



The Chairman & Clerk to Panel on Health Services
Panel on Health Services
Legislative Council
Legislative Council Complex 1
Legislative Council Road Central
Hong Kong

23rd Floor Gloucester Tower
15 Queen's Road Central
Hong Kong
T +852 2845 6639
F +852 2845 9099

www.herbertsmithfreehills.com

Our ref
6461/12474/31012325
Your ref

Date
12 June 2018

Second Letter

By email

Dear Sirs,

Scientific Information and Studies relating to electronic cigarettes and heated tobacco products

We act for British-American Tobacco Company (Hong Kong) Limited and we write further to our letter dated 11 June 2018 ([LC Paper No. CB\(2\)1578/17-18\(18\)](#)). Terms defined in our letter shall have the same meaning herein.

We enclose herewith a copy of the May Submission ([LC Paper No. CB\(2\)1402/17-18\(01\) \(Revised\)](#)) that we have summarised in our letter dated 11 June 2018 for the Panel members' easy reference. We should be grateful if you could kindly table a copy of the same for the Panel members' reference.

Please feel free to contact us should you have any queries.

Yours faithfully,

Herbert Smith Freehills

Encl

Regional Managing Partner □ Asia
J J G D'Agostino

Managing Partner - Greater China
M F Tai

A R W Aitken
D J Byrne Hill +
J S Caen
H E Cassidy
S J Chapman
J M Copeman +

M C Emsley
D A Geiser
W R Hallatt
R W M Hunt
W W H Ku
H H S Lau

M H M Li
K S H Sanger
J Sung
G H Thomas
T C P Tong
K A Wombolt

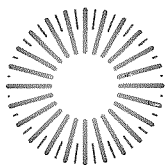
**Senior Registered Foreign
Lawyers:**
D Logofet *

Senior Consultants:
S M Loi
J M Siu
M K Wallace

**Senior Registered
Foreign Lawyers:**
P D Kiesselbach *

+ Not resident in Hong Kong

*Admitted in England and Wales



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Our ref
6461/12474/31012325
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Date
16 May 2018

By email and by hand

Dear Sirs,

Scientific Information and Studies relating to electronic cigarettes and heated tobacco products

We act for British-American Tobacco Company (Hong Kong) Limited ("**BATHK**").

We note that the Legislative Council's Panel on Health Services ("**Panel**") has listed in agenda item III of the Panel's meeting on 21 May 2018 (the "**Meeting**") to discuss the proposed study on issues relating to electronic cigarettes ("**e-cigarettes**") and heated tobacco products. We are writing on behalf of BATHK to provide the relevant scientific information and studies on e-cigarettes and heated tobacco products for the Panel's consideration at the Meeting and should be grateful if you could kindly table a copy of this letter for the Panel members' references.

1. TOBACCO HARM REDUCTION

1.1 The idea of tobacco harm reduction is not new, and is based on a well-established public health concept that seeks pragmatic ways to minimize the impact of an inherently risky activity or behavior.¹ An increasing number of experts in the scientific and public health

¹ We note, also, that tobacco harm reduction is a component of the WHO Framework Convention on Tobacco Control ("**FCTC**"), to which Hong Kong is a party by way of extension. Article 1(d) of the FCTC defines "*tobacco control*" as "*a range of supply, demand and harm reduction strategies that aim to improve the health of a population by eliminating or reducing their consumption of tobacco products and exposure to tobacco smoke*" (emphasis added).

Regional Managing Partner - Asia
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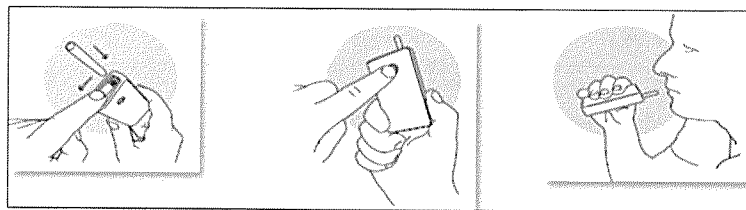


community are now advocating for a harm reduction approach as the way forward to help over a billion people worldwide² who continue to smoke despite the known health risks.

- 1.2 British American Tobacco plc ("**BAT**") has long been working to develop potentially less risky products that can help reduce the public health impact of smoking and has invested in a whole new generation of alternative products, including e-cigarettes which contain no tobacco at all and Tobacco Heating Products ("**THPs**"), which are devices that heat rather than burn tobacco.
- 1.3 Scientists widely agree that it is primarily the toxicants found in cigarette smoke (largely released through the combustion of tobacco) that cause smoking related diseases³ – not the nicotine itself.⁴ Products that involve no combustion are likely to emit far fewer and lower levels of toxicants compared to conventional cigarettes and have the potential to be significantly less harmful.

2. **TOBACCO HEATING PRODUCTS (THP)**

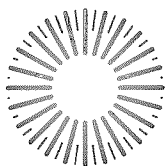
- 2.1 When a cigarette is lit, it burns, temperature reaches more than 800°C, and burning tobacco generates toxicants in the smoke. As stated above, inhaling these smoke toxicants is the primary cause of smoking-related diseases such as lung cancer.
- 2.2 On the other hand, THPs heat tobacco (typically at between 240-350 °C or lower but not at a temperature high enough to burn it) to produce a nicotine-containing aerosol (known colloquially as "*tobacco vapour*") composed mainly of water, humectant (e.g. glycerol), nicotine and flavourings. This is fundamentally different to the smoke emitted from a lit cigarette.
- 2.3 *glo*, one of BAT's THPs, comprises of an electronic battery powered device which heats specially designed tobacco sticks (Neostiks™) to approximately 240°C. The consumer inserts the Neostiks™ into the *glo* device and turns it on by means of a button which initiates the heating of the tobacco. Once the initial heating phase is completed, the Neostiks™ is ready to be vaped.



² <http://www.who.int/news-room/fact-sheets/detail/tobacco>

³ See, for example, statements by the International Agency for Research on Cancer ("**IARC**"), the UK Royal College of Physicians (2016), [Nicotine without smoke: Tobacco harm reduction](#), and the [Truth Initiative](#).

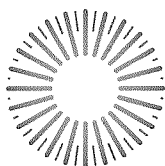
⁴ The UK National Institute of Health and Care Excellence ("**NICE**"), for example, has concluded that "*most health problems are caused by other components in tobacco smoke, not by the nicotine.*" NICE (2013), [Smoking: Harm Reduction](#), Available [here](#).



- 2.4 When used as directed and intended Neostiks™ neither ignite nor burn. The electronically-controlled heating, in combination with the uniquely processed tobacco, prevents combustion from occurring. The Neostiks™ is not smoked; it does not combust and produces no ash. This reduction in temperature, and the fact there is no burning, results in the aerosol produced by *glo* containing fewer toxicants, the majority of which are at significantly lower levels than in cigarette smoke. This offers the potential for significant harm reduction when compared to cigarettes.
- 2.5 The science BAT has done to date on *glo* shows that it emits approximately 90-95% less toxicants⁵ than the smoke of a reference cigarette in terms of the nine harmful toxicants the World Health Organisation recommends to reduce in cigarette smoke⁶. Further research on the *glo* product shows:-
- 2.5.1 **Fewer and lower levels of toxicants:** a series of analyses comparing the chemical composition of *glo* tobacco vapour with that of smoke was conducted. The results reveal the relatively simple composition of *glo* tobacco vapour compared to conventional cigarette smoke. Most cigarette smoke toxicants could not be detected in the *glo* tobacco vapour.
- 2.5.2 **Reduced biological impacts:** a system that allows living cells grown in the lab to be exposed to aerosols was used so as to mimic the way human lung cells are exposed to aerosols in real life. It was shown that *glo* tobacco vapour has a much-reduced or no biological impact on cells in the lab as compared to conventional cigarette smoke. Unlike cigarette smoke, *glo* tobacco vapour was not toxic to human airway cells and did not cause mutations in DNA or promote the development of tumours in the tests used. In many case, the results were similar to those obtained when the cells were exposed to air.
- 2.5.3 **Reduced second hand emissions:** indoor air quality and the tobacco odour of an environmentally controlled room were analysed. In the air sampled from the *glo* room, most toxicants measured could not be detected at all. Overall, the results reveal substantial reductions in numbers and levels of environmental toxicants for *glo* use compared to cigarette smoking.

⁵ 'British American Tobacco publishes a series of studies supporting the reduced-risk potential of *glo*' published by Dr Marina Murphy of British American Tobacco in November 2017. Also see Forster et al., (2017) Assessment of novel tobacco heating product THP 1.0. Part 3: Comprehensive chemical characterisation of harmful and potentially harmful aerosol emissions. Available [here](#). This is an independently peer-reviewed study, published in the journal of Regulatory Toxicology and Pharmacology.

⁶ This is a comparison between the smoke from combusted tobacco in a standard 3R4F reference cigarette (approximately 9 mg tar) and the vapour from heated tobacco in *glo*, in terms of the nine types of harmful components the World Health Organization recommends to reduce. See also (1) Statement on the toxicological evaluation of novel heat-not-burn tobacco products by Committee on Toxicity – COT2017/04; December 2017; and (2) Toxicological evaluation of novel heat-not-burn tobacco products – non-technical summary.



- 2.6 Please refer to the series of papers published in a special issue of the independently peer-reviewed scientific journal *Regulatory Toxicology and Pharmacology* for further information⁷.
- 2.7 Some public health authorities have recognised the reduced-risk potential of THPs in general compared to traditional combustible cigarettes, whilst acknowledging the need for more research. For example:
- 2.7.1 In 2018, Public Health England ("PHE"), an executive body of the UK Department of Health, published an evidence review of e-cigarettes and THPs in which it concluded that "[c]ompared with cigarette smoke, heated tobacco products are likely to expose users and bystanders to lower levels of particulate matter and harmful and potentially harmful compounds."⁸ The PHE (2018) report also noted that there are widespread "misperceptions" about the comparative potential risks of various nicotine and novel tobacco products, which need to be addressed and corrected, and which impede some consumers from moving to products with reduced-risk potential.⁹ This underscores the importance of ensuring that consumers have access to accurate information about these products.
- 2.7.2 Scientists also widely acknowledge that smoking related diseases are caused largely by the toxicants found in cigarette smoke – not the nicotine itself.¹⁰ Hence, the Food and Drug Administration hopes that "we can all see the potential benefits to addicted cigarette smokers, in a properly regulated marketplace, of products capable of delivering nicotine without having to set tobacco on fire".¹¹ Please also refer to the enclosed report for a summary of the relevant evidence.¹²
- 2.7.3 In 2017, the UK Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment ("COT") published a toxicological evaluation of two THPs on the market in the UK, in which it found that "[i]nvestigations on both products showed a decrease in the harmful and potentially harmful compounds (HPHCs) in the aerosol generated by the device to which the user would be exposed, compared to the HPHCs in the mainstream smoke from a conventional cigarette. For both products, there were some HPHCs where the reduction was approximately 50%, but the reduction in a number of other HPHCs was greater

⁷ <https://www.researchgate.net/search?q=Assessment%20of%20tobacco%20heating%20product%20THP1.0;https://www.sciencedirect.com/journal/regulatory-toxicology-and-pharmacology/vol/93/suppl/C>

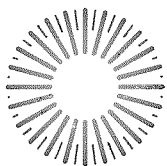
⁸ PHE (2018), *Evidence review of e-cigarettes and heated tobacco products 2018: A report commissioned by Public Health England*.

⁹ PHE (2018), *Evidence review of e-cigarettes and heated tobacco products 2018: A report commissioned by Public Health England*, at Chapter 4.

¹⁰ British American Tobacco (2017), 'ANDS role in supporting public health strategies', section A.

¹¹ Gottlieb S, *Protecting American Families: Comprehensive Approach to Nicotine and Tobacco*, July 2017.

¹² British American Tobacco (2017), 'ANDS role in supporting public health strategies'.



*than 90%, with many of the compounds being below the limits of detection or quantification for the assays used.*¹³

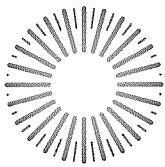
- 2.8 As part of BAT's product stewardship BAT has undertaken a series of chemical and toxicological studies, focussing both on what the product is made of and the tobacco aerosol that it produces. These data are available to scientists and regulators.¹⁴ We also enclose a paper entitled "Tobacco Heating Products glo: measurement of mainstream emissions" and a paper entitled "Tobacco heating products overview of the scientific assessment of glo" both prepared by BAT for a summary of the ingredients and emissions of Neostiks™.
- 2.9 Given that tobacco sticks, including Neostiks™, are not smoked when used as intended with THP devices, and in light of their harm reduction potential, they should not be treated in the same way as cigarettes. This approach is currently under consideration by New Zealand, where the Ministry of Health is "*considering how best to apply risk-proportionate regulation across all tobacco products including smoked tobacco, smokeless tobacco and vaping products*"¹⁵. Tobacco products are currently regulated under the Smoking (Public Health) Ordinance. BATHK is of the view that the Government should align its treatment of the tobacco containing consumables with that of "other tobacco products" under the Dutiable Commodities Ordinance accordingly.¹⁶
3. **E-CIGARETTES**
- 3.1 Devices such as e-cigarettes contain no tobacco at all, do not rely on combustion, and, as a consequence, no smoke or tobacco tar is formed when the e-liquid is "vaped". An increasing number of health experts agree that vaping e-cigarettes that are manufactured to robust quality and safety standards are less harmful than smoking tobacco.
- 3.2 **An increasing number of health experts agree that vaping is less harmful than smoking tobacco:**
- 3.2.1 The PHE (2018) report reiterated that "[v]aping poses only a small fraction of the risks of smoking and switching completely from smoking to vaping conveys

¹³ COT (2017), *Statement on the toxicological evaluation of novel heat-not-burn tobacco products*. Available [here](#).

¹⁴ See www.bat-science.com.

¹⁵ <https://www.health.govt.nz/our-work/preventative-health-wellness/tobacco-control/vaping-smokeless-including-heated-tobacco>

¹⁶ Under Part II of Schedule 1 to the Dutiable Commodities Ordinance, tobacco is classified under four categories, namely cigarettes, cigars, Chinese prepared tobacco and all other manufactured tobacco except tobacco intended for the manufacture of cigarettes. "Cigarette" is defined as "*any roll of tobacco capable of being smoked by itself not being a cigar*" (emphasis added). The definition of "cigar" also requires it to be "*capable of being smoked by itself*" (emphasis added). Unlike cigarettes and cigars which produce smoke via a process of self-sustained combustion, when used as intended with glo the tobacco in Neostiks does not combust and produces an aerosol very different to cigarette smoke. Hence, Neostiks do not fall under the definition of cigarettes and cigars. It is not "Chinese prepared tobacco" either as they are not "*prepared in the traditional Chinese manner from tobacco leaf grown in China*". The only appropriate classification of Neostiks would be "all other manufactured tobacco".



*substantial health benefits over continued smoking. Based on current knowledge, stating that vaping is at least 95% less harmful than smoking remains a good way to communicate the large difference in relative risk unambiguously so that more smokers are encouraged to make the switch from smoking to vaping. It should be noted that this does not mean e-cigarettes are safe." The PHE (2018) report also found that there have been "no identified health risks of passive vaping to bystanders."*¹⁷

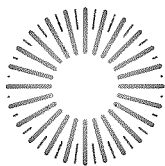
- 3.2.2 The Scottish National Health Service in collaboration with several other public health bodies and NGOs, including Action on Smoking and Health Scotland, Cancer Research UK, and the UK Centre for Tobacco and Alcohol Studies, published a statement in 2017 in which it stated that "[t]here is now agreement based on the current evidence that vaping e-cigarettes is **definitely less harmful** than smoking tobacco. Although most e-cigarettes contain nicotine, which is addictive, vaping carries less risk than smoking tobacco. Thus, it would be a good thing if smokers used them **instead** of tobacco."¹⁸ (emphases in original)
- 3.2.3 A study funded by Cancer Research UK (2017),¹⁹ analysed the nicotine, carcinogen, and toxin exposure in long-term e-cigarette and nicotine replacement therapy users over a year. This study, which is the first long-term study of its kind, found that people who swapped smoking regular cigarettes for e-cigarettes or nicotine replacement therapy for at least six months, had much lower levels of toxic and cancer causing substances in their body than people who continued to use conventional cigarettes.
- 3.2.4 A study by Levy et al., (2017)²⁰ modelled the population impact in the future if more smokers in the US switched to e-cigarettes. They estimated that taking into account several parameters such as cessation, initiation and relative harm, switching cigarette smokers to e-cigarette use over a 10-year period would lead to 1.6 to 6.6 million fewer premature deaths in the US under a pessimistic and optimistic scenario respectively. The authors concluded that "a strategy of replacing cigarette by e-cigarette use can yield substantial gains, even with conservative assumptions about related risks. Most important, an e-cigarette substitution strategy provides the justification to redouble efforts to target cigarette use, as it is called for by the WHO Framework Convention for Tobacco Control."

¹⁷ PHE (2018), *Evidence review of e-cigarettes and heated tobacco products 2018: A report commissioned by Public Health England, at Chapter 4.*

¹⁸ <http://www.healthscotland.scot/publications/e-cigarettes-consensus-statement>.

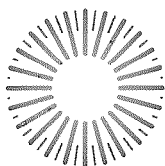
¹⁹ Shahab et al., (2017) *Nicotine, Carcinogen, and Toxin Exposure in Long-Term E-Cigarette and Nicotine Replacement Therapy Users.* *Ann Intern Med*, 390-400.

²⁰ Levy et al., (2017) *Potential deaths averted in USA by replacing cigarettes with e-cigarettes.* *Tobacco Control.* Aug 30.



