*	329.3±5.1	381.7±13.2**	373.0±7.9***
Hepatocellular vacuolisation	0.7±0.4	1.5±0.2*	1.2±0.3	1.4±0.3	0.8±0.4	1.8±0.8

Data are from Wong *et al*[1] and are presented as mean±SEM.
*P<0.05 relative to sham; **P<0.01 relative to sham; ***P<0.001 relative to sham; ****P<0.01 relative to 3R4F.
†Normalised to body weight and reported as $\times 10^{-4}$.
ALT, alanine aminotransferase.

Lauren Chun,[1] Farzad Moazed,[1] Michael Matthay,[1,2,3] Carolyn Calfee,[1,2,3] Jeffrey Gotts[1]

[1]Department of Medicine, University of California, San Francisco, San Francisco, California, USA
[2]Cardiovascular Research Institute, University of California, San Francisco, San Francisco, California, USA
[3]Department of Anesthesia, University of California, San Francisco, San Francisco, California, USA

Correspondence to Dr Jeffrey Gotts, Department of Medicine, University of California, San Francisco, San Francisco, CA 94143, USA; jeffrey.gotts@ucsf.edu

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Heated tobacco products likely appeal to adolescents and young adults

Karma McKelvey,[1] Lucy Popova,[2] Minji Kim,[3] Benjamin W Chaffee,[4] Maya Vijayaraghavan,[5] Pamela Ling,[3] Bonnie Halpern-Felsher[1]

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[1]Division of Adolescent Medicine, Department of Pediatrics, Stanford University, Palo Alto, California, USA
[2]School of Public Health, Georgia State University, Atlanta, Georgia, USA
[3]Center for Tobacco Control Research and Education, University of California, San Francisco, California, USA
[4]Division of Oral Epidemiology and Dental Public Health, University of California, San Francisco, California, USA
[5]General Internal Medicine, Zuckerberg San Francisco General Hospital, University of California, San Francisco, California, USA

Correspondence to
Dr Bonnie Halpern-Felsher, Department of Pediatrics, Division of Adolescent Medicine, Stanford University, Palo Alto CA 94402, USA; bonnieh@stanford.edu

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ABSTRACT

Background Beginning in the 1960s in the USA and globally since 1998, tobacco companies have beenaggressively promoting heated tobacco products (HTP). In 2016, Philip Morris International (PMI) applied to the US Food and Drug Administration (FDA) seeking authorisation to market their IQOS HTP system and flavoured 'HeatSticks' in the USA as a modified-risk tobacco product (MRTP).

Methods We systematically evaluated the publicly available data PMI submitted to FDA in its MRTP application to determine whether PMI's IQOS product meets the US Tobacco Control Act's standard for MRTP claims. We examined whether PMI provided sufficient data showing tobacco users will not initiate with IQOS, that youth will not misperceive the MRTP-related claims being made concerning IQOS, and how youth perceive health risks associated with IQOS.

Results PMI's own studies failed to provide evidence that youth, including non-users and former users, will not find IQOS appealing, will not initiate use of IQOS and will not perceive these products as risk-free. Further, PMI did not refer to independent studies conducted among adolescents which could influence their conclusions. Finally, their studies suffered from design and implementation flaws and cannot be relied on to support the proffered claims.

Conclusion PMI's own data and available evidence from scientific studies conducted independent of the tobacco industry regarding how novel tobacco products are currently being marketed suggest that introduction of IQOS will result in adolescent and young adult non-users initiating tobacco use with IQOS and could also increase poly-use of IQOS along with other tobacco products.

INTRODUCTION

Beginning in the 1960s in the USA and globally since 1998, tobacco companies have been developing heated tobacco products (HTP)[1 2]; in 2017, tobacco companies began aggressive worldwide promotion of HTPs. In December 2016, Philip Morris International (PMI) submitted an application seeking the US Food and Drug Administration's (FDA) authorisation to market their IQOS HTP system and flavoured 'HeatSticks' in the USA as a modified-risk tobacco product (MRTP). In the application, PMI sought to make three claims in consumer marketing: (1) switching completely from cigarettes to the IQOS system can reduce the risks of tobacco-related diseases, (2) switching completely to IQOS presents less risk of harm than continuing to smoke cigarettes and (3) switching completely from cigarettes to the IQOS system significantly reduces your body's exposure to harmful and potentially harmful chemicals.

In accordance with the Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act),[3] when considering whether a new tobacco product such as HTPs should be introduced into the US market, the FDA must consider what impact the new products and its related marketing will have on adolescents (ages 10–17) and young adults (ages 18–25), including providing clear evidence about the effect the HTP and related marketing will have on adolescents and young adults (AYA) who are not using tobacco (including never and former tobacco users); whether the new product and related marketing will influence initiation; how AYA consumers *actually use* the HTP; evaluation of consumers' understanding and perceptions of the HTP, including its MRTP claims, labelling, marketing and advertising; and consumers' beliefs about the health risks of using the HTP relative to other tobacco products.

In this paper, we systematically evaluate the publicly available data that PMI submitted to the FDA in its MRTP application to determine whether PMI's IQOS meets the US Tobacco Control Act's standard for making their MRTP claims. In particular, we examine whether PMI provided sufficient data to show whether AYA who are not using tobacco (including never and former tobacco users) will initiate tobacco use with the new IQOS HTP product, whether HTP use among AYA consumers results in reduced levels of harm based on how they actually use the product, and whether AYA correctly understand the risks of HTP relative to other tobacco products.[4]

Because PMI studies provide no evidence on adolescents, we brought in evidence from other tobacco products, particularly e-cigarettes. Unlike regular combustible cigarettes, HTP heat sticks use an electronic heat source to create nicotine-containing aerosols to be inhaled by the user. The resemblance of the HTP device and process is similar to that of e-cigarettes which heat nicotine-containing liquids to generate aerosols. As such, HTPs are considered a form of e-cigarettes in Japan,[5] Korea[1] and Italy.[6] PMI, in their own studies on perceptions, used e-cigarettes for comparison with IQOS (and showed the products were rated similarly).[4] These similarities in consumer perceptions are particularly important because the subjective perceptions and beliefs are what primarily drives consumer behaviour, rather than the physical product features, particularly among adolescents.

Table 1 Systematic evaluation of evidence required by the Tobacco Control Act and evidence provided by PMI vs extant evidence to support or refute MRTP claims

Evidence required by Tobacco Control Act	PMI's evidence	Extant evidence as of 1 June 2018
Will IQOS and its marketing increase the likelihood that AYA *non-users* (including never users and former tobacco products users) will start using the product?	PMI did not provide this evidence. PMI claimed that in a premarket setting, the effect of IQOS on initiation among non-users could not be assessed. Instead, PMI used 'behavioural intentions' among adults as a proxy for behaviour.	Large proportions of non-users are using IQOS and other non-cigarette tobacco products. Studies have found evidence of gateway from e-cigarettes to combusted tobacco products. Intentions are not a suitable proxy for actual behaviour, especially for adolescents.[10–13 48 55–57 77 96]
Does IQOS expose consumers to the claimed reduced level of harm considering how consumers *actually use* IQOS, including concurrent use of multiple nicotine or tobacco products?	Given that dual and poly use were the prevailing patterns in the PMI studies, PMI did not demonstrate that IQOS, as actually used by consumers, reduced levels of harm.	Epidemiological evidence suggests that for other non-cigarette tobacco products, switching completely has not been the most common outcome.[48 77]
Does IQOS advertising or labelling enable the public to comprehend the information concerning modified risk in the context of total health and in relation to all of the diseases and health-related conditions associated with the use of tobacco products and cessation aids?	PMI's application did not include information from studies with adolescents younger than 18. In PMI's studies, adult never-smokers had higher perceived risks of IQOS use compared with current or former smokers. They perceived risks of IQOS as lower than those of combusted cigarettes, but similar to health risks of e-cigarettes.	Extensive literature on adolescents conducted independently of the industry that PMI could have, but did not, present on current, former and non-users of cigarettes demonstrates the need to consider both perceptions of risks and benefits.[15] The actual marketing of IQOS to date in countries other than the USA demonstrates that PMI has not adequately protected against use by non-smokers and suggests that the product's name, physical appearance, flavours and retail environment will appeal to young people.[11 13 14 16–25 68 97]

AYA, adolescents and young adults; MRTP, modified-risk tobacco product; PMI, Philip Morris International.

Finally, given that PMI's MRTP application and their referenced data come mostly from the USA and that PMI is asking permission to market IQOS in the USA, our study largely focuses on US data. However, this study can help inform regulation of other HTP products globally, including whether new HTP products should be approved for sale under explicit or implicit reduced risk claims and marketing in light of how reduced-risk claims are perceived by the public.

METHODS

As part of the public comment process for all FDA MRTP applications submitted from 24 May 24 2017 to 24 January 2018, the FDA made the majority of PMI's MRTP application materials for HTP available online on a rolling basis.[4] We analysed the MRTP application materials and researched the available literature to determine whether PMI's claims concerning IQOS could be supported. The following sections of the PMI MRTP application were analysed in whole or in part: (1) Executive Summary; (2) Module 3: Product Description and Formulation; (3) Module 4: Labels, Labeling, and Advertising; (4) Module 6: Summaries of All Research Findings and (5) Module 7: Scientific Studies and Analyses, including product analyses (7.1), preclinical studies (7.2), studies in adult human subjects (7.3), populations health impact model (7.4) and mechanistic and systems toxicology studies.[4] Considered outside the scope of the present investigation were Module 1 (cover letters), Module 2 (table of contents) and Module 5 (environmental impact), as none contained data germane to the questions addressed in this study.

RESULTS

Table 1 summarises the evidence required by the Tobacco Control Act[3] to make modified risk claims and the evidence provided by PMI in support thereof, including (1) the effect of IQOS marketing on non-users; (2) actual use of the IQOS product and (3) consumer and potential consumer perceptions of IQOS. Table 1 also provides extant evidence on these issues from the literature. For more details on the evidence required and provided by PMI, please see the expanded table in the online supplementary appendix.

PMI's application did not provide any scientific evidence regarding the effect that IQOS and its marketing could have on the likelihood that adolescents who are currently non-tobacco users or who are former tobacco users will start using IQOS (table 1). Instead, PMI claimed that they could not conduct studies on the actual use of IQOS among adolescents, and thereby conducted studies of adults that relied on 'behavioural intention', defined as 'a person's perceived likelihood or subjective probability that he or she will engage in a given behavior,' as a proxy to predict MRTP use behaviours. While many decision-making theories such as Social Cognitive Theory,[7] the Health Belief Model,[8] The Theory of Reasoned Action[9] and The Theory of Planned Behavior[9] have argued that people's behaviours are largely shaped by their intentions to engage in that behaviour, more recent studies[10–13] have shown that these models do not accurately or fully predict adolescent behaviour, including tobacco use.

Further, there is concern regarding the packaging of IQOS and its potential impact on AYA use. IQOS packaging resembles iPhones and other high-end smartphones, where the device and parts are neatly placed in moulded plastic trays inside a glossy white box (figure 1). Piper Jaffray's 11 October 2017 'Taking Stock with Teens' survey of 6100 US teens showed that Apple's iPhone continues to rise in popularity among teens, with 78% of US teens saying they owned an iPhone, and 82% of teens saying their next smartphone will be an iPhone.[14] Adding to these concerns, the IQOS flagship stores in Seoul, Korea, visited in June 2017, look remarkably similar to high-end technology brand stores such as Apple or Microsoft stores in the USA (figures 2 and 3).[1] There is concern that this similarity in appearance to popular personal electronic devices could increase appeal among AYA (the most frequent users of such tech-based devices) and especially since as marketed the IQOS device itself is more similar to a (familiar and low risk) mobile electronic device than a (harmful) tobacco product such as cigarettes. That



Figure 1 Packaging of IQOS (top: picture taken by Minji Kim) resembles that of a high-end smartphone (bottom: Apple iPhone 7; source: www.phonearena.com).



Figure 3 IQOS Flagship store in Amsterdam, Netherlands, September 2017 (photo by Minji Kim).

said, the HeatSticks themselves bear the Marlboro brand and are clearly identifiable as a tobacco product. Packaging and marketing IQOS similarly to non-tobacco products could reduce perceptions of harm. The global experience with e-cigarette marketing demonstrates that perceptions of reduced harm are an important selling point of new products.[11 13 15–27] Another example is JUUL, a pod-based e-cigarette which looks like a USB stick.[28 29] The similarity with a popular consumer technology (USB stick) is another reason for JUUL popularity among adolescents, who are able to 'stealth vape' in school without teachers noticing.[30–32]



Figure 2 IQOS Flagship store in Seoul, Korea, June 2017 (photos by Minji Kim).

PMI also did not demonstrate that IQOS, as actually used by consumers, would 'benefit the health of the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products,' of whom AYA are a major group (table 1). For example, it is widely established that AYA are most likely to use flavoured tobacco products, as we have seen with e-cigarettes, little cigars, smokeless tobacco, and hookah.[19 22 33–41] IQOS HeatSticks currently come in three flavours, Marlboro HeatSticks, Marlboro Smooth Menthol HeatSticks and Marlboro Fresh Menthol HeatSticks. PMI was negligent in their review of the existing literature which shows that exposure to flavour-focused tobacco marketing and reduced risk claims attract AYA never-smokers to initiate tobacco use.[19 22 33–42] While PMI's application is silent on whether or not there will be more flavours of IQOS in the future, tobacco companies have considerable and well-documented experience developing and using flavours to increase the appeal of cigarettes, e-cigarettes, cigars, and smokeless tobacco to young people.[39 41 43–47] Given this history,[39 41 43–47] knowing that the flavoured and menthol products appeal to AYA <<PLEASE ADD REFS 19, 22, 33-41 HERE >>, it is highly likely that PMI will apply this expertise to IQOS <<PLEASE DELETE THESE REFS HERE>> .[11 13 15–27 33 35–42 48]

Finally, PMI did not provide sufficient evidence concerning perceptions of HTP products, including potential adolescent, young adult and adult consumers' beliefs about the MRTP claims, health risks, and cessation claims. There is an extensive literature showing that whether or not there is evidence of a product (most notably e-cigarettes) being safer than combustible cigarettes, if adolescents believe a product is safer (i.e., in the absence of clear evidence and consistent warnings), they are more likely to try and use the product which is an undesired population-level outcome (table 1).[15 18 25 49] <<PLEASE ALSO ADD REF 48 TO THIS LIST>> For example, many e-cigarette users (including AYA who have not smoked conventional cigarettes and those who are at low risk of smoking cigarettes) started using e-cigarettes

because they perceived them as less harmful (i.e., 'reduced risk') compared with cigarettes.[15 16 18 21 49 50] This could be explained, at least in part, by how e-cigarettes were marketed online.[26 51] Websites that compared cigarettes with e-cigarettes stated that e-cigarettes were cleaner (95% of the websites), cheaper (93% of the websites), could be used to circumvent indoor clear air policies (71% of the websites), and could aid in smoking cessation (64% of the websites).[52] These data suggest that marketing strategies for IQOS that could reduce perceptions of harm are likely to increase appeal to AYA. In fact, PMI in their 'IQOS Brand Voice Guidelines' is already marketing HTP as cleaner than cigarettes and states as an 'upside' to using their product: 'It produces less of a smell and no ash, so it's less invasive'. In Japan and Switzerland, the marketing was focused more on cleanliness and 'Clinical purity,' rather than direct claims on health benefits or reduced health risks.[53] In Canada,[54] PMI is promoting IQOS on their own cigarette packs saying 'Why burn tobacco when you can heat it? Real tobacco. Free of Smoke & Ash.'

DISCUSSION

PMI's application to the FDA to market IQOS as a MRTP in the USA ignores the likely effects IQOS and its marketing may have on AYA. PMI fails to provide a sufficiently comprehensive view of how marketing IQOS would benefit the health of the population as a whole and would significantly reduce harm and the risk of tobacco-related disease. PMI failed to provide adequate evidence concerning the effect that IQOS and its marketing will have on the likelihood that *non-users* (including never users and former tobacco products users) will start using the product bearing the proposed marketing claims. There are several problems with the evidence that was presented in PMI's application.

Behavioural intentions are a poor proxy for actual tobacco use behaviour among AYA

PMI used behavioural intentions as a proxy to predict MRTP use behaviours, claiming that the effect of IQOS on initiation among non-users could not be assessed in a premarket setting. However, the literature clearly shows that intentions are a poor proxy for actual behaviour, especially among adolescents.[8–12 55 56] While adolescents may not have an active plan or intention to use tobacco, they often find themselves in situations in which they would consider using even though they were originally committed to avoiding tobacco. Such willingness to use tobacco is a much better predictor of tobacco use than intentions and should be used in studies examining whether and why an adolescent would use any tobacco product.[12 55 57] Hence, not only is it incorrect to claim the impact of marketing cannot be assessed, especially considering PMI is already engaged in marketing IQOS around the world,[1 58] it is also incorrect to assume intentions are the primary drivers of behaviour, especially for adolescents.

Existing independent research studies on other tobacco products should have been presented

Companies are expected to provide evidence of population-level harms and benefits that could result from their MRTP application being reviewed by the FDA. Because those under age 18 are part of the population (and usually their initiation of the product results from actions requested in applications such as the instant MRTP application by PMI) and would be affected by population-level harms, the FDA unquestionably needs information on how those under 18 could be affected by any action resulting from an MRTP application.

Still, PMI cited no studies conducted among adolescents younger than 18, effectively ignoring the fact that most tobacco product use begins before age 18.[50] There is no reason to expect that initiating IQOS would be any different, particularly in light of the fact that levels of other tobacco product use, including e-cigarettes, are highest among AYA.[42 59–63] While neither PMI nor any other tobacco company should be permitted to conduct research on youth below the legal age for tobacco use (21 to be conservative) because the companies could use the information to design marketing campaigns to attract them to their products, it is not credible for PMI to argue that it does not know about or has not reviewed the literature on adolescents' use of other tobacco products, including e-cigarettes. Instead, PMI could conduct and present findings from a comprehensive literature review to inform their conclusions. There is a rich evidence-base of studies conducted among adolescents, independent of the tobacco industry, that PMI failed to review, including data on current, former and non-users of cigarettes[11 13 15–18 21–27 33–42 57] that will help us understand adolescents' intentions and willingness to use novel, non-cigarette tobacco products analogous to IQOS.

Appeal to adolescents of devices with flavours and high-tech look should have been addressed

Adolescents' decisions to adopt use of any tobacco product are based on several considerations, including whether the product appeals to them; the product's flavour, smell and taste; the product's perceived harm or reduced harm; and the ease and location of use.[15 16 18 25 29 64–66] Just as e-cigarettes, particularly the JUUL-style, promoted with a modern, high-tech image and harm reduction and 'smokeless' messages, appeal to adolescents, it is likely that IQOS, marketed in a similar manner, will also appeal to adolescents. It is especially concerning that the IQOS packaging and retail stores as shown in figures 1-3 closely mimic Apple's iPhone and other savvy, high-tech electronic products which might increase appeal to AYA never-smokers.

Flavour or 'taste' is one of the most commonly used marketing techniques to entice AYA to use a product.[67] In particular, sweet and salty flavours are used to promote food (mostly candy and snacks) to children and exposure to flavoured products and ads for such products is positively associated with AYA consumption.[40 68 69] Research on other products such as cigars,[70 71] e-cigarettes,[16 34 38] smokeless tobacco[50 72] and waterpipe[73 74]comports with these findings.[36 68 70]Flavours are frequently used in online e-cigarette marketing and boost user interaction and positive emotion.[23 75] Further, compared with ads for unflavoured tobacco products, flavoured e-cigarette advertisements elicit greater appeal and interest in buying and trying e-cigarettes.[40] The appeal of ads for flavours has been linked to rapid and persistent adoption of e-cigarettes among AYA; and 75% of US AYA stated they would not use e-cigarettes without flavours.[76] Questions regarding the appeal of IQOS flavours to AYA who have never used a tobacco product were left unanswered in PMI's MRTP application.

Concept of 'switching completely' poorly understood

PMI's proposed marketing claims are contingent on the phrase 'switching completely from cigarettes to IQOS' which is incongruent with PMI's own evidence regarding how consumers will *actually use* IQOS, as well as existing epidemiological evidence for related products. Epidemiological evidence suggests that for other non-cigarette tobacco products, switching completely has been an uncommon occurrence. Among US adults who use

e-cigarettes, 75%–82% use it in combination with at least one other form of combustible tobacco.[48 77] Similarly, AYA smokers who use novel tobacco products often use two or more kinds of tobacco products concurrently.[42 63 78–82]

Evidence of AYA understanding and perceptions should have been presented

PMI failed to provide evidence concerning AYA understanding and perceptions of HTP products, including labelling, marketing, advertising, MRTP claims, health risks, and cessation. Tobacco use studies among AYA show perceptions that e-cigarettes present less risk than cigarettes predicts e-cigarette use, even among non-smokers.[15–18 34 42 60 83–93] Adolescents report believing that e-cigarettes are safer than cigarettes, can help people quit smoking conventional cigarettes and contain no or just limited amounts of nicotine.[15–18 34 42 60 83–93] Adolescents also consider e-cigarettes to be trendier, more prevalent and more acceptable than conventional cigarettes.[15–18 34 42 60 83–93] <<PLEASE JUST INCLUDE REFS 15-18 HERE; DELETE THE OTHERS FOR THIS LIST ONLUY>> The lowest perceptions of harm and the most positive attitudes regarding e-cigarettes have been reported among adolescents who have used e-cigarettes.[10 16 25 64 88 94 95] Given the similarities between IQOS and e-cigarettes, including the newer JUUL-style (electronic, hi-tech and claims of reduced harm, a better alternative to cigarettes, no 'smoke'), it is reasonable to hypothesise that IQOS will be popular among AYA because they will make similar assumptions about the risks associated with IQOS, and will be willing to initiate and use IQOS. Perceptions of IQOS and e-cigarettes might be very different due to the differences in products; however, at least from risk perception perspective, IQOS studies themselves show similar levels of perceived risk for e-cigarettes and HTP.

Finally, with any reduced risk claims made by the tobacco industry, it is important to consider whether the evidence is from *independent studies*, versus studies conducted by the industry or influenced or paid for by that industry. Independent studies, as well as an accurate assessment of the extant literature, will better inform whether HTP products will influence tobacco use and misperceptions, with the ultimate goal of improving public health.

LIMITATIONS

In the absence of a research base for IQOS in the USA, we relied on analogous data from e-cigarette research. While an imperfect analogy, we feel the global regulatory atmosphere that largely treats HTP and e-cigarettes similarly, the parallels in devices such that both HTP and e-cigarettes heat and aerosolise tobacco or tobacco components and/or flavours for inhalation by the user, and the similar marketing techniques for HTP and e-cigarettes allow for reasonable analogies to be made and conclusions to be reached.

CONCLUSION

When evaluating whether IQOS or any HTP or new tobacco product should be allowed to come to market, one must consider that adolescents who otherwise would not have used any tobacco product might find the new product appealing, and thus likely will initiate tobacco use with this tobacco product. This is especially likely given AYA's attraction to flavoured tobacco products, the appeal of novel and technology-centric products among adolescents and the tendency for the public at large, including AYA, to misinterpret reduced harm claims. PMI completely ignored all the evidence that flavoured products attract AYA and that they will find the IQOS flavours appealing and therefore will be more likely to use them. The tobacco industry could and should use data available from experiences with other tobacco products, such as with e-cigarettes, that have been collected completely independently of the tobacco industry, to draw reasonable inferences about how the HTP product would affect AYA. No regulatory authority throughout the world should allow any new tobacco product to come to market without solid, independent evidence clearly showing that the new product will not appeal to AYA, misinform AYA about risks or encourage use of multiple tobacco products. Failing to account for these effects make it possible that the overall population impact of introducing new HTP (and other new tobacco products) would be negative even if they pose lower individual risks compared with smoking a cigarette.

What this paper adds

- This is the first independent analysis examining whether Philip Morris International's (PMI) proposed marketing of their new IQOS heated tobacco products (HTP) in the USA will appeal to adolescents.
- PMI's own studies failed to provide evidence that reduced risk perception among youth will not lead to increased use of these products.
- PMI did not refer to an important body of existing, independent research that could influence their conclusions.
- Based on PMI's research and evidence from other non-cigarette tobacco products (e.g., e-cigarettes), HTPs should not be labelled or sold as a modified-risk tobacco product.

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IQOS labelling will mislead consumers

Karma McKelvey,[1] Lucy Popova,[2] Minji Kim,[3] Lauren Kass Lempert,[3] Benjamin W Chaffee,[3,4] Maya Vijayaraghavan,[3,5] Pamela Ling,[3] Bonnie Halpern-Felsher[1]

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[1]Department of Pediatrics, Division of Adolescent Medicine, Stanford University School of Medicine, Palo Alto, California, USA
[2]School of Public Health, Georgia State University, Atlanta, Georgia, USA
[3]Center for Tobacco Control Research and Education, University of California, San Francisco, California, USA
[4]Division of Oral Epidemiology and Dental Public Health, University of California, San Francisco, California, USA
[5]General Internal Medicine/Zuckerberg San Francisco General Hospital, University of California, San Francisco, California, USA

Correspondence to
Dr Bonnie Halpern-Felsher, Department of Pediatrics, Division of Adolescent Medicine, Stanford University School of Medicine, Palo Alto, CA 94402, USA;
bonnie.halpernfelsher@stanford.edu

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ABSTRACT

Background Philip Morris International (PMI) continually expands and diversifies their nicotine product portfolio, which includes IQOS, a heated tobacco product. In December 2016, PMI filed a modified risk tobacco product (MRTP) application with the US Food and Drug Administration (FDA), seeking authorisation to market IQOS in USA with three claims of reduced harm: 'switching completely from conventional cigarettes to the *IQOS* system…' (1) 'can reduce the risks of tobacco-related diseases;' (2) 'significantly reduce[s] your body's exposure to harmful or potentially harmful chemicals;' and (3) 'presents less risk of harm than continuing to smoke cigarettes.' Consumers may misunderstand what is meant by 'switching completely'.

Methods We critically reviewed study reports submitted to FDA by PMI in support of proposed marketing claims in its MRTP application for IQOS and focused on the statement that switching completely to IQOS reduces risk.

Results We found deficiencies with evidence provided by PMI supporting their assertions that: current smokers will understand what is meant by the phrase 'switching completely'; the proposed claims will not decrease smokers' intentions to quit; and IQOS users will in fact 'switch completely' from smoking cigarettes to using IQOS. The studies and measurement instruments employed by PMI suffer from design flaws and their reporting of associated findings is misleading.

Conclusion Consumers will not understand the condition of the claims—that they must quit using cigarettes completely to achieve the inferred health benefits of IQOS. Rather, they are likely to misunderstand the unsupported claims of reduced risks to mean IQOS are harm-free.

INTRODUCTION

As tobacco companies increasingly expand and diversify their nicotine product portfolio,[1] new heated tobacco products (HTPs), also known as heat-not-burn products, that heat modified cigarettes to produce an aerosol for inhalation have been introduced worldwide,[2–4] including Philip Morris International's (PMI's) IQOS.[2 5] As of February 2018, PMI's marketing in several countries claims that because IQOS heats tobacco sticks, not burns them, it poses lower risks than regular combustible cigarettes. These claims have already been made explicitly on PMI's website and in interviews with the media.[6 7] In December 2016, PMI filed a modified risk tobacco product (MRTP) application with the US Food and Drug Administration (FDA), seeking authorisation to market IQOS in USA with three claims, each addressing a particular section of FDA regulation for MRTP applications (see table 1)—two focused on claims of reduced risk, and one focused on the claim of reduced exposure. These claims are provided to participants by PMI in its studies as 'Available Evidence to Date' to discern consumer perceptions of the proposed claims in light of 'warnings' also provided by PMI.

Tobacco companies' history of manipulating scientific studies and interpretation of findings makes it imperative that independent scientists examine the study designs, underlying data and conclusions from all tobacco industry-drive studies, including those involving IQOS and MRTP claims.[8] It is also necessary to bring in research from other fields or with other tobacco products to help inform the regulatory agencies on the potential effects of the new tobacco products and proposed marketing claims. For example, to help inform its decision regarding IQOS, FDA would be well served to consider the recent and well-documented experience with e-cigarettes. In particular, exposure to electronic cigarette ('e-cigarette') advertisements has been shown to cause increases in smoking urges among adult former and current smokers, reduce adolescent never-smokers' perceived risks of regular cigarettes, and to be associated with increased odds of e-cigarette and cigarette use in both cross-sectional and longitudinal studies.[9 10]

In USA, FDA may issue a *risk modification order* permitting an MRTP to be commercially marketed only if the applicant has demonstrated that the product, as it is actually used by consumers, will: (1) Significantly reduce harm and the risk of tobacco-related disease to individual tobacco users. (2) Benefit the health of the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco (Tobacco Control Act section 911(g)(1)). If scientific evidence is not currently available to meet these standards, FDA may issue an *exposure modification order* permitting the marketing of an MRTP that claims to reduce or eliminate exposure to a substance if reduced morbidity or mortality is likely to be demonstrated in future studies and it would 'promote the public health' (Tobacco Control Act section 911(g)(2)). The labelling claims made for MRTPs seeking an exposure modification order must be limited to an explicit or implicit representation that: (1) The tobacco product or its smoke does not contain a substance. (2) The product or its smoke contains a reduced level of a substance. (3) The product presents reduced exposure to a substance in tobacco smoke (Tobacco Control Act section 911(g)(2)(A)(ii)). (See supplementary appendix A for details).

Table 1 Summary of the text provided to participants in Phillip Morris International's (PMI's) studies conducted to evaluate consumer understanding and associated behavioural effects of proposed claims for the IQOS heated tobacco product

Study: THS-PBA-05-RRC-US[17] (n=2255)	Study: THS-PBA-05-RRC2-US[18] (n=2247)	Study: THS-PBA-05-REC-US[19] (n=2272)
Available evidence to date: claim 1*	**Available evidence to date: claim 2***	**Available evidence to date: claim 3***
► The iQOS system heats tobacco but does not burn it. ► This significantly reduces the production of harmful and potentially harmful chemicals. ► Scientific studies have shown that switching completely from conventional cigarettes to the iQOS system can reduce the risks of tobacco-related diseases.	► Switching completely to iQOS presents less risk of harm than continuing to smoke cigarettes.	► The iQOS system heats tobacco but does not burn it. ► This significantly reduces the production of harmful and potentially harmful chemicals. ► Scientific studies have shown that switching completely from cigarettes to the iQOS system significantly reduces your body's exposure to harmful or potentially harmful chemicals.
Important warning:†	**Important warning:†**	**Important warning:†**
► Reduced risk does not mean no risk. The best way to reduce your risk of tobacco-related diseases is to completely quit tobacco use. ► HeatSticks contain nicotine, which is addictive. ► Using the iQOS system can harm your health.	► Less risk of harm does not mean no risk of harm. The best way to reduce your risk of tobacco-related diseases is to completely quit tobacco use. ► HeatSticks contain nicotine, which is addictive.	► It has not been demonstrated that switching to the iQOS system reduces the risk of developing tobacco-related diseases compared with smoking cigarettes. ► HeatSticks contain nicotine, which is addictive. ► Using the iQOS system can harm your health.

Source, PMI Research and Development. *6.4 Consumer Understanding and Perceptions.* 2015. Available at: https://www.accessdata.fda.gov/Static/widgets/tobacco/MRTP/PMP/PMP_MRTPA_FDA-2017.zip

*'Available evidence to Date'. Term used by PMI to refer to 'caveats on disease risk and addiction included in PMI Warnings'[6]

†'Important Warning'. Term used to refer to proposed warnings developed by PMI.

In making the determination of whether to issue either a risk modification or an exposure modification order, FDA must take into account the net 'benefit to the health of the population as a whole', considering 'the increased or decreased likelihood that existing users of tobacco products who would otherwise stop using such products will switch to the tobacco product that is the subject of the application' and 'the increased or decreased likelihood that persons who do not use tobacco products will start using the tobacco product that is the subject of the application' (Tobacco Control Act section 911(g)(4)). For an exposure modification order, the applicant must also demonstrate that actual consumer perception tests show that, 'as the applicant proposes to label and market the product, consumers will not be misled into believing that the product – (I) is or has been demonstrated to be less harmful; or (II) presents or has been demonstrated to present less of a risk of disease than one or more other commercially marketed tobacco products' (Tobacco Control Act section 911(g)(2)(B)(iii)).

Therefore, to obtain a risk modification order under US law allowing PMI to market IQOS with its proposed labelling and advertising claims, PMI must present scientific data demonstrating that switching completely from conventional cigarettes to IQOS significantly reduces harm and the risk of tobacco-related diseases. To obtain an exposure modification order allowing PMI to market IQOS with its proposed labelling and advertising claim, PMI must demonstrate that switching completely from cigarettes to IQOS significantly reduces consumers' exposure to harmful substances, and that actual consumer perception studies show that consumers understand that the product has *not* been demonstrated to be less harmful or present less risk of disease.

The goal of this paper is to critically review the reports on the studies PMI submitted as part of its MRTP application for IQOS to support their proposed marketing claims, with a particular focus on the statements that switching completely to IQOS reduces risk.[11]

METHODS

Beginning in May 2017, the FDA made most of PMI's MRTP application materials for their HTP available online on a rolling basis for public comment. Most of the materials, including PMI's actual studies, were not publicly available until November 2017. We reviewed and analysed PMI's IQOS MRTP application materials and researched the relevant available literature to evaluate the evidence to support PMI's claims. We reviewed sections in the application that are pertinent to the product advertisements, warning labels and PMI's reports of relevant studies. We examined these application documents to establish what PMI provided as evidence in support of their MRTP application and sought to determine whether such evidence was sufficient. To determine sufficiency, we reviewed study designs, reported study limitations, and determined whether conclusions were supported by the data. Methods used by PMI in their studies are discussed below within the context of the MRTP application claims.

We examined PMI's studies for evidence that tobacco consumers and non-consumers will accurately understand the risks of IQOS as conveyed by PMI's proposed claims and understand what is meant by 'switching completely'; that IQOS claims will not affect combustible tobacco users' intentions to quit; and that combustible tobacco users will completely switch to IQOS (see table 2 for overview of PMI studies).

RESULTS

PMI did not provide sufficient evidence of consumer understanding of the concept of switching completely

PMI conducted quantitative studies to test comprehension of and risk perceptions associated with their proposed modified risk claims (section 6.4).[11] Table 1 delineates PMI's designated study numbers, PMI's claims and what PMI termed 'available evidence' that were shown to participants. Studies were conducted among US adult consumers (n=6774 total for the three studies), who were stratified into five groups: smokers with no intention to quit, smokers with an intention to quit, former smokers, never smokers and never smokers from the legal smoking age to age 25 years. Participants were then randomised by stratum and exposed to different combinations of PMI proposed claims and warnings or to the current Surgeon General's warnings mandated for cigarettes: (1) 'Smoking causes lung cancer, heart disease, emphysema, and may complicate pregnancy;' (2) 'Quitting smoking now greatly reduces serious risks to your health;' (3) 'Smoking by pregnant women may result in fetal injury, premature birth, and low birth weight;' and (4) 'Cigarette smoke contains carbon monoxide'. Table 3 presents outcome measures used in these studies.

Table 2 Overview of studies conducted by Philip Morris International (PMI) in support of its MRTP application

Study name	Methodology	Study year	Stated study goal
THS-PBA-01-US	Qualitative and quantitative	December 2012–June 2014	Development and validation of psychometric instruments for 'Risk Perception' and 'Intent to Use for tobacco products'
THS-PBA-02-US	Qualitative	October-December 2013	Testing 9* potential 'plain text'† messages
THS-PBA-03-US	Quantitative	October-December 2014	Testing three potential 'plain text' messages selected from THS-PBA-02-US
THS-PBA-04-US	Qualitative	December 2014	Testing five potential branded‡ communication materials with claims selected from THS-PBA-02-US
THS-PBA-05-RRC-US	Quantitative	July 2015	Testing three branded communication materials with claim #1 'Reduced risks of tobacco-related diseases'
THS-PBA-05-RRC2-US	Quantitative	September 2015	Testing three branded communication materials with the claim #2 'Reduced risk of harm'
THS-PBA-05-REC-US	Quantitative	December 2015	Testing three branded communication materials with the claim #3 'Reduced body's exposure to harmful and potentially harmful chemicals'

*The table in the PMI document mentions 9 messages, but there were actually 13 different messages for phase I because there are two versions of some (A1, A2, B, C1, C2, D and so on). Phase II of the study tested seven messages.
†'Plain text' message describes the information communicated on the product.
‡Branded communication materials were brochure, pack, and direct mail piece with the iQOS commercial name and the Tobacco Sticks as HeatSticks with the Marlboro Brand.
MRTP, modified risk tobacco product.

While PMI emphasised that the majority of participants were able to select the 'correct' statement (indicating that the risk of tobacco-related diseases can be reduced by completely switching from cigarettes to IQOS), PMI did not test whether participants understood what 'switching completely' meant. PMI reported that after seeing the proposed claims, 62%–78% of all participants were able to identify the 'correct' statement, which indicated that the risk of tobacco-related diseases can be reduced by completely switching from cigarettes to IQOS. However, this question did not measure whether participants understood the phrase 'completely switching', rather it tested recognition of the terms 'reduced' and 'eliminates'; all response options included the phrase 'completely switch'. Still, PMI interpreted this finding to indicate participants understood the 'reduced' risks of IQOS compared with regular cigarettes. Further, to assess perceptions of their claims and the IQOS product, PMI created and used a new 18-item Perceived Health Risk Scale, a 7-item Perceived Addiction Risk Scale and a 2-item Perceived Harm to Others Scale. PMI reported that HTP was on average '8 and 22 points lower than conventional cigarettes on the 0 to 100 perceived health risk scale'.[12] Hence, PMI failed to demonstrate at least two important factors that FDA deemed critically important to its review of MRTP applications: (1) Whether consumers fully 'understand the modified risk claims and the significance of the information in the context of one's health'. (2) Whether consumers truly understand 'the health risks of using the product.'

PMI's studies of whether smokers will completely switch from cigarettes to IQOS

Premarket human behaviour studies (design and results)

PMI's proposed marketing claims were all contingent on the phrase 'switching completely' from cigarettes. PMI's application drew evidence from two groups of premarket studies in which adult daily cigarette smokers were provided with IQOS *HeatSticks* and asked to record their tobacco use over time. The 'Whole Offer Test' (WOT) studies were conducted in five countries (Japan, Italy, Germany, Switzerland and South Korea) and the study THS-PBA-07-US took place in USA (table 4).

Participants were instructed to record each instance of using IQOS or smoking a cigarette in an electronic (THS-PBA-07-US) or pencil-and-paper (WOT) diary. The WOT studies ran for 4 weeks; THS-PBA-07-US ran for 6 weeks. Participants were given access to IQOS free of charge and, presumably, purchased any cigarettes at their own expense.

The studies examined several behavioural patterns, based (presumably, but not explicitly) on the percentage of diary entries made for use of a cigarette or IQOS. There was no category for 'switching completely' from cigarettes to IQOS. The 'exclusive' IQOS category included individuals at 95%–100% IQOS use, not necessarily completely switched, and not counting tobacco products other than IQOS and cigarettes. Behaviours beyond 6 weeks, when *HeatSticks* were no longer available for free, were not examined.

In these PMI studies, switching from cigarettes to 'exclusive' (ie, 95%–100%) IQOS use was rare (table 5). In THS-PBA-07-US, among adult daily cigarette smokers who completed the 6-week follow-up period, only 6% (58/968) of participants achieved 'exclusive' IQOS use, defined by PMI as using IQOS ≥100 times during the study and having *HeatSticks* comprise ≥95% of total recorded amount of cigarettes smoked and *HeatSticks* used in week 6 (table 4). Only 3% (15/465) of study completers who also kept valid diaries throughout achieved exclusive use (per-protocol analysis), and among all completers who reported using IQOS ≥100 times, just 16% become exclusive users. Occurrence of exclusive IQOS use among study completers was similarly uncommon in other settings: Japan (13%), Italy (5%), Germany (8%), Switzerland (4%) and South Korea (15%).

Premarket human behaviour studies (limitations)

The WOT and THS-PBA-07-US studies did not provide sufficient evidence that a substantial portion of adult cigarette smokers will completely switch to IQOS, first and foremost because the outcome 'switching completely' (ie,100% IQOS use) was not reported. Additional limitations deserve mention. For example, participants were given access to IQOS *HeatSticks* free of charge but, presumably, purchased cigarettes, giving an economic advantage to IQOS over cigarettes that would not be present in a real world setting.

No efforts to validate the accuracy of the self-reports were described. There was no comparison group to evaluate how keeping a daily tobacco diary, regardless of access to IQOS, would affect cigarette consumption. Such validation is important, as it is well documented that individuals change their behaviour when asked to keep a running log, such as food diaries.[13 14] Given that approximately half the sample did not use the diaries to document tobacco use for the duration of the study, the validity of estimates based on the full sample is questionable.

PMI reported that the proportion of participants switching back to cigarettes from exclusive IQOS use was 'very low'. However, participants were not classified as switching back to

Table 3 Outcome measures in quantitative studies

Construct	Instrument	Example questions
Intent to use	The Intent to Use Questionnaire (ITUQ) ► Intention to try (ie, to sample at least once; two items) ► Intention to use (ie, for continued usage; two items) (Answers on a 6-point scale from 'Definitely Not' to 'Definitely')	Based on what you know about IQOS, how likely or unlikely are you to try IQOS? If you try IQOS and like it, and taking into consideration the prices that are shown on the material, how likely or unlikely are you to use IQOS regularly?
Change in intention to quit smoking	Yes/no questions based on Prochaska and DiClemente's Stages of Change model[31] measured before and after exposure to IQOS message to determine change in intention to quit smoking (four items—two for smoking, two for all tobacco products)	Are you seriously considering quitting smoking within the next 6 months? Are you planning to quit smoking in the next 30 days?
Comprehension	1. 'Global comprehension': overall comprehension of the IQOS message on exposure to harmful chemicals and risk of tobacco-related diseases of using IQOS. 2. 'Specific comprehension': comprehension of three specific parts of the IQOS message: the Intended Users Statement, Evidence Statement and Warning Statement. Both types of comprehension were assessed with multiple-choice questions, five response options were presented, with one correct option, three incorrect options and an option for 'don't know'.	Next, thinking about all of the information on the IQOS material, completely switching from conventional cigarettes to IQOS: a. Can increase the risk of tobacco-related diseases. b. Can reduce the risk of tobacco-related diseases (correct). c. Has the same risk of tobacco-related diseases. d. Can eliminate the risk of tobacco-related. diseases e. Don't know. What happens to tobacco when IQOS is used? a. It is burned. b. It remains at room temperature. c. It is cooled. d. It is heated but not burned (correct). e. Don't know.
Risk perception	The Perceived Risk Instrument-Personal Risk (PRI-P) comprised of two domains, each measured by a unidimensional scale: 1. Perceived Health Risk 18-item Scale 2. Perceived Addiction Risk 7-item Scale 3. Perceived Harm to Others (two separate questions) Answers were no risk, low risk, moderate risk, high risk, very high risk and don't know, and were later converted into a 0 to 100 scale (0=no risk and 100=very high risk)	If you were to start using IQOS, what do you think would be the risk, if any, to you personally of getting the following (sometime during your lifetime) because you use IQOS…losing some sense of taste, having heart disease, an earlier death, having sores of the mouth or throat, and so on. If you were to start using IQOS, what do you think would be the risk, if any, to you personally of experiencing the following because you use IQOS… being unable to quit cigarettes, feeling like you have to smoke cigarettes, and so on. If you were to start using IQOS, what do you think would be the risk, if any, to others because you use IQOS… harming others through your secondhand smoke, harming unborn baby.

Source, Adopted from Table 17 in the Executive Summary, p. 121.[15]

smoking (cigarettes) unless cigarettes comprised 70% of products used, and participants first had to be classified as 'exclusive' IQOS users, leaving only a fraction of the observation period remaining to switch back. Nonetheless, PMI concluded that IQOS 'has the potential to completely 'switch' a sizeable proportion of participants',[15] despite the fact that in these PMI studies, an unknown percentage (but no more than 3%–15%) of adult cigarette smokers with access to IQOS free of charge switched completely. Together, the potentially misleading and arbitrary product use definitions, non-validated measurement methods, lack of a comparison group, and differential financial cost between IQOS and cigarettes cast doubt on the real world relevance of these PMI behavioural studies, even had the occurrence of switching completely been more common.

PMI summary reports misrepresent their own data on the effects of message exposure on changing intentions to quit smoking

The executive summary of the MRTP application, referring to the results stated in the executive summary of PMI's MRTP application, reported the effect of the proposed claims on smokers' intentions to quit smoking cigarettes, stating that: 'most smokers did not change their intentions to quit, maintaining positive responses to quitting in a range of 83% to 97% across all arms of the study'. However, the study tables showed that PMI designated participants who lowered their intentions to quit from planning to quit in the 'next 30 days' to planning to quit within 'next 6 months' as 'did not change their intentions to quit'.[16] The disaggregated data show that among those who had intentions to quit in the next 30 days at baseline, between 7% and 24% reduced their intentions to 'quit within next 6 months' and an additional 3%–10% said they no longer plan to quit. Among those who planned to quit in the next 6 months at baseline, 5%–17% indicated they no longer had intentions to quit (see tables 4 and 6 for detailed findings). Similarly, the executive summary for studies THS-PBA-05-RRC, THS-PBA-05-RRC2 and THS-PBA-05-REC stated that smokers with intentions to quit 'did not appreciably change their stated intentions to quit smoking…' and listed proportions of participants who 'stated a change in intentions' between 3.2% for increased intentions and 11.8% for decreased intentions.[17–19] The detailed data in the tables show that among smokers who planned to quit within 30 days, after exposure 3%–24% deferred quitting to the next 6 months, and an additional 0%–10% changed to stating they never planned to quit. Further, detailed study results found in PMI results tables show much greater reductions in intentions to quit following exposure to IQOS messaging when compared with the results PMI emphasised in the executive summary.

PMI's perceived risk measures were flawed and incomplete

PMI's perceived risk instrument was flawed and the choice of their risk perception questions was seemingly guided by tobacco companies' goals rather than measures of validity.[8] In their Instrument, PMI measured absolute perceptions of risk for each product (separately for cigarettes, e-cigarettes and IQOS; for example, 'If you were to start [smoking/using e-cigarettes/using IQOS], what do you think would be the risk, if any, to you personally of experiencing the following because you [smoke

Table 4 Premarket human behaviour studies

	Duration	Participants started	Participants completed	Switch to 'Exclusive' IQOS use*	IQOS use category in the final study week (completed participants)				
					Exclusive† IQOS use	Predominant‡ IQOS use	Combined§ IQOS+cigarettes	Predominant¶ cigarette use	Exclusive** cigarette use
THS-PBA-07-US									
Analytical sample††	6 weeks	1106	968	6.0%	7.5%	7.0%	22.4%	28.2%	34.5%
On-protocol sample‡‡	6 weeks	1106	465	3.2%	6.5%	5.2%	20.8%	32.9%	34.6%
WOT - Japan									
Included sample§§	4 weeks	718	638	13.2%	13.6%	16.1%	32.3%	27.7%	10.2%
WOT - Italy									
Included sample§§	4 weeks	571	535	4.7%	5.2%	6.9%	37.9%	39.3%	10.7%
WOT - Germany									
Included sample§§	4 weeks	443	377	7.7%	8.5%	11.4%	27.3%	24.7%	28.1%
WOT - Switzerland									
Included sample§§	4 weeks	516	416	3.8%	4.3%	5.5%	39.4%	30.5%	20.2%
WOT - South Korea									
Included sample§§	4 weeks	936	843	15.3%	15.7%	21.5%	36.3%	17.3%	9.3%

*Recorded use of ≥100 *HeatSticks* during the study and *HeatSticks* comprised ≥95% of total cigarettes and *HeatSticks* recorded in the final week.
†Of cigarettes and *HeatSticks* recorded, *HeatSticks* comprised ≥95% of total.
‡Of cigarettes and *HeatSticks* recorded, *HeatSticks* comprised ≥70% but <95% of the total.
§Of cigarettes and *HeatSticks* recorded, *HeatSticks* comprised ≥30% but <70% of the total.
¶Of cigarettes and *HeatSticks* recorded, *HeatSticks* comprised ≥5% but <30% of the total.
**Of cigarettes and *HeatSticks* recorded, *HeatSticks* comprised <5% of the total.
††Analytical sample restricted to a subset of enrolled participants who met inclusion criteria and recorded ≥1 cigarette use during the 1-week baseline run-in period and ≥1 IQOS *HeatStick* use during the 6-week observation period (excludes 262 of 1368 initially enrolled participants).
‡‡Per-protocol sample restricted to participants who also documented tobacco use 39 days of the 42-day observation period and did not report IQOS use exceeding number of *HeatSticks* supplied by >5% or 20 units.
§§Sample restricted to participants who completed 26 of the 28 daily tobacco use diary entries (ranges from 81% to 93% of participants who were eligible to begin the 4-week studies based on willingness to use IQOS).
n/a=not applicable; nr, not reported; WOT, whole offer test.

cigarettes/use e-cigarettes/use IQOS]…'), rather than asking direct comparative questions (eg, 'Are (IQOS products) less harmful/equally as harmful/more harmful than (cigarettes)?'). A better approach would have been to use both types of questions. Not doing so unavoidably biased results. Further, PMI did not provide any information on how a particularly relevant population—youth—will perceive these claims.

PMI failed to include a control group in studies testing effects of claims and marketing materials

PMI's designs to assess perceptions and intentions to quit did not include a control group. A control group with no exposure to IQOS information or to marketing material without any modified risk claim but with a strong health-related warning would have allowed PMI to draw conclusions on the effects of the messages on perceptions of risk of IQOS, and on intent to use and intent to quit smoking. Without a control group it is impossible to tell whether the messages had an effect on intentions to quit, if the effect was a result of repeated testing, or if using messages without modified risk claims may have prevented or otherwise altered the reported reduction in intentions to quit smoking.

Table 5 Postexposure intentions to quit among smokers who intend to quit within the next 6 months at baseline

Row #	Study	Next 6 months	No intention	Increased intentions to quit (next 30 days)
1	PBA-03	79%–90%	5%–17%	0%–5%
2	PBA-05-RRC	80%–89%	7%–18%	0%–6%
3	PBA-05-RRC2	74%–98%	0%–21%	2%–6%
4	PBA-05-REC	76%–92%	7%–19%	0%–5%
5	Overall	74%–98%	0%–21%	0%–6%

Note. Showing proportion of respondents among those who originally reported intention to quit within the next 6 months (100%) and then chose each answer postexposure to PMI proposed claims. The range indicates the lowest and highest numbers among the different messages/arms used in each study. PMI reports data separately for each arm of the study, rather than presenting the average for the whole study.

DISCUSSION

We found deficiencies with the evidence provided by PMI in support of their assertions that current smokers will understand what is meant by the phrase 'switching completely'; that IQOS users will not in fact 'switch completely' from smoking cigarettes to using IQOS and may become 'dual users' of IQOS and cigarettes; and that their proposed claims will not decrease smokers' intentions to quit smoking. Further, the studies and measurement instruments employed by PMI suffer from design flaws and their reporting of associated findings is misleading.[16 20 21]

In their MRTP application, PMI included three proposed claims of reduced harm, risk and exposure that assert 'switching completely' from cigarettes to IQOS bestows health benefits.[11] According to the Tobacco Control Act section 911(g)(2)(B)(iii), in MRTP applications for exposure modification orders, the applicant is required to demonstrate that consumers will not be misled by claims in labels or advertising. In their MRTP application materials, PMI failed to provide evidence that current smokers will understand what is meant by the phrase 'switching completely'.

PMI did not provide adequate evidence of how and if people understood the phrase 'completely switching', as used in their claims. Instead, their research only tested recognition of the terms 'reduced' versus 'eliminates', because the questionnaire

Table 6 Postexposure Intentions to quit among smokers who intend to quit within the next 30 days at baseline

Row #	Study	Plan to quit in the next 30 days	Plan to quit in the next 6 months	No intention to quit	Total reduction
1	PBA-03	67%–90%	7%–24%	3%–10%	10%–33%
2	PBA-05-RRC	83%–95%	3%–18%	0%–3%	5%–17%
3	PBA-05-RRC2	73%–95%	3%–24%	2%–6%	5%–27%
4	PBA-05-REC	83%–97%	3%–15%	0%–7%	3%–17%
5	Overall	67%–97%	3%–24%	0%–10%	3%–33%

Note. Showing proportion of respondents among those who originally reported intention to quit within the next 30 days (100%) and then chose each answer postexposure to PMI proposed claims. The range indicates the lowest and highest number among the different messages/arms used in each study. PMI reports data separately for each arm of the study, rather than presenting the average for the whole study.

asked, after reading the warning labels of IQOS, whether the respondents think 'completely switching from conventional cigarettes to IQOS' results in (1) 'increase the risk of tobacco-related diseases', (2) 'reduce the risk of tobacco-related diseases', (3) 'the same risk of tobacco-related diseases', (4) 'eliminate the risk of tobacco-related diseases' (underlines added). There remains considerable concern that IQOS consumers and potential IQOS consumers will not fully understand there is a contingency to PMI's claim of modified risk—namely, that one must 'completely switch' from cigarettes to IQOS to benefit their health.

PMI also failed to test whether people understood that 'switching completely' refers to switching away from cigarettes; thus, there is concern that e-cigarette users could interpret the claim to mean switching away from any tobacco product, including e-cigarettes, to a HTP would reduce harm, despite there being no evidence that IQOS are less harmful to health than e-cigarettes.

The claim that switching completely to IQOS could reduce harm and tobacco-related diseases assumes that people who attempt to switch will be successful at cigarette smoking cessation. However, available data suggest that cigarette smokers who try to switch from cigarettes to other tobacco products or who use other tobacco products for smoking cessation are more likely to be nicotine-dependent and experience difficulty with smoking cessation compared with people who do not use these alternative tobacco products.[22] Further, PMI ignores evidence that smokers who use novel tobacco products such as e-cigarettes often use two or more tobacco products in combination instead of switching entirely. Indeed, PMI's own data on IQOS show substantial levels of combined use in their test populations, and epidemiological evidence demonstrates that for other non-cigarette tobacco products, switching completely is not the most common outcome. Among US adults who use electronic cigarettes, 75% to 82% use e-cigarettes in combination with at least one other form of combustible tobacco, and only 20% of e-cigarette users report switching completely from combustible cigarettes. Finally, PMI's proposed warnings do not specifically inform consumers that continuing to smoke while using IQOS could reduce the likelihood of quitting smoking.[23 24] As such, PMI's data do not support their MRTP claim, and instead both data presented by PMI and in the literature base support the idea that introducing any HTP product (including IQOS) will likely be harmful to population health.

Research on e-cigarettes indicates that some dual users of e-cigarettes and combustible cigarettes viewed reduction in smoking as equivalent to quitting, not recognising the need to switch completely.[23] The evidence base showing adult tobacco users have difficulty understanding modified risk 'warnings' such as 'light' or 'low tar' cigarettes is well known, widely accepted and was relied on in formulating the Tobacco Control Act of 2009. Moreover, such messages are also shown to be misinterpreted by youth.[25–27] When individuals do not adequately understand warning messages or receive vague messages, they often make assumptions that the tobacco product is safe and are therefore more likely to initiate and/or continue using the product.[26 28] In fact, the Tobacco Control Act, Section 2, Finding 40 states:

> The dangers of products sold or distributed as modified risk tobacco products that do not in fact reduce risk are so high that there is a compelling governmental interest in ensuring that statements about modified risk tobacco products are complete, accurate, and relate to the overall disease risk of the product.

PMI's studies failed to offer findings that users and potential users of IQOS will not harbour similar misperceptions as has been seen with e-cigarettes and other tobacco products.

PMI also failed to provide evidence that their proposed claims will not decrease smokers' intentions to quit smoking or that IQOS users will in fact 'switch completely' from smoking cigarettes to using IQOS.[15] Instead, the evidence provided by PMI showed that use of both cigarettes and IQOS would be the predominant pattern, rather than switching completely from smoking cigarettes to using the IQOS. The detailed reports for PMI's studies on the effect of exposure to their proposed warnings on intentions to quit did not present information separately for smokers who had intentions to quit in the next 30 days and those with intentions to quit in the next 6 months at baseline. Rather, they obfuscated findings that actually showed that postexposure to their proposed warnings, up to nearly a quarter of smokers who planned to quit in the next 30 days at baseline switched to planning to quit within the next 6 months, and up to an additional 10% no longer intended to quit. Similarly, up to 24% of smokers who had planned to quit within the next 6 months at baseline said they were never planning to quit postexposure. In multiple instances, PMI's MRTP application departs from standard practices in scientific reporting, leaving out important methodological details, using non-standard, non-validated measurement tools and definitions, and summarising findings in misleading ways. For example, in examining whether non-smokers would be interested in using IQOS, PMI inappropriately characterised data from limited qualitative studies as representative of consumer perceptions. In their Perceived Risk Instrument, PMI measured absolute perceptions of risk for each product (separately for cigarettes, e-cigarettes and IQOS), rather than asking direct comparative questions. Past research has found that when risks are measured for products separately, a greater proportion of people perceive alternative tobacco products as less harmful.[29] When comparative risk is measured with a direct question, a greater portion of participants respond that alternative tobacco products are equally as harmful as cigarettes.[29 30] Use of both types of measures is necessary to demonstrate their findings are not simply an artefact of their carefully designed measurement tool.

CONCLUSION

PMI failed to demonstrate that the proposed IQOS claims within their MRTP application, and especially statements regarding 'switching completely' (1) Will be interpreted as meaning that the potential health benefits of IQOS are contingent on one completely quitting cigarettes. (2) Will not result in widespread misperceptions that the IQOS product is a harm-free alternative to combustible cigarettes. (3) Will not lead to substantial product appeal (and subsequent use) among youth, non-smoking adults and former smokers. (4) Are consistent with the scientific evidence of actual harm and exposure. (5) Are consistent with how those marketing claims will be interpreted and perceived by potential consumers. (6) Will not mislead consumers, especially adolescents and young adults, about the health risks of IQOS and the relative risks compared with not using any tobacco product. FDA should deny PMI's MRTP application because it does not include sufficient evidence to address these points.

What this paper adds

- This study is among the first to critically review data submitted by Philip Morris International (PMI) as part of their modified risk tobacco product (MRTP) application to the Food and Drug Administration (FDA).
- PMI's studies did not provide sufficient evidence that heated tobacco products (HTP) users will completely switch from cigarettes to HTP or that consumers understand the proposed claims regarding exposure, harm and 'switching completely'.
- PMI's MRTP application does not satisfy FDA requirements that consumers will not be misled; therefore, HTP should not be allowed to be marketed with reduced risk claims.

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Awareness and use of heated tobacco products among US adults, 2016–2017

Amy L Nyman,[1] Scott R Weaver,[1,2] Lucy Popova,[1,3] Terry Frank Pechacek,[1,4] Jidong Huang,[1,4] David L Ashley,[1,5] Michael P Eriksen[1,4]

[1]School of Public Health, Tobacco Center of Regulatory Science (TCORS), Georgia State University, Atlanta, Georgia, USA
[2]Division of Epidemiology and Biostatistics, School of Public Health, Georgia State University, Atlanta, Georgia, USA
[3]Division of Health Promotion and Behavior, School of Public Health, Georgia State University, Atlanta, Georgia, USA
[4]Division of Health Management and Policy, School of Public Health, Georgia State University, Atlanta, Georgia, USA
[5]Division of Environmental Health, School of Public Health, Georgia State University, Atlanta, Georgia, USA

Correspondence to
Amy L Nyman, Tobacco Center of Regulatory Science (TCORS), School of Public Health, Georgia State University, Atlanta, GA 30302, USA; anyman@gsu.edu

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ABSTRACT

Introduction Although heated tobacco products (HTP) have been on and off the commercial market for the past three decades (eg, Premier, Eclipse and Accord), they have not received widespread consumer acceptance as an alternative to combustible cigarettes. This may change with recent product innovations, shifts in consumer preferences and the tobacco market landscape and a US regulatory environment that may permit an internationally available HTP to be sold in the USA, possibly with a reduced exposure or risk statement. This study examined the extent of awareness and use of HTP in the USA and assessed the characteristics of those aware of and using these products.

Methods Data came from the 2016 and 2017 Tobacco Products and Risk Perceptions Surveys of national probability samples of US adults, conducted online during September–October 2016 (n=6014) and August–September 2017 (n=5992). Weighted χ^2 tests and regression analyses examined changes in awareness and use of HTP between 2016 and 2017 and characteristics associated with awareness and use.

Results From 2016 to 2017, awareness of HTP among US adults increased from 9.3% to 12.4% (p<0.001), ever use increased from 1.4% to 2.2% (p=0.005) and current use increased two fold, from 0.5% to 1.1% (p=0.004). Men and adults under age 45 years had higher rates of awareness than women and those 45 and older, respectively. Non-white adults, cigarette smokers and both current and former users of electronic nicotine delivery systems were more likely to be using HTP.

