香港中區立法會道1號
立法會綜合大樓
香港特別行政區立法會
《2019年吸煙(公眾衞生)(修訂)條例草案》委員會主席
黃定光議員

尊敬的黃議員：

就邵家輝議員提出規管加熱煙的修訂
表示十分歡迎及支持
促請政府及議員接納此修訂

「規管加熱煙大聯盟」由一群來自多個行業及界別的團體或人士自發組成——包括由傳統煙轉用加熱煙的使用者、零售報販、旅遊業、餐飲業、酒吧業、美容美髮業、創意產業、保險業、專業服務業從業員等，旨在推動政府及立法會以「規管」代替「禁售」加熱煙。

最近，大聯盟得悉立法會邵家輝議員對《2019年吸煙(公眾衞生)(修訂)條例草案》提出修訂，將政府原訂通過《條例草案》落實全面禁止進口、製造或售賣訂明「另類吸煙產品」（包括「電子煙」及「加熱煙」）的安排，修改為容許「加熱煙草產品」在規管下可進口、製造或售賣。換言之，經邵家輝議員修訂後，「加熱煙草產品」與《吸煙(公眾衞生)條例》對其他煙草產品的規管大致相同。大聯盟對此修訂表示十分歡迎及支持，我們認為此舉反映邵議員吸納民間意見，是一個務實的做法，亦是平衡各持份者的有效方案。另外，此修訂也符合國際規管趨勢，包括內地以「規管」代替「禁止」的政策方針。

加熱煙及電子煙屬於兩種完全不同的產品，加熱煙內含煙草，與傳統香煙同屬煙草產品，加熱煙運作原理爲以不燃燒的形式加熱真的煙草；政府將加熱煙及電子煙混爲一談，並在容許傳統香煙合法銷售的情況下禁止加熱煙，明顯有違常理。

政府提出全面禁售加熱煙等產品，此舉與國際監管趨勢背道而馳，同時也剝奪了消費者選擇傳統煙替代產品的合法權利。大聯盟理解到現時全球有逾64個國家/地區基於科學理據讓加熱煙產品合法在當地銷售，其中美國食品及藥物管理局（FDA）在去年7月還正式授權其中一種加熱煙作為風險改良煙草產品出售，亦表明相關決定是「符合促進公共健康的原則」。

大聯盟也得悉在內地，國家對於加熱煙的態度，早在四年前開始已有明顯取態。國家煙草專賣局在2017年10月，率先發布了工作通告《關於開展新型捲煙產品鑒別檢驗工作的通知》，將"IQOS"、"Glo"、“Ploom”、“Revo”等4種產品列入新型捲煙產品目錄，此舉表明內地當局視加熱煙為煙草製品。另外，國家煙草專賣局在

2017 年 12 月對香煙定義做出了修訂，把原本「用捲煙紙包裹煙絲捲製而成供人們燃吸的煙草製品」修訂為「以全部或部分煙草為材料，用紙或其他材料包裹全部或部分煙草加工而成的，供人們燃吸或以其他方式抽吸的煙草製品，不包括雪茄煙」，修訂後，加熱煙正式屬於香煙的範圍，也啟示了往後加熱煙的規管模式將會參照傳統香煙。另外，國家工信部今年 3 月公布，由於電子煙等新型煙草製品涉及消費者權益、國家收入等，提出修改及完善電子煙等新型煙草製品規管，向社會公開徵求意見。國家就加熱煙及電子煙的多項政策，意味著內地也在監管新型煙草產品上「採取規管而非禁止的做法」，這也是國際上先進國家/地區的主流做法，香港特區政府應積極仿效。

根據報販業界的前線經驗，香港平均每四名吸煙人士當中就約有一人轉用加熱煙；政府方案是禁賣不禁食，一方面只會令加熱煙的走私活動變得更加猖獗，部分煙民被迫轉投黑市，也令報販經營會更困難；另一方面，若採取過於極端的「禁售」政策，部分加熱煙用家只會被迫重新選擇傳統香煙，不利於香港長遠的控煙目標。

香港有完善法例規管煙草產品，大聯盟認為只要將加熱煙納入現行控煙框架以進行規管，即可防止青少年接觸此類產品，同時令成年煙民可以有正規途徑購買這些產品。大聯盟認爲，參照傳統香煙規管模式處理屬煙草產品的加熱煙，合情合理。

大聯盟期望主席及各位議員能夠敦促政府在這段艱難時期從善如流，聽取意見，並督促政府瞭解民情，做到兼聽則明，聆聽各個業界等的聲音，就加熱煙制定務實和平衡的規管措施。

規管加熱煙大聯盟

2021 年 7 月 16 日

註：附件見「規管加熱煙大聯盟」成員名單

附件

規管加熱煙大聯盟

參與及支持團體：

1) 香港報販協會林長富主席
2) 全港報販大聯盟廖社青主席
3) 加熱煙用家關注組盧啟律先生
4) 旅遊業界代表崔定邦先生
5) 旅遊業界代表陳世棠先生
6) BOF 創辦人林肇濤(BOF 是一個支持香港創意工業的平台：內有文化藝術工作者、美容師及髮型師)
7) 香港酒吧業協會
8) 令和居酒屋 ReiwaIzakaya
9) OPPA 韓國燒肉店
10) 稻八日式火鍋炸物放題 InahachiShabuShabu
11) 陳儀興飲食集團:(旗下餐廳包括)
    -陳儀興玫瑰餐廳
    -陳儀興尚潮樓
    -陳儀興飯店(嘉悅)
    -陳儀興飯店(崇齡街)
    -陳儀興牛什粉麵茶餐廳(安泰)
    -陳儀興牛什粉麵茶餐廳(麗閣)

參與及支持的個別人士：

12) 香港城市大學研究生院朱國能教授
13) 家庭主婦何太
14) CalvinCheung(電訊業)
15) AlexCheung(飲食業)
16) CeciliaHui(美容業)
17) KimmyWong(會計業)
18) CocoDing(會計業)
19) KimeLau(航空業)
20) LokKwok(公共事業)

香港報販協會
Hong Kong Newspaper Hawker Association
109，2/F,Shanghai Street Yaumatei Kowloon Hong Kong

《2019 年吸煙(公眾衞生)(修訂)條例草案》委員會主席
黃定光議員 GBS, 太平紳士
電郵：bc_51_20@legco.gov.hk

督促政府吸納邵家輝議員修訂

正式規管加熱煙草產品、容許在本港銷售

尊敬的黃主席：

就立法會討論《2019 年吸煙(公眾衞生)(修訂)條例草案》一事，本會特此致函期望就政府立法全面禁止加熱煙一事發表意見及建議。

本會得悉有多項海外科學研究顯示加熱煙對吸煙者本身和公共健康的影響較傳統香煙為低。目前世界各地包括美國、加拿大、紐西蘭、歐洲、和日本等地，共有 64 個國家或地區，准許加熱煙在當地市場銷售予成年吸煙者，絕大部分都是發達國家和地區，而祖國對於規管加熱煙的立場也十分清晰，包括國家煙草專賣局在 2017 年 12 月對香煙定義作出修訂，令加熱煙正式屬於香煙的範圍，表達了往後將參照傳統香煙模式對加熱煙作出規管。而國家工信部亦在今年 3 月公布，由於電子煙等新型煙草製品涉及消費者權益及國家收入等事宜，因此提出修改及完善有關的規管問題，已向公眾徵求意見。本會要求當局能參考以上主流國家地區做法規管加熱煙。

本會最近留意到，代表批發及零售界別的立法會議員邵家輝，在六月尾的法案委員會上，就政府一刀切禁止方案提出了修訂，要求政府容許「加熱煙草產品」在規管下可進口、製造或售賣，本會對此修訂表示歡迎及贊成，並藉此意見書，要求政府應積極吸納邵議員的修訂方案，盡快「規管」加熱煙。

近兩年，香港受社會事件和新型冠狀病毒病疫情連環打擊，本會評估，業界生意累積至今已下跌最少７成，部份報檔更被迫結業。而隨著紙媒步入寒冬，香煙已經成為了報販主要銷售物品之一，也是我們的主要收入來源。本會認為，加熱煙根本就是加熱的煙草產品，既然傳統香煙可以出售，當局也絕對可以規管加熱煙在港合法售賣，令基層報販可以增加合法收入。相反，若一刀切禁止售賣加熱煙，只會令走私問題更嚴重，變相助長黑市，對小商販不公道。本會認為，政府和反煙團體以為一刀切禁止可以杜絕加熱煙在香港出現，這是不切實際的想法，禁賣不禁食，只會令走私無日無之，只有讓加熱煙產品在一個受監管形式下合法售賣給成年吸煙人士，這才是符合社會實況和面對事實的做法。

要防止青少年接觸加熱煙，本會認為加強教育才是上策，並且透過前線零售商、報販有效把關，絕不把任何煙草產品賣給未成年人士，才能夠合力有效阻止青少年接觸吸煙產品。

香港報販協會

Hong Kong Newspaper Hawker Association

109，2/F,Shanghai Street Yaumatei Kowloon Hong Kong

本會重申，規管加熱煙草產品納入現行煙草框架進行規管，只售予成年吸煙人士，報販可以憑藉售賣加熱煙收回已流入黑市的收入，政府亦可以正式徵收稅款，與此同時，吸煙人士可以有選擇低害的煙草產品，實屬三贏之舉，期望政府三思，用規管取代全禁。

香港報販協會主席

林長富

2021 年 7 月 12 日

HERBERT SMITH FREEHILLS

Clerk to Bills Committee on Smoking (Public Health) (Amendment) Bill 2019
Legislative Council Secretariat
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

By email and by hand

Our ref
6461/12474/31012325
Your ref

Date
20 July 2021

Dear Sirs

Submission on the Smoking (Public Health) (Amendment) Bill 2019

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

We refer to our previous written submissions on behalf of BATHK including most recently our letter dated 8 April 2021, in which we have set out BATHK's opposition to the Smoking (Public Health) (Amendment) Bill 2019 (the "**Bill**"). BATHK maintains its position that the Bill is (amongst other things) irrational on the basis that it bans products that are potentially less harmful than traditional cigarettes, including electronic cigarettes ("**e-cigarettes**") and tobacco heating products ("**THPs**"), and ignores the potential harm reduction benefits associated with the use of such products as supported by scientific and other evidence.

