Smoke-free alternatives to cigarettes

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Technology that we and others have developed makes it possible to shift the tobacco and nicotine market towards a future in which cigarettes are replaced by less harmful, yet satisfying, smoke-free alternatives

Dr Moira Gilchrist, Vice President of Scientific and Public Communications at PMI Science, discusses how technology is enabling a shift in the tobacco and nicotine market towards a future in which cigarettes are replaced by smoke-free alternatives.

The Marlboro Man was one of the most iconic and impactful symbols of the past century. Tough, hardworking, self-sufficient and an advert for one of the biggest causes of death in the UK – cigarettes – he is both reviled and revered by all those who remember Phillip Morris International's (PMI) advertising sensation.

Today, the reality about the Marlboro Man is certainly darker; at least four of the actors who played him have died of smoking-related diseases, and this is a stark reminder of the health risks associated with cigarettes.

That is why Dr Moira Gilchrist, Vice President of Scientific and Public Communications at PMI Science has made a pledge to eradicate the Marlboro Man's memory in aid of PMI's transition to a smoke-free future with smoke-free alternatives to cigarettes.

Throughout her twenty year career in Science, Moira has been dedicated to driving breakthroughs to encourage adult smokers to switch to a less harmful smoke-free alternatives to the combustible cigarettes that the Marlboro man promoted.

With a £3.3bn (~€3.7bn) research budget, over the last ten years Moira and her team have developed revolutionary technology and 'Risk Reduced Products', and here she tells *SciTech Europa* about some of these new developments and why they are so important.

What would you say is the legacy of the '+Marlboro Man'? How have changes to advertising practices and regulations helped to address this, at least in part?

History shows us that cigarette smoking is addictive and can cause certain diseases such as lung cancer, cardiovascular disease, and emphysema. The well-known risks of smoking have led regulators to impose more restrictions and higher excise taxes on cigarettes than

on any other consumer product. It is clear that public policy and regulations should continue to dissuade people from starting to smoke and encourage cessation, and we support regulatory measures that have these objectives.

But it is equally clear that millions of men and women will continue to smoke – according to the World Health Organization (WHO), there will still be about a billion smokers ten years from now. What's the plan to address the needs of these men and women? The answer, in our view, is innovation – in products and in policies.

We are working to design smoke-free alternatives for a smoke-free future, our priorities are changing. Technology that we and others have developed makes it possible to shift the tobacco and nicotine market towards a future in which cigarettes are replaced by less harmful, yet satisfying, smoke-free alternatives.

What would you say have been the biggest breakthroughs in developing these less harmful smoke-free alternatives?

The biggest breakthrough for our smoke-free products has been to eliminate the element of fire. Some people have focused on the fact that our heated tobacco products contain tobacco, which is often cast as the 'demon leaf', but today not all tobacco products are the same. Tobacco is not inherently that harmful unless burnt to generate smoke, which contains thousands of chemicals. When any organic material is combusted – tobacco leaves, candle wicks, charcoal for a grill and so on – the organic compounds transform into thousands of new compounds that make up smoke. Many of these compounds are harmful to health. When we heat tobacco at a temperature below 400ºC, we eliminate or minimise the production of these harmful chemicals compared with what is found in the smoke from a burning cigarette. Eliminating the combustion of tobacco is key.

Building a better product is so much easier when you can begin with a basic principle like this.

What have been your own biggest achievements and challenges thus far with regard to research into this area?

The design and implementation of our product assessment programme – that is, how we scientifically assess the risk profile of our new products versus cigarettes – was both the biggest challenge and the biggest achievement because it had never been done before. It was inspired by practices used in the pharmaceutical industry, which was my background before I joined PMI, as well as the draft guidance the US Food & Drug Administration issued in 2012.

Myself and many of my colleagues in our R&D team brought tools and techniques from the pharma industry and have applied them to the scientific assessment of our smoke-free products. We designed a comprehensive assessment program, where every step builds upon the one before it, continually clarifying the potential a product has to make a positive impact on individual and public health.