Conclusions Awareness and use of HTP in the USA are increasing. These products are more familiar to men and younger adults and may be being used disproportionately by racial/ethnic minorities. With increases in HTP availability and the potential for reduced-risk claims ahead, surveillance of patterns and consequences of use by both smokers and non-smokers is needed.

INTRODUCTION

Heated tobacco products (HTP), also called 'heat-not-burn' tobacco products, contain tobacco that manufacturers claim is heated to temperatures that are below the level of combustion,[1] even though recent research has called this into question.[2] Users inhale a nicotine-containing aerosol created by heating the tobacco materials, instead of smoke from combustion,[3] thereby reducing the intake of chemicals previously identified by Food and Drug Administration (FDA) as harmful or potentially harmful but increasing the levels of certain other constituents.[4–7]

HTP have been manufactured and commercially available in the USA since the 1980s but have not experienced widespread commercial success. However, the historically lacklustre consumer adoption and market failures may give way to increased appeal and consumer acceptance owing to recent product innovations, shifts in consumer preferences and the tobacco market landscape and a US regulatory environment that might soon permit an internationally available HTP to be sold in the USA, and possibly with a reduced exposure or reduced risk statement. Although many electronic nicotine delivery systems (ENDS), which typically contain no tobacco, have held promise as less-toxic substitutes for cigarettes,[8] many smokers have rejected them as unsatisfying and not similar enough in feel to cigarettes.[9 10] In contrast, HTP have a taste and nicotine delivery profile similar to combustible cigarettes.[9] Some HTP, such as TEEPS by Philip Morris International (PMI), which uses an ignited heat source, also have an appearance and feel similar to cigarettes that may make them more appealing to smokers as substitutes for the combustible cigarette. However, some early independent research found that smokers did not perceive IQOS, another HTP from PMI that uses an electronically (battery) powered heat source, as delivering the same taste and nicotine intensity as cigarettes.[11]

Currently sold in markets in at least 30 countries,[12] the IQOS HTP by PMI has generated considerable consumer and market interest, as well as concerns among tobacco control proponents and policy makers.[13] In South Korea, where IQOS has been available since May 2017, and in numerous other locations, PMI has sold the products in spacious, sleek stores resembling those for other high tech devices and employed sophisticated marketing strategies to engage potential users.[14 15] Few studies of prevalence of the IQOS or other HTP awareness and use have been conducted. A 2017 survey of respondents ages 15 years and older in Italy, where IQOS has been available since 2014, found 19.5% of respondents were aware of IQOS and 1.4% have tried it.[16] In Japan, where IQOS has been available since November 2014 and is now sold nationally along with competing HTP from Japan Tobacco and British American Tobacco (but no nicotine-containing ENDS),[17] prevalence of current IQOS use increased dramatically (from 0.3% in 2015 to 3.6% in 2017) following publicity on a popular television show in April 2016.[12 18] Japanese Google searches for HTP have also increased substantially since 2015.[19]

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In the USA, PMI has applied to the FDA for IQOS to make claims as a Modified Risk Tobacco Product (MRTP).[1 20] MRTPs are those tobacco products that are 'sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products'.[21] Between May and November 2017, the FDA made the PMI MRTP application materials available online, and they were still accepting public comments on the application as of April 2018.[20] Studies conducted by PMI affiliates have claimed that IQOS produces fewer harmful constituents than combustible cigarettes,[22] though other studies have demonstrated that these products still contain and produce toxic constituents,[1 23] some of which may be present in even greater amounts in IQOS[7] and that users are not necessarily at lower levels of risk.[24] A meeting of the FDA's Tobacco Products Scientific Advisory Committee was held on 24 and 25 January 2018, during which PMI's MRTP application was debated. The ensuing discussion by the committee focused on concerns that the evidence presented by PMI was not adequate to support making modified risk or exposure claims. Unlike new tobacco product authorisation, modified risk authorisation restricts the use of modified risk claims to a limited time period, following which the applicant must demonstrate that the product and the modified risk claims continue to meet the statutory standard.

Given the popularity of HTP in Japan and elsewhere, it is expected that the commercial introduction of these products in the USA will impact consumers of nicotine and tobacco products.[9] To our knowledge, there have not yet been any published studies of the prevalence of awareness and use of HTP in the USA. Early understanding of the characteristics of HTP users in the USA may indicate the trajectory these products are likely to take in the future. Of particular importance is smoker interest in HTP and whether HTP might replace ENDS as a preferred substitute (or complement) for combustible cigarettes. Also worthy of investigation are the demographic characteristics of the earliest adopters of HTP. Our data serve to provide a baseline view of HTP use and trends against which to compare subsequent use following market shifts and regulatory actions.

METHODS

Study sample and procedures

Data come from the 2016 and 2017 Tobacco Products and Risk Perceptions Surveys, annual, cross-sectional surveys of a probability sample with oversample of current cigarette smokers drawn from GfK's KnowledgePanel. Survey participants were adults ages 18 years and older and were selected with probabilities proportional to size after application of the panel demographic poststratification weight. At the sampling stage, the 2017 sample excluded anyone who completed the 2016 Tobacco Products and Risk Perceptions Survey. Data collection occurred during September and October of 2016 and during August and September of 2017. Computers with internet access were provided for those recruited panellists who did not have them. All participants received a cash equivalent of $5 for their participation.

In 2016, 8125 KnowledgePanel members were invited to participate in the survey: 7157 members from the general population sample, of which 76.2% completed the screener and 5445 qualified for the survey and 968 members from the smoker oversample, of which 73.6% completed the screener and 616 qualified for the main survey by confirming their current smoking status. Of the 6061 qualified completers, 47 cases were excluded due to refusing to answer more than half of the survey questions, yielding an analytic sample of 6014 cases. A final stage completion rate of 74.0% was obtained for the 2016 sample.

In 2017, 8229 KnowledgePanel members were invited to participate in the 2017 survey: 7270 members from the general population sample, of which 75.1% completed the screener and 5455 qualified for the survey and 959 members from the smoker oversample, of which 68.1% completed the screener and 578 qualified for the main survey by confirming their current smoking status. Of the 6033 qualified completers, 22 cases were excluded due to refusing to answer more than half the survey questions and 19 were removed due to low duration or being flagged twice for highly improbable or incompatible responses, yielding an analytic sample of 5992 cases. A final stage completion rate of 72.8% was obtained for the 2017 sample.

A study-specific poststratification weight was computed using an iterative proportional fitting (raking) procedure to adjust for survey non-response as well as for oversampling of smokers. Demographic and geographic distributions from the most recent Current Population Survey were employed as benchmarks for adjustment, and included sex, age, race/ethnicity, education, household income, census region and metropolitan area.

Measures

Awareness and use of HTP

In both the 2016 and 2017 surveys, all participants were shown images of Revo and IQOS HTP, chosen as examples of some types of HTP, along with the following description: 'Heat-not-burn' uses leaf tobacco like traditional cigarettes. However, these products heat the tobacco to a lower temperature than traditional cigarettes to avoid burning the tobacco. When heated, they produce aerosol with nicotine, similar to electronic cigarettes. Depending on the specific product, the tobacco is heated by either a flame (with a lighter or match) or a battery. Some brands are Eclipse, Accord, Premier, Ploom, Revo and IQOS with Marlboro Heat Sticks. Participants were then asked if they had ever seen or heard of any HTP before this study. Those who reported being aware of the products were next asked if they had ever used HTP, even one or two puffs. If they answered affirmatively, they were asked if they now use it 'every day', 'some days', 'rarely' or 'not at all'. Those who reported using HTP 'every day', 'some days' or 'rarely' were classified as current users, while those who had ever used HTP, but now use it 'not at all', were classified as former users.[25]

Cigarette smoking

Participants who reported smoking at least 100 cigarettes in their lifetime were asked, 'Do you currently smoke cigarettes every day, some days, or not at all?'. Current smokers were those who responded 'every day' or 'some days', and former smokers were those who responded 'not at all'. Those who reported that they had not smoked at least 100 cigarettes in their lifetime were considered never smokers.

ENDS use

Participants who were aware of ENDS were asked if they had ever used ENDS, even one or two times. Ever users of ENDS were then asked if they now use them 'every day', 'some days', 'rarely' or 'not at all'. Those who responded 'not at all' were classified as 'former ENDS users' while those who responded 'every day', 'some days', or 'rarely' were classified as 'current ENDS users'.

Quit status and quit intentions

We created a three-level quit status variable consisting of former smokers, unsuccessful quitters and those who have never tried to quit. Current smokers were asked, 'In the past, have you ever made a serious attempt to quit smoking? That is, have you stopped smoking for at least one day or longer because you were trying to quit?'. Those who answered 'yes' were classified as unsuccessful quitters, while those who answered 'no' were classified as those who have never tried to quit. Current smokers were also asked to select the statement that best describes when and if they plan to quit smoking. Responses were then grouped into four categories, 'intend to quit in the next month', 'intend to quit in the next 6 months', intend to quit sometime in the future, but not in the next 6 months' and 'never plan to quit' to form a four-level quit intentions variable.

Early adopter propensity

Participants were asked to select whether they agreed 'not at all', 'somewhat', 'a lot' or 'completely' with each of three statements: 'I usually try new products before other people do', 'When I shop, I look for what is new' and 'I like to be the first among my friends and family to try something new'. The composite measure ranged from a low score of 3 (responding 'not at all' to all three statements) to a high score of 12 responding 'completely' to all three statements).

Participant sociodemographics

Participant sociodemographics used in analyses included sex, age, education level, race/ethnicity and annual household income and were obtained from profile surveys administered by GfK to KnowledgePanel members.

Statistical analysis

Where temporal change was not being examined or patterns of associations did not differ, data from the 2016 and 2017 surveys were pooled to improve statistical precision and power. Analyses were conducted using IBM SPSS with Complex Samples module (V.25) to obtain weighted point estimates and 95% CIs for sample sociodemographics, awareness and use of HTP, overall and by sample characteristics, quitting status and quitting intentions. Associations among awareness and use of HTP, sample characteristics, quitting status and quitting intentions were measured by weighted multivariable logistic regression models and Rao-Scott χ^2 tests.

RESULTS

Estimates of the population sociodemographic characteristics, smoking status and ENDS use for 2016 and 2017 are shown in table 1. In 2017, there was a significantly greater proportion of adults who currently smoked cigarettes ($p=0.003$) and who currently used ENDS ($p<0.001$) than in 2016. Adults in 2017 also reported greater propensity to be an early adopter of new products ($p=0.001$) than in 2016.

Table 2 compares awareness and use of HTP between 2016 and 2017. In 2017, 12.4% of all adults had heard of them, 2.2% had ever used them and 1.1% reported current use of HTP. Among all adults, awareness ($p<0.001$), ever use ($p=0.005$) and current use ($p=0.004$) increased significantly between 2016 and 2017.

Shown in table 3 are the proportions of awareness, ever use and current use of HTP by sample characteristics, as well as the adjusted ORs for sample characteristics and HTP awareness and use, for the 2016 and 2017 data combined. Adjusting for all other factors, men and those younger than age 45 years had greater odds of awareness of HTP than women and those 45 years and older, respectively. Non-white participants had greater odds of ever and current use of HTP, compared with white participants. Current cigarette smokers were nearly twice as likely to have ever used HTP as never smokers. Both former and current users of ENDS were more likely to be aware of, have ever used or be current users of HTP than those who have never used ENDS. Similarly, early adopters of new products had greater odds of awareness, ever use and current use of HTP.

Table 4 displays associations between quit status and quit intentions with awareness, ever use and current use of HTP, for the 2016 and 2017 samples. Former smokers in 2016 had lower odds of ever or current use of HTP compared with smokers who had never tried to quit. In 2017, smokers who had made quit attempts had increased odds of ever using HTP compared with smokers who had never tried to quit. Among current smokers in 2016, those who had plans to quit either in the next month or next 6 months were more than twice as likely to be aware of HTP than smokers with no plans to quit. Smokers in 2016 with plans to quit in the next 6 months also had greatly increased odds of currently using HTP compared with those with no plans to quit. There were no significant differences in awareness or use of HTP by quit intentions in 2017.

DISCUSSION

Though HTP products have not yet achieved widespread use, the number of US adults who are aware of and using these products is rapidly increasing. In 2017, ever and current use were still uncommon, 2.2% and 1.1%, respectively, though the proportion for current use had more than doubled since 2016. These numbers correspond to over 7 million people in the USA ever trying and over 3.5 million currently using HTP. If patterns of usage follow those occurring in Japan, we can expect these numbers to increase substantially following commercial introduction of IQOS. Analysts predict rapid sales growth in the USA, similar to that of Japan, over the next few years.[9 14] Caution should be used when extrapolating from the Japan example; however, as there are notable ways in which the Japanese market is different from the US market. Commercially available ENDS in Japan do not contain nicotine,[12] making ENDS less competitive with other tobacco and nicotine-containing products. Government regulations are also less stringent in Japan.[17]

PMI's MRTP application to the FDA outlines the 'considerations (that) will ensure that the product benefits the health of the population as a whole'.[20] Included are the stipulations that 'an MRTP should not increase initiation among non-users of tobacco products, and hence should not appeal to former users and never users' and 'an MRTP should not have a significant impact on the decision of a smoker who would otherwise quit smoking'.[20] PMI then cites studies that purport to show that IQOS is not attractive to adult never smokers and 'minimally attractive' to adult former smokers.[20] While our data do show that current smokers have thus far had significantly greater odds of using HTP, there are small numbers of never and former smokers who have tried and are currently using these products. In Italy, while current cigarette smokers and current ENDS users have the highest rates of HTP (IQOS) use, a small proportion of non-smokers have tried the products as well.[16] Though the number of both the Italian and US survey participants who have used HTP is small, roughly half of the Italian sample who used IQOS and just under half of the US sample who ever used any HTP are either never or former cigarette smokers. We do not know

Table 1 Participant sociodemographics

	2016		2017		
	Unweighted n	Weighted %/mean (95% CI)	Unweighted n	Weighted %/mean (95% CI)	P values*
Total	6014	–	5992	–	
Sex					
Male	3013	48.0 (46.5 to 49.6)	2987	48.1 (46.6 to 49.6)	0.923
Female	3001	52.0 (50.4 to 53.5)	3005	51.9 (50.4 to 53.4)	
Age (years)					
18–29	981	20.8 (19.5 to 22.3)	1092	20.8 (19.5 to 22.1)	0.992
30–44	1213	24.8 (23.5 to 26.2)	1183	24.9 (23.6 to 26.4)	
45+	3820	54.3 (52.8 to 55.9)	3717	54.3 (52.7 to 55.8)	
Education					
Less than high school	297	10.8 (9.6 to 12.1)	326	10.8 (9.7 to 12.1)	0.961
High school	1781	29.3 (27.9 to 30.6)	1345	28.9 (27.5 to 30.4)	
Some college	1876	28.8 (27.5 to 30.2)	2014	28.6 (27.4 to 29.9)	
College graduate or more	2060	31.1 (29.8 to 32.5)	2307	31.6 (30.3 to 33.0)	
Race/ethnicity					
White, NH	4434	65.1 (63.5 to 66.6)	4365	64.3 (62.8 to 65.9)	0.919
Black, NH	547	11.8 (10.8 to 12.9)	600	11.8 (10.8 to 12.8)	
Hispanic	672	15.3 (14.1 to 16.6)	639	15.8 (14.6 to 17.2)	
Other, NH	361	7.8 (6.9 to 8.9)	388	8.0 (7.1 to 9.1)	
Income					
Less than $30 000	1486	20.7 (19.6 to 22.0)	1290	19.1 (18.0 to 20.3)	0.067
$30 000–$99 900	3144	47.4 (45.9 to 49.0)	2961	47.0 (45.6 to 48.5)	
$100 000+	1384	31.8 (30.3 to 33.4)	1741	33.9 (32.4 to 35.3)	
Cigarette smoking status					
Never	3107	59.7 (58.2 to 61.2)	3061	56.4 (54.9 to 57.8)	0.003
Former	1619	27.1 (25.8 to 28.4)	1660	28.7 (27.3 to 30.0)	
Current	1288	13.2 (12.3 to 14.1)	1271	15.0 (14.0 to 16.0)	
ENDS use status					
Never	4821	83.9 (82.7 to 85.0)	4664	79.7 (78.5 to 80.9)	0.000
Former	792	10.7 (9.8 to 11.7)	786	11.8 (10.8 to 12.8)	
Current	390	5.4 (4.8 to 6.1)	542	8.5 (7.7 to 9.4)	
Early adopter propensity†	4832	5.11 (5.03 to 5.19)	5612	5.28 (5.22 to 5.35)	0.001

*χ^2 test.
†Range from 3 to 12.
ENDS, electronic nicotine delivery systems; NH, non-Hispanic.

whether the former smokers who have used HTP did so before or after they stopped smoking.

PMI also claims that their test communications about the products had no significant impact on the intention of adult smokers to quit smoking.[20] However, because their experimental studies did not include a control group, they cannot make causal claims on whether the messages had any impact on cessation.[26] Furthermore, between 3% and 33% of participants who had intentions to quit before exposure to the messages reported lower intentions to quit after they saw the messages about IQOS with modified risk claims.[26] It is possible that using messages without modified risk claims or combining the claims with stronger warnings (such as pictorial warning labels) might have prevented this decline in intentions to quit smoking.

Table 2 Awareness and use of HTP among US adults

	2016 n=6014		2017 n=5992		
	Unweighted n	Weighted % (95% CI)	Unweighted n	Weighted % (95% CI)	P values*
Aware of HTP	560	9.3 (8.4 to 10.2)	730	12.4 (11.4 to 13.4)	<0.001
Ever used HTP	88		142		
Among all US adults		1.4 (1.1 to 1.8)		2.2 (1.8 to 2.7)	0.005
Among those aware of HTP		14.8 (11.6 to 18.8)		17.8 (14.6 to 21.5)	0.243
Currently use HTP	36		61		
Among all US adults		0.5 (0.4 to 0.7)		1.1 (0.8 to 1.5)	0.004
Among those aware of HTP		5.6 (3.8 to 8.0)		8.6 (6.3 to 11.7)	0.076

*χ^2 test.
HTP, heated tobacco product.

Table 3 Characteristics associated with HTP product awareness and use, among US adults, 2016 and 2017

		Aware of HTP		Ever used HTP		Currently use HTP	
	n	%/Mean (95% CI)	AOR† (95% CI)	%/Mean (95% CI)	AOR† (95% CI)	%/Mean (95% CI)	AOR† (95% CI)
Sex							
Male	5998	13.4 (12.3 to 14.5)	1.67 (1.42 to 1.95)***	2.0 (1.6 to 2.6)	1.34 (0.92 to 1.96)	0.8 (0.6 to 1.2)	1.13 (0.63 to 2.04)
Female	5999	8.5 (7.7 to 9.3)	REF	1.6 (1.3 to 2.0)	REF	0.8 (0.5 to 1.0)	REF
Age (years)							
18–29	2069	13.9 (12.1 to 15.9)	1.58 (1.26 to 1.97)***	3.0 (2.3 to 4.1)	1.57 (0.92 to 2.66)	1.5 (1.0 to 2.4)	1.89 (0.89 to 4.00)
30–44	2394	13.4 (11.9 to 15.1)	1.50 (1.24 to 1.81)***	2.6 (2.0 to 3.4)	1.34 (0.84 to 2.15)	1.2 (0.8 to 1.8)	1.16 (0.59 to 2.29)
45+	7534	8.5 (7.8 to 9.2)	REF	0.9 (0.7 to 1.2)	REF	0.3 (0.2 to 0.5)	REF
Education							
<High school	622	12.6 (9.9 to 15.9)	1.15 (0.79 to 1.66)	3.6 (2.4 to 5.4)	1.51 (0.72 to 3.17)	1.6 (0.8 to 3.0)	1.50 (0.46 to 4.93)
High school	3121	10.7 (9.4 to 12.1)	1.09 (0.86 to 1.39)	1.8 (1.3 to 2.5)	1.22 (0.64 to 2.34)	0.9 (0.5 to 1.4)	1.64 (0.61 to 4.43)
Some college	3888	10.3 (9.2 to 11.5)	0.95 (0.78 to 1.15)	1.9 (1.4 to 2.4)	1.21 (0.68 to 2.15)	0.8 (0.5 to 1.1)	0.99 (0.44 to 2.21)
College graduate or more	4366	10.9 (9.9 to 12.0)	REF	1.1 (0.8 to 1.5)	REF	0.5 (0.3 to 0.8)	REF
Race/ethnicity							
White, NH	8794	10.2 (9.4 to 10.9)	REF	1.3 (1.0 to 1.5)	REF	0.4 (0.3 to 0.6)	REF
Black, NH	1143	11.1 (9.2 to 13.4)	1.08 (0.84 to 1.39)	2.0 (1.3 to 3.0)	1.39 (0.83 to 2.32)	1.2 (0.7 to 1.9)	2.54 (1.24 to 5.21)*
Hispanic	1311	13.6 (11.5 to 15.9)	1.09 (0.87 to 1.38)	3.4 (2.4 to 4.8)	2.09 (1.29 to 3.37)**	1.6 (0.9 to 2.7)	2.82 (1.36 to 5.86)**
Other, NH	749	10.5 (7.9 to 13.7)	1.00 (0.70 to 1.41)	2.7 (1.5 to 4.8)	2.57 (1.23 to 5.35)*	1.5 (0.6 to 3.3)	3.95 (1.29 to 12.07)*
Income							
Less than $30 000	2770	12.7 (11.1 to 14.4)	1.14 (0.88 to 1.48)	3.2 (2.5 to 4.2)	1.71 (0.92 to 3.19)	1.5 (1.0 to 2.3)	1.13 (0.50 to 2.57)
$30 000–$99 900	6102	10.3 (9.4 to 11.2)	0.92 (0.75 to 1.13)	1.8 (1.4 to 2.3)	1.32 (0.73 to 2.41)	0.7 (0.5 to 1.1)	0.84 (0.40 to 1.79)
$100 000+	3125	10.5 (9.3 to 11.8)	REF	0.9 (0.6 to 1.4)	REF	0.4 (0.3 to 0.8)	REF
Cigarette smoking							
Never	6161	9.6 (8.7 to 10.6)	REF	0.8 (0.5 to 1.1)	REF	0.3 (0.2 to 0.6)	REF
Former	3278	10.8 (9.6 to 12.1)	1.21 (1.00 to 1.47)	1.3 (0.9 to 1.9)	1.20 (0.64 to 2.25)	0.5 (0.3 to 1.1)	1.25 (0.51 to 3.04)
Current	2558	15.9 (14.1 to 17.9)	1.16 (0.91 to 1.47)	7.0 (5.7 to 8.5)	1.96 (1.14 to 3.37)*	3.1 (2.3 to 4.2)	1.57 (0.81 to 3.04)
ENDS use							
Never	9485	9.3 (8.6 to 10.1)	REF	0.4 (0.3 to 0.6)	REF	0.2 (0.1 to 0.3)	REF
Former	1578	15.0 (12.8 to 17.5)	1.45 (1.14 to 1.85)**	6.4 (4.9 to 8.2)	11.51 (6.20 to 21.36)***	0.8 (0.4 to 1.6)	4.04 (1.28 to 12.75)*
Current	932	21.5 (18.3 to 25.0)	1.78 (1.36 to 2.33)***	10.9 (8.6 to 13.7)	14.87 (7.84 to 28.19)***	8.1 (6.1 to 10.7)	35.97 (13.55 to 95.50)***
Early adopter propensity‡	10 437	5.72 (5.56 to 5.88)	1.08 (1.04 to 1.12)***	6.56 (6.15 to 6.98)	1.13 (1.04 to 1.22)**	6.97 (6.35 to 7.59)	1.14 (1.02 to 1.28)*

***P<0.001; **p<0.01; *p<0.05.
†Adjusted OR for sex, age, education, race/ethnicity, income, cigarette smoking, ENDS use and early adopter propensity.
‡Range from 3 to 12.
ENDS, electronic nicotine delivery systems; HTP, heated tobacco product; NH, non-Hispanic.

Smokers with concrete plans to quit were more likely to be aware of HTP than those with no plans to quit in 2016, but not in 2017, possibly indicating that media coverage of HTP may have contributed to expanding awareness beyond only those with intentions to quit smoking. Smokers in 2017 who had unsuccessfully tried to quit were more than twice as likely as those who have never tried to quit to have used HTP, which may indicate that HTP are increasingly being explored as quit aids among smokers who were unsuccessful with other cessation tools. We do not yet know the patterns in which HTP are being used by these groups; specifically, whether these products will be used only temporarily as smokers are trying to quit, if they will continue to be used as a substitution for quitting tobacco products entirely, or if they will be used concurrently with cigarettes, indefinitely. Careful monitoring of product uptake among non-smokers and of use among smokers trying to quit will be essential.

It is not surprising that current smokers in the USA are more likely to be aware of and using these products than those who have never smoked. More strikingly, those who have used ENDS, and current ENDS users, particularly, have much higher odds of having used HTP than never users of ENDS. It remains to be seen whether dual users of ENDS and HTP will find one product more satisfying and switch completely to that. It is also possible that smokers who have never tried (or who have tried but rejected) ENDS may consider trying HTP.

PMI's and our study did not evaluate the appeal of IQOS to youth, to whom these products should not appeal. Given the experience with ENDS in the USA, it is reasonable to assume that HTP would be appealing to youth and young adult newer smokers[27] ENDS are similar to HTP in that both are alternatives to cigarettes promoted by emphasising lack of smoke and reduced harm. As rates of ENDS use have been increasing rapidly in the USA since they were first introduced

Table 4 Awareness and use of HTP by quit status and quit intentions among current and former smokers, among US adults, 2016 and 2017

		Aware of HTP		Ever used HTP		Currently use HTP	
	n	% (95% CI)	AOR† (95% CI)	% (95% CI)	AOR† (95% CI)	% (95% CI)	AOR† (95% CI)
2016	6014						
Among current and former smokers (n=2904):							
Quit status							
Former smokers	1619	9.5 (8.0 to 11.3)	1.06 (0.63 to 1.77)	1.0 (0.6 to 1.7)	0.24 (0.10 to 0.56)**	0.2 (0.1 to 0.5)	0.14 (0.03 to 0.60)**
Unsuccessful quitters	895	13.9 (11.2 to 17.1)	1.54 (0.90 to 2.64)	5.1 (3.5 to 7.3)	0.95 (0.44 to 2.04)	2.7 (1.6 to 4.5)	1.49 (0.48 to 4.63)
Never tried to quit	390	9.7 (6.3 to 14.7)	REF	5.4 (2.9 to 10.0)	REF	1.9 (0.6 to 5.5)	REF
Among current smokers (n=1279):							
Quit intentions							
In next month	207	15.3 (9.7 to 23.3)	2.53 (1.05 to 6.08)*	9.2 (4.6 to 17.4)	4.29 (0.87 to 21.12)	3.3 (1.2 to 8.7)	7.05 (0.91 to 54.80)
In next 6 months	210	14.7 (9.4 to 22.2)	2.38 (1.00 to 5.67)*	8.1 (4.6 to 14.1)	3.85 (0.84 to 17.67)	6.0 (2.9 to 12.0)	15.85 (2.45 to 102.38)**
Future but not next 6 months	672	12.6 (9.7 to 16.3)	1.97 (0.95 to 4.09)	4.0 (2.3 to 6.6)	1.62 (0.40 to 6.53)	1.6 (0.7 to 3.8)	3.49 (0.52 to 23.41)
Never plan to quit	190	6.5 (3.6 to 11.5)	REF	2.3 (0.7 to 7.1)	REF	0.5 (0.1 to 2.2)	REF
2017	5992						
Among current and former smokers (n=2928)							
Quit status							
Former smokers	1660	12.0 (10.2 to 13.9)	0.95 (0.60 to 1.51)	1.7 (1.0 to 2.6)	0.48 (0.20 to 1.15)	0.9 (0.4 to 1.9)	0.58 (0.15 to 2.22)
Unsuccessful quitters	931	20.1 (16.9 to 23.8)	1.54 (0.99 to 2.41)	9.8 (7.4 to 12.7)	2.46 (1.24 to 4.87)*	4.1 (2.6 to 6.4)	2.25 (0.81 to 6.25)
Never tried to quit	337	17.0 (12.4 to 22.9)	REF	6.1 (3.4 to 10.7)	REF	2.8 (1.3 to 6.3)	REF
Among current smokers (n=1266)							
Quit intentions							
In next month	231	20.3 (13.9 to 28.6)	1.02 (0.53 to 1.96)	9.9 (5.6 to 17.0)	1.72 (0.62 to 4.79)	5.2 (2.1 to 12.4)	1.51 (0.40 to 5.69)
In next 6 months	219	18.5 (13.0 to 25.7)	0.94 (0.49 to 1.78)	7.8 (4.5 to 13.2)	1.45 (0.52 to 4.02)	4.2 (1.9 to 9.0)	1.25 (0.37 to 4.22)
Future but not next 6 months	645	18.2 (14.6 to 22.6)	0.83 (0.48 to 1.42)	8.9 (6.3 to 12.4)	1.40 (0.58 to 3.41)	3.1 (1.7 to 5.6)	0.83 (0.26 to 2.62)
Never plan to quit	171	21.1 (14.5 to 29.7)	REF	6.5 (3.0 to 13.2)	REF	3.2 (1.3 to 7.8)	REF

***P<0.001; **p<0.01; *p<0.05.
†Adjusted OR, adjusted for sex, age, education, race and income.
HTP, heated tobacco products.

into the market, so it is likely that HTP will enjoy the same popularity.

Our data show that minority adults in the USA are significantly more likely than non-Hispanic white adults to have ever used and to be current users of HTP, even when controlling for other demographic characteristics. These findings have no precedent in the literature, as prevalence studies of these products in other countries presumably used more racially homogeneous samples. As HTP are introduced in the USA and gain popularity, it will be important to monitor this trend. The Japanese study from 2015 found that use of HTP was higher among younger people,[18] and our current data appear to uphold that pattern, at least for awareness of these products. This is not surprising, as younger people are more likely to be aware of and interested in new or innovative technology, and this extends to innovative tobacco products as well.[28] A separate Japanese study of education level and HTP use found no clear associations, though a larger sample size of HTP users may have produced different results.[29] Usage trends among racial and ethnic minorities, younger people and those with varying levels of education could amplify tobacco-related health disparities and should be monitored as use of HTP products becomes more widespread in the USA.

Limitations

Our study is not without limitations. Our measures of HTP awareness and use featured images and descriptions of only some types and brands of HTP, and some of these products are no longer available. It is possible that some participants who were aware of or had used or were currently using HTP did not reply in the affirmative because they did not see their particular brand or recognise that the product they used fit within this definition. This measure is not specific enough to capture awareness and use of any one brand or type of HTP, but rather only of HTP generally. HTP have also been used for consuming marijuana, and though our survey description of HTP refers to use with tobacco, it is possible that some respondents reported on their use of HTP with marijuana. Our survey also did not explore where the products are being purchased (eg, online vs in stores, within the USA vs outside the USA). We did not measure risk perceptions, reasons for use, duration or intensity of use or satisfaction with HTP. Additionally, although our total sample size was large, the low prevalence of HTP use may have limited statistical power for some analyses and did not permit a finer-grain description of the sociodemographics and tobacco use characteristics of HTP users.

CONCLUSIONS

Based on current international experience, the latest generation of HTP could have a substantial impact on the US tobacco market. Significant increases in awareness and use are already apparent, with evidence that awareness is highest among men and young adults and that these products are being used in greater proportions by racial minorities.

Cigarette smokers and ENDS users also have higher odds of both awareness and use than non-users. Continued surveillance is needed, including further exploration of the perceptions and other characteristics associated with use,and the effects of HTP use on patterns of use of other nicotine and tobacco products.

What this paper adds

- Heated tobacco products (HTP) are being marketed aggressively and gaining popularity in many countries, and Philip Morris International is seeking Food and Drug Administration authorisation to market its IQOS HTP as a modified risk product in the USA.
- Little is known about current levels of awareness and use of HTP among US adults or the characteristics of those using these products.
- Our nationally representative survey data from 2016 and 2017 show that awareness and use of HTP are low, but increasing, among US adults.
- Awareness is higher among men, younger adults, smokers and users of electronic nicotine delivery systems (ENDS), while racial and ethnic minorities, cigarette smokers and ENDS users currently have the greatest odds of using HTP in the USA. Continuing surveillance is needed, in order to monitor potential patterns and purposes associated with HTP use.

Contributors All authors conceptualised the study and approved the final version of the manuscript. ALN ran the analyses, wrote the first draft of the manuscript and revised subsequent drafts. SRW and JH provided statistical guidance, interpretation of results and contributed to writing, reviewing and revising drafts of the manuscript. LP, TFP, and DLA contributed to interpretation of results, writing, reviewing and revising drafts of the manuscript. MPE oversaw design of the parent study, reviewed manuscript drafts and provided feedback on analyses and revisions.

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Data sharing statement Per the data sharing agreement with the NIH, the data that support the findings of this study will be made publicly available via a third-party data repository upon conclusion of the grant funding period. The data are also available from the principal investigator (MPE) on reasonable request.

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Impact of modified risk tobacco product claims on beliefs of US adults and adolescents

Sherine El-Toukhy,[1] Sabeeh A Baig,[2] Michelle Jeong,[2,3] M Justin Byron,[2,4] Kurt M Ribisl,[2,3] Noel T Brewer[2,3]

[1]Intramural Research Program, National Heart, Lung, and Blood Institute, The National Institutes of Health, Bethesda, Maryland, USA
[2]Department of Health Behavior, University of North Carolina, Gillings School of Global Public Health, Chapel Hill, North Carolina, USA
[3]Lineberger Comprehensive Cancer Center, University of North Carolina, Chapel Hill, North Carolina, USA
[4]Department of Family Medicine, School of Medicine, University of North Carolina, Chapel Hill, North Carolina, USA

Correspondence to
Dr Noel T Brewer, Department of Health Behavior, Gillings School of Global Public Health, University of North Carolina, Chapel Hill, NC 27599, USA; ntb@unc.edu

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ABSTRACT

Objective Under US law, tobacco product marketing may claim lower exposure to chemicals, or lower risk of health harms, only if these claims do not mislead the public. We sought to examine the impact of such marketing claims about potential modified risk tobacco products (MRTPs).

Methods Participants were national samples of 4797 adults and 969 adolescent US smokers and non-smokers. We provided information about a potential MRTP (heated tobacco product, electronic cigarette or snus). Experiment 1 stated that the MRTP was as harmful as cigarettes or less harmful (lower risk claim). Experiment 2 stated that the MRTP exposed users to a similar quantity of harmful chemicals as cigarettes or to fewer chemicals (lower exposure claim).

Results Claiming lower risk led to lower perceived quantity of chemicals and lower perceived risk among adults and adolescents (all $p<0.05$, Experiment 1). Among adults, this claim led to higher susceptibility to using the MRTP ($p<0.05$). Claiming lower exposure led to lower perceived chemical quantity and lower perceived risk (all $p<0.05$), but had no effect on use susceptibility (Experiment 2). Participants thought that snus exposed users to more chemicals and was less safe to use than heated tobacco products or electronic cigarette MRTPs (Experiments 1 and 2).

Discussion Risk and exposure claims acted similarly on MRTP beliefs. Lower exposure claims misled the public to perceive lower perceived risk even though no lower risk claim was explicitly made, which is impermissible under US law.

INTRODUCTION

Attempts to market products as safer alternatives to conventional cigarettes or as smoking cessation tools date back to the 1950s. The tobacco industry aimed to appeal to health-conscious consumers[1] and respond to declining cigarette smoking rates[2 3] attributable to tobacco control efforts (eg, smoke-free laws, media campaigns, taxation)[4] and growing antismoking norms.[5] Some tobacco companies made claims that their tobacco products cause less harm or deliver lower levels of chemicals than conventional cigarettes. For example in the early 2000s, Brown & Williamson advertised their Advance Lights as 'A step in the right direction. All of the taste … Less of the toxins'[6] and Vector claimed their Omni cigarettes to be 'The only cigarette to significantly reduce carcinogens that are among the major causes of lung cancer'.[7] More recently, electronic cigarette (e-cigarette) marketing has often claimed e-cigarettes to be safer than combusted cigarettes.[8–10] Such advertising claims of reduced exposure to harmful chemicals and reduced risk of harm lower public perceptions of harm and increase willingness to try these products.[11–17]

After decades of misleading reduced risk claims,[18] the 2009 US Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act) provided a regulatory framework in which tobacco companies could introduce and market tobacco products with lower exposure or risk claims only after a review and obtaining a marketing order from the US Food and Drug Administration (FDA).[19] Under the law, products with these claims are 'modified risk tobacco products' (MRTPs), defined as products 'sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products.'[20]

According to US law, applicants for MRTP status can qualify through one of two legal pathways.[21] For the first pathway, a manufacturer can qualify by demonstrating that the product, as used by consumers, lowers harm or risk of tobacco-related diseases compared with other tobacco products (modified risk pathway, Section 911(g)(1)).[22 23] Alternatively, for the second pathway, a manufacturer can qualify by demonstrating that the product or its smoke is free of or contains reduced levels of harmful chemicals, but only if such claims do not mislead the public to believe the product poses less harm than other commercially available products (modified exposure pathway, Section 911(g)(2)).[22 23] In 2014, Swedish Match North America filed the first MRTP application for 10 of their General snus products.[24] The FDA did not grant the Swedish Match request for MRTP status.[24 25] In 2016, Philip Morris International filed an MRTP application for its IQOS heated tobacco product.[26] In January 2018, FDA's Tobacco Product Scientific Advisory Committee voted that Philip Morris International's application did not demonstrate reduced risks of disease. The FDA is also reviewing an MRTP application by Reynolds American for its Camel Snus.[27] E-cigarettes are another tobacco product for which future modified-risk applications are likely.

The purpose of our study was to examine the impact of marketing claims about exposure and risk for potential MRTPs. We hypothesised that modified risk claims would lower perceptions of chemical quantity and health harm, and increase susceptibility to use an MRTP. Similarly, we hypothesised that modified exposure claims would lower perceptions of chemical quantity, lower perceived

risk of health harm and increase use susceptibility. Of particular importance would be whether exposure claims lower perceived risk in the absence of explicit claims of lower risk, which would prevent a product from gaining an MRTP status under US law.

METHODS

Participants

Participants were national samples of US adults and adolescents. The Carolina Survey Research Laboratory (CSRL) used sampling frames with coverage for 96% of US households, oversampling geographical areas, households and individuals to ensure adequate representation of smokers. CSRL recruited 4964 adults aged 18 years or older using both random digit dialling (of landlines and cell phones) and respondent-driven sampling approaches from August 2016 to May 2017. Separately, CSRL recruited 975 adolescents aged 13–17 years using random digit dial and list-assisted sampling frames from August 2016 to May 2017. The response rate was 39% for adults and 33% for adolescents. Adults provided consent verbally; adolescents' parents or guardians provided consent verbally on behalf of their adolescents, who provided their assent verbally. The analytical sample comprised the 4797 adults and 969 adolescents who were correctly randomised and responded to all outcomes. Additional details about the survey methodology are available elsewhere.[28 29]

Procedures

We conducted two between-subjects factorial experiments. In Experiment 1, we randomised 2352 adults and 480 adolescents to receive one message that varied by (a) risk claim (less harmful than cigarettes, as harmful as cigarettes, no statement (control)) and (b) potential MRTP type (IQOS heated tobacco product, Apollo e-cigarette, Swedish snus), which we also refer to as product type. For example, a message about snus read, 'I am going to describe a new type of moist tobacco called Swedish snus. It comes in a small pouch that goes under your lip. Suppose the FDA approves a label saying that Swedish snus is less harmful than cigarettes.'

In Experiment 2, we randomised 2445 adults and 489 adolescents to receive one message that varied by (a) exposure claim (20% less than cigarettes, 90% less than cigarettes, similar to cigarettes (control)) and (b) potential MRTP type (same as in Experiment 1). To increase the generalisability of the findings, the scenarios used one of three randomly selected chemicals (arsenic, carbon monoxide, formaldehyde). An example message about IQOS was, 'I am going to describe a new type of cigarette called IQOS. It makes less smoke because it warms the tobacco without burning it. Suppose the FDA approves a label saying that IQOS exposes you to 90% less arsenic than cigarettes.'

Measures

We adapted survey items from previous studies, or for new items, cognitively tested them.[30] The survey measured perceived chemical quantity with the following item, 'Do you think that using [product] would expose you to…' The 4-point response scale ranged from 'almost no harmful chemicals' (coded as 1) to 'a lot of harmful chemicals' (coded as 4). The survey assessed perceived risk of health harm using the following item, 'If you used [product] regularly for the next 10 years, how likely do you think it is that you would eventually develop serious health problems?' The 4-point response scale ranged from 'not at all likely' (1) to 'extremely likely' (4). This item includes the four components required to accurately gauge perceived risk: who is at risk, for what hazard, over what period of time, given a person's behaviour.[31] The survey measured susceptibility to use the potential MRTP, 'If one of your best friends was to offer you [product], would you try it?' The 4-point response scale ranged from 'definitely not' (1) to 'definitely yes' (4).

The survey also collected demographic data including education (for adolescents, maternal education). The survey assessed numeracy (ability to understand and use numeric information) using the item: 'In general, which of these numbers shows the biggest risk of getting disease?' Response options were: 1 in 10, 1 in 100 or 1 in 1000.[32] We categorised adults as current smokers if they had smoked 100 or more cigarettes in their lifetime and currently smoke some days or every day.[33] We categorised adolescents as current smokers if they had smoked at least 1 day in the past 30 days.[34]

Data analysis

We analysed the data using R (V.3.4.3).[35] All statistical tests were two tailed and used a critical alpha of 0.05. In randomisation checks, only 25 associations of 80 models were significant ($p<0.05$) confirming that demographics, numeracy and smoking status were equally distributed across experimental conditions.

We conducted 2×3 between-subjects analyses of variance. Analyses combined categories for risk claim (less harmful than cigarettes vs as harmful as cigarettes or no statement) in Experiment 1 and exposure claim (similar to cigarettes vs 20% less or 90% less) in Experiment 2 because the combined categories showed the same pattern of results. We further examined statistically significant main effects of potential MRTPs with post hoc t-tests comparing IQOS and the e-cigarette to Swedish snus, using Bonferroni adjustments. Finally, we used linear regression models to examine whether perceived quantity and perceived risk mediated the relationship between independent variables and susceptibility to use MRTPs as a dependent variable. Analyses bootstrapped total, direct and mediated effects with 1000 iterations.

RESULTS

The samples were 55% female, 67% white, 91% non-Hispanic and 70% non-smokers (table 1). Less than one-third had a high school diploma or equivalent or earned US$25 000 or less in annual income. Mean age for adults was 46 (SD=17) years and 45 (SD=17) years in Experiments 1 and 2, respectively. Mean age for adolescents was 15 (SD=1) years in both Experiments 1 and 2.

Experiment 1: lower risk claim

Perceived chemical quantity. Among adults, claims that an MRTP was less harmful than cigarettes led to lower perceived chemical quantity compared with claims that an MRTP was as harmful as cigarettes or when there was no statement ($p<0.001$) (table 2; figure 1). Perceived chemical quantity differed among the products ($p<0.001$); post hoc t-tests showed higher perceived chemical quantity for Swedish snus than for IQOS ($p<0.001$) and the e-cigarette ($p<0.001$) (figure 2). Adolescents showed the same pattern of results for the experimental manipulations.

Perceived risk of health harm. Lower risk claims led to lower perceived risk of harm among adults ($p<0.001$). Perceived risk differed among the products ($p<0.001$); post hoc t-tests showed Swedish snus elicited higher perceived risk of harm than IQOS ($p<0.001$) and the e-cigarette ($p<0.001$). Adolescents again showed the same pattern of results as adults except that snus and IQOS did not differ.

Table 1 Sample characteristics

	Experiment 1		Experiment 2	
	Adults (n=2352)	Adolescents (n=480)	Adults (n=2445)	Adolescents (n=489)
	%	%	%	%
Age (years)				
13–17	–	100	–	100
18–25	15.2	–	17.5	–
26–34	14.5	–	16.0	–
35–44	16.7	–	16.2	–
45–54	18.2	–	17.3	–
55–64	21.6	–	19.4	–
65+	13.7	–	13.6	–
Male	45.0	50.0	45.5	49.0
Race				
White	67.1	79.2	67.2	82.4
Black or African-American	21.6	14.0	22.3	11.5
American Indian or Alaska native	3.9	1.3	3.6	1.0
Asian or Pacific islander	2.4	2.0	2.3	0.6
Other	5.0	3.5	4.6	4.5
Hispanic	8.7	6.7	8.1	5.7
Education				
<High school	12.0	4.8	9.6	5.1
High school diploma or equivalent	26.2	18.8	25.7	17.5
Some college	20.3	12.4	21.7	11.2
Associate degree	10.4	11.0	10.6	12.1
Bachelor's degree	19.1	33.0	19.8	34.0
Master's degree	9.3	15.8	9.1	15.4
Professional or doctorate degree	2.7	4.3	3.5	4.7
Low numeracy	31.8	24.2	29.7	21.4
Income per year				
US$0–US$24 999	31.0	–	29.8	–
US$25 000–US$49 999	24.6	–	26.5	–
US$50 000–US$74 999	17.9	–	18.5	–
US$75 000–US$100 000	11.5	–	10.5	–
>US$100 000	15.0	–	14.7	–
Current smoker	26.7	3.5	25.7	2.0

Among adults, missing data for income and education were 5% in Experiments 1 and 2. Among adolescents, missing data were less than 5% for age in Experiment 2 and 9% and 8% for mother's education in Experiments 1 and 2, respectively. Missing data for other characteristics were minimal.

Susceptibility to use potential MRTP. Lower risk claims elicited higher susceptibility to use the product among adults ($p<0.001$). Use susceptibility differed among the products ($p<0.001$); post hoc t-tests showed use susceptibility was lower for Swedish snus than for IQOS ($p<0.001$) and the e-cigarette ($p<0.001$). Among adolescents, risk claims and product type had no effect on use susceptibility. Interactions with smoking status were not statistically significant.

Table 2 Impact of lower risk and lower exposure claims

		Perceived quantity		Perceived risk		Use susceptibility	
		Adults	Adolescents	Adults	Adolescents	Adults	Adolescents
	df	F	F	F	F	F	F
Experiment 1							
Risk claim	1	31.8**	21.5**	12.9**	10.1*	14.1**	0.4
Product	2	50.0**	10.6**	19.7**	8.6**	31.4**	0.5
Risk claim×product	2	1.6	0.7	0.3	1.5	0.2	1.2
Experiment 2							
Exposure claim	1	82.6**	35.3**	21.6**	5.2*	3.1	0.0
Product	2	8.4**	5.5*	8.9*	2.9	30.6**	1.3
Exposure claim×product	2	1.9	0.4	2.1	0.7	0.6	1.9

Experiment 1: n=2352 adults and 480 adolescents. Experiment 2: n=2445 adults and 489 adolescents. df=degrees of freedom.
*P<0.05, **P<0.001.

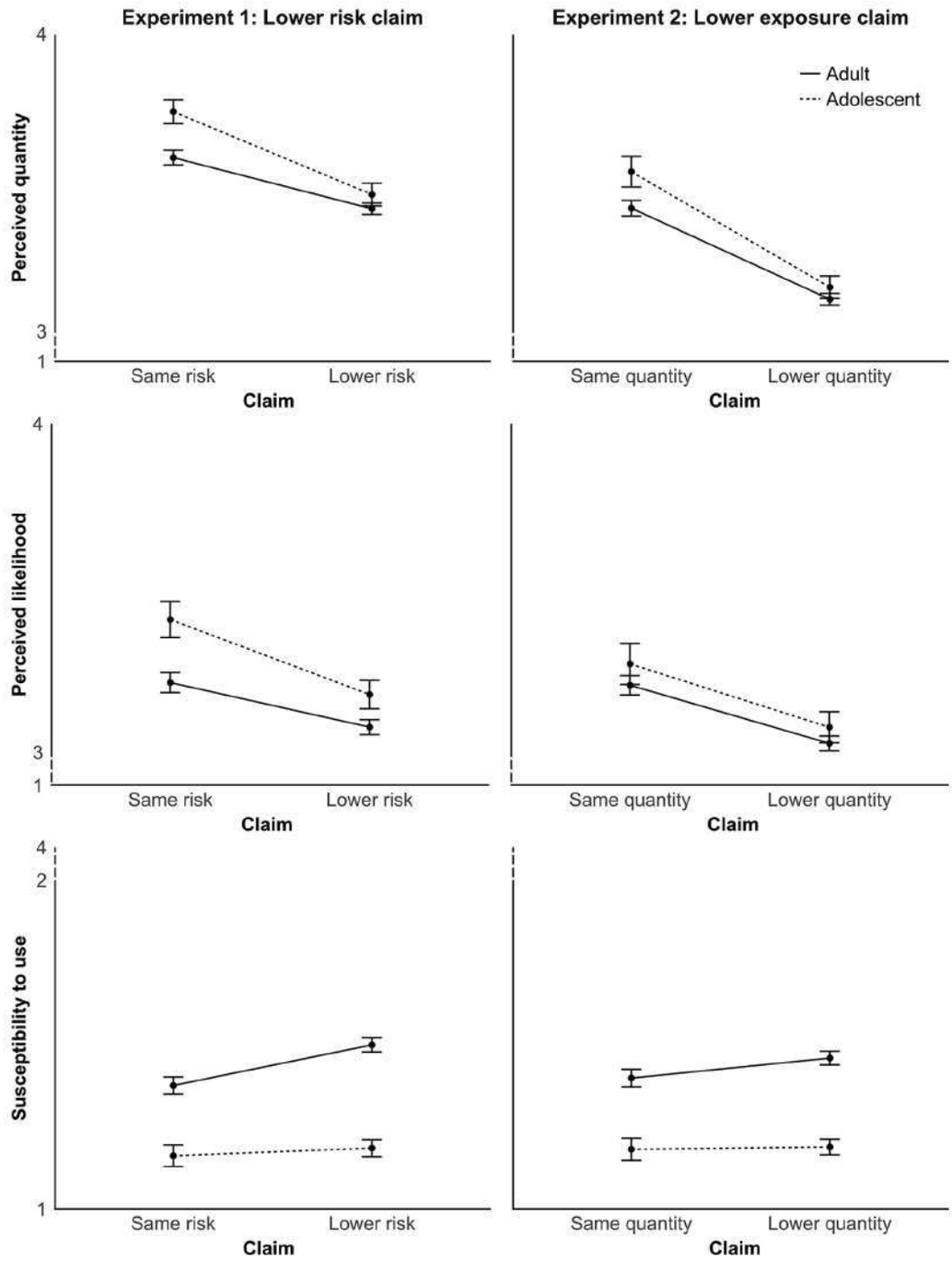


Figure 1 Impact of lower risk claim (Experiment 1) and lower exposure claim (Experiment 2). Error bars show standard errors.

Mediation. Claims that an MRTP was less harmful than cigarettes elicited lower perceived chemical quantity, which in turn, was associated with greater use susceptibility among adults (mediated effect =0.07 , p <0.001; table 3). Similarly, the claims elicited lower perceived risk, which was associated with greater use susceptibility (mediated effect=0.05, p<0.001). The two constructs also mediated the effect of product type on susceptibility among adults. Although risk claims and product type did not change adolescents' susceptibility to use, analyses showed the same pattern of mediation as among adults. The correlation between the mediators, perceived chemical quantity and perceived risk, was r=0 . 53 among adults and r=0.54 among adolescents (both p values < 0.001).

Experiment 2: lower exposure claim

Perceived chemical quantity. Among adults, claims that an MRTP exposed users to fewer chemicals led to lower perceived chemical quantity compared with the claim that an MRTP had chemical quantities similar to cigarettes (p<0.001) (table 2; figure 1). Perceived chemical quantity differed among the products (p<0.001); post hoc t-tests showed higher perceived chemical quantity for use of Swedish snus than IQOS (p=0.002) and

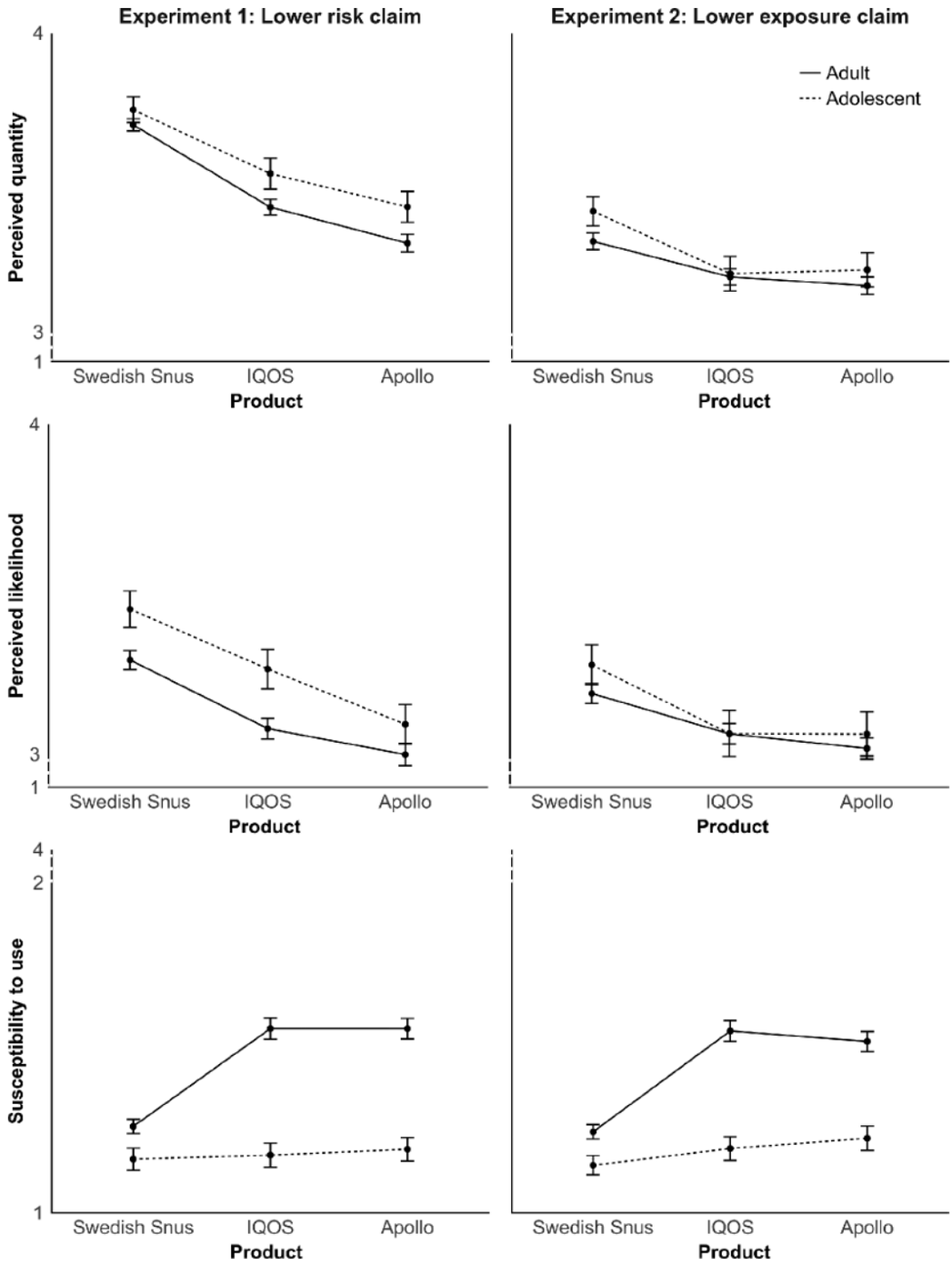


Figure 2 Impact of potential modified risk tobacco product. Error bars show standard errors.

the e-cigarette ($p<0.001$). Adolescents showed the same pattern of results as adults.

Perceived risk of health harm. Claims that an MRTP exposed users to less chemicals lowered adults' perceived risk of health harm ($p<0.001$). Perceived risk differed among the products ($p<0.001$); post hoc t-tests showed perceived risk was higher for use of Swedish snus than IQOS ($p=0.005$) and e-cigarettes ($p<0.001$). Exposure claims had a similar effect on adolescents, but product type had no effect.

Susceptibility to use potential MRTP. Exposure claims did not change use susceptibility among adults or adolescents. Among adults, use susceptibility differed among the products ($p<0.001$); post hoc t-tests showed lower susceptibility to use Swedish snus than IQOS ($p<0.001$) or the e-cigarette ($p<0.001$). Among adolescents, use susceptibility did not vary among the products. Interactions with smoking status were not statistically significant.

Mediation. Although claims of lower exposure did not change adults' susceptibility to use an MRTP, the claims led to lower perceived chemical quantity, which was associated with greater use susceptibility (mediated effect=0.09, $p<0.001$; table 3). Similarly, claims of lower exposure led to lower perceived risk, which was associated with greater use susceptibility (mediated effect=0.06, $p<0.001$). The two constructs also mediated the effect of product type on use susceptibility among adults. While risk claims and product type did

Table 3 Path coefficients from mediation analysis for the effects of lower risk and lower exposure claims on susceptibility to use MRTPs

	Perceived quantity					Perceived risk				
	a	b	c	c′	Mediated effect	a	b	c	c′	Mediated effect
EXPERIMENT 1										
Adults (n=2352)										
Risk claim	−0.17**	−0.41**	0.12*	0.05	0.07**	−0.14**	−0.34**	0.12**	0.08*	0.5**
IQOS versus snus	−0.28**	−0.40**	0.30**	0.19**	0.11**	−0.21**	−0.33**	0.30**	0.23**	0.07**
E-cigarettes versus snus	−0.40**	−0.40**	0.30**	0.14**	0.16**	−0.29**	−0.33**	0.30**	0.20**	0.09**
Adolescents (n=480)										
Risk claim	0.28**	−0.17**	−0.02	−0.02	0.05**	−0.23*	−0.20**	0.02	−0.02	0.05*
IQOS versus snus	−0.21*	−0.17**	−0.01	−0.02	0.04**	−0.18*	−0.20**	0.01	−0.02	0.04*
E-cigarettes versus snus	−0.33**	−0.17**	−0.03	−0.03	0.06**	−0.35**	−0.20**	0.03	−0.04	0.07**
EXPERIMENT 2										
Adults (n=2445)										
Exposure claim	−0.31**	−0.29**	0.06	−0.03	0.09**	−0.18**	−0.31**	0.06	0.01	0.06**
IQOS versus snus	−0.12*	−0.27**	0.31**	−0.27**	0.03**	−0.12*	−0.30**	0.31**	0.27**	0.04*
E-cigarettes versus snus	−0.15**	−0.27**	0.27**	−0.23**	0.04**	−0.17**	−0.30**	0.27**	0.22**	0.05**
Adolescents (n=489)										
Exposure claim	−0.39**	0.19**	0.01	−0.07	0.07**	−0.19*	−0.18**	0.01	−0.03	0.04*
IQOS versus snus	−0.21*	0.17**	0.05	0.01	0.04*	−0.21*	−0.18**	0.05	0.01	0.04*
E-cigarettes versus snus	−0.20*	0.17**	0.08	0.05	0.03*	−0.21*	−0.18**	0.08	0.04	0.04*

a=path from independent variable to mediator. b=path from mediator to dependent variable. c=path from independent variable to dependent variable (total effect). c'=cpath adjusted for mediator (direct effect).
*P<0.05, **P<0.001.
MRTPs, modified risk tobacco products.

not change adolescents' susceptibility to use, lower exposure claims and product type showed similar mediation effects as among adults. The correlation between perceived chemical quantity and perceived risk was r=0.47 among adults and r=0.49 among adolescents (both p values<0.001).

DISCUSSION

Tobacco product claims about reduced exposure to harmful chemicals and health risk had similar impact on the beliefs of four diverse samples of US adults and adolescents. A key finding was that claims of lower exposure led to lower perceived risk of harm from MRTP use, even in the absence of an explicit claim of reduced risk. This linkage makes it extremely unlikely that, absent actual evidence of reduced risk, reduced exposure claims can be allowed under the Tobacco Control Act without misleading consumers. Adults' susceptibility to use MRTPs increased in response to lower risk claims but not in response to lower exposure claims whereas adolescents were not affected by either claim, suggesting some impact of claims on behaviour.

With respect to policy, a modified exposure claim would probably not satisfy US regulations for MRTP marketing.[23] The intent of the law is to proactively ensure 'that statements about MRTPs are complete, accurate and relate to the overall disease risk of the product' because the 'dangers of products sold or distributed as MRTPs that do not in fact reduce risk are so high.'[36] National samples of adults and adolescents misinterpreted modified exposure claims as showing reduced risk. Accordingly, the modified exposure pathway (section 911(g)(2)) is not likely to be a viable legal mechanism to introduce and market MRTPs that reduce exposure without actually reducing risk. In contrast, in our studies the public interpreted modified risk claims as intended, which suggests a modified risk claim for a product that truly does reduce risk compared with other products would appear to satisfy US regulatory requirements with respect to public understanding.[23] In addition, per the law, applications would need to back up the risk claim with clear evidence of reduction in health harms to support an issuance of a risk modification order under section 911(g)(1).[23] Finally, our findings about use susceptibility suggest that, should the FDA issue a risk or exposure modification order, the agency should first require measures to minimise initiation among non-users and multiple tobacco product use among current users.