By this letter, we write to address the following:

1. The Government's response to issues raised at the Bills Committee's meeting 23 February 2021 (LC Paper No. CB(2)917/20-21(02) (the "**Government's Response to the February Meeting**"), in particular the Food and Health Bureau's reference to the World Health Organization's ("**WHO**") brief on THPs published in 2020 (the "**WHO Brief**"); and

2. The Government's response to issues raised at the Bills Committee's meeting 30 March 2021 (LC Paper No. CB(2)1198/20-21(02)) (the "**Government's Response to the March Meeting**").

We would be grateful if you could kindly table a copy of this letter for consideration by the members of the Bills Committee.

If you have any questions, please feel free to contact our Mr Dominic Geiser or Mr Trevor Ho.

1. THE GOVERNMENT'S RESPONSE TO THE FEBRUARY MEETING AND THE WHO BRIEF

1.1 In the Government's Response to the February Meeting, the Food and Health Bureau referred to the WHO Brief and stated that "*there is no available evidence to conclude whether [THP] use is associated with any long-term clinical outcome, positive or negative, from exposure to the mainstream emission*" (paragraph 3).

1.2 We are not aware of the type and nature of evidence considered by the WHO in making the above statement. However, we note that the WHO Brief was published in or around May 2020.[1] Accordingly, the WHO may not have considered the latest body of evidence on the harm reduction benefits offered by e-cigarettes and THPs, published since May 2020 and some of which have been set out in our letter dated 8 April 2021 and BATHK's previous written submissions. We respectfully urge the Bills Committee to re-consider such submissions in detail.

1.3 In particular, we would like to draw the Bills Committee's attention to the following international studies mentioned in our letter dated 8 April 2021:

1.3.1 In the report titled "Vaping in England: an evidence update including vaping for smoking cessation" issued in February 2021 by Public Health England,[2] it was recognised that alternative nicotine delivery devices, such as nicotine vaping products, could play a crucial role in reducing the enormous health burden by cigarette smoking (at page 10). It was also noted that "*[a] safety review by the Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT)[3] concluded that* ***the risk of adverse health effects from vaping products is expected to be much lower than from cigarettes"*** (page 11; emphasis added); and

1.3.2 In New Zealand, the Ministry of Health launched a new harm reduction campaign called "Vape to QuitStrong" on 7 March 2021 to encourage people to quit smoking tobacco by switching to vaping.[4] The campaign states that "*[r]esearch shows that 'most toxins responsible for health damage from smoking are absent in e-cigarette aerosol and that those that are present are there at much lower levels ...than in tobacco cigarettes'*"[5] and "*[m]any of the cancer-causing chemicals are produced from burning tobacco in cigarettes or roll-your-own tobacco. If you're a smoker, switching to vaping will greatly decrease your risk of cancer*".[6]

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[1] https://www.euro.who.int/en/health-topics/disease-prevention/tobacco/news/news/2020/5/who-launches-reports-on-novel-tobacco-products-to-help-bridge-gap-between-science-and-policy.

[2] https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/962221/Vaping_in_England_evidence_update_February_2021.pdf. Public Health England is an executive agency of the Department of Health and Social Care, the Government of the United Kingdom.

[3] The COT is a committee of independent experts that provides advice to the Food Standards Agency, the Department of Health and Social Care and other Government Departments and Agencies of the Government of the United Kingdom.

[4] https://www.hpa.org.nz/campaign/vape-to-quitstrong.

[5] https://vapingfacts.health.nz/the-facts-of-vaping/risks-of-vaping/does-vaping-cause-cancer.html, citing the Public Health England's report "Evidence review of e-cigarettes and heated tobacco products 2018" published in February 2018.

[6] https://vapingfacts.health.nz/the-facts-of-vaping/risks-of-vaping/does-vaping-cause-cancer.html.

1.4 Further, the following international studies provide additional evidence of the long-term harm reduction benefits offered by the use of e-cigarettes and THPs:

1.4.1 According to research published by the National Cancer Centre of Tokyo, Japan in November 2020, it was found that *"[e]xposure to aerosol from [THP]s in a designated smoking room under usual conditions is estimated to be tolerable since the lifetime cancer risk is expected to be below a [Virtually Safe Dose (which is a method of cancer risk assessment adopting the standard of 'the amount causing carcinogenesis at a probability of 1/100,000')] of 10^{-5} (1/100,000), which is three orders of magnitude lower than that for cigarettes smoked under the same conditions*".[7] The research was based on the nicotine concentration results obtained from a pilot exposure assessment conducted by the Japanese Ministry of Health, Labour and Welfare; and

1.4.2 According to research published in *The Journal of Internal and Emergency Medicine* on 1 July 2021, it was found that "*complete[ly] switching from cigarette smoking to using a THP could reduce the risk of smoking-related diseases*" (see paragraph 1.8 below).

1.5 As to the WHO's finding that there was no available evidence regarding the long-term clinical outcome of using THPs, it appears that the WHO was only commenting on two studies conducted by Philip Morris International ("**PMI**"). However, it is unclear whether the WHO had considered other studies regarding the positive long-term harm-reduction benefits of the THPs (as mentioned above), as well as the health effects of other products manufactured by other manufacturers.

1.6 The WHO's caveats regarding the finding of a lower level of toxicants in the emission of THPs also only made reference to certain reports submitted by PMI (see Section 2 below).

1.7 As mentioned in our previous submissions (in particular, our letter to the Secretary for Food and Health dated 28 November 2019), the Government's approach in relying on the test result of only one product from a particular manufacturer, namely iQOS produced by PMI, as justification to impose a blanket ban on all other products from a range of different manufacturers (including our client) which affects a number of industries, is plainly unfair and irrational. Each product could be very different and carry different risk levels. For example, whilst we understand that iQOS heats the tobacco stick up to 350°C, we are instructed that our client's *glo* product heats tobacco sticks, known as Neostiks, at a significantly lower temperature of approximately 240°C and consequently would be likely to produce fewer toxicants and lower levels of those toxicants. The substance and composition of Neostiks may also be different with that of the corresponding tobacco sticks manufactured for use with iQOS. There are also other THPs in the international market which the Government has ignored and failed to consider. Accordingly, it is entirely inappropriate for the Government to have failed to properly consider the health effects of all types of products before introducing the Bill.

1.8 On 1 July 2021, new research was published in *The Journal of Internal and Emergency Medicine* regarding the long-term harm-reduction benefits of *glo.* The research involved conducting a randomised, controlled study with healthy adult, volunteer smokers using *glo*

[7] https://www.mdpi.com/1660-4601/17/22/8319/htm.

over a period of 6 months. It found that "*complete[ly] switching from cigarette smoking to using a THP [i.e. glo] could reduce the risk of smoking-related diseases*" and that the research data "*add[s] support to the body of evidence suggesting that THPs are potential MRTPs [i.e. modified risk tobacco product] and also support the notion that the deleterious health impacts of cigarette smoking may be reduced in smokers who completely switch to using THPs*".

1.9 A copy of the research is enclosed herein for the Bills Committee's reference; it can also be accessed via https://link.springer.com/article/10.1007/s11739-021-02798-6?fbclid=IwAR2TyixgX3W9AxiY043Uacvu9Kmyg25ZKlLGhe-m_9NWh6esuTMJLYg2Gw8.

1.10 The new research shows that our client's *glo* could potentially reduce conventional smokers' exposure to certain toxicants and indicators of potential harm related to certain smoking-related diseases.

1.11 BATHK strongly believes that this research highlights the need for the Government to conduct a comprehensive assessment of all types of products from different manufacturers, instead of merely relying on the test results of a single particular product of its choice.

2. THE GOVERNMENT'S RESPONSE TO THE MARCH MEETING

2.1 One of the WHO's caveats regarding their finding of a lower level of toxicants in the emission of THPs is that "*[t]he reports submitted by PMI to the FDA include levels of 57 other constituents that are not included in the FDA's list of HPHCs. The level of 56 of them was higher in IQOS emissions than in conventional cigarettes. Their levels were double those in the reference conventional cigarettes for 22 compounds and more than 10 times higher for seven. It appears that IQOS reduces exposure to some toxicants but elevates exposure to other substances. A number of these substances belong to chemical classes that are known to have significant toxicity, but in general, there is limited information on the toxicity of many of them (22)*" (page 10).

2.2 In the Government's Response to the March Meeting, the Food and Health Bureau set out a list of 80 chemical substances which were either present in higher concentration in aerosols of PMI's iQOS products or not found in conventional cigarette smoke (the "**List**").

2.3 With respect, the List does not justify the Government's proposed total ban on THPs for the following reasons.

2.4 *First,* the List consists of chemical substances present in PMI's iQOS products. We repeat our submission at paragraph 1.7 above that it is wholly inappropriate, and unfair to other manufacturers including our client, for the Government to have failed to properly consider the health effects of all types of products by testing them before introducing the Bill.

2.5 *Second*, the difference in concentration of the chemical substances between the aerosols of PMI's iQOS products and cigarette smoke is unclear. If the difference is only minimal, the Government must clarify why such chemical substances can be emitted by traditional

cigarettes but not THPs. It is also unclear which chemical substances are present in higher concentration in aerosols of PMI's iQOS products, and which are not found in conventional cigarette smoke at all.

2.6 *Third*, there is no evidence regarding the potential health effects (if any) of such chemical substances. For example, it is entirely unclear as to whether (i) these chemical substances are harmful and, if so, at what concentration; and (ii) they are more harmful if they are emitted from THPs instead of conventional cigarettes. It should be noted that the Food and Health Bureau concluded in the Government's Response to the March Meeting that "*FDA's reviews indicated that toxicology/carcinogenicity/genotoxicity data for many of the chemicals are either not available or insufficient for evaluation of their impacts on health*".