- 3.2.5 *"Nicotine is not a carcinogen; there is no evidence that sustained human use of nicotine alone increases the risk of cancer."*²¹ According to a 2016 report by the UK Royal College of Physicians ("RCP"), as most of the harm caused by smoking arises not from nicotine but from other components of tobacco smoke, the health and life expectancy of today's smokers could be radically improved by encouraging as many as possible to switch to a smoke-free source of nicotine. The report does recognise *"concerns that e-cigarettes are not hazard free are justified, but this hazard could be minimised by a combination of technological development and appropriate regulation."*
- 3.3 **Vaping may be an effective way for people to quit smoking. BAT does not market its e-cigarettes as cessation devices. However, BAT is aware that a growing number of public health authorities have embraced their use as such:**
- 3.3.1 The PHE (2018) report found that *"[i]n the first half of 2017, quit success rates in England were at their highest rates so far observed and for the first time, parity across different socioeconomic groups was observed. It is plausible that EC [e-cigarettes] have contributed to this"* and that *"[w]hile caution is needed with these figures, the evidence suggests that ECs have contributed tens of thousands of additional quitters in England."*²²
- 3.3.2 The UK National Health Service ("UK NHS") supports the use of e-cigarettes in quit-attempts, referring to e-cigarettes on its "Stop smoking treatments" website, and stating that *"research has found that e-cigarettes can help you give up smoking, so you may want to try them rather than the medications listed above..."*²³ During October 2017, the annual TV campaign to encourage people to stop smoking did, for the first time, feature e-cigarettes as viable option to stop smoking.²⁴
- 3.3.3 A briefing note by Cancer Research UK (2016), "E-Cigarettes in Stop Smoking Services" recommends that *"[S]top Smoking Services are currently seeing a reduction in the number of clients and one contributing factor is likely to be the increase in e-cigarette use. These services should be accepting of e-cigarette use and support those who wish to use them alongside behavioural support as an aid to stop smoking. Services should provide patients with basic information and advice about e-cigarettes. This will maximise the reach of the service and improve e-cigarette users' chances of stopping smoking."*²⁵
- 3.3.4 The RCP has stated that *"smokers who use nicotine products as a means of cutting down on smoking are more likely to make quit attempts. Promoting wider*

²¹ UK Royal College of Physicians (2016), *Nicotine without smoke: Tobacco harm reduction*.
²² PHE (2018), *Evidence review of e-cigarettes and heated tobacco products 2018: A report commissioned by Public Health England, at Chapter 4*.
²³ [http://www.nhs.uk/conditions/smoking-\(quitting\)/Pages/Treatment.aspx](http://www.nhs.uk/conditions/smoking-(quitting)/Pages/Treatment.aspx) .
²⁴ <https://www.youtube.com/watch?v=28alsV4ya5A>.
²⁵ Cancer Research UK (2016), *E-Cigarettes in Stop Smoking Services*. Available at: https://www.cancerresearchuk.org/sites/default/files/e-cig_in_sss_0.pdf.



*use of consumer nicotine products, such as e-cigarettes, could therefore substantially increase the number of smokers who quit.*²⁶

3.4 Claims that vaping is a gateway for young people into smoking are, to date, unfounded:

3.4.1 The PHE (2018) Report found that "[d]espite some experimentation with these devices among never smokers, EC are attracting very few young people who have never smoked into regular use" and that "EC do not appear to be undermining the long-term decline in cigarette smoking in the UK among young people."²⁷

3.4.2 A UK study by Bauld et al., (2017)²⁸ which assessed recent trends in ever and regular use of e-cigarettes and tobacco smoking among 11-16 year olds, found that their "findings indicate that there is no evidence of e-cigarettes driving smoking prevalence upwards. This is important, and suggests that fears about e-cigarettes as a gateway to more youth becoming smokers are not currently justified, at least in the UK."

3.4.3 An annual survey of young people in Great Britain aged between 11 and 18, commissioned by Action on Smoking and Health UK ("**UK ASH**"), has shown that regular e-cigarette use remains rare and indicates that it is unlikely they are acting as a gateway into smoking²⁹.

3.4.4 The RCP concluded that "All the UK evidence, and almost all the international evidence, on the use of e-cigarettes by children and young people to date indicates that concerns about e-cigarettes helping to recruit a new generation of tobacco smokers through a gateway effect are, at the least to date, unfounded."³⁰

3.5 An increasing number of international public health bodies and experts are calling for balanced regulation of e-cigarettes because of their real potential to contribute to public health strategies:

3.5.1 Most recently, in February 2018 PHE opined that "[r]egulations need to balance the risks of e-cigarettes with their potential benefits – and achieve key aims of reducing smoking and continuing to avoid uptake of e-cigarettes by non-smokers. This requires keeping them under regular review and evaluating their impact".³¹

²⁶ UK Royal College of Physicians (2016), Nicotine without smoke: Tobacco harm reduction.

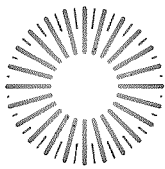
²⁷ PHE (2018), Evidence review of e-cigarettes and heated tobacco products 2018: A report commissioned by Public Health England.

²⁸ Bauld et al., (2017) Young People's Use of e-cigarettes across the United Kingdom: Findings from Five Surveys 2015-2017. International Journal of Environmental Research and Public Health, 14(9):973.

²⁹ ASH fact sheet-Use of electronic cigarettes among children in Great Britain, Action on Smoking and Health UK, October 2016.

³⁰ UK Royal College of Physicians (2016), Nicotine without smoke: Tobacco harm reduction.

³¹ PHE (2018), Evidence review of e-cigarettes and heated tobacco products 2018: A report commissioned by Public Health England.

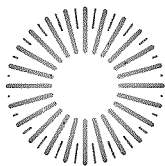


- 3.5.2 In October 2017 the British Psychological Society published a briefing on e-cigarettes, which recommended that regulators should "[u]se policy interventions and fiscal measures to raise the cost of smoking and reduce the cost of e-cigarettes. Continue to increase taxes, smoke-free regulation and purchasing barriers for cigarettes but regulate the reduced risk product less heavily. For e-cigarettes, avoid taxation and 'vape-free' legislation and promote unrestricted advertising of factual information"; and that they should "[r]egulate to promote product development" so as to "allow e-cigarettes to further evolve and improve so they are safer, more appealing and satisfying for more smokers. This means allowing higher nicotine strength e-liquid to remain on the market where there is no evidence to suggest harm, and avoid unnecessary burdensome and costly procedures for manufacturers so they can focus on improving the safety and efficacy of their products."³²
- 3.5.3 In August 2016 the RCP released a comprehensive analysis of nicotine and e-cigarettes in its report "Nicotine without smoke: Tobacco harm reduction".³³ In this report the RCP recommended that "in the interests of public health it is important to promote the use of e-cigarettes, NRT and other non-tobacco nicotine products as widely as possible as a substitute for smoking in the UK."
- 3.5.4 In 2016, the potential use of e-cigarettes in a public health strategy was also recognised in a guidance document on the use of e-cigarettes in public places and workplaces published by PHE. Its authors concluded that "[w]e believe e-cigarettes have the potential to make a significant contribution to its achievement. Realising this potential depends on fostering an environment in which e-cigarettes can provide a route out of smoking for England's eight million smokers, without providing a route into smoking for children or non-smokers."³⁴ The PHE report proposes five key principles intended to "guide the development of evidence-based policies that maximise the potential for e-cigarettes to improve public health while managing the risks in any particular setting." These principles are:
- (A) make clear the distinction between vaping and smoking;
 - (B) ensure policies are informed by the evidence on health risks for bystanders;
 - (C) identify and manage risks of uptake by children and young people;
 - (D) support smokers to stop smoking and stay smokefree; and

³² British Psychological Society (2017), *Changing Behaviour: Electronic Cigarettes*. Available at: <https://beta.bps.org.uk/sites/beta.bps.org.uk/files/Policy%20-%20Files/Changing%20behaviour%20-%20electronic%20cigarettes.pdf>.

³³ UK Royal College of Physicians (2016), *Nicotine without smoke: Tobacco harm reduction*.

³⁴ Public Health England (2016), *Use of e-cigarettes in public places and workplaces – Advice to inform evidence-based policy making*, available at <https://www.gov.uk/government/publications/use-of-e-cigarettes-in-public-places-and-workplaces>.



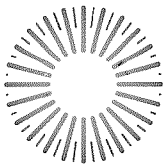
- (E) support compliance with smokefree law and policies.³⁵
- 3.5.5 Some governments and other public health bodies have also actively supported e-cigarettes as part of their tobacco harm reduction activities, encouraging people who do not want to stop smoking to switch to e-cigarettes. For example:
- (A) The U.K. Government's Tobacco Control Plan 2018³⁶ states that the evidence is increasingly clear that e-cigarettes are significantly less harmful to health than smoking tobacco and commits Public Health England to: *"provide evidence based guidance for health professionals to support them in advising smokers who want to use e-cigarettes or other nicotine delivery systems to quit"*.
- (B) A New Zealand Ministry of Health position statement on E-cigarettes, published in October 2017, suggest that recent decisions taken by the government have increased the focus on harm reduction with an aim to support smokers to switch to significantly less harmful products like e-cigarettes, and *"[t]he Ministry of Health encourages smokers who want to use e-cigarettes to quit smoking to seek the support of local stop smoking services. Local stop smoking services provide smokers with the best chance of quitting successfully and should support smokers who want to quit with the help of e-cigarettes."*³⁷
- (C) The UK NHS supports the use of e-cigarettes in quit-attempts, referring to e-cigarettes on its *"Stop smoking treatments"* website, and stating that *"[r]esearch has found that e-cigarettes can help you give up smoking, so you may want to try them rather than the medications listed above..."*³⁸ In 2017, the UK NHS-backed "Stoptober" campaign also featured e-cigarettes in its televised adverts, and stated on its website that *"[e]-cigarettes are a great way to help combat nicotine cravings and carry a fraction of the risk of cigarettes."*
- (D) A briefing by the National Centre for Smoking Cessation and Training ("**NCSCT**") (2016) which was prepared in partnership with Public Health England, states that *"[s]top smoking services should be open to e-cigarette use in people keen to try them to help them quit. This is*

³⁵ Public Health England, *E-cigarettes in public places and workplaces: a 5-point guide to policy making*, available at <https://www.gov.uk/government/publications/use-of-e-cigarettes-in-public-places-and-workplaces/e-cigarettes-in-public-places-and-workplaces-a-5-point-guide-to-policy-making>.

³⁶ [https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/630217/Towards a Smoke free Generation - A Tobacco Control Plan for England 2017-2022_2 .pdf](https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/630217/Towards_a_Smoke_free_Generation_-_A_Tobacco_Control_Plan_for_England_2017-2022_2.pdf).

³⁷ <http://www.health.govt.nz/our-work/preventative-health-wellness/tobacco-control/e-cigarettes>.

³⁸ [http://www.nhs.uk/conditions/smoking-\(quitting\)/Pages/Treatment.aspx](http://www.nhs.uk/conditions/smoking-(quitting)/Pages/Treatment.aspx).



especially so in those who have tried and failed to quit using licensed stop smoking medicines."³⁹

- (E) A briefing note by Cancer Research UK (2016), "*E-Cigarettes in Stop Smoking Services*" recommends that "[S]top Smoking Services are currently seeing a reduction in the number of clients and one contributing factor is likely to be the increase in e-cigarette use. These services should be accepting of e-cigarette use and support those who wish to use them alongside behavioural support as an aid to stop smoking. Services should provide patients with basic information and advice about e-cigarettes. This will maximise the reach of the service and improve e-cigarette users' chances of stopping smoking."⁴⁰

3.5.6 We are aware that a 2016 report of the WHO raises a number of concerns over the potential health risks of e-cigarettes and the risks that they present to effective tobacco control policy.⁴¹ However, this report has been heavily criticised. For example, the UK Centre for Tobacco and Alcohol Studies, an independent network of 13 universities which conducts research, teaching and policy work into tobacco and alcohol, published a commentary on the WHO report, which concludes that the report: "*fails to deliver the equipoise required for dispassionate formulation of public health policy. The report also contains **factual errors and misinterpretations of evidence** available in the public domain...*"⁴². The WHO also acknowledged that "[i]f the great majority of tobacco smokers who are unable or unwilling to quit would switch without delay to using an alternative source of nicotine with lower health risks, and eventually stop using it, this would represent a significant contemporary public health achievement."⁴³

3.6 **A proportionate approach to regulation of e-cigarettes would be more appropriate and should be based on the following principles:**

3.6.1 **Classification as consumer (not medicinal) products:** Medicinal products, including smoking cessation products, are subject to restrictive, cumbersome and lengthy approval processes which stifle innovation of the product category. E-cigarettes should be classified as consumer products so that they are readily accessible by adult consumers as an alternative to tobacco products, and so that they are subject to a level of regulation and oversight that ensures product safety

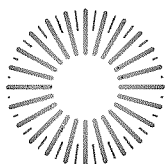
³⁹ NCSCT (2016), *Electronic cigarettes: A briefing for stop smoking services*. Available at: http://www.ncsct.co.uk/publication_electronic_cigarette_briefing.php.

⁴⁰ Cancer Research UK (2016), *E-Cigarettes in Stop Smoking Services*. Available at: https://www.cancerresearchuk.org/sites/default/files/e-ciq_in_sss_0.pdf.

⁴¹ WHO FCTC (2016), *Report on Electronic Nicotine Delivery Systems ("ENDS") and Electronic Non-Nicotine Delivery Systems ("ENNDS") to the seventh session of the Conference of the Parties*, available at http://www.who.int/fctc/cop/cop7/FCTC_COP_7_11_EN.pdf.

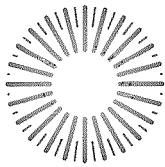
⁴² Available at <http://ukctas.net/news/commentary-on-WHO-report-on-ENDS&ENNDS.html>

⁴³ WHO FCTC (2016), *Report on Electronic Nicotine Delivery Systems ("ENDS") and Electronic Non-Nicotine Delivery Systems ("ENNDS") to the seventh session of the Conference of the Parties*, available at http://www.who.int/fctc/cop/cop7/FCTC_COP_7_11_EN.pdf at paragraph 5.



whilst allowing scope for manufacturers to continue to develop the product category and to deliver the best possible reduced-risk alternatives to conventional cigarettes.

- 3.6.2 **Quality & safety standards:** The government should collaborate with the industry and other stakeholders to develop high product standards, based on robust science to reassure consumers and regulators that the products on the market meet appropriate criteria with regards to quality and safety. These should include provisions relating to e-liquid content, safe refilling of e-liquid tanks, aerosol content, product stability, content labelling, device safety and child proofing.
 - 3.6.3 **Responsible marketing to adults only:** As above, BATHK believes that advertising and promotional activities should only be directed at adults. Given the reduced risk potential of these products (discussed above), the Government should develop marketing guidelines that ensure that manufacturers adhere to responsible marketing practices, whilst enabling communication with adult consumers regarding the attributes of these products. The Government should also enable manufacturers to make comparative claims, provided that such claims are factually accurate and substantiated.
 - 3.6.4 **Freedom to collaborate & communicate:** The public and private sectors need to work together to accurately communicate the benefits of potentially lower-risk products, including e-cigarettes, so that consumers are able to make informed decisions.
 - 3.6.5 **Distribution freedoms:** For e-cigarettes to fulfil their true potential as a viable alternative to cigarettes, they should be widely available in all the retail channels where smokers buy their cigarettes, including online.
 - 3.6.6 **Innovation freedoms:** Product improvement and innovation will further improve product functionality and quality as the category grows to enable the development of a compelling range of products for adult consumers.
 - 3.6.7 **Tax & excise:** As e-cigarettes do not contain tobacco, they should not be subject to excise. The imposition of excise would increase their price and reduce consumers' incentive to continue to switch from conventional cigarettes to e-cigarettes.
- 3.7 We also enclose a copy of a report prepared by Ernst & Young LLP, which provides an objective review of the various literatures on the use of e-cigarettes, for the Panel's consideration.
4. **CONCLUSION**
- 4.1 In view of the above, BATHK respectfully invites the Panel and the Government to study the science and evidence relating to e-cigarettes and THPs before introducing any proposed regulations. In this connection, BATHK is happy to provide further information



and is prepared to work together with the Panel and the Government to establish regulatory regimes that reflect the risk profile of these products.. Please feel free to contact us should you have any queries.

Yours faithfully,

Henry Smith Freehills

Encls.

Enclosures

1. 'British American Tobacco publishes a series of studies supporting the reduced-risk potential of glo' published by Dr Marina Murphy of British American Tobacco (November 2017)
2. Statement on the toxicological evaluation of novel heat-not-burn tobacco products by Committee on Toxicity – COT2017/04 (December 2017)
3. Toxicological evaluation of novel heat-not-burn tobacco products – non-technical summary by Committee on Toxicity – COT2017/04 (December 2017)
4. British American Tobacco (2017), 'ANDS role in supporting public health strategies' (September 2017)
5. 'Tobacco heating products overview of the scientific assessment of glo' prepared by British American Tobacco
6. 'Tobacco heating products glo: measurement of mainstream emissions' prepared by British American Tobacco
7. Ernst & Young LLP (2017), 'Electronic Nicotine Delivery Systems: Review of scientific literature 2011-2016' (February 2017)

CONTACT:

Dr Marina Murphy British American Tobacco
Marina_murphy@bat.com | +44(0)7711 150135



BRITISH AMERICAN
TOBACCO

FOR IMMEDIATE RELEASE

British American Tobacco publishes a series of studies supporting the reduced-risk potential of glo

- glo, a tobacco heating product (THP), heats rather than burns tobacco
- Studies reveal that the numbers of toxicants and the levels at which they are detected in glo emissions are significantly lower than those in cigarette smoke
- In contrast to cigarette smoke, studies reveal glo vapour to have little or no impact on human cells in the lab, in some cases having the same impact as air
- Based on these and other test results, glo has the potential to be significantly reduced risk compared to cigarettes

November 2017, Southampton, UK: Scientists at British American Tobacco have conducted a series of tests that help establish glo as having the potential to be reduced risk compared to traditional cigarettes. glo is a tobacco-heating product that heats rather than burns tobacco and does not produce cigarette smoke. It is currently available in five markets: Japan, Korea, Switzerland, Canada and Russia.

The tests used were specifically developed to help assess the relative risk of products like glo. The tests included analysing how people use glo, the content of the vapour and what that vapour does to cells in certain laboratory tests. The results are combined to create an overall picture that reveals glo vapour to be relatively simple compared to cigarette smoke and to have much less, or no (depending on the particular test used), impact on cells in the lab compared to smoke.

“A key part of our company strategy is developing and commercialising a range of products that offer consumers potentially less risky alternatives to conventional cigarettes,” said Dr James Murphy, Head of Reduced Risk Substantiation at British American Tobacco. “This is a rapidly evolving category and both consumers and regulators rightly want as much information as possible about the products available. That is why we believe a science-based approach is vital to gathering the evidence we need to demonstrate the reduced-risk potential of glo,” Murphy said.

Test One - What's in the Vapour?

Understanding what is in the vapour produced by glo is important because it will show what a consumer may be exposed to when they use the product. It will also reveal the difference in toxicant emissions between glo vapour and cigarette smoke.

It is widely understood that it is the toxicants in smoke that cause most smoking-related diseases. Removing combustion from the equation, thereby removing smoke and reducing the number and levels of smoke toxicants, should, therefore, theoretically go some way towards



creating a potentially reduced-risk product. glo does not produce smoke because it heats rather than burns tobacco.

Scientists at BAT first studied how people used glo and used this information to programme puffing robots in the lab. The robots then puffed on glo to produce vapour in a realistic way.