Several risk perception findings in our studies are likely to be generalisable beyond the context of MRTPs. First, the public infers that both risk and exposure are lower when they hear that either one is lower. Our participants perceived lower risk claims for MRTPs as indicating lower quantities of harmful chemicals and less health harm, consistent with previous studies.[11 13 16] Our findings and previous studies also show claims of reduced quantities of chemicals are associated with lower perceived harm.[12–14 17] Perceived risk and perceived chemical quantity were also highly correlated in our studies. Second, perceived risk is surprisingly responsive to claims about products and chemical amounts even in the absence of explicit reduced risk claims. Perceived risk is fairly insensitive to pictorial warnings and many other persuasion approaches.[37 38] Yet, perceived risk changed in response to our experimental manipulations of exposure and risk claims, and MRTP type. It is reasonable for the public to think of lower exposure claims to be relevant to and influence the assessment of MRTP harm.[39] Third, the public is quite susceptible to being misled about tobacco products. Exposure claims were misleading to our study participants. Tobacco companies have successfully misled the public on many topics for decades.[12 13 16] Disclaimers are unlikely to remedy these misperceptions as evidenced by industry-sponsored studies[26] and by external scientists.[40]

Exposure and risk beliefs mediated all pathways to susceptibility to use MRTPs in both experiments and age groups,

which is broadly consistent with our hypotheses. However, only risk claims changed use susceptibility and only among adults. Nonetheless, the results raise some concerns about uptake of MRTPs given that susceptibility is a risk factor for tobacco use behaviour.[41] This is concerning given the detrimental health effects of multiple (vs single) tobacco product use[42] and those of any tobacco use compared with non-use.[43] Among current tobacco users, MRTP marketing claims might encourage multiple tobacco product use. Previous studies show that users of non-cigarette tobacco products are less likely to quit[44] and are more likely to progress to smoke cigarettes in addition to or instead of these alternative tobacco products.[45 46] Among non-users, MRTP marketing claims might encourage initiation of tobacco use. This is particularly relevant to youth and their perceptions of potential MRTPs such as IQOS and e-cigarettes. Existing evidence on e-cigarettes shows that they appeal to youth because of their trendiness, youth-oriented flavours and social appeal.[47] Literature on adolescents' tobacco use shows that experimentation with non-cigarette tobacco products is a predictor of future cigarette smoking[48] and multiple tobacco product use,[49] and that adolescents who initiate tobacco use are more likely to continue using tobacco in their adulthood and experience its negative health effects over a longer period.[50]

Our studies' strengths include national samples, inclusion of adults and adolescents, use of experimental designs, and replication of many of our findings across the samples. Limitations include the use of brief descriptions of the products, some of which may have been new to participants, and not examining actual product use. Using three tobacco products currently on the market increases the relevance of our results. Additional research is needed to replicate our findings with other candidate MRTPs, both existing and proposed.

CONCLUSION

Accuracy of claims and public comprehension of health risks associated with MRTPs are a requirement of US law.[19] At long last, the Tobacco Control Act shifts the burden to tobacco manufacturers to demonstrate with scientific evidence that the issuance of an MRTP order under the Tobacco Control Act section 911 would be appropriate for the protection of the public health. Our national samples of adults and adolescents understood modified risk claims as intended. However, they misinterpreted modified exposure claims as communicating lower risk even when there was no explicit claim of lower risk, suggesting that this may not be a viable pathway under the law.

What this paper adds

- The US Tobacco Control Act allows marketing of tobacco products as causing less exposure to harmful chemicals only if this claim does not mislead the public into believing the product presents reduced risk of health harm.
- Claims of lower exposure and lower risk acted similarly, with both leading to lower perceived quantity of harmful chemicals and lower perceived risk of health harm.
- Absent concurrent evidence of reduced risk, claims of lower exposure are intrinsically misleading.
- Claims of lower exposure do not satisfy US legal requirements for modified risk tobacco products.

Contributors NTB, KMR, SAB and MJB designed the experiment. SAB conducted the analyses and SE-T led writing of the manuscript. All authors were involved in analysis and interpretation of data, as well as critical revision of the manuscript for important intellectual content.

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Competing interests None of the authors have received funding from tobacco product manufacturers. NTB and KMR have served as paid expert consultants in litigation against tobacco companies. The other authors declare no conflicts of interest.

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Research paper

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Examining perceptions about IQOS heated tobacco product: consumer studies in Japan and Switzerland

Elizabeth C Hair,[1,2] Morgane Bennett,[1,3] Emily Sheen,[4] Jennifer Cantrell,[2,5] Jodie Briggs,[1] Zoe Fenn,[4] Jeffrey G Willett,[1] Donna Vallone[1,2,5]

[1]Schroeder Institute, Truth Initiative, Washington, DC, USA
[2]Department of Health, Behavior and Society, Bloomberg School of Public Health, Johns Hopkins University, Baltimore, MD, USA
[3]Department of Prevention and Community Health, Milken Institute School of Public Health, The George Washington University, Washington, DC, USA
[4]Flamingo, London, UK
[5]College of Global Public Health, New York University, New York, NY, USA

Correspondence to
Dr Elizabeth C Hair, Schroeder Initiative, Truth Initiative, Washington, DC, USA; ehair@truthinitiative.org

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ABSTRACT

Objective To examine consumer perceptions, attitudes and behaviours regarding the heated tobacco product, IQOS, as well as to document the product's marketing strategies to determine its potential for appealing to youth and young adults.

Method Truth Initiative, in collaboration with Flamingo, collected qualitative data via: (1) expert interviews, (2) semiotic analysis of IQOS packing and marketing materials, and (3) 12 focus groups with adults in Switzerland (ages 19–44 years; June 6–9, 2016) and Japan (ages 20–39 years; June 22–24, 2016) (n=68 for both groups).

Results Expert interviews and IQOS packing and marketing analyses revealed the product is being marketed as a clean, chic and pure product, which resonated very well in Japan given the strong cultural values of order, cleanliness, quality and respect for others. Focus groups results indicated Japanese IQOS users used the product for socialising with non-smokers. Focus group participants in both Japan and Switzerland reported lower levels of satisfaction with the product relative to combustible cigarettes, although many found the product packaging to be appealing. While participants identified several benefits and barriers related to IQOS, few reported any potential health benefits of use compared with combustible tobacco products.

Conclusion IQOS was marketed as a sophisticated, high tech and aspirational product. Because youth and young adults are more interested in such product positioning, this approach raises some concern about youth appeal. This research shows cultural factors appeared to affect the appeal of this messaging, indicating that prevalence and uptake data will likely not be similar from country to country.

INTRODUCTION

The heated tobacco product (HTP), IQOS, is a battery-powered, pen-like device that delivers nicotine to users by heating tobacco. This device was developed by Phillip Morris International (PMI) and released to the market in 2014. Users operate it by inserting a 'HeatStick', a rod of tobacco that is electrically heated to a high temperature without igniting and combusting like a traditional combustible cigarette. According to PMI, nicotine is delivered to the user through this heating process with a taste similar to a traditional combustible cigarette.[1] These devices are entering markets at a time when e-cigarette popularity is beginning to wane, and research suggests e-cigarette users are dissatisfied with the lack of rapid nicotine delivery and 'throat-hit' that come from combustible tobacco use.[2] The use of real tobacco in IQOS may make this new device a more appealing alternative to those looking for a seemingly less harmful alternative to combustible tobacco. Tobacco executives appear to be aware of this opportunity and prepared to take advantage of it, with PMI CEO reportedly stating HTPs are the 'greatest growth opportunity in the years to come, which we believe has the very real potential to transform the industry'.[3]

IQOS is marketed as a clean alternative to cigarettes using online promotional materials that present the device as sophisticated, high tech and providing all the benefits of smoking but less ash and odour.[1] IQOS products were first test-marketed in Japan and Italy in 2014 and are now being test-marketed in 30 countries around the world, including Switzerland.[4] Japan, however, remains the only country that has seen a national roll-out of IQOS. A longitudinal online survey of youth and adults in Japan found less than 1% of respondents had ever used an IQOS device from January to March 2015. However, that percentage doubled in 2016 and reached 3.6% by February 2017, with an estimated 3 million people in Japan using IQOS.[4] Analysis of Google search data revealed dramatic increases in searches for HTPs between 2014 and 2017 in Japan, a further indication of the rapid growth in interest and popularity of the products.[5] Surveys of Italian youth and adults revealed that almost 20% were aware of IQOS, and 2.3% reported intentions to try the device in the future.[6] Another indication of the growing popularity of IQOS is its increasing share of the tobacco product market, reaching over 13% of the market share of all tobacco products in Japan by October 2017.[7]

In 2016, PMI filed an application to the US Food and Drug Administration (FDA) for IQOS to be marketed as a modified risk tobacco product in the USA. To date, FDA continues to accept comments to the PMI application.[8] In January 2018, the FDA Center for Tobacco Products, Tobacco Products Scientific Advisory Committee rejected PMI's claim that IQOS is less harmful than cigarettes. However, the committee did concede that evidence suggests that 'switching completely from cigarettes to the IQOS system significantly reduces your body's exposure to harmful or potentially harmful chemicals'.[9] Given the ongoing review of PMI's application, and the product's growing popularity and expansion into worldwide markets,[10] the current study was designed to explore knowledge, attitudes, beliefs and marketing strategies related to IQOS use in Japan and Switzerland.

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METHODS

Original data were gathered by Truth Initiative, a US-based non-profit public health organisation focused on tobacco prevention, and Flamingo, an insight and brand consultancy firm based in the UK, via expert interviews, product and marketing analyses and focus groups.

Expert interviews

Expert interviews were conducted with professionals working in youth culture and youth and young adult tobacco and electronic nicotine delivery system use in order to gain insight into how IQOS might translate into markets. Experts were identified via desk research and included an ethnographer specialising in e-cigarettes and young adult smoking and an editor at Vice.com who specialises in youth culture. These experts were selected to ensure both an academic and a cultural lens on smoking and were financially incentivised for their time. Questions asked via a structured discussion guide encouraged experts to explain their understanding of youth smoking culture to unpack the differences between what cigarettes and e-cigarettes represent in culture. Experts were also asked to hypothesise how IQOS might fit into cultures and markets, based on their understanding of tobacco and e-cigarettes. This process provided key information to better understand how IQOS's marketing fits into broader cultural landscapes. Questions covered areas such as, 'what attracts young people to smoking and vaping today?' and 'where do you see the future of smoking – what will keep it relevant for young people?'.

Interviews were audio-recorded and transcribed. Transcripts were analysed by two Flamingo semioticians who specialise in connecting product attributes with broader cultural trends. The two researchers performing the analyses differed in their level of involvement with the project (ie, one was closely involved in the design and implementation of the study, while the other was not) in order check the reliability of study findings. A thematic analysis approach was used to place interview findings into cultural contexts, informed by additional research on youth websites, such as Vice.

Product and marketing analysis

An analysis of IQOS packaging (font, colour scheme, pack and product shape and claims) and advertisements (claims, colours, font and visuals) was also conducted to document the brand positioning and use of terminology. Field workers visited IQOS stores in Tokyo and Zurich, the majority of which were located within close proximity to train stations to ensure high volume of foot traffic and collected print marketing materials and photographs of point-of-sale marketing. The stores visited represented a convenience sample of IQOS retailers in the two cities.

Focus groups

Results of the expert interviews and IQOS product and marketing analyses were used to inform the focus group guides. Twelve focus groups (six in each country) were conducted in Japan and Switzerland during June 2016. These were stratified according to age (18–19 years, 20–25 years and 26–44 years in Lausanne and Zurich, Switzerland; 20–24 years, 25–29 years and 30–39 years in Nagoya, Japan) and segmented by attitudes to IQOS. A total of 68 participants from both countries were recruited through social media posts, telephone lists and at retail venues that sold IQOS. The cities of Lausanne and Zurich were selected as they were the first cities in Switzerland where IQOS was available, and Nagoya was selected because it was the location IQOS was initially launched. Recruitment criteria included age (segmented as described above), smoking habits, attitudes to smoking and willingness to talk freely on the subject in a group setting. Participants were recruited to fit within the following smoking categories: (1) those who had fully converted to IQOS use from cigarettes, (2) dual users of both IQOS and cigarettes, (3) those who had tried and rejected IQOS and (4) those who were aware of IQOS but had never tried it. Focus groups included a set of open-ended questions related to respondents' combustible tobacco smoking habits (eg, 'What occasions do you smoke? Who with? What? Why? Do you smoke other things on different occasions? Why/Why not?') and IQOS perceptions (eg, 'How did you discover it? What were your initial impressions? How has your opinion changed?'), usage (eg, 'What moments do you use IQOS? Any moments where you'd be less likely to use it? Why? Why not?') and behaviours (eg, 'How does it compare using IQOS versus regular cigarettes? Has it changed your routine at all? How do you find it to hold?'). Questions also examined receptivity to IQOS marketing and promotional message themes (eg, 'What (if any) communications have you seen for the product? What stands out in your mind? Why? Have you attended any IQOS events? If so, describe the event to me. How did it make you feel?').

Focus groups were audio-recorded and transcribed. Transcriptions were analysed by Flamingo through the four thematic lenses that resulted from the semiotic packaging analysis and expert interviews: cleanliness, customisation, next generation smoking and sociability (see Results section for more details). The analysis team at Flamingo consisted of three qualitative researchers in the UK (at different levels of closeness to the project to maintain objectivity), two semiotics team members (also at different levels of closeness to the project) and two qualitative research/semiotics hybrids in Japan (who had conducted the Japanese interviews). Analysis methods included recurring sentiment and attitudinal analysis, through which patterns in participants' emotional reactions to the four themes were analysed across markets, and examination of linguistic themes, through which emotive language used was explored in detail in order to identify additional themes.

RESULTS

Expert interviews

The expert interviews helped define and examine the intersection of smoking and youth culture, unearthing insights such as: technology's most important role for young people is as an emotional facilitator, and today's youth are more wedded to technology than any previous generation, across all aspects of their lives. One expert stated, 'My younger siblings grew up with Facebook and Snapchat and they grew up not knowing anything else […] I feel like they don't understand offline etiquette'. Two key spaces emerged from these expert interview discussions around youth culture: freedom and control—a tension between using technology as freedom of expression, to pursue emotional desires, and set yourself apart, but also to control your body, organise your life and uncover the processes behind the goods they consume. The expert interviews suggested that vaping speaks to the freedom space (rebellion, smoke, 'hackable' nature of the device and no clear rules), while IQOS would likely sit more in the control space (clean lines, official branding, not 'hackable' or flexible in terms of flavour).

Product and marketing analysis results

Analysis of marketing strategies revealed a comprehensive effort to promote IQOS as a sophisticated and aspirational product in

both Japan and Switzerland. IQOS promotional efforts centred around presenting the product in a clean, controlled, minimalist environment during invitation-only pop-up events in dedicated spaces. These events introduced the product by employing brand ambassadors to showcase the product and answer questions with free samples. These brand representatives highlighted the sleek, exclusive 'iPhone' style and quality of IQOS products, as well as the benefits of reduced ash and odour. An analysis of the product's marketing and advertising in both countries identified four key message themes: cleanliness, customisation, comparisons with combustible smoking and sociability. The overarching message architecture focused on the concept of modernising traditional smoking by promoting themes of control and freedom from the negative aspects of combustible tobacco smoking. Analysis of the product packaging revealed eight additional themes, specific to the device: clinical purity, a closed system, premium design, sensory invitations, nostalgia for combustible tobacco smoking, stability, familiar technology and normalisation. For example, the product's 'clinical purity' allowed smokers to control offensive factors like smoke and ash, distinguishing the product from combustible cigarettes. At the time of data collection, any potential health benefits associated with IQOS use were not included on the product packaging or marketing materials in either country. Some marketing materials in Switzerland contained the health message, 'This tobacco product can harm your health and is addictive'.

IQOS marketing efforts in both countries were also found to highlight product factors that are similar to traditional combustible cigarettes in an effort to invoke familiarity and nostalgia for smoking. Marketing materials highlight the similarity of the product's taste and behavioural process to combustible cigarettes, the similarity between the size of HeatSticks and combustible cigarettes and the charging mechanism to an old-fashioned cigarette lighter. Additionally, IQOS products are occasionally displayed next to combustible cigarettes in stores.

Focus group results

Focus group participants in Japan consistently reported IQOS as a clean, chic and pure product, indicating the effectiveness of the marketing strategy. Respondents primarily reported using IQOS when socialising with groups of non-smokers where the use of combustible cigarettes could infringe on smoke-free social situations. One respondent commented, 'Most of my friends have little kids and I started feeling uncomfortable smoking around them. So now I am only using IQOS'. Participants also reported using the product in places where smoking combustible cigarettes may leave an unwanted residue in an area. One participant stated, 'I like smoking IQOS while watching the TV with my family at home. IQOS is the best for smoking in the house because it creates no ash or odour'. Japanese participants also commented on the cumbersome process of using IQOS. For these respondents, taking along the charger and HeatSticks can be bulky and burdensome. Nonetheless, Japanese focus group participants found the packaging of the product to be appealing. Even non-users unimpressed by descriptions of the device were intrigued when presented with the actual product, indicating that the product's sleek appearance blended well with existing tech devices. Younger non-users commented that price could be a potential barrier, but after analysis of the focus group conversations, this in fact served to contribute to the overall cache of the product as luxurious and prestigious.

In Switzerland, the product's promise of freedom was subverted by the realities of using an HTP. Swiss respondents complained about the charging and cleaning of IQOS. Focus group results suggested a view of smoking combustible cigarettes as a tool for self-expression, and it appeared that the IQOS's promotional efforts failed to resonate in this culture. In reference to smoking combustible cigarettes, one young adult participant stated, 'I guess it's the time where you have that sense of freedom, you're doing something the teachers don't want you to do'. Many focus group participants reported initiating smoking combustible tobacco products to impress friends, rebel against authority figures (eg, teachers and parents) or set a trend. Several participants reported that the product did not provide the same level of intensity as smoking combustible cigarettes, and thus, comparisons with combustible cigarettes made by IQOS were not deemed credible. Swiss participants also cited the milder taste and reduced sensory cues as barriers to continued use. One Swiss participant commented, 'There's just something about that after-work drink, I need a proper cigarette with it. Same with coffee; cigarettes just "go" with coffee'.

Focus group participants in both countries identified several benefits of IQOS use, including less throat discomfort, appealing packaging, cleanliness, lack of ash and smoke and more social acceptability. Participants commented on the novelty of the product as both an advantageous 'conversation starter' for some, as well as 'ostentatious' by others. Participants in both locations also identified several barriers to using the device, including a strange or unpleasant taste and smell, unfamiliar appearance, high maintenance and high cost. Some who had previously smoked combustible cigarettes noted that the product was cumbersome because it could not be held like a traditional combustible cigarette. Among participants in both countries, few identified any potential health benefits of IQOS use compared with combustible tobacco products, and many expressed that the product still felt unfamiliar and complicated to use.

DISCUSSION

Findings from this exploratory study suggest HTPs, like IQOS, may appeal to consumers, particularly within cultures that value cleanliness, exclusivity and high tech appearances. Others who perceive combustible tobacco use as an expression of freedom, and individualism may be deterred by the price of the product, its cumbersome utility, high maintenance and unfamiliar taste, smell and appearance. The consumer research presented here suggests consumer reception of IQOS may differ depending on culture. Similar cultural differences have been observed in the acceptance and use of snus as a harm reduction tool. While evidence suggests snus may be an effective harm reduction method among Swedish smokers, the same has not been found in the USA.[11 12]

Consistent with the current study, PMI's research that was presented in their modified risk tobacco product application to the US FDA suggested there is more interest in IQOS in Asian markets compared with European markets.[13] This suggests usage patterns and IQOS acceptance are likely to significantly vary from country to country. However, the popularity of e-cigarettes in the USA and the potential for HTPs to become a more appealing alternative to current e-cigarette users highlights the need to further monitor the launch of novel HTPs, like IQOS, in US markets.

Evidence from tobacco industry executives suggests a strong desire and interest in heavily promoting HTPs in order to take advantage of the declining consumer interest in combustible tobacco products and e-cigarettes.[2] As was historically

done with combustible cigarette promotions,[14] the marketing strategies used by PMI for HTPs may seek to capitalise on the products' potential among youth and young adults in the USA—a group for whom combustible cigarette use continues to decline.[15] Marketing efforts to portray HTPs as sleek, exclusive items akin to iPhones could find success among American teens and young adults, and researchers are already warning of growing interest and potential demand within new markets.[5 16]

What this paper adds

- To our knowledge, this is the first study of IQOS conducted independent of a tobacco company to provide a brief overview of the marketing and promotional efforts, as well as consumer responses related to the heated tobacco product (HTP), IQOS, in Japan and Switzerland.
- Tobacco industry executives have indicated significant interest in developing and promoting novel HTPs, like IQOS. Given the probable increasing effort by the industry to promote HTPs, and the pending application for IQOS to be marketed as a modified risk tobacco product in the USA, findings are key in understanding how this product may be promoted and how to counter these efforts for at-risk groups, particularly youth and young adults.

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Awareness, experience and prevalence of heated tobacco product, IQOS, among young Korean adults

Jinyoung Kim,[1] Hyunjae Yu,[2] Sungkyu Lee,[3] Yu-Jin Paek[1,4]

[1]Southern Gyeonggi Regional Smoking Cessation Centre, Hallym University, Anyang, Republic of Korea
[2]School of Communication, Sogang University, Seoul, Republic of Korea
[3]National Tobacco Control Centre, Korea Health Promotion Institute, Seoul, Republic of Korea
[4]Department of Family Medicine, Health Promotion Center, Hallym University Sacred Heart Hospital, Anyang, Republic of Korea

Correspondence to
Dr Sungkyu Lee, National Tobacco Control Centre, Korea Health Promotion Institute, Seoul 04554, Republic of Korea; wwwvince77@gmail.com

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ABSTRACT

Introduction Philip Morris International introduced 'IQOS' to the Korean market in June 2017. To monitor the use of IQOS among young Korean adults, we identified their awareness, experience and current use of IQOS.

Methods Three months after the introduction of IQOS in Korea, we conducted an online survey with 228 general young adults, aged 19–24 years.

Results 87 participants (38.1%) were aware of IQOS, 13 (5.7%) were IQOS ever users and 8 (3.5%) were current IQOS users. All the current IQOS users were triple users of conventional cigarettes and electronic cigarettes (e-cigarettes). There were no IQOS-only users and one IQOS ever user was a non-cigarette smoker. Among the eight current IQOS users who smoked 9.1 conventional cigarettes a day on average, four smoked 10–20 HEETS sticks a day. The current IQOS users decided to use IQOS because they believed it was less harmful or to stop smoking. The current conventional cigarette smokers were much more likely to be aware of IQOS (OR 4.496; 95% CI 2.185 to 9.250) and to be IQOS ever users (OR 11.649; 95% CI 1.024 to 132.564).

Conclusion Awareness, experience and use of IQOS among young Korean adults were relatively higher than among their Japanese counterparts. Current IQOS users were more likely to smoke conventional cigarettes and/or e-cigarettes, which contradicts the tobacco industry's claims that conventional cigarette smokers will switch to heated tobacco products. Until obtaining robust evidence concerning heated tobacco products, the government should regulate the tobacco industry's marketing tactics and health claims.

INTRODUCTION

Philip Morris International (PMI) introduced its heated tobacco product, IQOS, to the Korean market in June 2017. After their market success in Japan, the company penetrated the Korean market by establishing two flagship stores in Seoul and signing a contract with CU—Korea's largest convenience store chain with 1654 locations in the capital city and 7946 nationwide—to sell IQOS and packs of modified cigarettes, named HEETS.[1]

PMI offered discount coupons to customers who registered on their IQOS website (www.myiQOS.com). With these coupons, the price of a device can be discounted by 20% and the warranty period can be extended from 6 to 12 months.[1] The company has marketed their heated tobacco product as a harm reduction product and it advertised that IQOS reduces harmful substances by approximately 90% on average compared with conventional cigarettes which are sold in the Korean market (figure 1).[2] This assumes that Korean smokers' behaviour reflects these marketing tactics.[3] It is not hard to find IQOS users on the streets of Korea.

Korea has been successful in enforcing tobacco control policies. Tobacco tax increased in 2015 and pictorial health warnings were introduced on cigarette packages in 2016. The smoking prevalence among adult men decreased to 40.7% in 2016 from 66.3% in 2001.[4] However, the introduction of new types of tobacco products, such as heated tobacco products, to the Korean market can threaten this achievement. Although there are many current smokers who can quit and be free from nicotine addiction with existing tobacco control policies and programmes, the tobacco industry claims that they developed alternative products, such as heated tobacco products, to continue cigarette smoking. The industry tries to hold on to their customers with 'harm reduction' strategies.[5]

Three months after the introduction of IQOS in the Korean market, the government and Congress were confused about IQOS while preparing to define the product and impose taxes on it. Due to this situation, the public has been exposed to marketing messages generated by the tobacco company. There is an urgent need to collect data related to IQOS to develop effective policies regarding heated tobacco products.

The purpose of this study was to identify awareness, experience and current use of the heated tobacco product, IQOS, among Korean adults aged 19–24 years. The results of this study can contribute to helping the government to prepare appropriate regulations to control such products.

METHODS

In September 2017, three months after the introduction of IQOS in Korea, we carried out an online survey to identify the awareness, experience and prevalence of the new product, IQOS, among young Koreans. We recruited 228 general adults aged 19–24 years, which included 114 men and 114 women, from an online survey panel, which was managed by a survey company, EMBRAIN (http://www.embrain.com/eng/). The study participants were defined by age and gender. The online survey consisted of 24 questions and only took 10–15 min to complete. If there were questions that were not answered, participants could not complete the survey. The survey company, EMBRAIN, provided online points, which can be exchanged for cash or gifts, to participants who completed the survey.

Conventional cigarette smoking questions were: 'Have you ever smoked in your life?' (none/less than 100 cigarettes/more than 100 cigarettes) and 'Do you currently smoke?' (yes/no). Electronic



Figure 1 The IQOS ad on top of the shelf in a convenience store claims, 'IQOS reduces harmful substances by approximately 90% on average compared to conventional cigarettes which are sold in the Korean market' (photo taken by Dr Jinyoung Kim).

cigarette (e-cigarette) use questions were: 'Have you ever used e-cigarettes?' (yes/no) and 'Have you used e-cigarettes in the past 30 days?' (yes/no). IQOS use questions were 'Have you ever used IQOS?' (yes/no) and 'Have you used IQOS in the past 30 days?' (yes/no). The IQOS awareness question was 'Are you aware of IQOS?'

We included several demographic variables because these variables could be associated with IQOS use: age, education level (using the question, 'What is the highest *educational* qualification that you have completed?') and monthly allowance (using the question, 'How much money do you spend a month?'). Response options for educational level were 'high school', '2 year college degree' and '4 year college degree'. Response options for monthly allowance were 'none', 'less than 50 000 won' (equivalent to approximately US$50), '50 000 to 99 999 won', '100 000 to 149 999 won' and 'more than 150 000 won'. We also asked about the amount of IQOS daily use and the reason that current IQOS users decided to use it.

Data analyses were performed using SPSS software, V.21.0 for Windows (SPSS).

RESULTS

Among the participants, those aged 23 years old were the largest group with 27.2%, followed by those aged 24 years old with 21.5%, and those aged 22 years old with 20.6%. The mean age and SD of the male participants and female participants were 22.3 years old (±1.4) and 22.0 years old (±1.5), respectively. A total of 53.1% of all participants were university students and 16.2% of participants were college students. The remaining 70 participants' (30.7%) education level was a high school degree. More than half of participants (57.9%) lived in Seoul, the capital city, or Gyeonggi Province. Almost one-third (30.7%) of participants spent between 50 000 and 99 999 won a month. 18.0% and 19.7% spent 100 000–149 999 won or more than 150 000 won, respectively. The number of current conventional cigarette smokers in this study sample was 38 (33.3%) among men and 39 (34.2%) among women. Among the participants, 20 men (17.5%) and 14 women (12.3%) were current e-cigarette users.

Table 1 shows the awareness, experience and current use of IQOS among the study group.

Eighty-seven participants (38.1%) were aware of IQOS. More men (52.9%) were aware of IQOS than women (47.1%), but the difference was not statistically significant ($p=0.495$). IQOS awareness was significantly higher for conventional cigarette smokers (57.5% vs 42.5% for non-cigarette smokers; $p<0.0001$). Among participants who were aware of IQOS, 25 (28.7%) were current e-cigarette users, while 62 (71.3%) did not use e-cigarettes ($p<0.0001$).

Thirteen participants (5.7%) had tried IQOS; nine of these were men and four were women. Almost every IQOS ever user (12 out of 13) was also a current conventional cigarette smoker and the one non-current cigarette smoker was a never smoker. In addition, 10 of the 13 IQOS ever users were current e-cigarette users. There were eight current IQOS users (3.5%) among all the participants and all current IQOS users were triple users of conventional cigarettes and e-cigarettes.

Although the current IQOS users were few, we analysed their daily IQOS use and reasons for IQOS use. Among the eight current IQOS users, four participants smoked less than 10 HEETS sticks a day, but the other four participants smoked 10–20 HEETS sticks a day. Six current IQOS users decided to use the product because they believed that heated tobacco products were less harmful and less smelly compared with conventional cigarettes. Two out of eight current IQOS users used it to stop smoking. They believed that IQOS was a smoking cessation aid.

Multivariable logistic regression analysis indicated that current conventional cigarette smokers were much more likely to be aware of IQOS (OR 4.496; 95% CI 2.185 to 9.250) and to be IQOS ever users (OR 11.649; 95% CI 1.024 to 132.564) than non-smokers. Men, older participants and those with a high monthly allowance and higher education levels were more likely to be aware of IQOS and to become IQOS ever users, although the differences were not significant. In addition, the OR for being IQOS ever users among current e-cigarette users was 9.647 (95% CI 1.632 to 57.013).

DISCUSSION

In 2014, PMI introduced IQOS in Japan. Compared with Ploom, which is another type of heated tobacco product manufactured by Japan Tobacco International, the growth of IQOS in Japan was relatively very rapid. After a big success in Japan, PMI accessed the Korean market in 2017 with similar marketing tactics to that used in Japan. Once the product was marketed in Korea, the media focused on IQOS and introduced it as the equivalent of the 'iPhone' in the field of the tobacco business.

A previous study found that 48% of Japanese people were aware of IQOS, 6.6% had ever used it and 1.3% had used it in the last 30 days in 2015, one year after its introduction in the Japanese market.[6] Later research conducted in 2017 found that 3.6% of Japanese people were current IQOS users.[7] The prevalence of IQOS use in Japan has increased almost threefold in the last 2 or 3 years. The study also found that 4.7% of Japanese people used at least one type of heated tobacco product or e-cigarettes; of these, 72% smoked conventional cigarettes.[7] Unlike the tobacco industry's claim that current cigarette smokers can switch from conventional cigarettes to heated tobacco products, it was found that most IQOS users were triple or dual users of conventional cigarettes and/or e-cigarettes.

Table 1 Awareness, experience and prevalence of IQOS among the Korean young adults and multivariable association of IQOS awareness and ever use

			Univariate association between IQOS awareness/ever use/current use and sociodemographic characteristic and smoking behaviour						Multivariable association of IQOS awareness and ever use	
			IQOS awareness (n=87)		IQOS ever use (n=13)		Current IQOS use (n=8)		IQOS awareness	IQOS ever use
Factor	Category	n (228)	n (%)	P values	n (%)	P values	n (%)	P values	OR (95% CI)	OR (95% CI)
Gender	Female	114	46 (52.9)	0.495	9 (69.2)	0.153	6 (75.0)	0.569	Ref	Ref
	Male	114	41 (47.1)		4 (30.8)		2 (25.0)		1.10 (0.59 to 2.05)	3.11 (0.67 to 14.30)
Age (mean±SD)		228	22.31±1.43	0.279	21.92±1.12	0.526	21.50±0.93	0.082	1.12 (0.89 to 1.40)	0.80 (0.46 to 1.37)
Education level	High school	121	27 (31.0)	0.497	4 (30.8)	0.770	2 (25.0)	0.850	Ref	Ref
	2-year college degree	37	11 (12.6)		3 (23.1)		2 (25.0)		0.70 (0.25 to 1.96)	0.84 (0.10 to 6.78)
	4-year college degree	70	49 (56.3)		6 (46.2)		4 (50.0)		1.51 (0.71 to 3.20)	1.22 (0.22 to 6.68)
Monthly allowance (KRW)	None	49	14 (16.1)	0.076	1 (7.7)	0.028	0 (0.0)	0.386	Ref	Ref
	Less than 50 000 won	39	13 (14.9)		1 (7.7)		1 (12.5)		1.65 (0.59 to 4.61)	1.72 (0.06 to 50.87)
	50 000–99 999 won	54	17 (19.5)		3 (23.1)		1 (12.5)		1.28 (0.49 to 3.29)	3.63 (0.23 to 57.01)
	100 000–149 999 won	41	20 (23.0)		1 (7.7)		1 (12.5)		1.59 (0.60 to 4.27)	0.37 (0.02 to 9.47)
	More than 150 000 won	45	23 (26.4)		7 (53.8)		5 (62.5)		1.00 (0.36 to 2.80)	1.95 (0.17 to 22.78)
Conventional cigarette smoking	Never smoker	151	37 (42.5)	0.000	1 (7.7)	0.000	0 (0.0)	0.188	Ref	Ref
	Current smoker	77	50 (57.5)		12 (92.3)		8 (100.0)		4.50** (2.19 to 9.25)	11.65* (1.02 to 132.56)
E-cigarette use	Never e-cigarette user	194	65 (71.3)	0.000	3 (23.1)	0.000	0 (0.0)	0.012	Ref	Ref
	Current e-cigarette user	34	25 (28.7)		10 (76.9)		8 (100.0)		2.99* (1.11 to 8.07)	9.65* (1.63 to 57.01)

KRW is South Korea's currency, the won (1000 won=US$1).
*P<0.05; **P<0.0001.

Korea has experienced a similar situation to that of Japan. Compared with a Japanese study,[6] which was carried out 1 year after the introduction of IQOS in the Japanese market, awareness of IQOS (48% in Japan vs 38.1% in Korea) and ever-use of IQOS (6.6% in Japan vs 5.7% in Korea) were slightly lower. However, since there were similar percentages of current IQOS users in Korea (3.6% in Japan vs 3.5% in Korea), urgent action is needed to tackle the rapid growth of heated tobacco product use in Korea.

Given that the sample size of the present study was relatively smaller than previous studies in Japan, there is a limitation in directly comparing the results. However, if we consider that our study was carried out just 3 months after the introduction of IQOS in the Korean market, we could assume the IQOS growth in Korea has been much faster compared with its growth in Japan. According to the announcement of the Ministry of Finance, the market share of heated tobacco products, including IQOS, British American Tobacco's Glo, and KT&G's (the largest tobacco company in Korea) lil, reached 9.1% of the total sale of tobacco products in Korea.[8]

Importantly, our study found that none of the IQOS current users had switched from conventional cigarettes to IQOS. In addition, among 13 IQOS ever users, one ever user smoked neither conventional cigarettes nor e-cigarettes. This can be explained in that IQOS might possibly be a gateway product for tobacco use among never smokers. Similarly, a recent study describing the Italian experience of heated tobacco products reported that nearly half (45%) of Italian IQOS current users and over half (51%) of Italian people who were interested in IQOS were never smokers.[9]

In our sample, there were many conventional female cigarette smokers, although the smoking prevalence among Korean female adults was low. This might affect the finding that there was no significant difference in awareness of IQOS between men and women.

Not surprisingly, we found that all current IQOS users in the sample were current conventional cigarette and e-cigarette users. This is similar to the finding of a Japanese study.[7] In addition, four out of eight current IQOS users consumed 10–20 HEETS sticks a day, while they smoked 9.1 conventional cigarettes a day on average. Considering that Korean adult smokers aged 19–29 years old smoke 10.8 cigarettes a day on average,[4] dual users of conventional cigarettes and IQOS in our study sample were exposed to more nicotine and other tobacco-related toxic substances. Although six out of eight decided to replace their tobacco products with heated tobacco products with the faith that IQOS was less harmful and can be used as a smoking cessation aid, these triple users' total nicotine absorption and toxic exposure from conventional cigarettes, e-cigarettes and IQOS can be really high and cause serious adverse effects to their health.

This study has a limitation in that the sample was small, and thus the findings should be interpreted carefully. Nevertheless, this study is likely to remain valuable because it analysed the early influence of IQOS on young Korean adults.

CONCLUSIONS

Due to aggressive marketing activities by the tobacco industry, awareness, experience and use of heated tobacco products, particularly among young adults, have rapidly increased. Additionally, smokers readily believe that heated tobacco products are less harmful and would help them quit smoking. Current IQOS users are more likely to smoke conventional cigarettes and/or e-cigarettes, which contradicts the tobacco industry's claims that conventional cigarette smokers will switch to heated tobacco products.

What this paper adds

- Awareness, experience and use of IQOS among young Korean adults were relatively higher than among their Japanese counterparts.
- IQOS users decided to use the product because they believed it was less harmful and would help them quit smoking. All the current IQOS users were triple users of conventional cigarettes and electronic cigarettes, which contradicts the tobacco industry's claims that conventional cigarette smokers would switch to heated tobacco products.

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IQOS campaign in Israel

Laura J Rosen,[1] Shira Kislev[2]

[1]Department of Health Promotion, School of Public Health, Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel
[2]The National Initiative to Eradicate Smoking (Smoke-Free Israel), Ramat Raziel, Israel

Correspondence to
Dr Laura J Rosen, Department of Health Promotion, School of Public Health, Tel Aviv University, Ramat Aviv 69978, Israel; rosenl@post.tau.ac.il

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INTRODUCTION

At present, IQOS, Philip Morris's (PM's) heated tobacco product, is being test-marketed in 30 countries worldwide.[1] Similarly to electronic cigarettes,[2] regulation varies widely by country. In the USA, for example, sales and marketing of IQOS are currently prohibited by the Food and Drug Administration's (FDA's) premarket approval structure, pending a decision by the FDA.[3] Canada allows marketing, and has been termed a 'dark market' due to its strong tobacco advertising ban in combination with its categorisation of IQOS as a tobacco product.[4] Italy, by contrast, has exempted IQOS from its comprehensive ban on cigarette advertising and also from the graphic warnings which are required on cigarettes.[5]

This paper describes the entry of IQOS into Israel, and its marketing campaign (see Figure 1). In 2016, when the IQOS campaign began, the adult smoking prevalence was 21.6%.[6] Israel was a signatory to the Framework Convention on Tobacco Control (FCTC), had a governmentally approved tobacco control plan, national legislation for smoke-free public indoor and outdoor places and high levels of taxation.[7] A partial advertising ban was in place which prohibited advertisement of tobacco products on television and radio, and in print press publications directed at youth.[7] No premarket regulatory mechanism existed for any tobacco or nicotine product, and Israel did not have any distinct category for emerging tobacco and nicotine products.

During the first half of 2016, PM communicated directly with officials from the Ministries of Health and Finance via high-level meetings and letters prior to marketing of IQOS to the public.[6] This is consistent with PM's global strategy.[8] Following these meetings, the Ministry of Health (MOH) sent a letter to the Tax Authority defining IQOS as a new product which did not fall under existing tobacco regulation.[9] PM began advertising IQOS online in December 2016. In January 2017, online sales began, and in February 2017, retail sales began. Initially, the cost was about US$100 for IQOS plus 10 packs of HEETs (HEETS, or Heat Sticks, are the cigarette-like product inserted into the IQOS holder).

The classification of IQOS as a product not subject to existing tobacco legislation was challenged in the Supreme Court with three petitions. The first petition, filed on 12 March 2017 by Dubek, a local tobacco company, demanded that IQOS be defined as a tobacco product, with taxation equal to that on cigarettes.[10] The second petition was filed on 19 March 2017 by the Israel Association for Progressive Democracy, and also demanded that IQOS be defined as a tobacco product, subject to existing regulations on tobacco products.[11] The Supreme Court then requested clarification from the MOH regarding IQOS's status. On 2 April 2017, the MOH responded that IQOS should be regulated under existing tobacco legislation, as requested by the petitioners. The third petition was filed on 15 November 2017 by two advocacy organisations: The Israel Association for a Progressive Democracy and the National Initiative to Eradicate Smoking (Smoke Free Israel). They demanded that the Minister of Finance sign the bill to tax IQOS.[12] On 17 January 2018, the Minister of Finance signed the tax order for IQOS, and on 13 March 2018, following an 83–0 vote in the plenary of the Knesset, IQOS was taxed at the same rate as cigarettes.[13]

THE IQOS MARKETING CAMPAIGN

We observed five distinct advertising elements which were used in two separate campaigns, one for policy-makers, and another for the public. Examples of the advertisements are shown in figure 2A–F.

The five campaign elements

1. *PM's 'Smoke-free Israel Vision'* embodied the main concept of the entire campaign and was part of PM's global campaign for a Smoke-Free World.[14] It framed the emerging tobacco and nicotine products as being fundamentally different from the combusted cigarette and promoted the idea that PM was taking a global leadership role in pursuing a world without smoke (figure 2A).
2. *The harm-reduction* element focused on transitioning smokers from combustible to non-combustible products. The claim that non-combustible products were risk-reduced compared with cigarettes appeared as part of this element. PM referred to the harmful chemicals in cigarette smoke as the main cause of tobacco-attributable illness, proposed alternatives and quoted from the FDA and the WHO (figure 2B). The advertisements did not state that the original WHO and FDA statements did not endorse any particular product, type of product or company in their original statements.
3. *IQOS status*: PM proposed that non-combustible products should enjoy a different status for the purpose of regulation due to the harm reduction (figure 2C).
4. *Taxation policy*: The content of messages regarding taxation policy were specific to Israel policy, though not specific to IQOS (figure 2C).
5. *The classic product element* was aimed at the public, and was similar to IQOS marketing elsewhere. Messages included: 'IQOS: This changes everything' (in English), TRUE (tobacco taste),

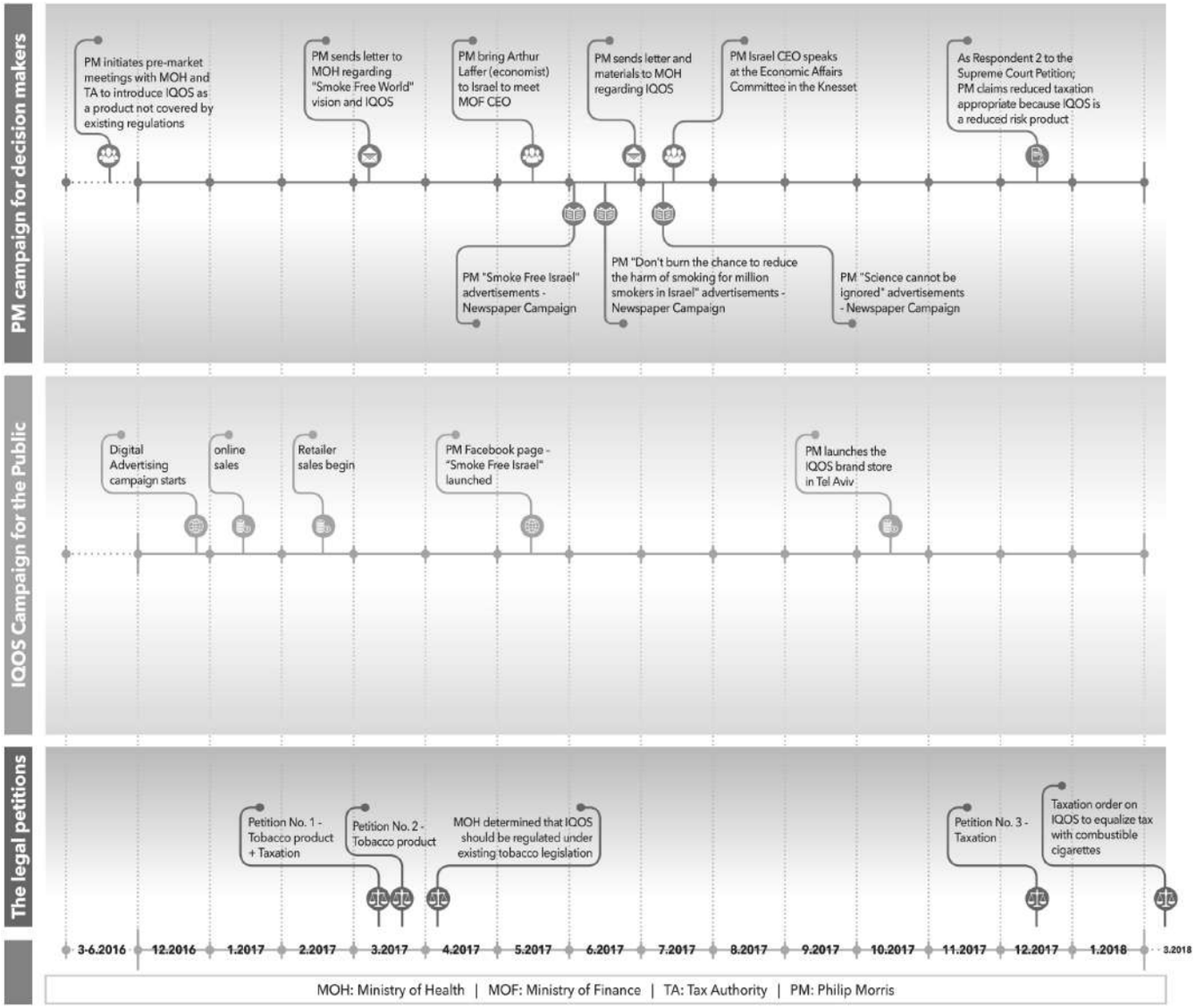


Figure 1 Timeline of IQOS campaign in Israel.

REAL (tobacco experience), 'No fire/No smoke/No ash/Less smell/Unlike cigarettes/CLEAN' (figure 2D,E,F).

The two campaigns

We observed two distinct campaigns.

The *Policy Makers Campaign* began with contacts between PM and governmental officials prior to advertisement or sales of IQOS to the Israeli public, and continued postmarketing. On 5 March 2017, these actions were complimented by a letter sent by PM to the MOH regarding their 'Smoke-Free World Vision' and IQOS.[15] Advertisements in the print press were a key element of the campaign: these were publicised in the weekend editions of papers over many weeks, often in full or half-page advertisements. The earliest advertisements featured the Smoke-Free Israel Vision (figure 2A), often with text only, without pictures and without any mention of IQOS at all. In the Smoke-Free Vision ads, the PM logo was present, but not prominently. At the bottom of the advertisements were black boxed warnings. The warnings provided at the time of IQOS's launch in Israel were placed voluntarily by PM, with messages such as 'Medical researches suggest that cigarettes cause addiction' (figure 2A,D). These advertisements used the identical style and font as governmentally required tobacco product warnings, but did not use the governmentally approved set of warnings and did not attribute them to the MOH. After IQOS's status had changed to that of a tobacco product, the black boxes included MOH-approved warnings for cigarettes and were attributed to the MOH.

Further actions in the campaign for decision-makers were reactive to the Supreme Court petitions and decisions. In March 2017, following the two first petitions by Dubek and the Israel Association for Progressive Democracy, PM placed large advertisements in the printed press demanding that the MOH 'review our science' and 'inform Israeli adult smokers about the findings in an objective and transparent manner' (figure 2B). Once IQOS was defined as a tobacco product, the battle for preferential taxation, on the basis of PM's risk-reduction argument, ensued. PM sent world-famous economist Arthur Laffer to meet with officials in the Ministry of Finance regarding taxation.[16] PM further addressed the issue in well-funded print press campaigns, made possible, even after definition of IQOS as a tobacco product, by the lack of a tobacco advertising ban in the print press. The 'Don't burn the chance to reduce the harm of smoking'



Figure 2 (A) Advertisement in English (B) Advertisement in English (C) Translation of Hebrew to English: A future without smoke in Israel. Why prevent adult smokers in Israel from having better alternatives to smoking cigarettes? The harmful chemicals in cigarette smoke are the primary cause of disease due to smoking. New smokeless tobacco products are better alternatives for smokers who plan to continue smoking. Taxation of new smokeless tobacco products at the same rate as cigarettes, at rates substantially higher than taxes on roll-your-own cigarettes, will be a serious impediment to those smokers who want to switch to these products. If this is done, Israel will be the only country in the world where these products are sold which tax them equally with cigarettes. Smoke-free products are not risk free. The best way to reduce health risks from smoking is to stop using tobacco altogether. Follow us on Facebook page Smoke Free Israel. In black box: WARNING: Medical research has shown that cigarettes lead to addiction (D) Advertisement in English (E) Translation of Hebrew to English: This is going to change your living room. No ash. Less smell. Want to know more? To schedule an appointment, press here. This product is for adult smokers >18 only (F) Translation of Hebrew to English: True tobacco taste. This product is for adult smokers > 18 only. Warning: Smoking causes premature ageing of facial skin. The Ministry of Health.

advertisement, which appeared as full page ads, argued in favour of lower taxation. As the battle intensified, PM presented data in the advertisements about taxation policies in other countries, suggesting that if Israel did move to equalise taxation, it would be the only country in the world with equal taxation (figure 2C).

The Public Campaign, which began with the IQOS launch, started with a widely disseminated digital marketing campaign[17] which included photos of the product and short text messages. The word IQOS and the phrase 'This changes everything' appeared, in English only, on many advertisements. This differed

from the other terms which were in Hebrew (except in advertisements in the English press, some of which are presented here). Pop-ups appeared regularly on internet sites and as people opened their smartphones or popular news websites. This was later complemented by print press advertising with similar types of messages. Other components of the campaign included a unique Facebook page under the slogan 'Smoke Free Israel' and cars with advertising messages. Package inserts advertising IQOS appeared in cigarette packages. Journalists were flown to Switzerland by PM. As an example of coverage, the report in a local English paper by a reporter flown by PM to Switzerland mentioned the words 'harm reduced' or 'less harm' 12 times in a single article, described reduced exposure to toxicants and quoted PM executives extensively.[18] IQOS was also distributed to celebrities.[19 20] A flagship IQOS store, closely resembling Apple iPhone stores, was opened in Tel Aviv on October 2017.

IMPLICATIONS

1. In countries such as Israel, which neither require premarket approval nor have clear product definitions for emerging products, the following types of industry behaviour may occur:
   a. The entry of IQOS and/or other non-combustible tobacco or nicotine products may be accompanied by campaigns aimed at both policy-makers and the public.
   b. Prior to market entry, the tobacco industry may try to define emerging products as belonging to a new type of product not covered by existing tobacco laws, even if the product label clearly states that it is a tobacco product. This is particularly important if the terminology used in local laws is based on use of the term 'smoking' which PM claims is distinct from 'vaping'.
   c. PM may focus on its 'smoke-free vision' which is not specific to a single product or type of product, or it may emphasise a particular product.
   d. If the product is not defined as a tobacco product subject to tobacco warnings under local laws, PM may voluntarily place warnings on the product and use the identical style and font as for locally required warnings, but with messages which would not necessarily be approved by local authorities. For example, the warning stating that 'research suggests that cigarettes cause addiction' (figure 2A,D), which was used during the IQOS campaign, may cause people to doubt the well-established evidence regarding the addictiveness of cigarettes. Introducing doubt into the public debate is consistent with the tobacco industry's previous behaviour.[21]
   e. PM may 'change gears' during the course of the campaign, in response to regulatory proposals, in its efforts to obtain advantageous policies.
   f. In countries where FCTC Article 5.3 is adhered to but there is a lack of a complete advertising ban, PM will be able to communicate directly with policy-makers through the media, even if IQOS is defined as a tobacco product.
   g. In its promotional strategy, PM may selectively cite favourable policies in other countries, as well as statements made by major health organisations.
2. Because only a small minority of countries in the world have complete implementation of FCTC obligations,[22] and even fewer have premarket regulation of tobacco and nicotine products, there is worldwide vulnerability to poorly regulated industry marketing, advertisement and promotion of non-combustible tobacco and nicotine products. The absence of comprehensive, enforced marketing bans on all tobacco and nicotine products, which include digital and social media, and restrictions on health claims, are specific areas of vulnerability.

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Modelling the impact of a new tobacco product: review of Philip Morris International's Population Health Impact Model as applied to the IQOS heated tobacco product

Wendy B Max,[1,2] Hai-Yen Sung,[1,2] James Lightwood,[3] Yingning Wang,[1,2] Tingting Yao[1,2]

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[1]Institute for Health and Aging, School of Nursing, University of California, San Francisco, California, USA
[2]Department of Social and Behavioral Sciences, School of Nursing, San Francisco, California, USA
[3]Department of Clinical Pharmacy, School of Pharmacy, San Francisco, California, USA

Correspondence to
Professor Wendy B Max, Institute for Health and Aging, University of California, San Francisco, CA 94118, USA; wendy.max@ucsf.edu

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ABSTRACT

Objectives We review the Population Health Impact Model (PHIM) developed by Philip Morris International and used in its application to the US Food and Drug Administration (FDA) to market its heated tobacco product (HTP), IQOS, as a modified-risk tobacco product (MRTP). We assess the model against FDA guidelines for MRTP applications and consider more general criteria for evaluating reduced-risk tobacco products.

Methods In assessing the PHIM against FDA guidelines, we consider two key components of the model: the assumptions implicit in the model (outcomes included, relative harm of the new product vs cigarettes, tobacco-related diseases considered, whether dual or polyuse of the new product is modelled, and what other tobacco products are included) and data used to estimate and validate model parameters (transition rates between non-smoking, cigarette-only smoking, dual use of cigarettes and MRTP, and MRTP-only use; and starting tobacco use prevalence).

Results The PHIM is a dynamic state transition model which models the impact of cigarette and MRTP use on mortality from four tobacco-attributable diseases. The PHIM excludes morbidity, underestimates mortality, excludes tobacco products other than cigarettes, does not include FDA-recommended impacts on non-users and underestimates the impact on other population groups.

Conclusion The PHIM underestimates the health impact of HTP products and cannot be used to justify an MRTP claim. An assessment of the impact of a potential MRTP on population health should include a comprehensive measure of health impacts, consideration of all groups impacted, and documented and justifiable assumptions regarding model parameters.

INTRODUCTION

Philip Morris International (PMI) submitted an application to the Food and Drug Administration (FDA) to market its heated tobacco product (HTP), IQOS, as a modified-risk tobacco product (MRTP) in the USA, arguing that because the product does not actually burn tobacco, it will have a reduced impact on health compared with cigarettes. PMI used a computational model they developed, the Population Health Impact Model (PHIM),[1] to estimate the potential impact of this IQOS marketing on public health. While the application was denied by the FDA, the proliferation of purported reduced harm products suggests the need for an understanding of how to assess the impact on population health of new tobacco products.

No models specifically consider the health impact of IQOS, but several simulation models analyse the impact of two tobacco products on population health. These models evaluate the impact of a reduced-risk tobacco product on population health by comparing a factual scenario (considering cigarette use only) with a counterfactual scenario, in which the new product is introduced. None of the models consider the impact of other tobacco products. Details of the models, the assumptions they are based on and their findings are summarised in online supplement 1 and online supplement table 1. Four models compared the health effects of cigarettes with e-cigarettes (or a vaporised nicotine product), measuring health effects either as an index[2] or as mortality.[3–6] Two of these models reported a net positive impact on health[3 4 6] while two reported net population harm.[2 5] All four research teams assumed that e-cigarettes were safer than cigarettes by factors ranging from 5% to 30%, but they differed in their assumptions about the impact of e-cigarettes on cigarette smoking initiation and cessation. Three studies analysed the impact of introducing a non-specified MRTP on cigarette smoking and mortality. Each study reported a potential reduction in mortality,[7–9] though one study indicated that mortality could increase if the MRTP were 50% as risky as cigarettes and 50% of initiates were never smokers.[8] One study[10] evaluated the impact of promoting use of the smokeless product snus on a health index, and concluded that promoting snus as a safer product than cigarettes is not likely to result in population health benefits.

These models illustrate how different assumptions about what is included in the model as well as the data sources for estimating transition rates and tobacco use prevalence lead to varying conclusions about the net impact of a new product. These model characteristics will be reviewed for the PHIM.

PMI's multiple tobacco product model, the PHIM, was refined for its application for IQOS. This paper reviews the FDA guidelines for MRTP applications and assesses whether the PHIM as used in the IQOS MRTP application meets the criteria the FDA has developed to determine whether or not the impact of IQOS on population health justifies the introduction of the product as an MRTP. We also consider more generally the criteria for

assessing the impact of a new tobacco product on population health.

METHODS

We evaluate the PHIM as published[1 11] and as submitted for marketing IQOS as a MRTP[12 13] against FDA guidelines for MRTP applications.[14] In our evaluation, we consider two key components of the model: the assumptions implicit in the model (outcomes included, relative harm of the new product vs cigarettes, tobacco-related diseases considered, whether dual or polyuse of the new product is modelled, and what other tobacco products are included) and data used to estimate and validate model parameters (transition rates between non-smoking, cigarette-only smoking, dual use of cigarettes and MRTP, and MRTP-only use; and starting tobacco use prevalence).

The FDA issued draft guidelines for MRTP applications in March 2012.[14] The guidelines specify that 'scientific studies submitted by the applicant "should contain an overall assessment of the potential effect that the marketing of the product as proposed may have on tobacco-related morbidity and mortality". (p21)[14] The guidelines further recommend that the potential impact on mortality and morbidity be assessed for seven population groups and exposure patterns.(p22)[14]

RESULTS

The PMI PHIM

The PHIM, developed by PMI researchers and their collaborators, is described briefly here and in more detail in online supplement 2. The PHIM is a dynamic state transition model which models the impact of cigarette and MRTP use on mortality. It follows a cohort aged 15 and older for 20 years. The PHIM consists of a prevalence component ('P-component') and an epidemiological risk component ('E-component').[1] The P-component models changes in the distribution of cigarette and/or MRTP use occurring in a hypothetical population over a defined period. The model compared a null (ie, no MRTP) scenario and an MRTP scenario.(p88)[1] For each scenario, transition probabilities for initiation, reinitiation and cessation of smoking and of product switching (including dual cigarette/MRTP use) are estimated from historical cigarette smoking prevalence data, and premarket Perception and Behavioral Assessment studies conducted by PMI.[12] The E-component uses the tobacco use patterns from the P-component along with estimates of the relative risk (RR) of death for lung cancer, ischaemic heart disease (IHD), stroke and chronic obstructive pulmonary disease (COPD) to estimate mortality using published estimates of RR for smoking and assumptions about how much less risky MRTP use is compared with smoking.

Sensitivity analyses vary assumptions about initiation and reinitiation of tobacco use; transition rates between smoking, MRTP and dual use; time frames; and the RR of the MRTP versus cigarettes.

Comparison of IQOS MRTP application with FDA guidelines

Impact of IQOS on morbidity

The PHIM does not include any measure of morbidity, such as incident or prevalent cases of tobacco-related illness. One way of quantifying the impact of morbidity is through healthcare costs which incorporate the severity and time course of illness, and would include hospitalisations, outpatient care, medications and other services. No estimates of healthcare costs are made in the PHIM.

Impact of IQOS on mortality

The PHIM considers mortality from four diseases caused by smoking—lung cancer, IHD, stroke and COPD.

The base case in the IQOS MRTP application assumes that compared with cigarettes, sole MRTP use is 80% less risky and dual use of MRTP and cigarettes is 40% less risky than cigarette smoking alone. The RR of death for dual use of cigarettes and IQOS is assumed to be the midpoint of the risk of cigarette smoking and the risk of IQOS use.(p19)[12] To simulate the mortality impact on the US population, the model uses smoking prevalence from 1990 projected through 2010.

Impact of IQOS on different types of individuals

We next assess how the PHIM treats the seven population groups and exposure patterns recommended for consideration by the FDA.(p22)[14] More detailed descriptions are contained in online supplement table 2.