2.7 Relevantly, the FDA's assessment of iQOS states that among the 80 chemical substances identified in the List, 4 are possibly carcinogenic, 30 are identified by the applicant as Generally Recognized as Safe, and 46 additional ingredients (mostly flavoring ingredients).[8] In particular:

2.7.1 As regards the possible carcinogenic substances, "*[t]he explanation provided by [PMI] does not support a conclusion that these pose no risk to IQOS users;* ***however the levels of exposure to these possible carcinogens appear low and when considered with other data does not preclude a conclusion the products are appropriate for protection of public health***" (emphasis added; page 32); and

2.7.2 As regards the Generally Recognized as Safe substances, "*[t]he data provided by [PMI] is not sufficient to support their conclusion that these compounds pose no risk to IQOS users;* ***however, although there is potential for genotoxicity with some of these compounds, the exposure levels appear low and the available data does not preclude a conclusion the products are appropriate for protection of public health***" (emphasis added; page 32).

2.8 *Fourth,* and in any event, we again urge the Bills Committee to consider the latest, substantial body of evidence regarding the harm reduction benefits offered by the use of e-cigarettes and THPs, instead of relying on a single review of a particular product conducted in 2016.[9]

3. CONCLUSION

3.1 BATHK respectfully urges the Government to amend the Bill from imposing a total ban on THPs to establishing a fair, evidence-based regulatory regime that properly reflects the risk profile of e-cigarettes and THPs including their potential harm reduction benefits. BATHK

[8] The FDA's Technical Project Lead Preview of the Premarket Tobacco Product Application: https://www.fda.gov/media/124247/download. Also see the FDA's Scientific Review of the Modified Risk Tobacco Product Application at page 32: https://www.fda.gov/media/139796/download.

[9] The references to the FDA's Technical Project Lead Preview of the Premarket Tobacco Product Application, and the FDA's Scientific Review of the Modified Risk Tobacco Product Application, are set out in footnotes 2 and 3 of the Government's Response to the March Meeting respectively.

also urges the Government to conduct laboratory testing on BATHK's products, and take the testing results into account in formulating any revisions or modifications to the Bill.

3.2 In order to establish a regulatory regime which is consistent with international practice, the Government may draw on the other countries' experience in legalising and regulating e-cigarettes and THPs – in this regard, according to the latest information available to BATHK, a total of 64 countries and regions/markets allow THPs to be sold and some of them (such as the United Kingdom and New Zealand), in fact, endorse them as low-risk alternatives to conventional smoking.

Yours faithfully,

Herbert Smith Freehills

Encl.

Cc: Secretary for Food and Health
Food and Health Bureau
18/F, East Wing
Central Government Offices
2 Tim Mei Avenue, Tamar
Hong Kong
(By email and by hand)

For the attention of Professor Sophia Chan, JP

Internal and Emergency Medicine
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IM - ORIGINAL

Changes in biomarkers after 180 days of tobacco heating product use: a randomised trial

Nathan Gale[1] · Michael McEwan[1] · Oscar M. Camacho[1] · George Hardie[1] · Christopher J. Proctor[2] · James Murphy[3]

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Abstract

The aim of this study was to investigate whether biomarkers of exposure (BoE) and potential harm (BoPH) are modified when smokers switch from smoking cigarettes to exclusive use of a tobacco heating product (THP) in an ambulatory setting. Participants in this randomised, controlled study were healthy volunteer smokers assigned either to continue smoking or switch to a THP, and a control group of smokers who abstained from cigarette smoking. Various BoE and BoPH related to oxidative stress, cardiovascular and respiratory diseases, and cancer were assessed at baseline and up to 180 days. In continuing smokers, BoE and BoPH remained stable between baseline and day 180, while THP users' levels of most BoE reduced significantly, becoming similar to those in controls abstaining from cigarette smoking. Also at 180 days, significant changes in numerous BoPH, including total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, 8-epi-prostaglandin F2α type III, fractional concentration of exhaled nitric oxide and white blood cell count, were directionally consistent with lessened health impact. Our findings support the notion that the deleterious health impacts of cigarette smoking may be reduced in smokers who completely switch to using THPs.

Keywords Cigarette smoking · Tobacco heating product · Biomarkers of exposure · Biomarkers of potential harm · Modified risk tobacco product

Introduction

Cigarette smoking is linked to the development of numerous diseases including lung cancer, cardiovascular disease and chronic obstructive pulmonary disease [1]. Smoking-related disease risk is correlated to daily cigarette consumption and the number of years since smoking initiation and is due to inhalational exposure to smoke toxicants that transfer into cigarette smoke during tobacco combustion [1−6]. While quitting smoking reduces disease risk [1], and large proportions of smokers report wanting to quit smoking and make cessation attempts [6], fewer than one in ten smokers successfully quit smoking annually [7]. For those who are either unwilling or unable to quit smoking, a tobacco harm reduction (THR) approach has been proposed [6]. Fundamentally, THR relies on the proposition that the health burden of smoking at the individual and population levels can be reduced by encouraging smokers to switch to novel nicotine and tobacco products that may support combustible cigarette displacement [8], and while not being risk free would reduce or eliminate exposure to toxicants [8, 9] and potentially reduce smoking-related harms.

Cigarette smoke contains more than 8700 identified chemicals [5], many of which may contribute to disease development [10]. The US Institute of Medicine (IoM) has proposed that the development of potential reduced-exposure products (PREPs) which yield lower emissions of some toxicants compared with conventional cigarettes could be expected to result in reduced toxicant exposure in smokers who completely switch to using them [4, 6]. Aerosols from tobacco heating products (THPs) exhibit lower machine yields of toxicants compared to cigarette smoke [11]. Clinical studies examining smokers who switch to using THPs have demonstrated reductions in exposure, in some cases to

✉ Nathan Gale
nathan_gale@bat.com

1 British American Tobacco (Investments) Limited, Research and Development, Regents Park Road, Southampton SO15 8TL, UK

2 DoctorProctorScience Limited, 157 Cavendish Meads, Sunninghill, Ascot SL5 9TG, UK

3 R. J. Reynolds Tobacco Company, 401 N Main Street, Winston-Salem NC27101, USA

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a degree approaching or matching that of smoking cessation [12−14]. Despite these exposure reductions and demonstrations that novel tobacco products may be PREPs, what is not fully established is whether switching to using THPs leads to measurable changes in the health impacts of smoking. One approach to assess the potential health impacts of switching is to measure biomarkers of potential harm (BoPH) [15, 16] in clinical studies involving switching smokers. BoPH assessment has been defined as "measurement of an effect due to exposure; these include early biological effects, alterations in morphology, structure, or function, and clinical symptoms consistent with harm" [15]. Studies utilising BoPH can help determine whether a PREP can be considered a modified risk tobacco product (MRTP) [16] and may form a substantial component of regulatory submissions to regulators such as the US Food and Drug Administration (FDA) when requesting authorization to market a novel product as a MRTP [16, 17].

The aim of this current study is to examine changes in BoE and BoPH in smokers who switch to using a THP relative to those who continue to smoke combustible cigarettes, over a period of 12 months. We have recently reported BoE changes at day 90 of this study [12], and here we report both BoE and BoPH findings up to day 180.

Methods

Study design

This was a randomised, controlled, parallel group, open-label, ambulatory clinical study carried out at four sites in the UK (Belfast, London, Leeds and Merthyr Tydfil). Favourable opinion (which is equivalent to Institutional Review Board (IRB) approval) was given by the NHS Health Research Authority, Wales Research Ethics Committee 2 (reference number 17/WA/0212). The study was conducted in compliance with the ethical principles of the Declaration of Helsinki, Good Clinical Practice (International Council for Harmonisation (ICH) E6 Consolidated Guidance, April 1996) and UK laws, including those relating to the protection of participants' personal data. Written informed consent was obtained from all participants prior to their participation in the study and before undergoing any study procedures, including screening assessments. A full description of the study design and protocol has been published previously [18]. This study is registered with ISRCTN (ISRCTN81075760).

Participants

During a screening visit, potential participants were assessed. Eligible participants were healthy male or female adult current smokers (self-reported daily smoking of 10–30 non-menthol factory-manufactured or roll-your-own cigarettes for at least 5 consecutive years) or never-smokers aged 23−55 years. Smoking status was verified using urinary cotinine (> 200 ng/mL) and exhaled breath carbon monoxide (eCO; ≥ 7 ppm). The cotinine cut-off used was based on the ability to discriminate between social/intermittent smoking and regular smoking [19]. Main inclusion criteria were no clinically relevant abnormal findings on physical examination, vital signs assessment, electrocardiogram, clinical laboratory evaluations or lung function tests, and medical history. The main exclusion criteria were refusal of individuals or their partners of childbearing potential to use effective methods of contraception for the duration of the study; females who were pregnant/breastfeeding; blood donation ≥ 400 mL within 12 weeks (males) or 16 weeks (females) prior to study start; acute illness requiring treatment within 4 weeks prior to study start; regular use of any nicotine/tobacco products other than commercially manufactured filter cigarettes and/or roll-your-own cigarettes up to 14 days before screening; use of any medications/substances (other than tobacco) which interfere with the cyclo-oxygenase pathway or are known to be strong inducers or inhibitors of cytochrome P450 enzymes, up to 14 days or five half-lives of the drug prior to study start. Participants who were never-smokers or were planning to quit in the next 12 months could be included but were eligible only for the never-smoker or cessation groups, respectively.

Study procedures and randomisation

A study design schematic has been published previously [18]. Following screening procedures, smokers completed a tobacco use history questionnaire and the Fagerström Test for Cigarette Dependence (FTCD) [20]. At Visit 1 (baseline), participants underwent safety assessments prior to randomisation. Ambulatory 24-h urine samples and spot blood samples were taken for BoE and BoPH analysis, eCO and fractional concentration of exhaled nitric oxide (FeNO) measurements were made, and spirometry was performed. Smokers not intending to quit were also allowed to try the THP to experience the product to which they might be randomised. Participants could decide whether to continue to participate in the study following this trial.

Randomisation schemes were computer-generated by Covance Clinical Research Unit (Leeds, UK) using a pseudo-randomisation permutation procedure (PROC PLAN procedure in SAS® Version 9.4) for the continue smoking group (Group A) and the switch to THP group (Group B) and provided to the study centres. Randomisation lists were stratified by sex and age categories (23–40 years and 41–55 years). Participants were assigned to groups in blocks of eight, with two participants allocated to Group A and six

to Group B within each block [21]. Participants intending to quit were assigned without randomisation to the cessation group (Group D), and an attempt was made to achieve a balance by sex and age. Never-smokers were assigned to Group E.