One of the biggest achievements in our research so far has been to demonstrate that our electrically heated tobacco product (commercialised as IQOS), exposes smokers who switch to it to significantly lower levels of harmful chemicals compared with cigarette smoke.

The technology in IQOS is built on the basic principle previously mentioned: it doesn't burn tobacco. Instead, the tobacco is precisely heated by a blade that's controlled by electronics. It produces lower levels of harmful chemicals, which means smokers are exposed to lower levels of chemicals than when they use cigarettes. But we don't rely just on the basic principle that eliminating combustion is better. We carefully tested our hypothesis within the framework of our scientific product assessment programme over many years. We have measured that IQOS produces on average 90-95% lower levels of harmful chemicals compared to a standard reference cigarette.

When we look at all of the evidence generated in our scientific studies – the so-called 'totality of evidence' – it clearly points toward a significant reduction in risk compared with continued smoking.

What role will such electronic tobacco heating systems play a role moving forwards? Where will your research priorities lie when you look to develop this further?

Heated tobacco products provide a more familiar experience to people who smoke than products without tobacco. There is no single product that will appeal to all smokers, which is why it is so important to have a range of products, including those with real tobacco, where each one can be an acceptable alternative to cigarettes.

This is why we won't stick just with electronically heated tobacco – we've also developed another heated tobacco product, TEEPS, which uses a carbon tip to heat the tobacco rather than a heating blade. It looks and feels more like a cigarette for those who are looking for that familiarity. And our ongoing research right now also includes smoke-free products without tobacco, which will provide consumers an even wider range of products to choose from.

What are your thoughts on recent developments in the industry, such as Public Health England claiming that vaping should be widely encouraged as a way to help people quit smoking? What more would you like to see being done?

I think that any product with evidence that it is or is likely to be safer than continued cigarette smoking should be promoted to current smokers who would otherwise continue to smoke, and they should be encouraged to switch completely to these products. Obviously, smoking cessation remains the best choice, but as mentioned earlier many smokers will simply not quit. E-cigarettes are a great option, and we have e-cigarettes in our own smoke-free product portfolio. The challenge is that e-cigarettes don't work for everyone.

I'd like to see the regulations and public acceptance expand to embrace not just e-cigarettes, but every smoke-free product that is backed by science. This is how we will see the biggest positive impact on public health.

Dr Moira Gilchrist

Vice President of Scientific and Public Communications

PMI Science

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TEEPS

pmi.com/smoke-free-products/teeps-carbon-heated-tobacco-product

Carbon Heated Tobacco Product

Heating Tobacco **Through Innovation**

Through intensive research and development, we have managed to create another breakthrough heated tobacco product. Just like *IQOS*, it releases flavors and nicotine without combustion, but it heats the tobacco with an **alternative heat source**. This new product has a pressed carbon heat-source that is separate from the tobacco and, using patented *HeatControl Technology*, provides an effective and controlled temperature transfer to create a nicotine-containing vapor.

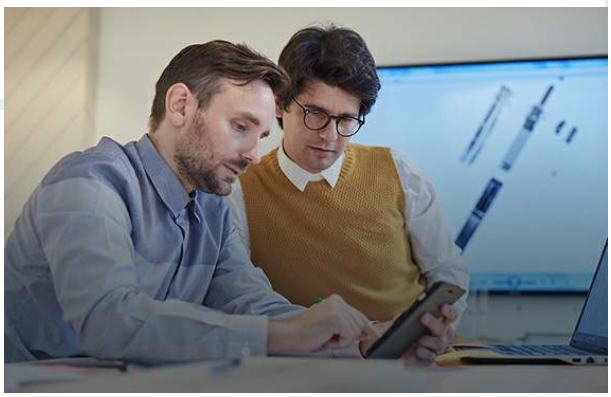
How does *TEEPS* work?

The carbon heat source at the end of *TEEPS* is ignited. This lights the carbon heat source, which supplies the energy used to heat, not burn, the tobacco.

Once the carbon heat source is lit, heat is transferred to a uniquely processed tobacco plug, **designed for heating and not for smoking**. The patented design of *TEEPS* prevents tobacco from burning. The consumer puffs on *TEEPS* to inhale a flavorful nicotine-containing vapor until the end of the experience.