This vapour was then passed through filters, which on visual inspection reveal the stark difference between glo vapour and smoke from cigarettes, see Figure 1. However, when understanding what's in an aerosol, what you can't see can be just as important as what you can see.

For this reason, a series of further analyses were conducted comparing the chemical composition of glo vapour with that of smoke. The results reveal the relatively simple composition of glo vapour compared to conventional cigarette smoke. An example of the kinds of results obtained can be seen in Figure 2. Scientists found substantial reductions in the numbers and levels of toxicants in the glo vapour for all toxicant groups measured. In fact, most cigarette smoke toxicants could not be detected in the glo vapour. Overall, there are around 90-95% less toxicants in glo vapour, so it should in principle expose consumers to less toxicants compared to smoke*.

Test Two - Vapour vs Smoke

A further batch of tests was employed to compare glo vapour with smoke in terms of the impact on living cells in the lab.

Puffing robots were again used, but this time in combination with a special system that allows living cells grown in the lab to be exposed to aerosols. One such system was developed to mimic the way human lung cells are exposed to aerosols in real-life. Using this system, it was shown that glo vapour has a much-reduced, or no (depending on the test used), biological impact on cells in the lab, compared to conventional cigarette smoke.

Unlike cigarette smoke, glo vapour was not toxic to human airway cells and did not cause mutations in DNA or promote the development of tumours in the tests used*. In many cases, the results were similar to those obtained when the cells were exposed to air.

Test Three – Second-Hand Vapour?

Cigarette smoke enters the environment when smokers exhale but also when cigarettes smoulder, which they do even when not being actively smoked. glo is different from cigarettes in that it doesn't smoulder between puffs, as it does not burn tobacco. However, there is often a visible vapour cloud produced when people use products like glo. Because of this, perhaps it is not surprising that some people ask the question: is there anything in the exhaled vapour that by-standers should be worried about?

For this reason, scientists at BAT analysed indoor air quality and the tobacco odour of an environmentally controlled room where volunteers used glo over a period of four hours. Air from the room was sampled and compared to air from the room when volunteers smoked cigarettes as well as air from the room when no products were used. These tests were



conducted in the room at different air flows, to simulate a home, office or hospitality environment.

In the air sampled from the glo room, most toxicants measured could not be detected at all. Overall, the results reveal substantial reductions in numbers and levels of environmental toxicants for glo use compared to cigarette smoking*. Additionally, tobacco odour on hair, clothes and skin was not an issue in the room when people used glo.

Assessing Reduced Risk

When taken together the results of these, and other studies, show that there is a wide gap between glo and conventional cigarettes in terms of the aerosols they produce, with glo emitting substantially reduced numbers and levels of certain known toxicants as compared to those from conventional cigarettes. glo vapour also has much-reduced or no biological impact on human cells in the biological tests performed as compared to cigarette smoke.

This means that when ranked along an emissions spectrum, cigarettes are at one end of a spectrum (high toxicant levels) and glo is at the other end (low toxicant levels).

'When taken together with the reduced levels of responses seen in the biological tests, these results place cigarettes and glo at opposite ends of an emissions spectrum, although more long-term studies will be needed to substantiate if this translates to a reduction in risk,' said Murphy.

Does this mean that glo is safer than cigarettes?

One test alone cannot prove reduced risk. However, taken together these initial results indicate that glo has the potential to be substantially reduced risk compared to cigarettes. However, we are in the process of conducting longer term studies to better understand these products and until these studies are completed, we cannot say at this stage that these products are less harmful than other tobacco products.

"We've long been committed to research in this area and to communicating to consumers and regulators that the information on our products is based on sound, evidence-based science. This is just the beginning," Murphy said.

These results were published in a special issue of the Journal [Regulatory Toxicology and Pharmacology](#).

British American Tobacco's Commitment to NGPs

British American Tobacco has invested more than US\$2.5 billion over six years in developing and commercialising a world-leading portfolio of products in the Next Generation Products (NGPs) category. British American Tobacco currently has NGPs in 16 markets, with three of four consumers using THPs in Tokyo using glo, BAT has a bold ambition to realise revenue of more than £5bn from NGPs by 2022.

ENDS

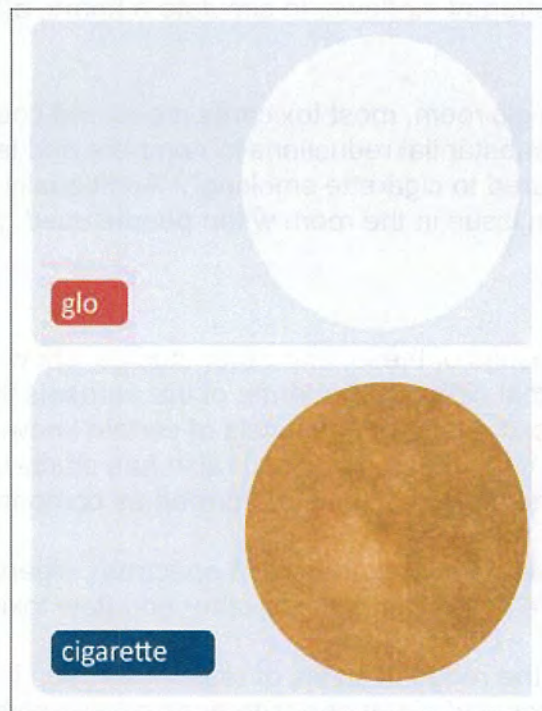


Figure 1: Filter pads with glo aerosol (top) and smoke from a reference cigarette (bottom).

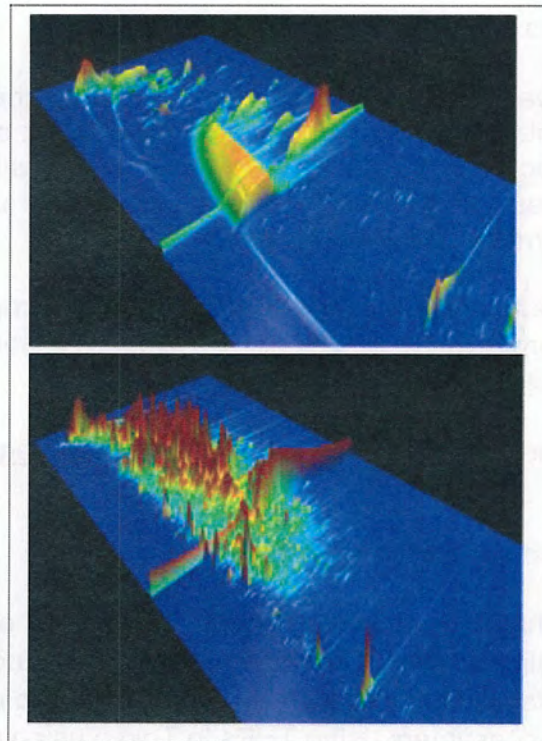


Figure 2: The number of peaks in the top graph (glo) are smaller than in the bottom graph (cigarette) reflecting the fact that glo produces a simpler aerosol, contains less compounds than smoke from a cigarette (bottom).



NOTES to Editors

About British American Tobacco: British American Tobacco is a global tobacco and next generation product company with brands sold in more than 200 markets. It employs more than 50,000 people worldwide and has over 200 brands in its portfolio, with its cigarettes chosen by one in eight of the world's one billion smokers. Leading global brands include Dunhill, Kent, Pall Mall and Lucky Strike.

About Next Generation Products (NGP): Next Generation Products is part of the British American Tobacco Group and is focused on developing and delivering high-quality alternative nicotine and tobacco products for adult smokers in the key areas of Vapour and Tobacco Heating Products. For more information see www.goVype.com and www.bat-science.com.

About Tobacco Harm Reduction: The only way to avoid the risks associated with tobacco use is not to consume tobacco at all, and the best way to reduce the risks is to stop using tobacco. However, the concept of harm reduction is increasingly being considered in relation to tobacco use. Harm reduction is about finding practical ways to minimise the health impact of an inherently risky activity or behaviour, without seeking to stop it entirely. It is a key element of BAT's business strategy and is being discussed by some regulators. We think it's important to work towards producing consumer-acceptable, potentially reduced risk products. We believe that tobacco regulatory policies should include harm reduction approaches for the millions of adults globally who will continue to consume tobacco products.

The Public Health Impact of e-cigarettes and other Next-Generation Products: Many in the public health community believe e-cigarettes offer great potential for reducing the public health impact of smoking. Public Health England, an executive body of the UK Department of Health, recently published a report saying that the current expert estimate is that using e-cigarettes is around 95% safer than smoking cigarettes. The Royal College of Physicians have said that the public can be reassured that e-cigarettes are much safer than smoking and that they should be widely promoted as an alternative to cigarettes.

Whats in the vapour? The results reported here are based on a comparison between the smoke from combusted tobacco in a standard 3R4F reference cigarette (approximately 9 mg tar), and the vapour from heated tobacco in glo, in terms of the 9 types of harmful components which the World Health Organisation recommends to reduce in cigarette smoke.

* These qualities do not necessarily mean this product is less harmful than other tobacco products



**COMMITTEES ON TOXICITY, CARCINOGENICITY AND MUTAGENICITY OF
CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT
(COT, COC and COM)**

**Statement on the toxicological evaluation of novel heat-
not-burn tobacco products**

Introduction

1. The COT, with support from the COC and the COM, was requested to assess the toxicological risks from novel heat-not-burn tobacco products, and compare these risks to those from conventional cigarettes. This assessment will provide the Department of Health (DH) and Public Health England (PHE) with a general opinion on the toxicological risks of such products. It will not fulfil any regulatory function of PHE.

2. To date, two novel heat-not-burn tobacco products have been notified to PHE in accordance with the Tobacco and Related Products Regulations 2016.

What are novel heat-not-burn tobacco products?

3. Novel tobacco products are defined in The Tobacco and Related Products Regulations 2016 as a tobacco product which –

- a. Is not a cigarette, hand rolling tobacco, pipe tobacco, waterpipe tobacco, a cigar, a cigarillo, chewing tobacco, nasal tobacco or tobacco for oral use; and
- b. Is first supplied by the producer after 19th May 2014.

4. In heat-not-burn tobacco products, processed tobacco is heated instead of being burnt as is the case for conventional tobacco products. Under the definition in the Tobacco and Related Products Regulations 2016, these are therefore novel tobacco products, and hence are required to be notified to PHE. In this evaluation, the Committees have considered the two heat-not-burn tobacco products which had been notified to PHE by November 2016, and which are available on the UK market.

5. A recent consultation by HM Treasury¹, noted there is a range of heat-not-burn tobacco products, where:

- a. processed tobacco is heated directly to produce vapour
- b. processed tobacco is designed to be heated in a vaporiser
- c. devices produce vapour from non-tobacco sources, where the vapour is then passed over processed tobacco in order to flavour the vapour

6. The two products assessed by the Committees fall into the first and last of these groups, and as a result the temperature to which the tobacco is heated varies considerably between them. This may result in differences in the potential health outcomes. For one product, where the tobacco is heated directly, a maximum heating temperature of up to 350 °C was reported, while for the other product, in which the tobacco is heated by a vapour, the maximum temperature of the tobacco was reported to be less than 50 °C. For comparison, when tobacco in cigarettes is burnt it reaches temperatures of at least 800 °C.

Information obtained

7. The Committees reviewed data submitted to the EU Common Entry Gateway, the EU portal through which manufacturers submit information to the competent authorities of each Member State as per the requirements of the Tobacco & Related Products Regulations 2016, which transposes the EU Tobacco Products Directive (2014/40/EU).

8. To facilitate the discussion, a consolidated list of the types of information needed by the Committees to undertake their assessment was produced. The two manufacturers of products notified in the UK before November 2016 were asked to present the data they hold addressing these information needs to a joint discussion session of the COT, COC and COM held on 16th May 2017. The list of Committees' information needs is appended to this statement at Appendix 1.

9. In addition to the manufacturers' data, a literature search was undertaken to identify any available independent data on these products.

Available data

10. Of the two products considered, there was a marked difference in the amount of data available from the manufacturers on which the Committees could base their assessment. Only limited information on these products is available from independent sources.

¹ Tax treatment of heated tobacco products, published 20 March 2017: <https://www.gov.uk/government/consultations/tax-treatment-of-heated-tobacco-products/tax-treatment-of-heated-tobacco-products> (accessed 19/06/2017)

Exposure

11. Investigations on both products showed a decrease in the harmful and potentially harmful compounds (HPHCs) in the aerosol generated by the device to which the user would be exposed, compared to the HPHCs in the mainstream smoke from a conventional cigarette². For both products, there were some HPHCs where the reduction was approximately 50%, but the reduction in a number of other HPHCs was greater than 90%, with many of the compounds being below the limits of detection or quantification for the assays used.

12. The Committees also requested data on additional contaminants from the devices themselves, as this had been identified as a possible area of concern for e-cigarettes. The available data presented and discussed with the manufacturers provided no evidence for exposures other than from compounds also present in conventional cigarette smoke.

13. The design of the devices means that any potential sidestream emissions from them will be very different to those from the burning tip of conventional cigarettes. In terms of environmental exposure to bystanders, indoor air following use of the heat-not-burn tobacco products has been assessed by both manufacturers, and compared with background and environments where conventional cigarettes (market brands) have been used. These assessments showed that while some of the measured components increased above background with the use of the heat-not-burn tobacco products, much greater increases occurred across all the measured components (volatile organic compounds, combustion related markers and tobacco smoke related markers including nicotine) following use of conventional cigarettes.

Toxicity data

14. In compiling the list of information requested by the Committees for this evaluation, there was a focus on cancer, mutagenicity, respiratory-related health effects, cardiovascular and liver effects.

15. The greatest contrast in the available data for the two products provided by the manufacturers was with respect to the type of toxicity data available. For both products however, two genotoxicity tests had been undertaken. For one product where tobacco is directly heated, *in vivo* study data were available for some endpoints with further work planned as well as some *in vitro* data, while for the other product where the tobacco is heated by a vapour, information was available from *in vitro* studies only.

² Throughout the statement, unless otherwise stated, comparison was between the product and the Kentucky 3R4F reference cigarette.

Epidemiological data

16. Both products are already available on the market in the UK and other countries around the world. Post-market surveillance is being undertaken by both manufacturers in these countries.

17. In addition, for the product where tobacco is directly heated epidemiology studies have been undertaken, mostly relating to the pattern of use rather than on health. Studies are continuing and the manufacturer's aim is to assess the impact on human health, directly or indirectly, compared to people who continue to use their preferred market brand of conventional cigarettes.

Committees' discussion

18. The Committees have considered only the two products notified in the UK, which therefore does not cover all three of the types of product outlined in the HM Treasury consultation on taxation of heated tobacco products.

19. A number of differences were identified between the two products, including the temperature to which the tobacco is heated, which will potentially have an impact on the number and amount of compounds that become volatilised and can be inhaled by the user. There is also a difference in the source of the nicotine in the aerosol. In the product where the tobacco is heated directly, the nicotine is derived from the tobacco in the device, while for the other product the nicotine is (mainly) within the liquid, which is aerosolised and passed through the tobacco.

20. The Committees noted the difference in the amount of toxicological and related data available for the two products, influencing the certainty of conclusions across the range of heat-not-burn tobacco products.

21. The request for the Committees to assess the absolute risk of heat-not-burn tobacco products was not possible to address. While there are data available on risks associated with cigarette smoking, it is not possible to extrapolate from these studies as the relative concentrations of the HPHCs in tobacco smoke are different to those in the aerosol from heat-not-burn tobacco products. Further, information on the quantitative contribution of specific compounds to the risk from exposure to conventional cigarettes and their emissions is not available.

22. The data, both from manufacturers and the limited independent sources, indicated that the aerosol generated from these novel products contains HPHCs, some of which are mutagenic and carcinogenic. The normal recommendation of the Committees is that exposure to such chemicals is kept as low as reasonably practicable, but there would be a likely reduction in risk for smokers deciding to use heat-not-burn tobacco products compared with continuing to smoke cigarettes as the exposure to HPHCs is reduced. Nevertheless using heat-not-burn tobacco products would involve a greater risk compared to stopping smoking completely.

23. A reduction in risk would be expected to be experienced by bystanders where smokers switch to heat-not-burn tobacco products.

24. The Committees were concerned over the potential for non-smokers including children and young people, who would not otherwise start to smoke cigarettes, to take up using these products as they are not without risk. There was also concern over whether use of these products would lead people to take up smoking cigarettes. Though outside the Committees' remit, monitoring of the number of non-smokers who take up use of heat-not-burn tobacco products, and their age profile, would be useful, and also if it could be determined whether in the absence of heat-not-burn tobacco products they would have taken up smoking.

25. The data considered by the Committees was not sufficient to comment on the relative risks of heat-not-burn tobacco products and e-cigarettes. This is of interest in case people switch from e-cigarettes to heat-not-burn tobacco products, and the Committees noted the potential that if people perceive e-cigarettes as safe this perception could transfer to heat-not-burn tobacco products, despite a lack of data on which to establish this. It was noted that for the product where a heated vapour is drawn over the tobacco for flavour, there are similarities with e-cigarettes, so some of the potential concerns that the COT has scoped out for e-cigarettes may also apply to this product (see TOX/2016/25). Consideration of these two aspects could be made when the COT e-cigarette work is taken forward.

26. The Committees considered the potential risks from use of these products during pregnancy. The current UK advice to pregnant women is to stop smoking entirely. However, the advice states: "If using an e-cigarette helps you to stop smoking, it is much safer for you and your baby than continuing to smoke" (NHS, 2017). There is no toxicity data for heat-not-burn tobacco products on the risk to the unborn child following use by the mother. Based on exposure to compounds of concern being reduced with heat-not-burn tobacco products compared to conventional cigarettes, the Committees considered that, though the aim should be for pregnant women to stop smoking entirely, the risk to the unborn baby is likely to be reduced if using these products during pregnancy instead of smoking. The Committees cannot presently comment on the relative risks of use of heat-not-burn tobacco products compared to e-cigarettes during pregnancy.

27. It was emphasised that nicotine itself is addictive, and can have harmful effects on health. In addition, users of any nicotine product would use the product in such a way, and in such quantity, as to achieve a similar effect to that they were used to from their previous smoking products. Depending on the concentrations of nicotine in different products, relative exposure to other compounds of concern could be increased or decreased in the process of achieving the desired nicotine effect. For example, a user might take a fewer or greater number of puffs, or use these products more often or for longer than they did with conventional cigarettes.

Committees conclusions and recommendations

28. Tobacco smoking and smokeless tobacco for oral or nasal use are carcinogenic to humans, and have been classified by IARC as Group 1 carcinogens.