1. *Tobacco users who switch from other commercially marketed tobacco products to the proposed product*. The PHIM considers switching only from cigarettes. PMI acknowledges that other tobacco products are not considered in their model, arguing that there is no evidence to indicate that IQOS users will switch from other tobacco products.(p7)[12]
2. *Tobacco users and non-users who, after adopting the proposed product, switch to or switch back to other tobacco products that may present higher levels of individual health risk*. The PHIM assumes that each month 0.1% of IQOS users will switch to cigarette smoking, but that after a year of IQOS use virtually no users will become cigarette smokers or dual users. They also assume that 10% of dual IQOS/cigarette smokers will become sole cigarette smokers each month (p14)[12] (online supplement table 4).
3. *Tobacco users who opt to use the proposed product rather than cease tobacco use altogether*. PMI indicates that this group was 'considered by a specific analysis in which current conventional cigarette smokers who would otherwise have switched to MRTP or to dual use, quit instead'.(p5, Module 7.4)[13] PMI indicates that 'here, the reduction in deaths associated with MRTP introduction was estimated to be about 11 times greater in males and about 13 times greater in females than that for the basic analysis'.(p5, Module 7.4)[13]
4. *Tobacco users who opt to use the proposed product rather than an FDA-approved tobacco cessation medication*. PMI indicates that this is 'outside the present scope of the model'. (p5, Module 7.4)[13]
5. *Non-users who initiate tobacco use with the proposed product, such as youth, never users, former users*. The PHIM assumes that uptake of the IQOS HTP will be limited among youth because of the relatively high cost. It assumes that the per cent of never-smokers who will initiate tobacco use with IQOS each month ranges from 0.05% to 0.08% (after 25 years), and that the rate drops with age, with no one initiating use after age 35 (p13, Module 6.5) [12] (online supplement table 3). The model assumes that reinitiation rates of former smokers with IQOS range from 0.01% for youth aged 15–19 years to 0.08% for older adults (aged 75–79 years) after more than 25 years (p13, Module 6.5)[12] (online supplement table 3).
6. *Tobacco users who use the product in conjunction with other tobacco products*. The PHIM assumes that few smokers or IQOS users will become dual users (p14, Module 6.5)[12] (online supplement table 4) and that fewer than 0.02% of never tobacco users and fewer than 0.04% of former smokers will

become dual users (p13, Module 6.5)[12] (online supplement table 3).

7. *Non-users who experience health risks from the product*. Risk to non-users is not considered in the PHIM.

DISCUSSION

The PHIM is similar in structure to many of the published models reviewed which are all dynamic in nature and model state transitions in tobacco use over time, with the exception of one steady state model.[2] The PHIM focuses on mortality as the outcome measure as do all but two models which included a health effects index.[2 10] The PHIM models the population aged 15 and older, an improvement over some of the models which focus on a subgroup of the population. It follows the population for 20 years which is reasonable for MRTP application purposes, and is in line with the published models which use varying time horizons from 10 to 84 years.

However, the PHIM analysis of IQOS has some important limitations that are apparent in reviewing the model against FDA recommendations. Morbidity-related outcomes are omitted, mortality is underestimated, transition rates used in the model are based on PMI perception studies and the model uses data for the USA in 1990 as a starting point. The role of other tobacco products such as e-cigarettes and impact on non-users are not considered. Thus, the analysis of IQOS does not fully satisfy FDA guidelines for MRTP applications, and results in an overestimation of the benefit of IQOS on population health.

Morbidity is ignored

The PHIM does not include any measures of morbidity, such as tobacco-related disease incidence or tobacco-attributable healthcare costs, though this is an FDA requirement. Morbidity costs are more than half of total costs of cigarette smoking for high-income countries,[15] so this omission is potentially serious.

Mortality is underestimated

The clinical results presented for US adults to justify the lower RR of mortality for IQOS versus cigarette use do not show statistically significant improvements in the biomarkers of harm that PMI assessed in actual people who used HTP (with a single exception).[16] This contradicts the assertion of reduced harm, and does not justify the 70%–90% reductions in risk assumed in the PHIM. The RR of mortality for IQOS compared with cigarettes is a critical parameter in the model and a smaller reduction in harm should be used in the analyses.

The RRs of mortality from smoking used in the PHIM are based on multicountry studies rather than those published by the 2014 US Surgeon General and based on US cohorts.[17] PMI's sensitivity analyses indicate that the proportion of smoking-attributable deaths from the four causes for men would increase 15% (2005–2009) if based on the RRs from the Surgeon General report,[11] with less of a change for women. The Surgeon General estimates, which are more current and vetted through a more thorough process of independent peer review than the PHIM estimates, are more appropriate and should be used in these analyses.

The PHIM assumes that the RR of dual use of IQOS and cigarettes is the midpoint of the two RRs. However, there is some evidence that dual users of cigarettes and e-cigarettes have greater risks of negative health outcomes than sole cigarette users,[18] suggesting that there could be greater risks for dual users of IQOS and cigarettes and that the PHIM model may underestimate the number of deaths attributable to dual use.

The inclusion of only four smoking-attributable diseases in the PHIM further reduces the estimates of mortality from IQOS versus cigarette use. At least 22 causes of death for adults[19] and 4 causes of death for infants[20] have been causally linked to cigarette smoking. PMI acknowledges that the 'overall estimates of deaths saved due to the introduction of IQOS would have to be increased about 50% to give an estimate for all smoking-related diseases combined'.(p41)[12]

Given that mortality is the main measure of population health used in the PHIM, the use of low RRs and the inclusion of only four causes of death will result in an overestimate of the benefit of IQOS introduction as an MRTP which will greatly impact the results.

Assumptions about transition rates are not well justified

The PHIM uses transition probabilities for smoking dating back to 1986 for 12 countries. PMI does report an adjustment for poor model forecast performance through 2005 but does not report the methodology or provide documentation of the model predictions against historical data. Other models use more recent data, document the methodology and report the predictive performance against historical data. For example, Warner and Mendez[6] validate their model to US data through 2015, and Levy *et al*[3] calibrate their model using US data through 2010. The absence of an explanation of methodology and documentation for the PHIM predictive performance is a serious weakness because poor forecasts of status quo and alternative scenarios may bias the results.

Transition probabilities for IQOS initiation, reinitiation, cessation and product switching are based on PMI perception surveys. The only empirical data available are from Italy, but these data report on ever use and are thus not comparable with the PHIM estimates.[21] Youth have initiated tobacco use with e-cigarettes at high rates,[22] and may find the IQOS product to be similarly appealing. Flavours, electronic features and perceptions of harm are factors that are important determinants of adolescent decisions regarding tobacco use, and IQOS is likely to appeal to them on all these characteristics.[23] The PHIM assumption that youth uptake will be limited because of the relatively high cost ignores the use of coupons to reduce prices, a common tobacco industry pricing strategy, and also ignores shared use among users. Recent estimates suggest that the prevalence of sharing e-cigarette devices among adolescents over the previous 30 days exceeds 70%.[24]

The PHIM makes optimistic assumptions about cigarette smoking cessation rates associated with IQOS use, assuming that 0.4%–1.5% of smokers will quit smoking each month due to IQOS use,(Module 6.5)[12] (online supplement table 3) a relatively high rate in light of evidence that many IQOS users continue to smoke cigarettes, including PMI's own finding that 36% of Japanese IQOS users use another tobacco product.[25] Recent research has produced evidence for the USA that, with the current regulatory environment and smoking behaviours, e-cigarettes do not increase smoking cessation in the general population greater than what would have occurred without them.[26] Furthermore, the potential effectiveness of e-cigarettes in aiding smoking cessation may depend greatly on the level of the smoker's nicotine dependence.[27] This is also likely to impact the effectiveness of IQOS in cessation, but is not acknowledged in the PHIM.

The potential gateway effect of IQOS is not fully considered. There is evidence for youth and young adults that e-cigarette use increases subsequent uptake of cigarette smoking.[28] PMI

indicates in its application that IQOS mimics cigarette smoking better than e-cigarettes or vaping because of more rapid nicotine delivery, suggesting that IQOS may be much more effective at addicting youth and young adults to nicotine as well as increasing transitions to cigarette smoking. A net increase in nicotine addiction and cigarette uptake among adolescents and young adults is a realistic possibility that the PHIM does not consider.

Transition rates are one of the key parameters in the model, and their correct estimation is critical to the results.

The model uses the 1990 US population and smoking prevalence as the starting point for the simulations

The PHIM simulates the health impact on the population starting with a baseline population and smoking prevalence representative of the USA in 1990.(Module 6.5.2.2)[12] It is not clear why 1990 data was used, when smoking prevalence was much greater than in more recent years; data for 2015 were readily available at the time of the analyses. Other published models use more recent prevalence data from 2000,[8] 2006,[10] 2011[6] and 2016.[3] The use of 1990 prevalence is likely to lead to higher than actual smoking-attributable costs and higher expected benefits from IQOS.

The PHIM ignores other tobacco products, such as e-cigarettes

The population health results would be different if the PHIM comparison were between IQOS and a lower-risk product such as e-cigarettes. There are reasons to expect that e-cigarette users may find IQOS to be a tempting and attractive product, and ignoring the role of e-cigarette use in a model of the population health impact of IQOS will lead to an incomplete analysis.

The PHIM assumes very low rates of transition to dual use, contrary to empirical evidence from other countries showing that many of those individuals who use IQOS will continue to use their previous product. In Japan, where IQOS products are now available, over one-third of IQOS users are polyusers, most of whom also smoke cigarettes.[25] Dual use of electronic tobacco products (HTP products including IQOS, Glo and Ploom Tech, or non-nicotine e-cigarettes) and combustible cigarettes was reported by 3.4% of Japanese internet survey respondents in 2017.[29] Thus, actual evidence of dual IQOS and cigarette use indicates that the assumptions of dual use rates in the PHIM are too low.

Impact of IQOS on non-users is not considered

Ignoring the impact on non-users who experience health risks from IQOS is not reasonable. Empirical evidence already exists for second-hand exposure from HTP aerosol. A Greek study found that nicotine levels for IQOS aerosol were greater than those in e-cigarettes at low puff duration, though lower than tobacco cigarettes.[30] Another study using an animal model that exposed rats to cigarette smoke and IQOS aerosol at levels that were relevant to real-world human exposure levels found that both exposures resulted in similar vascular impairment.[31] There is also direct evidence of negative health impacts from exposing human non-users to HTP aerosol. In Japan, 49% of never-to-bacco users and 41% of former tobacco users exposed to second-hand HTP aerosol reported symptoms including general illness, eye discomfort or a sore throat.[29]

Children are particularly likely to be impacted by exposure to HTP products. They may suffer negative health effects when exposed to their parents' second-hand aerosol, as they are when exposed to second-hand cigarette smoke.[32–34] A Canadian study found that children suffered respiratory effects from exposure and digestive effects of ingestion of e-cigarettes.[35] Women who use IQOS while pregnant may cause lifelong health impacts for their children, as is the case for women who smoke cigarettes or use snuff while pregnant.[20 36 37] Another potential risk from IQOS use is fires and explosions, such as those that occur with e-cigarettes. Ignoring the health impact of IQOS on non-users overestimates the benefit of IQOS as an MRTP. While this impact may be of a smaller magnitude than the impact on users of IQOS or cigarettes, the impact on non-users is recommended by the FDA for consideration.

CONCLUSION

The PHIM has a structure not unlike other simulation models reviewed. However, because it is used to justify the marketing of a tobacco product as a MRTP, it must satisfy FDA guidelines that other models are not subject to. The FDA is likely to receive a number of applications for MRTP orders in the coming years, and it is important that reasonable criteria be established for reviewing them. Future analyses of the impact of new tobacco products used for social decision-making such as regulatory actions should consider all relevant and substantial social effects. This includes both morbidity and mortality that arise from a comprehensive list of tobacco-attributable diseases. Model-based estimates need to carefully document methods for estimating key parameters such as transition rates and to validate model's predictive performance. Also, the effects of policy on all populations that will be affected should be included in the analyses, including non-tobacco users who will suffer health effects. These recommendations are relevant for the evaluation of new tobacco products as well as potential harm-reduction products more generally.

PMI, through its analysis of IQOS using the PHIM, has not shown that this product would 'significantly reduce harm and the risk of tobacco-related disease to individual tobacco users;

What this paper adds

- Heated tobacco products (HTP), also referred to as heat-not-burn products, are not currently marketed in the USA and their impact on the health of the US population is not known.
- Philip Morris International developed a Population Health Impact Model that they used to estimate the potential impact of marketing an HTP, IQOS, as a modified-risk tobacco product (MRTP) in the USA.
- Because the model is used to support an MRTP application, the Food and Drug Administration guidelines indicate that it should include the impact of the new product on morbidity and mortality, and the impact on seven population groups and exposure patterns. However, the model underestimates mortality, omits morbidity measures, excludes impacts on non-users and underestimates the impact on other groups. Therefore, the model underestimates the potential impact of IQOS on the population as a whole and does not justify marketing the product as an MRTP.
- An assessment of the impact of a new tobacco product on population health should include a comprehensive measure of health impacts, consideration of all groups impacted, and documented and justifiable assumptions regarding model parameters such as the relative harm of the new product compared with existing products and transition rates between tobacco use categories.

and benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products'.(p3)[14] As new tobacco products are introduced into US and worldwide markets, particularly those that purport to be less harmful than currently used products, models of population health impacts will play an important role. The PMI PHIM as applied to the marketing of IQOS as a MRTP illustrates some of the potential pitfalls of analysis that should be avoided.

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Light and mild redux: heated tobacco products' reduced exposure claims are likely to be misunderstood as reduced risk claims

Lucy Popova,[1] Lauren Kass Lempert,[2] Stanton A Glantz[2,3]

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[1]School of Public Health, Georgia State University, Atlanta, Georgia, USA
[2]Center for Tobacco Control Research & Education, University of California, San Francisco, California, USA
[3]Department of Medicine, Cardiovascular Research Institute, Philip R. Lee Institute for Health Policy Studies, Helen Diller Family Comprehensive Cancer Center, University of California, San Francisco, San Francisco, California, USA

Correspondence to
Dr Lucy Popova, School of Public Health, Georgia State University, Atlanta, GA 30302, USA; lpopova1@gsu.edu

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ABSTRACT

Introduction Heated tobacco products (HTPs) are being marketed in several countries around the world with claims that they are less harmful than combusted cigarettes, based on assertions that they expose users to lower levels of toxicants. In the USA, Philip Morris International (PMI) has submitted an application to the Food and Drug Administration (FDA) in 2016 seeking authorisation to market its HTPs, IQOS, with reduced risk and reduced exposure claims.

Methods We examined the PMI's Perception and Behavior Assessment Studies evaluating perceptions of reduced risk claims that were submitted to the FDA and made publicly available.

Results Qualitative and quantitative studies conducted by PMI demonstrate that adult consumers in the USA perceive reduced exposure claims as reduced risk claims.

Conclusion The data in the PMI modified risk tobacco product IQOS application do not support reduced risk claims and the reduced exposure claims are perceived as reduced risk claims, which is explicitly prohibited by the FDA. Allowing PMI to promote IQOS as reduced exposure would amount to a legally sanctioned repeat of the 'light' and 'mild' fraud which, for conventional cigarettes, is prohibited by the US law and the WHO Framework Convention on Tobacco Control.

INTRODUCTION

Heated tobacco products (HTPs), also called heat-not-burn products, are tobacco products that heat tobacco to temperatures that avoid combustion and produce a nicotine aerosol that is inhaled by smokers and may also generate side-stream emissions.[1] As of February 2018, HTP entrants into the global market included Philip Morris International's (PMI)'s 'IQOS', British American Tobacco's 'Glo', Japan Tobacco's 'Ploom Tech' and RJ Reynolds' revamped 'Eclipse'. Because of the growing evidence of severe negative health effects of smoking and smokers' concerns about their health, tobacco companies have been motivated to create 'safer cigarettes' since the 1960s, and in 1988 they first introduced HTPs, marketing them as less harmful than combusted cigarettes. While HTPs produce different toxic chemicals than combusted cigarettes,[2] the human health effects of HTPs are not completely understood and the evidence that PMI submitted to the US Food and Drug Administration (FDA) revealed that, in terms of the clinical biomarkers of disease[3] or pulmonary and immune toxicity,[4] IQOS was not significantly different from cigarettes.

As of February 2018, the new HTPs, like PMI's IQOS, were being sold in multiple countries around the world in minimalist high-tech looking stores that resemble Apple stores.[5–7] Advertisements and marketing materials for IQOS emphasise both its superiority over combustible cigarettes (in terms of cleanliness and customisability) and similarity to them (in terms of product's taste, size and providing similar behavioural experience).[6] Claims about health benefits or lower risks of IQOS are not emphasised in the marketing materials and some of the materials carry minimal health warnings, such as 'This tobacco product can harm your health and is addictive'[6] or it is 'not risk-free or a safe alternative to cigarettes but it is a much better choice than smoking.'[7] Before IQOS is introduced into the US market, PMI needs the FDA's permission. The 2009 Family Smoking Prevention and Tobacco Control Act[8] (FSPTCA) assigns the FDA authority to regulate the manufacturing, marketing and distribution of tobacco products in the USA. Tobacco manufacturers may seek authorisation from FDA to market products with claims that they reduce risks of tobacco-related diseases compared with other tobacco products currently on the market.

To obtain FDA authorisation to market a product as a 'modified risk tobacco product' (MRTP), a company must submit an MRTP application to FDA. FDA may issue one of two types of orders permitting such marketing: (1) a 'risk modification order' or (2) an 'exposure modification order'.[9 10] For a *risk modification* order, a company must provide scientific evidence that the product 'as actually used by consumers will (1) significantly reduce harm and the risk of tobacco-related disease to individual users and (2) benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products.'[10] When such scientific evidence is not available and cannot be obtained without long-term epidemiological studies, an *exposure modification* order can be issued if the company demonstrates that such an order would be appropriate for promoting public health (once again taking into account both users and non-users) and that lower levels of harmful chemicals in the product will likely result in reduced death and disease among individual tobacco users. Under the exposure modification order, the marketing claim can only state that the product has lower levels of or is free of a certain substance. Furthermore, a company needs to demonstrate that "consumers will not be misled into believing that the product is […] less harmful or presents […] less of a risk of disease than

one or more other commercially marketed tobacco products."[9] The FSPTCA puts the burden on the MRTP applicant, not the FDA, to demonstrate that the product presents reduced risk or reduced exposure and to demonstrate that consumers do not perceive reduced exposure claims as reduced risk claims.

Long before the MRTP process was enacted in 2009, tobacco companies had been misleading the public with reduced exposure claims since the 1950s, asserting that filtered and low-tar cigarettes[11] gave smokers 'less tar and nicotine',[12] a reduced exposure claim. 'Light' and 'mild' cigarettes have been marketed to smokers concerned about their health and positioned as an alternative to quitting smoking.[13–15] Even though advertisements for light and mild cigarettes almost never explicitly stated that they would reduce risk of tobacco-related disease, people who saw these advertisements with reduced exposure claims perceived these cigarettes to have lower health risks than regular cigarettes.[16 17]

Furthermore, these cigarettes did not result in lower levels of exposure to harmful chemicals for users. Tobacco companies created them with microscopic ventilation holes in the filters to draw in air and reduce machine-measured tar and nicotine, which gave the appearance that these products delivered lower emissions to the user.[18 19] However, the cigarette companies designed these products so that smokers would compensate for dilution of the smoke by blocking ventilation holes with their lips, taking larger puffs or taking more frequent puffs.[20–23]

This inherently deceptive nature of reduced exposure and reduced risk ('light' and 'mild') marketing claims was at the core of the US Department of Justice's Racketeer Influenced and Corrupt Organization (RICO) Act lawsuit against the major cigarette companies for defrauding the public about the dangers of smoking and which essentially became the basis of the FSPTCA's MRTP provisions. In August 2006, Federal Judge Gladys Kessler held[24] that the tobacco companies, including Philip Morris, violated RICO by fraudulently covering up the health risks associated with smoking and for marketing their products to children. Judge Kessler found that the companies "have engaged in and executed – and *continue to engage in and execute* -- a massive 50 year scheme to defraud the public, including consumers of cigarettes, in violation of RICO [emphasis added]." In her 1683-page opinion with extensive Findings of Fact, Judge Kessler found, among other fraudulent acts, that Philip Morris and other tobacco companies deceptively marketed cigarettes characterised as 'light' or 'low tar', while knowing that those cigarettes were at least as hazardous as 'full flavoured' cigarettes; misled smokers, former smokers and non-smokers to believe that these cigarettes were safer and deliberately targeted the youth market (see table 1 for examples of relevant findings). Importantly, the court found that there was a reasonable likelihood that defendants would continue to violate RICO in future.

Following the 2006 RICO decision, in 2009, Congress recognised and described the tobacco companies' use of reduced exposure claims to mislead the public and Judge Kessler's findings in 14 of the 49 Findings for the FSPTCA.[10] Of particular relevance, Congressional Finding 40 states: "The dangers of products sold or distributed as modified risk tobacco products that do not in fact reduce risk are so high that there is a compelling governmental interest in ensuring that statements about modified risk tobacco products are complete, accurate, and relate to the overall disease risk of the product."

Given the long history of the tobacco industry using reduced exposure claims to mislead consumers into believing that the products in question have reduced risk, most notably through the use of 'light' and 'mild' cigarette claims, it is important to evaluate to what extent the modified risk claims for the new HTP products are based on scientific evidence and whether reduced exposure claims are perceived by consumers as reduced risk claims. This paper uses the materials in the PMI MRTP application made public by the FDA to evaluate these claims.

Table 1 Relevant findings from Racketeer Influenced and Corrupt Organization case

"According to [Brand Manager of Marlboro from 1969 to 1972, James] Morgan, Philip Morris made a calculated decision to use the phrase 'lower tar and nicotine' even though its own marketing research indicated that consumers interpreted that phrase as meaning that the cigarettes not only contained comparatively less tar and nicotine, but also that they were a healthier option."	[24] Para 2402, p. 888
"Morgan, who later became CEO of Philip Morris, further explained in 2002 that rather than relying on the tar and nicotine numbers from the FTC Method, 'the major influence in people's perceptions in the tar of a cigarette would have come from the marketing positioning of a brand as opposed to people literally reading the FTC [tar and nicotine figures]."	[24] Para 2403, p. 888
Philip Morris and the other tobacco companies knew that "many smokers who were concerned and anxious about the health risks from smoking would rely on the health claims made for low tar cigarettes as a reason, or excuse, for not quitting smoking"	[24] Para 2627, p. 971

METHODS

We examined the materials in the PMI MRTP applications to FDA[25] for its HTP IQOS system and Heatstick products (PMI also refers to IQOS as Tobacco Heating System (THS) 2.2 in these materials). On 5 December 2016, PMI submitted its MRTP applications asking the FDA to authorise marketing of IQOS with reduced risk and reduced exposure claims. Our analysis is based on the Executive Summary[26] and Module 7: Scientific Studies and Analyses,[27] specifically Section 7.3 Studies in Adult Human Subject (7.3.2 Perception and Behavior Assessment (PBA) Studies), studies THS-PBA-02-US, THS-PBA-03-US, THS-PBA-04-US and THS-PBA-05-REC-US. We report PMI's findings on the consumer perceptions of reduced exposure claims.

RESULTS

To develop and evaluate marketing messages and materials with reduced risks and reduced exposure claims, PMI conducted Consumer PBA Studies (table 2). Participants were recruited by phone from proprietary databases maintained by local research agencies, which include people interested in participating in market research. Participants' smoking status was based on self-report.

Qualitative studies

PMI's qualitative studies (THS-PBA-02-US and THS-PBA-04-US) were conducted by TNS Qualitative. Focus groups and individual interviews were conducted in person, in facilities with one-way mirrors with PMI representatives observing the studies. They followed discussion guides and employed 'visual aids' to position products on relative risk and interest to use scales. Focus groups lasted 2.5 hours, while individual interviews took 1.5 hours. Participants evaluated various messages containing either reduced exposure or reduced risk claims. In THS-PBA-02-US, they evaluated 13 messages in focus groups in Phase 1 (Online Supplementary 1), which were subsequently modified

Table 2 Philip Morris International's (PMI)'s Consumer Perception and Behavior Assessment (PBA) Studies in the USA

Study name	Methodology	Location	Study year	Participants	Age	Materials
THS-PBA-02-US	Qualitative 20 focus groups (n=113) 37 individual interviews	Boston, MA Chicago, IL Charlotte, NC Phoenix, AZ	Oct–Dec 2013	S-NITQ, S-ITQ, FS, NS*	21+	Nine potential 'plain text'† messages‡
THS-PBA-03-US	Quantitative (n=1713)	Chicago, IL Marlton, NJ Phoenix, AZ Atlanta, GA	Oct–Dec 2014	S-NITQ, S-ITQ, FS, NS	LA+	Three potential 'plain text'† messages selected from THS-PBA-02-US
THS-PBA-04-US	Qualitative 28 individual interviews	Chicago, IL Phoenix, AZ	Dec 2014	AS, FS, NS	18+	Five potential branded§ communication materials with claims selected from THS-PBA-02-US
THS-PBA-05-RRC-US	Quantitative (n=2255)	Paramus, NJ Dallas, TX St Louis, MO Los Angeles, CA	Jul 2015	S-NITQ, S-ITQ, FS, NS	LA+	Three branded§ communication materials with claim #1 'Reduced risks of tobacco-related diseases'
THS-PBA-05-RRC2-US	Quantitative (n=2247)	Marlton, NJ Chicago, IL Tampa, FL Denver, CO	Sep 2015	S-NITQ, S-ITQ, FS, NS	LA+	Three branded§ communication materials with the claim #2—'Reduced risk of harm'
THS-PBA-05-REC-US	Quantitative (n=2272)	Framingham, MA San Diego, CA St Louis, MO Baltimore, MD	Dec 2015	S-NITQ, S-ITQ, FS, NS	LA+	Three branded§ communication materials with the claim #3 'Reduced body's exposure to harmful and potentially harmful chemicals'

*Never smokers participated only in Phase 2 of THS-PBA-02-US.
†'Plain text' message describes the information communicated on the product.
‡The table in the PMI document says nine messages, but the file (Online Supplementary 1) for Phase 1 shows 13 messages because there are two versions of some (A1, A2, B, C1, C2, D and so on). Phase 2 tested seven messages (Online Supplementary 2).
§The branded communication materials were brochure, pack and direct mail piece with iQOS commercial name and the Tobacco Sticks as HeatSticks with the Marlboro Brand.
AS, adult smokers; FS, adult former smokers; LA, legal smoking age; NS, adult never smokers; S-ITQ, adult smokers with the Intention to quit; S-NITQ, adult smokers with no intention to quit.
Source: adapted from table 1 Overview of the Studies from PMI Research and Development[51] (p. 7).

into seven messages for testing with individual interviews in Phase 2 (Online Supplementary 2).

Participants frequently equated reduced exposure claims with reduced risk, conflating the reduction in chemicals with lower chances of developing tobacco-related health issues. For example, female smoker (21–34 years old, Phoenix) stated: "It reduces your body's exposure to the chemicals… that would be my biggest take-away… it suggests that it is better for you than a traditional cigarette." When asked to clarify: (Better—In what way?), she specified: "It's the lesser of two evils; it's a better bad choice… It reduces harmful chemicals which is likely to reduce your chances of getting a tobacco-related disease."

While the PMI's claims that reduced exposure does not mean reduced harm tried to address this issue, some people found this juxtaposition of a claim of reduced exposure and no reduced harm confusing and hard to believe, which reduced credibility of the message source. Female smoker (21–35 years old, Boston) explained: "It says to me that if you smoke this or if you use this thing, you're still at risk of getting all those diseases that they claim it reduces your exposure to… The way it's worded… I'm not buying into it. It's kind of doubletalk… […] It's flip flopping, saying it will reduce but you still might get it, or … It's just weird, it doesn't make me want to use it at all, now that I'm reading this… This makes me less likely to use it, because I'm… almost mad that it tries to claim that it… has benefits, but it really doesn't."

The THS-PBA-02-US Study report concludes that all messages (both reduced risk and reduced exposure claims) were perceived by participants as statements about lower harm. In Phase 2, three out of seven messages were reduced exposure claims. For all three reduced exposure messages, the PMI's report stated that participants perceived IQOS to be a lower risk than conventional cigarettes because the tobacco is heated, not burned, which results in reduced 'exposure to harmful chemicals' (pp. 31, 34) and 'the absence of smoke and second-hand smoke' (p. 37).[28] For the four reduced risk messages, the report similarly concluded that the product was 'perceived to be a lower risk than conventional cigarettes' (pp. 40, 42, 44, 46) by 'reducing the production of harmful chemicals found in cigarette smoke and providing a possible chance of reducing the risk of tobacco-related diseases' (pp. 44, 46).[28]

The fact that PMI's report does not distinguish perception of reduced risk and reduced exposure provides additional evidence that reduced exposure claims are viewed as reduced risk claims.

The findings from the second qualitative study (THS-PBA-04-US) that assessed reduced risk and reduced exposure claims in the context of marketing materials (brochure, pack and direct mail) portray a similar picture. The study report concludes that "There is a clear recognition that this is an innovative product that heats, rather than burns, the tobacco using electronic technology combining the tobacco taste satisfaction of CC's [conventional cigarettes] with hygiene benefits (less odor, no ash, less mess) and the potential to reduce the risk to health compared to smoking conventional cigarettes."[29] Also, "Understanding is generally consistent across all label, labeling and marketing material and subject groups."[29]

In this second qualitative study, reduced exposure claims in combination with the information that IQOS does not reduce risk of tobacco-related disease (presented as 'Important Warning') were also perceived as confusing and contradictory, but still made participants rate the risk as moderate, below the

risk of conventional cigarettes. Some participants were able to articulate that reduced exposure does not mean reduced risk:

> "It's still as risky as smoking a cigarette. It does not mean a reduction in the risk of developing tobacco related diseases… Tobacco related diseases are what you get from smoking cigarettes. It's telling me that even though it scientifically reduces my body's exposure to these chemicals, I have the exact same risk of developing a tobacco-related disease." (female adult smoker, 26–35 years old, Chicago).

Yet others were still very optimistic about the product that offers reduced risk, particularly appreciating the implications of reduced exposure as the ability to use HTPs in smoke-free places:

> "There's still a risk, so we all know we can't get anywhere besides-you can't get anywhere, you can't even hide from that, so there's going to be risk. But it's just a better way of smoking a cigarette. It gives you a better option. 'Real tobacco, no fire, tobacco heating system', so obviously trying to make it a better way of smoking, make it better for you to smoke at your workplace, school, anywhere. So yeah, that's what I get from it. Well, they give you the less odor, no fire. It even tells you-it gives you a little hint that it will be better for the people that's around you worrying about affecting them, so that's good." (male adult smoker, 18–25 years old, Phoenix).

In summary, PMI's qualitative studies demonstrate that US adults understand reduced exposure claim to mean that the lower levels of harmful chemicals in the product means reduced risk of health harms.

Quantitative studies

PMI reports results of two quantitative studies (THS-PBA-03-US and THS-PBA-05-REC-US, see table 2 for details) that were conducted by Covance Market Access Service. Quantitative studies were five-arm parallel group experiments, where each arm corresponded to the different message condition tested in the study. Studies used computer-assisted self-interviews (with computer-assisted personal interviews for more in-depth questions in THS-PBA-03-US) and lasted 45 min on average. The outcome measures used in these studies are presented in table 3. For the purpose of our study, we focus on the measures PMI used to assess global comprehension and risk perceptions because they indicate to what extent reduced exposure claims are perceived as reduced risk claims.

In THS-PBA-03-US, five different text-based messages were evaluated: four contained reduced exposure claims and one had a reduced risk claim (figure 1). Participants were randomised into five groups, where each group saw one of the messages. For the measure of global comprehension, the proportion selecting the answer 'Reduces the risk of tobacco-related diseases' was 18% for reduced exposure Message 3, 28% (Message 2), 32% (Message 1) and 35% (Message 4). For all perceived risk measures (health risk to self (figure 3), addiction risk and risk to others), participants rated IQOS lower in risk than cigarettes for all messages, whether it was a reduced exposure message or a reduced risk message.

In THS-PBA-05-REC-US, participants evaluated marketing materials with a reduced exposure warning: a brochure, a pack

Table 3 Outcome measures in quantitative studies

Construct	Instrument	Example question
Intent to Use	The Intent to Use Questionnaire ► Intention to Try (ie, to sample at least once; two items) ► Intention to Use (ie, for continued usage; two items) (Answers on 6-point scale from 'Definitely Not' to 'Definitely').	Based on what you know about IQOS, how likely or unlikely are you to try IQOS? If you try IQOS and like it, and taking into consideration the prices that are shown on the material, how likely or unlikely are you to use IQOS regularly?
Change in Intention to Quit Smoking	Yes/No questions based on Prochaska and DiClemente's Stages of Change model (Prochaska and DiClemente 1982) measured before and after exposure to THS 2.2 message to determine change in Intention to Quit Smoking (four items).	Are you seriously considering quitting smoking within the next 6 months?
Comprehension	1. 'Global comprehension': overall comprehension of the THS 2.2 message on exposure to harmful chemicals and risk of tobacco-related diseases of using THS 2.2. 2. 'Specific comprehension': comprehension of three specific parts of the THS 2.2 message: the Intended Users Statement, Evidence Statement and Warning Statement. Both types of comprehension were assessed with multiple choice questions; five response options were presented, with one correct option, three incorrect options and an option for 'don't know'.	1. Thinking about all of the information on the card, would you say that compared with cigarettes, using THS 2.2: a. Has a greater risk of tobacco-related diseases b. Reduces the risk of tobacco-related diseases c. Has not been demonstrated to reduce the risk of tobacco-related diseases (correct) d. Eliminates the risk of tobacco-related diseases e. Don't know 2. What happens to tobacco when IQOS is used? a. It is burned b. It remains at room temperature c. It is cooled d. It is heated but not burned (correct) e. Don't know
Risk Perception	The Perceived Risk Instrument-Personal Risk comprised of two domains, each measured by a unidimensional scale: 1. Perceived Health Risk 18-item scale 2. Perceived Addiction Risk 7-item scale 3. Perceived Harm to Others (two separate questions) Answers were no risk, low risk, moderate risk, high risk, very high risk and don't know and were later converted into a 0–100 scale (0=no risk and 100=very high risk).	1. If you were to start using IQOS, what do you think would be the risk, if any, to you personally of getting the following (sometime during your lifetime) because you use IQOS… losing some sense of taste, having heart disease, an earlier death, having sores of the mouth or throat and so on. 2. If you were to start using IQOS, what do you think would be the risk, if any, to you personally of experiencing the following because you use IQOS… being unable to quit cigarettes, feeling like you have to smoke cigarettes and so on. 3. If you were to start using IQOS, what do you think would be the risk, if any, to others because you use IQOS… harming others through your secondhand smoke, harming unborn baby.

Source: adapted from table 17 in the Executive Summary, p. 121.[26]

Message 1	Message 2	Message 3	Message 4	Message 5
Evidence Statement 1 (reduced exposure)	Evidence Statement 1 (reduced exposure)	Evidence Statement 2 (reduced exposure)	Evidence Statement 2 (reduced exposure)	Evidence Statement 3 (reduced risk)
• When tobacco is burned, it produces many harmful or potentially harmful chemicals. • THS 2.2 heats tobacco but does not burn it • With the except ion of nicotine, with THS 2.2 there is a significant reduction in the production of harmful or potentially harmful chemicals	• When tobacco is burned, it produces many harmful or potentially harmful chemicals. • THS 2.2 heats tobacco but does not burn it • With the except ion of nicotine, with THS 2.2 there is a significant reduction in the production of harmful or potentially harmful chemicals	• THS 2.2 heats tobacco but does not burn it • This significantly reduces the production of harmful or potentially harmful chemicals • Scientific studies have shown that switching completely from cigarettes to THS 2.2 significantly reduces your body's exposure to harmful or potentially harmful chemicals	• THS 2.2 heats tobacco but does not burn it • This significantly reduces the production of harmful or potentially harmful chemicals • Scientific studies have shown that switching completely from cigarettes to THS 2.2 significantly reduces your body's exposure to harmful or potentially harmful chemicals	• THS 2.2 heats tobacco but does not burn it • This significantly reduces the production of harmful or potentially harmful chemicals • Scientific studies have shown that switching completely from cigarettes to THS 2.2 can reduce the risks of tobacco-related diseases
WARNING A	Warning B1	WARNING A	Warning B2	Warning C
• **It has not been demonstrated** that switching to THS 2.2 reduces the risk of developing tobacco-related diseases compared to smoking cigarettes • THS 2.2 tobacco sticks contain nicotine which is addictive • Using THS 2.2 can harm your health	• A significant reduction in the production of harmful chemicals, compared to cigarettes, **does not mean a reduction in the risk of tobacco-related diseases** • THS 2.2 tobacco sticks contain nicotine which is addictive • Using THS 2.2 can harm your health	• **It has not been demonstrated** that switching to THS 2.2 reduces the risk of • developing tobacco-related diseases compared to smoking cigarettes • THS 2.2 tobacco sticks contain nicotine which is addictive • Using THS 2.2 can harm your health	• A significant reduction in the your body's exposure to harmful chemicals compared to cigarettes, **does not mean a reduction in the risk of tobacco-related diseases** • THS 2.2 tobacco sticks contain nicotine which is addictive • Using THS 2.2 can harm your health	• Reduced risk **does not mean no risk**. The best way to reduce your risk of tobacco-related diseases is to completely quit tobacco use • THS 2.2 tobacco sticks contain nicotine which is addictive • Using THS 2.2 can harm your health

Figure 1 Reduced exposure and reduced risk messages used in study THS-PBA-03-US. Note: same messages are indicated by the same colour. PBA, Perception and Behavior Assessment.

and a direct mail piece (figure 2). In this study, all materials had a reduced exposure claim, but it was paired with either a Surgeon General (SG) warning for cigarettes or a PMI-developed warning for IQOS communicating that reduced exposure does not mean reduced risk, that IQOS contains addictive nicotine and that IQOS can be harmful ('PMI Important Warning' in figure 2). Participants were randomised into five groups: (1) brochure with SG warning, (2) brochure with PMI warning, (3) pack with the SG warning, (4) pack with PMI warning and (5) direct mail piece with PMI warning.

Between 26% of participants (brochure with a PMI warning) and 58% (pack with SG warning) selected an answer that using IQOS reduces the risk of tobacco-related diseases for the global comprehension measure. An additional 0.8–2.6% answered that it 'eliminates the risk of tobacco-related diseases.' The proportion of participants who answered 'don't know' was 3.1–12.3%. In sum, a large proportion of participants who saw the reduced exposure messages selected answers indicating that tobacco-related disease risk is reduced by switching from cigarettes to IQOS.

For the measures of perceived risk to self, IQOS was rated lower than cigarettes. IQOS was rated similar in perceived risks to e-cigarettes for all measures of perceived risk (figure 3).

Participants also consistently rated IQOS as lower in perceived risk of addiction than combusted cigarettes, even though the marketing brochure did not contain any information on how IQOS compared with cigarettes in terms of addiction risk. PMI's report speculated that participants might be inferring lower perceived addiction risk for IQOS based on the information about reduced exposure to harmful chemicals.[30]

PMI's study report[31] concluded, "In general, reduced exposure messages may present a greater challenge than reduced risk messages on comprehension of disease risk" (p. 74). "It appears likely that consumers will typically infer a degree of reduced disease risk, even where such inferences are explicitly contradicted by warning statements" (p. 76).[31] The report suggested that reduced exposure claims for IQOS "may present an apparent contradiction between (1) reductions in HPHCs [harmful or potentially harmful chemicals identified by the FDA in conventional cigarettes] and (2) a lack of reduced risk for disease" where participants have a hard time reconciling these claims. The report referred the FDA MRTP Draft Guidance, which also acknowledged that "there may be challenges to constructing appropriate claim language that conveys the potential benefits of the product to tobacco users and does not convey that the product is less harmful than other tobacco products.[9] In summary, PMI's quantitative studies corroborated the findings from qualitative studies that US adults perceive reduced exposure claims as reduced risk claims.

DISCUSSION

PMI proposed to market IQOS with reduced exposure and reduced risk claims in the USA. PMI's own qualitative and quantitative studies consistently show that reduced exposure claims are likely to be perceived as reduced risk claims and will,

Reduced Exposure Claim (REC) and associated Warnings (Tested in study THS-PBA-05-REC-US)

AVAILABLE EVIDENCE TO DATE:

- The *iQOS* system heats tobacco but does not burn it.
- This significantly reduces the production of harmful and potentially harmful chemicals.
- Scientific studies have shown that switching completely from cigarettes to the *iQOS* system significantly reduces your body's exposure to harmful or potentially harmful chemicals.

SURGEON GENERAL'S WARNINGS:

- Smoking Causes Lung Cancer, Heart Disease, Emphysema, And May Complicate Pregnancy.
- Quitting Smoking Now Greatly Reduces Serious Risks to Your Health.
- Smoking By Pregnant Women May Result in Fetal Injury, Premature Birth, And Low Birth Weight.
- Cigarette Smoke Contains Carbon Monoxide.

PMI IMPORTANT WARNING:

- It has not been demonstrated that switching to the *iQOS* system reduces the risk of developing tobacco-related diseases compared to smoking cigarettes.
- *HeatSticks* contain nicotine, which is addictive.
- Using the *iQOS* system can harm your health.



Figure 2 Reduced exposure message and an example of marketing materials from study THS-PBA-05-REC-US. In study THS-PBA-05-REC-US, all marketing materials carried a reduced exposure claim. PBA, Perception and Behavior Assessment; PMI, Philip Morris International.

therefore, mislead the public. While few studies outside the tobacco industry evaluated consumer perceptions of reduced risk or reduced exposure claims for non-cigarette tobacco products,[32–34] the results were similar. El-Toukhy *et al*[34] found that modified exposure claims reduced perceived risks of snus and e-cigarette products among adults and adolescents. These results indicate that perceptions of exposure and risk are highly correlated and communication about one— either lower risk or lower exposure—reduces perceptions of both risk and chemical exposure.

The conclusion that consumers interpret reduced exposure information as reduced harm seems to hold across different contexts and tobacco products. The tobacco industry's 'reduced exposure' claims are perceived as indicators of lower harm, as demonstrated by the PMI's studies reviewed here and by research on 'light' and 'mild' descriptors.[16 17] Furthermore, studies on different ways to communicate amounts of harmful chemicals in cigarettes consistently show that consumers misinterpret quantities of harmful chemicals as indicators of health risks.[35 36] This misperception holds regardless of the way the information on reduced exposure is presented: graphically, numbers only, or numbers with additional information, such as common use of these chemicals.[37]

The tobacco industry has a long history of using reduced exposure claims to mislead consumers into believing that the products in question have reduced risk, most notably through the use of 'light' and 'mild' cigarette claims.[24] Therefore, it is particularly important that the FDA and comparable authorities elsewhere in the world take care not to give legal sanction for PMI or other tobacco companies to market their IQOS or other similar products to mislead the public in the same way that it and other tobacco companies have done with earlier products. In particular, IQOS and other HTPs should not be permitted to be marketed with labelling or advertising that claims or implies modified exposure because the PMI's own studies demonstrate that consumers perceive reduced exposure claims as reduced risk claims. Both US law (FSPTCA, 911(g) and 903)[10] and the Framework Convention on Tobacco Control[38] (FCTC) and FCTC's

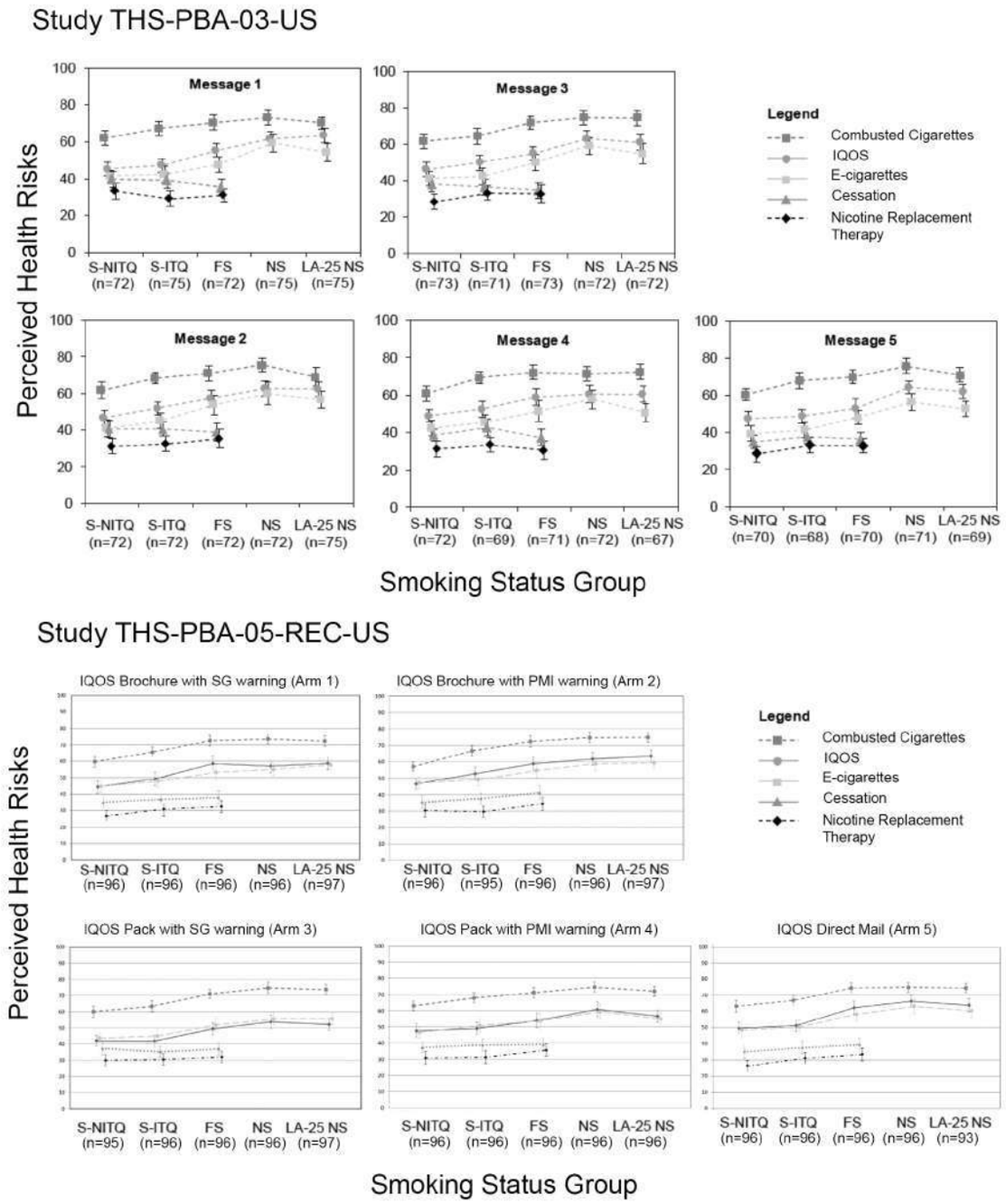


Figure 3 Participants in a quantitative study (THS-PBA-03-US, top panel) perceived health risk of IQOS to be significantly lower than health risks of combusted cigarettes, regardless of whether they saw a reduced exposure claim (Messages 1–4) or a reduced risk claim (Message 5)[31] (p. 68). Similarly, participants in THS-PBA-05-REC-US (bottom panel) rated perceived health risks of IQOS lower than combusted cigarettes for all marketing materials with reduced exposure claim[30] (pp. 56, 72, 86). Note: answers were no risk, low risk, moderate risk, high risk, very high risk and don't know and were later converted into a 0–100 scale (0=no risk and 100=very high risk). Error bars represent 95% CIs from the mean. Connecting lines are only to highlight clustering of outcomes for each comparator along the y-axis across IQOS messages. Abbreviations for Smoking Status Group: FS , adult former smokers; LA-25 NS , adult never smokers aged between their state legal smoking age (18 or 21) to 25 years; NS , adult never smokers; PBA, Perception and Behavior Assessment; PMI, Philip Morris International; SG, Surgeon General; S-ITQ, adult smokers with the intention to quit combusted cigarettes; S-NITQ, adult smokers with no intention to quit combusted cigarettes.

Guidelines for Implementation[39] prohibit tobacco product labelling that is false or misleading, especially labelling that would mislead consumers to believe that the product is less harmful than other products.[40]

Even though tobacco companies almost never marketed light and mild cigarettes with explicit claims of reduced health risks, promotions focused on reduced exposure (lower tar and nicotine) made smokers believe they were reducing their health risks

by switching to light cigarettes.[13–17] Later, tobacco companies went further to promote light and mild cigarettes with aspirational messages, linking light cigarettes to highly desirable places and situations, such as style, relaxation and sophistication.[41] PMI is using the same playbook in marketing IQOS around the world by promoting IQOS as sophisticated and aspirational,[7]emphasising the themes of cleanliness, customisation and sociability.[6] Based on what we have learnt from marketing of light cigarettes and natural tobacco,[42–44] as well as the results of PMI's own research, it is likely that these claims will also be understood by consumers as reduced risk claims.[34]

Limitations and directions for future research

We report findings from PMI's qualitative and quantitative studies, relying primarily on the summary reports for each study rather than re-analysing the raw data. Our study is limited by the shortcomings of the original studies. For example, it is possible that participants in the qualitative studies perceived reduced exposure claims as reduced risk claims in part because they were exposed to all claims during their focus groups or interviews. These studies focused on more intensive message processing under conditions of participants paying attention to the messages. In the real world, these claims might be processed differently, and the resultant perceptions might be different. Future research should investigate how understanding of reduced exposure and reduced risk claims varies under situations of limited attention and unmotivated processing. Combining reduced risk/exposure claims with warning information that comes from a different source (such as the government) might result in differential processing by various people and more studies need to be done with warnings attributed to various sources to evaluate whether the findings were the artefacts of these specific claims.

Another area worth examining is the role of the source of modified risk information. The PMI's studies do not report on who the consumers attributed the claims to; however, given what we know, understanding whether consumers think this information comes from FDA or from tobacco companies would play an important role. Past research found that consumers (including tobacco users) generally trust FDA and generally distrust tobacco companies.[45] Furthermore, attributing reduced risk claims to FDA might make consumers mistakenly believe that the government endorsed these products and further reduce their risk perceptions, resulting in less informed decision making in the marketplace.[33]

CONCLUSION

PMI's MRTP application for IQOS makes reduced risk claims about IQOS that, like its earlier 'light' and 'mild' claims that were deemed fraudulent in the RICO case, are not substantiated by PMI's own internal research reported in its application.[2–4] Several of the other papers in this supplement indicate that IQOS is not significantly less harmful than combusted cigarettes[2–4 46 47] and that while IQOS had lower levels of pulmonary cytotoxicity[48] and carcinogens[49] than combusted cigarettes, they were higher than those of e-cigarettes. Therefore, the limited evidence on the health risks of HTPs does not support the much lower levels of perceived harm that PMI's consumer studies found. Even the evidence for the reduced exposure claim is questionable because PMI's data show *higher* levels of exposure than conventional cigarettes to some toxins.[2]

In the MRPT application, PMI makes an argument that the 'reduction in exposure to toxicants provides the foundation for the reduced harm rationale for this product as an MRTP', which further indicates that they do not currently have evidence aside from the data on reduced emissions to demonstrate effects on health. However, this is exactly what FDA says is not sufficient to show reduced risk, that is, to demonstrate that IQOS 'significantly reduce[s] harm and the risk of tobacco-related disease to individual users.' On 25 January 2018, the FDA Tobacco Products Scientific Advisory Committee (TPSAC) voted not to accept Philip Morris' claims that IQOS is less harmful than cigarettes (with 8 'No's and 1 'Abstain'). The TPSAC found (on an 8 to 1 vote) that the evidence presented by PMI demonstrated its reduced exposure claim, but unanimously rejected the idea that PMI demonstrated that consumers accurately understand the risks of IQOS. The important point is that the evidence from consumer studies clearly indicates that even a reduced exposure claim does not meet the regulatory criteria because consumers will understand such a claim as a reduced risk claim.

PMI's reduced exposure claims in its labelling and marketing for IQOS and similar claims for HTPs made by other companies are likely to be misunderstood as reduced risk claims. Therefore, FDA and other regulatory agencies in other countries should not permit PMI or any other tobacco company to market IQOS with reduced exposure claims. If PMI and other tobacco companies are allowed to make confusing (if not deliberately deceptive) claims in its labelling and/or advertising, it is likely to result in consumers being misled into believing HTPs are endorsed by regulatory agencies or into misunderstanding HTP's harmfulness.[50] In short, despite PMI's contradictory statements,[26] the actual reports, transcripts and data submitted by PMI to FDA provide substantial evidence that consumers perceive reduced exposure claims as reduced risk claims. Allowing PMI to promote IQOS as reduced exposure would amount to a legally sanctioned repeat of the 'light' and 'mild' fraud which, for conventional cigarettes, is prohibited by the US law and the FCTC.

What this paper adds

- The US Food and Drug Administration can authorise marketing of tobacco products as causing less exposure to harmful chemicals or lowering health risks. The law requires that claims of lower exposure do not mislead the public into believing the product presents reduced risk of health harm.
- The evidence in Philip Morris International's qualitative and quantitative studies submitted as part of its modified risk tobacco product application reveals that adult consumers in the USA perceive reduced exposure claims as reduced risk claims.
- Without evidence of reduced risk, claims of lower exposure are inherently misleading because they will be interpreted as reduced risk claims even if they do not explicitly make reduced risk claims.

Contributors All authors conceptualised the study, contributed to the writing and revision and approved the final version of the manuscript. LP and LKL analysed the data.

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Invisible smoke: third-party endorsement and the resurrection of heat-not-burn tobacco products

Jesse Elias,[1] Pamela M Ling[1,2]

[1]Center for Tobacco Control Research and Education, University of California, San Francisco, California, USA
[2]UCSF Department of Medicine, Division of General Internal Medicine, San Francisco, California, USA

Correspondence to
Dr Pamela M Ling, Department of Medicine, University of California San Francisco School of Medicine, San Francisco, CA 94143, USA;
Pamela.Ling@ucsf.edu

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ABSTRACT

Background Tobacco companies are introducing new 'heat-not-burn' cigarettes in dozens of countries. Historically, these products failed commercially, and independent researchers contested their health claims. The most prominent early heat-not-burn cigarette was RJ Reynolds's (RJR's) Premier, introduced in the USA in 1988. Curiously, *The Lancet* endorsed Premier as a 'near-perfect low tar cigarette' in a 1991 editorial, 2 years after Premier had been removed from the market. We examined the context of this endorsement.

Methods To ascertain what RJR knew about this endorsement, we systematically searched and analysed previously secret RJR documents in public archives and triangulated the industry document data with other published work.

Results RJR had a long-standing interest in collaborating with outside scientists to endorse potentially reduced harm cigarettes. The author of *The Lancet* editorial had previously corresponded with RJR regarding Premier's health effects and market potential. Internally, RJR regarded *The Lancet*'s editorial, its stance on novel tobacco products, and its endorsement of Premier as major successes. While the editorial came too late to save Premier, RJR saw future business opportunities for novel products if endorsed by health authorities.

Conclusions Endorsement by high-impact medical journals and health authorities may be critical in helping heat-not-burn' products succeed where previous attempts have failed. Conflicts of interest influenced these endorsements in the past. Health leaders and academic journals should consider both conflicts of interest and the ethics of endorsing tobacco product substitution, as tobacco companies simultaneously work to promote cigarette smoking and undermine tobacco control globally.

BACKGROUND

Since the 1960s, the tobacco industry has developed 'safer' products to attract health-conscious smokers and improve its public image.[1] Major tobacco companies have recently expanded their product portfolios to include alternative nicotine products, such as electronic cigarettes (e-cigarettes) and 'heat-not-burn' cigarettes.[2] In 2015, Philip Morris International (PMI), British American Tobacco (BAT), RJ Reynolds (RJR; now owned by BAT) and Japan Tobacco International (JTI) all launched heat-not-burn products in dozens of countries.

Heat-not-burn cigarettes have a near 30-year record of dismal market performance.[3 4] RJR introduced the first heat-not-burn product—Premier 'smokeless' cigarettes—in the USA in 1988. RJR internally hoped Premier would 'address the growing pressures cigarette smokers face on the subjects of smoking and health, environmental tobacco smoke, and other issues related to the social acceptability of smoking'.[5] In an internal memo to employees, RJR's President of Development Richard Kempe described Premier as 'one of the most important projects any of us will be involved in during our professional lives…because the success of this project could easily result in a tremendous long-term competitive advantage to RJR and would clearly have a substantial impact on the industry as we know it'.[6] Smokers nonetheless widely rejected the product's taste, smell and difficulty of use. Having invested $300 million ($635 million inflation-adjusted to 2018), RJR removed Premier from test markets after only 6 months.

In 1991, 2 years after Premier's failure, *The Lancet* published an editorial praising Premier's ability to deliver nicotine with fewer carcinogens.[7] The editorial called for health authorities, particularly in the UK, to promote cigarettes that delivered nicotine with as little accompanying tar as possible. As one of the earliest examples of an influential journal promoting a novel tobacco product, *The Lancet*'s endorsement of Premier provides important context for the tobacco industry's current pursuit of health authority endorsements for its new products.[8] Though the 1991 editorial appeared after Premier's demise, RJR viewed *The Lancet*'s position as promising evidence that some health authorities would support novel tobacco products, and that with such endorsements, consumers might accept future products.

METHODS

We analysed previously secret internal tobacco industry documents available through the Truth Tobacco Industry Document Library (https://industrydocuments.library.ucsf.edu/tobacco/) between January 2016 and February 2017. In seeking to identify why *The Lancet* endorsed Premier in 1991, we combined qualitative analytical methods with iterative search strategies.[9–11] Initial keyword searches included: 'Lancet' AND 'Premier'; 'Nicotine use after the year 2000'; 'editorial' AND 'Premier' and 'Chemical and Biological Studies of a Cigarette that Heats Rather than Burns Tobacco'. On learning that two historians attributed the anonymous editorial to Michael Russell,[2 12] we conducted further searches with keywords including: 'Michael Russell', 'MAH Russell' and 'Russell' AND 'Premier'. We conducted snowball searches to locate related documents using reference (Bates) numbers, file locations, dates and individuals mentioned in pertinent documents. Triangulation with online search engines and

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news coverage (eg, Google News) generated data that helped resolve and contextualise questions raised by the documents. We repeated iterative searches until keywords and documents yielded only previously viewed documents, suggesting saturation. This analysis is based on a final set of 196 documents.

RESULTS

In a 1988 internal memo, RJR insisted that in its marketing of Premier, the company was:

> [N]ot claim[ing] that the cigarette is 'safe' or 'safer'… [instead] we have used the word 'cleaner'… This is not a therapeutic claim… Premier's tobacco-heating technology is a breakthrough that 'changes the very composition of the smoke – substantially reducing many of the controversial compounds found in smoke of tobacco-burning cigarettes.'[13]

RJR President and CEO for West Germany, Peter Fischer, stressed that, when meeting with policy makers, RJR's scientific representatives should 'concentrate on "tar"/condensate related scientific aspects of [Premier] thereby avoiding to address [sic] the remaining nicotine and CO issues'[14] which, if independently interrogated, might lead scientists to refute Premier's implicit health claims as 'cleaner'.

Legally restricted from making health claims, RJR depended on the scientific community and media to make those claims on its behalf. Proctor notes that Premier's marketing campaign included 'one-on-one briefings with university presidents, medical school deans, science writers, and medical organizations, along with politicians and "opinion leaders" throughout the world'.[1]In a confidential 1987 planning document, Fischer discussed strategy to 'insure [sic] a successful product launch' for Premier, recommending RJR 'build strong support for the product concept among scientific, regulatory and political constituencies'.[14]

In 1990, to garner scientific and public support for Premier, Donald deBethizy, a senior toxicologist and Vice President of Research and Development at RJR, published a paper with nine other RJR scientists that compared the nicotine absorption, urine mutagenicity and carcinogens in mainstream smoke from Premier to a conventional cigarette.[15] According to the paper—entitled "Chemical and Biological Studies of a Cigarette that Heats Rather than Burns Tobacco"—all chemical and carcinogen levels, save formaldehyde, were lower among Premier smokers.[16] The authors attributed these reductions to Premier's smoke, reported as consisting of more than 90% water, glycerol and propylene glycol.[15]

The Lancet endorses Premier

Before its publication in the *Journal of Clinical Pharmacology*, deBethizy's paper was rejected by the *Journal of the American Medical Association*[17] and the *New England Journal of Medicine*.[18] In October 1989, deBethizy submitted the paper to *The Lancet*, hoping for 'better luck in England',[19] despite the product already having been pulled from US shelves 8 months earlier.[20] *The Lancet* also rejected the paper on the grounds that its printing in the journal was 'not justifiable'.[21] In the rejection letter, *The Lancet* editor David Sharp nonetheless called the paper 'a substantial study… [that] deserves to be published in full'.[21] Sharp proposed a future editorial about Premier should a different journal publish the article.[21] Over a year later, deBethizy notified *The Lancet* of the paper's publication in the *Journal of Clinical Pharmacology* and requested the editorial.[16]

In this follow-up letter, deBethizy argued that Premier 'speak[s] directly to the call by the Frogett (sic) Committee in Great Britain for reduced "tar" to nicotine ratio cigarettes'[16] The Froggatt Committee was, since Peter Froggatt's appointment as chair, the informal name of the Independent Scientific Committee on Smoking and Health (ISCSH; earlier known as the Hunter Committee). The ISCSH served as the UK government's chief scientific advisory body on the issue of smoking and health through the 1970s and 1980s and was openly advised by major British tobacco manufacturers.[22] Effectively, deBethizy, an RJR scientist, used the authority of the ISCSH, which was under industry influence, to stress to *The Lancet* the importance of RJR-funded findings on Premier (an RJR product). In his letter, deBethizy set Premier in a framework promoting tobacco product substitution:

> The public health community in the US has not been receptive to these prototypes, taking the position that prohibition of smoking is the only avenue that should be pursued. We believe that this is a short-sighted approach which ignores the projections that by the year 2000, forty million Americans and an even greater number worldwide will choose to smoke…. We feel that cigarettes that heat tobacco will provide an alternative to smokers who choose to smoke despite warnings that adverse health effects may arise from smoking.[16]

While we found no return correspondence from *The Lancet*, the journal published the editorial 6 months later.[7] Historians Virginia Berridge and Mark Elam[2 12] attribute this editorial's authorship to Michael Russell, one of Britain's most prominent tobacco scientists during the second half of the 20th century . We found no evidence of collaboration between RJR and Michael Russell regarding the content of this editorial.