Similar to *IQOS*, *TEEPS* heats tobacco to release its true taste. Because the tobacco is heated and not burned, the level of harmful chemicals is significantly reduced compared to cigarette smoke.

How long will PMI be in the cigarette business?



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 Please direct comments or questions to [english@hani.co.kr] Original Korean

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Short Communication Open Access

Heated Tobacco Products Create Side-Stream Emissions: Implications for Regulation

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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

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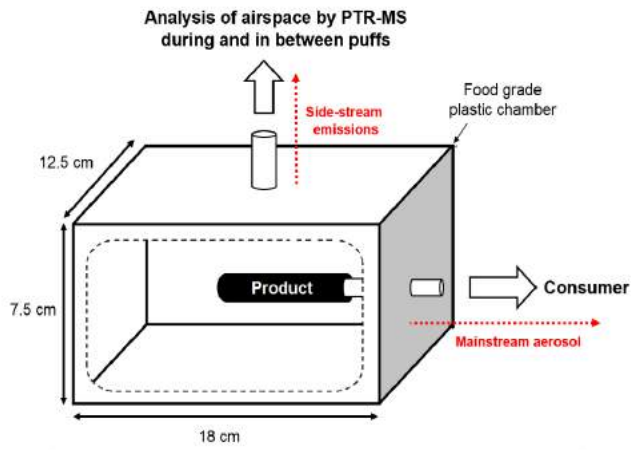

Figure 1: Schematic representation showing experimental set-up and the side-stream emissions capture chamber.

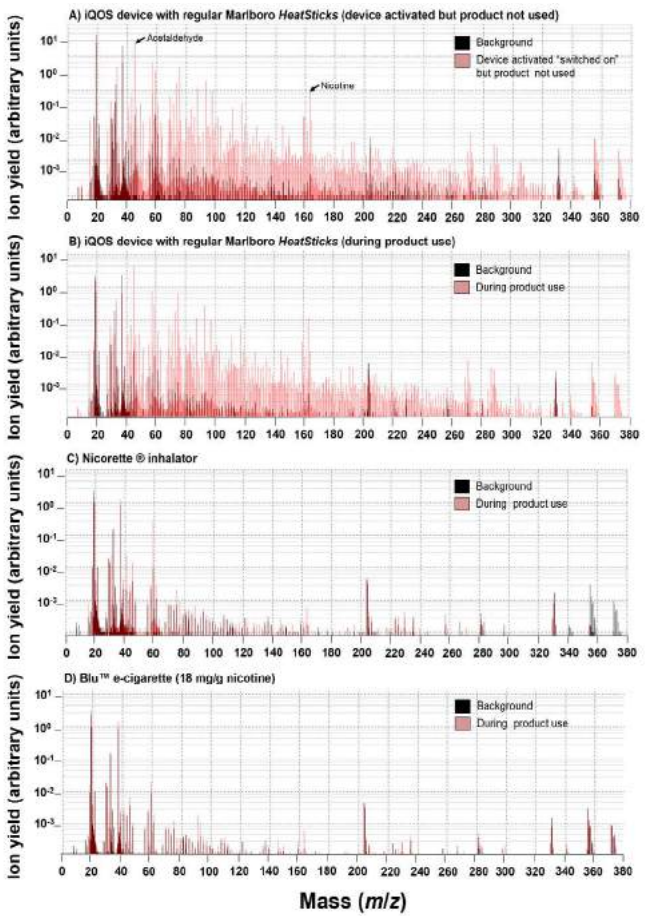

Figure 2: Representative PTR-MS mass spectra of the VOCs released to the airspace for (**A**) iQOS with regular Marlboro *HeatStick* when activated "switched on" but product not actively puffed and (**B**) during consumer use of the iQOS device with regular Marlboro *HeatSticks*; (**C**) during consumer 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

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

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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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Philip Morris hides data in plain sight on dangers of new heat-not-burn product

theconversation.com/philip-morris-hides-data-in-plain-sight-on-dangers-of-new-heat-not-burn-product-87636

Stanton Glantz

For as long as smoking has been known to cause cancer and other diseases, Big Tobacco has worked to avoid the truth about its deadly and highly addictive products.