29. The aerosol generated by heat-not-burn tobacco products contains a number of compounds of concern, some of which are carcinogens, and there will be a risk to the health of anyone using these products.

30. For non-smokers who start to use these products, this will be an increase in risk, compared to if the products were not used. The Committees were particularly concerned for young people, who do not smoke, starting to use these products, due to the potential for longer exposure over the remainder of their lives compared to adults and to possible differences in sensitivity.

31. As the exposure to compounds of concern in the aerosol is reduced compared to conventional cigarette smoke, it is likely that there is a reduction in risk, though not to zero, to health for smokers who switch completely to heat-not-burn tobacco products.

32. The risks associated with use of heat-not-burn tobacco products cannot be quantified due to gaps in the information available and uncertainties in the dose-response relationship of the chemicals and potential adverse health outcomes. In addition, the levels of the different compounds in the aerosol vary compared to the levels in smoke from conventional cigarettes and therefore it is not possible to extrapolate from epidemiological data on smoking risks, particularly given the complexity of the interactions that occur between these compounds in producing adverse health effects.

33. As these products contain nicotine and are designed to deliver similar levels of nicotine to conventional cigarettes, their use will not reduce nicotine exposure or its risk to health and possibility of addiction from nicotine.

34. Most of the data on heat-not-burn tobacco products has been provided by the product manufacturers. To date there has been limited independent confirmation of the manufacturers' findings, and for public health reassurance the Committees consider it important to obtain independent verification of the manufacturers results.

35. Further information on the population impact of availability of these products should be collected, including uptake of these products by smokers and non-smokers and their age profile, whether product switching or dual use occurs including with e-cigarettes, uptake of smoking as a result of use of these products by non-smokers, and overall population exposure, including bystanders, to compounds of concern.

36. In addition to the requested comparison of novel heat-not-burn tobacco products with conventional cigarettes, it is of interest to compare the risks from these products to those from e-cigarettes. This will be borne in mind when the COT considers e-cigarettes, but is not possible to address based on the data presented to the Committees as part of the current evaluation.

37. Overall, the Committees conclude that while there is a likely reduction in risk for smokers switching to heat-not-burn tobacco products, there will be a residual risk

and it would be more beneficial for smokers to quit smoking entirely. This should be part of any long-term strategy to minimise risk from tobacco use.

COT, COC and COM
COT 2017/04; December 2017

References

NHS (2017). Stop smoking in pregnancy. Available:
<http://www.nhs.uk/conditions/pregnancy-and-baby/pages/smoking-pregnant.aspx>
(accessed 07/09/2017)

COT Statement 2017/XX – Appendix 1

COMMITTEES ON TOXICITY, CARCINOGENICITY AND MUTAGENICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COT, COC and COM)

Toxicological evaluation of novel heat-not-burn tobacco products

List of COT, COC and COM information needs for assessment of novel heat-not-burn tobacco products sent to the manufacturers of products notified to Public Health England by November 2016.

Information needs for COT, COM and COC evaluation of heat not burn tobacco products

Cigarette smoking has been associated with many health problems; for example addiction, cancer, and cardiovascular effects. In evaluating heat not burn products we wish to consider both hazard identification of aspects that may be new to heat not burn products (for example nanoparticles and device related issues) as well as comparing risk for known chemicals, and considering the risks associated with combined use of burn and heat not burn products.

Aspects relating to the Tobacco containing product:

- Constituents and Chemical composition
- Additives
- Temperature of heating, and chemical processes occurring at that temperature
 - How these differ from heating and burning processes occurring in conventional cigarettes – i.e. what is new chemistry

Aspects relating to the delivery device

- Releases (e.g. metals – nickel in particular was mentioned)
- What is the overlap with devices such as e-cigarettes, and any devices assessed by MHRA

Exposure

- Chemicals in the mainstream 'smoke'
- Nicotine levels
- Chemicals released to the environment

- What the user is inhaling
- What is in the air surrounding the user including what is exhaled by the user, resulting in passive/bystander exposure
- What is in the general environment as a result of use of the product

- How is air quality assessed
 - What particulate matter is in the aerosol
 - What nanoparticles arise from use
 - Other chemicals released during and after use

- Likely age groups for anticipated use – attractiveness of use to younger age groups
- Appropriate use levels
- Accidental exposure, and routes of exposure – especially to children
- Potential for deliberate mis-use or overdose – e.g. reports of use of e-cigarette fluids as eye drops

- Cumulative exposures, including to nicotine, arising from use in conjunction with conventional or electronic cigarettes
- Consider potential for formation of cancer-causing chemicals as a result of combination e.g. with dietary chemicals even if no longer present in 'smoke'

Health effects

For each set of data it is important to know how the evaluation or tests were carried out, e.g. according to standard methods or otherwise. COT, COM and COC would require documentation of the methods and statistical analyses undertaken, as well as dose response data on the biological effects observed.

- Acute effects
 - Mutagenicity endpoints e.g.
 - DNA Strand breaks
 - Clastogenicity
 - Aneuploidy
 - Gene mutation (Point mutation, Deletion, Rearrangement or Recombination)
 - Genotoxicity test types (Bacterial, Mammalian in vitro or in vivo, Site of contact – oral and respiratory, Target organ, Germ cell)
- Chronic effects
 - Cancer effects
 - Respiratory toxicity
 - Lung lipid metabolism
 - Systemic toxicity
 - Hepatotoxicity
 - Cardiovascular toxicity
- Sensitisation potential
- Systems biology data
- Epidemiological data
- Volunteer studies or Clinical assessment
 - Pharmacokinetics and Pharmacodynamics
 - Biomarkers assessed – including relevant early markers
 - Cancer
 - Cardiovascular
- Post Market Assessment
- Specific toxicity effects of nicotine at the exposure levels resulting from use of these products

**COMMITTEES ON TOXICITY, CARCINOGENICITY AND MUTAGENICITY OF
CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT
(COT, COC and COM)**

**Toxicological evaluation of novel heat-not-burn tobacco
products – non-technical summary**

Introduction

1. The COT, with support from the COC and the COM, was requested to assess the toxicological risks from novel heat-not-burn tobacco products, and compare these risks to those from conventional cigarettes.
2. To date, two novel heat-not-burn tobacco products have been notified to PHE in accordance with the Tobacco and Related Products Regulations 2016.

What are novel heat-not-burn tobacco products?

3. In heat-not-burn tobacco products, processed tobacco is heated in a controlled device instead of being burnt as is the case for conventional tobacco products.
4. A recent consultation by HM Treasury¹ noted there is a range of heat-not-burn tobacco products where:
 - a. processed tobacco is heated directly to produce vapour
 - b. processed tobacco is designed to be heated in a vaporiser
 - c. devices produce vapour from non-tobacco sources, where the vapour is then passed over processed tobacco in order to flavour the vapour
5. The two products assessed by the Committees fall into the first and last of these groups, and as a result the temperature to which the tobacco is heated varies considerably between them. For one product where the tobacco is heated directly, a maximum heating temperature of up to 350 °C was reported, while for the other product in which the tobacco is heated by a vapour, the maximum temperature of the tobacco was reported to be less than 50 °C. For comparison, when tobacco in cigarettes is burnt it reaches temperatures of at least 800 °C.

¹ Tax treatment of heated tobacco products, published 20 March 2017:
<https://www.gov.uk/government/consultations/tax-treatment-of-heated-tobacco-products/tax-treatment-of-heated-tobacco-products> (accessed 19/06/2017)

Information obtained

6. The two manufacturers of products notified in the UK before November 2016 were asked to present the relevant toxicity data they hold. In addition to the manufacturers' data, a literature search was undertaken to identify any available independent data on these products. This was very limited.

Exposure

7. Investigations on both products that were assessed by the Committees, showed a decrease in the harmful and potentially harmful compounds (HPHCs) to which the user would be exposed, compared to the HPHCs from a conventional cigarette². For both products, there were some HPHCs where the reduction was approximately 50%, and the reduction in other HPHCs was greater than 90%.

8. The Committees also requested data on additional contaminants from the devices themselves. The available data presented and discussed with the manufacturers provided no evidence for exposures other than from compounds also present in conventional cigarette smoke.

9. The design of the devices means that any potential sidestream emissions from them will be very different to those from the burning tip of conventional cigarettes. In terms of environmental exposure to bystanders, assessments showed that while some of the measured components increased above background with the use of the heat-not-burn tobacco products, much greater increases occurred following use of conventional cigarettes.

Toxicity data

10. In compiling the list of information requested by the Committees for this evaluation, there was a focus on cancer, respiratory, cardiovascular and liver-related health effects.

Epidemiological data

11. Both products are already available on the market in the UK and other countries around the world. Post-marketing surveillance is being undertaken by both manufacturers in these countries, but it is too early for epidemiological information on health impacts to be available.

Committees' discussion

12. A number of differences were identified between the two products notified in the UK, the most obvious being the temperature to which the tobacco is heated, which will potentially have an impact on the number and amount of compounds that thereby become volatile and can be inhaled by the user. There is also a difference in the source of the nicotine. In the product where the tobacco is heated directly, the

² Throughout the statement, unless otherwise stated, comparison was between the product and the Kentucky 3R4F reference cigarette.

nicotine is derived from the tobacco in the device, while for the other product the nicotine is present within the liquid that is aerosolised and passed through the tobacco.

13. The Committees were unable to assess the absolute risk of heat-not-burn tobacco products given the nature of the data available.

14. The data indicated that the aerosol generated from these products contains HPHCs, some of which are mutagenic and carcinogenic, and therefore there will be some risk to health from use of these products. The normal recommendation of the Committees is that exposure to such chemicals is kept as low as reasonably practicable, but it was recognised that these products could provide harm reduction for people who would otherwise smoke cigarettes.

15. There would likely be a reduction in risk for conventional smokers deciding to use heat-not-burn tobacco products instead of smoking cigarettes. However, stopping smoking entirely would lead to the greater reduction in risk.

16. A reduction in risk would also be experienced by bystanders where smokers switch to heat-not-burn tobacco products.

17. The Committees were concerned over the potential for non-smokers including children and young people, who would not otherwise start to smoke cigarettes, to take up using these products, as they are not without risk. There was also concern over whether the use of these products would lead to cigarette smoking by non-smokers. Information on this should be obtained before the overall impact on public health can be assessed.

18. The data considered by the Committees was not sufficient to comment on the relative risks of heat-not-burn tobacco products and e-cigarettes, though this is of interest.

19. The Committees considered the potential risks from use of these products during pregnancy. The current UK advice³ to pregnant women is to stop smoking entirely. However, the advice states: "If using an e-cigarette helps you to stop smoking, it is much safer for you and your baby than continuing to smoke". There is no direct data on the risk to the unborn child following use of heat-not-burn tobacco products by the mother. Based on reduced exposure to compounds of concern with heat-not-burn tobacco products compared to conventional cigarettes, the Committees considered that, though the aim should be for pregnant women to stop smoking entirely, the risk to the unborn baby is likely to be reduced if using these products during pregnancy instead of smoking.

20. The Committees emphasised that nicotine itself is addictive, and can have harmful effects on health. In addition, users of any nicotine product would use it in such a way, and in such quantity, as to achieve a similar effect to that they were used to from their previous smoking products. Depending on the concentrations of

³ Stop smoking in pregnancy. Available at: <http://www.nhs.uk/conditions/pregnancy-and-baby/pages/smoking-pregnant.aspx> (accessed 07/09/2017)

nicotine in different products, relative exposure to other compounds of concern could be increased or decreased in the process of achieving the desired nicotine effect. For example a user might take a fewer or greater number of puffs, or use these products more often or for longer than they did with conventional cigarettes.

Committees' conclusions

21. It is well recognised that using tobacco is carcinogenic and its use has other harmful effects on human health.
22. Using heat-not-burn tobacco products involves breathing in a number of compounds of concern, some of which are carcinogens.
23. The levels of the different compounds in the aerosol from heat-not-burn tobacco products are different to the levels in smoke from conventional cigarettes.
24. Heat-not-burn tobacco products contain nicotine and are designed to deliver similar levels of nicotine to conventional cigarettes; their use will not reduce nicotine exposure or the risk to health from and possibility of addiction to nicotine.
25. The Committees conclude that there will be a risk to health from using heat-not-burn tobacco products.
26. It is currently not possible to quantify this risk. Heat-not-burn tobacco products are new and there is insufficient data available to enable a full assessment.
27. The exposure to compounds of concern in using heat-not-burn tobacco products is reduced compared to that from conventional cigarette smoke. It is likely that there is a reduction in overall risk to health for conventional smokers who switch to heat-not-burn tobacco products.
28. While the Committees conclude there is a likely reduction in risk for smokers switching to heat-not-burn tobacco products, a risk remains and it would be more beneficial for smokers to quit smoking entirely.
29. A reduction in risk would be expected to be experienced by bystanders where smokers switch to heat-not-burn tobacco products.
30. The risk to the unborn child from use of these products by mothers during pregnancy is difficult to quantify and current NHS advice is to stop smoking entirely. The Committees consider that the risk to the unborn baby is likely to be reduced if these products were used during pregnancy instead of smoking, although the aim should be to stop smoking entirely.
31. Overall, the Committees conclude there are toxicological risks from novel heat-not-burn tobacco products though data on impacts to human health is very limited. Compared with the known risks from conventional cigarettes, they are probably less harmful. Even so, smokers would do better to quit entirely.

There is a growing body of evidence that non-combustible Alternative Nicotine Delivery Systems (ANDES) are potentially less harmful to health than cigarettes, and may play a powerful role in reducing smoking prevalence and the associated health impacts of smoking. Enactment of a balanced regulatory policy is crucial to realising the potential benefit of these products.

A. The harm caused by smoking is primarily attributable to the constituents of tobacco smoke and not nicotine itself, and there is a need to recognize the public health potential of less harmful nicotine products for smokers who do not want to quit nicotine use.

“it’s the other chemical compounds in tobacco, and in the smoke created by setting tobacco on fire, that directly and primarily cause the illness and death, not the nicotine.” Dr Scott Gottlieb, US FDA commissioner, July 2017.¹

Scientists widely agree that it’s largely the toxicants found in cigarette smoke that cause smoking related diseases – not the nicotine itself. Public health organisations, including the International Agency for Research on Cancer (IARC), the UK’s Royal College of Physicians and the UK’s National Institute for Health and Care Excellence (NICE) generally agree that nicotine, while addictive, is not the primary cause of smoking-related diseases and the harm of smoking is primarily caused by other constituents of tobacco smoke. IARC states that nicotine does not cause cancer directly,² and NICE has stated that “nicotine inhaled from smoking tobacco is highly addictive. But it is primarily the toxins and carcinogens in tobacco smoke – not the nicotine – that cause illness and death.”³

While smokers are aware of the risk of smoking, some find it difficult or do not want to quit nicotine. The challenge has been in providing alternative nicotine products that appeal to smokers and expose them to less toxic chemicals than cigarettes. A report by the UK Royal College of Physicians states that, “as most of the harm caused by smoking arises not from nicotine but from other components of tobacco smoke, the health and life expectancy of today’s smokers could be radically improved by encouraging as many as possible to switch to a smoke-free source of nicotine”⁴.

B. There are decades of research demonstrating that Swedish snus is substantially safer than smoking and Sweden has shown that a majority of smokers may, given the availability of a socially acceptable and affordable reduced risk alternatives, switch from smoked tobacco to a non-combusted alternative nicotine product.

“Snus has both contributed to decreasing initiation of smoking and, when used subsequent to smoking, appears to facilitate smoking cessation. All these effects suggest that the availability and use of snus has been a major factor behind Sweden’s record-low prevalence of smoking and the lowest level of tobacco-related mortality among men in Europe.”⁵

Swedish snus is an oral tobacco which many experts agree involves substantially less health risk than cigarette smoking. Sweden was the first country to fund an educational campaign on the risk of

¹ Gottlieb S, Protecting American Families: Comprehensive Approach to Nicotine and Tobacco, July 2017.

² <https://cancer-code-europe.iarc.fr/index.php/en/ecac-12-ways/tobacco/199-nicotine-cause-cancer>

³ Smoking: harm reduction (PH45), NICE, UK – last reviewed March 2017.

⁴ *Nicotine without smoke: Tobacco harm reduction*, a report by the Tobacco Advisory Group of the UK Royal College of Physicians, April 2016

⁵ Ramström L., Int. J. Environ. Res. Public Health 2016, 13(11), 1110

smoking, and at the same time taxed snus at a lower level than cigarettes.⁷ In the latest Eurobarometer survey (March 2017),⁶ Sweden boasted the lowest level of daily smoking prevalence by far in Europe (5%) while EU wide daily smoking prevalence is 24%. Snus has regained popularity in Sweden over cigarettes from 1970 and has consistently grown over time since then. While the overall daily consumption of tobacco (including snus) in Sweden is close to the daily consumption of the EU as a whole (25%), Sweden had the lowest level of lung cancer and COPD mortality (two diseases for which the main risk factor is smoking) in 2016 out of 10 comparable countries.⁷ Tobacco as a risk factor for death in Sweden fell by 11.5% between 2005 and 2016, ranking 5th as a risk factor in 2016 as compared to 3rd in 2005.⁹ In 2017, Sweden counted the most ex-smokers in the EU, at 41% compared to the EU average of 26%.⁸ The Swedish experience with snus helps prove the concept that smokers can transition to non-combusted alternative nicotine delivery systems, with consequent decreases in smoking prevalence and the number of deaths associated with smoking.

C. A more recent innovation, e-cigarettes, is increasingly being recognized as also having the ability to drive down smoking prevalence.

“Changes in prevalence of e-cigarette use in England have been positively associated with the success rates of quit attempts.”⁸

The UK government has recognised the potential role that e-cigarettes (and other novel products which expose users to less toxic chemicals) can have in reducing smoking prevalence, in its latest tobacco control strategy for England.⁹ The government does not tax nor regulate e-cigarettes as strictly as cigarettes and the latest stop smoking campaign in England featured e-cigarettes as one of the ways to quit smoking. E-cigarettes have been positively associated with successful quit smoking attempts in England and smoking prevalence has fallen to 16% in 2017, the second lowest in the EU, after Sweden.⁸ The latest evidence review of e-cigarettes undertaken by Public Health England (PHE), an agency of the UK Department of Health, concludes that quit smoking success rates in England are at the highest rates ever observed and that it is plausible that e-cigarettes are contributing to this. According to PHE, “the evidence suggests that [e-cigarettes] have contributed tens of thousands of additional quitters in England annually”.¹⁰

D. The most recent evidence review by Public Health England (PHE) has reiterated that vaping is likely to carry a small fraction of the risk compared to smoking for users that switch completely.