Michael Russell

Michael Russell is oft-quoted as stating, 'people smoke for nicotine but they die from the tar'.[23] A psychiatrist by training, Russell is today widely regarded[24 25] as influential in British health organisations'[26–28] and authorities'[29 30] promotion of e-cigarettes for long-term nicotine maintenance and cessation purposes. One of the first researchers to identify nicotine as the primary reason for which smokers became addicted, Russell was an early developer of and advocate for nicotine replacement therapy.[31] Among other proposals, Russell promoted medium and high nicotine, low tar cigarettes so as to avoid smokers' 'compensation', a phenomenon in which low-tar cigarette smokers inhale more deeply to obtain nicotine, thereby ingesting as much, if not more tar and negating any 'health' benefits of low-tar cigarettes.[23]

In the late 1970s, Russell collaborated with BAT on two 'safer' cigarette studies[32] and received £55,000 (£300,850 inflation adjusted to 2018) in funding to conduct a third joint study, testing medium nicotine, low tar cigarettes.[33–36] Russell acknowledged this 'strong relationship with BAT' and their 'help with some funding' in a 2004 interview with *Addiction*, commenting that maintaining relationships with tobacco companies was common practice among researchers at the time.[37] Russell also engaged extensively with RJR about Premier's 'positive aspects',[38] both prior to the product's release and following its failure (box 1).

In August 1988, Russell requested 3000 Premier cigarettes from RJR to conduct a study measuring 'nicotine, cotinine and carboxyhemoglobin levels in persons smoking Premier'.[39]On RJR's approval of his study in October 1988, Russell stated that the 'publication of results in an English Medical Journal', showing Premier to have fewer carcinogens than regular cigarettes, 'could go a long way to raising interest here [i.e. in the UK] and casting a favorable light on things'.[40] The first time RJR attempted to send Premier cigarettes to Russell, however, British customs

Box 1 Events prior to *The Lancet* editorial favouring Premier

August 1988: Michael Russell writes to RJ Reynolds (RJR) requesting 3000 Premier cigarettes for 'a week-long study with 10–12 male smokers… [to] monitor plasma, nicotine, cotinine and carboxyhemoglobin levels in persons smoking Premier'.[39] Jack Blanchard, Director of Scientific Relations at RJ Reynolds, saw this correspondence as a 'result of discussions that Dr. Russell had with several of us on this topic…last month'.[41] Blanchard suggests to Wallace Hayes, Vice President of Research at RJR, that research scientist Donald J. deBethizy interact with Russell to facilitate these studies.[41]
October 1988: On RJR's approval of his study, Russell states that the 'publication of results in an English Medical Journal', showing Premier to be healthier than regular cigarettes, 'could go a long way to raising interest here and casting a favorable light on things'.[40]
November 1988: Premier introduced to American test markets.
February 1989: Premier withdrawn from American test markets.
February 1989: deBethizy *et al* manuscript sent to Martin Cline at UCLA for comment; Cline suggests RJR to submit the paper to the *New England Journal of Medicine*, and failing that the *Journal of the American Medical Association* (*JAMA*).[71]
February 1989: deBethizy paper submitted to the *JAMA*, which rejects it.[17]
July 1989: deBethizy paper submitted to *New England Journal of Medicine*, which rejects it.[18]
August 1989: Wallace Hayes, coauthor and Vice President of Research at RJR, sends a copy of the paper and recent articles on Premier to Michael Russell, whom he thanks in a letter for his 'encouragement regarding Premier'.[72]
October 1989: deBethizy submits paper to *The Lancet*.[19]
November 1989: *The Lancet* rejects the paper, but editor David Sharp proposes a future editorial on Premier should the article be published elsewhere.[21]
January 1990: deBethizy submits paper to *Journal of Clinical Pharmacology*, on recommendation by Eliot Vessel.[73]
August 1990: deBethizy paper published in *Journal of Clinical Pharmacology*.[73]
December 1990: deBethizy alerts *The Lancet* to the article's publication, hoping the journal will follow up on its initial interest in writing an editorial about Premier.[16]
January 1991: Russell writes to RJR proposing future tests on Premier that he could lead were funding from RJR granted.[42 74]
May 1991: Editorial praising Premier (attributed to Russell) appears in *The Lancet*.[7]

detained them. Russell consequently proposed to Wallace Hayes, RJR Vice President of Research and Development that RJR send the cigarettes to Russell directly, the associated fees for which Russell could pay, and for which RJR could later reimburse him. Russell suggested he could then ' "lose" records of this [reimbursement]' such that no 'note would be kept in the Heathrow customs that could eventually be traced to your company'.[40] We were unable to determine if Russell ever received the cigarettes or conducted the study. While RJR internally planned to coordinate discussions between Russell and deBethizy,[41] we found no evidence of subsequent discussions between the two.

In January 1991, Russell met with RJR executives again, to whom he proposed additional studies on Premier, which 'would of course need to be funded, and we [i.e. Russell's research team] would be interested to consider this when the time is ripe from your [i.e. RJR's] point of view'.[42] Russell noted that it would not even be necessary for these studies to demonstrate 'that harmfulness is reduced in any direct way' but that it would be 'sufficient initially to simply show that when people switched [to Premier] their blood nicotine levels are if anything lower'.[42] In that letter, Russell also mentioned having done a 'preliminary study with [Premier] cigarettes that we purchased ourselves'.[42] This preliminary study may have been the basis for a 1993 paper that Russell coauthored in *Thorax*, showing lower average nicotine, carbon monoxide and tar intake among Premier smokers.[43]

Four months after this January 1991 correspondence, the anonymous editorial, 'Nicotine Use After the Year 2000', appeared in *The Lancet*, praising Premier as a 'near-perfect low tar cigarette'.[7] In the tradition of newspapers, *The Lancet* publishes unsigned editorials, occasionally from outside authors whose opinion reflects the journal's editorial board and represents the position of *The Lancet*. Russell's editorial urged the British government to promote the long-term, recreational and even addictive use of nicotine as a cessation therapy provided the nicotine could be delivered alongside as little tar as consumers found acceptable.[7] Such products should then be made 'as acceptable and palatable as possible, advertised, actively promoted with health authority endorsement, and given tax advantages over tobacco'.[7] In the same month, Russell published an article in the *British Journal of Addiction*, in which he promoted a nasal nicotine spray and nicotine lozenge as potential 'long-term alternatives to tobacco that makes the virtual elimination of tobacco a realistic target'.[44] Using near-identical wording to that employed in *The Lancet* editorial, Russell argued that such products should be made as palatable and acceptable as possible and actively promoted on the open market to enable competition with conventional cigarettes. He stated the products would also need health authority endorsement, tax advantages and support from the anti-smoking movement if tobacco use is to be gradually phased out altogether.[44]

Russell also advised RJR in correspondence to seek advice about introducing Premier into the UK market from Peter Froggatt, Chairman of the ISCSH.[42] Initially receptive, Froggatt ultimately decided to neither endorse Premier nor lobby for its entrance into the UK market.[45] Premier was never marketed in the UK.

RJR reacts

A month after *The Lancet* editorial appeared, deBethizy sent an interoffice memo stressing to colleagues that:

> [T]he position on nicotine advocated in this editorial is a major departure from the position taken by the public health community in the US…[indicating] a willingness on the part of some prominent physicians to propose tobacco product modification as an essential component to a realistic public health policy on smoking and health.[46]

deBethizy saw this difference between American and British attitudes towards potentially reduced harm tobacco products as a major business opportunity. In September 1991, deBethizy and one of his coauthors, David Doolittle, cited *The Lancet*'s endorsement of Premier in a letter to RJR President James Johnston. deBethizy and Doolittle advocated that the company should continue to market products that specifically respond to consumers' increasing 'health consciousness,' in order to 'stabiliz[e] or revers[e] market decline'.[47] As health concerns around smoking intensified, the two scientists argued that the 'long-term vitality' of RJR would depend on repositioning cigarettes to

address these concerns. The letter stated, 'one can only imagine the market share' that such products, 'uniquely perceived…as less hazardous', stood to secure.[47]

RJR executives again acknowledged the importance of third-party endorsements after Premier was removed from the market. In 1993, Russell wrote to Carl Ehmann, RJR's Research Director, arguing that RJR should not abandon Premier or similar potentially reduced harm products.[48] Ehmann responded that RJR was confident it could redress Premier's shortcomings and introduce a similar product that smokers would accept.[49] Nonetheless, Ehmann stated that the company's

> ability to market such a product [in the future] will be dependent upon more rational scientists, like yourself, speaking up and encouraging such concepts. Otherwise, we will be at the mercy of anti-smoking zealots who mistakenly believe they can engineer a smoke-free society and therefore have no interest in products which address the very issues about which they are concerned.[49]

DISCUSSION

A major UK medical journal's endorsement of a defunct American tobacco product was aided by an enthusiastic scientist's cooperation with RJR tobacco company. This scientist's conflict of interest with the maker of Premier should have been, at the very least, disclosed by both Russell and *The Lancet*. Russell's conduct (eg, soliciting funding from RJR and stating *a priori* that publication of the study results in an English journal could go a long way to 'casting a favorable light on things';[40] offering to ' "lose" records' of reimbursement from RJR,[40] and suggesting RJR pay him to undertake research on a product he later anonymously endorsed while representing *The Lancet*[42]) raises serious questions of integrity. It is unclear whether these conflicts of interest were disclosed to the journal, or why the journal offered to write the editorial for a paper they deemed 'not justifiable' for publication in *The Lancet*. Current industry communications attribute new prodcuts' public health impact to consumer acceptance,[50] framed publicly more simplistically than their internal research,[51] as the product of nictoine, taste and the user's associated 'ritual'.[52] Our analysis, however, suggests that health-authority backing will also be central in determining whether the next generation of heat-not-burn devices succeeds where previous attempts have failed.

The industry document database consists mainly of documents produced during litigation and is not a complete archive. As such, we may have missed relevant information, particularly information contained in documents that the industry has withheld on the grounds of trade secrets or client/lawyer privilege.[53] Nonetheless, the documents we have analysed provide a window into prominent RJR scientists' and executives' candid discussions of a potentially reduced harm product. These insights may help public health professionals craft policy that anticipates reiterations of the tobacco industry's promotional strategies for its newest crop of products.

While Premier was a commercial failure, the industry has continued to pursue potentially reduced risk tobacco products.[54] The major tobacco companies have adopted 'harm reduction' language to promote their product portfolios.[55] In 2014, PMI introduced its heat-not-burn product IQOS in Italy and Japan, before expanding to 30 other markets within 2 years. In 2015, BAT and JTI launched heat-not-burn products in Japan. In December 2016, PMI filed an application to the Food and Drug Administration so that it may market IQOS as a modified risk tobacco product in the USA.[56] PMI now claims that its 'vision… is that these [reduced-harm] products will one day replace cigarettes',[57] and in September 2017 announced it would commit $1 billion to the establishment of the 'Foundation for a Smoke-Free World'.[58] Wells Fargo analyst Bonnie Herzog has predicted that heat-not-burn products could displace 'up to 30 percent of the combustible cigarette industry in developed markets by 2025',[59] although sales for IQOS, the current industry leader, began to plateau in the first quarter of 2018.[60]

The industry has also continued courting public health endorsement of its new products. PMI's 'Foundation for a Smoke-Free World' claims to want to combat cigarette smoking via public health partnerships and the promotion of new products.[58] Part of the foundation's launch included publication of an article in *The Lancet*,[8] penned by Derek Yach, a former WHO official who previously worked in tobacco control. While many oppose the Foundation,[61] and *The Lancet* also published a comment by public health advocates voicing concerns,[62] *The Lancet* editorial board failed to support the WHO's strong stance against industry cooperation in their accompanying editorial.[63]

Nearly 1000 peer-reviewed papers based on tobacco industry documents, as well as the US District Court's ruling that the tobacco companies violated the Racketeer Influenced Corrupt Organizations Act[64] demonstrate the folly of partnership with the tobacco industry. August public health organisations, authorities and journals that believe 'the best science must lead to better lives'[65] should consider the ethics of endorsing tobacco industry attempts to preserve profits[66] with products claimed to be, but not yet demostrated as reduced risk,[67] while simultaneously continuing to both aggressively promote cigarettes and undermine tobacco control worldwide.[68] Public health practitioners should also bear in mind past experience with industry-backed 'safer' cigarettes (eg, filtered and low-tar) that served to undermine and delay tobacco control efforts.[69 70] Endorsements from health leaders and regulatory authorities may be the key factor in determining current heat-not-burn products' commercial

What this paper adds

What is already known on this subject

- The tobacco industry has long viewed the endorsement of external authorities as necessary to the success of its potentially reduced harm products.
- In 1991, *The Lancet* endorsed RJ Reynolds' (RJR) heat- not-burn cigarette, Premier, as a safer alternative to traditional cigarettes.
- While Premier failed commercially, the support of potentially reduced harm tobacco products as substitutes continues among some public health organisations and authorities, and is aggressively promoted by tobacco and electronic cigarette manufacturers.

What this paper adds

- The author of *The Lancet*'s editorial had previously collaborated with and advised RJR on Premier.
- While the editorial appeared after Premier was removed from the market, RJR internally regarded *The Lancet*'s stance on Premier as both opening a critical business opportunity for harm-reduced products and as an important departure from health authorities in the USA.
- Endorsements by respected health leaders are likely to play a critical role in determining new heat-not-burn tobacco products' commercial fate and may help the newest crop of modified tobacco products succeed where previous attempts have failed.

succcess, as well as the tobacco industry's future legitimacy as it promotes new products.

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Revolution or redux? Assessing IQOS through a precursor product

Jesse Elias,[1] Lauren M Dutra,[1,2] Gideon St. Helen,[1,3] Pamela M Ling[1,4]

[1]Center for Tobacco Control Research and Educaion, University of California, San Francisco, California, USA
[2]Center for Health Policy Science and Tobacco Research, RTI International, Berkeley, California, USA
[3]UCSF Department of Medicine, Division of Clinical Pharmacology, San Francisco, California, USA
[4]UCSF Department of Medicine, Division of General Internal Medicine, San Francisco, California, USA

Correspondence to
Dr Pamela M Ling, Department of Medicine, University of California San Francisco School of Medicine, San Francisco CA 94143, USA;
Pamela.Ling@ucsf.edu

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ABSTRACT

Background Philip Morris International (PMI) currently claims that its heated tobacco product, IQOS, reduces health risk by reducing users' exposure to harmful and potentially harmful constituents present in tobacco smoke. Given the tobacco industry's long history of misrepresenting and obfuscating research, independent assessment of PMI's claims is important. Analysis of Accord, a failed but strikingly similar precursor to IQOS, may help contextualise PMI's claims in its Modified Risk Tobacco Product (MRTP) application.

Methods We analysed previously secret internal Philip Morris (PM) and PMI documents, public communications and MRTP application.

Results PM marketed Accord as a 'cleaner' tobacco product in an attempt to address smokers' growing health concerns without making explicit health claims. While PM communications asserted that Accord reduced users' exposure to harmful constituents, company scientists and executives consistently stressed to both regulators and the public that such reductions did not render Accord safer. IQOS's design and marketing are similar to Accord's. On the basis of aerosol chemistry data, IQOS reduces user exposure to some compounds compared with Accord but raises them for others.

Discussion IQOS appears to be a variant of Accord without consistent improvements in exposure to aerosol toxic compounds. In contrast to PM's past claims for Accord, PMI now claims in its MRTP application that IQOS reduces health risk. This shift in stance is likely not the result of any toxicological difference between Accord and IQOS, but rather a change in the social and regulatory landscape permitting these claims.

BACKGROUND

The tobacco industry has developed heated tobacco products since the 1960s.[1] When these 'safer' offerings have been marketed, consumers have generally rejected the products' poor taste, smell and user experience.[2] As of May 2018, however, a heated tobacco product from Philip Morris International (PMI), IQOS, had won at least moderate consumer acceptance in several of the 31 countries in which it was available.[3] By early 2018, IQOS had captured nearly 15% of the national tobacco market share in Japan, 2 years after its introduction.[4] Despite the continued predominance of conventional cigarettes to company profit,[3] PMI publicly frames IQOS as presaging the company's supposed departure from the cigarette business altogether.[5]

In promoting IQOS, PMI has attempted to foster a perception of the product as reduced risk. The company's public communications and warning label statements claim that switching completely to IQOS is a safer alternative to smoking cigarettes.[6] In an attempt to court favourable regulation, taxation and exemptions from smoke-free ordinances for IQOS, PMI has begun promoting the product's purported benefits in meetings with national health authorities.[7] In December 2016, PMI submitted a multi-million page Modified Risk Tobacco Products (MRTP) application to the US Food and Drug Administration (FDA).[8] If approved, PMI will be able to market IQOS in the USA as a reduced risk alternative to conventional cigarettes.

Given the tobacco industry's well-documented history of misrepresenting and obfuscating its research,[2] independent assessment of PMI's claims is important. While PMI's internal data and business strategy on IQOS are largely unknown, internal Philip Morris (PM) documents discussing Accord—a failed, but similar heat-not-burn precursor to IQOS—are available in public archives. We compared available documents detailing product design, exposure data and safety claims PM made for Accord to data and claims submitted as part of the IQOS MRTP application. Our aims were to compare product design characteristics; determine if IQOS exposure levels were demonstrably and consistently improved compared with Accord; and learn how PM understood the extent to which reductions in exposure to harmful constituents reduced harm to users.

METHODS

Between October 2013 and January 2016, we searched industry documents (available through the Truth Tobacco Industry Document Library; https://industrydocuments.library.ucsf.edu/tobacco/) detailing tobacco companies' development of various heat-not-burn tobacco product prototypes. Between January 2017 and May 2018, this dataset was expanded with additional iterative searches[9–11] focused specifically on Accord, with initial keyword searches including "Accord market*," "Accord research," "Accord consumer," "Accord science," and related terms drawn from earlier searches, such as "electrically heated cigarette smoking system" (EHCSS) and "EHCSS." We then conducted snowball searches to locate related documents using reference (Bates) numbers, file locations, dates and individuals mentioned in pertinent documents, and by refining subsequent searches with Boolean operators and year and publication type filters. Iterative searches were repeated until keywords and documents yielded only previously viewed documents, suggesting saturation.

To ensure documents' internal consistency, all documents were organised thematically and chronologically, and relevant documents were

compared with relevant sections of PMI's MRTP application available on the FDA's website.[8] Triangulation with online search engines, news coverage, public statements made by PMI (most often found at http://www.pmi.com) and internal PMI documents obtained by Reuters (accessible at https://www.documentcloud.org/public/search/projectid:_2033738) generated data that helped resolve and contextualise questions raised by the documents. Having reviewed over 1,000 documents, this analysis is based on a final collection of 200 documents.

RESULTS

Accord origins and specifications

Through the late 1980s and early 1990s, public health consensus on the negative health effects and addictiveness of smoking led to smoke-free policies and the broader social denormalisation of smoking.[12] In response to these pressures, RJ Reynolds introduced its 'clean smoke' heated tobacco product, Premier, in 1988.[13] Although similar to a conventional cigarette, Premier heated tobacco, instead of burning (combusting) it, producing an aerosol for inhalation.[14 15] Industry scientists hypothesised that such products presented a lower health risk to users: because tobacco was not combusted, smokers might beexposed to fewer respiratory irritants and carcinogens.[1] Marketed as a 'smokeless', 'cleaner' cigarette, Premier was widely rejected by consumers and pulled from shelves within 4 months of its release.

In response to Premier, PM began developing reduced-risk tobacco products of its own.[2 13 16] A 1990 presentation introduced Project Beta, a battery-operated device that would heat rather than burn tobacco.[17] Through Project Beta, PM developed the heat-not-burn product, Accord (internally referred to as an electrically heated smoking system (EHCSS)).[18] Accord comprised a short, low-tar cigarette (in 3 and 6 mg tar versions) and a battery-powered lighter into which the user inserted the short cigarette. On the user's puffing, the tobacco in the cigarette would heat, generating a tobacco-flavoured aerosol for inhalation. Retailing at US$77 (inflation-adjusted to 2018), Accord was packaged for sale as part of a kit that included Accord's special cigarettes (sold at prices comparable to regular cigarettes), the product's heating device and an instructional video (table 1).[16]

Table 1 Component comparison: Accord and IQOS

	Accord	IQOS
Product description	'… [Accord is] an electrically heated cigarette smoking system, comprised of a lighter/heater, which supplies power to the system, and a cigarette designed to be used only with the lighter/heater … activation occurs as the smoker takes a puff. The flow of the puff is detected by a sensor, which then activates the blade-heating cycle. The electronic system in the lighter/heater synchronizes puffing and energy to the blades. The result is that the cigarette delivers eight puffs to the smoker on demand, one for each blade.'[36]	'To operate … the user inserts a Tobacco Stick into the holder and turns on the device by means of a switch. This initiates the heating of the tobacco via the heating blade inserted into the tobacco plug. The tobacco neither ignites nor burns. The electronically controlled heating, in combination with the uniquely processed tobacco, prevents combustion from occurring. The holder supplies heat to the Tobacco Stick through the heating blade for a fixed period of approximately six min and allows up to fourteen puffs to be taken during that time.'[61]
Health claims	'The Accord product has not been proven to be safer. Substantial reductions in certain harmful compounds have not been proven to lead to a reduction in smoking-related diseases.'[41]	'[IQOS] heats tobacco but does not burn it. This significantly reduces the production of harmful and potentially harmful chemicals. Scientific studies have shown that switching completely from cigarettes to [IQOS] can reduce the risks of tobacco-related diseases.'[61]
Tobacco material	Tobacco, glycerol, water, ammonium magnesium phosphate, pectin, beta-cyclodextrin	Tobacco, glycerol, water, guar gum, cellulose, and propylene glycol
Cigarette configuration	62 mm (overall length) 32 mm (tobacco plug)	45 mm (overall length) 12 mm (tobacco plug)
Tobacco weight (mg/cig)	407.6	314
Tar (mg/cig)	3.0	19.4
Nicotine (mg/cig)	0.2	1.29
Filters	A low-efficiency filter (30 mm), containing a segment of activated carbon-in-paper	A polylactic acid filter (18 mm) and a low-density cellulose acetate mouthpiece filter similar to the filter of a conventional cigarette
Tube	Hollow acetate tube	Hollow acetate tube
Paper	Outer paper Tipping paper	Outer paper Tipping paper
Retail price	US$77 (inflation adjusted to 2018)	US$110
Heater description	'The heater is equipped with an array of eight blades made from an iron-aluminide alloy, one blade for each of the eight possible puffs per cigarette …. activation occurs as the smoker takes a puff. The flow of the puff is detected by a sensor, which then activates the blade-heating cycle.'[18]	'The Holder heats the tobacco using a ceramic blade, which is pushed into the tobacco plug [upon insertion]. The Holder has a small battery, which stores enough energy for a single experience (ie, complete use of one Tobacco Stick). The power to the heating element is controlled by an embedded electronic system, which ensures that the temperature follows a pre-defined heating profile for each puff regardless of the user's puffing behaviors. The Holder needs to be recharged prior to each Tobacco Stick use. The Holder is activated by a simple button and its status is conveyed through an interface that includes a colored LED.'[61]
Peak temperature (°C)	500	310–350
Heating blade thickness (mm)	8	0.36
Puffs per charge	13 cigarettes (eight puffs each)	14 puffs per cigarette or 6 minutes of use (whichever comes first), after which the Holder must be recharged in the portable case before a new tobacco stick can be used. Portable case can charge Holder 20 times before needing re-charge.

Accord marketing

In October 1998, PM introduced Accord in 16–20 stores in Richmond, Virginia (the location of a major PM manufacturing facility), expanding to 120 stores within 3 months.[19] In the same year, PM released Accord in Osaka, Japan, under the name 'Oasis'. The tobacco industry has long marketed its 'cleaner' (eg, low-tar) products in Japan due to perceptions that Japanese smokers value cleanliness and are more willing than consumers in other countries to embrace new technologies.[13 20] During Accord's first three years on the market, consumer awareness remained limited, and sales and retention were low.[21] Dual use of Accord with conventional cigarettes was also high: 86% of those who smoked Accord used the product for between one-quarter and one-half of their tobacco use; and only 9% of Accord users used the product for 75% or more of their tobacco use.[22] PM attributed this 'situationa[l]/occasiona[l]' use to the product's poor taste, higher price than conventional cigarettes, unfamiliar operating system and unconventional appearance.[21 22]

PM characterised Accord smokers as favouring product characteristics related to 'hygiene or consideration of others,'[23] and attributed the little success that Accord enjoyed to its perception as a 'cleaner' product that would not irritate others.[21] To attract hygiene-conscious consumers, one Accord advertisement read, 'Less smoke around you. Virtually no lingering odor. And no ashes', all of which rendered Accord 'a whole new way to smoke'.[24] Another ad (figure 1) showed a couple sitting together on the same lounge chair while the man holds an Accord device, the woman seemingly unperturbed by any foul smell or smoke.

While PM emphasised Accord's 'cleanliness' in consumer communications,[25] the company also went to great lengths to clarify that such 'cleanliness' did not render the product safer than conventional cigarettes. In an advertisement accompanying

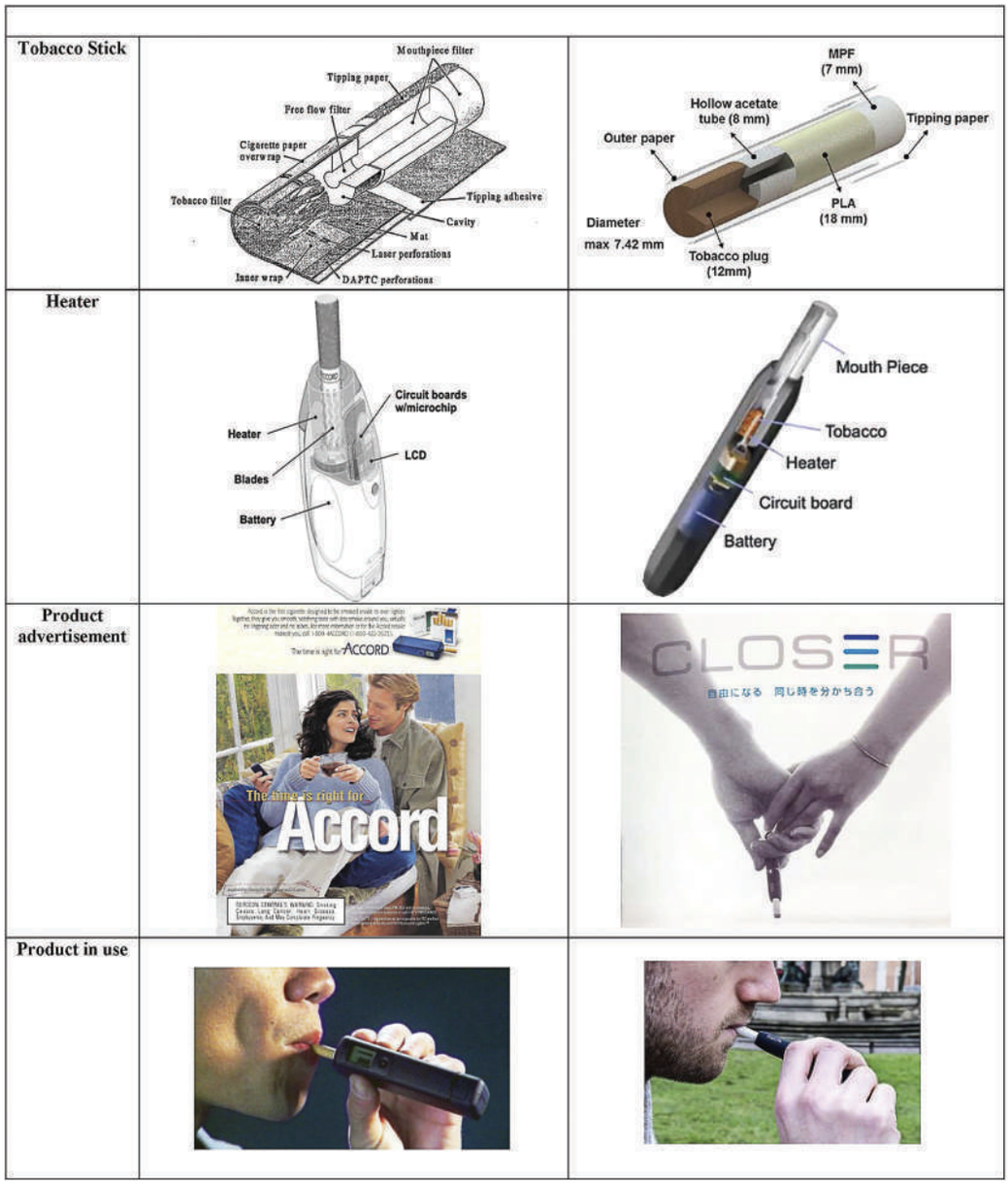


Figure 1 Visual comparison of Accord and IQOS tobacco stick, heating device structure, advertising and product demonstration. Photo credit for Product in Use images: www.vaping360.com and WGBH Educational Foundation.

the Accord Kit, PM stated that while 'Accord reduces certain harmful smoke compounds you inhale … [(such] reductions … have not been proven to lead to a reduction in smoking-related diseases'.[26] After asserting that Accord reduces carbon monoxide exposure by 98% compared with an ultra-light cigarette, PM asked rhetorically in the same brochure, 'Are we saying that Accord is a "safer" cigarette? No.'[26] The brochure also stated that 'public health authorities do not endorse either smoking fewer cigarettes or switching to lower-yield brands or a cigarette that heats rather than burns tobacco as a satisfactory way of reducing risk'.[26 27] This is consistent with past and current research showing that the extent to which reduced exposure leads to reduced harm is unclear.[28 29] Despite these clarifications, a 2003 PM presentation to the company's 'New Products Committee' reported that on average 11% of consumers exposed to Accord advertisements believed Accord to be less harmful than other cigarettes.[30]

Outside of PM, research on Accord's safety was limited. Two independent studies compared Accord smokers' CO intake and heart rate to those of cigarette smokers, and found both levels to be lower in the Accord users.[31 32] However, nicotine uptake for Accord smokers was slower than conventional cigarettes, leading smokers to 'compensate'; that is, inhale more deeply to extract more nicotine, thereby negating any health benefits of lower tar cigarettes.[31]

The significance of these findings, however, was undercut by the product's scant adoption. By 2003, PM had spent over $400 million in operating expenses and almost $70 million (inflation-adjusted to 2018) in capital expenses in developing subsequent versions[33] of Accord.[34] One PM study found that both Japanese and American consumers rejected Accord (although acceptance was higher in Japan) because of its taste ('hard to draw, perceived harshness, not enough taste, not enough puffs per cigarette') and inconvenience ('charging time, cigarettes per charge').[35] Accord also required smokers to adopt a new routine (eg, buying a new brand of cigarettes, recharging the battery pack), while the device itself required 'enhanced consumer support, product maintenance, spare parts, technology acceptance and product education', which most users found burdensome.[22] PM discontinued Accord in 2006 after 8 years on the market.

PM's pursuit of normalisation

Accord was designed as a potentially reduced exposure product (PREP), with PM clarifying in external company communications that reduced exposure did not indicate reduced risk.[36] While PM contracted an advertising company to draft harm reduction advertisements for Accord in the USA, these advertisements were ultimately not used,[12] perhaps because tobacco companies were legally barred from making reduced risk or reduced exposure claims while Accord was available.[37] PM marketed the product instead as a low-smoke alternative,[16] likely hoping to imply to consumers that Accord was safer than conventional cigarettes.

In 2000, as part of efforts to improve the company's beleaguered image, PM began lobbying for legislation that would grant the FDA authority over tobacco.[38] In 2001, 3 years after PM introduced Accord, the Institute of Medicine (IoM, now National Academies of Sciences, Engineering and Medicine) conditionally endorsed PREPs as potentially capable of reducing user risk.[39] Believing that reduced risk products could help 'normalise' the company,[27 40] PM echoed IoM policy recommendations in arguing that potential legislation should create separate classifications for reduced exposure products and reduced risk products. This distinction would enable PM to make reduced exposure claims for products like Accord, without having to wait for long-term evidence finding exposure reduction sufficient to indicate risk reduction.[27] The proposed legislation failed to pass Congress in 2004.

In 2007, a year after PM discontinued Accord , Kenneth Podraza, Vice President of Research and Development at PM USA, wrote to the Surgeon General in an effort to gain government endorsement of Accord. 'In the absence of FDA regulation', Podraza stated that PM 'now turn[ed] to you for guidance', asking that the Office of the Surgeon General determine if Accord is a PREP,[41] likely in the hopes that the Surgeon General's designation of Accord as reduced exposure would generate increased consumer acceptance of either Accord (should it be reintroduced), or of future, similar products. The tobacco industry has long viewed third-party endorsements of industry products as crucial to those products' success.[2 42] Podraza attributed Accord's commercial failure to both consumer rejection and the company's 'inability to communicate a potential reduced exposure message'.[41]

Reiterating PM's previous communications on Accord, Podraza clarified that while Accord may be a PREP it nonetheless 'has not been proven safer [as] substantial reductions in certain harmful compounds have not been proven to lead to a reduction in smoking-related diseases'.[41] Podraza concluded his letter stating that PM would continue to develop future potentially reduced-risk products that smokers would hopefully accept.[41] We found no evidence that the Surgeon General responded to Podraza. In 2008, PM briefly test-marketed a near-identical product, 'Heatbar' in Switzerland and Australia.[16 43 44]

IQOS and Accord product design

In 2014, PMI introduced a new heated tobacco product, IQOS, in Italy and Japan. IQOS's moderate success in several markets as of 2018 is at least partly attributable to the current social and regulatory landscape. When Accord was available, public health authorities were unwilling to deem safe, new, unpopular products designated as 'cleaner' by the industry.[2] Since 2007, however, as the popularity of electronic cigarettes (e-cigarettes) increased,[45–47] several prominent public health organisations[48–51] and health authorities[52 53] have promoted e-cigarettes as safer alternatives to cigarettes. In the USA, the 2009 Family Smoking Prevention and Tobacco Control Act granted the FDA authority to regulate all tobacco products.[54] As part of this legislation, tobacco manufacturers could, for the first time, market preapproved products as 'modified risk tobacco products'.

In addition to its distinct context, IQOS has several notable design differences from Accord. IQOS cigarettes have more nicotine and more than six times as much tar per cigarette as Accord cigarettes. IQOS's HeatSticks are shorter than Accord's cigarettes (45 mm vs 62 mm), as is its tobacco plug (12 mm vs 32 mm). IQOS cigarettes also have less tobacco per cigarette than Accord (314 mg vs 407.6 mg), are burned at a lower temperature (~350°C vs 500°C) and the product kit is approximately US$40 more expensive (inflation adjusted to 2018) than Accord's (table 1).

The products also share a number of similarities. Like Accord, IQOS maintains the core technology of heating rather than burning tobacco, which purportedly lowers users' exposure to harmful or potentially harmful constituents (HPHCs)—constituents linked to the most serious effects of tobacco use (eg, cancer, cardiovascular disease, respiratory effects, addiction). Both products work by activating a heating blade (eight iron-aluminide

alloy blades for Accord and one ceramic blade for IQOS), which then warm(s) the adjacent tobacco, and both products' electronic systems control the temperature of the blade and delimit the amount of puffs the user takes per cigarette (figure 1).

IQOS and Accord advertising

IQOS's marketing has also resembled Accord's. A 2016 internal training for employees managing IQOS's social media presence revealed that, like Accord, IQOS is partially targeted at the hygiene-conscious, particularly 'those who want to reduce risks to their young families'.[55] PMI alerted employees that, as occurred with Accord, consumers may be turned off by the product's 'learning curve', different 'taste and satisfaction levels' and the required time commitment, estimated at 3 weeks, to become accustomed to the product experience.[55] Nonetheless, PMI stated in the same document that IQOS would 'change the way legal-age smokers smoke for the better'.[55]

PMI also expects a number of indirect benefits to accrue to the company if consumers perceive IQOS to be safer than cigarettes. This is consistent with PM's hopes for earlier reduced risk products.[27 40] A 2014 internal PMI document entitled '10 year Corporate Affairs Objectives and Strategies' frames IQOS as a key component in 'normalising' PMI's business more broadly, transforming the company into a 'trusted and indispensable partner … bringing solutions to the table'.[56] In gaining the trust of the public and regulators, PMI hoped to both regain access to broader regulatory discussions from which it is currently excluded and reverse the trend of 'PMI/industry de-normalization … [so as] to drive future growth'.[56]

Such normalisation efforts will be most successful if smokers switch completely to IQOS. Nonetheless, research on corporate social responsibility programmes has shown that tobacco companies can use purported gestures of goodwill (such as developing 'safer' products) to increase access to policymakers and generate support for industry activity regardless of a given programme's effectiveness.[38 57 58] In IQOS's case, the mere manufacture of a potentially safer product may be enough to earn PMI influence.[59 60]

Comparing IQOS and Accord aerosol chemistry

In December 2016, PMI submitted a multi-million-page MRTP application to the FDA for the company to market IQOS in the USA with reduced-risk claims.[8] While PM consistently clarified that reductions in exposure did not reduce user risk , PM's spin-off company, PMI, now claims that such reductions in exposure do indeed reduce user risk, asserting that 'switching completely [from cigarettes to IQOS] presents less risk of harm than continuing to smoke cigarettes'.[61]

Internal documents and statements by PMI scientists contradict these reduced risk claims about IQOS. In October 2015, an internal newsletter for Philip Morris Japan stated that while 'the 'Tobacco Vapor' generated by the use of iQOS contains significantly lower levels of harmful or potentially harmful compounds', PMI has nonetheless 'not reached the point where we can say that it is 'less harmful for adult smokers and those around them'[62] (figure 2). In 2018, four former PMI scientists and researchers that worked on IQOS also claimed that the product's reduction of certain compounds does not necessarily render IQOS safer.[63]

To assess one measure on which PMI bases IQOS's claims of reduced exposure and thus reduced risk, we compared aerosol chemistry data from PM's Scientific Data Summary (SDS) of Accord with information provided in PMI's MRTP application for IQOS. PM assembled the SDS to detail Accord's product specifications and clinical and non-clinical research findings. An 'evolving document … intended for scientific and regulatory discussions',[36] PM compiled the report from 2002 to 2006 to support reduced-risk claims for the Accord,[64] perhaps anticipating US governmental regulation of tobacco and the creation of a regulatory mechanism through which manufacturers could make reduced-exposure and/or reduced-risk claims for preapproved products.[27] Despite detailing reductions in HPHC exposure compared with reference cigarettes, PM stated in later versions of the SDS that the company made neither a reduced exposure claim for Accord,[36] nor a reduced risk claim, stating that 'reduc[ing] exposure to potentially harmful smoke constituents [did] not … establis[h] whether the product decreases the hazard of smoking.'[36]

In both PM's SDS for Accord and PMI's MRTP application for IQOS, industry scientists quantified levels of HPHCs in the products' mainstream aerosol. PMI frames IQOS as safer than conventional cigarettes partly because levels of 58 constituents (PMI-58) were lower in IQOS mainstream aerosol relative to 3R4F reference cigarette mainstream smoke. The MRTP application for IQOS does not report data on 18 compounds included in the SDS for Accord, many of which are nitrosamines and polycyclic aromatic hydrocarbons, all of which are known toxicants (table 2).

The MRTP application presents percent reduction of HPHC yields from IQOS compared with that of 3R4F reference cigarette on a per cigarette/stick basis as well as normalised by nicotine yields (per nicotine basis). The SDS for Accord provides only absolute HPHC yields. In addition, because Accord and IQOS were compared to different reference cigarettes (2R4F and 3R4F, respectively), which have different smoke constituent yields, the percent reductions of Accord and IQOS to their respective reference cigarettes are not comparable. Thus, we compared constituent yields from Accord and IQOS on a per stick basis, using values reported in the SDS for Accord and MRTP for IQOS (table 3). Based on levels of 25 constituents measured in both Accord and IQOS mainstream aerosol, 8 constituents appeared to be higher in Accord emissions while 17 appeared to be higher in IQOS emissions. When normalized by the weight of tobacco in the product, IQOS exposures were higher for 12 constituents and lower for 13 compared to Accord.

DISCUSSION

While Accord was a commercial failure, IQOS is situated in a distinct social and regulatory landscape, which may increase its chances of success. The decline of cigarette consumption in developed markets, the increased popularity of e-cigarettes, select public health endorsements of e-cigarettes and the creation of a legal mechanism in the USA through which manufacturers can now make reduced risk claims may all have increased both consumers' willingness to try new tobacco products, and PMI's willingness to designate new products as safer than conventional cigarettes. In 2017, PMI announced the establishment of a US$1 billion foundation dedicated to partnering with public health and promoting PMI's portfolio of reduced harm products, chiefly IQOS.[65]

Despite PMI's claims of IQOS's novelty,[66] the product appears to be a successor of Accord on the basis of product design, marketing and aerosol chemistry. Both products work by inserting a modified cigarette into a holder that heats, rather than burns tobacco. Both products' marketing implies reduced harm relative to cigarettes. While PMI claims that IQOS is



Figure 2 Excerpt from an internal October 2015 Philip Morris Japan newsletter. To clarify employee understanding of IQOS, a mock employee asks: '… iQOS has a less harmful impact on health, right?' The company expert replies, 'No no no! While these [ambient air reductions] are important results, we have not reached the point where we can say that it is "less harmful" for both adult smokers and those around them.'[74]

Table 2 Compounds listed in Philip Morris' Scientific Data Summary for Accord but not Philip Morris International's modified risk tobacco product application for IQOS

Polycyclic aromatic hydrocarbons	Benzo[b]fluoanthene, Benzo[k]fluoanthene, Benzo[j]fluoanthene, Ideno[1,2,3 cd]pyrene, Dibenz[a,h]pyrene, Dibenz[a,l]pyrene, Dibenz[a,e] pyrene, 5-methylchrysene
N-nitrosamines	N-Nitrosodimethylamine (NDMA), N-Nitrosoethylmethylamine (NEMA), N-Nitrosodiethylamine (NDEA), N-Nitrosodi-n-propylamine (NDPA), N-Nitrosodi-n-butylamine (NDBA), N-Nitrosopyrrolidine (NPYR), N-Nitrosopiperidine (NPIP)
Aliphatic nitrogen compounds	2-nitropropane
Aromatic amines	o-anisidine, 2-naphthylamine

reduced risk largely because it reduces users' exposure to harmful constituents, IQOS does not drastically improve users' exposure to toxic compounds than relative to Accord. PMI's claims for IQOS's comparative safety on the basis of reduced exposure are further undermined by internal documents from PMI's parent company: as late as 2007, PM executives and scientists claimed that reductions in exposure did not render Accord safer than conventional cigarettes.

One limitation of this study is that the Truth Tobacco Industry Documents Library is fragmented and incomplete, as it primarily comprises documents released through litigation. As a result, we may have missed documents relevant to our analysis, including information contained in the archive's many 'restricted' documents, which the industry protects under attorney/client privilege.[67] Given these limitations, there may be unreported differences in product design, marketing and aerosol chemistry between Accord and IQOS that could have informed our analysis.

Table 3 Comparison of Accord and IQOS constituent yields on a per cigarette basis based on data from Philip Morris' Scientific Data Summary and Philip Morris International's modified risk tobacco product application

Constituent	IQOS (abs. value)	Accord (abs. value)	3R4F (abs. value)	2R4F (abs. value)	IQOS (% of 3R4F)	Accord (% of 2R4F)	Ratio IQOS/Accord (abs. values)
1,3-Butadiene (µg)	0.207	2.2	89.2	36.7	0.23	5.99	0.09
4-Aminobiphenyl (ng)	7.8	0.113	3.21	1.24	243.0	9.1	69.0
Acetaldehyde (µg)	192	114	1602	670	12.0	17.0	1.68
Acetamide (µg)	2.96	0.592	13	4.72	22.8	12.5	5.00
Acrolein (µg)	8.32	16.2	158	61	5.3	26.6	0.51
Acrylonitrile (µg)	0.145	0.415	21.2	15.1	0.68	2.75	0.35
Benz[a]anthracene (ng)	2.65	<0.13	28.4	10.8	9.3	<1.20	>20.4
Benzene (µg)	0.452	0.413	77.3	53.7	0.58	0.77	1.09
Benzo[a]pyrene (ng)	0.736	<0.13	13.3	7.75	5.5	<1.68	>5.66
Carbon Monoxide (mg)	0.347	0.564	29.4	14.3	1.18	3.94	0.62
Catechol (µg)	14	4.53	84.1	45.9	16.6	9.87	3.09
Formaldehyde (µg)	14.1	7.41	79.4	18.6	17.8	39.8	1.90
Isoprene (µg)	6.55	35.4	891	386	0.74	9.17	0.19
Lead (ng)	2.23	<0.676	31.2	12	7.15	<5.63	>3.30
Nicotine (mg)	1.29	0.21	1.74	0.934	74.1	22.5	6.14
Nitrogen oxides (µg)	14.2	28.6	538	298	2.64	9.60	0.50
NNK (ng)	7.8	<12	244.7	150	3.19	<8.00	>0.65
NNN (ng)	10.1	15.2	271	166	3.73	9.16	0.66
o-Toluidine (ng)	1.1	0.773	96.2	56.6	1.14	1.37	1.42
Phenol (µg)	1.47	<0.01	15.6	8.27	9.42	<0.12	>147.0
Proprionaldehye (µg)	10.8	4.94	109	54.7	9.91	9.03	2.19
Styrene (µg)	0.577	0.176	13.9	5.85	4.15	3.01	3.28
Toluene (µg)	1.42	1.26	129	80.4	1.10	1.57	1.13
Tar (mg)	19.4	2.27	25	10.3	77.6	22	8.55
Total particulate matter (mg)	30.2	3.56	41.4	12.6	72.9	28.3	8.48

For all ratio values that are under one, IQOS has less of the given compound than Accord on a per stick basis. For all values that are over one, IQOS has more of the given compound than Accord on a per stick basis. IQOS reduces levels of 8 constituents compared with Accord, but raises them for 17 others. When normalized by the weight of tobacco in the product, IQOS exposures were higher for 12 constituents and lower for 13 compared to Accord.

Similarly, we were only able to analyse one part of PMI's MRTP application. Nonetheless, the results of this analysis suggest that PMI's new claims of reduced health risk for IQOS are more likely the product of the current regulatory environment rather than a substantive improvement in the tobacco product's harm profile compared with its precursor, Accord. Scientific evidence supporting reduced harm claims based solely on reduced exposure remains in.[28 29]

To prove that IQOS is safer than combustible cigarettes, PMI must show that IQOS 'significantly reduce[s] harm and the risk of tobacco-related disease to individual tobacco users and benefit[s] the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products'.[68] Studies related to health effects range from lab-based smoking machine studies to assess constituent concentrations in products and aerosols/smoke; in vitro and in vivo toxicology studies; clinical and human pharmacology studies to examine the subjective and health effects of product use in lab and ambulatory settings; and epidemiological studies to examine the longer-term effects of these products relative to smoking. Though PMI has conducted several of these studies with favourable results, studies must also address effects on youth uptake, and product appeal to former-smokers and never-smokers to determine population-level health effects. Given the lack of long-term data on the individual and population health effects of IQOS, we remain sceptical of PMI's claims of reduced risk through the use of predictive models.

Other independent research on IQOS has also contested IQOS's claims of comparative safety.[69–72] In analysing PMI's MRTP application, independent researchers have noted that PMI's conclusions of reduced population-level risk are based on data that factor in neither concerns of gateway effects for youth,[73] nor secondhand smoke and dual use.[74] Despite public communications about targeting solely adult smokers who would not otherwise quit,[75] PMI has so far marketed IQOS much like an upscale tech gadget,[6] offered primarily in countries with declining smoking prevalence and rising cessation rates.[76]

At the individual level, IQOS appears to cause damage to endothelial function, and the liver and the immune system at levels comparable to conventional cigarettes.[77 78] In addition to showing toxicology yields from only a limited range of HPHC's present in IQOS's aerosol,[79] 22 of the constituents in the MRTP application had yields more than 200% higher than those present in conventional cigarettes, while another 7 had yields more than 1000% higher.[79] PMI's medical tests on human subjects also demonstrate 'no statistically detectable difference between IQOS and conventional cigarettes for 23 of the 24 biomarkers of potential harm'.[80] In January 2018, the FDA's Tobacco Products Scientific Advisory Committee concluded that PMI had not proven IQOS to be safer than conventional cigarettes.[81]

This paper joins these analyses in casting doubt on PMI's health claims for IQOS. Based on product specifications, marketing and aerosol chemistry, IQOS appears to represent less of a technical breakthrough than it does an attempt to capitalise

on a social and regulatory landscape more favourable than a similar precursor product's. When the regulatory environment prohibited reduced risk claims, PMI's parent company consistently stated that reduced exposure did not mean reduced risk. The FDA should take PM at its word.

What this paper adds

What is already known on this subject

- Philip Morris International (PMI) claims that IQOS reduces users' risk by reducing their exposure to harmful and potentially harmful constituents.
- From 1998 to 2006, PMI's parent company, Philip Morris (PM), marketed a strikingly similar heated tobacco product, Accord, with little commercial success.

What important gaps in knowledge exist on this topic

- Independent assessment of PMI's health claims for IQOS important, given the tobacco industry's long history of misrepresented and manipulated research.
- Analysis of internal communications surrounding Accord may help shed light onto PMI's understanding of IQOS.

What this paper adds

- PM scientists and executives consistently stated that Accord reduced users' exposure to harmful constituents but that these reductions did not render Accord safer than conventional cigarettes.
- IQOS's design and marketing are similar to Accord's.
- We found that when comparing the aerosol chemistry test results between Accord and IQOS there was not a consistent reduction in exposure to toxicants, calling into question PMI's current safety claims for IQOS, which are made on the basis of reduced exposure.

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Heated tobacco products: another tobacco industry global strategy to slow progress in tobacco control

Stella A Bialous,[1,2] Stanton A Glantz[3]

[1]Center for Tobacco Control, UCSF, San Francisco, California, USA
[2]Social and Behavioral Sciences, School of Nursing UCSF, San Francisco, California, USA
[3]Division of Cardiology, University of California, San Francisco, San Francisco, California, USA

Correspondence to
Dr Stella A Bialous, Center for Tobacco Control, University of California, San Francisco, CA 94143-1390, USA;
stella.bialous@ucsf.edu

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ABSTRACT

There has been a global decline in tobacco consumption that, if continued, will negatively impact the tobacco industry's profits. This decline led the industry to invent and market new products, including heated tobacco products (HTP). HTP are an extension of the industry's strategies to undermine government's tobacco regulatory efforts as they are being promoted as part of the solution for the tobacco epidemic. Under the moniker of 'harm reduction', the tobacco companies are attempting to rehabilitate their reputation so they can more effectively influence governments to roll back existing tobacco control policies or create exemptions for their HTP. Rolling back tobacco control policies will make it easier for the companies to renormalise tobacco use to increase social acceptability for all their products. When regulations are absent or when loopholes exist in classifying HTP as a tobacco product (thus subject to all tobacco control regulations), the industry's marketing of HTP is making these products more visible to the public and more accessible. Governments need to ensure that HTP are regulated as tobacco products or drugs and reject partnerships with the tobacco companies to promote 'harm reduction'. The tobacco companies remain the vector of the tobacco-caused epidemic and cannot be part of the global tobacco control solution.

INTRODUCTION

As of April 2018, Philip Morris International (PMI), British American Tobacco (BAT) and Japan Tobacco International (JTI) were aggressively promoting their 'heated tobacco products' (HTP, also called 'heat-not-burn' heated tobacco, smoke-free tobacco and other 'less risky' products around the world (table 1). Marketing for these products and media accounts of HTP launches in different countries explicitly state or imply that they are safer than cigarettes.[1–6] In a few instances, marketing materials claim that HTP are potentially helpful to smokers who want to quit.[6]

In the USA, claims of reduced risk (what US law calls a Modified Risk Tobacco Product or MRTP) must be approved by the Food and Drug Administration (FDA) before a tobacco company can market a product with reduced exposure or risk claims.[7] In December 2016, PMI submitted a request to the FDA to market IQOS, one of its HTP as a MRTP, claiming that it is a reduced risk tobacco product. The application to sell in the USA without these claims falls under a different process.[7] In particular, despite evidence to the contrary in their MRTP application,[8–10] PMI claimed that smokers who switch completely to IQOS would experience a reduction in the health-related risks associated with smoking.[11 12] In January 2018, the FDA Tobacco Product Scientific Advisory Committee recommended against FDA approval of reduced risk claims for IQOS.[13] This paper provides an overview of the global HTP market, the marketing claims that tobacco companies are making when promoting HTP, and the policy implications of HTP within the context of the tobacco industry's ongoing efforts to disrupt tobacco control progress. IQOS and the other HTP products represent a continuation of the tobacco industry's documented strategies to undermine effective tobacco control, including successful implementation of the WHO Framework Convention on Tobacco Control (FCTC).

Plans to rapidly introduce heated tobacco products

As of April 2018, the industry was rapidly introducing new HTP.[14 15] In December 2014, PMI became the first company to make a large-scale launch of HTP, promoting IQOS. In Italy, rapid market penetration led to an increase in IQOS use, including intent to use IQOS among non-smokers and long-term former smokers who would otherwise remain tobacco-free.[16 17] In the case of never smokers, HTP has the potential to cause harm, despite the tobacco companies' claim to the contrary.[16] The finding that non-smokers and former smokers are using IQOS illustrates how the introduction of HTP can compound the harms caused by other tobacco products.

PMI built a US$120 million production facility in Switzerland and announced, in June 2017 the building of a US$320 million facility in Germany[5] focused entirely on the development and production of HTP. PMI announced plans to double production capacity from 50 billion heatsticks (the disposable tobacco stick that fits in the IQOS device) in 2017 to 100 billion sticks in 2018.[15] In Japan, IQOS quickly gained market share, reaching 10% of the tobacco market in less than 1 year. In 2017, JTI responded with the launch of Ploom TECH,[1] followed by BAT's glo.[18]

We do not know the exact number of countries where the tobacco industry is seeking approval to introduce HTPs in 2018, but a 115 page 2014 presentation by PMI Research and Development titled 'Reduced Risk Products Briefing'[19] released by Reuters[14] indicates that PMI aimed to reach 50 markets by the end of 2018. It appears that PMI selected the top 50 markets after considering volume of cigarettes sold, existing product regulation, the 'economical, political and legal environment' and likelihood of commercial success.[19] BAT stated on its website in 2017 that it planned to have its 'potentially reduced risk products' in 40 markets

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Table 1 Availability of HTP by major cigarette company and country of availability (January 2018)

Company	Product	Year launched	Countries/Comments
British American Tobacco[91]	iFuse* glo	2015 2016	Romania, Japan, Switzerland, Canada, South Korea, Russia
China National Tobacco Corporation / SMTA[92]	Not reported	Not launched	A few of the companies claim to have over 30 patents of HTP and continue to be engaged in research and development of these products. But none yet are in the market.
Imperial Brands[93]	Not reported	Not launched	Focusing on e-cigarettes at the moment, claims to have options to launch when it deems that time is right
Japan Tobacco International[31]	Ploom TECH†	2016	Japan, Switzerland
KT&G Corp.[94]	lil	2017	South Korea
Philip Morris International‡ [6]	IQOS TEEPS§	2014 Not yet launched	Canada, Guatemala, Colombia, Czech Republic, Denmark, France, Germany, Greece, Israel, Italy, Kazakhstan, Lithuania, Monaco, Netherlands, Poland, Portugal, Romania, Russia, Serbia, Slovak Republic, Slovenia, Spain, Switzerland, Ukraine, UK, South Africa, South Korea, Japan, New Zealand

*It is unclear that iFuse will remain in the market in Romania, where Glo was introduced in 2018.
†Ploom TECH is described as a hybrid between a HTP and a vaporiser. It is to be used with Mevius capsules. Mevius is one of JTI's best-selling cigarette brands. The capsules contain tobacco which are then heated by vapour.
‡PMI website states that it is developing a new heated nicotine delivery product that has no tobacco, STEEM, among other 'reduced risk' products.
§ We do not know what TEEPS stands for, it is not included in the product's description (https://www.pmi.com/smoke-free-products/teeps-carbon-heated-tobacco-product).
HTP, heated tobacco product.

by the end of 2018.[4] In April 2018, PMI shares dropped in value subsequent to its announcement of an earlier than expected plateauing of the Japanese IQOS market.[20]

Regulatory considerations

A 2017 Reuters investigation found that before launching IQOS in a country, PMI engaged with high level government officials in attempts to convince regulators that IQOS had health benefits and therefore should not be subject to the same regulatory restrictions as cigarettes, including marketing, labelling and taxation.[14] As Martin King, PMI's Asia President told *Asia Times* in a 2017 interview: 'Ensuring the right market infrastructure and regulatory frameworks are in place is essential to our overall launch schedule for Asia. Fundamentally, any potentially less-harmful alternative to cigarettes needs to be recognised by regulators and consumers as different from cigarettes—taxed differently, labelled differently, and with the freedom to communicate the product attributes openly; only then can smokers have the information they need to encourage them to switch to a smoke-free alternative' .[2] Similarly, in 2017 Ruth Dempsey, PMI's Director for Regulatory and Scientific Affairs, told the Costa Rican newspaper *Imprensa Libre* that existing regulations in some countries make it difficult for PMI to launch IQOS and suggested that countries needed to change their regulatory frameworks to allow PMI to communicate with consumers and explain the advantages of IQOS.[3]

In 2017 in Colombia, the Vice President of PMI affiliate Coltobaco, Humberto Mora, lamented that legislation they supposed to treat HTP differently than other tobacco products did not pass a Senate Committee. He stated that lacking specific regulation, the company's goal was to ensure that minors did not buy the product.[21] Mora also claimed that HTP did not generate any toxic components associated with cardiovascular diseases and cancer.[22]

In March 2017, the Ministry of Health of Israel allowed IQOS to enter the market without any restrictions that are applicable to cigarettes and exempted from the tax scheme for other tobacco products.[23] These decisions generated a strong protest from health advocacy groups who filed a court case to protest the Ministry's decision.[24] The announcement also ran counter previous statements by the Health Ministry's legal advisor. In January 2018, the Ministry reversed its position and convinced the Minister of Finance to announce that HTPs would be taxed similarly to cigarettes.[25]

As of April 2018, there were a range of regulatory approaches to HTP and most of the countries being targeted by the industry for launching HTP were facing the challenge of regulating HTP under existing tobacco control laws that may not explicitly include HTP, which may have made it easier for the companies to open up loopholes in existing laws to evade regulations that apply to all other tobacco products. At a minimum, all claims of harm reduction must be proven with robust, independent evidence,[26] and all regulatory measures of the FCTC should be applicable to the packaging, taxation, sales and marketing of HTP.[7]

Marketing heated tobacco products

Marketing of these products, and claims being made about them, need to be regulated.[7 27] In 2016 in Japan, the appearance of IQOS in a popular television programme was followed by a rapid increase in IQOS use, highlighting the need to regulate HTP marketing and use.[28] The agency that represented the TV celebrities that included IQOS on their television show stated that 'they received absolutely no payment from Philip Morris or affiliated companies' to discuss IQOS on their show'.[29] In Canada, where marketing restrictions exists, PMI is using a series of direct to consumers marketing strategies, including events, and claims of a 'smoke-free future', highlighting the need for governments to develop regulatory framework around marketing claims.[30]

The tobacco companies are using a series of claims in the marketing of HTP. Both in websites and statements to the media and investors, HTP are presented as less harmful but not risk-free. Some media accounts of product launches state that HTP reduce the levels of harmful tobacco components by 90%–95% compared with cigarettes, while others emphasise the lack of odour or visible emissions as part of marketing campaigns. It is important to note that as of April 2018, there is no evidence to confirm this claimed 90%–95% lower level of harm. Other marketing claims highlight that these products produce no smoke, that is, are smoke-free. Implied in these claims, in ads and stores globally, is that smokers should switch from cigarettes to these new, allegedly less harmful, products.