All participants attended the clinic on days 30, 60, 90 and 180 (Visits 2, 3, 4 and 7), at which the same samples were collected as Visit 1. In addition to eCO measurements made at these visits, eCO was also measured on days 120 and 150 (Visits 5 and 6) and values reported here are the mean of these 2 measurements.

All participants received a Research Ethics Committee-approved financial reimbursement for taking part in the study, which was set by the clinical site in accordance with their usual level of stipend for taking part in this type of study and was dependent on the number of procedures each participant underwent. Smokers were reminded of the risks associated with smoking prior to enrolment and informed that they were free to voluntarily quit smoking and/or withdraw from the study at any time. Any participant who decided to quit smoking was directed to appropriate stop smoking services.

Adverse and serious adverse events were monitored throughout the study period by open questioning at each study visit and by encouraging participants to spontaneously report such events by telephone should they occur between study visits. Reported adverse events were recorded in source data and on electronic case report forms and coded according to MedDRA Version 20.0. Adverse events were any medical event, irrespective of being related to the investigation products. Serious adverse events were defined as those resulting in death, threatening to life, requiring hospitalisation/prolongation of hospitalisation, resulting in disability and/or in congenital anomaly or birth defect.

Investigational products

Participants in Group A were required to purchase their own usual-brand cigarettes. Those in Group B received the glo THP device and Neostick tobacco consumables (British American Tobacco, Southampton, UK) free of charge. These products have been described previously [12, 22]. In brief, the glo THP electronically heats a small tobacco consumable (Neostick) to a temperature of approximately 245 °C. This eliminates the combustion of tobacco but facilitates the release of nicotine in an aerosol which the user inhales [12].

At study visit 1, participants randomised to Group B were provided by clinic staff with the study THP and tobacco consumables (one Neostick being equivalent to one cigarette) equivalent to 150% of their average number of cigarettes consumed per day (CPD) as self-reported at screening, with the possibility of more (up to a total of 200% of original CPD consumption) before visit 2 by visiting the study site. At visits 2–12, product usage was assessed by return of all empty, part-used, and unused packs of THP consumables, and the next allocation of consumables was supplied at 120% of the usage in the previous period, up to the limit of 200% of pre-screening consumption. At visit 13, as well as all empty, part-used and unused packs of THP consumables, participants were asked to return the study THP device, chargers and other accessories supplied for use in this study. The 200% limit was chosen to support naturalistic product use behaviour following switching to THP use due to possible difference in nicotine yield from usual brand cigarettes, but to avoid large increases in the consumption of free tobacco products which has been reported previously in similar studies [23, 24]. Full accountability records for study products (THP device and consumables) were maintained by staff at the clinical site.

Group D participants devised a cessation strategy with the Investigator, which included nicotine replacement therapy (NRT) and/or varenicline provision if requested, alongside cessation counselling.

Compliance

Participants were instructed of the importance of exclusively using their randomised product (Groups A and B) or of not smoking cigarettes or using nicotine products (Groups D and E) other than NRT (Group D). Participants were asked to report any non-compliance using electronic or paper diaries and were informed that compliance assessments would be conducted at each study visit. Assessment of compliance in Group B was achieved by measuring levels of a haemoglobin adduct of acrylonitrile (*N*-(2-cyanoethyl) valine; CEVal) as a marker of combusted tobacco exposure. Acrylonitrile is found in cigarette smoke but is below the detection limit in the THP emissions and has no common environmental source. Thresholds for CEVal used to deduce compliance were calculated based on a previous study [21, 23].

Use of concomitant medication by study participants was recorded by study site staff. If a prohibited concomitant medication which could affect BoE/BoPH was taken, the participant's data for the timepoint(s) affected by that concomitant medication were not included in any analyses.

Biomarkers of exposure

BoE to selected cigarette smoke constituents in 24-h urine collections were measured at baseline and days 30, 60, 90, and 180; this paper reports BoE levels on days 90 and 180. Laboratory analyses of urine and blood BoE were carried out at ABF GmbH (Planegg, Germany). Details of the bioanalytical methods have been published previously [13]. All BoE assessed in this study have been assessed as fit for purpose in cigarette smoke exposure studies using criteria

such as the availability of suitable assay techniques, sample stability, reproducibility, differential levels between smokers and non-smokers, and the kinetics of reversibility with either smoking cessation or changes in tobacco product use [25].

BoE measured in 24-h urine samples were total nicotine equivalents (TNeq; nicotine, cotinine, 3-hydroxycotinine and their glucuronide conjugates); total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL); total N-nitrosonornicotine (NNN); 3-hydroxypropylmercapturic acid (3-HPMA); 3-hydroxy-1-methylpropylmercapturic acid (HMPMA); S-phenylmercapturic acid (S-PMA); monohydroxybutenylmercapturic acid (MHBMA); 2-cyanoethylmercapturic acid (CEMA); 4-aminobiphenyl (4-ABP); *o*-Toluidine (*o*-Tol); 2-aminonaphthalene (2-AN); 1-hydroxypyrene (1-OHP); and 2-hydroxyethylmercapturic acid (HEMA). Additionally, eCO in exhaled breath and CEVal in whole blood were measured. The smoke constituent associated with each BoE, and details of the limit of detection and lower and upper limits of quantification for each BoE measured, have been reported previously [12].

Biomarkers of potential harm

BoPH were assessed in urine (11-dehydrothromboxane B2 [11-dTx B2], 8-epi-Prostaglandin F2a type III [8-Epi-PGF2α type III]), whole blood (white blood cell [WBC] count), plasma (soluble intercellular adhesion molecule-1 [sICAM-1]), serum (high-density lipoprotein [HDL]), and exhaled breath (FeNO). Additionally, forced expiratory volume in 1 s (FEV_1) was assessed using spirometry. Indications associated with each BoPH have been reported previously [18, 21]. BoPH selection was based on a number of criteria, including association of the BoPH to the risk of developing a smoking-related disease, previously reported differences in BoPH levels between smokers and non-smokers, existence of a dose–response relationship between cigarette consumption and BoPH levels, and reversibility and kinetics after smoking cessation [26]. Furthermore, the selected BoPH have been assessed in prior studies examining the impact of switching from cigarette smoking to using novel nicotine products on individual health markers [27–29]. While NNAL is generally used as a BoE to the cigarette smoke toxicant 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), it is also considered to be a BoPH for smoking-related lung cancer risk due to its tobacco specificity, its carcinogenicity, and its predictive value for lung cancer risk [30–33]. Laboratory analyses of urine and blood (whole, plasma, and serum) BoPH were carried out at Celerion (Lincoln, NE, USA) and Covance (Harrogate, UK and Geneva, Switzerland). sICAM-1 was measured using an electrochemiluminescence immunoassay (Meso Scale Diagnostics, Rockville, MD, USA). FeNO was measured using a NIOX VERO™ device (Circassia Ltd, Oxford, UK) and spirometry was measured using a 6600 Compact™ Expert Workstation Spirometer (Vitalograph Ltd, Buckingham, UK). WBC counts were performed using an automated hematology sampling procedure (Covance). HDL was assessed using homogenous enzymatic colorimetry (Roche Diagnostics, Mannheim, Germany). 11-dTx B2 and 8-Epi-PGF2α type III were assessed using gradient ultra-high-performance liquid chromatography on an ACQUITY UPLC BEH C18 analytical column (Waters, Elstree, UK) following mixed mode solid phase extraction. Negative ions were monitored on a QTRAP 5500 (SCIEX, Macclesfield, UK) in multiple reaction monitoring mode.

Endpoint analysis

Changes in BoE only were expected at day 90, therefore NNAL excretion was pre-specified as the primary endpoint for between-group statistical comparisons at day 90, with the remaining BoE assigned as secondary endpoints. This inferential statistical analysis was to be repeated at day 180 for any BoE endpoint which did not reach significance at day 90. 8-Epi-PGF2α type III was pre-specified as the primary BoPH endpoint at day 180, with 11-dTx B2, FeNO and WBC also included in the inferential statistical analysis as secondary endpoints. Whilst also assigned as secondary study endpoints, sICAM-1, HDL and FEV_1 were not planned for inclusion in the formal statistical analysis.

Statistical methods

A full statistical analysis plan including power calculation methods has been published previously [21]. Based on the power calculation, 466 smokers in total were enrolled, with the objective of having a minimum of 50 participants complete the study in full (i.e., through to day 360, with no major protocol deviations) in each of Groups A, B (CEVal-compliant) and D. 40 never-smokers were also enrolled with the aim of 30 such participants completing the study, since this was considered sufficient to characterise biomarker levels in a never-smoker population.

Analyses were conducted on the per-protocol (PP) and CEVal-compliant populations; for details of participant composition in data tables refer to Supplementary Table 1. In summary, BoE and BoPH levels were computed at each timepoint, and changes from baseline at day 90 and/or day 180 between the THP switching group (Group B) and the continued smoking group (Group A) compared using specific contrast tests from statistical models adjusted for baseline measurements. Data are presented separately for the CEVal-compliant (indicated by CEVal levels in Group B < 78 pmol/g Hb at day 90 and < 54 pmol/g Hb at day 180) and the per-protocol (i.e., all participants who had a valid assessment of a biomarker variable and completed the study

to the relevant timepoint without major protocol deviations) populations.

Alpha level across timepoints was adjusted using the O'Brien-Fleming approach [34] with overall value set at 0.0006 and 0.0151 for days 90 and 180, respectively. Any primary endpoint yielding a significant outcome at any timepoint was not to be statistically assessed at subsequent timepoints and its alpha level would be equally divided among the remaining primary endpoints. NNAL was significant at day 90; its day 180 alpha level was therefore distributed between the other primary endpoints, and as one primary endpoint (AIx) was removed from the study, a conservative approach was taken, leaving $\alpha = 0.00755$ at day 180. Multiplicity adjustment for family-wise error was performed using Holm's method [35].