“Vaping poses only a small fraction of the risks of smoking and switching completely from smoking to vaping conveys substantial health benefits over continued smoking. Based on current knowledge, stating that vaping is at least 95% less harmful than smoking remains a good way to communicate the large difference in relative risk unambiguously so that more smokers are

⁶ Eurobarometer, report 458, issued May 2017: March 2017 survey data.

⁷ <http://www.healthdata.org/sweden>

⁸ Beard E *et al*, BMJ 2016;354:i4645 <http://dx.doi.org/10.1136/bmj.i4645>

⁹ Towards a smokefree generation, A tobacco control plan for England, Department of health, July 2017.

¹⁰ McNeill A, Brose LS, Calder R, Bauld L & Robson D (2018). Evidence review of e-cigarettes and heated tobacco products. A report commissioned by Public Health England. London: Public Health England.

encouraged to make the switch from smoking to vaping.”¹¹ Public Health England, February 2018, based on their previous evidence review report published in 2015, and a review of all peer reviewed literature published since then as well as survey data and other government's databases and reports.

The PHE report is the result of one of the most extensive reviews of peer reviewed literature, surveys, reports and databases undertaken and by a highly respected public body.

The PHE Report also concluded:

- One assessment of the published data on emissions from cigarettes and e-cigarettes calculated the lifetime cancer risks. It concluded that the cancer potencies of e-cigarettes were largely under 0.5% of the risk of smoking.
- Comparative risks of cardiovascular disease and lung disease have not been quantified but are likely to be also substantially below the risks of smoking. Among e-cigarette users, two studies of biomarker data for acrolein, a potent respiratory irritant, found levels consistent with non-smoking levels.
- There have been some studies with adolescents suggesting respiratory symptoms among e-cigarette experimenters. However, small scale or uncontrolled switching studies from smoking to vaping have demonstrated respiratory improvements.

A report by the UK Royal College of Physicians also concluded that: "... in the interests of public health it is important to promote the use of e-cigarettes, NRT (*Nicotine Replacement Therapy*) and other non-tobacco nicotine products as widely as possible as a substitute for smoking in the UK."¹²

There is a growing consensus that e-cigarettes expose users to much lower levels of toxic chemicals. One study that compared exposure to nicotine, tobacco-related carcinogens, and toxins among smokers of combustible cigarettes and former smokers with more than 6 months use of e-cigarettes, found that long-term e-cigarette-only use is associated with substantially reduced levels of measured carcinogens and toxins relative to smoking only combustible cigarettes. The authors also found no evidence that long-term e-cigarette-only use was associated with greater levels of carcinogens or toxins than NRT-only use.¹³ Taking into account several parameters such as cessation, initiation and relative harm, a recent model estimated that switching cigarette smokers to e-cigarette use over a 10-year period would lead to 1.6 to 6.6 million fewer premature deaths in the US under a pessimistic and optimistic scenario respectively.¹⁴

E. The emerging scientific evidence about Tobacco Heating Products (THP), also known Heat not Burn (HNB), is also pointing towards the potential for substantially reduced risk compared to cigarettes.

¹¹ McNeill A, Brose LS, Calder R, Bauld L & Robson D (2018). Evidence review of e-cigarettes and heated tobacco products. A report commissioned by Public Health England. London: Public Health England.

¹² *Nicotine without smoke: Tobacco harm reduction*, a report by the Tobacco Advisory Group of the UK Royal College of Physicians, April 2016.

¹³ Shahab L. *et al.*, *Annals of Internal Medicine*, Vol. 166 No. 6, 21 March 2017

¹⁴ Levy DT, *et al.* *Tob Control* 2018;27:18–25. doi:10.1136/tobaccocontrol-2017-053759

“It is likely that there is a reduction in overall risk to health for conventional smokers who switch to heat-not-burn tobacco products”.¹⁵ UK Committee on Toxicity, December 2017.

“The available evidence suggests that heated tobacco products may be considerably less harmful than tobacco cigarettes.”¹³ Public Health England, February 2018.

Given the understanding that it is the toxicants in cigarette smoke that cause most smoking-related diseases, THPs which remove burning tobacco and smoke from the equation and thereby reduce the number and levels of toxicants, should theoretically lead to a potentially reduced-risk product. Emerging evidence, assessed by PHE and the UK government’s Committee on Toxicity seems to support this theory. The evidence base will continue to evolve but it is clear that THPs are yet another consumer acceptable option for current smokers to consume nicotine and at the same time avoid cigarette smoke.

F. A ban on the use of all flavours will undermine the public health potential of new potentially reduced risk tobacco and nicotine products.

Scientific research conducted so far suggests that flavours are not what attracts young people to e-cigarettes. For example, in a study by Shiffman et al., (2015)¹⁶ teenagers were asked to rate their interest in using e-cigarettes on a scale of 0-10 and were offered a list of flavours. They reported minimal interest in flavours (average = 0.41 out of 10), much less so than adult smokers (1.73 out of 10), and their interest did not vary much across flavours.

This is supported by a study by Pepper et al., (2013)¹⁷ which analysed whether adolescent males were willing to try e-cigarettes, and specifically looked at whether there was a difference in respondents' willingness to try plain versus flavoured varieties. The study found that “[t]he same proportion of respondents were willing to try plain e-cigarettes or to try flavored e-cigarettes.”

However, the availability of flavoured e-cigarettes can be an important component for some smokers looking for an alternative to conventional cigarettes. This is further supported by a study by Farsalinos et al., (2013) which found that “[t]he average score for importance of flavours variability in reducing or quitting smoking was 4 (“very important”)” and that “the majority of participants stated that restricting variability of flavours would make the EC experience less enjoyable while almost half of them answered that it would increase craving for tobacco cigarettes and would make reducing or completely substituting smoking less likely.” The study concluded that “EC liquid flavourings play a major role in the overall experience of dedicated users and support the hypothesis that they are important contributors in reducing or eliminating smoking consumption.”¹⁸

In short, research to date finds that flavours are an important part of the attraction for adults to switch from smoking to vaping but are a generally irrelevant consideration for teenagers.

¹⁵ Toxicological evaluation of novel heat-not-burn tobacco products – non-technical summary, UK Committee on Toxicology, December 2017.

¹⁶ Shiffman et al., (2015) *The impact of flavor descriptors on non-smoking teens' and adult smokers' interest in electronic cigarettes*. *Nicotine Tob Res* 17(10)

¹⁷ Pepper et al., (2013) *Adolescent Males' Awareness of and Willingness to Try Electronic Cigarettes*, which found that flavours did not increase the attractiveness of e-cigarettes to teenagers.

¹⁸ Farsalinos et al., (2013) *Impact of Flavour Variability on Electronic Cigarette Use Experience: An Internet Survey* 11/47673130_2

Public health experts have also confirmed the importance of maintaining the availability of flavoured products. For example:

- The ex-director of UK anti-smoking charity ASH UK, Clive Bates has stated that "[n]on-users should understand that flavours are an important aspect of vaping and integral to the experience. They are also part of a migration away from tobacco. Initial switchers tend to favour tobacco flavours but gradually move on to non-tobacco flavours often as part of a permanent switch from smoking."¹⁹
- Jeff Stier, a Senior Fellow at the National Center for Public Policy Research in Washington DC, has also stated that: "we're also beginning to see scientific data pointing to the benefits of flavours helping people not only quit smoking, but more importantly, stay off cigarettes." He further added that "[h]umans learn by association. When we associate the pleasure of nicotine with the burnt tobacco, we think we like burnt tobacco. What flavors help us do is disassociate the pleasure of the nicotine with the burnt tobacco."²⁰

G. Many specialists in the areas of tobacco control, nicotine science and public health policy are calling for balanced regulation of ANDS because of their potential to contribute to the reduction of smoking prevalence and the projected health impacts of tobacco consumption. Regulation should enable novel nicotine product innovations to enhance their ability to compete with cigarettes and drive down smoking prevalence.

*"Armed with the recognition of the risk continuum, and the reality that all roads lead back to cigarettes as the primary cause of the current problem, we need to envision [...] a world where less harmful alternative forms, efficiently delivering satisfying levels of nicotine, are available for those adults who need or want them."*²¹ Dr Scott Gotlieb, FDA commissioner, July 2017

*"There is a need for regulation to reduce direct and indirect adverse effects of e-cigarette use, but this regulation should not be allowed significantly to inhibit the development and use of harm-reduction products by smokers."*²² UK Royal College of Physicians, April 2016.

Given the potential public health benefit of ANDS, these products need a regulatory framework that is different from cigarettes and encourage smokers to switch, such as lower taxes, factual advertisement and a wider range of flavours. It is also important that a broad range of products is available to appeal to the range of different preferences of smokers. Regulation is critical to creating responsible growth and consumer access and awareness. Such regulation should be evidence based, proportionate, take account of the relative risks of products and not treat these products in the same way as combustible tobacco.

¹⁹ Counterfactual, February 2015. www.clivebates.com

²⁰ <http://www.jeffstier.org/18998/q-a-defending-electronic-cigarettes-to-the-white>

²¹ Gottlieb S, Protecting American Families: Comprehensive Approach to Nicotine and Tobacco, July 2017.

²² *Nicotine without smoke: Tobacco harm reduction*, a report by the Tobacco Advisory Group of the UK Royal College of Physicians, April 2016



tobacco heating products
overview of the scientific
assessment of

glo



bat-science.com



tobacco heating products

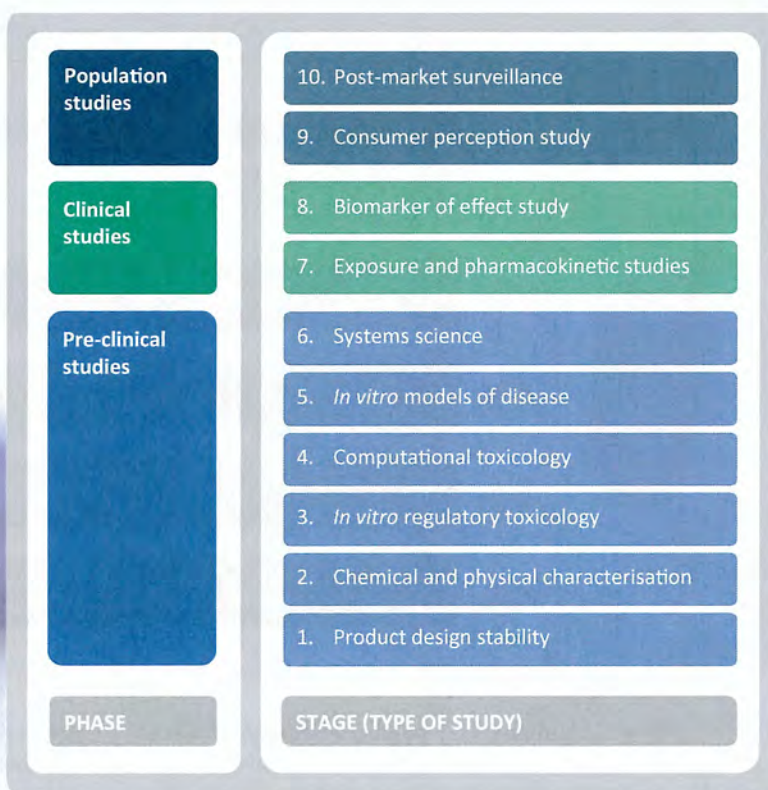
In the UK several public health agencies have advocated a potential role for Tobacco Heating Products in tobacco harm reduction.

It is widely known that cigarette smoking causes many human diseases including cardiovascular disease, lung disease and cancer. Novel tobacco products with reduced yields of toxicants compared with cigarettes, such as tobacco heating products (THPs),

snus and electronic cigarettes (ECs), may hold great potential for reducing the risks associated with tobacco use for smokers who choose to swap to only using such products instead of cigarettes. In the UK some public health agencies have advocated a potential role for Tobacco Heating Products in tobacco harm reduction. In 2017, the UK Independent Scientific Committee on Toxicity were asked by the UK Department of Health to study data on Tobacco Heating Products. They concluded: "As the expo-

sure to compounds of concern in the aerosol is reduced compared to conventional cigarette smoke, it is likely that there is a reduction in risk, though not to zero, to health for smokers who switch completely to heat-not-burn tobacco products." They acknowledged that the actual risks associated with the use of heat-not-burn tobacco products cannot be quantified for a number of reasons, such as due to gaps in the information available and that further research is required to verify the findings [Committee On Toxicology, 2017] Furthermore, a recent publication from Public Health England (PHE) concluded "The available evidence suggests that heated tobacco products may be considerably less harmful than tobacco cigarettes", but "more harmful than e-cigarettes" [McNeill, 2018] Again PHE highlighted that more independent research is needed on THPs.

substantiating risk



At British American Tobacco we risk assess all our next generation products before launch. In terms of THP consumables, ingredients are sourced at the high purity. Flavours are food grade as a minimum and any ingredient that is a carcinogen, a mutagen or a reproductive toxicant is excluded from recipes. Furthermore, regulations in the EU under the revised Tobacco Product Directive (TPD), require manufacturers to submit dossiers of information on their products disclosing ingredients and ensuring that electrical safety testing has been successfully completed and that the product has the requisite

electrical safety certificates. Additionally, suitable device materials that do not leach chemicals during consumer use are selected to augment product safety.

Claims on these novel products such as 'reduced exposure' and 'reduced risk' should be substantiated using a weight of evidence approach based on a comprehensive scientific assessment. The US Food and Drug Administration (FDA), has provided draft guidance outlining a framework to assess novel products as Modified Risk Tobacco Products (MRTP) [FDA 2012]. In October 2017 the Italian government trans-

posed the European Union Tobacco Products Directive (EU TPD) to include a regulatory framework, whereby [in a similar manner as the US] manufacturers could submit dossiers to potentially support [health-related] claims on heated tobacco products that could be printed on product packaging. Based on this, we previously proposed a scientific framework (Figure 1) comprising pre-clinical, clinical, and population studies to assess the risk profile of novel tobacco products [Murphy 2017].

Figure 1/ Scientific framework for assessing the risk profile of glo



TOXICOLOGICAL STUDIES

TOXICANTS OF INTEREST (CIGARETTE V GLO)



3%

WHO (9 PRIORITY TOXICANTS)

4%

FDA (18 PRIORITY TOXICANTS)

4%

HEALTH CANADA (MAIN 44 TOXICANTS)

4%

FDA (93 HARMFUL AND POTENTIALLY HARMFUL CONSITUENTS)

100% = CIGARETTE

We have published a series of 10 papers to date, that describe both the operation of a new commercial THP (glo) and its assessment in a series of pre-clinical clinical and population based studies [Proctor 2018]. With no combustion and maximum heating of the tobacco to $240^{\circ}\text{C} \pm 5^{\circ}\text{C}$ in glo, the tobacco consumable did not form any ash as is found with cigarette smoking [Eaton 2018]. The emissions of glo correspondingly showed around 90–95% fewer tested toxicants than those measured in cigarette smoke.^a Furthermore, a range of analyses of physical properties concluded that the aerosol

produced was respirable. [Forster 2018a] The environmental emissions were substantially reduced when consumers used glo compared with when they smoked cigarettes, to the extent that for the majority of measured constituents, the environmental emissions were at similar levels as those from the baseline measurements, when the consumers were not using any products. Furthermore, the PM10 measurement of the aerosol would conform with the recommended WHO outdoor air limit of $10 \mu\text{g}/\text{m}^3$. This reduction in environmental emissions led to a reduction in the tobacco odour on hands, hair and fabric being perceived

from using glo compared with smoking cigarettes under a set of laboratory tests. The reduction in environmental emissions and tobacco odour with glo were measured versus both a flue-cured blended cigarette and US-blended cigarettes. [Forster 2018b] A series of *in vitro* toxicological studies indicated that glo was non-mutagenic, showed no tumour promotion activity [Thorne 2018] and elicited a substantially reduced cytotoxic response that was 97% reduced relative to the response from cigarette smoke [Jaunky 2018]. A separate study that used a high-content screening approach with eight end

Figure 2/ Average reduction in toxicant levels in the aerosol of glo relative to a scientific reference cigarette

^a This is a comparison between the smoke from combusted tobacco in a 3R4F scientific reference cigarette (approximately 9 mg/cig 'tar'), and the vapour from heated tobacco in glo, in terms of the nine types of harmful components which the World Health Organisation recommends to reduce in cigarette smoke."