Reduced harm

In a July 2017 press release, JTI also claimed a 99% reduction on a list of tobacco product constituents that have been identified as harmful by WHO's Tobacco Product Regulation Expert Group.[31] In a December 2017 press release, BAT made a similar claim for its HTP, glo, in Romania, where in addition to the 90%–95% reduction in harmful components, BAT claimed that the new product was aligned with WHO's recommendations for regulating tobacco products content.[32] BAT qualified the 90%–95% claim with a footnote stating that this was based on an analysis of nine 'harmful components' in cigarettes that the WHO had identified as target for reduction. WHO responded with a statement in February 2018, stating that WHO was 'in no way endorsing BAT's product nor the company's claims concerning the product'.[33]

Smoke-free

In 2017 in South Africa,[34 35] PMI emphasised HTP as 'smoke-free' in its marketing. At the opening of an IQOS store in Cape Town PMI capitalising on the fact that South African law does not require 100% smoke-free public places (by allowing for designated smoking areas), Blaine Dodds, Head of Marketing for Reduced Risk Products at Philip Morris South Africa stated that the company was

> extremely excited to partner with these malls which have agreed to allow the trial of this product indoors. The HeatSticks or heated tobacco units inserted in the IQOS device are not ignited, only heated and therefore do not generate smoke. The indoor air quality is not negatively impacted by the aerosol. This affords PMSA the opportunity to leverage the area of the store to demonstrate a smoke-free future to South Africans.[34]

A footnote in the press release that quotes Dodds states that 'IQOS is not risk free. The best way to reduce tobacco related health risks is to quit tobacco use altogether'.[34]

A June 2017 JTI press release emphasised the lack of odour from Ploom TECH in an effort to ensure that indoor use is not restricted.[1]

In sum, by 2018, the tobacco companies were promoting HTP, globally as a reduced harm product and an option to address the tobacco epidemic. As in previous attempts of the tobacco industry to be a stakeholder in tobacco control,[36–39] these marketing efforts were providing the tobacco companies with access to decision makers and opinion leaders, continuing the industry's efforts to influence the policy process to protect its profits.

Scientific and political engagement

The tobacco companies use HTP products as part of their broader political and public relations activities to position them as 'partners' to address the tobacco epidemic rather than as the vectors that are causing it. This is a similar strategy previously used by the tobacco industry to promote itself as a partner of public health in reducing the harms of tobacco, while obfuscating the scientific evidence pointing that harm reduction is achieved through tobacco control policies that decrease consumption.[39]

PMI's 2014 internal '10 year Corporate Affairs Objectives and Strategies'[40] released as part of a series of investigations by Reuters outlines PMI's strategies to support its 'combustible and reduced risk (RPP) product businesses'. The strategy document provided a series of examples of activities to renormalise its business to regain access to the political and policy discussions related to tobacco control. One of the key objectives was to 'establish PMI as a trusted and indispensable partner, leading its sector and bringing solutions to the table'. Another key objective was to 'define and pave the way for the right fiscal and regulatory frameworks to secure PMI's RPP portfolio as the pathway for future growth'.[40]

According to this 'confidential internal use only' plan, PMI's 'external engagement' plans were:

1. Establish the concept of harm reduction as legitimate public policy in tobacco regulation.
2. Establish the legitimacy of tobacco companies to be a part of the regulatory debate on RRPs [reduced risk products]('part of solution').
3. Leverage PMI's innovation and scientific research to establish credibility with stakeholders.
4. Identify and engage non-traditional third party stakeholders/allies (e-cigarette manufacturers and retailers, adult consumers of RPP products, tobacco harm reduction advocates, scientific community) globally and locally.
5. Develop compelling messages and materials to support our advocacy on RPP issues.
6. Amplify and leverage the debate on harm reduction around global events (eg, COP6).
7. Continue to engage with regulators globally.[40]

As discussed below, these strategies echo the tobacco industry's decades-long efforts to undermine tobacco control and present itself as an 'indispensable' partner in all policy discussions.

The 2014 presentation by PMI titled 'Reduced Risk Products Briefing'[19] released by Reuters[14] (figure 1) described how PMI planned to invoke the tobacco industry's usual tools to influence the scientific and policy debate around tobacco control: funding of science, global media and public relations campaigns, use of consultants and support for individuals and groups that it perceives as adequate spokespeople for the company's message.[41–46]

PMI released a full-page advertisement in newspapers on 2 January 2018 in the UK claiming that PMI was 'trying to give up cigarettes'.[47] In the ad, PMI explicitly expressed a desire to partner with local and national governmental authorities to support cessation services, including seeking 'governmental; approval to insert, directly into our cigarette packs, information on quitting and on switching'.[47] The advertisement did not mention HTP directly, but did pledge to 'expand the availability of new, alternative products in the UK'.[47] PMI also launched a website, nominally to communicate with smokers about quitting regular cigarettes called 'smoke-free future' (only available for consumers in the UK as of April 2018). PMI's communications surrounding HTP emphasised the company's nominal goal of a smoke free future, which is similar to the name of the Foundation for a Smoke-Free World PMI created and funded in 2017.

Foundation for a smoke-free world

As an apparent element of PMI's plan to expand the market for its HTP as well as rehabilitate the company's reputation, in 2017 PMI committed almost US$1 billion (US$80 million per year for 12 years[48]) to create the Foundation for a Smoke-Free World.[49] The foundation website stated that its goal was to ultimately eliminate smoking worldwide and 'advancing the dialogue on smoking cessation and harm reduction'.[49] The foundation website also stated that it was in the process of developing a research agenda, after which it would release a call for research proposals. The new foundation has a strong goal of promoting HTP as a harm reduction alternative to smoking, in alignment with PMI's strategy to engage with the scientific community and 'amplify' the debate on harm reduction.[36 37]

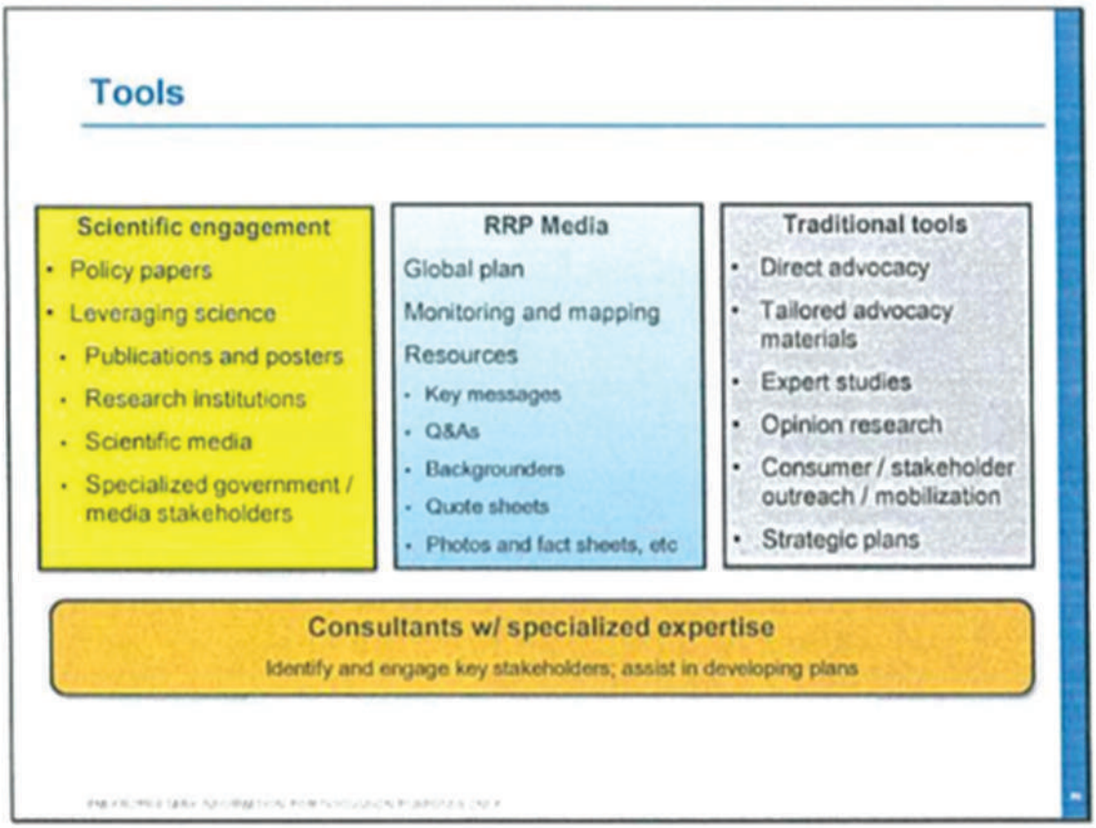


Figure 1 PMI's tools to expand access to markets for its alleged reduced risk products (Slide 22 of a 125 slide presentation titled 'Reduced Risk Products Briefing'[18]) released by Reuters[14] as part of a series of reports on PMI activities. PMI, Philip Morris International.

PMI's motives for creating the foundation were questioned by every major health authority group in the world, including the WHO, Union for International Cancer Control and the Union.[50–52] In January 2018, the deans of 17 schools of public health in the USA and Canada issued a statement declaring that their school would not collaborate with the foundation because they considered funding from the Foundation as being funding from the tobacco industry, which these schools have rejected. Several scholars[37 53] identified the foundation as another tobacco industry public relations campaign, similar to previous foundations or research institutes the industry had created in the past to serve its political and public relations needs. The criticism also focused on the questionable independence of the foundation from PMI[54] and questioned the real intent behind the foundation's research agenda. Like its predecessor organisations, the foundation captured a few scientists and academics to promote an agenda that overlaps significantly with PMI's agenda, although research awards had not been announced as of April 2018.

DISCUSSION

The launching of the latest incarnation of HTPs is a reprise[55] of similar efforts in the past to use similar products to undermine tobacco control, particularly efforts that present the tobacco industry as a harm reduction partner.

As early as the 1960s, the tobacco companies developed alternative tobacco products with the goal of supplementing the cigarette market with products. A few of these products, such as RJ Reynolds (now Reynolds America, part of BAT) *Premier* and *Eclipse* and Philip Morris' *Accord* and *HeatBar* were marketed but received poor ratings from customers, were commercial failures and were withdrawn.[55] It is possible the companies were not more aggressive in making 'reduced harm' claims on new products because of legal concerns: Claiming that the new products were safer would amount to an admission that cigarettes were dangerous, opening the door for litigation and political difficulties for the tobacco industry, including FDA regulation of new products and cigarettes in the USA.[56–58] In addition, the FCTC did not ban cigarettes, one of the tobacco industry's fears. All these factors laid the foundation for the wave of HTP reduced risk claims in several countries that accompanied new HTP products starting around 2014. The introduction of these new products may also have been a response to the growing popularity of e-cigarettes beginning around 2007 after independent companies introduced them before the major multinational tobacco companies entered the e-cigarettes market.[55 57] Furthermore, the global decline of cigarette consumption and decrease in adult smoking prevalence (from 24% in 2007 to 21% in 2015), combined with the success of tobacco control, including implementation of the FCTC,[59–62] may also have lead the tobacco companies to consider alternative products to protect their profits and political interests. HTP serves both purposes by keeping consumers using the companies' tobacco products while providing the industry with an avenue to lobby for exemptions from FCTC and similar national regulations by claiming that HTP would be good for public health.[58] The PMI announcement in the UK[47] has been identified as integral to the overall tobacco industry strategy to present a changed image to the public while continuing to promote nicotine addiction.[36]

In the 1990s, with growing pressure from litigation in the USA and increasing engagement of the WHO in supporting tobacco control globally, the tobacco industry worked to create divisions within tobacco control while seeking to reposition itself politically as part of the 'solution' to the problems created by tobacco use.[44] Philip Morris' Project Sunrise, initiated in 1995, outlined a clear strategy to target certain individuals within the tobacco control community, question their credibility and integrity and work with them to promote alternative policy options that would be less harmful to the interests of the tobacco industry.[38] Project Sunrise implemented Philip Morris' 10-year strategy to position itself as a 'responsible' company and a partner in tobacco control efforts, which would give heightened access to decision makers and the possibility to influence tobacco control regulations. Despite Philip Morris' efforts, global tobacco control did advance, with the FCTC entering into force in 2005.[43]

Since Project Sunrise, the tobacco industry has deployed a range of strategies to interfere with tobacco control, as described by the WHO.[45 46] Among these strategies are efforts to create an image of 'social responsibility' and a commitment to work in partnership with governments to advance tobacco control, although neither of these initiatives have had any impact other than a public relations campaign for the tobacco industry.[46 63–66] Another significant strategy the tobacco industry used in the early 2000s was to promote voluntary, self-regulation in an effort to prevent the FCTC from entering into force. This voluntary self-regulation focused on marketing and youth smoking prevention programmes (YSP). Both voluntary marketing regulation and industry-sponsored YSP have been demonstrated to be ineffective in addressing the tobacco epidemic.[43 67–71]

An integral part of the tobacco industry's efforts is to promote a variety of its products in ways that imply, overtly or not, that they pose less harm than conventional cigarettes. Such misleading discourse accompanied the launch of cigarette filters, machine-measured lower-tar cigarettes, non-cigarette tobacco products such as snus and other smokeless tobacco.[39 72 73] All these efforts sought to avoid marketing restrictions and influence policy makers to support self-regulation instead of a mandatory and more restrictive regulatory framework.[42 43 46] Scientific evidence, on the other hand, demonstrated that filters, decreasing the number of cigarettes smoked a day or switching to a different type of cigarette are not viable risk reduction options. Similarly, as of 2018, the tobacco industry was producing its own science, and planning to fund scientists, in an effort to create evidence to support its claims.

However, emerging science indicated that HTP are unlikely to be any 'healthier' than conventional cigarettes, including scientific data submitted by PMI as part of its MRTP application to the FDA.[8 10 74–77] The industry's claims are often speculative, emphasising the 'potential' for these new products to either reduce harm or reduce risk of tobacco use.[78 79] Additionally, research has demonstrated that despite claims that there is not burning of tobacco, pyrolysis and charring occurs when using IQOS, releasing highly toxic formaldehyde cyanohydrin.[80] Others have shown that while there is a reduction is some toxic compounds, when comparing IQOS with regular cigarettes, these are not removed, and the clinical impact of exposure remains to be assessed.[81] Nonetheless, the tobacco industry appears to be determined in using a 'harm reduction' frame in order to gain access to the policymaking table.

The tobacco industry's use of the 'harm reduction' framework also serves to fracture the tobacco control movement, leaving it without a unified voice to communicate with the public, the media and with policy makers on the strategies to advance tobacco control. The concept of harm reduction has traditionally been embraced in several public health fields such as clean needles for injectable drug use and has been explored by some tobacco control experts in the past,[82] with enthusiasm for the possibility of harm reduction growing with the widespread availability of electronic cigarettes in certain markets.[83–85] The tobacco industry frames harm reduction as a common ground with health advocates and a possible entry point to influence legislation and regulation of tobacco products.[39 86 87]

As described by Peeters and Gilmore,[39] the 2001 Institute of Medicine report on the potential tobacco harm reduction (that was heavily influenced by industry interests[88]) appears to have provided support for tobacco industry efforts to reframe harm reduction as a viable tobacco control policy option and, more importantly, to position itself as pivotal to achieving such harm reduction goals. Thus, in the past decade and a half, the tobacco industry became a vocal proponent of tobacco harm reduction and has invested millions of US dollars in research and development of new products, such as HTP, which the tobacco industry is now using to gain access to scientists, opinion leaders and decision makers as a 'solution' to address the tobacco epidemic. Elias and Ling[89] describe the role the tobacco industry played a role in funding the earliest efforts to promote 'clean nicotine' for harm reduction and conclude that the tobacco industry will continue to seek endorsement from health authorities to its proposition of HTP as a 'harm reduction' strategy.

If HTP manufacturers were seriously concerned about addressing the tobacco epidemic, they would immediately withdraw from dozens of court cases where they are challenging governments' right to implement policies that protect the public's health. Moreover, none of the tobacco companies that are promoting HTP have made any effort to actually reduce tobacco harm by curtailing marketing of tobacco products and has continued to vigorously oppose tobacco control measures and the implementation of the FCTC at national, regional and international levels.

FCTC Article 5.3

Governments that are a Party to the FCTC are urged to consider the regulatory options provided by the treaty when confronted with the tobacco industry's pressure to enter new markets. There is nothing in the language of the treaty that precludes treating HTP as all other tobacco products (or a drug delivery system), including restriction of use in public places, applying labelling requirements, marketing restrictions and taxes.[7] Additionally, Parties to the FCTC that choose to accept the tobacco industry as a stakeholder in addressing the tobacco epidemic are in breach of Article 5.3. Article 5.3 and its implementation guidelines[90] clearly state that there is an 'irreconcilable conflict of interest' between health policy and the tobacco industry. It further states that the tobacco industry is not, and could not, be a partner of governments in the implementation of tobacco control measures. Thus, governments must not engage, or participate, in tobacco industry-led 'harm reduction' efforts.

CONCLUSION

The introduction of the latest generation of HTP appears to be the latest chapter in the decades-old tobacco industry strategy of working to create partnerships with governments and health advocates, presenting these alleged 'harm reduction' products

as an option to address the tobacco epidemic. While health authorities should keep an open mind if independent compelling evidence that a true harm reducing tobacco product is developed and could support a harm reduction policy strategy, they should also keep in mind that the past has demonstrated that partnerships with industry benefit the corporate interests of the tobacco industry and harms countries' health and development. The evidence available to date does not convincingly demonstrate that the available HTPs will simply replace conventional cigarettes among current smokers without attracting youth or even that these products will substantially reduce health risks among users. Nevertheless, the tobacco industry has a well-developed media, public relations and scientific strategy to undermine tobacco control through HTP. It is reaching out to governments and scientists to co-opt them to promote HTP.[14] LMICs, and scientists in these countries, are vulnerable to the appeal of industry funding and must be supported in resisting partnering with the industry and, for countries that are Parties to the FCTC, breaching its international commitments. It is unclear what impact, if any, multilateral trade agreements will have on the expansion of HTP markets or the regulation of these new products.

Despite the rapid introduction of HTPs, as of April 2018, the vast majority of countries did not yet have these products, which creates a window of opportunity to address the tobacco industry's latest 'harm reduction' offensive. But, time is of essence. The FCTC provides a legal framework that encourages countries to take a series of measures regarding novel tobacco products, from banning entry into market, to regulating advertisement, sales, packaging and use[7] allowing Parties to address HTP before these products enter the market in an unregulated fashion.

What this paper adds

- ► After decades of increasing, global cigarette consumption is falling following implementation of the evidence-based policies in the WHO Framework Convention on Tobacco Control (FCTC).
- ► The tobacco companies are promoting heated tobacco products (HTP) as harm reduction as part of their effort to be 'part of the solution' to the tobacco epidemic.
- ► The tobacco companies are using strategies that they have used for decades to fracture tobacco control and promote tobacco 'harm reduction' in an attempt to renormalise tobacco use.
- ► Tobacco companies are introducing HTP in markets with little or no regulatory or marketing restrains despite the fact that reduced risks claims are unproven and likely false.
- ► All FCTC regulatory measures should apply to HTP.
- ► Governments in countries where HTP are not available should keep them out and if allowed in the market at all should be under the strict regulatory framework defined by the FCTC.

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Heated tobacco product regulation under US law and the FCTC

Lauren Kass Lempert,[1] Stanton A Glantz[1,2]

[1]Center for Tobacco Control Research and Education, University of California San Francisco, San Francisco, California, USA
[2]Division of Cardiology, Department of Medicine, University of California San Francisco, San Francisco, California, USA

Correspondence to
Lauren Kass Lempert, Center for Tobacco Control Research and Education, University of California San Francisco, San Francisco, CA 94143, USA; Lauren.Lempert@ucsf.edu

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ABSTRACT
Tobacco companies are marketing new 'heated tobacco products' (HTPs) composed of battery-powered holders, chargers and tobacco plugs or sticks. The non-tobacco HTP components have escaped effective regulation under many countries' tobacco control laws because they are packaged and sold separately from the tobacco-containing components. In the USA, HTPs cannot be marketed unless the Food and Drug Administration determines that allowing their sale would be 'appropriate for the protection of the public health'. Philip Morris International (PMI) is seeking permission to market its IQOS HTP in the USA with 'modified risk tobacco product' (MRTP) claims that it reduces exposure to harmful substances and is less harmful than other tobacco products. However, PMI has not submitted adequate scientific evidence required by US law to demonstrate that the product is significantly less harmful to users than other tobacco products, that its labelling would not mislead consumers, or that its marketing—with or without MRTP claims—would benefit the health of the population as a whole. Parties to the WHO Framework Convention on Tobacco Control (FCTC) must take measures to reduce tobacco use and nicotine addiction, and prevent false or misleading tobacco product labelling, advertising and promotions; the introduction of new HTPs must be assessed according to these goals. All components of HTPs should be regulated at least as stringently as existing tobacco products, including restrictions on labelling, advertising, promotion and sponsorship, sales to minors, price and taxation policies and smokefree measures. There is nothing in US law or the FCTC that prevents authorities from prohibiting HTPs.

'Heated tobacco products' (HTPs), also known as 'heat-not-burn' products,[1] use battery-powered systems to heat sticks of compressed tobacco, flavours and other chemicals to produce a nicotine aerosol to create a 'nicotine hit' that imitates cigarette smoking.[2] A commercial failure in previous decades,[1] major tobacco companies now promote HTPs in many countries as less harmful alternatives to conventional cigarettes, including Philip Morris International's (PMI) 'IQOS', Japan Tobacco International's 'Ploom TECH' and British American Tobacco's (BAT) 'glo'.[3]

The US Family Smoking Prevention and Tobacco Control Act[4] (TCA) assigned the Food and Drug Administration (FDA) authority to regulate tobacco products, including modified (reduced) risk tobacco products (MRTP). The TCA requires premarket authorisation of all tobacco products (Section 910)[4] and does not permit manufacturers to market tobacco products with claims that they are 'modified risk tobacco products' (ie, the product is sold to reduce harm or the risk of tobacco-related disease, or to reduce consumers' exposure to harmful substances) without first demonstrating to FDA that these claims are supported by scientific evidence. (Section 911)[4] FDA must refer all MRTP applications (MRTPA) to its Tobacco Products Scientific Advisory Committee (TPSAC) which must report its recommendations (which are advisory only) to FDA. (Section 911(f))[4]

Outside the USA, the WHO Framework Convention on Tobacco Control[5] (FCTC, the USA is not a party), and its implementing guidelines[6] provide frameworks for parties to enact implementing national legislation, including prohibitions on misleading advertising (Article 11(1)(a))[5] (Article 11 Guidelines for Implementation)[6] and misleading packaging and labelling (Article 13(4)(a))[5] (Article 13 Guidelines for Implementation)[6] which serve similar purposes as MRTP review. Further, parties are 'encouraged to implement measures beyond those required' by the FCTC. (Article 2)[5]

When the TCA and FCTC were enacted, the tobacco companies were not marketing their current HTPs. This paper uses the specific case of IQOS to analyse how these regulatory frameworks do or should apply to HTPs and related reduced harm claims.

THE IQOS HTP IS AN INTEGRATED TOBACCO PRODUCT DESIGNED TO MAINTAIN NICOTINE ADDICTION

IQOS consists of three integrated components essential for its proper functioning: a holder (which heats the tobacco material via an electronically controlled heating blade), a charger (which recharges the holder after each use) and a tobacco stick ('HeatSticks' or 'HEETS') (figure 1). As PMI acknowledges, these three components collectively comprise IQOS[7]; the holder and charger have no independent function without the tobacco sticks, and the tobacco sticks cannot create a nicotine aerosol without the holder and charger. In its MRTP application, PMI describes the HeatStick as '*specifically designed to function with the holder* to produce an aerosol [emphasis added]'.[8]

PMI is taking advantage of this three-component design to package and sell the tobacco sticks separately from other IQOS components that do not contain tobacco, thereby evading existing tobacco control labelling, marketing and tax laws in some countries. For example, in Canada many chain convenience stores sell IQOS HEETS, but not the device itself, and store clerks inform customers to contact an IQOS representative to arrange for the

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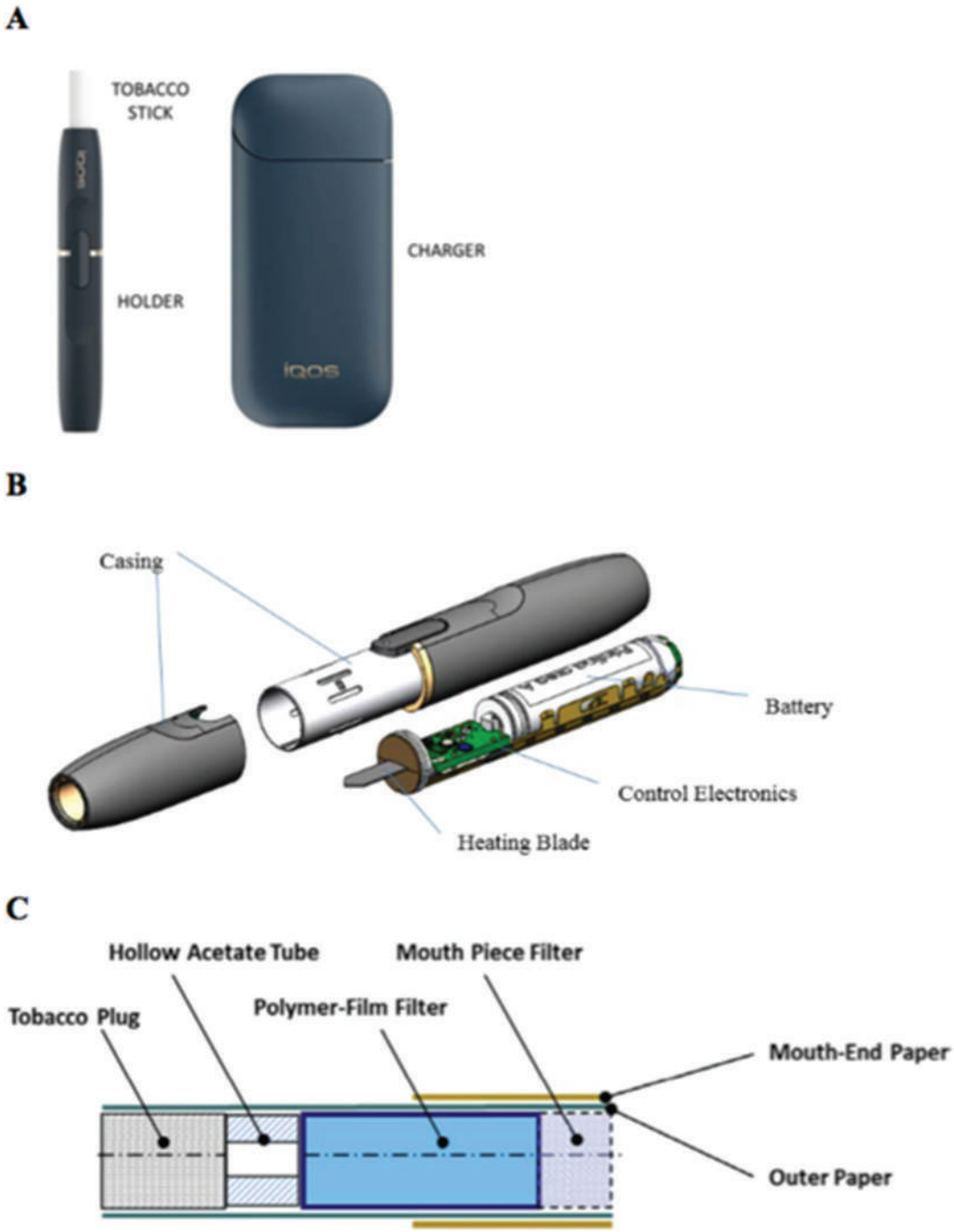


Figure 1 Schematic drawing of the IQOS showing its components (A), a schematic exploded view drawing of the holder (B), and a schematic cross-sectional view of the tobacco stick (C) (Executive Summary).[7]

device purchase.[9] In Korea,[10] PMI markets its IQOS holder, charger and related accessories in packages that do not contain the HEETS labelled only as 'IQOS' without any reference to tobacco or health warnings required on tobacco product packaging. PMI sells the HEETS in separate packages branded with Marlboro or other cigarette brands that include health warnings and comply with tobacco product packaging and labelling laws.

The product description of IQOS in PMI's MRTPA is heavily redacted,[7] but states that the IQOS holder contains an electronic chip (firmware) used to 'control the temperature', 'detect puffs' and conduct other functions that control the user's nicotine intake. (Module 3.1, Product Description)[7] PMI testified at the January 2018 TPSAC meeting that the IQOS device is able to capture data such as the number of puffs taken, but said this information is used for diagnostic purposes if the device is returned.[11] Additionally, PMI testified to TPSAC that IQOS's Bluetooth functionality is used to deliver messages to consumers such as 'you haven't used your IQOS device today' and to remind them to reorder tobacco HeatSticks.[11] The fact that IQOS measures a user's puff-by-puff heating profile,[11 12] integrates IQOS's Bluetooth capability with mobile phones and computers,[13] and automatically reminds consumers to continuously use the device and to reorder tobacco sticks[11] suggests that it calibrates the delivery of nicotine to ensure not only 'satisfaction', but also the potential for PMI to customise the dose, speed of delivery

and continuous use of nicotine to maximise addictive potential for individual users.[12 14 15]

REGULATION OF HTPS IN THE USA

How tobacco products are defined impacts how they are regulated.[16] The TCA defines 'tobacco products' as 'any product made or derived from tobacco that is intended for human consumption, *including any component, part, or accessory of a tobacco product*… [emphasis added]'. (Section 101(a))[4] IQOS (including the HeatSticks, holder and charger) falls squarely under the FDA's definition of 'tobacco product'; PMI does not dispute that its IQOS product (including all three components) is a 'tobacco product' under US law[7] and subject to most regulations that pertain to tobacco products (eg, premarket review (Section 910)[4]) and prohibition on distribution of free samples.[17]

The Deeming Rule, in which FDA took jurisdiction over tobacco products beyond cigarettes and smokeless tobacco, defines 'component or part' to include materials intended or expected to alter or affect the tobacco product's performance, composition or characteristics[18] and extends FDA's regulatory authority to cover all tobacco products meeting the definition of 'tobacco product' including HTPs and their components and parts.[19] Certain provisions of the Deeming Rule (eg, prohibition of sales to customers under age 18 and vending machine sales)[20] apply only to 'covered tobacco products' which 'excludes any component or part that is not made or derived from tobacco'.[18 20] The loophole FDA created in the Deeming Rule contradicts the clear definition of 'tobacco product' in the TCA[4] which includes '*any* component, part, or accessory'. The loophole creates opportunities for companies to sell IQOS devices to youth in violation of the law's intent.

Additionally, the Federal Cigarette Labeling and Advertising Act[21] (FCLAA) defines 'cigarettes' as 'any roll of tobacco wrapped in paper or in any substance not containing tobacco' and the regulations implemented under the TCA incorporated this definition.[18] Because the HeatSticks also meet the definition of 'cigarettes', additional restrictions that apply to cigarettes but not other tobacco products (eg, required cigarette warnings[22] and prohibition of advertising on electronic communication media[23]) should apply to the HeatSticks.

Before being permitted to market a new tobacco product in the USA, manufacturers must first receive premarket authorisation from FDA through a premarket tobacco product application (PMTA), a 'substantial equivalence' (SE) order or an exemption from SE. (Section 910(a)(2))[4] (The less rigorous SE pathway is not available to the current generation of HTPs because no HTPs with similar characteristics were marketed in the USA before 15 February 2007, (Section 910(a)(3))[24] and HTPs are not 'minor modifications' of any product that was marketed in the USA before 15 February 2007. (Section 905(j)(3))[24]) A PMTA applicant has the burden of showing that the product 'would be appropriate for the protection of the public health', determined with respect to 'the risks and benefits to the population as a whole, including users and nonusers', taking into account the increased or decreased likelihood that existing users will stop using tobacco products, and non-users will start using them. (Section 910(c)(4))[4] This stringent standard essentially requires the applicant to demonstrate that, on balance, 'allowing the sale of the new product would likely reduce tobacco-related harms'.[25] Additionally, FDA is required to deny a PMTA for any product whose proposed labelling is 'false or misleading in any particular'. (Section 910(c)(2)(C))[4]

Furthering its mission to protect the public health, the TCA aims to prevent the tobacco industry deception detailed in a US district court's holding that tobacco companies deliberately deceive and mislead consumers about the harmfulness of their products with labelling and marketing[26 27] and highlighted in the TCA's 'Findings' section. (Section 2)[4] In particular, the TCA gives FDA the authority to 'ensure that there is effective oversight of the tobacco industry's efforts to develop, introduce, and promote less harmful tobacco products'. (Section 3(4))[4]

The TCA defines an MRTP as 'any tobacco product that is sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed products.' (Section 911(b)(1))[4] To secure an order permitting sales of tobacco products with modified-risk claims, a manufacturer must submit an application (MRTPA) to FDA demonstrating that the product, as actually used by consumers, will 'significantly reduce harms and the risk of tobacco-related disease to individual tobacco users' and 'benefit the health of the population as a whole', taking into account both users and non-users of tobacco products. (Section 911(g)(1))[4] For products that cannot receive risk-modification orders, FDA may issue an exposure-modification order if the applicant has demonstrated that doing so 'would be appropriate to promote the public health' and the labelling and advertising is limited to representing that the product or its smoke is free of or contains a reduced level of a substance or presents a reduced exposure to a substance in tobacco smoke. (Section 911(g)(2)(A))[4] Additionally, for an exposure-modification order, the applicant must demonstrate among other things that: (1) the product as actually used by consumers will not expose them to higher levels of other harmful substances compared with similar types of tobacco products currently on the market and its use would reduce overall morbidity and mortality among users; and (2) based on testing of actual consumer perception, the proposed labelling and marketing will not mislead consumers into believing that the product is less harmful or presents less risk of disease than other commercially marketed tobacco products. (Section 911(g)(2)(B))[4] Furthermore, for both risk-modification and exposure-modification orders, FDA must ensure that 'any advertising and labeling concerning modified risk products enable the public to comprehend the information concerning modified risk and to understand the relative significance of such information in the context of total health' and tobacco-related harms. (Section 911(h)(1))[4]

The TCA authorises states to enact laws that are more stringent than TCA requirements, including measures 'prohibiting the sale, distribution, possession, exposure to, access to, advertising and promotion of, or use of tobacco products by individuals of any age'. (Section 916)[4]

The PMI IQOS MRTP application

In December 2016, PMI submitted a multimillion-page MRTPA to FDA seeking permission to market IQOS in the USA with two modified-risk claims ('switching completely from cigarettes to the IQOS system can reduce the risks of tobacco-related diseases' and 'switching completely to IQOS presents less risk of harm than continuing to smoke cigarettes') and one modified-exposure claim ('switching completely from cigarettes to the IQOS system significantly reduces your body's exposure to harmful and potentially harmful chemicals').[7] In January 2018, PMI presented its IQOS MRTPA to TPSAC, and TPSAC found that PMI's MRTPA failed to provide sufficient scientific evidence supporting its modified risk claims.[11 13]

In March 2017, PMI submitted a PMTA[28] seeking authorisation to market IQOS in the USA which is required whether or not IQOS is marketed with MRTP claims. Accordingly, if FDA rejects PMI's application to market IQOS with MRTP claims, FDA could still grant PMI's application to market IQOS in the USA without any such claims.

PMI's harm-reduction claims are based on the principle that it is the inhalation of complex combustion compounds in tobacco smoke that causes adverse health outcomes, and since the IQOS device purportedly heats but does not burn the proprietary tobacco stick to create an inhalable nicotine-containing aerosol, it is less harmful than cigarette smoke.[8] Contrary to these claims, harmful chemicals are created in the pyrolysis phase.[29]

US law (Section 911(g)(1))[4] places the burden on PMI to demonstrate that IQOS is appropriate for the protection of the public health before marketing it with MRTP claims and not on FDA or the public to demonstrate the product's harmfulness. However, a close reading of PMI's MRTPA reveals it did not meet this burden. PMI's own data fail to show consistently lower risks of harm in humans using IQOS compared with conventional cigarettes,[30 31] that IQOS is associated with pulmonary and immunomodulatory harms not significantly different from conventional cigarettes,[32 33] that IQOS use may be associated with hepatotoxicity and unexpected organ toxicity that has not been associated with conventional cigarettes[34 35] and that IQOS use does not necessarily avoid the adverse cardiovascular effects of conventional cigarette smoking.[36 37] In addition, data collected independently of PMI revealed IQOS does not consistently reduce exposure to harmful or potentially harmful chemicals.[29 38–42] Moreover, Reuters published a report in December 2017 identifying irregularities in PMI's IQOS research.[43 44] At its January 2018 meeting, TPSAC voted that PMI's MRTPA failed to provide scientific evidence supporting its modified risk claims.[13]

The evidence presented in PMI's MRTPA also failed to demonstrate a net public health benefit as required for both a PMTA order (Section 910(c)(4))[4] and a MRTP order. (Section 911(g)(1))[4] PMI did not demonstrate IQOS would benefit the health of the population as a whole, considering both users and non-users of tobacco products.[45 46] Of particular concern, PMI failed to consider whether youth or adolescents or other non-users are likely to initiate tobacco use with IQOS,[10 47 48] or whether users are likely to use IQOS concurrently with other tobacco products, rather than 'switch completely'.[32 47 49] Based on the evidence presented in PMI's MRTPA, TPSAC found that there would be a low likelihood that US smokers would completely switch to IQOS use.[13]

The TCA also requires PMI's MRTPA to include scientific studies demonstrating that consumers will understand the proposed advertising and labelling and not be misled into believing the product is less harmful than it actually is. However, the evidence presented by PMI indicates that the IQOS labelling or advertising will not ensure accurate consumer perceptions of risk, smokers will not understand they would need to switch completely to IQOS to secure the purported benefits, and consumers will likely view the reduced-exposure claims as reduced-risk claims, rendering them inherently misleading.[27 50 51] Independent research also demonstrates that adults and adolescents misinterpret reduced-exposure claims as communicating lower risk even when there is no explicit claim of lower risk.[52] TPSAC also found that PMI failed to demonstrate that consumers would accurately understand the risks of IQOS as conveyed in PMI's proposed MRTP labelling and advertising.[13]

If PMI cannot revise its application to demonstrate that marketing IQOS would actually be 'appropriate for the protection of the public health' and its proposed labelling would not be misleading, FDA would be required by statute to deny PMI's applications, and PMI would not be permitted to market IQOS with or without any related modified-risk claims.

FDA's decisions regarding PMI's IQOS applications will influence how other governments regulate HTPs and related reduced-risk claims throughout the world. Indeed, PMI stated in its 2018 annual report, 'We remain focused on our aspiration to see IQOS launched in the United States' and 'Future FDA actions may influence the regulatory approach of other governments'.[53]

REGULATION OF HTPS IN FCTC PARTY COUNTRIES

The objective of the FCTC is 'to protect present and future generations from the devastating health, social, environmental and economic consequences of tobacco consumption and exposure to tobacco smoke' and to reduce 'continually and substantially the prevalence of tobacco use'. (Article 3)[5] The 181 parties to the FCTC commit to implementing legislative and other measures 'for preventing and reducing tobacco consumption, nicotine addiction and exposure to tobacco smoke', (Article 5)[5] to inform every person of 'the health consequences, addictive nature and mortal threat posed by tobacco consumption', to prevent initiation and decreasing the consumption of tobacco products 'in any form', (Article 4)[5] and to prevent and reduce 'nicotine addiction' in addition to tobacco consumption. (Article 5)[5]

The FCTC provides strong and broad support for parties to adopt measures protecting the public from the dangers of HTPs. Although the FCTC (negotiated between 1999 and 2003) does not specifically discuss HTPs, it was not intended to be limited to conventional cigarettes, smokeless tobacco and other tobacco products being marketed at the time. The objective of the FCTC is unequivocally to protect '*future generations*' as well as present generations, (Article 3)[5] and it anticipates the introduction of new products that would be introduced after treaty negotiations concluded in 2003. FCTC Article 2 encourages parties to implement measures that go beyond and are stricter than those required by the FCTC. (Article 2)[5] Countries can choose various approaches to regulating HTPs consistent with FCTC's goals.

Regulating HTPs as tobacco products

FCTC Article 1 defines 'tobacco products' as 'products entirely or partly made of the leaf tobacco as raw material which are manufactured to be used for smoking, sucking, chewing or snuffing'. (Article 1)[5] Unlike the definition under US law, the FCTC's definition of 'tobacco product' does not explicitly include 'any component, part, or accessory of a tobacco product'. However, because HTPs are integrated products that are partly made of tobacco and are used for smoking or sucking, some countries may interpret their laws to consider HTPs as tobacco products. Significantly, in its own documents and marketing claims, PMI refers to its 'IQOS system' as one integrated tobacco product. PMI states that IQOS's tobacco sticks are 'specifically designed to function with the holder', and refers to IQOS interchangeably as 'IQOS', 'the IQOS system, consisting of the tobacco sticks, holder, and charger' and as 'the Tobacco Heating System'.[7] On its website, PMI markets the three main IQOS components as a singular tobacco product, the IQOS 'tobacco heating system'.[54]

The fact that HTPs are considered 'tobacco products' under the FCTC is confirmed in several statements issued by the Convention Secretariat.[55] In 2016, the FCTC Conference of the Parties

(COP), the treaty's governing body, stated that 'All new and emerging tobacco products should be regulated under the WHO FCTC. This should include products such as vaporizers and any other novel devices which can be used for tobacco consumption and are not classified as electronic cigarettes.'[56] A 2017 WHO information sheet on HTPs stated, 'all forms of tobacco use are harmful, including HTPs', and recommended, 'HTPs should be subject to policy and regulatory measures applied to all other tobacco products, in line with the WHO FCTC.'[57]

In September 2017, the FCTC Convention Secretariat addressed the introduction of new tobacco products such as HTPs and stated that parties are obligated under the FCTC to treat these and 'other novel tobacco or nicotine products' that may emerge in the same way other tobacco products are regulated.[55] Thus, parties should include HTPs in all restrictions currently applied to other tobacco products, including but not limited to regulation of the product's contents and disclosures, packaging and labelling requirements, comprehensive bans (or severe restrictions) on product advertising, promotion and sponsorship, protections from exposure to the product's smoke/aerosol, prohibitions on sales to minors, and price and tax measures.

In March 2017, Israel became the first country to regulate IQOS as a tobacco product and apply all tobacco product restrictions to IQOS,[58] and in March 2018 Israel's Finance Committee approved applying Israel's cigarette tax to IQOS.[59]

Prohibiting HTPs

The simplest and most effective way to deal with HTPs under the FCTC would be to prohibit the introduction of HTPs which is supported by the FCTC's goals, including protecting future generations from the devastating health consequences of tobacco consumption, (Article 3)[5] preventing the initiation of tobacco products 'in any form' (Article 4)[5] and preventing and reducing 'nicotine addiction'. (Article 5)[5] Historical arguments against banning cigarettes (eg, that it would lead addicted smokers to seek nicotine elsewhere and create a black market)[60] do not apply to a ban on products like HTPs that have yet to be introduced or are as yet a minor segment of the nicotine market.

By introducing IQOS or other HTPs, tobacco companies are likely to increase tobacco consumption, increase nicotine addiction, increase initiation among youth and non-smokers,[61 62] undermine efforts to denormalise and significantly reduce tobacco use,[63] and create a new market of tobacco products that once established will be difficult to control. PMI has introduced IQOS in some markets where it is treated differently from cigarettes under existing regulatory frameworks, allowing it to advertise IQOS and engage in intensive one-to-one marketing to switch current smokers to IQOS which would not be permitted under those countries' FCTC-aligned tobacco control legislation.[9 60] The fact that IQOS could be programmed to maximise addictive potential (discussed above) is of particular concern.

Recent experience with e-cigarettes suggests that introducing new, highly addictive tobacco products where cigarettes are available may increase initiation and encourage dual use, especially among youth, and sustain nicotine addiction in violation of the FCTC's principles.[64–66]

Some FCTC parties have already effectively banned HTPs. For example, in 2015 Singapore banned emerging tobacco products including e-cigarettes and devices that are smoked or mimic smoking.[67]' In Australia, nicotine is a scheduled poison, so products containing nicotine for human consumption are prohibited unless for 'human therapeutic use' (cigarettes are grandfathered).[68]

Definitions in national implementing legislation

The statutory systems of each of the 181 parties to FCTC differ, and the legal mechanisms for drafting, amending or interpreting laws will be specific to each country. Because many parties enacted national legislation to implement the FCTC before the current generation of HTPs were being marketed, some countries' laws use definitions of 'tobacco products' that are ambiguous with regard to HTPs. Removing any ambiguity or potential for misunderstanding will make it more difficult for tobacco companies to claim there are loopholes that exempt HTPs or any HTP components from tobacco control laws.

As discussed above, tobacco companies are seeking to take advantage of this ambiguity by disassembling their integrated tobacco products and selling the components that do not contain tobacco in separate packages and even separate stores to evade labelling and advertising laws. Parties to the FCTC should ensure that all of the tobacco control measures contained in the FCTC apply to all components of the HTP system, whether sold as a single system or as separate components.

Analogous to the situation where IQOS holders and chargers are sold separately from IQOS tobacco sticks, hookah waterpipes are often sold separately from hookah tobacco. Responding to the potential problems this poses in regulating warning labels, in November 2016 COP issued a decision stressing the need for all parties to fully implement all FCTC articles in all aspects of waterpipe use.[69] We found one country, Turkey, whose labelling laws explicitly require health warnings to be placed on hookah bottles and waterpipe tobacco packages.[70]

Countries should interpret their definitions to include HTPs (and other new tobacco products), and, if necessary to avoid ambiguity, amend their definitions, for example, 'tobacco products' means products entirely or partly made of tobacco which are manufactured to be used for inhaling, smoking, sucking, chewing, snuffing or by any other means (see, eg, definitions of 'tobacco products' found in Thailand, the Philippines, Cambodia, Oman and Uganda).[71] Alternatively, countries could add language to clarify that their existing definitions of tobacco products include components like the US definition, and ensuring that all regulations that apply to tobacco products also apply to their components. COP should issue an opinion recommending that parties subject HTPs to all FCTC regulatory measures applied to tobacco products and prohibit tobacco industry attempts to evade these measures.

Countries could also clarify and broaden the definition of 'smoking' in their laws. The FCTC Article 8 Guidelines recommended defining 'smoking' as 'being in possession or control of a lit tobacco product regardless of whether the smoke is being actively inhaled or exhaled'. (Article 8)[6] Countries that adopted this language should change the definition so that it would clearly include HTPs. This could be accomplished by explicitly adding HTPs to the definition of smoking. COP should issue a decision recommending all parties to ensure their definition of 'smoking' includes HTPs and other new tobacco products that may emerge.

Packaging, advertising and marketing

FCTC Article 11 requires parties to adopt measures that prohibit packaging and labelling that promotes a tobacco product 'by any means that are false, misleading, deceptive or likely to create an erroneous impression about its characteristics, health effects,

hazards or emissions', including any figurative or other sign 'that directly or indirectly creates the false impression that a particular tobacco product is less harmful than other tobacco products'.[72] FCTC defines 'tobacco advertising and promotion' to mean 'any form of commercial communication, recommendation or action with the aim, effect or likely effect of promoting a tobacco product or tobacco use either directly or indirectly'. (Article 1(c))[5] FCTC's Article 13 advertising, promotion and sponsorship provisions (Article 13(2))[5] urge parties to adopt comprehensive bans of all tobacco product advertising, promotion and sponsorship to reduce consumption of tobacco products. The Article 13 Guidelines for Implementation (Article 13)[6] underscore that such a 'comprehensive ban' applies to *all* kinds of tobacco promotion without exception, including *indirect* advertising, acts that are likely to have a promotional effect and commercial communications. For example, in addition to traditional media and internet advertisements, Article 13 'advertising, promotion and sponsorship' restrictions include display of tobacco products at points of sale, packaging and product features (including colours, logos, pictures and materials), brand stretching and corporate social responsibility campaigns. (Article 13)[6]

The Article 13 Guidelines are particularly relevant to current IQOS promotions, including its 'smoke-free future' campaign[73] and its product features and marketing that appeal to youth and adolescents, including using packaging that uses colours, logos and materials that mimic iPhones, and selling IQOS in stores that imitate Apple computer stores.[9 10 61 62] It is important to recognise that any advertising or promotion of IQOS, including in particular promotions of the holder alone or any other IQOS component that has been separated for marketing purposes from the essential tobacco sticks, is promoting tobacco within the meaning of the FCTC because it is not only *likely* to promote a tobacco product or use, but its *specific aim* is to promote use of the IQOS tobacco sticks (HeatSticks or HEETS). Neither the IQOS holder nor the IQOS tobacco sticks have any utility other than when used together. Following this reasoning, in April 2018, Lithuania's tobacco regulator fined a PMI subsidiary for advertising the IQOS device, determining the device is subject to the same advertising restrictions as other tobacco products[74] based on its view that 'this device can only be used to smoke tobacco products'.[75]

As of May 2018, PMI was promoting IQOS as a less harmful alternative to cigarettes.[3 9 50 60 76] Because these claims have not been substantiated with scientific evidence, they violate FCTC's Article 11 and Article 13 prohibitions. PMI's 'smoke-free future' campaign[73] appears designed to renormalise tobacco use, rather than to treat tobacco dependence or promote the end of tobacco.[63] In February 2018, WHO issued a statement condemning BAT's promotional statements for its glo HTP implying that WHO endorsed glo as a less harmful alternative to conventional cigarettes and said, 'There is no evidence to demonstrate that HTPs are less harmful than conventional tobacco products.'[77]

In countries that cannot enact comprehensive bans, Article 13(4) states that at a minimum, parties shall prohibit 'all forms of tobacco advertising, promotion and sponsorship that promote a tobacco product by any means that are false, misleading or deceptive or likely to create an erroneous impression about its characteristics, health effects, hazards, or emissions'. (Article 13(4))[5] Under this provision, countries should prohibit PMI from all forms of advertising or promoting IQOS. In the absence of such a prohibition, at a minimum, countries should not permit PMI to market IQOS with unsubstantiated explicit or implicit claims that it is safer than conventional cigarettes, including through using deceptive packaging or colours to alter consumers' perceptions of the product's harmfulness.[78–83]

Since scientific evidence does not support PMI's reduced risk claims about IQOS, they are false, misleading and/or deceptive and likely to create misperception about IQOS's health impacts, just as 'light' and 'mild' claims were found to mislead consumers.[26 27] Therefore, they are prohibited under Articles 11 and 13.

CONCLUSION

Tobacco manufacturers are using unsubstantiated claims of reduced health risks associated with their new HTPs and aggressive marketing campaigns that are especially effective among youth and adolescents to introduce and market their latest versions of supposedly 'safer cigarettes'. The companies have not provided evidence to demonstrate that these new products are actually less harmful, and there is evidence that the companies' marketing claims mislead consumers. Companies have tried to evade existing laws intended to regulate tobacco products, including HTPs, by breaking apart the products and selling the components separately.

Because the tobacco sticks can only be used when attached to the HTP heating devices, sales prohibitions, youth access and advertising and labelling laws (including FCLAA restrictions that apply to cigarettes in the USA) should apply to the complete HTP system, including all components. Loopholes in laws and regulations (including the FDA's Deeming Rule) that would allow HTPs to evade tobacco control restrictions if the holder is sold separately from the tobacco stick should be eliminated. PMI's aggressive marketing techniques for IQOS using targeted

What this paper adds

- Many tobacco companies are developing heated tobacco products (HTPs) that are being marketed with unsubstantiated claims of reduced harm compared with conventional cigarettes.
- Companies have sold the non-tobacco components of HTPs separately from the tobacco-containing components to exploit ambiguity in governments' 'tobacco product' definitions to evade tobacco control laws and public health restrictions.
- Philip Morris International has not submitted the adequate scientific evidence required by US law demonstrating that marketing IQOS in the USA would be 'appropriate for the protection of the public health', or demonstrating that IQOS is significantly less harmful to users than other tobacco products, that its labelling would not mislead consumers or that its marketing—with or without modified risk claims—would benefit the health of the population as a whole.
- The WHO Framework Convention on Tobacco Control (FCTC) provides a strong framework for parties outside the USA to enact and enforce laws to effectively regulate HTPs; parties should revise their laws to remove ambiguity and ensure that HTPs are covered by national laws.
- The USA and parties to the FCTC should ensure that all components of HTPs are regulated at least as stringently as tobacco products and are subject to all tobacco control laws that apply to other tobacco products, including restrictions on misleading labelling, advertising, promotion and sponsorship, sales to minors, price and taxation policies, and smokefree measures.

customer interventions and sophisticated technologies to capture data, monitor use and convert customers should concern privacy and public health advocates. Policy-makers in places that do not prohibit the sale of HTPs should amend or enact comprehensive tobacco control laws that ensure HTPs are captured for the purposes of all tobacco product restrictions under the TCA and FCTC measures, including smokefree laws, advertising, promotion and sponsorship, packaging and labelling, taxation, and content regulation as appropriate. Under no circumstances should HTPs be treated less strictly than combustible tobacco products.

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Tobacco Control



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Study finds heat-not-burn cigarettes no less harmful than ordinary cigarettes

koreabiomed.com/news/articleView.html

June 7, 2018

HOME Policy

Study finds heat-not-burn cigarettes no less harmful than ordinary cigarettes

The Ministry of Food and Drug Safety Thursday dispelled the misconception of heat-not-burn cigarettes being healthier than ordinary cigarettes, publishing the results of an independent study done in Korea.



The Ministry of Food and Drug Safety published study findings on heat-not-burn cigarettes that found them not less harmful than ordinary tobacco.

Heat-not-burn cigarettes, which the public has often perceived as being less harmful to health than ordinary tobacco, were found to have more tar than the latter, and have the same nicotine content, the ministry said. “There were no evidence to show heat-not-burn cigarettes to be less harmful than

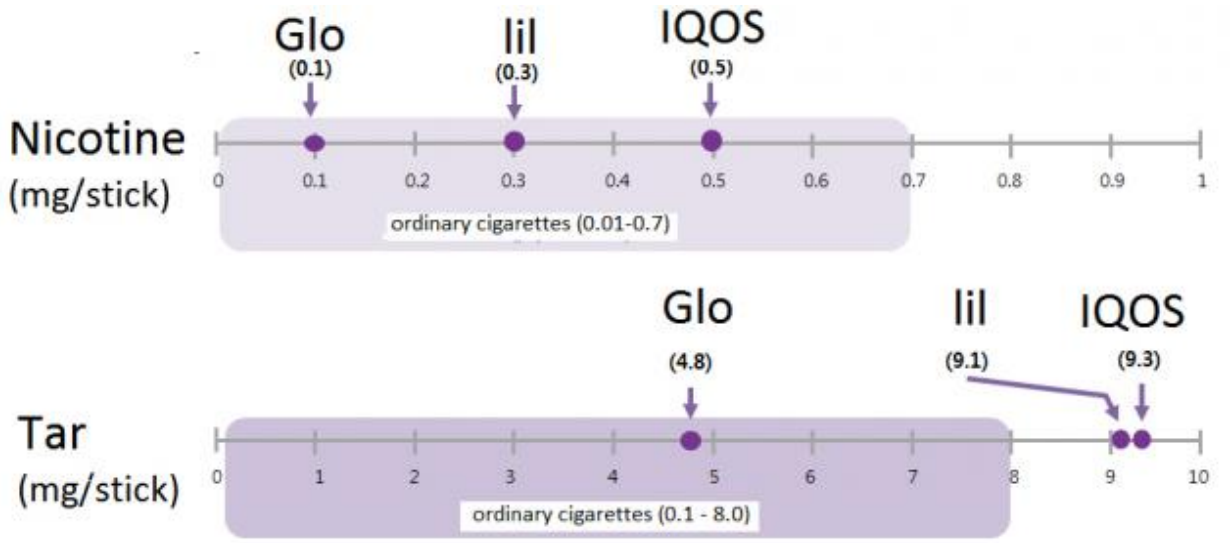
ordinary cigarettes," it added.

The study, aimed to provide correct information about heat-not-burn cigarettes substances for the public, screened six carcinogens and 11 other harmful substances, including nicotine and tar, excreted from 3 heat-not-burn cigarettes on the Korean market -- Philip Morris's IQOS, British American Tobacco's Glo and KT&G's Lil.

Researchers used the standards of the International Organization for Standardization and the method employed by Health Canada and had results verified by an independent evaluation committee composed of 11 professors, the ministry said.

Findings showed heat-not-burn cigarettes had up to five human carcinogens, including benzopyrene and benzene. The ministry pointed out that heat-not-burn cigarettes, like ordinary tobacco, can cause various illnesses, such as cancer.

Heat-not-burn cigarettes also had similar levels of nicotine as conventional products while two brands of e-cigs had higher tar content. Philip Morris' iQOS had the highest nicotine and tar levels out of the three, the ministry noted.



Source: Ministry of Food and Drug Safety

"The tar content of two heat-not-burn cigarettes was higher than ordinary tobacco, which indicates they could have other harmful substances not found in the latter," it said.

The ministry also said heat-not-burn cigarettes do not help people quit smoking as nicotine is an addictive substance. The overall harmfulness of e-cigs additionally depends on factors such as duration and amount of smoking, inhaling amount and depth as well as other smoking habits, it said.

yjc@docdocdoc.co.kr

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Korea vs. HNB cigarette makers

theinvestor.co.kr/view.php

▶주메뉴 바로가기

▶본문 바로가기

The Korea Herald

[THE INVESTOR] The Korean government has ruled that heat-not-burn cigarettes are not less harmful than conventional cigarettes. The findings appear to run counter to what the tobacco makers say.

On June 7, the Ministry of Food and Drug Safety said that HNB cigarettes contain less toxicants compared to conventional cigarettes, but that they can still cause serious diseases including cancer, and therefore it is hard to say that they are less harmful.



PMI's IQOS.

In particular, it said that two of the brands -- Philip Morris International's IQOS and KT&G.'s Lil -- release more tar than conventional cigarettes. The data showed that IQOS and Lil release 9.3 mg and 9.1 mg of tar on average,respectively, which is higher than the 0.1-8.0 mg of traditional cigarettes. British American Tobacco's Glo releases 4.8 mg of tar on average, the ministry said.

It also said that while it's impossible to compare the two types of cigarettes due to their limited sources, this also means considering that cigarettes contain more than 7,000 kinds of hazardous chemicals, HNB cigarettes may be even more harmful than meets the eye.

As of April this year, 9.4 percent of Korean smokers switched to HNB cigarettes, according to the ministry's data. Philip Morris Korea is the biggest player with up to a 60 percent market share, followed by KT&G and BAT. Below are the response from the three HNB cigarette makers and some consumers.

Phillip Morris Korea: The ministry's results are misleading. First of all, tar is a term that indicates all elements, excluding water and nicotine, that are released when burning tobacco. So it is not a synonym for "harmful component." It also can't be used as a measure for HNB cigarettes since they aren't burned to be smoked. Moreover, the quality of vapor released by HNB cigarettes and conventional cigarettes are completely different, so it's impossible to compare.

BAT Korea: Tar is not synonymous with "harmful element." It's just a term used for all the combined components produced when burning conventional cigarettes. Just because it has more tar, it does not mean it is more harmful. The ministry should have indicated specifically what elements in HNB cigarettes vapor are more harmful. Furthermore, when comparing the nine harmful elements designated by the WHO, the ministry's findings show that HNB cigarettes contain less toxicants.

KT&G: We will have to look into the ministry findings more closely. We are however, also concerned about the definition of tar, and how it should be interpreted in HNB cigarettes.



HNB cigarette smokers:

Kim Gi-woong, a Lil user says, “I switched to HNBs thinking they would be less harmful. But now it seems like the cigarette makers duped us. I don’t know what to trust.”

Lee Joo-ho, an IQOS user says, “I got more confused. The government says that it is as harmful as traditional cigarette while also saying that it contains less amount of toxicants.”

Song Eun-suk, also an IQOS user says, “Since it’s hard to figure what to trust, I guess I will just continue to smoke IQOS just because they smell less.”

'Smoking e-cigarettes just as harmful as conventional ones'

koreatimes.co.kr/www/nation/2018/12/119_259963.html

December 7, 2018



By Kim Hyun-bin

Controversy over the safety of using electronic cigarettes has stirred in the country after the government released a report stating e-cigarettes contained five harmful substances that could cause cancer. Cigarette manufacturing company Philip Morris filed a lawsuit against the Ministry of Food and Drug Safety over the report.

Some 27 countries around the world including the United States, China and Hong Kong have

some restrictions on e-cigarettes claiming they contain harmful substances. However, this is not the case in Korea where sales are through the roof, especially among young people.

According to the Ministry of Economy and Finance over 230 million packs of e-cigarettes were sold between January and September this year, making up over 9 percent of total cigarette sales. Only two million packs were sold in the second quarter of last year, but that number skyrocketed 44 fold in the second quarter of this year to 87 million.

Since Philip Morris launched its IQOS e-cigarettes in May 2017 it has sold over 32 million packs as of September this year.