Data for some of the BoE and BoPH endpoints were better represented by a log-normal distribution than a normal distribution. Therefore, after back transformation to the original scale, ratios of geometric mean partial least squares and confidence intervals were calculated. For NNN, several extreme values were present and an ancillary analysis was performed using a non-parametric (Kruskal–Wallis) test, to avoid distributional assumptions.

Missing values were not imputed and values below the analytical limit of detection or lower limit of quantification were replaced with half of the threshold values. Data analysis was performed using SAS® Version 9.4.

Results

Participant demographics

The first participant was enrolled onto the study on 7th March 2018, and recruitment was completed on 31st March 2019. Of smokers with no intent to quit, 79 were randomised to Group A and 197 to Group B, and 190 smokers intending to quit were enrolled into Group D. Of these, 20 in Group A, 70 in Group B, and 81 in Group D were withdrawn before or missed their day 180 visit. Thus, 59, 127, and 109, respectively, were included in the day 180 analysis. 40 never-smokers were enrolled into Group E; 3 of these participants withdrew from the study prior to the Day 180 visit and as such 37 are included in the day 180 analysis.

Brief demographic details for participants in all groups are presented in Supplementary Table 2. The average age of participants in each group ranged from 37 to 40 years of age, and the overall male:female gender split was 180:152 with only minor differences between groups. Self-reported baseline cigarette consumption was broadly similar across Groups A, B and D, as was total FTCD score. Participants were predominantly white (86.4–89.9% depending on study group), and there were no notable differences in age, weight or BMI between study groups.

Cigarette and neostick consumption

In Group A, self-reported cigarette consumption at all timepoints up to day 180 remained largely similar to that reported at screening (Table 1). In Group B, consumption of Neosticks was slightly higher than usual brand combustible cigarette consumption reported at screening and in Group A at all timepoints but remained stable over time to day 180 (Table 1). In Groups B and D, self-reported cigarette consumption was very low following either switching to the THP (Group B) or being required to abstain from all nicotine/tobacco product use (Group D).

Compliance

CEVal measurement indicated compliance in 97 (76%) of the 127 participants in Group B reaching Day 180. Although only used, as planned, to specify a compliant subset of Group B, CEVal levels in Group D participants would indicate compliance in 80 (73%) of the 109 participants in this group reaching Day 180. At baseline, only three never-smokers had CEVal concentrations above the assay LLOQ of 2 pmol/g globin; their concentrations were 2.4, 2.5 and 5.5 pmol/g globin. At Day 90, all but two never-smokers (3.5 and 4.6 pmol/g globin) had CEVal concentrations below the assay LLOQ. At Day 180, only four never-smokers had CEVal concentrations at or above the assay LLOQ (4.6, 2.6, 2.0 and 2.0 pmol/g globin).

Biomarkers of exposure and of potential harm

Time-series data for the two BoE and BoPH assessed as primary endpoints (NNAL and 8-Epi-PGF2α type III) among CEVal-compliant participants in Group B and among the per-protocol population in Groups A, D and E are presented in Fig. 1. Levels of NNAL (Fig. 1A) in Group A remained similar to baseline over time. In contrast, levels were reduced by approximately 50% in Group B (switch to THP) and approximately 80% in Group D (cessation) by day 30, with these exposure reductions maintained at similar levels between days 30 and 180. For 8-Epi-PGF2α type III, levels trended towards a slight reduction between baseline and day 180 in Group A, whereas in Groups B and D levels reduced gradually to a greater extent over time, with a total drop of approximately 29% and 17% by day 180, respectively (Fig. 1B). In Group E, both NNAL and 8-Epi-PGF2α type III levels remained constant over time (Fig. 1).

Statistical analyses of the differences in BoE and BoPH changes from baseline between groups A and B in the CEVal-compliant PP population are presented in Table 2;

Table 1 Consumption data for study participants in the day 180 per-protocol population

Numbers	Group A (continue to smoke)			Group B (switch to THP[a])			Group D (cessation)		
	Baseline	Day 90	Day 180	Baseline	Day 90	Day 180	Baseline	Day 90	Day 180
CC consumption[b]									
Number of participants	59	59	59	127	122[d]	122[d]	109	100[d]	104[d]
Mean (SD)	18.0 ± 5.2	17.3 ± 5.3	17.4 ± 4.6	17.9 ± 5.1	0.2 ± 1.4	0.0 ± 0.1	18.1 ± 5.4	0.1 ± 0.7	0.0 ± 0.1
Minimum	10.0	7.4	8.7	10.0	0.0	0.0	10.0	0.0	0.0
Maximum	30.0	30.0	27.8	30.0	15.5	0.7	30.0	6.7	0.7
Neostick consumption[c]									
Number of participants	–	–	–	–	123[e]	127	–	–	–
Mean (SD)	–	–	–	–	20.8 ± 9.0	21.9 ± 9.7	–	–	–
Minimum	–	–	–	–	0.7	0.4	–	–	–
Maximum	–	–	–	–	53.5	53.8	–	–	–

Data were recorded at ± 3 days up to day 90 or ± 14 days after day 90 due to individual participant visit scheduling. For cigarette consumption, data were averaged using daily self-reported consumption across all days between the relevant study clinic visits. Baseline combustible cigarette consumption data were self-reported by participants at screening. For THP consumption, the number of Neosticks dispensed at a participant visit minus the number of sticks returned at the subsequent visit was divided by the number of days between the two visits

[a]*THP* tobacco heating product

[b]Average number of conventional cigarettes (CC) smoked per day

[c]Average number of neosticks used per day

[d]Some participants failed to self-report consumption data (see Supplementary Table 1)

[e]Consumption data for four participants could not be calculated at Day 90 (see Supplementary Table 1). For details of participant composition refer to Supplementary Table 1

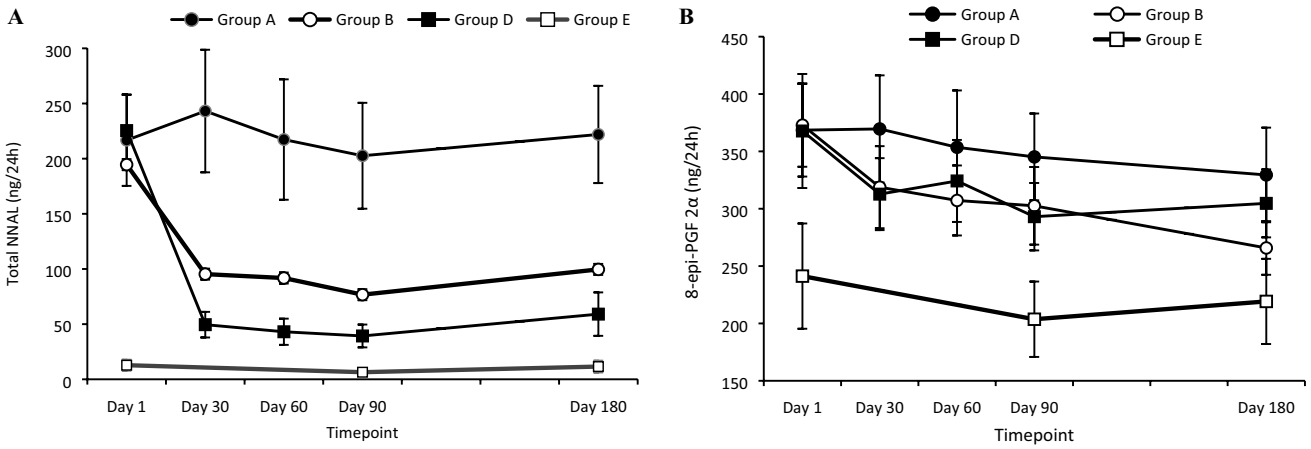

Fig. 1 Time-series plots of changes in primary endpoints in the day 180 per-protocol population. Data are means ± 95% confidence intervals for the BoE Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL; panel **A**) and the BoPH 8-epi-Prostaglandin F2a type III (8-Epi-PGF2α type III; Panel **B**). Data shown are for the Day 180 PP population (CEVal-compliant for Group B), excluding any invalid data points (e.g., urine collection issues, prohibited concomitant medication) and, for panel **B**, two extreme outliers (2543 and 2190 ng/24 h) for Group E. Therefore $N = 52–56$ (Group A), 84–90 (Group B), 97–107 (Group D), 31–36 (Group E). Group A, continue to smoke combustible cigarettes; Group B, switch to THP; Group D, cessation; Group E, never smokers

the BoE analyses were only performed on day 180 data if differences at day 90 were not significant, as per the SAP. A complete listing of mean BoE levels in Group A and CEVal-compliant Group B at baseline, day 90 and day 180 is presented in Supplementary Table 3. For those BoPH for which inferential statistical analyses were not performed (sICAM-1, HDL and FEV_1) descriptive statistics are presented in Table 3. Reductions in the levels of all BoE were seen in Group B between baseline and day 180. When compared to changes in Group A, the reductions in the THP group were statistically significant at day 90 for NNAL, 3-HPMA, HMPMA, MHBMA, HEMA, 4-ABP,

Table 2 Between-group statistical analysis of change from baseline in BoE and BoPH in the CEVal-compliant per-protocol population