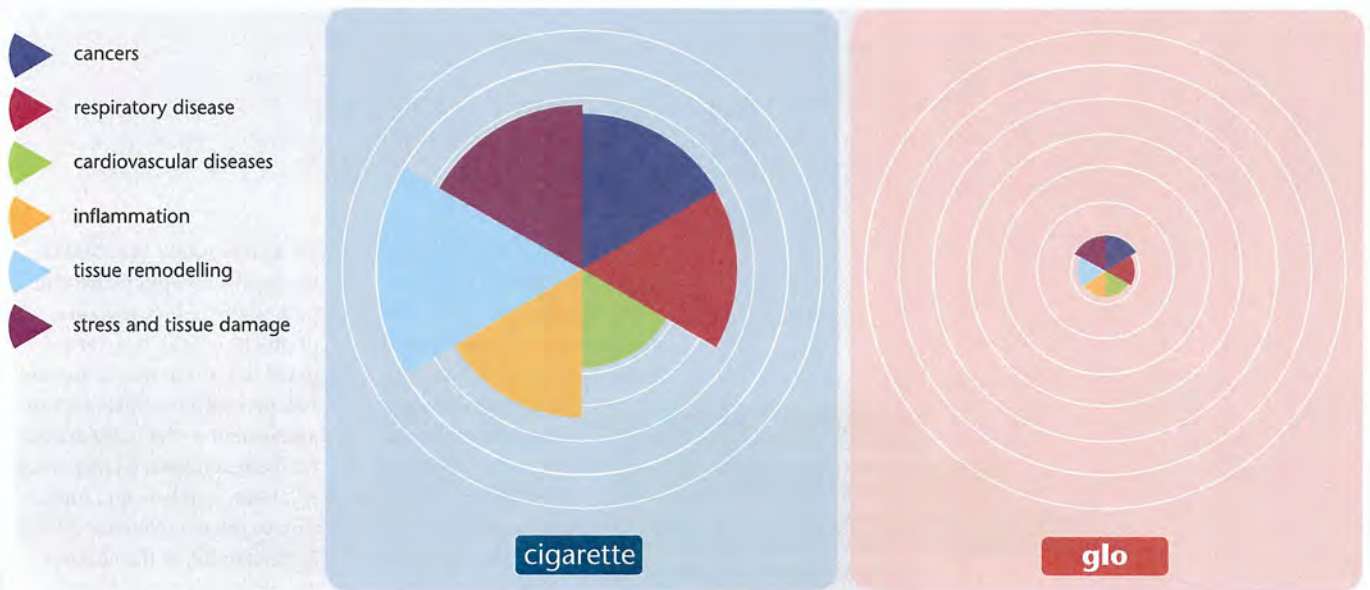


Figure 3/ In laboratory tests, glo promotes substantially less disease relevant gene changes in comparison to a scientific reference cigarette, 3R4F

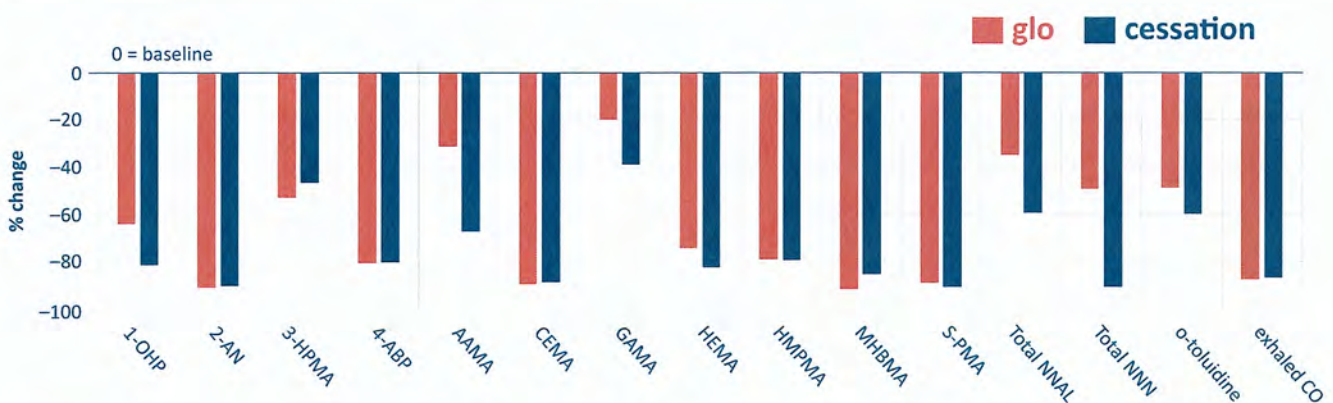


Figure 4/ Reduction in biomarkers of exposure for smokers who switched to glo or stop smoking completely (cessation) relative to continued smoking

points showed similar substantially reduced responses for glo relative to the cigarette control [Taylor 2018]. Furthermore, an *in vitro* systems biology assessment of glo showed that disease relevant mechanisms and endpoints were greatly reduced in comparison to cigarette smoke [Minet 2018]. Additionally, using the concept of the model risk continuum, the emissions and toxicological responses from glo were compared relative to cigarettes, other commercially available THPs and

an e-cigarette [Murphy 2018]. The responses for glo in the studies were similar to the other Next Generation Products (the commercial THPs and the e-cigarette), which were all substantially reduced relative to the cigarettes [Murphy 2018]. Consumption levels were measured in Japan for smokers who switched to glo, in terms of the number of Neostik used daily. The number of Neostiks used daily, did not increase in comparison to their daily cigarette consumption before the switch

[Gee 2018]. Furthermore, in two short term, week long clinical studies conducted in Japan [Gale 2018] and the UK [McEwan 2018], consumers uptake of nicotine was less when using glo in comparison to smoking, measured using pharmacokinetics, suggesting a lower abuse liability potential. Additionally, consumers were exposed to fewer toxicants when using glo in comparison with smoking, measured using biomarkers of exposure and in some cases, levels were reduced to

a high-content screening approach with eight end-points showed similar substantially reduced responses for glo aerosol

those observed when subjects stopped smoking completely [Gale 2018 and McEwan 2018]. We have recently commenced a year-long clinical study in the UK measuring consumer's exposure over a 90 day period and a variety of disease relevant risk indicators over a 360-day period, to assess individual potential risk reduction. Furthermore, a range of pre- and post-market studies

are also required to substantiate them as products that can potentially reduce risk on a population level. It is anticipated that these would include risk perception studies and an assessment of the population's (current smokers, former smokers, never smokers etc) intention to use glo [Murphy 2017]. Furthermore, in the absence of epidemiology, analytical modelling techniques will also be used to assess the impact of glo on public health [Hill 2016].



CONCLUSION

Public Health authorities in the UK have reported that Tobacco Heating Products (THPs) have the potential to be less harmful to health than cigarettes. We have conducted a series of pre-clinical and clinical studies on a THP, glo in comparison to scientific reference and commercial cigarettes. The results from these studies when considered in their totality are in line with the findings of PHE and COT and demonstrate that glo has the potential to be a reduced risk product in comparison to cigarettes. Longer term clinical and population studies will be required to confirm this potential to demonstrate risk reduction.

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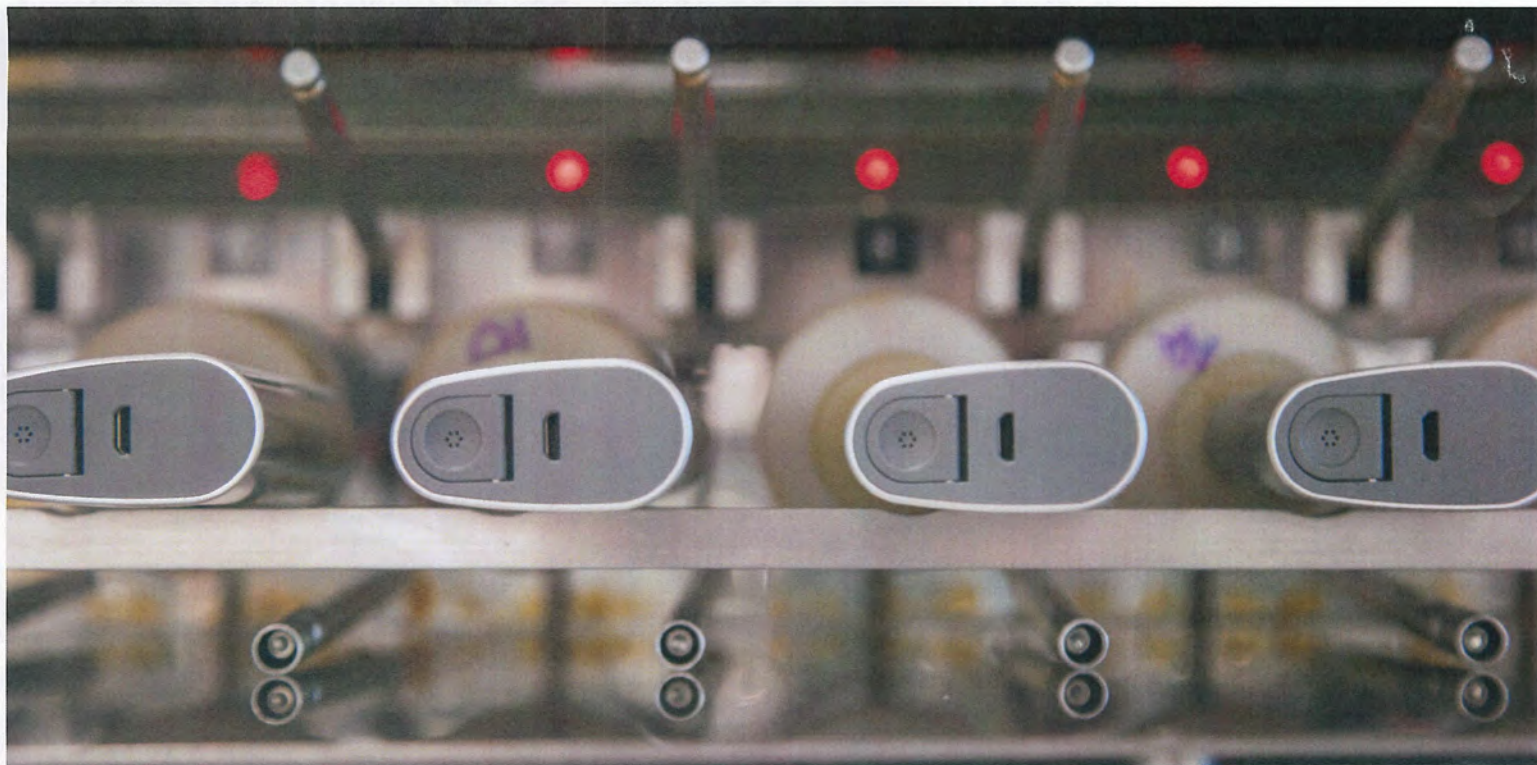
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Tobacco Heating Products
**glo: measurement of
mainstream emissions**





glo heats rather than combusts tobacco, forming much fewer individual compounds and lower levels of the toxicants associated with cigarette smoke.

what exactly is glo?

Cigarettes (Figure 1a) contain tobacco which when lit, combust at temperatures between 600 ~ 900°C forming smoke which is comprised of greater than 6,500 individual compounds [Rodgman and Perfetti, 2013], of which about 150 are known as toxicants [Fowles and Dybing, 2003]. It is these toxicants which are the main drivers of smoking related diseases.

glo is a novel Tobacco Heating Product (THP), which

comprises a tobacco consumable rod called a Neostik (Figure 1b), which is inserted into an electrical heating device (Figure 1c). glo heats the Neostik to a maximum temperature of 245°C [Eaton, 2017], much below the temperature of cigarette combustion (>600°C). It therefore heats rather than combusts the tobacco, forming much fewer individual compounds and lower levels of the toxicants associated with cigarette smoke.

Figure 1/ Illustration of a) a cigarette, b) a Neostik and c) glo Tobacco Heating Product with a Neostik inserted in its heating chamber



PRODUCT	REGIME	PUFF VOLUME (ML)	PUFF DURATION (S)	PUFF INTERVAL (S)	VENTILATION OCCLUSION	REFERENCE
Standard puffing regime (ISO)						
3R4F	ISO	35	2	60	0%	[ISO 4387:2000]
glo	ISO*	35	2	60	0%	cf. [ISO 4387: 2000]*
Intensive puffing regime (Health Canada Intense, HCI)						
3R4F	HCI	55	2	30	100%	[Health Canada 1999]
glo	HCI*	55	2	30	N/A	cf. [Health Canada 1999]*

*While there are no ISO and Health Canada methods for Tobacco Heating Products, these cigarette methodologies can be adapted to give comparative values for THPs

Table 1/ Summary of puffing regimens used for measuring the emissions from 3R4F cigarette and glo tobacco heating product

MEASURING EMISSIONS



Emissions refer to what is emitted by a product (be it smoke or vapour) when that product is being used (smoked or vaped). Understanding what is in the emissions is important because it gives an indication of what a person may be exposed to when they use the product.

Emissions are measured using laboratory based puffing engines programmed to operate according to a specific plan, or “puffing regime”, that prescribes the frequency of puffs, the duration of each puff and the size/volume of the puff. The puffing machines are used to collect smoke produced by a reference cigarette (3R4F) and heated tobacco vapour from glo. There are two standard puffing regimes that are widely used, the International Standards Organisation (ISO) puffing regime, and a so-called intensive puffing regime designed by Health Canada (Table 1). The Health

Canada Intense (HCI) regime may be considered to reflect extreme consumer use for cigarette smoking. This method is in regulatory usage today for reporting cigarette smoke yields in Canada. Mainstream cigarette smoke yields are often printed on cigarette packs, summarizing the emissions of Nicotine Free Dry Particulate Matter (NFDPM - , sometimes referred to as ‘tar’ for cigarettes), nicotine and Carbon Monoxide. These emissions are measured using laboratory based smoke machines set at the ISO puffing regime (Table 1). There are currently no standard methods for measuring Tobacco Heating Product emissions, though glo can be measured using these regimes for comparative purposes. Some adaptation of these regimes are required when testing non-combustible products, for example lighting steps do not apply and ventilation blocking may not be possible due to device construction. When modified the regimes are denoted with a “-m”.

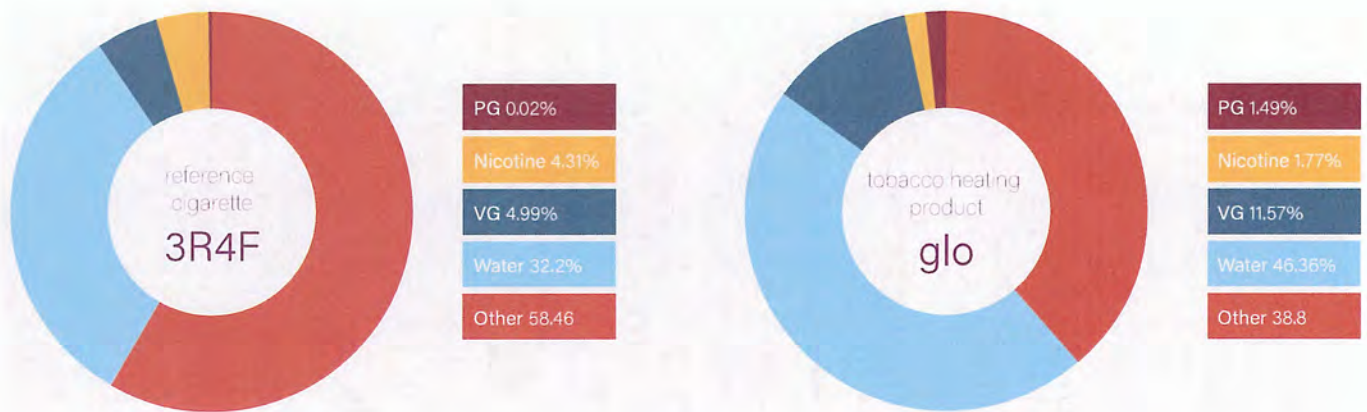


Figure 2/ Composition of the emissions from 3R4F smoke and glo tobacco vapour measured at the HCl machine puffing regimen

MAINSTREAM AEROSOL EMISSIONS

A comparison of the emissions was made between a reference cigarette, 3R4F (smoke) and glo (heated tobacco vapour) using the ISO machine puffing regimen; the data are shown in Table 2.

Cigarette smoke has quantifiable levels of NFDPM, nicotine and carbon monoxide as shown in Table 2. The levels of CO in particular from the reference cigarette demonstrates that combustion has occurred. glo on the other hand, does not combust tobacco and while NFDPM and nicotine can be quantified, there is no detectable level of the combustion gas carbon monoxide in the aerosol as no combustion has occurred*.

Table 3 provides a comparison of a wider group of emissions from 3R4F smoke and the glo heated tobacco vapour using the more intensive HCl regime [Murphy 2017]. The results are outlined below and include information on the water, nicotine, Glycerol, Propylene Glycol and total particle content (TPM) of the aerosols.

A major difference between the

PRODUCT	NFDPM (mg/stick)	NICOTINE (mg/stick)	CARBON MONOXIDE (mg/stick)
3R4F	9.4	0.7	12
glo	4.1	0.15	Below Detection Limit

Table 2/ Emissions from a 3R4F cigarette and glo using the ISO puffing regimen

ingredients in a cigarette and the Neostik is the amount of glycerol and propylene glycol used for the Tobacco Heating Product. These compounds distill into cigarette smoke and into glo vapour when the products are used. This and the fact that glo heats rather than burns tobacco suggests that the heated tobacco vapour produced by glo is very different to the smoke produced by burning a cigarette, as illustrated in Figure 3.

* Figure 2 illustrates the composition of the different aerosols measured under ISO conditions.



PRODUCT	TPM (mg/stick)	OTHER (mg/stick)	WATER (mg/stick)	NICOTINE (mg/stick)	GLYCEROL (mg/stick)	PROPYLENE GLYCOL (mg/stick)	CARBON MONOXIDE (mg/stick)
3R4F	46.9	27.42	15.1	2.02	2.34	0.02	32
glo	26.1	10.13	12.1	0.46	3.02	0.39	Not quantified

Table 3/ Mainstream aerosol yields from 3R4F cigarette and glo tobacco heating product measured under an intense puffing regime.