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.

They have also developed products that avoided burning, including products thatheat the tobacco without combustion, e-cigarettes and even nicotine replacement therapy.

Philip Morris International's IQOS is the latest entry into this sweepstakes.

IQOS is a hand-held electric device that generates its nicotine aerosol by heating a stick of ground tobacco and chemicals without setting the tobacco on fire. IQOS does not burn the tobacco, so it produces fewer toxic chemicals than a cigarette.

A man smokes an IQOS. ThamKC/Shutterstock.com

Because IQOS is a new tobacco product, it needs the Food and Drug Administration's approval to sell it in the United States. Philip Morris submitted its massive application to the FDA on May 24, 2017. As required by law, FDA has made most of the application available for the public to review. The FDA will then consider the comments to determine if IQOS "as it is actually used by consumers, will significantly reduce harm and the risk of tobacco-related disease to individual users" and to the population as a whole. FDA can approve IQOS only if it meets this standard.

As someone who has worked in tobacco control for decades, I plowed through the application to see what information Philip Morris presented. To my surprise, I found (and told the FDA) that Philip Morris's own application shows that in American people there is no statistical difference in the harm caused by IQOS product and traditional cigarettes.

Bad stuff gets in your lungs either way

Like cigarettes (and e-cigarettes), IQOS uses an aerosol of ultrafine particles to deliver the nicotine. These ultrafine particles cause heart and lung disease.

And 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. This effect is why smoke-free environments are followed by big drops in heart attacks despite the fact that secondhand smokers breathe in much less smoke that the smokers.

Nevertheless, Philip Morris is aggressively marketing IQOS all over the world 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."

Independent research has found higher levels than Philip Morris claims. Fewer toxic chemicals, however, do not necessarily translate into lower harm.

In the United States, Philip Morris 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."

To support these claims, Philip Morris's application presents data on toxic chemicals and effects in animals. Most important, Philip Morris reports medical tests that doctors use to assess people's health in people using IQOS.

These 24 medical tests include blood (cholesterol, inflammation, oxidative stress), blood pressure and lung function. They are the most important information in the application because they represent direct evidence of how IQOS affects people who use them.

A health hazard by any other name

I closely examined Philip Morris's results. They show that there is no statistically detectable difference between IQOS and conventional cigarettes in these medical tests in the Americans Philip Morris studied.

Like all medical tests, there is uncertainty in the results. This range of uncertainty is what statisticians call the 95 percent confidence interval and journalists call "the margin of error."

For 23 of the medical tests, the margin of error in the tests to discern the difference between IQOS and conventional cigarettes included a zero (i.e., no difference). So neither we nor the FDA can be 95 percent confident that IQOS are better for people than conventional cigarettes in those cases.

Moreover, when using the conventional 95 percent confidence standard, one would expect 5 percent of the tests to yield false positives or 1 out of 24 tests. That is exactly what Philip Morris reported.

In other words, Philip Morris's own data demonstrate that IQOS is no different from conventional cigarettes in terms of effects on these medical tests in American people.

Too hot to cook your turkey

This is not surprising, because IQOS heats the tobacco to 660° Fahrenheit (350° Celsius). That's well below the 1,100°F for combustion, but it is still hot enough to cause chemical reactions known as pyrolysis. Pyrolysis is what turns a turkey baked at 350°F into Thanksgiving dinner. Imagine if you had eaten a turkey cooked at IQOS's 660°F!

These conclusions are based on taking Philip Morris's results at face value, ignoring the fact that the tobacco industry, including Philip Morris, has a long history of manipulating

scientific study designs and statistical analysis to get the results they want.

And there is already independent evidence that IQOS compromises functioning of arteries, a key risk factor for heart disease and heart attacks, as badly as a cigarette.

Because Philip Morris's medical tests in humans failed to show that IQOS "as it is actually used by consumers, will significantly reduce harm and the risk of tobacco-related disease to individual users," I believe the FDA must deny Philip Morris's application to protect the public health.