Biomarker (units)	Group[a]	*N*[b]	Day	LS[c] mean or GLS[d] mean ratio compared to baseline[e]	Difference between groups (CI)[e,f]	*p* value[g]
Total NNAL[e,h] (ng/24 h)	A	55	90	0.89	0.50 (0.33, 0.75)	< 0.0001
	B	97		0.44		
Total NNN[e,i] (ng/24 h)	A	55	90	0.84	0.51 (0.24, 1.10)	0.0025
	B	97		0.43		
Total NNN[e,i] (ng/24 h)	A	53	180	0.97	0.64 (0.37, 1.10)	0.0276
	B	85		0.62		
3-HPMA[e,j] (µg/24 h)	A	55	90	1.00	0.30 (0.19, 0.48)	< 0.0001
	B	97		0.30		
HMPMA[e,k] (µg/24 h)	A	55	90	0.85	0.29 (0.19, 0.44)	< 0.0001
	B	97		0.25		
MHBMA[e,l] (µg/24 h)	A	55	90	1.05	0.11 (0.05, 0.23)	< 0.0001
	B	97		0.11		
HEMA[e,m] (µg/24 h)	A	55	90	0.83	0.52 (0.30, 0.88)	< 0.0001
	B	97		0.43		
4-aminobiphenyl (ng/24 h)[e]	A	55	90	0.86	0.29 (0.19, 0.42)	< 0.0001
	B	97		0.25		
2-aminonaphthalene (ng/24 h)[e]	A	55	90	0.88	0.15 (0.09, 0.25)	< 0.0001
	B	97		0.13		
o-Toluidine (ng/24 h)[e]	A	55	90	1.01	0.36 (0.24, 0.52)	< 0.0001
	B	97		0.36		
1-hydroxypyrene (ng/24 h)[e]	A	55	90	1.15	0.37 (0.24, 0.57)	< 0.0001
	B	97		0.42		
FeNO[e,n] (ppb)	A	54	180	0.99	1.52 (1.20, 1.93)	< 0.0001
	B	93		1.51		
WBC[e,o] count (10^9/L)	A	56	180	0.99	0.85 (0.76, 0.94)	< 0.0001
	B	93		0.84		
eCO[p,q] (ppm)	A	62	120/150	15.06	−13.37 (−16.20, −10.54)	< 0.0001
	B	112		1.69		
TNeq[p,r] (mg/24 h)	A	55	90	−1.67	−3.11 (−8.74, 2.53)	0.0550
	B	97		−4.77		
TNeq[p,r] (mg/24 h)	A	53	180	−4.70	−1.13 (−5.21, 2.95)	0.4529
	B	85		−5.84		
S-PMA[p,s] (µg/24 h)	A	55	90	−0.74	−2.84 (−4.51, −1.18)	< 0.0001
	B	97		−3.58		
CEMA[p,t] (µg/24 h)	A	55	90	−2	−158 (−212, −103)	< 0.0001
	B	97		−159		
11-dTx B2[p,u] (ng/24 h)	A	53	180	−100	−173 (−399, 53)	0.0396
	B	85		−274		
8-Epi-PGF2α[p,v] (ng/24 h)	A	53	180	−41	−76 (−144, −7)	0.0032
	B	85		−116		

All analyses, except for eCO, were performed using biomarker levels at baseline (day 1) and on either day 90 or day 180, as indicated. eCO was analysed as the difference between the means of absolute values on days 120 and 150

[a]Group A, continue to smoke combustible cigarettes, Group B, switch to THP

[b]*N*, number of participants (for details of participant composition refer to Supplementary Table 1)

[c]*LS* least squares

[d]*GLS* geometric least squares

[e]GLS mean and ratio shown for data log-transformed prior to calculation of change from baseline

[f]*CI* confidence interval: 99.94% CI shown for day 90; 99.245% CI shown for day 180

[g]Significance threshold 0.0006 on day 90 and 0.00755 on day 180

Table 2 (continued)

[h]*NNAL* 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol

[i]*NNN N*-nitrosonornicotine

[j]*3-HPMA* 3-hydroxypropylmercapturic acid

[k]*HMPMA* 3-hydroxy-1-methylpropylmercapturic acid

[l]*MHBMA* monohydroxybutenyl-mercapturic acid

[m]*HEMA* 2-hydroxyethylmercapturic acid

[n]*FeNO* fractional exhaled nitric oxide

[o]*WBC* white blood cell

[p]LS mean and difference shown for untransformed data

[q]*eCO* exhaled carbon monoxide

[r]*TNeq* total nicotine equivalents (nicotine, cotinine, 3-hydroxycotinine and their glucuronide conjugates)

[s]*S-PMA* S-phenylmercapturic acid

[t]*CEMA* 2-cyanoethylmercapturic acid

[u]*11-dTx B2* 11-dehydrothromboxane B2

[v]*8-Epi-PGF2α* 8-epi-prostaglandin F2α type III

Table 3 Descriptive Statistics for sICAM-1, HDL and FEV1 at Baseline (day 1), Day 90 and Day 180 in the Day 180 CEVal-compliant per-protocol population

Biomarker (units)	Group[a]	*N*[b]	Day 1	Day 90	Day 180
sICAM-1[c] (ng/mL)	A	58–59	474.3 (444.4, 504.2)	491.0 (454.9, 527.1)	501.8 (463.6, 540.0)
	B	94–97	464.4 (437.6, 491.1)	428.0 (409.1, 447.0)	433.2 (410.3, 456.1)
HDL[d] (mmol/L)	A	58–59	1.39 (1.29, 1.49)	1.39 (1.28, 1.49)	1.37 (1.26, 1.49)
	B	94–97	1.41 (1.34, 1.48)	1.49 (1.41, 1.57)	1.48 (1.40, 1.56)
FEV_1%pred[e]	A	55–58	91.5 (88.5, 94.5)	90.1 (87.0, 93.1)	88.1 (85.1, 91.0)
	B	89–93	91.9 (89.7, 94.2)	92.8 (90.5, 95.1)	93.0 (90.8, 95.1)

Data are means with lower and upper 95% confidence intervals in parentheses

[a]Group A continue to smoke combustible cigarettes, Group B, switch to THP

[b]*N*, number of participants (for details of participant composition refer to Supplementary Table 1)

[c]*sICAM-1* soluble intercellular adhesion molecule-1

[d]*HDL* high-density lipoprotein

[e]*FEV_1%pred* forced expiratory volume in 1 s percentage of predicted

2-AN, *o*-Tol, 1-OHP, eCO, S-PMA and CEMA (Table 2). Changes from baseline for NNN or TNeq were not statistically significant between Groups A and B at days 90 or 180 following multiple comparisons adjustment (Table 2). In the case of NNN, this was despite reductions in exposure from baseline in Group B of 57% at day 90 and 38% at day 180 (Table 2), compared with reductions in Group A of 16% at day 90 and 3% at day 180. One potential reason for the lack of statistical significance for NNN levels between Groups A and B is that NNN levels in Group B were skewed due to an extreme observation at day 180 (456.26 ng/24 h) relative to the mean group B value of 11.34 ng/24 h. A Kruskal–Wallis test suggested reductions in exposure to NNN in Group B ($p = 0.0103$) compared to continued smoking, and this reduction was enhanced ($p = 0.0061$) after removal of the most extreme value in Group B, in the absence of multiple comparison adjustments.

Regarding BoPH in the Group B CEVal-compliant PP population, 8-Epi-PGF2α type III levels and WBC count were reduced, and FeNO was elevated, between baseline and day 180. These effects were significant when comparing Groups A and B (Table 2). Levels of 11-dTX B2 were lower at day 180 than at baseline in Group B. Despite this reduction being over two-and-a-half times that seen in Group A, the comparison with Group A did not reach statistical significance (Table 2).

For other BoPH, for which only descriptive statistics were generated, favourable directional trends were seen over time in participants who switched to using the THP (Group B; Table 3). Thus, compared to baseline sICAM-1 was lower on days 90 and day 180 while both HDL and FEV_1 were increased. This contrasted with elevation of sICAM-1 and reductions in HDL and FEV_1 over time in continued smokers (Group A).

Complete listings of mean BoE levels in Groups A, B, D and E at baseline, day 90 and day 180, and statistical analyses of BoE and BoPH data, in the total PP population are presented in Supplementary Tables 4 and 5. There

were no major differences in statistical outcomes between the total PP and CEVal-compliant PP populations. Thus, significant differences were seen at day 90 between Groups A and B for reductions in the BoE NNAL, 3-HPMA, HMPMA, MHBMA, HEMA, 4-ABP, 2-AN, *o*-Tol, 1-OHP, eCO, S-PMA and CEMA, and for the changes in the BoPH 8-Epi-PGF2α type III, FeNO and WBC count at day 180. As seen in the CEVal-compliant PP population, the reduction in 11-dTx B2 neared statistical significance in the PP population. Finally, there were no major differences in the descriptive statistics for the BoPH sICAM-1, HDL and FEV_1 between the PP and CEVal-compliant PP populations (Supplementary Table 6).

Adverse events

Up to Day 180, exposure period adverse events occurred in 329 participants, including 5 serious adverse events considered unrelated to any study product. The most frequently reported adverse event was headache, and the majority of adverse events were mild or moderate in severity.

Discussion

In a previous publication of a planned, interim analysis of a subset of study participants at day 90 from this study, and also in a publication assessing data from a 5-day confinement study, we demonstrated significant reductions in exposure to a number of cigarette smoke toxicants in smokers switching to using the THP [12, 13]. These exposure reductions were correlated with the lower THP emissions compared to cigarette smoke and approached those seen with smoking cessation for a number of the BoE examined. Here, we build on those observations by reporting reductions in BoE in the full population of study participants at day 90 while also demonstrating that exposure reductions persisted at day 180. The day 180 BoE reductions were to a degree similar to that in the smoking cessation group in the per-protocol population (Supplementary Table 5). Importantly, we also demonstrate that exposure reductions in those switching to using the THP were accompanied by significant changes in BoPH, which are associated with disease risk and therefore considered to indicate changes in smoking-related harm [15], compared with those who continued smoking. Furthermore, although no formal statistical analyses have been performed and descriptive statistics have been presented, it is notable that in the per-protocol population changes in BoPH at Day 180 were directionally similar in the THP switching group to those seen in the smoking cessation group.

When compared with continued smoking, significant reductions were seen between baseline and day 180 for 8-Epi-PGF2α type III (a prostaglandin associated with systemic oxidative stress and implicated in smoking-related disease progression [36–38]) and white blood cell count (an inflammatory marker indicative of cardiovascular disease risk [39]), while FeNO (an indicator of airway inflammation, lung health and vascular tone [40]) levels were significantly increased. Furthermore, urinary NNAL levels were significantly reduced between baseline and day 180 and while this indicates a reduction in exposure to the tobacco-specific nitrosamine NNK, urinary NNAL levels are also considered a biomarker for lung cancer risk [30, 32, 33]. Of interest, although as per the SAP the statistical significance was not assessed, we observed an increase in HDL at day 90 and day 180 in the THP switching group. Given the rough proportionality of increased HDL levels with reduced CVD risk, this change could be biologically relevant [41]. Overall, taking our BoE and BoPH findings into account our data are indicative that complete switching from cigarette smoking to using a THP could reduce the risk of smoking-related diseases.