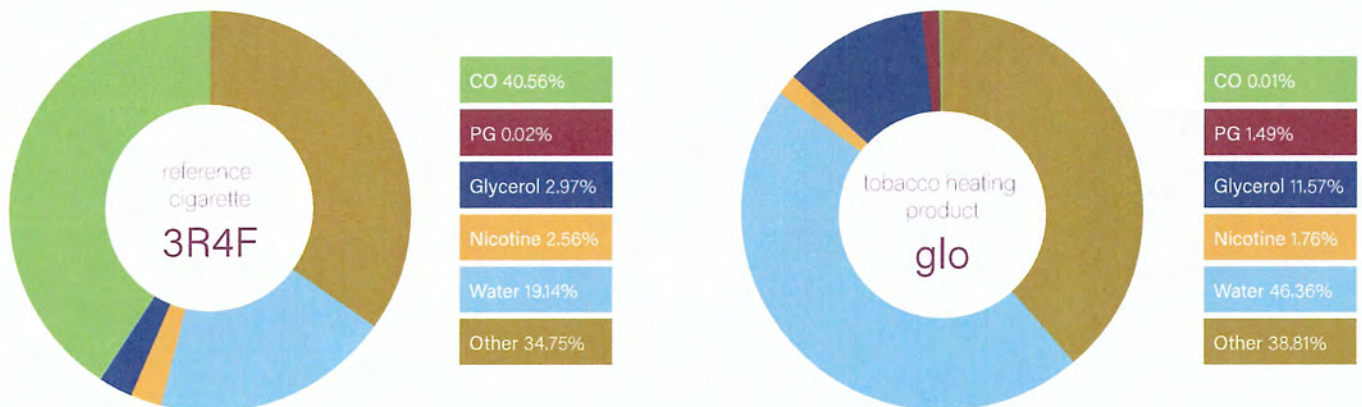
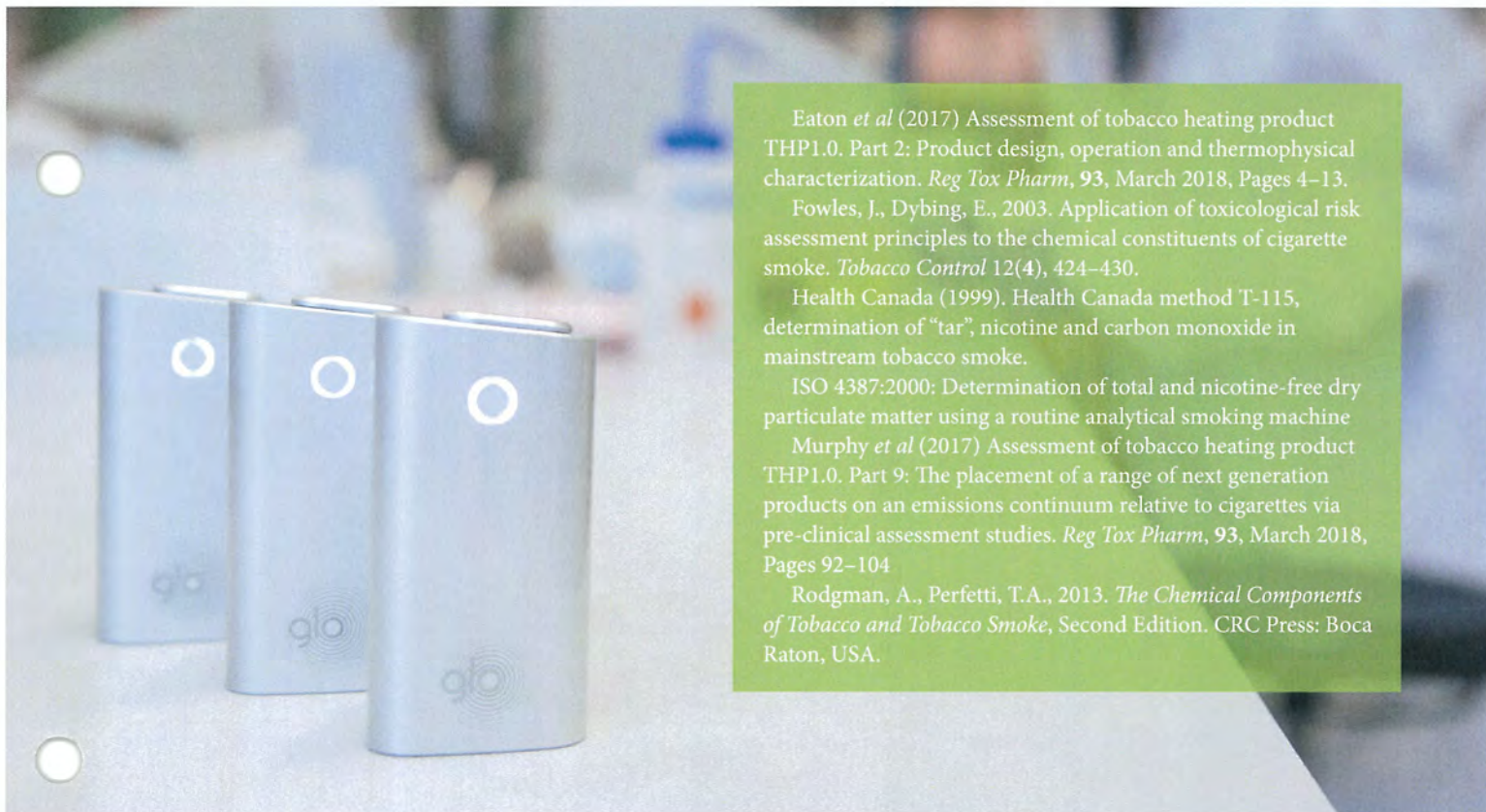


Figure 3/ Composition of the emissions from 3R4F smoke and glo tobacco vapour measured at the HCL machine puffing regimen (inclusive of Carbon Monoxide, CO)



@BAT_Sci

Electronic Nicotine Delivery Systems

Review of scientific literature
2011-2016

February 2017



We have taken an evidence based approach to answering eight key stakeholder questions

What are ENDS?

Electronic Nicotine Delivery Systems (ENDS, often referred to as e-cigarettes) do not contain tobacco. They work by heating a liquid typically containing nicotine in a solution of either propylene glycol (PG) and/or vegetable glycerin (VG). The heat atomises the liquid, turning the solution into a vapour. The resulting vapour is inhaled, delivering the nicotine to the user. The heating element is only activated when the puffing of the user activates a sensor, or manually by the user, and as such vapour is only produced when the device is in active use.

There are broadly three categories of ENDS:

- ▶ **Closed systems:** these contain enough liquid for a defined number of uses after which they are discarded as the canister holding the liquid is inaccessible.
- ▶ **Reusable closed systems:** these devices can be refilled with fresh liquid via replacement of a cartridge, allowing for different types/flavours of liquid to be used, and the battery can be recharged.
- ▶ **Open systems:** these allow for greater customisation by the user, including the ability to refill with a greater variety of e-liquids, as well as making adjustments to voltage and nicotine concentration.

ENDS are similar to but, for the purposes of this document, distinct from ENNDS (Electronic Non-Nicotine Delivery Systems).

The scope of this report

Since ENDS first entered the American and European markets in 2006, there has been an ongoing debate in the public health community as to the potential risks and benefits associated with their use. Public Health England believes ENDS to be 95% less harmful than conventional cigarettes and the Royal College of Physicians has also noted their potential public health benefits, but other organisations such as the World Health Organisation (WHO) and the US Surgeon General, while accepting ENDS should be available for sale as a regulated products, have been more reluctant to advocate their use. The mainstream media discourse is even more varied.

The purpose of this paper is to objectively review and distil the key findings from the extant academic literature on ENDS.

In doing this we have defined and addressed eight key questions.

Key questions

User health risks and benefits

1. How do the health impacts of ENDS compare to combustible tobacco?
2. What is nicotine and what are its effects on health?
3. Are there any other health risks or benefits associated with the use of ENDS?
4. Do ENDS help with smoking cessation?
How effective are they?

Broader risks and benefits

5. Are there any indications that exhaled vapour can be dangerous to bystanders?
6. How safe are ENDS devices and liquids?

Social risks and benefits

7. Do ENDS act as a gateway to smoking? Are they re-normalising smoking?
8. Which groups are using ENDS?

Our approach

We conducted a pragmatic literature review of the available evidence. We considered evidence both for and against the use of ENDS, and summarised the findings; drawing conclusions based on the balance and quality of research.

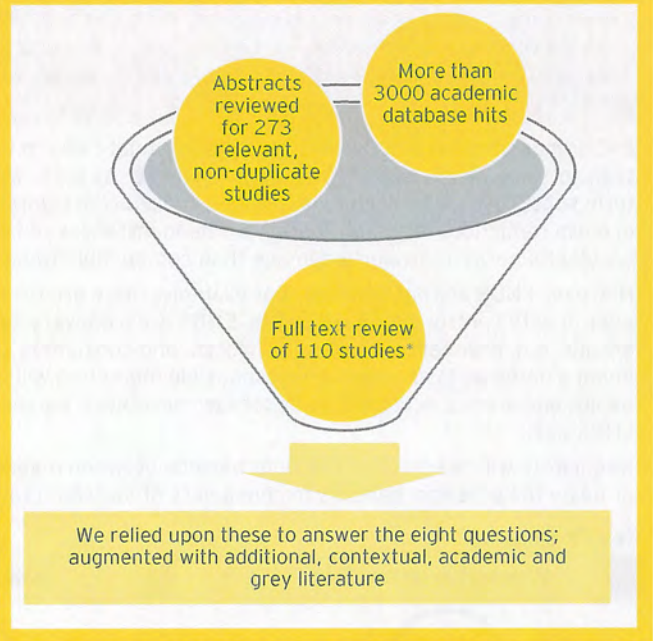
In order to conduct our literature review, searches were performed on the Medline database and Google Scholar. In addition, supplementary evidence was collected from governmental and NGO websites including the World Health Organisation, the US Centers for Disease Control and Prevention, Public Health England, and the Royal College of Physicians.

We reviewed only articles published in the English language between January 2011 and July 2016, which were subjected to inclusion and exclusion criteria.

A step by step approach was used to filter the articles, as set out in the diagram opposite. The remaining articles were appraised for quality using an adapted version of the Cochrane methodology.

A more detailed method statement has been produced and published alongside this report as Appendix A.

Our evidence gathering/filtering process



* All studies taken forward have been published and peer reviewed.



Executive summary



Since Electronic Nicotine Delivery Systems (ENDS) first entered the market, there has been an ongoing debate as to their potential risks and benefits. While Public Health England (PHE) has stated it believes ENDS to be 95% less harmful than conventional cigarettes other organisations such as the World Health Organisation (WHO) have been more reluctant to advocate their use (for example, in their August 2016 report). In the media the discourse is even more confused and contradictory. The purpose of this literature review is to provide an objective view based on the current evidence base. We found:

ENDS appear to have significant potential for public health benefit. The vapour from ENDS contains significantly lower levels of toxicants and carcinogens than cigarette smoke. As such, whether they are used as a short term smoking cessation aid, a long term substitute for cigarettes or a means of reducing cigarette consumption through dual use, they have the potential to result in harm reduction. Although there have been instances of battery malfunction ENDS also appear to be less likely to cause accidental harm or property damage than combustible tobacco products.

However ENDS are not risk free. For example, there are toxicological concerns such as the risk of accidental poisoning and poor quality control over ingredients. ENDS are a delivery system for nicotine, which does pose intrinsic health risks for some groups, e.g. pregnant women and children, and consumers should be made aware of this. We found little evidence of ENDS being a gateway to smoking, but responsible marketing will be required to ensure ENDS remain of net benefit to population health and are not accessed by underage consumers. Further research is also needed, in particular on the long term effects of ENDS use.

Regulators will need to find the right balance between managing these risks and avoiding overregulation, which could reduce or delay the potential benefits to consumers of switching to ENDS from cigarettes and other tobacco products.

Key Findings

<p>Alternative to smoking</p>  <p>ENDS users reduce their cigarette consumption by 77% on average</p>	<p>Reduced Hazard</p>  <p>36% of accidental fire fatalities in England are due to combustible tobacco; switching to ENDS could help reduce this, despite instances of battery malfunction</p>	<p>Nicotine Risk</p>  <p>ENDS contain nicotine which should be avoided by certain groups such as pregnant women and children</p>
<p>Potential Harm Reduction</p>  <p>ENDS vapour contains significantly lower levels of toxicants and carcinogens than cigarette smoke</p>  <p>Studies suggest that smokers with conditions like COPD or asthma switching to ENDS see improvements in lung function</p>		<p>Toxicological Concerns</p>  <p>For example those related to accidental poisoning, poorly designed products and lack of quality control on ingredients</p>

ENDS in the media: consumers are faced by conflicting messages

"E-cigarette ads may cause children to underestimate smoking risks - study"
Guardian

"Study finds vaping can help smokers cut down"
Irish Examiner

"E-cigarettes' effect on public health an open question, which the FDA will try to answer"
LA Times

"British study: Physicians give e-cigarette their blessing"
Spiegel

"E-cigarettes 95% less dangerous than tobacco"
Bild

"E-cigarettes are no safer than smoking tobacco scientists warn"
The Telegraph

"E-cigs much safer than normal smokes - study"
New Zealand Herald

"Electronic cigarette smoking harmful to children and pregnant women"
La Stampa

"Ban the use of e-cigarettes in public, demand doctors"
Times

"Doctor lobbies for legal 'life saving' via e-cigarettes"
The Australian

"The health dangers of e-cigarettes maybe worse than we think"
Herald Sun

"Royal College of Physicians says e-cigarettes can prevent almost all the harm from smoking"
Forbes

"E-cigs aiding 2.6mn to give up smoking"
Daily Mirror

"E-cigarettes contribute to increased tobacco use by teens"
Reuters

"Vaping IS better than smoking - and one of the best ways in 50 years of improving the world's health"
Daily Mail

"The dangers of e-cigarettes: should they be banned in public places?"
L'Obs

"Smoking electronic cigarettes during pregnancy alters the foetus"
El Mundo

"Quit smoking, start vaping and save your life"
Sunday Times

"There is no evidence that 'vaping' helps to quit smoking"
El Pais

"Yes, e-cigarettes help to stop smoking"
Le Soir

Q1: How do the health impacts of ENDS compare to combustible tobacco?

Key findings

The evidence suggests the health risks of ENDS are likely to be fewer and less severe than those associated with combustible tobacco products. The prospect of consumers switching from combustible tobacco products to ENDS has the potential to yield significant benefits to public health in terms of harm reduction.

Regulatory and policy implications

Encouraging smokers to switch to ENDS (where cessation attempts have been unsuccessful) in order to achieve harm reduction. Avoid overregulation which might decelerate switching.

Areas for further study

Continued monitoring of long term effects of ENDS.

Cigarette consumption poses real risk of serious disease

The types of harm that can be caused by cigarette consumption are well documented. These include several types of cancer including lung cancer; cardiovascular conditions such as coronary heart diseases; other conditions of the lungs such as COPD¹; and for many people smoking is difficult to quit.

ENDS appear significantly less harmful

ENDS contain nicotine but not tobacco, and there is no combustion. Instead a liquid is heated to create a vapour which is inhaled. The current evidence base suggests that ENDS may present considerably fewer risks than cigarette smoking. ENDS vapour contains significantly lower levels of toxicants and carcinogens than tobacco smoke² suggesting lower risk of cancer and other conditions associated with smoking. Further studies have found other indicators of harm are reduced when using ENDS as opposed to smoking cigarettes:

- ▶ Levels of fraction exhaled carbon monoxide (a poison), which become elevated when smoking cigarettes, remaining at baseline levels when using ENDS³ (note though that these findings related to non-nicotine devices).
- ▶ Use of ENDS resulting in no increase in white blood cell count, in contrast to smoking and passive smoking which do elicit a response from the body's immune system⁴.
- ▶ While conventional cigarettes increased heart rate, blood pressure and carboxyhaemoglobin, ENDS had less impact on these clinical measurements⁵.

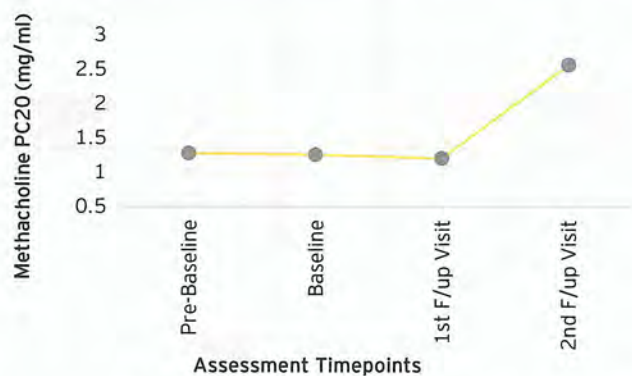
Based on the current available evidence, including a study by Nutt et al., Public Health England recently suggested that ENDS are **95% less harmful** than combustible cigarettes^{6, 7}.

Some studies have indicated that, as with smoking cessation⁸, switching from cigarettes to ENDS can lead to reduction in clinical measurements of adverse acute health effects⁹.

Smokers switching to ENDS were found to show relative improvements in clinical measurements reflecting the severity of conditions such as COPD, asthma and hypertension, e.g. by 1.7, 2.2 and 1.9 times respectively^{10,11}.

Lung function improvement after 12 months in smoking asthma sufferers (adapted from Polosa 2014)

A significant improvement in lung function, a doubling in the quantity of methacholine needed to induce constriction in patients' airways by the second follow up, 12 months after baseline at which ENDS use began.



While many of the risks associated with smoking may be reduced, there are some other risks associated with ENDS, for example device and e-liquid safety, and these are covered on pages 9 and 12 of this document.

It should be noted that due to the relatively recent introduction of ENDS the current evidence base is limited and further research is needed, in particular in relation to their long term health impacts.

Q2: What is nicotine and what are its effects on health?

Key findings

Nicotine is the addictive stimulant found in tobacco products. The evidence suggests that nicotine in isolation has far fewer harmful effects than smoking. The health risks associated with nicotine in and of itself include issues of foetal and child development and exacerbation of existing long term health conditions such as diabetes.

Regulatory and policy implications

Ensuring appropriate packaging and labelling of nicotine containing e-liquids as per other nicotine products such as patches and gums.

Areas for further study

Ongoing monitoring of effects of long term nicotine consumption via non-tobacco products such as ENDS.

Nicotine alone is less risky than tobacco

In considering the health risks and benefits of ENDS, it is important to understand the impact of nicotine. Nicotine is the addictive stimulant found in cigarettes and other tobacco products. It is naturally occurring in tobacco (it is not added).

Several other delivery systems for nicotine exist, such as gums and patches, which have been developed for the express purpose of helping smokers with cessation by providing an alternative to smoking; these are termed nicotine replacement therapies (NRTs).

While tobacco is associated with conditions such as cancers, COPD and cardiovascular disease, nicotine as distinct from tobacco is not associated with the majority of the adverse effects of smoking¹².

But it poses risks, particularly for some groups

However, nicotine is not entirely risk free, especially for certain groups:

- ▶ **Expectant mothers and children:** nicotine has been linked to foetal and child development issues such as impaired or altered brain, lung and sexual organ development¹³⁻¹⁹.
- ▶ **Diabetics:** nicotine exposure affects insulin resistance, hindering management of diabetes²⁰.
- ▶ **Individuals with muscular-skeletal conditions:** there is a link between nicotine exposure and low bone mineral density in middle-aged and elderly patients resulting in increased frequency of hip fracture²¹.

Some groups claim potential health benefits

Conversely some groups have been observed to derive a health benefit from nicotine use, such as people with:

- ▶ Parkinson's disease²²⁻²³;
- ▶ Ulcerative colitis²⁴; and
- ▶ Schizophrenia²⁵.

It should be noted that these observations have been made by a limited number of studies, and that nicotine is not an accepted therapy for any of these conditions.

However, it is important to consider that for individuals who do wish, for whatever reason, to continue accessing nicotine ENDS offer a means of achieving this with potentially reduced harm compared to the alternative of continued tobacco consumption.



Q3: Are there any other health risks or benefits associated with the use of ENDS?

Key findings

Additional health risks associated with ENDS include those related to misuse by users and/or issues of poor product design and manufacturing by producers of ENDS and e-liquids. These include dangerous emissions, such as high levels of formaldehyde (a type 1 carcinogen) when ENDS are used at unusually high voltages, and some instances of use of flavourings in e-liquids which while safe for ingestion, become dangerous when inhaled. The main benefits remain potential harm reduction from reduced tobacco consumption.

Regulatory and policy implications

The introduction and enforcement of appropriate product quality and safety standards to manage these risks.

Areas for further study

The rapidly evolving ENDS market means the evidence base with regards to product safety and quality considerations needs to be continually refreshed.

Dangerous emissions at high voltages

Some ENDS allow for voltage to be adjusted, creating more heat and as such more vapour. When used at low/standard voltages ENDS emit levels of formaldehyde and acetaldehyde (both carcinogens) that are below the legally allowed thresholds for workplace exposure, and significantly below the levels found in cigarette smoke. However, when voltages are increased the levels of emission increase significantly to levels similar to or in the case of formaldehyde higher than those found in cigarette smoke^{19,26-27}.