Philip Morris's application did include one accurate statement: "The best way to reduce your risk of tobacco-related diseases is to completely quit tobacco use." Of course, if people did that, Philip Morris would not make any more money from them.

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iQOS: evidence of pyrolysis and release of a toxicant from plastic

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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.

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

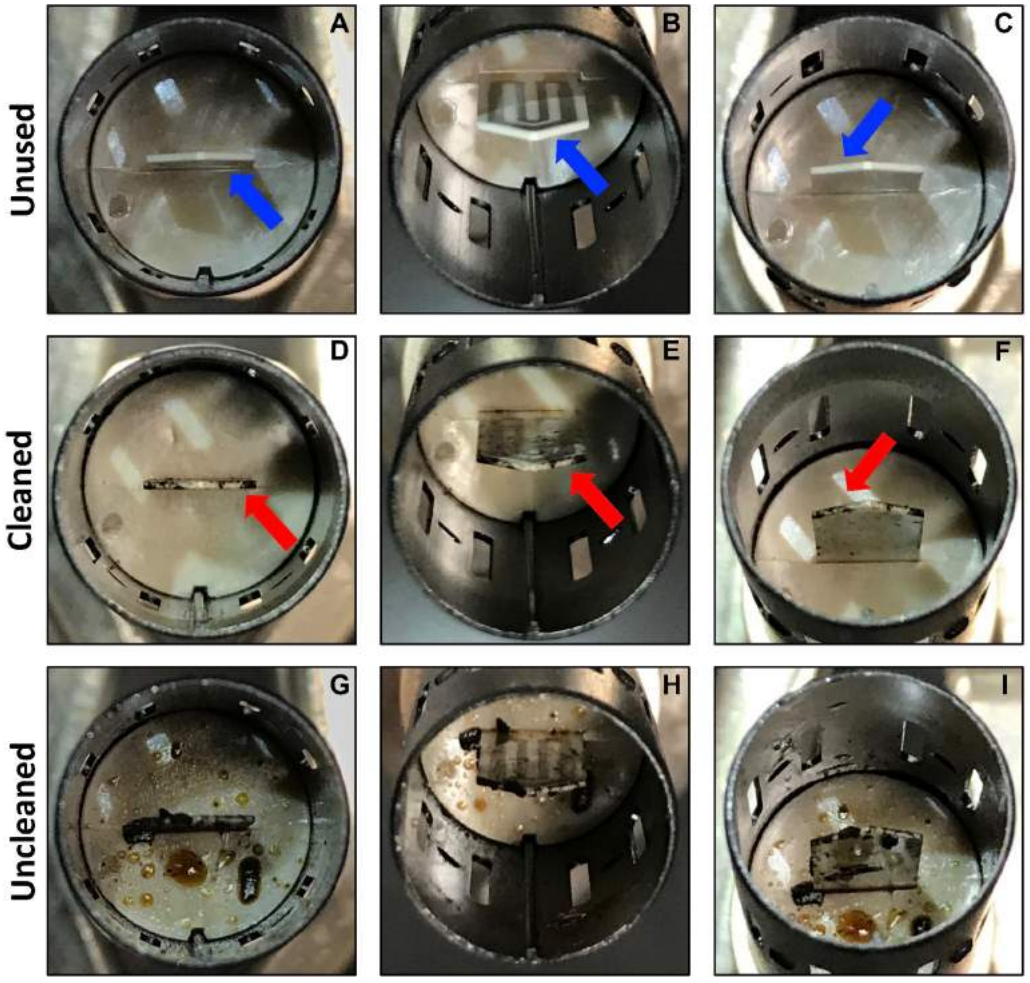

Figure 2 Internal view of the I quit original smoking holder. (A–C) Clean, unused holder showing heater (blue arrows). (D–F) Used holder that was cleaned after every use; black residue remains on heater (red arrows). (G–I) Used holder that was not cleaned between uses (10 uses).

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).