While the criteria under which a tobacco product may be considered a reduced exposure or reduced risk tobacco product have not been fully defined, the US IoM and the FDA [16, 17] have indicated one potential criterion, observation of a statistically significant difference in BoE and BoPH in those switching to using a novel product compared with continued smoking, and similarity of effect size compared with cessation may also be considered a criterion [16]. Indeed, the FDA recently authorized the marketing of a THP as a MRTP with 'Reduced Exposure information' based in part on these criteria [42]. Many of the BoE examined in this study meet either or both of these criteria, as do the BoPH 8-Epi-PGF2α type III, WBC count, FeNO, NNAL, 11-dTx B2, sICAM-1, HDL and FEV_1 which all changed favourably in the THP switching group. Furthermore, the BoPH changes meet a criterion of biological relevance suggested by Chang et al. [15] such that differences > 10% can distinguish between smokers and non-smokers. Our findings add to the body of evidence suggesting that THPs are potentially MRTPs when compared to combustible cigarette smoking. Our findings may also provide insight into the utility of certain biomarkers for assessing changes in smoking-related disease risk. For example, one of the BoPH assessed in this study, 8-Epi-PGF2α type III, showed a large degree of variability between timepoints, even within the never-smoker group (Fig. 1). This has also been observed previously in other switching studies [23]. While the reasons for such variability cannot be ascertained, potentially this could be due to 8-Epi-PGF2α type III being a general marker of systemic oxidative stress, and therefore being susceptible to change due to factors other than changes in cigarette smoking status (e.g., other risk factors or seasonal disorders). While such variability may hinder data analysis and interpretation, it does give insight into how future studies should be designed

to take into account such variability, for example by ensuring an adequate sample size.

While a previous study reported BoPH changes in smokers switching to using a THP [27], self-reported compliance was as low as 50%. Furthermore, cigarettes could have constituted up to 30% of tobacco products used in participants defined as complete THP switchers. These issues lessened the ability to detect changes in BoPH. A strength of this current study is the use of a biochemical measure (CEVal) and pre-determined thresholds to determine compliance [21], allowing us to define a group of complete switchers in which to assess biomarker changes. Additionally, in this study, we were able to maintain compliance at higher levels using both participant selection (high intentions to quit smoking in the abstinence group) and participant monitoring. It is notable in this regard that potentially due to this maintenance of compliance there were no major differences in our findings between the CEVal-compliant and the per-protocol analysis populations.

While the degree of compliance and its accurate assessment are strengths of our study, there are some limitations of the study and our findings. While we provide evidence of both acute [12] and sustained reductions in BoE and BoPH in smokers switching to THP use, the findings do not necessarily indicate changes in population-level exposure or risk, particularly if within those populations smokers do not switch completely and instead switch to dual-using cigarettes and THPs. Secondly, the generalizability of our findings may be limited since the study involved a young, healthy population and a small sample size. Larger, future studies in other populations are needed to improve the generalisability and strengthen our conclusions regarding reduced disease risk. Furthermore, while BoE for a number of smoke toxicants linked with smoking-related disease were reduced, and these were associated with favourable changes in BoPH covering a spectrum of smoking-related diseases, only limited conclusions can be drawn regarding whether switching to THP use reduces smoking-related morbidity and mortality. Such information can only come from prospective longer-term epidemiological and/or cohort studies.

In summary, the data presented here build on our prior work by demonstrating that exposure changes in smokers switching to using the THP were sustained and extend this finding by demonstrating that these exposure reductions were associated with beneficial changes in disease risk biomarkers covering several smoking-related diseases. While the use of THPs is likely not risk-free and may be addictive due to nicotine delivery to users, and given that to eliminate the risks associated with cigarette smoking the best course of action for a smoker to take is to completely abstain from the use of any tobacco products [1], our study gives an insight into the potential beneficial effects of smoking-related disease reduction in smokers switching to using THPs. This is illustrated by the similarity in BoE in smokers who switched to using the THP or who quit all tobacco/nicotine use. When taking into account established criteria for risk reduction, our data add support to the body of evidence suggesting that THPs are potential MRTPs and also support the notion that the deleterious health impacts of cigarette smoking may be reduced in smokers who completely switch to using THPs. Further research, including assessments of disease endpoints such as cardiac or respiratory events in smokers who switch to using THPs, may be able to further determine this risk reduction potential.

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Author contribution Conceptualization, Nathan Gale, Michael McEwan, Oscar Camacho, George Hardie, Christopher Proctor and James Murphy; data curation, Nathan Gale, Michael McEwan, Oscar Camacho and George Hardie; formal analysis, Nathan Gale, Michael McEwan, Oscar Camacho and George Hardie; funding acquisition, Christopher Proctor and James Murphy; investigation, Nathan Gale, Michael McEwan, Oscar Camacho, George Hardie, Christopher Proctor and James Murphy; Methodology, Nathan Gale, Michael McEwan, Oscar Camacho, George Hardie, Christopher Proctor and James Murphy; project administration, Nathan Gale and Michael McEwan; software, Oscar Camacho; Supervision, George Hardie, Christopher Proctor and James Murphy; validation, Nathan Gale, Michael McEwan, Oscar Camacho, George Hardie, Christopher Proctor and James Murphy; visualization, Nathan Gale; writing—original draft, Nathan Gale, Michael McEwan and Oscar Camacho; writing—review and editing, Nathan Gale, Michael McEwan, Oscar Camacho, George Hardie, Christopher Proctor and James Murphy.

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Data availability Deidentified participant-level data will be available on request in SDTM format. This data will be available immediately following publication for at least 5 years. Data will be available to anyone who wishes access to the data and for any purpose. Requests for data should be made to clinical_info@bat.com and data requestors must sign a data access agreement.

Declarations

Conflict of interest NG, MM, OMC and GH are current employees of British American Tobacco (Investments) Limited, which was the sponsor and funding source of this study. JM was an employee of British American Tobacco (Investments) Limited at the time of the study and is a current employee of R. J. Reynolds Tobacco Company. CJP was

an employee of British American Tobacco (Investments) Limited at the time of the study and is currently contracted by British American Tobacco (Investments) Limited to provide consultancy services. The British American Tobacco Group is the manufacturer and holder of the intellectual property rights of the investigational product used in this study.

Ethics approval This study was granted a Favourable Opinion (equivalent to Institutional Review Board approval) by NHS Health Research Authority Wales Research Ethics Committee 2 (reference number 17/WA/0212).

Informed consent All participants provided written informed consent before enrolment into the study, including agreeing for the results to be published.

References

1. National Center for Chronic Disease Prevention and Health Promotion (US) Office on Smoking and Health (2014) The health consequences of smoking—50 years of progress: a report of the Surgeon General. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, Atlanta
2. IARC (2007) Tobacco control: reversal of risk after quitting smoking. In: IARC handbooks of cancer prevention, vol 11. IARC, Lyon
3. Doll R, Peto R, Wheatley K et al (1994) Mortality in relation to smoking: 40 years' observations on male British doctors. Brit Med J 309:901–911
4. Institute of Medicine (2001) Clearing the smoke—assessing the science base for tobacco harm reduction. National Academies Press, Washington, DC
5. Perfetti T, Rodgman A (2011) The complexity of tobacco and tobacco smoke. Beitr Tabakforsch Int 24:17
6. Stratton K, Shetty P, Wallace R, Bondurant S (2001) Clearing the smoke: the science base for tobacco harm reduction–executive summary. Tob Control 10:189–195
7. Babb S, Malarcher A, Schauer G et al (2017) Quitting smoking among adults—United States, 2000–2015. MMWR Morb Mortal Wkly Rep 65:1457–1464
8. Royal College of Physicians (2016) Nicotine without smoke. Tobacco harm reduction. A report by the Tobacco Advisory Group of the Royal College of Physicians. Royal College of Physicians, London
9. Public Health England (2018) Evidence review of e-cigarettes and heated tobacco products 2018. A report commissioned by Public Health England. PHE Publications, London
10. Food and Drug Administration (2012) Harmful and potentially harmful constituents in tobacco products and tobacco smoke; established list. Docket No FDA-2012-N-0143. Fed Reg 77:20034–20037
11. Forster M, Fiebelkorn S, Yurteri C et al (2018) Assessment of novel tobacco heating product THP1.0. Part 3: comprehensive chemical characterisation of harmful and potentially harmful aerosol emissions. Regul Toxicol Pharmacol 93:14–33
12. Gale N, McEwan M, Camacho OM et al (2021) Changes in biomarkers of exposure on switching from a conventional cigarette to the glo tobacco heating product: a randomized, controlled ambulatory study. Nicotine Tob Res 23(3):584–591
13. Gale N, McEwan M, Eldridge AC et al (2019) Changes in biomarkers of exposure on switching from a conventional cigarette to tobacco heating products: a randomized, controlled study in healthy Japanese subjects. Nicotine Tob Res 21(9):1220–1227
14. Haziza C, de La Bourdonnaye G, Donelli A et al (2020) Reduction in exposure to selected harmful and potentially harmful constituents approaching those observed upon smoking abstinence in smokers switching to the menthol tobacco heating system 22 for three months (part 1). Nicotine Tob Res 22(4):539–548
15. Chang CM, Cheng YC, Cho TM et al (2019) Biomarkers of potential harm: summary of an FDA-sponsored public workshop. Nicotine Tob Res 21:3–13
16. Institute of Medicine (2012) Scientific standards for studies on modified risk tobacco products. The National Academies Press, Washington, DC, p 370
17. Food and Drug Administration (2012) Modified risk tobacco product applications. Draft guidance for industry. Docket No. FDA-2012-D-0071. Fed Reg 77:20026–20030
18. Newland N, Lowe FJ, Camacho OM et al (2019) Evaluating the effects of switching from cigarette smoking to using a heated tobacco product on health effect indicators in healthy subjects: study protocol for a randomized controlled trial. Intern Emerg Med 14:885–898
19. Shiffman S, Li X, Dunbar MS et al (2015) Social smoking among intermittent smokers. Drug Alcohol Depend 154:184–191
20. Fagerström K (2012) Determinants of tobacco use and renaming the FTND to the Fagerstrom test for cigarette dependence. Nicotine Tob Res 14:75–78
21. Camacho OM, Hedge A, Lowe F et al (2020) Statistical analysis plan for "A randomised, controlled study to evaluate the effects of switching from cigarette smoking to using a tobacco heating product on health effect indicators in healthy subjects." Contemp Clin Trials Commun 17:100535
22. Eaton D, Jakaj B, Forster M et al (2018) Assessment of tobacco heating product THP1.0. Part 2: product design, operation and thermophysical characterisation. Regul Toxicol Pharmacol 93:4–13
23. Shepperd CJ, Newland N, Eldridge A et al (2015) Changes in levels of biomarkers of exposure and biological effect in a controlled study of smokers switched from conventional cigarettes to reduced-toxicant-prototype cigarettes. Regul Toxicol Pharmacol 72:273–291
24. Shiffman S, Scholl S (2018) Increases in cigarette consumption and decreases in smoking intensity when nondaily smokers are provided with free cigarettes. Nicotine Tob Res 20:1237–1242
25. Gregg EO, Minet E, McEwan M (2013) Urinary biomarkers of smokers' exposure to tobacco smoke constituents in tobacco products assessment: a fit for purpose approach. Biomarkers 18:467–486
26. Scherer G (2018) Suitability of biomarkers of biological effects (BOBEs) for assessing the likelihood of reducing the tobacco related disease risk by new and innovative tobacco products: a literature review. Regul Toxicol Pharmacol 94:203–233