But according to the government, a problem is that e-cigarettes are popular among teenagers and this popularity is spreading.

According to the Korea Centers for Disease Control and Prevention's "Young Adults' Health Condition Report," the smoking rate among middle to high school students rose to 6.7 percent from 6.4 percent last year. Some 9.4 percent of male students smoked, down from 9.5 percent in 2017. However, the female smoking rate rose from 3.1 percent to 3.7 percent in the same period.

Among both genders, 43 percent smoked e-cigarettes — more among male students than their female counterparts.
Experts say e-cigarettes are popular among teenagers as there is less of an odor compared to conventional cigarettes. Most of the students smoke discreetly as they fear getting caught by teachers and parents.

Also cigarettes are sold in most convenience stores, and the country's distribution of these has contributed to making Korea one of the top three markets for IQOS sales.

"The fact that they are easily bought in convenience stores, and there is no odor and harm done to other people are crucial factors as to why it they are so popular in Korea," an official from Philip Morris said.

Some want the government to take the initiative in banning ads in convenience stores targeting young people.

In its Framework Convention Alliance for Tobacco Control, the World Health Organization's (FCTC) recommends all member nations to ban cigarette advertisements in convenience stores.

New Zealand, England, Australia, Canada and Thailand do this and even ban the display of cigarettes on shelves.

The U.S. government has also started a crackdown on youth smoking and slapped more restrictions on products called "Juul" a liquid e-cigarette from stores, as the government deemed it easier for underage smokers to buy these from convenience stores.

A recent Washington Post report citing U.S. government statistics stated that there was a rise of 77 percent of high school students who smoke electronic cigarettes since last year and 50 percent increase for middle school students.

The IQOS has not yet met requirements to be marketed in the U.S. and China. In May 2017, Philip Morris requested the U.S. Food and Drug Administration (FDA) to approve its IQOS as a "less harmful cigarette," however, the approval has been postponed for over 18 months.

Philip Morris claims that its IQOS reduces the chances of death and contracting diseases. However, the FDA advisory committee said there was no scientific evidence proving this to be the case.

Fierce legal battle

The Ministry of Food and Drug Safety and the local unit of global tobacco giant Philip Morris is expected to face a fierce legal battle once a court hearing date is set.

Philip Morris filed a lawsuit after the ministry announced in June that five cancer-causing substances were found in heat-not-burn tobacco products sold here, with the level of tar exceeding that of conventional cigarettes.

The ministry announced the results after testing Philip Morris' IQOS, British American Tobacco's Glo and Lil from local cigarette maker KT&G Corp.
Philip Morris sued the ministry for declining to provide information on its research methods.

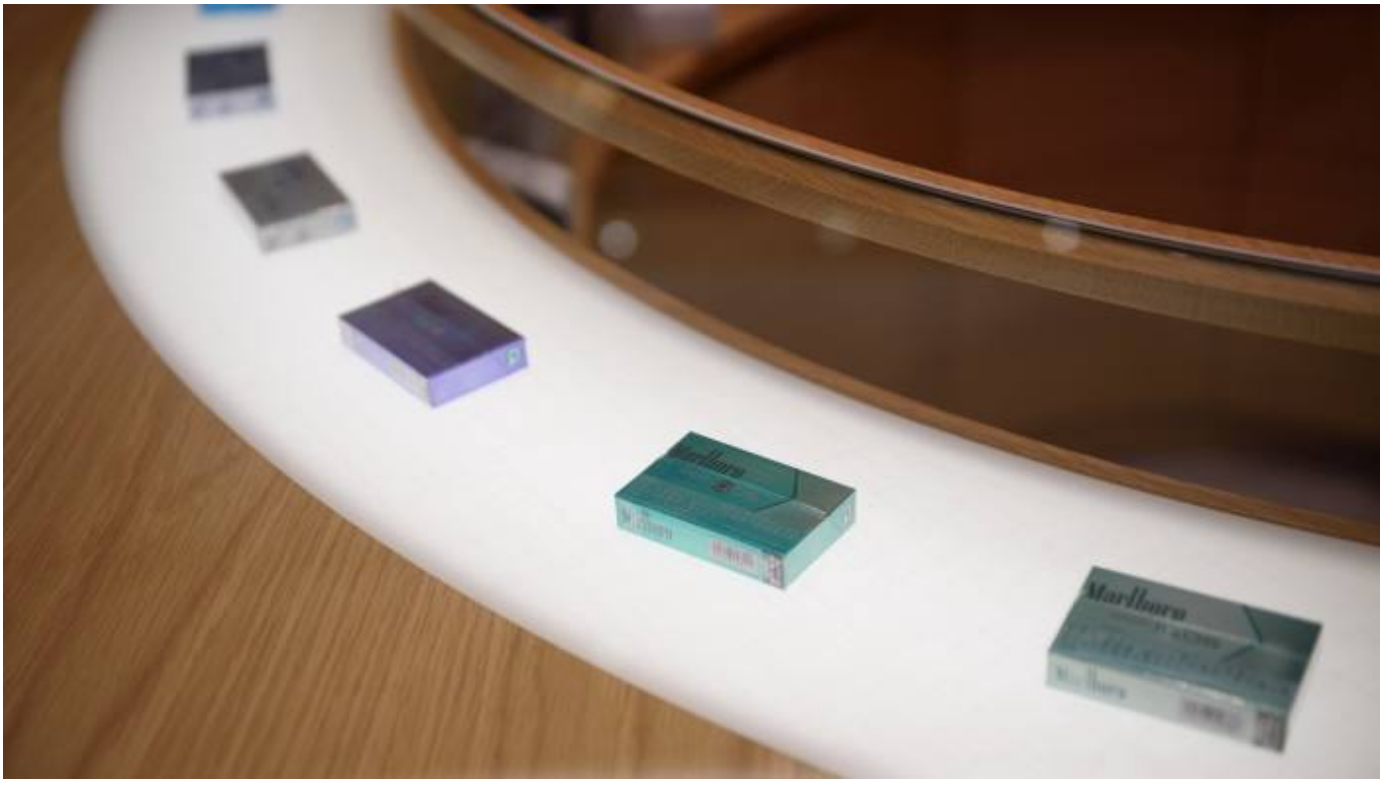
Philip Morris sues Seoul over ecigarette information disclosure

FT ft.com/content/c3a286ec-c54e-11e8-8670-c5353379f7c2

1 October 2018

Philip Morris International Inc
Lawsuit comes amid concern sales could be hit in important Asia market





Marlboro Heatstick packs made by Philip Morris © Bloomberg

Song Jung-a in Seoul

October 1, 2018
Philip Morris International has filed a lawsuit against the South Korean government, demanding the disclosure of detailed information on Seoul's recent test results of harmful substances found in electronic cigarettes.

The lawsuit against the Ministry of Food and Drug Safety follows its announcement in June that five cancer-causing substances were found in heated tobacco products, with the level of tar detected in some of them far exceeding that of conventional cigarettes.

The ministry tested heated tobacco devices including PMI's IQOS, British American Tobacco's Glo, and Lil, made by leading South Korean cigarette maker KT&G Corp.

The unusual lawsuit against the South Korean regulator underlines PMI's concern that sales of ecigarettes in one of its key markets in Asia could take a hit, right as it is struggling to convince older and more conservative smokers to make the switch.

Seeking to rebut the ministry's findings, PMI said its alternative tobacco product had lower levels of harmful substances than conventional ones, and that tar was a concept specific to cigarette smoke and should not apply to its smoke-free product.

"Because of the ministry's announcement, smokers and their relatives are confused over using alternative tobacco products that are less harmful than conventional ones," the company said in a statement on Monday.

Recommended

PMI filed the case with the Seoul Administrative Court after it said it was denied relevant information on the ministry's test results, including the experimental data and the method of analysis, even though South Korean law requires key health information to be shared with the public.

"This lawsuit is part of our effort to clear such confusion and misunderstanding by disclosing the ministry's information transparently according to the law," said Brian Kim, the company's vice-president.

The ministry declined to comment on the lawsuit.

The company behind the Marlboro brand has been betting on smokeless devices for growth as health-conscious consumers increasingly abandon traditional cigarettes. PMI touts its IQOS product by highlighting that the tobacco is heated rather than burnt, thus reducing the levels of harmful chemicals while maintaining a flavourful nicotine-containing vapour.

The cigarette-like device, which heats disposable tobacco-packed sticks, has quickly gained popularity among young smokers in South Korea. PMI has sold 1.9m units as of May this year, after launching IQOS in the country in May 2017, with about 1m South Korean smokers estimated to have switched to the smokeless product.

The global market for heated tobacco devices was estimated at $6.3bn last year, with analysts projecting an average annual growth rate of more than 20 per cent for the next five years. IQOS had 7.3 per cent of South Korea's tobacco market in the first three months of this year.

Get alerts on Philip Morris International Inc when a new story is published

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Philip Morris' IQOS cigarettes to carry risk warnings first in Korea

theinvestor.co.kr/view.php

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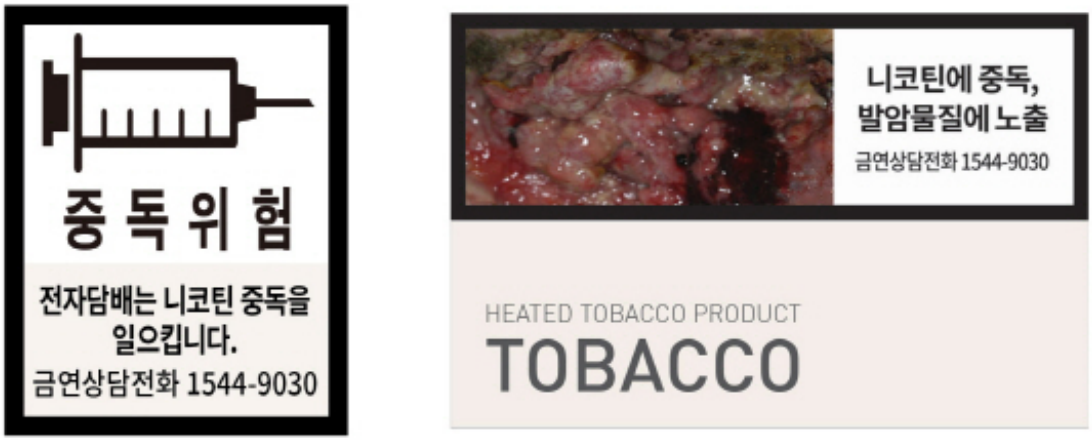
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The Korea Herald

Retail & Consumer

[THE INVESTOR] The Korean government plans to enforce heat-not-burn cigarettes like Philip Morris' popular IQOS sticks to carry a risk warning from December, reigniting disputes over the health hazards of tobacco alternatives here.

Tobacco companies immediately resisted the unprecedented decision -- the first of its kind around the world.



Korea plans to replace the current needle image (left) with a picture of cancer-ridden organs as a warning claim for HNB cigaretttes.

The Health Ministry said on May 14 graphic warnings have to be put on all cigarettes packets, including HNB products, from Dec. 23 regardless of the controversy about its effectiveness.

“Even Philip Morris’ own investigations show that harmful elements do exist in HNB cigarettes, so we are mandating a warning image on their products,” a ministry official told The Investor on condition of anonymity.

As of now, HNB products carry a needle image to warn of risks but it will be replaced with a picture of cancer-ridden organs. Before it is enforced, the ministry said it will hold public hearings to gauge different views till June 4.

If implemented, Korea will be the first country to enforce this on HNB cigarettes that the producers say contain lower levels of toxic chemicals than regular cigarettes. It has not yet been verified whether it translates into lower rates of tobacco-related diseases.

“Korea is the first country to do so. The situation is different from other countries. The decision was made based on a surging number of HNB cigarette smokers here,” the official added.

In Korea, the market share of HNB products has more than doubled to 8.6 percent from 3 percent since the first product -- Philips Morris’ IQOS -- hit the market in June last year.

“The government’s decision is not based on scientific grounds. We express serious concerns,” the Korea Tobacco Association, a lobby group consisting of KT&G, the leading Korean tobacco maker, along with international tobacco makers like Philip Morris and British American Tobacco, said in a statement.

Philips Morris which has seen a surge in sales largely due to the popular IQOS device and HEETS sticks here also expressed its concerns.

“We worry the warning images could discourage smokers from turning to HNB cigarettes that are less harmful to health,” a Philip Morris spokesperson said.

KT&G which has its own brand HB Lil, was a bit cautious about the government’s decision, saying the tobacco association’s statement does not exactly reflect its own stance. A company official declined to comment due to sensitivity of the issue.

Industry watchers say related disputes could continue for some time because Korea’s drug safety agency has not yet concluded its research on the harmfulness of HNB cigarettes. The Ministry of Food and Drug Safety started research in July last year but the results are being delayed possibly due to mixed results from around the world.

Early this year, the US Food and Drug Administration concluded that HNB cigarettes reduce exposure to harmful or potential harmful chemicals but the agency has not yet announced its findings on whether they actually reduce the risk of tobacco-related disease. The World Health Organization has said all forms of tobacco, including HNB products, use harmful ingredients and they should be subject to regulatory surveillance.

By Song Seung-hyun (ssh@heraldcorp.com)

Korea counters Philip Morris' info disclosure lawsuit

koreaherald.com/view.php

November 26, 2018

Korea counters Philip Morris' info disclosure lawsuit

By Yonhap

- Published : Nov 26, 2018 - 09:54
- Updated : Nov 26, 2018 - 09:54

South Korea's food and drug watchdog said Monday it has filed a response to Philip Morris Korea Inc.'s lawsuit over the disclosure of information on its research on harmful substances found in alternative tobacco products.

The Ministry of Food and Drug Safety said it has selected a local law firm to prepare for a legal battle with Philip Morris after filing a statement to the Seoul Administrative Court on Saturday.



IQOS (Yonhap)

The ministry and the local unit of global tobacco giant Philip Morris are expected to engage in a fierce legal battle once the court sets a hearing schedule.

The lawsuit came after the ministry said in June that five cancer-causing substances were found in heat-not-burn tobacco products sold in the local market, with the level of tar detected in some of them exceeding that of conventional cigarettes.

The ministry made the announcement after investigating Philip Morris' IQOS, British American Tobacco's Glo and lil from leading South Korean cigarette maker KT&G Corp.

Four months later, Philip Morris sued the ministry for declining its request to provide relevant information on its research results, including the method of analysis and the experimental data.

Philip Morris has claimed that its new tobacco product provides lower levels of harmful compounds than conventional ones and that the measurement of tar is an inappropriate standard to analyze the health impact of the new heat-not-burn products, whose popularity has been growing fast here.

The ministry expressed its displeasure at the lawsuit, saying Philip Morris Korea has skipped several administrative procedures to iron out differences and calling it a marketing ploy to promote its heat-not-burn tobacco brand. (Yonhap)

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JUUL electronic cigarette products linked to cellular damage

medicalxpress.com/news/2019-04-juul-electronic-cigarette-products-linked.html

APRIL 9, 2019

by University of California - Riverside



Credit: CC0 Public Domain

Little is known about the potential health effects of JUUL e-cigarette products that have recently risen in popularity, especially among adolescents. The Food and Drug Administration, or FDA, has a growing concern about this uptick in their use because these electronic cigarettes deliver nicotine—a highly addictive stimulant, with potential to affect the still-developing adolescent brain.

A research team led by Prue Talbot, a professor in the Department of Molecular, Cell and Systems Biology at the University of California, Riverside, and James F. Pankow, a professor of chemistry as well as civil and environmental engineering at Portland State University, Oregon, has now found that nicotine concentrations are higher in JUUL electronic cigarettes than in any of the hundreds of other electronic cigarette products the team analyzed.

"The nicotine concentrations are sufficiently high to be cytotoxic, or toxic to living cells, when tested in vitro with cultured respiratory system cells," said Talbot, the director of the UCR Stem Cell Center. "JUUL is the only electronic cigarette product we found with nicotine concentrations high enough to be toxic in standard cytotoxicity tests. A big concern is that its

use will addict a new generation of adolescents to nicotine."

Study results appear in *Chemical Research in Toxicology*.

JUUL e-cigarettes are made by JUUL Labs, an electronic cigarette company. JUUL use is widespread among middle and high school students.

The research team made a second finding: Although each flavor of the JUUL pod—eight different flavors are available—has relatively few flavor chemicals, several of these chemicals are present in high concentrations.

"Some JUUL flavor pods have sufficiently high concentrations of flavor chemicals that may make them attractive to youth," Pankow said. "We still need to determine if JUUL products will lead to adverse health effects with chronic use."

"We found some flavor chemicals, such as ethyl maltol, also correlate with cytotoxicity, but nicotine seems to be the most potent chemical in JUUL products, due to it very high concentration," Talbot said.

The nicotine found in JUUL products is currently, on average, about 61 milligrams per milliliter of fluid in pods—equivalent to more than one pack of conventional cigarettes.

Talbot is hopeful that the FDA will limit the permissible concentration of nicotine in electronic cigarette products.

"The FDA is trying to prevent sales of JUULs to those under 21, but these products still find their way into high schools," she said. "Our data reinforce the need to prevent adolescents from using products with these extremely high nicotine concentrations."

"Despite advertisements promoting e-cigarettes and JUUL products as smoking cessation tools, studies have shown, concerningly, that increasing use of these products among youth and adolescents can serve as gateways to tobacco and other substance abuse," said Julie Chobdee, the coordinator of the Wellness Program at UCR, who did not participate in the study.

Talbot explained that various flavor chemicals present in e-cigarette refill fluids, such as diacetyl, cinnamaldehyde, menthol, and ethyl vanillin, are popularly found in sweet, buttery/creamy and fruity/citrus e-liquids.

"Depending on their concentrations in the products, these chemicals can elicit varying toxic effects, as has been noted in case reports and laboratory studies," she said. "For example, diacetyl is a flavoring ingredient commonly found in popcorn. Inhalation of diacetyl, however, can cause a serious lung disease called bronchiolitis obliterans."

More information:
Esther E Omaiye et al, High Nicotine Electronic Cigarette Products: Toxicity of JUUL

Fluids and Aerosols Correlates Strongly with Nicotine and Some Flavor Chemical Concentrations, *Chemical Research in Toxicology* (2019). DOI: 10.1021/acs.chemrestox.8b00381

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Article

High Nicotine Electronic Cigarette Products: Toxicity of JUUL Fluids and Aerosols Correlates Strongly with Nicotine and Some Flavor Chemical Concentrations

Esther E Omaiye, Kevin J. McWhirter, Wentai Luo, James F. Pankow, and Prue Talbot

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High Nicotine Electronic Cigarette Products: Toxicity of JUUL Fluids and Aerosols Correlates Strongly with Nicotine and Some Flavor Chemical Concentrations

Esther E. Omaiye MS[†¶], Kevin J. McWhirter BS[‡], Wentai Luo PhD[‡§], James F. Pankow PhD[‡§] and Prue Talbot PhD[¶]*

[†]Environmental Toxicology Graduate Program, University of California Riverside, California, USA

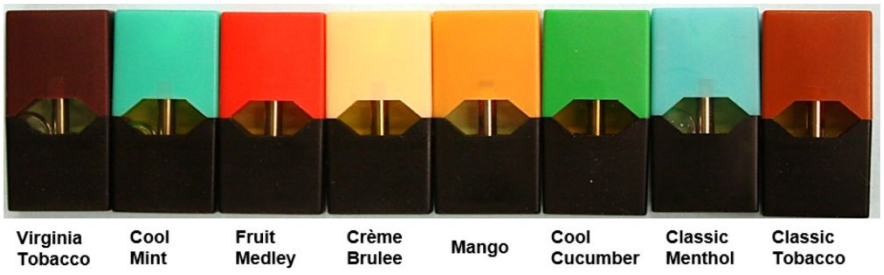
[‡]Department of Civil and Environmental Engineering, Portland State University, Portland, Oregon, USA

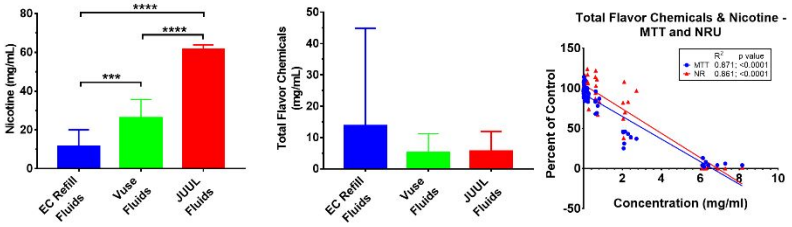
[§]Department of Chemistry Portland State University. Portland, Oregon, USA

¶Department of Molecular, Cell and Systems Biology. University of California, Riverside, California, USA

KEYWORDS. Nicotine, JUUL, EC fluids, cytotoxicity, flavor chemicals, GC-MS

For TOC Only


Virginia Tobacco
Cool Mint
Fruit Medley
Crème Brulee
Mango
Cool Cucumber
Classic Menthol
Classic Tobacco


Nicotine (mg/mL)
****
****
***
EC Refill Fluids
Vuse Fluids
JUUL Fluids
Total Flavor Chemicals (mg/mL)
Total Flavor Chemicals & Nicotine - MTT and NRU
Percent of Control
Concentration (mg/ml)
MTT 0.871; <0.0001
NR 0.861; <0.0001

ABSTRACT

While JUUL electronic cigarettes (ECs) have captured the majority of the EC market with a large fraction of their sales going to adolescents, little is known about their cytotoxicity and potential effects on health. The purpose of this study was to determine flavor chemical and nicotine concentrations in the eight currently marketed pre-filled JUUL EC cartridges ("pods") and to evaluate the cytotoxicity of the different variants (e.g., "Cool Mint" and "Crème Brulee") using in vitro assays. Nicotine and flavor chemicals were analyzed using gas chromatography-mass spectrometry in pod fluid before and after vaping and in the corresponding aerosols. 59 flavor chemicals were identified in JUUL pod fluids, and three were >1 mg/mL. Duplicate pods were similar in flavor chemical composition and concentration. Nicotine concentrations (average 60.9 mg/mL) were significantly higher than any EC products we have analyzed previously. Transfer efficiency of individual flavor chemicals that were >1 mg/mL and nicotine from the pod fluid into aerosols was generally 35 - 80%. All pod fluids were cytotoxic at a 1:10 dilution (10%) in the MTT and neutral red uptake assays when tested with BEAS-2B lung epithelial cells. Most aerosols were cytotoxic in these assays at concentrations between 0.2 and 1.8%. The cytotoxicity of collected aerosol materials was highly correlated with nicotine and ethyl maltol concentrations and moderately to weakly correlated with total flavor chemical concentration and menthol concentration. Our study demonstrates that: (1) some JUUL flavor pods have sufficiently high concentrations of flavor chemicals that may make them attractive to youth, and (2) the concentrations of nicotine and some flavor chemicals (e.g. ethyl maltol) are high enough to be cytotoxic in acute in vitro assays, emphasizing the need to determine if JUUL products will lead to adverse health effects with chronic use.

INTRODUCTION

While cigarette smoking is declining in many countries, youth and adult use of e-cigarettes (ECs) has increased.[1-3] and EC sales are estimated to reach 3.6 billion dollars in 2018.[4] To appeal to consumers and improve nicotine delivery, ECs have evolved since their introduction into world markets about 10 years ago. Although original models looked similar to tobacco cigarettes and were often termed “cig-a-likes”,[5] some highly evolved models have large tanks and batteries with features that allow power control by the user.[6]

The JUUL brand is one of the newer entries into the EC market and is more similar to the “cig-a-like” products than to recently available tank/box mod styles.[7] JUUL has spurred the development of many competing single pod style atomizers designed to be used with refill fluids containing dissolved nicotine salts.[8,9] In June 2018, in the US, it was estimated that about 68% of current EC sales are JUUL products.[10] Middle and high school students, as well as young adults, make up a large fraction of JUUL consumers.[11] This demographic may be attracted to JUUL in part because of its

appealing compact design, which resembles a USB drive, and its ability to create relatively small clouds of aerosol making its use indoors and in schools difficult to detect.[12] Unlike many other EC fluids, JUUL products contain high concentrations of nicotine and sufficient acid to protonate most of the nicotine; lower free-base nicotine levels have been associated with increased palatability on inhalation.[13-15]

The JUUL system utilizes pre-filled EC fluid “pods”, originally sold exclusively by JUUL, but now offered by third parties. JUUL currently sells eight flavors of pods, which can be characterized as minty (“Cool Mint” and “Classic Menthol”), fruity (“Mango”, “Fruit Medley” and “Cool Cucumber”), sweet (“Crème Brulee”), and tobacco (“Classic Tobacco” and “Virginia Tobacco”). In spite of their sudden surge in popularity, relatively little has been reported on the chemicals delivered by JUUL products. We have previously shown that many other EC refill fluids contain very high concentrations of flavor chemicals[16,17] and that these concentrations are cytotoxic when tested in vitro with lung cells.[17-20]

The purposes of this study were to: (1) quantify nicotine concentrations in the eight flavor versions offered by JUUL and compare to those in other EC products, (2) identify and quantify the flavor chemicals in the eight flavor pods and compare to those in other EC products, (3) determine the transfer efficiency of nicotine and flavor chemicals into aerosols, and (4) test these products for cytotoxicity *in vitro* using human lung cells.

MATERIALS AND METHODS

Purchase of JUUL Products. The five original flavors of JUUL pods and three "limited edition" flavors were purchased online from the manufacturer's USA website. These were "Cool Mint", "Crème Brulee", "Mango", "Fruit Medley", "Virginia Tobacco", "Cool Cucumber", "Classic Menthol" and "Classic Tobacco" (see Supporting Information, S1). Products were inventoried and stored at room temperature until used. Manufacturer's label information stated that each JUUL Pod flavor contained 0.7 mL of flavored fluid at 5% nicotine.

Acquisition and Sampling of EC Refill Fluids. Nicotine concentrations (>1 mg/mL) of 66 EC refill fluids were obtained from previously published data. [27,29] In addition, 103 bottles of EC

refill fluids were purchased from product lines offered by manufacturers in Nigeria and the USA (see Supporting Information, S2). Products were inventoried and stored at room temperature until analyzed.

Aerosol Production and Capture Using an Impinger Method. Each JUUL Pod was pre-conditioned by taking 3 puffs prior to weighing the pods and making aerosol solutions. Aerosol generated from pod fluids was bubbled through and captured in either isopropyl alcohol for flavor chemical and nicotine analysis or basal cell culture medium for cytotoxicity evaluation. During method development, we determined that about 96% of the flavor chemicals in the aerosol was captured in the two impingers. The aerosol materials captured in a fluid will be referred to as "aerosol" in the remainder of the paper. Aerosols produced from different pod flavors were collected at room temperature in two tandem 125 mL impingers, each containing 25 mL of isopropanol or basal cell culture medium. A JUUL EC (battery and pre-filled pod) connected to a Cole-Parmer Masterflex L/S peristaltic pump was puffed using a 4.3 s puff duration,[21] interpuff interval of 60 s, and an air flow rate of 10 – 13 mL/s. To reduce the likelihood of "dry puffing", only ¾ of the pod fluid was vaped. The pods were weighed before and after

aerosol production to collect at least 15 mg for GC/MS analysis. Aerosol solutions were stored at −20 °C until shipped to Portland State University for analysis.

For the MTT assay, 6 total puff equivalents or TPEs (1 TPE = 1 puff/milliliter of culture medium) aerosol solutions were prepared in BEAS-2B basal medium and supplements were added after aerosol production. The complete medium was passed through a 0.2 μm filter, and aliquots were stored at -80 ºC until testing. Aerosols were tested at 0.02, 0.06, 0.2, 0.6, 2 and 6 TPE. To convert from TPE to percentage of the concentration of the pod fluid, the pod weight difference before and after aerosol collection was used to obtain the mg of fluid consumed. The weight (grams) of fluid consumed/puff of aerosol was calculated, and the density of the pod fluid was determined. Then the grams/puff were converted to milliliters using the density values. Finally, the percent for concentrations used in the aerosol cytoxicity assays was determined according to the equation: (Np x Vp)/Vm where Np is the number of puffs, Vp is the volume of 1 puff, and Vm is the volume of the medium.

Identification and Quantification of Flavor Chemicals in JUUL EC Pod Fluids and Aerosols. The pre-filled pod fluid obtained prior to aerosolization of the JUUL pod is referred to as “unvaped fluid”. The fluid left in the pod after the aerosol has been collected is referred to as “vaped fluid”. Unvaped fluids, vaped fluids and aerosols were analyzed using GC/MS. For each unvaped and vaped sample, 50 µL were dissolved in 0.95 mL of isopropyl alcohol (IPA) (Fisher Scientific, Fair Lawn, NJ). All diluted samples were shipped overnight on ice to Portland State University and analyzed using GC/MS on the day they were received. A 20 µL aliquot of internal standard solution (2000 ng/µL of 1,2,3-trichlorobenzene dissolved in IPA) was added to each diluted sample before analysis. Using internal standard-based calibration procedures described elsewhere,[22] analyses for 178 flavor-related target analytes were performed with an Agilent 5975C GC/MS system (Santa Clara, CA). A Restek Rxi-624Sil MS column (Bellefonte, PA) was used (30 m long, 0.25 mm id, and 1.4 µm film thickness). A 1.0 µL aliquot of diluted sample was injected into the GC with a 10:1 split. The injector temperature was 235 °C. The GC temperature program for analyses was: 40 °C hold for 2 min; 10 °C/min to 100 °C; then 12 °C/min to 280 °C and hold for 8 min at 280 °C, then 10 °C/min to 230 °C.

The MS was operated in electron impact ionization mode at 70 eV in positive ion mode. The ion source temperature was 220 °C and the quadrapole temperature was 150 °C. The scan range was 34 to 400 amu. Each of the 178 target analytes was quantitated using authentic standard material and an internal standard compound normalized multipoint calibration.

Cell Culture. Human bronchial epithelial cells (BEAS-2B) obtained from the American Type Culture Collection (ATCC) were cultured in Airway Epithelial Cell Basal Medium from ATCC (Manassas, VA) supplemented with 1.25 mL of human serum albumin, linoleic acid and lecithin (HLL supplement), 15 mL of L-glutamine, 2 mL of extract P, and 5.0 mL airway epithelial cell supplement from ATCC (Manassas, VA). Nunc T-25 tissue culture flasks were coated overnight with basal medium, collagen, bovine serum albumin and fibronectin prior to culturing and passaging cells. At 90% confluency, cells were harvested using Dulbecco's phosphate buffered saline (DPBS) for washing and incubated with 2 mL of 0.25% trypsin EDTA/DPBS and poly-vinyl-pyrrolidone for 3 mins at 37^{o}C to allow detachment. Cells were cultured in T-25 flasks at 75,000 cells/flask,

and the medium was replaced every other day. For the in vitro assays, cells were plated at 8,000 – 10,000 cells/well in pre-coated 96-well plates and allowed to attach overnight prior to a 24-hour treatment.

Cell Viability and Cytotoxicity Assays. The toxicities of unvaped and vaped pod fluids and their resulting aerosol fluids were determined using three assays. Treatments were performed over 3-fold dilutions with the highest concentration being 10% for the fluids and 6 TPE solutions for the aerosols, which ranged from 1.3 to 3%. Serial dilutions in culture medium were arranged in 96-well plates with negative controls placed next to the highest and lowest concentration to check for a vapor effect.[18] Cells were exposed for 24 hours before performing the MTT 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), Neutral Red Uptake, (NRU) and Lactate Dehydrogenase (LDH) assays.

The MTT cytotoxicity assay measures mitochondrial reductases which convert the water soluble MTT salt to a formazan that accumulates in healthy cells. Post 24-hours of treatment, 20 µL of MTT (Sigma-Aldrich, St Louis, MO) dissolved in 5 mg/mL of DPBS

(Fisher Scientific, Chino, CA) were added to each well and incubated for 2 hrs at 37ºC. Solutions were removed, and 100 µL of dimethyl sulfoxide (DMSO) (Fisher, Chino, CA) were added to each well and gently mixed on a shaker. The absorbance of control and treated wells was read against a DMSO blank at 570 nm using an Epoch micro-plate reader (Biotek, Winooski, VT). Each chemical was tested in three independent experiments.

The NRU assay measures the uptake of neutral red dye, which accumulates within the lysosomes of healthy living cells. A working solution of 4 µg of neutral red stock (4 mg NR/mL of PBS without Ca^{2}+ and Mg^{2}+) per mL of cell culture medium was prepared and incubated at 37ºC overnight to dissolve the neutral red. Following exposure of cells to treatments, all medium was removed, and cells were incubated with 150 µL of neutral red solution for 2 hours. Cells were washed with PBS and 150 µL of lysis buffer (50% EtOH/ 49% deionized H_2O/ 1% acetic acid) were added to each well and gently mixed to achieve complete dissolution. The absorbance of control and treated wells at 540 nm was recorded using an Epoch micro-plate reader (Biotek, Winooski, VT).

The LDH leakage assay measures the activity of lactate dehydrogenase released into the culture medium and is an indicator of cell death or cytotoxicity due to plasma membrane damage. Reagents and solutions were prepared using an in-house recipe developed by OPS Diagnostics (Sigma-Aldrich, St Louis, MO). 200 mM TRIS, pH 8 (22.2 g Tris-HCl and10.6 g Tris-base and 50 mM of lithium lactate (19.6 mg/mL) were prepared in water. Tetrazolium salt (INT) was dissolved in DMSO (33 mg/mL), phenazine methosulphate (PMS) was dissolved in water (9 mg/mL), and β-nicotinamide adenine dinucleotide (NAD) sodium salt was dissolved in water (3.7 mg/mL). All three reagents (INT, PMS and NAD) were used to make the INT/PMS/NAD solution. 50 µL of all reagents were added to 96-well plates followed by 50 µL of culture medium obtained from both treated and control cells. The absorbance of all wells was measured at 490 nm using an Epoch micro-plate reader (Biotek, Winooski, VT).

Statistical Analyses. All cytotoxicity assays were carried out using three independent experiments each with different passages of cells, and each experiment had triplicate points. Data were statistically analyzed with a one-way analysis of variance (ANOVA),

and each concentration was compared to the untreated control with Dunnett's post hoc test using Prism software (GraphPad, San Diego). For the nicotine concentration data, means were analyzed using an ANOVA followed by Bonferroni's post hoc test.

RESULTS

Identification of Flavor Chemicals in JUUL Pods. Fifty-nine of 178 flavor chemicals on our target list were identified and quantified in duplicates of the eight JUUL flavor pods (Figure 1). The duplicate data were generated using fluids from two different unvaped pods analyzed at different times. The total concentration of flavor chemicals in each product appears above each column. Abbreviations of JUUL pod names are on the *x*-axis, and safety classifications based on existing oral rat LD_{50} data[23] are on the *y*-axis. Within each safety classification, the chemicals are ranked from the most to least potent. Rat oral toxicity data were used for ranking because they were available for most chemicals in the heat map, while inhalation LD_{50} data were seldom available for rats or humans. Forty-three of the 59 chemicals had concentrations >0.01 mg/mL, 13 were >0.1 mg/mL, and 3 (menthol, vanillin and ethyl maltol) were >1.0 mg/mL. The

highest concentrations of menthol, vanillin and ethyl maltol in unvaped pod fluids were 15, 6.9 and 1.8 mg/mL, respectively. Duplicate pods were generally similar to each other, however, “Fruit Medley-1” contained five times the total flavor chemical concentration as its duplicate pod. The “Fruit Medley” sample at 0.3 mg/mL was similar to the “Classic Tobacco” and “Virginia Tobacco” samples, which were all lower than 0.5 mg/mL.

Nicotine and Total Flavor Chemical Concentrations in EC Products. JUUL pods contain solvents, flavor chemicals, and varying concentrations of nicotine. The nicotine concentrations in 66 refill fluids from previous studies, [27, 29] 103 EC refill fluids, 5 Vuse cartomizer fluids, and 8 JUUL pod fluids in the current study (Figure 2a) were evaluated. Nicotine concentrations in the EC fluids fell into one of three groups: (1) most products had 1.6 – 34.4 mg/mL (blue dots), (2) Vuse products had 18.9 – 38.8 mg/mL (green dots), and (3) JUUL had 59.2 – 66.7 mg/mL (red dots) (Figure 2a). The average concentration of nicotine was significantly higher in JUUL than in the other two groups (Figure 2b).

The total concentration of flavor chemicals was compared in 182 EC products (169 refill fluids, five Vuse cartomizer fluids and eight JUUL pod fluids) (Figure 2c). Concentrations in refill fluids were highly variable and ranged from 0.1 to 362.3 mg/mL. In contrast, concentrations in cartomizers and pods were similar and generally lower than in refill fluids. Vuse cartomizers had total flavor chemical concentrations ranging from 0.7 to 15.7 mg/mL, while JUUL pods ranged from 0.2 to 15.6 mg/mL.

Concentrations of Total Flavor Chemicals and Nicotine in JUUL Fluids and Aerosols.

The total concentration of flavor chemicals in unvaped pod fluids, vaped fluids, and aerosols ranged between 0.1 – 16.7, 0.1 – 14.7, and 0.1 – 9.1 mg/mL, respectively (Figure 3a). Transfer from the fluid to the aerosol was variable, but in general was over 50% efficient. Only fluids from “Cool Mint” and “Classic Menthol” pods had total flavor chemical concentrations >10 mg/mL. “Crème Brulee”, “Mango”, “Cool Cucumber” and “Fruit Medley” had total flavor chemical concentrations between 0.3 and 8.1 mg/mL, while the two tobacco flavors had negligible concentrations.

In JUUL products, nicotine concentrations averaged 60.9 mg/mL, 63.5 mg/mL and 41.2 mg/mL in unvaped, vaped, and aerosol samples, respectively (Figure 3b). Transfer efficiently for nicotine to the aerosol was between 56 – 75%.

Individual Flavor Chemicals and Transfer Efficiency. In comparison with other EC refill fluids that we have analyzed,[17] JUUL uses a small number of different flavor chemicals in their pods (Figure 4). Five of eight products had 1-2 flavor chemicals (menthol, vanillin or ethyl maltol) >1 mg/mL, and these were generally present in about equal concentrations in both unvaped and vaped fluids. Menthol was the major flavor chemical in four of the flavor pods ("Cool Mint", "Classic Menthol", "Cool Cucumber" and "Fruit Medley"), although its concentration varied with "Classic Menthol" having the highest concentration (14.9 mg/mL) and "Fruit Medley" the lowest (0.7 mg/mL). Vanillin and ethyl maltol were the major flavor chemicals in "Crème Brulee" and "Mango", respectively. "Classic Tobacco" had low levels of benzyl alcohol, while flavor chemicals were negligible in "Virginia Tobacco". These major flavor chemicals in each product

generally transferred well to the aerosol with transfer efficiencies ranging from 39 to 62%.

Cytotoxicity of JUUL Pod Fluids and Aerosols. Cytotoxicities of both fluids and aerosols were evaluated with BEAS-2B cells using the MTT, NRU, and LDH assays. Products were considered cytotoxic if they produced an effect that was 30 % less than the untreated control (referred to as the IC_{70}) in accordance with ISO protocol # 10993-5:2009(E) international standard.[24] JUUL pod fluids were cytotoxic in both the MTT and NRU assays for all pod flavors (Figures 5a-b and 5d-e). Generally, IC_{70}s and IC_{50}s were reached at fluid concentrations between 1-10% (Table 1), and all products produced a maximum effect at 10% (Figures 5a-b and 5d-e). Cytotoxicity was also observed in the MTT and NRU assays when cells were tested with JUUL pod aerosols (Figures 5c and 5f). The highest aerosol concentration of 6TPE, when converted to percentage concentration of pod fluid, ranged from 1.3% to 3.0% (Figure 5c and f). In the MTT assay, IC_{70}s for aerosols varied with different pod flavors and generally were reached between concentrations of 0.31% to a 1.8% (Table 1), which was considerably lower

than observed with the fluids. In the NRU assay, IC_{70}s were reached for five of the eight JUUL flavor pods (Table 2 and Figure 5 d and e). Aerosols from three flavors pods ("Classic Menthol", "Classic Tobacco", and "Virginia Tobacco") did not produce a significant effect. As seen in the MTT assay, aerosols were more toxic than the fluids in the NRU assay (Figures 5 a-f and Table 1 and 2).

With JUUL pod fluids and aerosols, little effect was seen in the LDH assay (Figures 5g-i), indicating that in general, fluids and aerosol treatments did not cause rupture of BEAS-2B plasma membranes.

Correlation between Nicotine Concentration, Flavor Chemical Concentration, and Toxicity. Since some flavor chemicals can cause cytotoxicity, especially at concentration >1 mg/mL,[17] linear regression analyses were performed to parse out the relative contribution of nicotine, total flavor chemicals, and individual flavor chemicals to the cytotoxicity observed with JUUL pod fluids and aerosols (Figures 6 and 7). For unvaped JUUL fluids, there was a high correlation between cytoxicity (percent of untreated control) and the concentration of nicotine plus total flavor chemicals in both the MTT (R^2

= 0.871; p<0.0001) and NRU (R^2 = 0.861; p<0.0001) assays (Figure 6a). When nicotine and flavor chemical concentrations were analyzed separately (Figures 6b and 6c), the correlation coefficient for nicotine concentrations alone versus cytotoxicity (R^2 = 0.879 for MTT) was almost equivalent to that of nicotine and flavor chemicals concentrations combined (R^2 = 0.871 for MTT). In contrast, total flavor chemical concentration alone (without nicotine) was only moderately/weakly correlated to cytoxicity (R^2 = 0.379 for MTT and 0.383 for NRU), nevertheless the correlation was significant (p<0.0001 for both MTT and NRU). The correlation between cytotoxicity and the concentrations of individual flavor chemicals found at concentrations >1 mg/mL was moderate for ethyl maltol and weak for menthol and vanillin (Figures 6d-f); nevertheless, all correlations were statistically significant (Figures 6d-f). A similar pattern of linear correlation and statistical significance was observed with vaped fluids in both the MTT and neutral assays (see Supporting Information, S2).

For JUUL aerosols, correlations between cytotoxicity and total chemicals (nicotine plus flavor chemicals) (Figure 7a), nicotine alone (Figure 7b), and ethyl maltol (Figure 7d)

were strong (R^2 > 0.75, except for two NRU R^2s which were > 0.45) and significant (all p<0.0001) (Figures 7a-b, and 7d). Flavor chemicals alone (Figure 7c) and menthol (Figure 7e) were weakly correlated to cytotoxicity (R^2 ranged from 0.099 to 0.361), while R^2 for vanillin was weak and not significant (p>0.05) (Figure 7f).

DISCUSSION

While the health complications associated with EC use are appearing in case reports and the infodemiological literature,[25,26] to date no health reports have been made for consumers of JUUL products. Nicotine concentrations were higher in JUUL pod fluids than in any of the 174 EC refill and cartomizer fluids that we have examined previously [27,29] (Figure 2a). Concentration-response curves for the JUUL fluids were remarkably similar among the flavor pods and reached a maximum effect in the MTT and NRU assays at a 10% concentration for all samples. Aerosols were more cytotoxic than fluids and reached a maximum response at concentrations between 0.2 and 1.8%%. Cytotoxicity of aerosols was strongly correlated with total chemical concentrations, nicotine concentration, and ethyl maltol concentration, which was 1.81 mg/mL in one

JUUL product. While we have previously reported that the concentrations of some flavor chemicals in some EC products are high enough to be cytotoxic,[19,20] JUUL pods are the only EC product that we have studied in which cytotoxicity can be attributed to the concentrations of both nicotine and a flavor chemical (ethyl maltol).

Only 1-2 flavor chemicals were present at concentrations >1 mg/mL in each JUUL product, similar to some refill fluids from other manufacturers that contained 1-4 flavor chemicals/product at 1 mg/mL or greater.[17] In general, the concentrations of individual flavor chemicals in JUUL products were relatively low compared to other cartomizer style EC and refill fluids.[16,17] Two exceptions were JUUL “Cool Mint” and “Classic Menthol”, which both had menthol concentrations >10 mg/mL. Others have reported that the minty flavors may be the most popular of the JUUL products,[3] which could be due to a stronger flavor imparted by their high concentrations of menthol or the effects of menthol on nicotine metabolism.[28] In contrast to the minty products, the two JUUL tobacco-flavored pods had very low concentrations of flavor chemicals. It is possible that the high concentration of nicotine and acid in JUUL pods imparts some flavor

features to the aerosol making the use of additional chemicals unnecessary in the "Classic Tobacco" and "Virginia Tobacco" pods or that the predominant aroma molecules for those flavor profiles were not included in the GC/MS target compounds. The low levels of flavor chemicals in most JUUL pods may reduce their odor, which would facilitate "stealth" use, a desirable feature among middle and high school students who vape in class or in rest rooms.[12]

The flavor chemicals that were present in JUUL pods at very low concentrations are likely co-constituents of the major flavor chemicals (i.e., menthol, vanillin and ethyl maltol) or may in some cases be added to impart subtle flavor accents. With respect to manufacturing practices, duplicate pods and packages were identical and contained similar flavor chemicals. However, during aerosol production, pods did not perform uniformly on the smoking machine, some pods produced low density aerosols, and some pods did not work at all. This inconsistency in puff production may also account for the relatively low transfer efficiencies seen with some pods.

Nicotine concentrations in the JUUL products were significantly higher than in any other EC cartomizers and refill fluids our laboratory has evaluated (total 174).[27,29] The average nicotine concentration in JUUL pods in our study (60.9 mg/mL) agrees well with our earlier report 61.6 mg/mL.[14] Other laboratories have reported similar values (56.2 mg/mL,[30] 75.6 mg/mL,[31] and 69 mg/ml [32]). The variation between labs may be due to differences in the analytical technologies used. A single JUUL pod contained more nicotine (56 - 66 mg) than a pack of cigarettes (2 mg/stick * 20 sticks = 40 mg/pack). The high concentrations of nicotine in JUUL EC is coupled to a high concentration of benzoic acid, which protonates nicotine making it less harsh when inhaled by users.[14,15] The combination of the high nicotine concentration and its protonation by benzoic acid likely facilitates JUUL use and subsequent addiction, especially of adolescent or naïve consumers of JUUL products. Concern about the potential for addiction to JUUL products is compounded by the report that only 37% of the past 30-day consumers were aware that JUUL products always contain nicotine.[33]

In contrast to nicotine, total flavor chemical concentrations were not unusually high in JUUL pods and were found over a relatively narrow range of concentrations (15.7 mg/mL being the highest). Currently marketed refill fluids, in contrast, have a much wider range of total flavor chemical concentrations with the highest we have detected being 362.3 mg/mL. Moreover, the high concentrations of flavor chemicals are cytotoxic when tested in vitro.[17] In this study, only one flavor chemical (ethyl maltol) was correlated with cytoxicity, as discussed below.

JUUL fluids and aerosols produced no significant effects in the LDH assay. Since this assay measures the release of LDH, a cytoplasmic enzyme, it is probable that treatment did not lyse cells or cause significant damage to the plasma membrane. In contrast, all pod fluids and most aerosols produced a cytotoxic response at a 10% concentration in the MTT and NRU assays. Our linear regression analysis showed that the nicotine and ethyl maltol concentrations in JUUL aerosols were high enough to account for most of the cytotoxicity observed with the MTT and NRU. Since nicotine concentrations were similar in all JUUL products and since cytoxicity can be attributed mainly to nicotine, the

concentration-response curves for JUUL fluids were all similar. In some prior work with other EC products that had lower nicotine concentrations, cytotoxicity was correlated with the flavor chemical concentration, not nicotine.[17,18,34] Ethyl maltol concentration, which was also strongly correlated with aerosol cytotoxicity, was highest in the Mango pods (1.57 mg/mL), which were more potent than “Crème Brulee” and “Virginia Tobacco” (Figures 5c, and 5f), which both had lower concentrations of ethyl maltol (0.65 mg/mL and 0.03mg/mL, respectively) (Figure 1).

In the NRU assay, the “Classic Menthol” and “Classic Tobacco” aerosol did not inhibit uptake relative to the control. This could be because the concentrations of the aerosol did not reach 10%, as they did with fluids. In addition, these were the only flavors that contained caffeine (Figure 1), which is a stimulant. The caffeine concentrations in “Classic Menthol” and “Classic Tobacco” aerosols were 0.037mM and 0.090 mM, respectively. These concentrations are similar to those reported to provide protection to cells in other models[35] and may explain our results with “Classic Menthol” and “Classic Tobacco” aerosol.

In summary, the current popularity of JUUL products has raised two major concerns for the FDA. The first is the likelihood that JUUL use, which is widespread among middle school and high school students, will addict a new generation of adolescents to nicotine. The second is that these adolescents will eventually migrate to tobacco products that may be more dangerous, such as conventional cigarettes. Our data clearly identify a third concern related to the high nicotine concentration in JUUL products, i.e., the potential for high levels of nicotine, as well as flavor chemicals such as ethyl maltol, to damage or even kill cells at the concentrations used in JUUL pods. Our exposures were acute and produced a maximal cytotoxic response that was strongly correlated with nicotine and ethyl maltol concentrations. It will be important in future work to determine if JUUL products, and other products containing nicotine salts, have adverse effects on consumers and if such effects lead to health problems with chronic use. In the meantime, the FDA could limit nicotine and flavor chemical concentrations in EC products.

ASSOCIATED CONTENT

Supporting Information

The supporting Information is available free of charge

Figure S1. Images of the eight JUUL pod flavors evaluated in this study (PDF)

Tables S1. Brand/Manufacturer and product names of 83 EC refill fluid products (PDF)

Figure S2, Relationship between cytoxicity of vaped pod fluids and concentrations of nicotine and the flavor chemicals (PDF)

AUTHOR INFORMATION

Corresponding Author

*Dr. Prue Talbot

Department of Molecular, Cell and Systems Biology, University of California, Riverside, CA.

Telephone: 951-850-7783

FAX: 951-827-4206

Email: talbot@ucr.edu

Author Contributions

PT, JFP and EO formed the concept and design of this study. Sample preparation, data collection and data processing were carried out by EO, WL, and KJM. Data were analyzed and interpreted by EO, WL, JFP, and PT. Writing and editing of the manuscript was done by EO, WL, KJM, JFP, and PT.

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TABLES

Table 1. IC_{70} and IC_{50} (mg/mL) of JUUL pod fluids and aerosols in the MTT Assay

	Unvaped Fluids		Vaped Fluids		Aerosols		
JUUL Pod Flavors[a]	**IC_{70}**	**IC_{50}**	**IC_{70}**	**IC_{50}**	**IC_{70}**	**IC_{50}**	**Highest Conc. (%)**
"Cool Mint"	0.92	2.17	0.79	1.25	0.31	0.64	2
"Cool Cucumber"	1.10	1.43	1.23	1.93	0.33	0.68	1.3
"Mango"	1.52	2.57	1.61	2.58	0.65	0.93	2.3
"Classic Menthol"	1.48	2.33	2.14	3.24	0.67	1.51	1.7
"Virginia Tobacco"	1.54	2.61	1.66	2.88	0.85	2.17	1.4
"Classic Tobacco"	1.60	2.37	1.87	3.07	0.89	1.67	1.4
"Fruit Medley"	1.52	2.70	1.35	2.00	1.01	1.42	3
"Crème Brulee"	1.03	1.97	1.27	2.06	1.80	2.90	3

a = order of pod flavors ranked according to IC_{70} of aerosols

Table 2. IC_{70} and IC_{50} (mg/mL) of JUUL pod fluids and aerosols in the NRU Assay

	Unvaped Fluids		Vaped Fluids		Aerosols		
JUUL Pod Flavors[a]	**IC_{70}**	**IC_{50}**	**IC_{70}**	**IC_{50}**	**IC_{70}**	**IC_{50}**	**Highest Conc. (%)**
"Cool Mint"	1.32	1.81	1.21	2.18	0.20	0.54	2
"Cool Cucumber"	1.65	2.55	1.70	2.77	0.42	0.68	1.3
"Mango"	3.08	3.75	1.61	3.75	0.65	0.89	2.3
"Fruit Medley"	2.29	3.50	1.35	3.11	1.39	1.98	3
"Crème Brulee"	3.68	4.88	3.75	5.07	1.52	3.23	3
"Classic Menthol"	4.28	5.09	2.14	4.30	> 1.7	> 1.7	1.7
"Classic Tobacco"	4.82	7.94	1.87	7.84	> 1.4	n/a	1.4
"Virginia Tobacco"	3.69	4.91	1.66	3.21	n/a	n/a	1.4

a = order of pod flavors ranked according to IC_{70} of aerosols

FIGURES

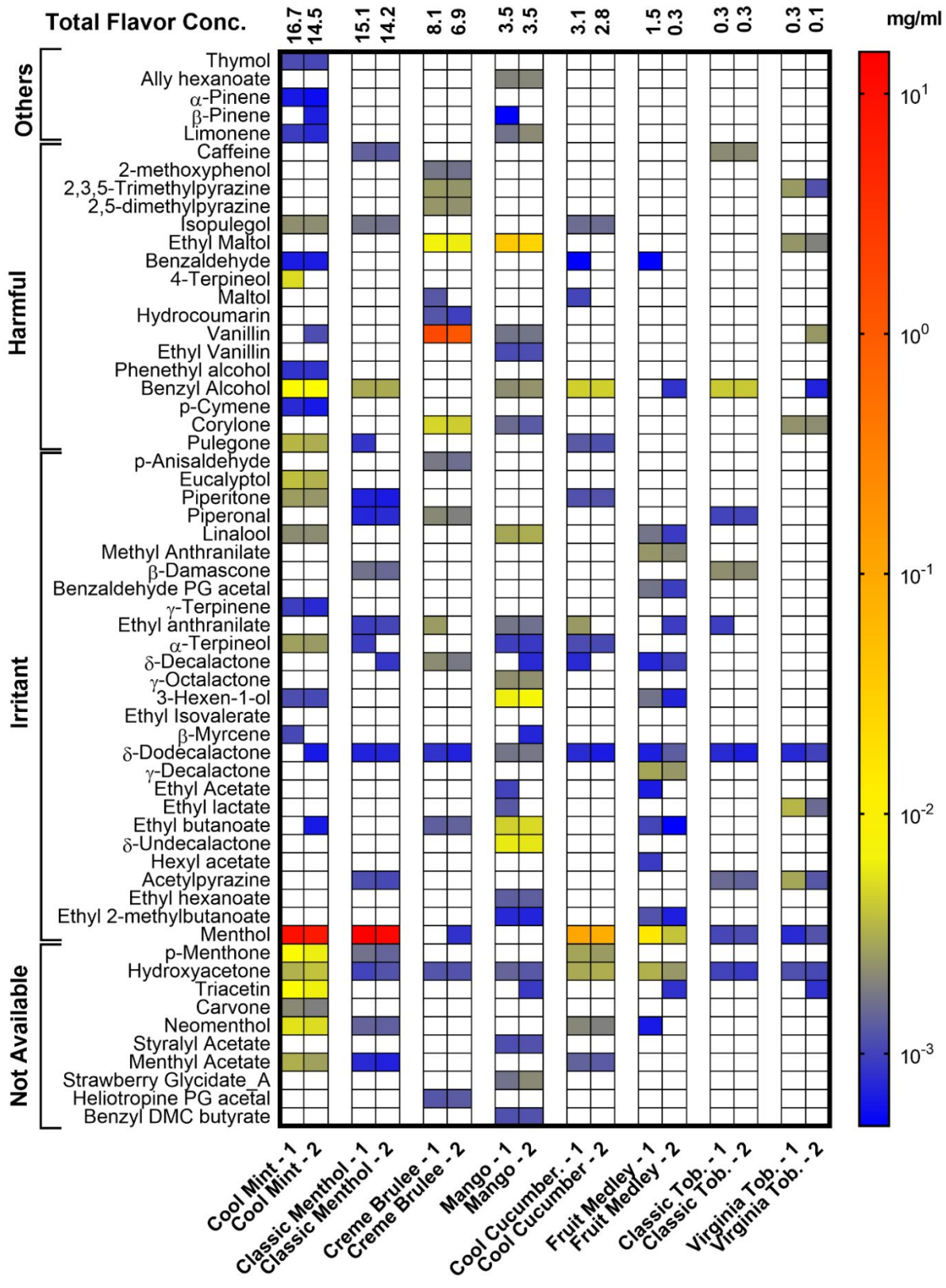

Total Flavor Conc.
16.7 14.5
15.1 14.2
8.1 6.9
3.5 3.5
3.1 2.8
1.5 0.3
0.3 0.3
0.3 0.1
mg/ml
Others
Harmful
Irritant
Not Available
Thymol
Ally hexanoate
α-Pinene
β-Pinene
Limonene
Caffeine
2-methoxyphenol
2,3,5-Trimethylpyrazine
2,5-dimethylpyrazine
Isopulegol
Ethyl Maltol
Benzaldehyde
4-Terpineol
Maltol
Hydrocoumarin
Vanillin
Ethyl Vanillin
Phenethyl alcohol
Benzyl Alcohol
p-Cymene
Corylone
Pulegone
p-Anisaldehyde
Eucalyptol
Piperitone
Piperonal
Linalool
Methyl Anthranilate
β-Damascone
Benzaldehyde PG acetal
γ-Terpinene
Ethyl anthranilate
α-Terpineol
δ-Decalactone
γ-Octalactone
3-Hexen-1-ol
Ethyl Isovalerate
β-Myrcene
δ-Dodecalactone
γ-Decalactone
Ethyl Acetate
Ethyl lactate
Ethyl butanoate
δ-Undecalactone
Hexyl acetate
Acetylpyrazine
Ethyl hexanoate
Ethyl 2-methylbutanoate
Menthol
p-Menthone
Hydroxyacetone
Triacetin
Carvone
Neomenthol
Styralyl Acetate
Menthyl Acetate
Strawberry Glycidate_A
Heliotropine PG acetal
Benzyl DMC butyrate
10^{1}
10^{0}
10^{-1}
10^{-2}
10^{-3}
Cool Mint - 1
Cool Mint - 2
Classic Menthol - 1
Classic Menthol - 2
Creme Brulee - 1
Creme Brulee - 2
Mango - 1
Mango - 2
Cool Cucumber. - 1
Cool Cucumber - 2
Fruit Medley - 1
Fruit Medley - 2
Classic Tob. - 1
Classic Tob. - 2
Virginia Tob. - 1
Virginia Tob. - 2

Figure 1. Heat map of flavor chemicals in eight duplicate JUUL pod fluids. Chemicals are ordered on the *y*-axis according to their toxicity (Others, Harmful, Irritant) based on LC_{50} data from rat oral exposures, and within each class, they are ranked from most to least toxic. The "Others" category on the *y*-axis represents chemicals that are corrosive, toxic, harmful, irritants as well as dangerous to the environment. JUUL products (*x*-axis) are ordered according to the total weight (mg/mL) of the flavor chemicals in each product with the highest concentration at the left. The total flavor chemical concentration (mg/mL) is indicated at the top of each column. The color gradient on the right shows the concentrations of the flavor chemicals in the heat map. Three chemicals (vanillin, ethyl maltol, and menthol) in the orange to red color gradient were ≥1 mg/mL in at least one product. JUUL pod code: Classic Tob. = "Classic Tobacco"; Virginia Tob. = "Virginia Tobacco". The numbers 1 and 2 with the JUUL pod codes designate the first and second pod tested.