In practice, Public Health England and others have suggested that such abnormally high voltages would result in an acrid taste, inferring that users themselves would not elect to use products at these unsafe voltages^{7,28}.

Some flavourings can be harmful

The e-liquid used in ENDS products is often flavoured in order to improve the experience of the user. There have been instances where common food additives, which are safe when ingested but which become dangerous when inhaled, have been used as flavourings for ENDS^{26, 29}.

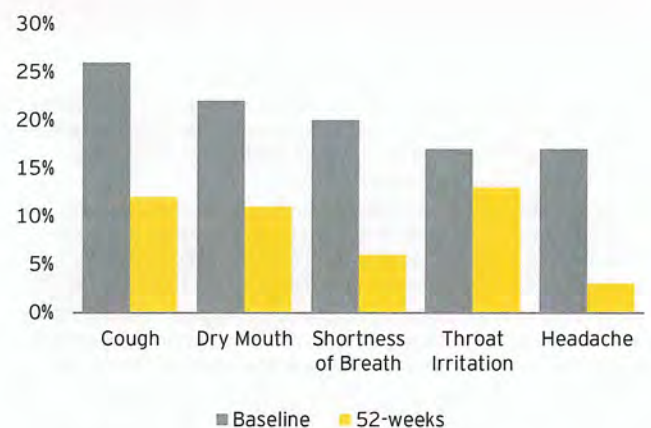
Misuse of flavourings in this way by some manufacturers of ENDS and e-liquids will need to be regulated through appropriate product standards in order to protect public health and avoid damaging public confidence in ENDS products, limiting their harm reduction potential.

Mild adverse effects diminish over time

A further benefit of ENDS relative to smoking is that mild adverse effects such as coughing, dry mouth, throat irritation, and shortness of breath diminish over time post switching³⁰.

Mild adverse events from ENDS (data from Caponnetto 2013)

Mild adverse effects of smoking observed at baseline, diminished significantly over 52-weeks.



Q4: Do ENDS help with smoking cessation? How effective are they?

Key findings

While sold as a consumer goods product, ENDS appear to be as effective or more effective than NRTs for smoking cessation. As with NRTs a significant number of users choose dual use, partially substituting cigarette consumption rather than full cessation.

Regulatory and policy implications

A balanced regulatory approach is required which avoids stifling the market and enables the benefits of ENDS as an alternative to smoking.

Areas for further study

Large randomised controlled trials with relevant comparators, e.g. comparison to nicotine replacement therapy products such as patches and gum.

ENDS can support smoking cessation

A criticism levelled at traditional NRTs is that while they provide a substitute to cigarettes in terms of delivering nicotine, they do not substitute the social, ritualistic or behavioural aspects of smoking. For this reason ENDS have been viewed as a potential means of supporting smoking cessation for individuals for whom traditional NRTs have been ineffective³¹. Studies have found this to be true to at least some extent:

- ▶ Early randomised controlled trials (RCTs) found users of ENDS are more likely to abstain from smoking than those using placebos³¹. These findings are similar to those previously observed in placebo-controlled trials of NRTs³².
- ▶ More recent studies have found that regular ENDS users attempting smoking cessation are six times more likely to report they have successfully stopped smoking than non-users, and that ENDS users report an average 77% reduction in cigarette consumption^{33, 34}.
- ▶ However, at least part of the reason for the success of ENDS in supporting smoking cessation appears to be due to the amount of nicotine they allow the user to consume. More modern modular devices, which allow the user control over nicotine levels have been found to be more effective than older models^{35, 36}.

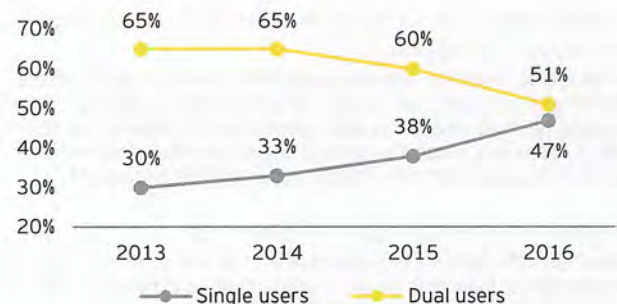
Dual use can also lead to harm reduction

As with NRT users, many ENDS users are dual users, substituting some of their cigarette consumption but not achieving full cessation³⁷. A number of studies have estimated that cigarette users taking up ENDS are roughly evenly split between those whose aim is cessation and dual users³⁸⁻⁴⁰.

Those who persist with dual use have been found to reduce their tobacco consumption by c. 50%³⁸, which could potentially result in a significant harm reduction benefit.

ENDS trends in single versus dual use (ASH 2016)

There is a convergence between single users (who used to smoke cigarettes but now only use ENDS) and dual users. Numbers of people who were never smokers using ENDS remains small (~2%). This suggests a trend of increased use of ENDS for the purpose of full smoking cessation over time.



There is less clarity however as to whether dual users are more or less likely to achieve full cessation in the longer term, with contradictory evidence emerging from a number of studies. This ranges from findings that compared to other groups dual users make more cessation attempts, to dual users being no more or less likely to achieve cessation, and even suggestions that dual users are less likely to achieve full cessation^{37, 41-43}.

Limitations of the evidence base

Many of the studies undertaken to date have limitations. These include use of cohort designs instead of RCTs, placebos instead of more relevant comparators such as NRTs and small sample size.

Q5: Are there any indications that exhaled vapour can be dangerous to bystanders?

Key findings

The evidence suggests that the potentially harmful substances found in the aerosol from ENDS are present at significantly lower levels than those which would be legal in the workplace, and at much lower levels than those found in second hand cigarette smoke.

Regulatory and policy implications

A number of bodies have mooted public place vaping bans. However, the evidence to date does not support a ban, and as such this would be a purely precautionary measure based upon concerns regarding the unknown. Before implementing a ban regulators must weigh up its value against the loss of potential harm reduction benefits derived from consumers switching from smoking to using ENDS if ENDS were to be subjected to similar regulation as cigarettes.

Areas for further study

More realistic testing of short and long term effects of exposure to vapour.

Second hand cigarette smoke has been associated with adverse health effects

Second hand cigarette smoke is comprised of both smoke from the burning end of a cigarette and the smoke exhaled by the user. Given that second hand smoke has been associated with adverse health effects, there is a natural desire to understand whether there are similar risks associated with ENDS vapour exhaled by users⁴⁴.

Aerosol from ENDS appears lower risk

Given that ENDS are only activated when the user puffs on them, the composition of vapour is similar to that inhaled by the user. This means that the areas of concern are similar:

- ▶ **Nicotine:** nicotine is dangerous to some groups, and a key benefit to banning smoking cigarettes in public places in the UK and other countries has been to protect these groups. Nicotine, and cotinine – a biomarker for nicotine – have been found in higher airborne levels in the homes of ENDS users versus non-smoking homes. The implication is that bystanders in those spaces will be at increased risk of nicotine exposure^{13,27,45-46}. However, studies investigating the air quality effects of ENDS usage have found that levels of nicotine released are 10 times lower than those emitted by cigarette smoking and not sufficient to cause health concerns^{47, 48}.

- ▶ **Formaldehyde and other harmful substances:** when used at abnormally high voltages ENDS can produce formaldehyde, which is a group 1 carcinogen, and ENDS vapour has been observed to contain other potentially harmful substances^{46, 49}. Studies have sought to ascertain whether these substances are produced in high enough concentration by ENDS to pose a health risk. Comparison of the levels of these substances to levels which workers can be legally exposed to in the workplace found they were significantly below the threshold limit values (TLVs). For example formaldehyde emitted from ENDS was found to be less than 5% its TLV¹⁹. The levels of risk associated with chemicals found in ENDS vapour have also been found to be significantly lower than those found in cigarette smoke⁵⁰.

On balance, the evidence suggests that the potentially harmful substances found in the aerosol from ENDS are present at significantly lower levels than those which would be legal in the workplace, and at much lower levels than those found in second hand cigarette smoke.

Limitations of the evidence base

The current evidence base is limited. Studies have been based on simulating the effects of ENDS on air quality using smoking machines, a limited set of ENDS products have been tested, and the cumulative long term effects of vapour on bystanders have not been tested.



Q6: How safe are ENDS devices and liquids?

Key findings

While lithium batteries of the type included in ENDS have been known to cause fires if overcharged, smokers products are the largest cause of accidental fire related fatality in the UK, and as such a shift towards ENDS could represent reduced hazard.

E-liquids are not intended for ingestion and can lead to poisoning if they are. Such cases have increased over time, with children being particularly at risk where, for example, child proofing of packaging is inadequate.

Regulatory and policy implications

The introduction and enforcement of appropriate product quality and safety standards, such as those set by the British Standards Institution, including child-resistant packaging for e-liquids and requirements for leak-proof containers.

Areas for further study

The design and range of ENDS products and liquids is rapidly evolving, meaning the evidence base with regards to appropriate measures of product safety and quality needs to be continually refreshed.

Ingestion of e-liquids has led to poisoning

ENDS are intended to deliver e-liquids by inhalation. E-liquids usually contain nicotine, water, propylene glycol, glycerin, flavourings and/or other additives; they are not intended for ingestion.

However, a number of cases of ingestion were reported to the poison centres in the UK and the US:

- ▶ In the US, the number of exposures from ENDS reported to poison centres has increased from one per month in September 2010 to 215 per month in February 2014 with more than half the cases relating to children under five years old⁵¹.
- ▶ In the UK, the data from National Poisons Information Service shows similar findings⁵².

Most poisoning cases were accidental and symptoms - which included vomiting, nausea, dizziness and abdominal pain - were usually short-lived⁵³. However, newer ENDS devices have replaced glycerol and propylene glycol with ethylene glycol, which increases health risks if ingested, owing to its toxicity for the kidneys and nervous system⁵⁴.

Device malfunctions lead to fires

ENDS, like many other consumer devices including mobile phones, use lithium batteries. Lithium is highly reactive and if the separators keeping the elements of the battery apart are damaged, there is a risk of internal short-circuit and a subsequent build-up of heat. This can result, in rare cases, in the battery catching fire.

Concerns have also been identified relating to product design and handling instructions; a market surveillance study in 2013-14, found that 6 out of 17 ENDS devices had no instructions for charging, and 8 out of 17 devices did not have a charging cut-off device and therefore did not meet the requirements of British Standard BS EN 62133:2013⁵⁵.

Cigarettes carry a greater fire hazard

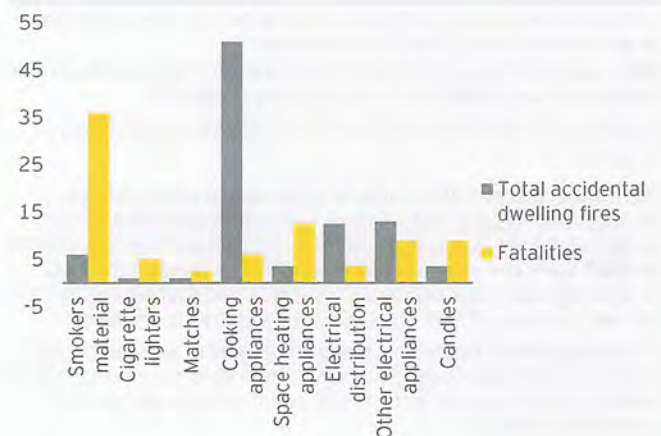
In England, there were 43 recorded call outs for fires related to ENDS in 2013 and 62 in 2014 (January till mid-November)⁵⁶.

By contrast, traditional smoking products were associated with 6% of accidental fires (1,878 fires) and 36% of accidental fire related fatalities (95 fatalities) in England over the 2014/15 reporting year⁵⁷.

This suggests there would be a net reduction in accidental fire related harm and damage as a result of smokers switching to ENDS.

Percentage of incidents and fatalities by selected sources of ignition in accidental dwelling fires, England 2014/15 (Home Office report, 2016)

Smokers materials are the largest cause of accidental domestic fire fatalities in the UK.



Q7: Do ENDS act as a gateway to smoking? Are they re-normalising smoking?

Key findings

The balance of evidence suggests that ENDS act as a substitute for cigarettes, not a gateway to smoking. While there is a correlation between ENDS use and smoking, only 1% of ENDS users are never-smokers.

At a population level increases in ENDS use have coincided with reductions in cigarette consumption.

Regulatory and policy implications

A balanced regulatory approach is required which enables the benefits of ENDS as an alternative to smoking while safeguarding young people.

Areas for further study

Studies specifically designed to give a clearer indication of causality.

The concept of a 'gateway' effect was originally developed to explain a developmental process of involvement in drugs in which certain drugs serve as a gateway for the use of other, usually more harmful substances.

Recent statistics suggest that prevalence of ENDS use has more than tripled among middle and high school students in the USA⁵⁸. This has led to debate as to whether ENDS might act as a gateway to smoking cigarettes, or if instead they are full or partial substitutes, used by young people in place of cigarettes.

ENDS users are more likely to smoke

Reports have found that young people who use ENDS are also likely to smoke cigarettes.

College students using ENDS were found to be 2.5 times more likely to also smoke tobacco than those who don't⁵⁹.

ENDS users were also found to be more likely to report an intention to smoke than non-ENDS users, even in young people⁶⁰⁻⁶³.

However, the evidence does not suggest a gateway effect

In the UK experimentation with ENDS has been found to be high amongst smokers and non-smokers, but that regular ENDS use is largely restricted to people who already smoked and that less than 1% of ENDS users had never smoked³⁸. Similarly, in the USA the CDC found that while experimentation with ENDS had doubled among 13-18 year olds, almost 90% of this cohort were already smokers⁶⁴.

This suggests that ENDS users being more likely to also smoke may not be a causal relationship, but rather the characteristics that attract someone to nicotine will attract them to any nicotine source be it cigarettes or ENDS.

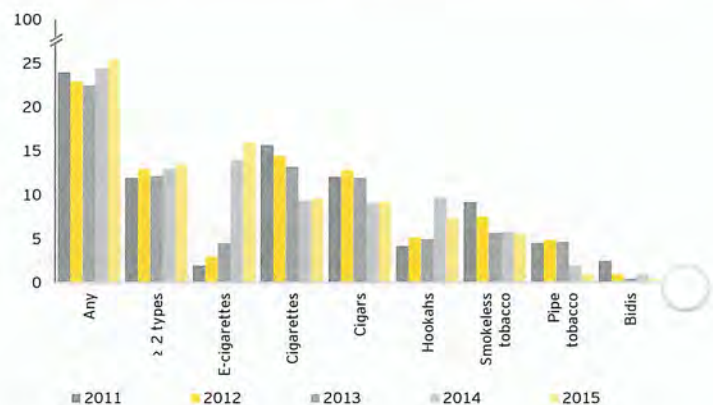
Overall there seems to be a substitution effect

While there is a correlation between ENDS use and smoking at the individual level, at a population level there appears to be a substitution effect between ENDS and cigarettes, with existing smokers moving towards ENDS. The national youth tobacco survey found that between 2011-2015 there were large increases in the use of ENDS at the same time as large decreases in cigarettes and cigar use by high school students in the USA⁵⁸.

The idea of the products being substitutes is supported by findings that bans on the sale of ENDS to minors in some US states have coincided with small increases in smoking rates⁶⁵.

Estimated percentage of high school students who currently use any tobacco products or ENDS (adapted from Singh et al. 2015)

ENDS and hookah use have increased in a non-linear fashion, while other products have seen decreases.



Q8: Which groups are using ENDS?

Key findings

Users of ENDS fall into two broad categories. Firstly adults, mostly under the age of 35, who use ENDS primarily for smoking cessation, as well as being curious about the flavours on offer. Secondly, younger users, who tend to also smoke, have previously smoked, and/or drink alcohol.

Regulatory and policy implications

Sales to minors should be restricted in order to reduce the risk of nicotine addiction.

Areas for further study

For young users, current literature avoids quantifying consumption, instead relying on self reported use. There is therefore difficulty in measuring ENDS consumption compared to cigarettes.

Adults are using ENDS to quit smoking

2.8 million British adults are now using ENDS, mostly aged 35 or under³⁸. The primary reason given for using ENDS is to cease or reduce smoking⁶⁶. Adult users in the UK tend to give four key reasons to explain why they prefer ENDS to cigarettes³⁸:

1. ENDS are perceived to be safer than cigarettes.
2. The vapour does not have a smell that lingers, making it socially more acceptable including for indoor use.
3. A wide variety of flavours are available.
4. They are perceived to have a recreational element.

Expanding on the use of ENDS for recreation, it has been noted that they create a sensory satisfaction making them more of a novelty than conventional cigarettes particularly for younger users⁶⁷.

US adult users give similar reasons for using ENDS⁶⁶:

1. Wanting to cease smoking.
2. Wanting to reduce the level of smoking.
3. Wanting to reduce the health risk associated with smoking.
4. Curiosity owing to different devices and flavours.

Experimentation with ENDS is currently rare amongst non-smoking young people

Although the likelihood of use does not differ across race or ethnicity, it is most often young males, rather than females, who have been found to use ENDS as is also commonly found in adults⁷.

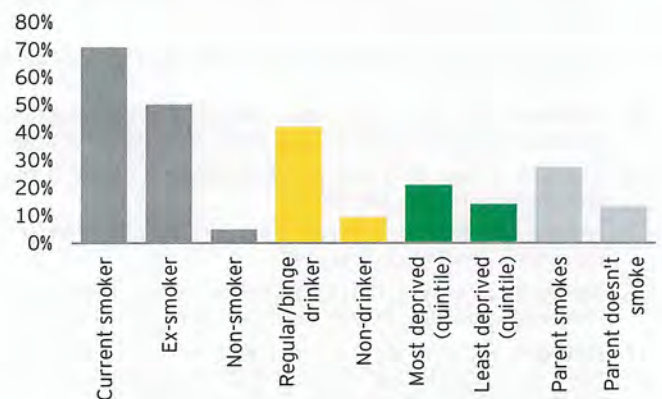
Experimentation with ENDS is currently rare amongst non-smoking young people in the UK, with only approximately 1% of 16-18 year old never-smokers having experimented with ENDS and few progressing to sustained use⁶⁸.

Approximately 12% of British youth (11-18 year olds) have ever tried ENDS. Regular use is more rare with 2% using ENDS at least monthly and 0.5% more than weekly. Only 0.3% of youth never-smokers use ENDS regularly (at least monthly)⁶⁹.

Other important correlations to ENDS consumption include having parents who smoke and consume alcohol. Adolescents who accessed ENDS are also particularly vulnerable to other forms of substance abuse, including binge drinking⁷⁰.

Factors associated with adolescent propensity to use ENDS (data from Hughes 2015)

Adolescents who use ENDS are also likely to be current or ex smokers or regularly consume alcohol.



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