27. Haziza C, de La Bourdonnaye G, Donelli A et al (2020) Favorable changes in biomarkers of potential harm to reduce the adverse health effects of smoking in smokers switching to the menthol tobacco heating system 2.2 for 3 months (part 2). Nicotine Tob Res 22:549–559
28. Lüdicke F, Ansari SM, Lama N et al (2019) Effects of switching to a heat-not-burn tobacco product on biologically relevant biomarkers to assess a candidate modified risk tobacco product: a randomized trial. Cancer Epidemiol Biomarkers Prev 28(11):1934–1943
29. Lüdicke F, Picavet P, Baker G et al (2018) Effects of switching to the menthol tobacco heating system 2.2, smoking abstinence, or continued cigarette smoking on clinically relevant risk markers: a randomized, controlled, open-label, multicenter study in sequential confinement and ambulatory settings (part 2). Nicotine Tob Res 20:173–182
30. Hatsukami DK, Benowitz NL, Rennard SI et al (2006) Biomarkers to assess the utility of potential reduced exposure tobacco products. Nicotine Tob Res 8:169–191
31. Ter-Minassian M, Asomaning K, Zhao Y et al (2012) Genetic variability in the metabolism of the tobacco-specific nitrosamine 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) to 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL). Int J Cancer 130:1338–1346
32. Xue J, Yang S, Seng S (2014) Mechanisms of cancer induction by tobacco-specific NNK and NNN. Cancers (Basel) 6:1138–1156
33. Yuan JM, Butler LM, Stepanov I, Hecht SS (2014) Urinary tobacco smoke-constituent biomarkers for assessing risk of lung cancer. Cancer Res 74:401–411
34. O'Brien PC, Fleming TR (1979) A multiple testing procedure for clinical trials. Biometrics 35:549–556
35. Holm S (1979) A simple sequentially rejective multiple test procedure. Scand J Stat 6:65–70
36. Campos C, Guzmán R, López-Fernández E, Casado Á (2011) Urinary biomarkers of oxidative/nitrosative stress in healthy smokers. Inhal Toxicol 23:148–156
37. Basu S, Helmersson J, Jarosinska D et al (2009) Regulatory factors of basal F_2-isoprostane formation: population, age, gender and smoking habits in humans. Free Radic Res 43:85–91
38. Morrow JD, Frei B, Longmire AW et al (1995) Increase in circulating products of lipid peroxidation (F2-isoprostanes) in smokers. Smoking as a cause of oxidative damage. N Engl J Med 332:1198–1203
39. Madjid M, Awan I, Willerson JT, Casscells SW (2004) Leukocyte count and coronary heart disease: implications for risk assessment. J Am Coll Cardiol 44:1945–1956
40. Cameli P, Bargagli E, Bergantini L et al (2020) Extended exhaled nitric oxide analysis in interstitial lung diseases: a systematic review. Int J Mol Sci 21:401–411
41. Soria-Florido MT, Schröder H, Grau M et al (2020) High density lipoprotein functionality and cardiovascular events and mortality: a systematic review and meta-analysis. Atherosclerosis 302:36–42
42. Food and Drug Administration (2020) FDA authorizes marketing of IQOS tobacco heating system with 'reduced exposure' information. https://www.fda.gov/news-events/press-announcements/fda-authorizes-marketing-iqos-tobacco-heating-system-reduced-exposure-information. Accessed 15 September 2020

香港吸煙與健康委員會
HONG KONG COUNCIL ON SMOKING AND HEALTH

香港中區立法會道 1 號
香港特別行政區立法會
《2019 年吸煙（公眾衞生）（修訂）條例草案》委員會

黃定光主席：

所有另類吸煙產品必須禁止 儘快通過條例草案

《2019 吸煙（公眾衞生）（修訂）條例草案》旨在禁止進口、製造或售賣另類吸煙產品，包括加熱煙草製品（加熱煙）。對於有議員提出修正案，建議規管而非禁止加熱煙，香港吸煙與健康委員會表示極度關注和強烈反對，並呼籲立法會應從速禁止所有另類吸煙產品包括加熱煙，及制定長遠全面禁煙的藍圖。

委員會重申，所有吸煙產品均會損害健康。無異於傳統捲煙，加熱煙本質亦是煙草產品，更可釋出濃度較高或不存在於傳統煙煙霧的有害物質。世界衞生組織、美國食物及藥物管理局、澳洲衞生部及意大利衞生部等醫學組織和衞生部門均已否定加熱煙的減害聲稱。世衞強調「從傳統捲煙轉用電子煙並不等於戒煙」，更何況是含有煙草而且較電子煙更為有害的加熱煙。

香港的吸煙率由有記錄以來的 23.3%降至近年 10.2%，是近 40 年逐步加強控煙工作的成果。規管而不禁止加熱煙形同准許更多吸煙產品在香港出售，勢將令吸煙常態化，妨礙降低吸煙率的努力，並讓煙草禍害持續蔓延。在邁向無煙香港的路上，政府應為吸煙人士提供已證實有效及安全的戒煙輔助，並非更多類型的吸煙產品。

我們希望立法會及法案委員會能從速回應社會對無煙香港的期望，儘快通過全面禁止包括加熱煙在內的另類吸煙產品，並進一步加強控煙措施，以持續降低吸煙率，保障公眾健康。

主席　　總幹事

湯修齊 MH 太平紳士　　黎慧賢 MPH

二零二一年七月二日
副本送：食物及衞生局局長、衞生署署長

香港灣仔皇后大道東183號合和中心44樓4402-03室
Unit 4402-03, 44/F., Hopewell Centre, 183 Queen's Road East, Wanchai, Hong Kong
電話Tel: +852 2185 6388　傳真Fax: +852 2575 3966　電郵Email: enq@cosh.org.hk
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香港中區立法會道1號

立法會綜合大樓

香港特別行政區立法會

《2019年吸煙(公眾衞生)(修訂)條例草案》委員會主席

黃定光議員

尊敬的黃議員：

港九新界販商社團聯合會（下稱本會）就《2019年吸煙(公眾衞生)(修訂)條例草案》(下稱吸煙修訂條例草案)的審議工作提交意見書。

本會自成立以來一貫堅持愛國愛港立場，致力為販商爭取合法權益，長期積極地參與香港各項重大社會事務，全力支持政府施政。本會的屬會數目現已超過90個，會員人數合共超過兩萬。本會一直關注吸煙修訂條例草案的審議工作，**是次來函希望積極建議政府盡快「規管」加熱煙，以平衡整體經濟、民生需求及公共衞生等多個角度出發，此舉也是令香港可以跟隨祖國及國際的大方向，實施務實而平衡的政策。**

自2019年中至今，香港先後受社會事件和新型冠狀病毒病疫情連環打擊下，經濟陷入深度衰退，各行業均面對異常沉重的經營壓力，本會屬下會員特別是報販同業也大受影響，靠經營報檔糊口的會員已是苟延一息，陷入了史無前例的困境。

隨着本港紙媒步入寒冬，報販亦唇亡齒寒，只能依靠銷售香煙、糖果等其他產品幫補。假若政府全面禁售加熱煙產品，只會令私煙問題惡化，既不能保障未成年人士，同時亦抹煞守法售賣煙草產品的基層小報販生存空間；相反，**政府只要嚴謹「規管」加熱煙，把同樣屬於煙草產品的加熱煙納入現行控煙框架，容許合法販商銷售，不單可以把流入黑市的收益正式轉入去基層小報販的口袋內，政府也可以正式把這類煙草產品徵收稅項。**

事實上，祖國及海外國家的發展也值得香港政府仿傚，根據貴 法案委員會多位議員曾經指出，全球已有 64 個國家容許加熱煙產品在規管下銷售；加上國家工信部今年三月就電子煙等新型煙草產品提出修改及完善有關的規管問題，觀乎中國政府及先進國家均對加熱煙等產品採取「規管」做法，積極建議香港政府實有必要加以參考及跟隨。

另外，本會一直留意，貴 委員會已先後召開十多次會議，曠日持久，

地 址: 灣仔駱克道368號百玲大廈十四樓R2
網 址: www.hkfha.org.hk
電 話: 2574 4779
電 郵: info@hkfha.org.hk
傳 真: 2574 8796

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在百業蕭條的慘況下，條例修訂工作實在不宜拖沓。**本會促請主席及各位議員，敦促政府體恤民情、從善如流，盡快將加熱煙納入現行控煙框架加以規管，並協助業界走出困局。**

港九新界販商社團聯合會

FEDERATION OF H.K. KLN., N.T. HAWKER ASSOCIATIONS 港九新界販商社團聯合會 ※

2021 年 7 月 12 日

地 址: 灣仔駱克道 368 號百玲大廈十四樓 R2
網 址: www.hkfha.org.hk
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