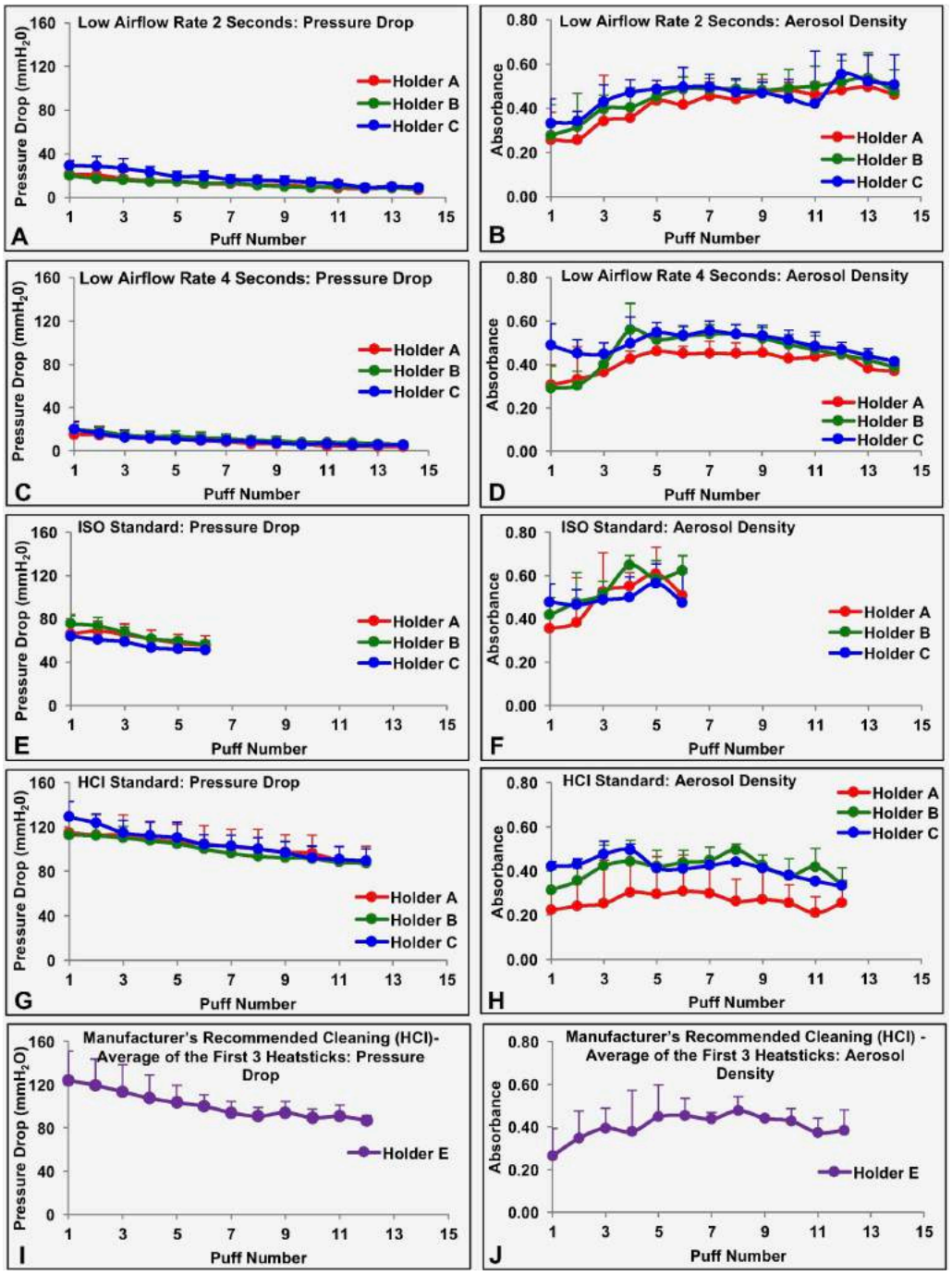

Figure 3 Performance characteristics of the I quit original smoking heat-not-burn system. (A, C, E, G and I) Pressure drop is plotted versus the puff number for five puffing protocols. (B, D, F, H and J) Absorbance is plotted versus puff number for the five puffing protocols. Each line of the graph represents 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