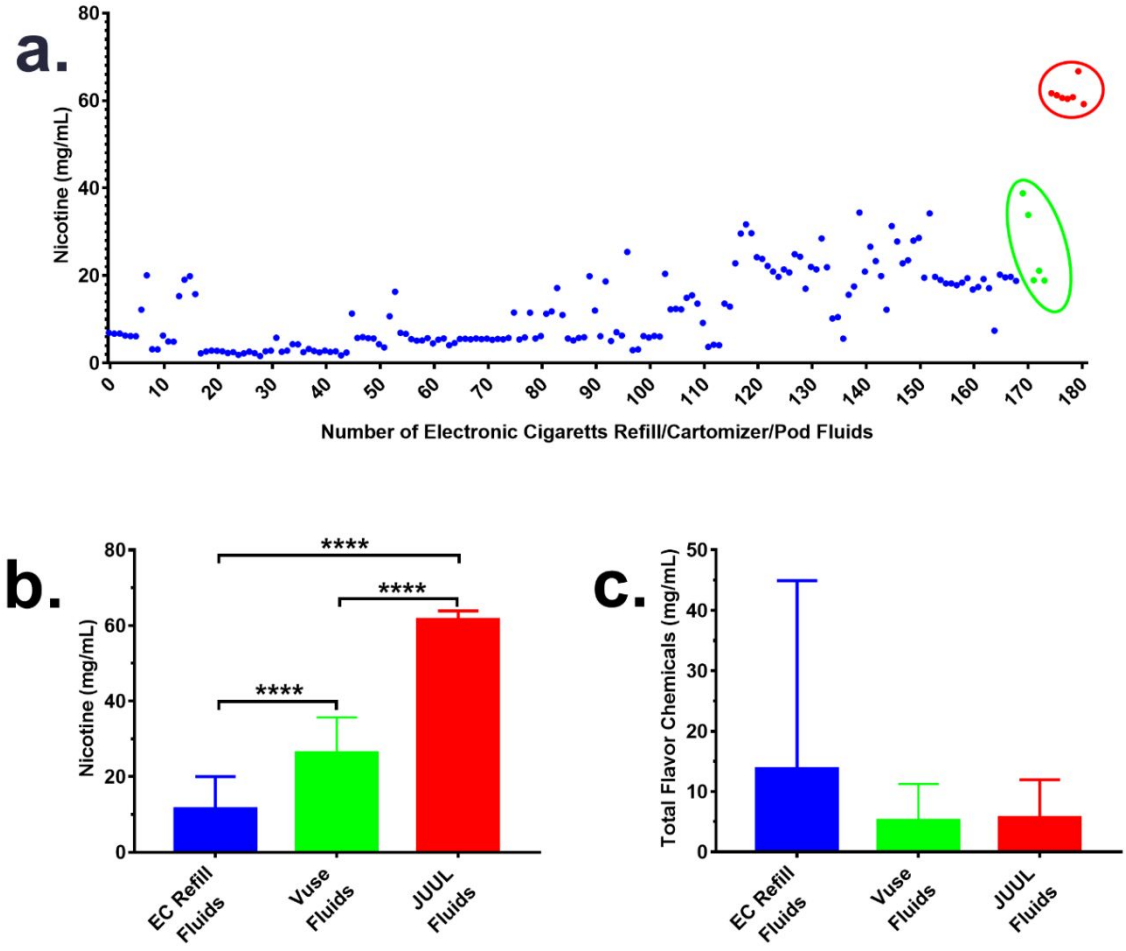


Figure 2. Nicotine and total flavor chemical concentrations in EC products. (a) Nicotine concentrations in 182 EC products. Red dots represent eight JUUL products; green dots represent 5 Vuse cartomizer fluids, and blue dots represent 169 refill fluids from 34 brands. The *y*-axis shows nicotine concentrations in each EC product listed on the *x*-axis. (b) The mean concentrations of nicotine in 169 EC refill fluids from 34 brands (blue bar), five Vuse cartomizers (green bar), and eight JUUL pods (red bar). The mean

concentrations of nicotine were significantly different in each group. **** = $p < 0.0001$. (c) The mean concentrations of total flavor chemicals in 169 EC refill fluids from 34 brands (blue bar), five Vuse cartomizers (green bar), and eight pod JUUL pods (red bar).

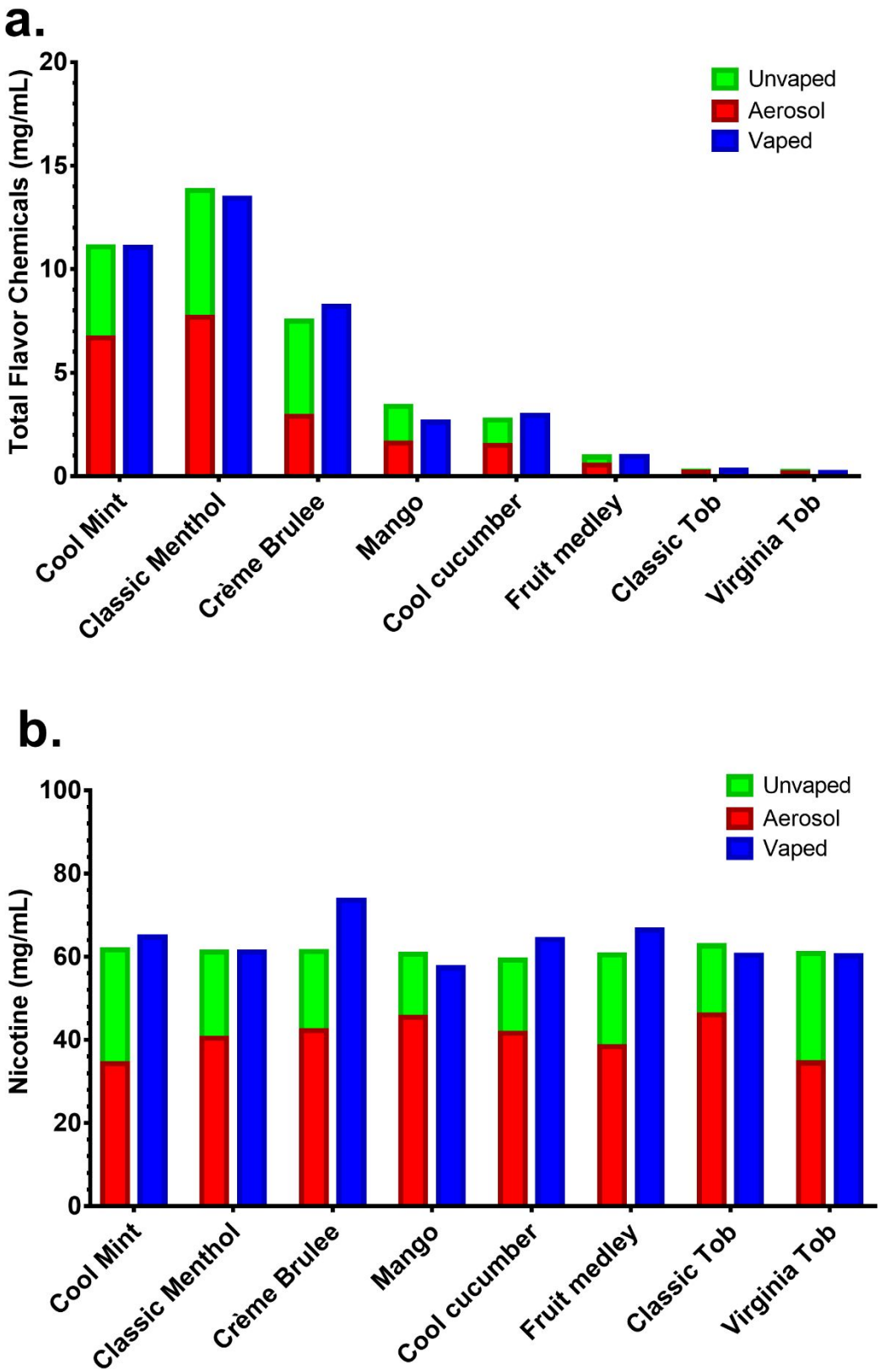

a.
Total Flavor Chemicals (mg/mL)
20
15
10
5
0
Unvaped
Aerosol
Vaped
Cool Mint
Classic Menthol
Crème Brulee
Mango
Cool cucumber
Fruit medley
Classic Tob
Virginia Tob
b.
Nicotine (mg/mL)
100
80
60
40
20
0
Unvaped
Aerosol
Vaped
Cool Mint
Classic Menthol
Crème Brulee
Mango
Cool cucumber
Fruit medley
Classic Tob
Virginia Tob

Figure 3. Total flavor chemical and nicotine concentrations in JUUL pod fluids and aerosols. (a) The total flavor chemical concentrations in unvaped pod fluids, vaped pod fluids, and aerosols. (b) Concentrations of nicotine in unvaped pod fluids, vaped pod fluids, and aerosols. The total flavor chemical concentrations and nicotine concentrations were very similar in the unvaped and vaped pod fluids. Each bar is mean concentration of two independent experiments.

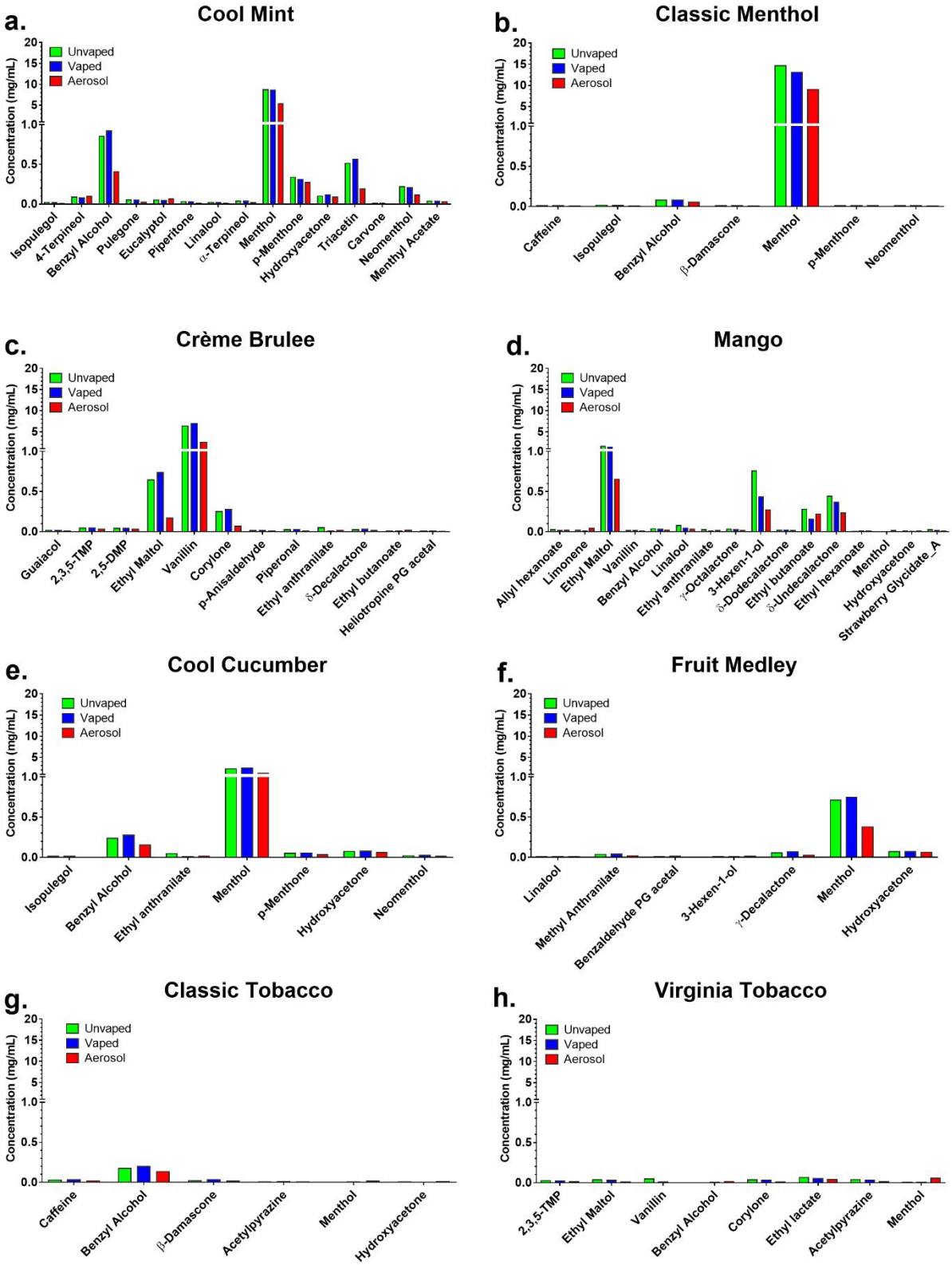

a.
Cool Mint
Unvaped
Vaped
Aerosol
Concentration (mg/mL)
Isopulegol
4-Terpineol
Benzyl Alcohol
Pulegone
Eucalyptol
Piperitone
Linalool
α-Terpineol
Menthol
p-Menthone
Hydroxyacetone
Triacetin
Carvone
Neomenthol
Menthyl Acetate
b.
Classic Menthol
Caffeine
Isopulegol
Benzyl Alcohol
β-Damascone
Menthol
p-Menthone
Neomenthol
c.
Crème Brulee
Guaiacol
2,3,5-TMP
2,5-DMP
Ethyl Maltol
Vanillin
Corylone
p-Anisaldehyde
Piperonal
Ethyl anthranilate
δ-Decalactone
Ethyl butanoate
Heliotropine PG acetal
d.
Mango
Allyl hexanoate
Limonene
Ethyl Maltol
Vanillin
Benzyl Alcohol
Linalool
Ethyl anthranilate
γ-Octalactone
3-Hexen-1-ol
δ-Dodecalactone
Ethyl butanoate
δ-Undecalactone
Ethyl hexanoate
Menthol
Hydroxyacetone
Strawberry Glycidate_A
e.
Cool Cucumber
Isopulegol
Benzyl Alcohol
Ethyl anthranilate
Menthol
p-Menthone
Hydroxyacetone
Neomenthol
f.
Fruit Medley
Linalool
Methyl Anthranilate
Benzaldehyde PG acetal
3-Hexen-1-ol
γ-Decalactone
Menthol
Hydroxyacetone
g.
Classic Tobacco
Caffeine
Benzyl Alcohol
β-Damascone
Acetylpyrazine
Menthol
Hydroxyacetone
h.
Virginia Tobacco
2,3,5-TMP
Ethyl Maltol
Vanillin
Benzyl Alcohol
Corylone
Ethyl lactate
Acetylpyrazine
Menthol

Figure 4. Concentrations of individual flavor chemicals in JUUL pod fluids and aerosols. (a) “Cool Mint”, (b) “Classic Menthol”, (c) “Crème Brulee”, (d) “Mango”, (e) “Cool Cucumber” (f) “Fruit Medley”, (g) “Classic Tobacco”, and (h) “Virginia Tobacco”. Most fluids contained 1-2 flavor chemicals >1 mg/mL, except the tobacco flavored products, which had very low concentrations of flavor chemicals. Flavor chemicals >1mg/mL transferred from unvaped pod fluids into the aerosols with 39 to 62% efficiency. Each bar is the mean concentration of two independent experiments.

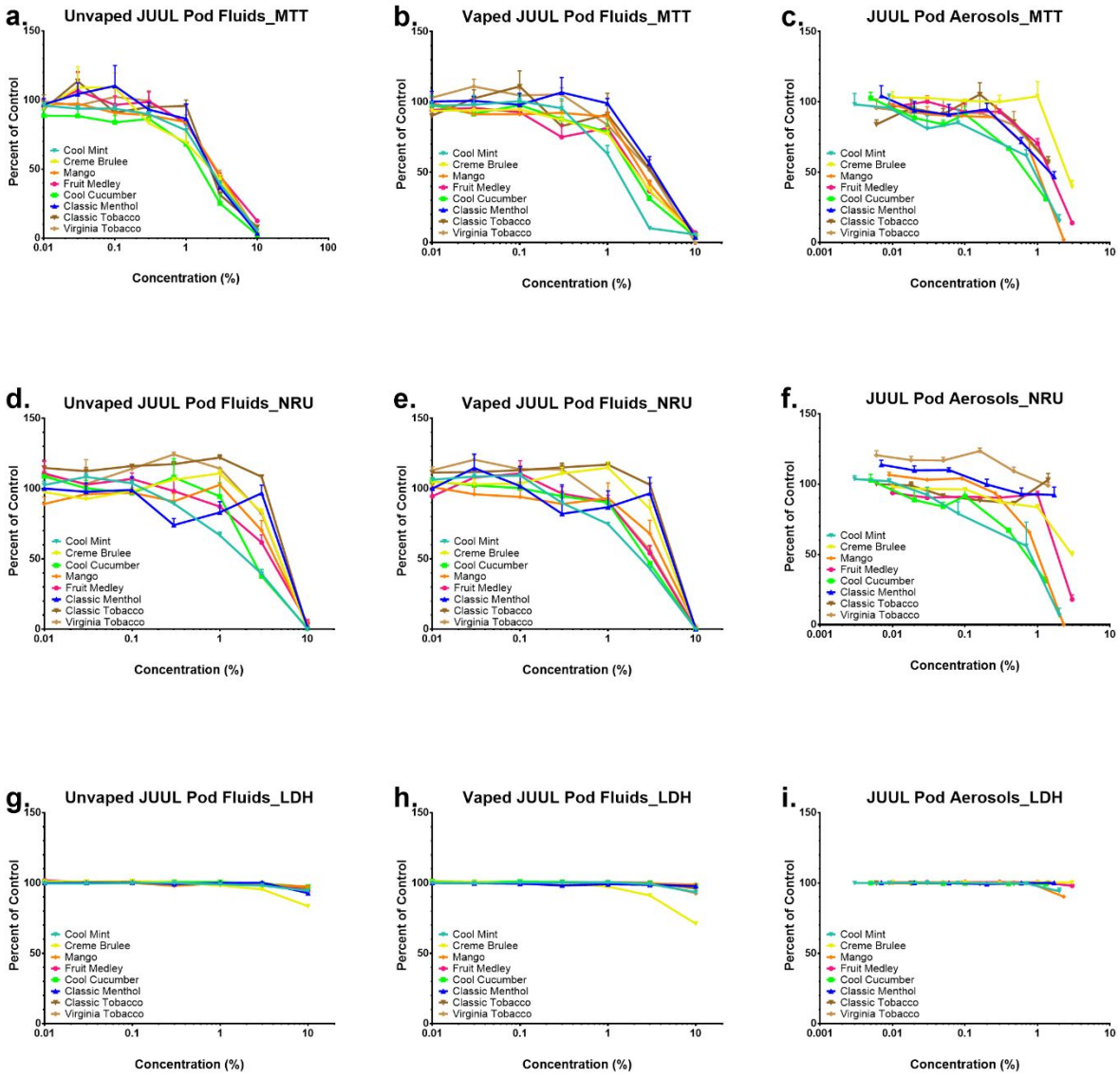


Figure 5. Concentration-response curves for BEAS-2B cells treated with JUUL pod fluids and aerosols. (a-c) MTT assay, (d-f) NRU assay, and (g-i) LDH assay for all eight pod variants. The *y*-axis shows the response of cells in each assay as a percentage of the

untreated control. Each point is the mean ± standard error of the mean for three independent experiments.

Relationships between Chemicals and Cytotoxicity of Unvaped Pod Fluids

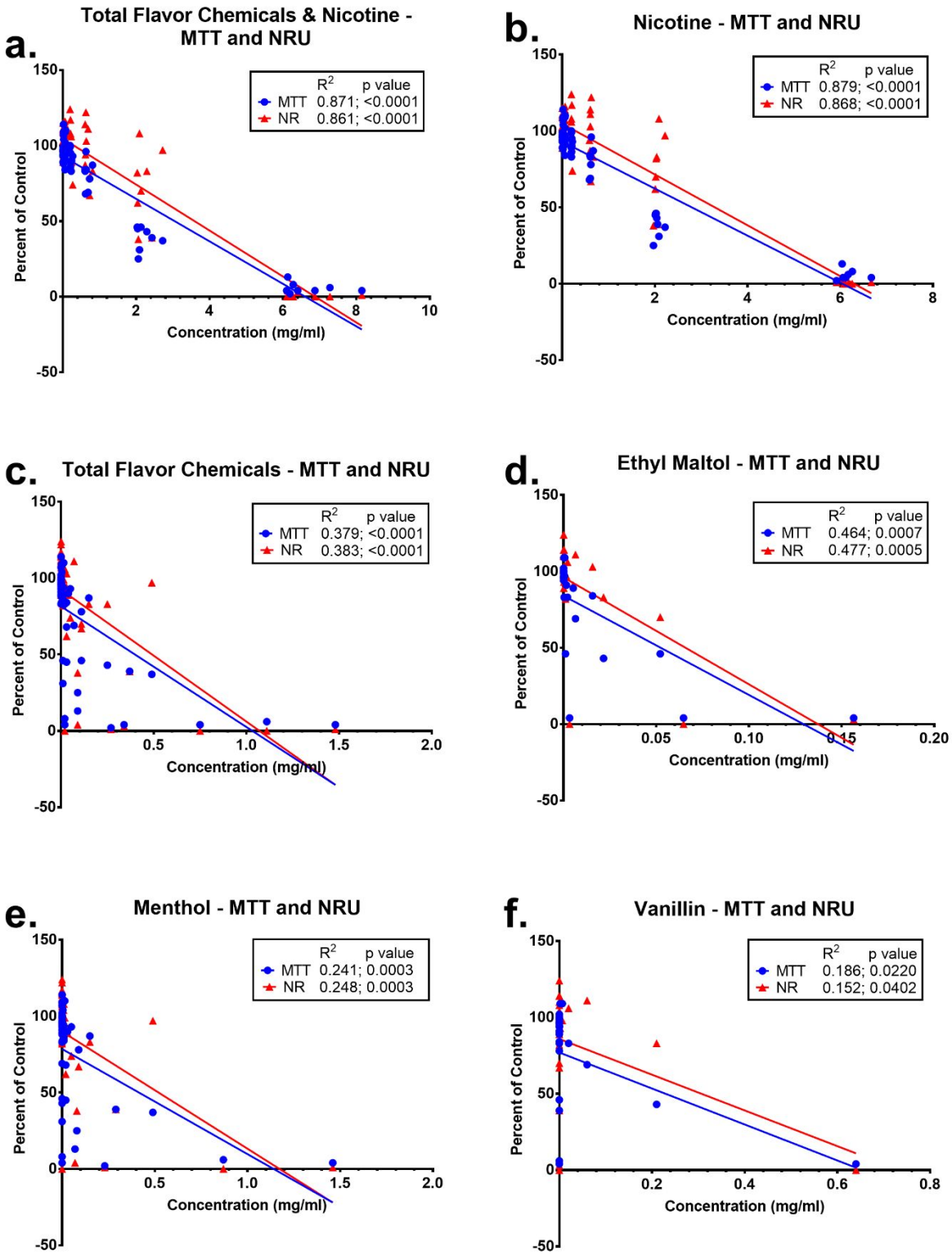


Figure 6. Relationship between cytoxicity of unvaped pod fluids and concentrations of nicotine and the flavor chemicals. Linear regression analysis for cytotoxicity (*y*-axis, expressed as a percentage of the untreated control) in the MTT and NRU assays versus the concentrations of: (a) total flavor chemicals and nicotine, (b) nicotine only, (c) total flavor chemicals only, (d) ethyl maltol, (e) menthol, and (f) vanillin. Blue dots and red triangles represent concentrations tested in the MTT and NRU assay, respectively. Cytotoxicity was strongly correlated with total concentration of chemicals (flavor chemicals and nicotine) and with nicotine concentration only and weakly to moderately correlated with the concentrations of total flavor chemicals, ethyl maltol, menthol and vanillin. All correlations were significant ($p<0.05$).

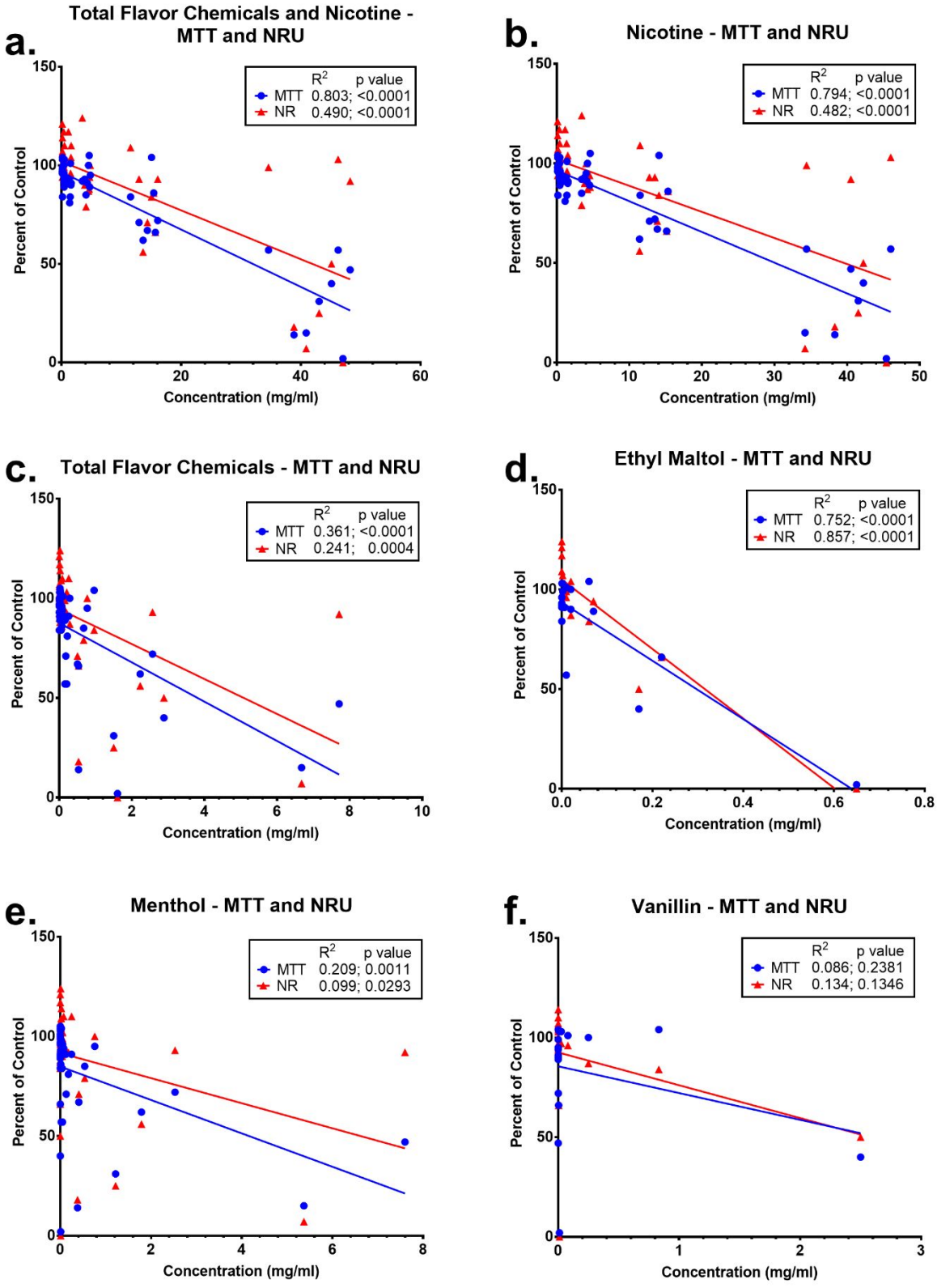

Relationships between Chemicals and Cytotoxicity of Aerosols
a.
Total Flavor Chemicals and Nicotine - MTT and NRU
R2 p value
MTT 0.803; <0.0001
NR 0.490; <0.0001
Percent of Control
Concentration (mg/ml)
b.
Nicotine - MTT and NRU
R2 p value
MTT 0.794; <0.0001
NR 0.482; <0.0001
Percent of Control
Concentration (mg/ml)
c.
Total Flavor Chemicals - MTT and NRU
R2 p value
MTT 0.361; <0.0001
NR 0.241; 0.0004
Percent of Control
Concentration (mg/ml)
d.
Ethyl Maltol - MTT and NRU
R2 p value
MTT 0.752; <0.0001
NR 0.857; <0.0001
Percent of Control
Concentration (mg/ml)
e.
Menthol - MTT and NRU
R2 p value
MTT 0.209; 0.0011
NR 0.099; 0.0293
Percent of Control
Concentration (mg/ml)
f.
Vanillin - MTT and NRU
R2 p value
MTT 0.086; 0.2381
NR 0.134; 0.1346
Percent of Control
Concentration (mg/ml)

Figure 7. Relationship between cytoxicity of pod aerosols and the concentrations of nicotine and the flavor chemicals. Linear regression analysis for cytotoxicity in the MTT and NRU assays versus the concentrations of: (a) total flavor chemicals and nicotine, (b) nicotine only, (c) total flavor chemicals only, (d) ethyl maltol, (e) menthol, and (f) vanillin. Blue dots and red triangles represent the concentrations tested in the MTT and NRU assay. Cytotoxicity (percent of control) was strongly correlated with the total concentration of chemicals (flavor chemicals and nicotine), nicotine concentration only, and ethyl maltol concentration. The correlations between cytotoxicity and the concentrations of total flavor chemicals and menthol were moderate and weak, respectively. The correlation between cytotoxicity and vanillin concentration was not significant.

Doctors Raising Eyebrows Over New Electronic Cigarette Ads

nbclosangeles.com/investigations/Troubling-Medical-Claims-in-Smokeless-Tobacco-Ads-by-Juul-509664401.html

By Lolita Lopez and Joshua Underwood-Davis

NBC4 I-TEAM

Vaping Company's Ads Under Fire

As more teens are vaping more than ever before, there's new scrutiny about the biggest player in the vaping game - Juul. Some say the company's latest advertisements may be making troubling medical claims. The I-Team found those claims have some health experts concerned. Investigative reporter Lolita Lopez explains for NBC4 News at 11 p.m. on Wednesday, May 8, 2019.

(Published Thursday, May 9, 2019)

As more teens are vaping than ever before, there's new scrutiny about the biggest player in the vaping game — Juul.

Some say the company's latest advertisements may be making troubling medical claims that the NBC4 I-Team found have some health experts concerned. The campaign is called "Make the Switch" and the ads are running on the Internet, TV and radio, featuring adults who currently smoke.

But some medical professionals are questioning the ads, asking if the ads imply that Juul can help people stop using cigarettes.

"If you're going to make a medical claim, we have laws about that," said Dr. Michael Ong, of the CA Tobacco Education & Research Oversight Committee.

LA City Cracks Down on Flavored Tobacco

A crackdown may be coming on flavored tobacco being sold to young people in Los Angeles. Lolita Lopez reports for the NBC4 News on Wednesday, April 10, 2019.

(Published Wednesday, April 10, 2019)

Ong says those laws would require clinical testing that vaping products haven't been subjected to. Ong says he thinks it's walking a fine line.

"I do think that it's problematic and that it does need more scrutiny to be determined is this truly a medical claim or not," he said.

In a statement to the NBC4 I-Team, Juul said it's "a switching product" and "not intended to be used as cessation products, including for the cure or treatment of nicotine addiction ..."

Teens Don't Realize How Much Nicotine They're Vaping: Study

Medical professionals aren't the only ones raising their eyebrow at these new ads. It's been decades since commercials aired featuring characters like the Marlboro Man.

The ads were banned from TV and radio more than 30 years ago, under the Public Health Cigarette Smoking Act.

"Probably about 70 or 80 percent of people alive today in America have probably never seen a tobacco ad on television," said Dr. Stanton Glantz, of the Center for Tobacco Control Research & Education.

Beverly Hills Moves Ahead With a Plan to Outlaw All Tobacco Sales

Glantz says the law hasn't caught up with technology.

"The definition of a cigarette is tobacco wrapped in paper," he said. "And Juul is not a cigarette. That means these ads are fair game."

They've been effective.

Juul is currently worth nearly $40 billion, getting a big financial boost at the end of last year from Altria, the makers or Marlboro.

"I think Juul's future really depends on what the public and the public health authorities do," Glantz said. "I think left unrestrained they're going to spread all over the world very quickly and they're gonna make a ton of money."

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AdChoices

NORTH CAROLINA v. JUUL LABS, INC.

Superior Court of Durham County

INTRODUCTION AND SUMMARY

Nicotine, which is highly addictive, is a neurotoxin — meaning it is poisonous to the human brain. The brains of teenagers are particularly vulnerable to nicotine and have what one study describes as "exquisite sensitivity" to nicotine's neurotoxic effects. Even small and brief exposures to nicotine can cause lasting neurobehavioral damage in adolescents.[1] When a teenager gets addicted to nicotine, it makes it much more likely that he or she will later become a user of traditional cigarettes or illegal drugs.[2]

Distributing e-cigarettes to minors is illegal in North Carolina and most other states.[3] Despite that, within the past year, use of e-cigarettes has increased among high-schoolers by 78%, and among middle-schoolers by 48%.

[1] Yael Abreu-Villaça, et al., *Nicotine is a neurotoxin in the adolescent brain: critical periods, patterns of exposure, regional selectivity, and dose thresholds for macromolecular alterations*, 979 Brain Research 114-28 (July 25, 2003), https://www.ncbi.nlm.nih.gov/pubmed/12850578.

[2] U.S. Department of Health, and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease, Prevention and Health Promotion, Office on Smoking and Health, *E-Cigarette Use Among Youth And Young Adults: A Report of the Surgeon General — Executive Summary* (2016), https://e-cigarettes.surgeongeneral.gov/documents/2016_SGR_Exec_Summ_508.pdf.

[3] North Carolina law makes it illegal to "distribute, or aid, assist, or abet any other person in distributing" electronic cigarettes to minors. N.C. Gen. Stat. § 14-313(b).

In 2017, in North Carolina, nearly 17% of all high school students—and more than 5% of all middle-schoolers—reported using an e-cigarette within the previous 30 days.[4] National studies show that the situation got even worse during 2018, with "alarming increases" in reported tobacco use among both middle and high school students between 2017 and 2018, primarily because of an increase in e-cigarette use.[5] Both the U.S. Surgeon General and the federal Food and Drug Administration (FDA) Commissioner have described underage use of e-cigarettes as an "epidemic."[6]

JUUL has played a central role in fostering the epidemic of e-cigarette use among youth. Over the past year, JUUL's share of the e-cigarette market has risen from 24% to 75%,[7] and its brand name is so well-known that it has

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[4] N.C. Department of Health and Human Services, Division of Public Health, Tobacco Prevention and Control Branch, *North Carolina Youth Tobacco Survey Middle & High School Fact Sheet* (2017), https://www.tobaccopreventionandcontrol.ncdhhs.gov/data/yts/docs/2017-YTS-FactSheet-FINAL.pdf.

[5] U.S. Food and Drug Administration, *Youth Tobacco Use: Results from the National Youth Tobacco Survey* (2018), https://www.fda.gov/tobacco-products/youth-and-tobacco/youth-tobacco-use-results-national-youth-tobacco-survey (content current as of June 6, 2018).

[6] U.S. Food and Drug Administration, FDA News Release: *FDA takes new steps to address epidemic of youth e-cigarette use, including a historic action against more than 1,300 retailers and 5 major manufacturers for their roles perpetuating youth access* (Sept. 12, 2018), www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm620184.htm*; see also* U.S. Department of Health and Human Services, Public Health Service, Surgeon General's Advisory on E-cigarette Use Among Youth (Dec. 18, 2018), https://e-cigarettes.surgeongeneral.gov/documents/surgeon-generals-advisory-on-e-cigarette-use-among-youth-2018.pdf.

[7] Truth Initiative, *Behind the Explosive Growth of JUUL* (Jan. 3, 2019), https://truthinitiative.org/news/behind-explosive-growth-juul.

become a verb (i.e., "Juuling," also known as "vaping," means to use an e-cigarette).

JUUL has long claimed that its e-cigarettes are intended only for adult smokers seeking to transition away from traditional cigarettes, even though it has not sought nor has the FDA granted a designation as an approved smoking cessation device. But the facts tell a very different — and sobering — story: teens aged 15 to 17 are far *more* likely to use JUUL than JUUL's supposed target demographic of 25- to 34-year-olds.[8]

It is no accident that JUUL has achieved such striking success in attracting underage users. JUUL's popularity among teens is the predictable result of JUUL's youth-focused business strategy. That strategy drove the development and design of JUUL's products, the ways in which they were marketed, and their methods of delivery.

In developing its e-cigarette products, JUUL deliberately designed the flavors, the look, and even the chemical composition of the e-cigarettes to appeal to youthful audiences, including minors. Belying its claimed "corporate mission" of helping experienced smokers wean themselves from traditional cigarettes, JUUL developed dessert- and fruit-like flavors

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[8] Truth Initiative, *The Youth E-Cigarette Epidemic: 5 Important Things to Know* (Nov. 14, 2018), https://truthinitiative.org/news/youth-e-cigarette-epidemic-5-important-things-to-know.

calculated to introduce tobacco in an appealing way to non-smokers, especially young people. To further ease new smokers into the habit, JUUL manipulated the chemical content of its e-cigarettes to make the vapor less harsh on the throats of young and inexperienced smokers. JUUL also created a sleek design for its smoking device that it knew would be attractive to young people, in part because it is easily concealable.

JUUL's focus on youth is also evident in its marketing. JUUL has consciously chosen social media platforms and marketing channels that are known to attract minors, has used models who look like teenagers or very young adults, and has sought out and paid youth-oriented sponsors and "influencers" popular among teenagers to spread the popularity of JUUL's youth-focused brand identity among the young.

After knowingly creating an e-cigarette product that appeals to minors and knowingly marketing that product in a way that attracts minors, JUUL pursued a sales strategy with a strong emphasis on internet-based sales, where the seller does not typically see the customer face-to-face and cannot directly confirm her age. In selling e-cigarettes online, JUUL has relied on age-verification techniques that it knows are ineffective, and has been slow to change its techniques, despite evidence that they are not working, in an effort to avoid creating "friction" with customers. In some instances, JUUL's management has encouraged its employees to actively avoid "digging around"

to ensure that underage users were not purchasing JUUL products. Because of JUUL's lackadaisical—and, at times, willfully blind—approach to age verification, enormous numbers of underage users have easily obtained JUUL products, often simply by ordering them online.

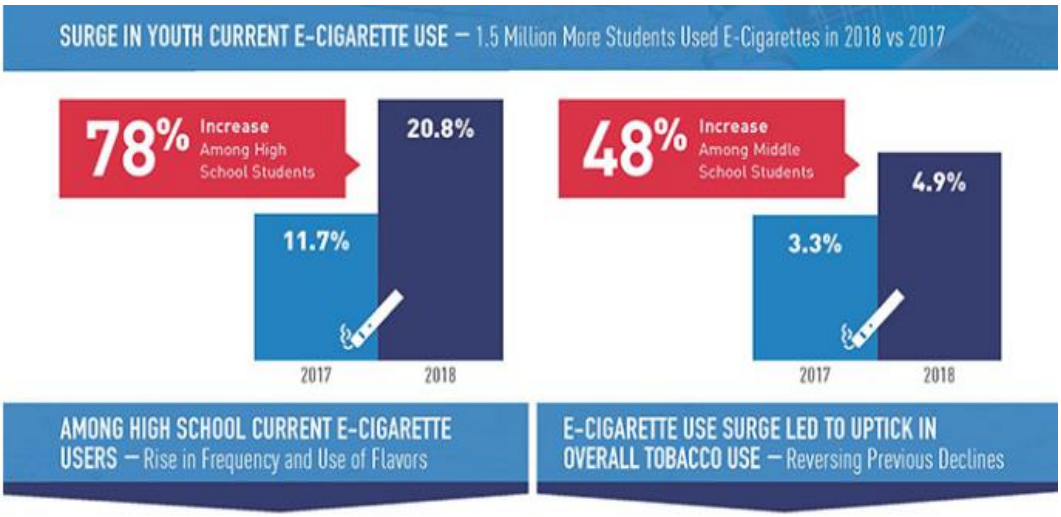
In a remarkably short span of time, JUUL has marketed, sold, and delivered millions of e-cigarette products to minors, helping reverse the historic decline in teen tobacco use that had occurred over the previous two decades. From 2000 to 2017, cigarette use among teens dropped from 28% to just above 5%.[9] But in 2018, due in large part to JUUL, there were 1.5 million new underage e-cigarette users.[10] Now, 27.1% of high school students and 7.2% of middle school students use tobacco products.[11]

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[9] U.S. Department of Health & Human Services, Office of Adolescent Health, *Adolescents and Tobacco: Trends* (2018), https://www.hhs.gov/ash/oah/adolescent-development/substance-use/drugs/tobacco/trends/index.html (content current as of May 1, 2019).

[10] A. LaVito, *CDC blames spike in teen tobacco use on vaping, popularity of Juul*, CNBC (Feb. 11, 2019), https://www.cnbc.com/2019/02/11/e-cigarettes-single-handedly-drives-spike-in-teen-tobacco-use-cdc.html.

[11] U.S. Food and Drug Administration, *2018 National Youth Tobacco Survey Finds Cause for Concern* (Nov. 2018) https://www.fda.gov/media/120063/download.



2018 National Youth Tobacco Survey[12]

At the same time JUUL has pursued a youth-focused business strategy, it has also routinely understated the strength of the nicotine in its products and downplayed their health risks. JUUL entered the e-cigarette market with among the highest nicotine potency of any product, a nicotine level so high that, in some countries, it is illegal for consumers of any age. JUUL has deceived consumers about that nicotine strength, has misrepresented the nicotine equivalency of its products to traditional cigarettes, and has understated the risks of addiction that occur with such powerful levels of nicotine.

JUUL's actions—designing, marketing, and selling e-cigarettes in ways that it knows will attract minors and deceptively downplaying the potency and danger of the nicotine in its e-cigarettes—are unfair, deceptive, and

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[12] *Id.*

illegal under North Carolina law. JUUL has harmed consumers throughout this State. The Attorney General brings this action on behalf of the State in an effort to put a stop to JUUL's wrongful actions and to hold JUUL accountable for them.

REQUEST FOR RELIEF

The State requests that the Court:

1. Preliminarily and permanently enjoin JUUL, its officers, directors, employees, and agents, and all those acting in concert with them, as follows:
    a. JUUL shall not offer, sell, deliver, or in any manner provide e-cigarette products to minors within this State.
    b. JUUL shall not facilitate, assist, or enable any individual or entity in offering, selling, delivering, or in any manner providing e-cigarette products to minors within this State.
    c. JUUL shall not offer, sell, deliver, or in any manner provide e-cigarette products within this State in any flavors other than tobacco or menthol through online sales.
    d. JUUL shall not facilitate, assist, or enable any individual or entity in offering, selling, delivering, or in any manner

providing e-cigarette products within this State in any flavors other than tobacco or menthol through online sales.

e. JUUL shall not engage in or participate in any marketing or advertising activities within this State, including on social media accessed within this State, involving e-cigarette products that are intended to or are known to be likely to appeal to minors, nor shall JUUL retain, facilitate, assist, enable, or encourage any other person or entity to engage or participate in such marketing or advertising activities within this State. Accordingly, JUUL, without limitation, shall not:

    i. Send marketing emails to any minors within this State;

    ii. Advertise outdoors (including window advertisement visible from the street or sidewalk) within 1,000 feet of schools and playgrounds in North Carolina;

    iii. Sponsor sports, entertainment, or charity events held in North Carolina;

    iv. Provide free or discounted samples, starter kits, or

e-cigarette products to consumers. In addition, JUUL may not provide automatic renewals or bulk orders to recipients less than 18 years of age;

v. Advertise in any fashion in media or outlets that primarily target or serve consumers under 30 years of age.

f. Within 30 days of entry of this order, JUUL shall produce to the State a confidential database containing all customer-related information, including but not limited to names, addresses, email addresses, telephone numbers, and any other information in JUUL's possession regarding any individual consumer that is under age 18 or that JUUL is unable to confirm is at least 18 years of age. Within 10 days of providing such information to the State, JUUL shall permanently delete all such information in its possession, including but not limited to all account information on JUUL's website and inclusion of such individuals on JUUL's email marketing lists.

g. JUUL shall not offer, sell, deliver, or in any manner provide e-cigarette products within this State that describe the nicotine potency of such products as calculated by

weight rather than by volume, or in a manner that misrepresents the nicotine potency of e-cigarette products as compared to combustible cigarettes.

h. JUUL shall not facilitate, assist, or enable any individual or entity in offering, selling, delivering, or in any manner providing e-cigarette products within this State that describe the nicotine potency of such products as calculated by weight rather than by volume or that misrepresents the nicotine potency of e-cigarette products as compared to combustible cigarettes.

2. Award civil penalties to the State from JUUL pursuant to N.C.G.S. § 75-15.2;

3. Disgorge JUUL's profits from its unfair or deceptive acts and practices to the State;

4. Award the State its costs, including a reasonable attorneys' fee, incurred by the investigation and litigation of this matter pursuant to N.C.G.S. § 75-16.1; and

5. Any and all further legal and equitable relief as the Court deems the State is entitled to receive.

Article from The Hong Kong Institute of Allergy www.medscape.com

Tobacco Companies Forced to Admit That Smoking Is Deadly

Roxanne Nelson, RN, BSN

November 28, 2017

Major US tobacco companies are finally having to admit that they have been deceiving the public about the dangers of tobacco.

Tobacco companies have been ordered by the courts to begin publishing "corrective statement" advertisements in major news outlets based in the United States.

The advertisements, which began running on November 26, will have to explain the adverse health effects of smoking and second-hand smoke, along with other topics.

However, the statements not only will focus on the health problems associated with tobacco use but will also require companies to admit that they "intentionally designed cigarettes with enough nicotine to create and sustain addiction."

These "corrective" statements must be disseminated via television and newspaper advertisements, and a schedule for the topic and dates of presentation has been set up.

"The most important thing about these ads is that they remind the public and policymakers that the tobacco industry is a rogue industry, build on a mountain of lies," said Vince Willmore, vice president of communications at Campaign for Tobacco-Free Kids. "They are a reminder that the horrific toll that cigarettes have taken did not happen by accident and are the result of the illegal and deceitful practices of the tobacco industry."

In an interview, Willmore told *Medscape Medical News* the hope is that the corrective statements will spur elective officials to take strong corrective action.

"The main goal is to inform the public about health harms related to cigarette smoking and to inform them of the behavior of the tobacco industry and then start a conversation," he said. "There has been a lot of coverage about these statements, and that in and of itself is very beneficial in informing the public."

Long Court Process

The proposed ads are the culmination of a long-running lawsuit that the US Department of Justice filed against the tobacco companies nearly 20 years ago, in 1999. A landmark 2006 judgment and opinion by US District Judge Gladys Kessler ruled that tobacco companies had violated civil racketeering laws (RICO) and engaged in a decades-long conspiracy to deceive the public about the health effects of smoking and their marketing to children.

In her 2006 verdict, Judge Kessler ruled that the tobacco companies "have marketed and sold their lethal products with zeal, with deception, with a singleminded focus on their financial success, and without regard for the human tragedy or social costs that success exacted.... Over the course of more than 50 years, defendants lied, misrepresented and deceived the American public, including smokers and the young people they avidly sought as 'replacement' smokers about the devastating health effects of smoking and environmental tobacco smoke."

Despite their internal knowledge, the tobacco companies (from 1964 onward) continued to deny and distort the serious health effects of smoking, said Judge Kessler. Even as recently as 2005 (the year before the judgment), they still refused to admit that smoking was linked to serious health problems.

The tobacco industry was also well aware that smoking and nicotine are addictive, but they publicly denied it and "continue to do so," she ruled. They have "concealed and suppressed research data and other evidence that nicotine is addictive."

In 2006, Judge Kessler ordered the tobacco companies to publish corrective statements on the five topics about which they deliberately mislead the public:

- The adverse health effects of smoking;
- The addictiveness of smoking and nicotine;
- The lack of significant health benefits from smoking "low tar," "light," "ultra light," "mild," and "natural" cigarettes (which have been deceptively marketed as less harmful than regular cigarettes);
- The manipulation of cigarette design and composition to ensure optimum nicotine delivery; and
- The adverse health effects of exposure to secondhand smoke.

However, during the 11 years since the ruling, the tobacco companies have repeatedly filed appeals and have tried to modify and delay publication of the corrective statements. The US Supreme Court declined to hear their appeal in 2010, and the appeal process finally ended this year, with the result that the tobacco companies were ordered to begin running the corrective statement ads.

The new court-ordered advertisements for television must contain one of the five corrective statements and run five times per week for 1 year, for a total of 260 spots. The ads must run during prime time (7 to 10 pm) and on one of the three major networks.

For newspapers, tobacco companies must purchase five full-page ads in the first section of the Sunday edition of the 50+ newspapers specified by the court. These include papers published in the Hispanic media and African American/community papers. Each of the ads will contain one of the five corrective statements.

Reacting to the news, the University of Texas MD Anderson Cancer Center in Houston issued a statement applauding the action, noting that it will be a significant step toward informing Americans about the addictive power of cigarettes and the harms of tobacco use.

"Although we have made tremendous progress in terms of reducing tobacco use, the CDC [Centers for Disease Control and Prevention] recently reported that 20% of adults in the U.S. still use tobacco products," Ernest Hawk, MD, vice president and chair, Division of Cancer Prevention and Population Sciences at MD Anderson, said in a statement.

"It's clear that we must continue to educate the public about the dangers of tobacco use, and these statements will be an important part of that process," added Dr Hawk.

Big Tobacco Changing Its Stripes?

The ads are coming at time when tobacco companies are resorting to a variety of measures to thwart progress in smoking cessation and reduction.

Philip Morris International, for example, is trying to rebrand itself as part of the solution by funding the Foundation for a Smoke-Free World, as reported previously by *Medscape Medical News*. Philip Morris will provide $80 million annually over the next 12 years, and the foundation will focus on funding critical research and finding ways to speed up science-based solutions to the current public health crisis involving 1 billion smokers worldwide.

While some have applauded the measure, many experts are skeptical at what appears to be an apparent conflict of interest. In a *Lancet* editorial commenting on Philip Morris putting up the funds for this Foundation, Martin McKee, CBE, MD, DSc, from the Department of Health Services Research and Policy, London School of Hygiene & Tropical Medicine, United Kingdom, and colleagues wrote: "Anybody who believes that they really do want to see a smoke-free world is, we argue, living in a fantasy world." In its reaction to the announcement, the American Cancer Society commented that the involvement of Philip Morris in this endeavor was just "a continuation of a decades-long effort to paint over tobacco's role in spreading death and misery around the globe." The company has the power to make a difference, they noted: It should "stop selling cigarettes."

At the same time, while government health policies to control tobacco use are gaining strength globally, the tobacco industry is not about to back off that quickly.

Instead, it has produced new products to replace conventional cigarettes — electronic cigarettes (e-cigarettes), electronic nicotine delivery systems (ENDS), and novel "heat not burn" (HNB) devices. Although these products claim to be less toxic than cigarettes, no epidemiologic data are yet available on lung cancer or other diseases.

The tobacco companies "lie and pretend to be reformed…and say that they want to see people stop smoking cigarettes," commented Willmore. "But at the same time, they are trying to interfere with efforts to control the use of tobacco, and continue to aggressively market and promote their products."

More Steps Needed

In July, the US Food and Drug Administration unveiled a new comprehensive plan for regulating tobacco and nicotine that will "serve as a multi-year roadmap to better protect kids and significantly reduce tobacco-related disease and death."

Included in their plan is to begin a public dialogue about lowering nicotine levels in combustible cigarettes to nonaddictive levels. Given that 90% of smokers begin before they are 18 years old, lowering nicotine levels could decrease the likelihood of addiction as well as helping current smokers to quit.

"That would help prevent kids from getting addicted," said Willmore, "And there are a lot more steps we would like them to take, such as banning menthol cigarettes and putting graphic warnings on cigarette packs."

Smoking rates are still high in parts of the United States, he added, and in some specific populations. "We need to reduce smoking and the death and disease it causes, in all states and for all Americans."

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From: Lai Wendy [redacted]
To: bc_54_18@legco.gov.hk
Cc: "Dr. Jane Chan" [redacted]

Date: Wednesday, May 29, 2019 05:44PM
Subject: HKEJ (信報) - Dr. Jane Chan's article on 22/5/19

History: This message has been forwarded.

Dear Ms. Shiu,

Kindly pass the following message and attached file to all Legislative Councillors.

Dear the Honorable Legislative Councillors,

I would like to forward my article which was published in 信報 last Wednesday (22 May 2019) for your kind reference. It is important that Hong Kong people wisely see through the tricks played by the tobacco industry.

With all my best wishes,

Dr. Jane Chan
Specialist in Respiratory Medicine

Attachments:
香港人不要被煙草業一而而再三的欺騙_陳真光.pdf

香港人不要被煙草業一而而再三的欺騙

陳真光
呼吸系統科專科醫生

市民熟悉的傳統香煙，源於 19 世紀後期至 20 世紀初，隨工業化進展而漸成大眾商業消費品，而駱駝牌就是當時風行一時的香煙牌子。儘管早於 20 世紀 50 年代醫學文獻就已提出吸煙與肺癌的關係，，美國聯邦政府卻於 1964 年終發表公共衞生服務諮詢委員會的「吸煙與健康」報告，首次確定吸煙與特定疾病之間關連，尤具劃時代意義。隨着愈來愈多科學證據證明，吸煙足以傷害人體所有器官，煙草公司為求自保，於是群起對抗，加以否認之餘，更刻意通過種種手法誤導公眾。此後 50 年間，美國公共衞生界與煙草業互相對壘，爭辯過程漫長而激烈。雙方以下兩次法律訴訟大和解協議，尤其值得一提：

一、 1998 年，美國四大煙草公司 – 奧馳亞（Altria)、雷諾士（R.J. Reynolds）、羅瑞拉德（Lorillard）、菲莫美國（Philip Morris USA) 與美國 46 個州之間達成和解，除了同意支付所有訴訟費，並會支付與煙草相關的醫療費用，永久補償各州之內與吸煙相關病患者的醫療費用，以及限制部份營銷手段。

二、 1999 年，美國司法部對煙草公司展開另一場漫長訴訟；2006 年，美國地區法官凱斯勒作出影響深遠的裁決，判定煙草公司違反民用敲詐勒索法（RICO），以歷時數十年的陰謀，向公眾隱瞞吸煙對健康的影響，更不惜對兒童推廣和銷售其產品。

上述判決清晰指出，煙草公司以欺詐手段推廣和銷售足以致命的產品，但求賺錢，而從未考慮到大眾和社會為消費此等產品而付出的代價。在超過半個世紀的過程中，作為被告，煙草公司欺騙美國公眾，使之淪為煙民，更不惜向年輕人推銷，以填補因吸煙致病甚或致命而流失的顧客。

判詞同時提及，儘管煙草公司內部早從 1964 年已知悉吸煙之害，但仍極力否認和扭曲吸煙對健康所產生的嚴重影響。即使在 2005 年，，亦即法院作出判決前一年，煙草界仍堅持同一立場。雖然明知吸煙和尼古丁令人上癮，煙草公司仍不斷極力公開否認，更進一步隱瞞和壓制科學研究數據以及其他相關證據。

2006 年，凱斯勒法官下令煙草公司，就他們故意誤導公眾的五大重點，發表「糾正聲明」：

(1) 吸煙對健康的不良影響；

(2) 吸煙和尼古丁的成癮性；

(3) 吸食所謂「低焦油」、「淡味」、「超淡味」、「柔和」、「天然」香煙（在宣傳中聲稱比傳統香煙危害較少），對健康根本並無顯著益處；

(4) 香煙設計和成份調配，均為確保吸煙者儘可能吸入尼古丁含量的操控手法；

(5) 接觸二手煙，同樣對健康構成不良影響。

然而，裁決實施以後 11 年間，煙草公司一再提出上訴，並試圖修改、推遲發佈「糾正聲明」。2010 年，美國最高法院推翻他們的上訴，而上訴程序最終在 2017 年 11 月結束，法院下令煙草公司立即發佈「糾正聲明」廣告，內容 必須解釋吸煙和二手煙的不良影響，以及其他相關議題，並必須承認他們「故意設計、製造尼古丁含量足以維持成癮性的香煙」。 此等「糾正聲明」必須透過不同主要媒體發佈，其中電視廣告必須包含「糾正聲明」五大重點之一，須在晚上 7 時至 10 時的黃金時段，在三個指定電視台之一播出，每週播放五次，總共播出 260 次。

至於報紙方面，煙草公司必須在法院指定的 50 多份報章的週日版，以五頁整版廣告形式發佈，其中必須包含「糾正聲明」五大重點之一。此等「糾正聲明」旨在向美國人強調香煙成癮和吸煙危害健康的訊息，指出吸煙的沉重代價並非偶然，而是煙草公司以非法手段欺騙大眾的結果。

與此同時，政府監控服用煙草的衞生政策，雖然正在全球各地有所進展，但煙草公司並未知所收斂，反而積極謀求轉型，從下列各種手段即可見一斑：

1. 自稱為負責任行業

舉例來說，菲利普莫里斯國際公司（Philip Morris International）在裁決後為求改善形象，一再通過無煙世界基金會提供資金，藉以將公司

塑造成推動解決方案的持份者，措施包括為期 12 年、每年投放八千萬美元資助科研，以加快尋求解決方案進程，化解當前全球吸煙者已為數 10 億的公共衞生危機。

雖然上述措施贏得部份人讚賞，但許多專家對其中的明顯利益衝突則有所保留。

a. 聯合國大會已經意識到，「煙草業與公共衞生之間存在根本的利益衝突。」「雖然他們吹噓一些新煙草產品具備『降低危害』效能，卻繼續在世界各地銷售其致命產品，在較貧窮國家尤其如此。」
（2018 年 5 月《Chest 期刊》）

b. 醫學期刊《The Lancet》論及：「任何相信他們確實希望看到無煙世界的人，無非是自欺欺人」。

c. 美國癌症協會評論，菲利普莫里斯國際參與有關措施，只是他們長達數十年經營的延續，亦即以煙草在全球散播死亡和痛苦的商業活動。

2. 品牌重塑延伸

品牌重塑是一種營銷策略，藉着為現行品牌創建的新名稱，以及種種術語，符號、設計或其中組合，目的是在消費者、投資者、競爭者，以及其他持份者的心目中，重新包裝，打造另一形象。

隨着愈來愈多國家禁止所有形式的煙草廣告，煙草公司發現有必要採取另類宣傳手法。品牌重塑延伸，是有助於實現促銷煙草產品目標的最有效手段之一，可以避免訴訟風險，更可從中引入新產品或服務，利用現有產品或服務的聲譽，兼收促銷現有產品以及新產品之效。

奧馳亞是菲莫美國的母公司，早於 2003 年，菲莫美國便重新命名為奧馳亞，名稱變更策略有利於掩蓋與煙草業務相關的負面影響，使公司在不損煙草利潤的情況下，改善及提高其形象。

3. 煙草公司力推新煙草產品

電子煙產品為數日多，其中包括煙草巨頭雷諾士旗下的 Reynolds Vapor Company 所生產的 Vuse、歐洲最大煙草公司英美煙草公司（British American Tobacco）出品 Vype、帝國煙草 (Imperial Brands) 於 2015 年收購並出產電子煙 Blu。奧馳亞擁有 MarkTen，2018 年 12 月奧馳亞完成收購 35%股權的 Juul 等等。

Juul 是目前美國最暢銷的電子煙，佔電子煙產品總銷售額 72%以上，尤其備受年輕人歡迎。Juul 聲稱其產品僅供成年吸煙者服用，但其推銷手法實與傳統煙草公司的慣技無異，而採用嶄新高科技設計，並從中加重尼古丁含量，旨在吸引以年輕人為主的新客戶，使他們成為電子煙的忠實信徒。

根據美國兒科學院，與其他電子煙盒相比，Juul 的尼古丁濃度幾乎高出其他電子煙兩倍。當大腦仍在發育階段，一旦接觸尼古丁，上癮愈容易愈迅速，因此年輕人要戒除煙癮亦難上加難。

年輕時對尼古丁上癮，實際上會導致大腦重塑，而降低對其他物質上癮的門檻。換句話說，年輕人愈早服用尼古丁，日後就愈有可能對其他藥物上癮。

4. 煙草業對加熱煙的失實之言

加熱煙是一種新式的尼古丁輸送系統，將一根小煙草棒以電子方式加熱至產生氣霧，而不是燃燒。 自 2014 年首次在日本名古屋和米蘭推出 IQOS 以來，菲利普莫里斯國際研發的 IQOS 在全球 30 多個市場銷售，現佔全球加熱煙總銷售額七成。

歐洲呼吸學會 (ERS) 在其有關加熱煙產品的立場文件中指出，煙草公司的新聞稿有誤導之嫌，因為其中聲稱加熱煙草產品的主要成份是水，而傳統香煙的主要成份則為焦油，更聲稱有害和潛在有害物質和毒性減低 90%至 95%。然而獨立研究發現，加熱煙中尼古丁和焦油含量幾乎與傳統香煙相同。

丙烯醛（有毒並帶刺激性）僅減少 18%，甲醛（潛在致癌物質）減少 26%，甲醛（潛在致癌物質）減少 50%，TSNAs（致癌物）水平較常規燃燒香煙減少五份之一。此外，發現潛在致癌物質二氫苊（acenaphthene）含量，幾乎高出傳統香煙三倍。

ERS 對加熱煙草產品的立場如下：加熱煙有害並足以令人上癮；足以打消吸煙者戒煙念頭；足以打消戒煙者遠離香煙的念頭；足以對非吸煙者和未成年人構成誘惑；足以構成吸煙重新正常化的風險；足以構成與傳統香煙一同服用的風險。

美國食物及藥物管理局（FDA）上月底正式批准 IQOS 加熱煙在美國發售，並指其中有毒成份含量較傳統香煙為低。但該局強調，所有煙草產品都可危害健康、令人上癮；非吸煙者不應基於批准加熱煙發售的決定而嘗試吸煙，況且 FDA 亦從無提及加熱煙屬「有害程度較輕」(less harmful) 的煙草產品。

結語

上文剖析煙草公司一直以來，如何施展將大眾蒙在鼓裡的手法，歷經半個多世紀，利用香煙中足以令人上癮的尼古丁成份，令煙草業客似雲來，而煙草產品卻同時對全球各地的公共衞生造成浩劫。即使屢受司法制裁懲戒，煙草公司仍力圖透過形象重塑，打造良心企業的外觀，其實暗渡陳倉，積極向容易對尼古丁上癮的年輕顧客入手。種種新式煙草產品，都並未能證實為「有害程度較輕」，各地政府尤須明察，以免誤受重施故技的奸商所蒙蔽。對於電子煙和加熱煙，香港必須全面實施禁制。

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