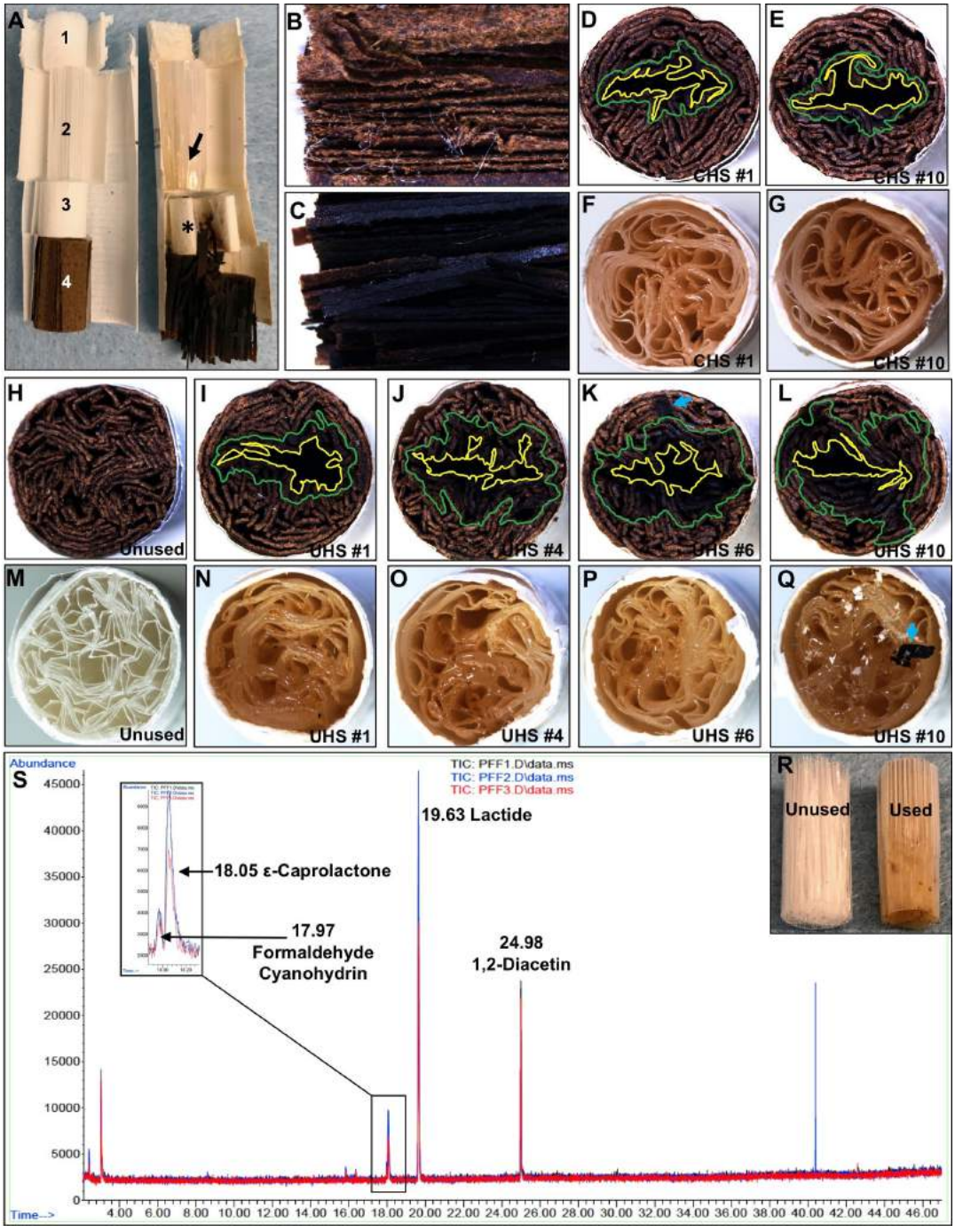

Figure 4 Charring of tobacco plug and melting of polymer-film filter. (A) Dissected heatsticks, each heatstick is composed of: (1) the low-density cellulose mouthpiece filter, (2) polymer-film filter, (3) hollow acetate tube and (4) tobacco plug. Heatsticks from left to right are unused stick with the 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.

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.

'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

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Notes

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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.

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.

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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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