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立法會衛生事務委員會主席
李國麟教授，SBS，JP

李主席勛鑒：

就衞生事務委員會 2018 年 5 月 21 日會議第三項議程「電子煙及加熱煙草產品相關事宜的研究建議」呈交資料

茲悉　貴會將於 2018 年 5 月 21 日會議上討論「電子煙及加熱煙草產品相關事宜的研究建議」一項。敝司忝為加熱煙草系統 *IQOS* 及加熱煙草產品 *Heatstick* 的生產商，願為促進有關加熱煙草產品的討論略盡綿力，謹此向　貴會上呈下列資料並懇請　李主席批准委員傳閱之，以茲參考：

#	資料	內容/摘要
1	香港《應貨稅品條例》下各類煙草產品之定義及 *Heatstick* 在國際市場上的應貨稅品分類	臚列《應貨稅品條例》中有關各類煙草產品的定義的條文及 *Heatstick* 在國際市場上的應貨稅品分類舉隅。
2	"Statement on the toxicological evaluation of novel heat-not-burn tobacco products" by the Committees on Toxicity (COT)	英國毒性委員會(COT)是一個獨立委員會，為英國政府提供與科學相關的意見。在此聲明中，COT 指出使用加熱煙草產品者所面對的有害或可能有害物的風險較吸食香煙者減少約 50%至 90%。
3	"Levels of selected analytes in the emissions of 'heat not burn' tobacco products that are relevant to assess human health risks" by Mallock et al.	由德國聯邦風險評估研究所[1]一組研究員進行的研究。該研究指出使用 *IQOS* 時並無燃燒現象發生，以及與香煙的煙霧相較，*IQOS* 氣霧中的九種有害及可能有害物質的份量減少 80%至超過 99%。另外，該研究亦指出因為汲取尼古丁不足而 [增加使用 IQOS] 至抵銷有害或可能有害物質的減少」的做法「幾無可能」。

敝司亦謹此概括下列因版權問題而未能將原本複製並上呈　貴會的文件之內容，以備查考：

#	資料	摘要

[1] 德國聯邦風險評估研究所是德國聯邦政府食品和農業部轄下的公共機構，負責為德國政府提供有關科學的意見。

1	"Comparison of Chemicals in Mainstream Smoke in Heat-not-burn Tobacco and Combustion Cigarettes" by Bekki et al.	由日本國立保健醫療科學院[2]一組研究員進行的研究。該研究發現香煙和 *IQOS* 的尼古丁含量雖然相當，惟使用 *IQOS* 時所產生的其他有害物質的份量則遠較燃點香煙時所產生的份量為低：煙草特有亞硝胺[3]的份量為香煙的五分之一，而一氧化碳的份量為香煙的百分之一。委員可透過以下鍵接閱讀此文件： https://www.jstage.jst.go.jp/article/juoeh/39/3/39_201/_pdf/-char/en
2	"Chemical Analysis and Simulated Pyrolysis of Tobacco Heating System 2.2 Compared to Conventional Cigarettes" by Li et al.	由中國國家煙草質量監督檢驗中心(CNTQSTC)[4]一組研究員進行的研究。該研究發現與作為水平參照的 3R4F 參考香煙相較，*IQOS* 氣霧中不少的有害或可能有害物質的份量均減少 90%以上；羰基、氨及 N-亞硝基新煙草碱[5]的份量則減低 50%至 80%。委員可透過以下鍵接訂閱此文件： https://academic.oup.com/ntr/advance-article-abstract/doi/10.1093/ntr/nty005/4793230?43directedFrom=fulltext

敝司殷望上述資料將有助　貴會研議有關加熱煙草產品的議題。耑此奉達，並頌
勛祺

菲利普莫里斯亞洲集團有限公司
香港及澳門企業事務部主管

贊家齊博士　謹啟
2018 年 5 月 14 日

[2] 日本國立保健醫療科學院為日本政府的研究和培訓機構，致力於改善日本公眾的健康。
[3] Tobacco-specific nitrosamines (TSNAs).
[4] 中國國家煙草質量監督檢驗中心是中國的一個監管機構，亦是世界衛生組織煙草實驗室網絡(TobLabNet)的其中一個成員。
[5] N'nitrosoanabasine.

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14th May, 2018

Prof Hon. Joseph Lee, SBS, JP
Chairman, Panel on Health Services, Legislative Council
Legislative Council Complex
1 Legislative Council Road
Central, Hong Kong

Dear Chairman Lee,

Submission of Information regarding Agenda Item III of the Health Services Panel Meeting on 21st May, 2018

I am writing with reference to agenda item III of the Health Services Panel meeting on 21st May, 2018: "Proposed study on issues relating to electronic cigarettes and heated tobacco products".

As the manufacturer of the tobacco heating system *IQOS* and tobacco consumable *Heatstick* (also known as "heat-not-burn (HnB) tobacco product), we believe we are in a position to aid the discussion on HnB-related topics by providing relevant information. We would therefore like to respectfully submit, and ask you to permit the Secretariat to circulate the following materials regarding HnB for the panel members' perusal and reference when discussing this agenda item during the meeting:

#	Item	Content/Explanatory Notes
1	Definition of Tobacco Products under the Dutiable Commodities Ordinance (DCO) in Hong Kong versus Classification in International Jurisdictions	Information showing the relevant parts of the DCO on the definitions of various tobacco products and some examples how *Heatsticks* are classified for excise in international jurisdictions.
2	"Statement on the toxicological evaluation of novel heat-not-burn tobacco products" by the Committees on Toxicity (COT)	COT is an independent scientific advice to the UK government. In the statement, COT concluded that people using HnB products were exposed to around 50% to 90% fewer harmful and potentially harmful chemicals compared with conventional cigarettes.
3	"Levels of selected analytes in the emissions of 'heat not burn' tobacco products that are relevant to assess human health risks" by Mallock et al.	A study conducted by a team of researchers of the Federal Institute for Risk Assessment (BfR)[1]. The study found no combustion takes place when using *IQOS*, and reductions in nine harmful and potentially harmful substances in the *IQOS* aerosol of 80% to more than 99% relative to cigarette smoke; and that "an increased consumption [of *IQOS*] aimed at compensating deficient nicotine delivery" that could overwhelm the reduction in harmful and potentially harmful substances is "unlikely".

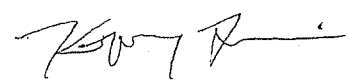
We would also like to provide a summary of the following papers that we regret not being able to share with the honourable Members in full due to copyright requirements:

[1] BfR is a public body under the German Federal Ministry for Food and Agriculture responsible for providing scientific advice to the German government.

#	Item	Summary
1	"Comparison of Chemicals in Mainstream Smoke in Heat-not-burn Tobacco and Combustion Cigarettes" by Bekki et al.	A study conducted by a team of researchers of the National Institute of Public Health of Japan [2]. The study found that while the concentrations of nicotine in both cigarettes and *IQOS* were almost the same, the levels of other harmful substances generated when using *IQOS* are significantly lower than those when burning cigarettes: TSNAs[3] was one-fifth of that of cigarettes, while carbon monoxide was a hundredth of that of cigarettes. Members may wish to read the full paper at https://www.jstage.jst.go.jp/article/juoeh/39/3/39_201/_pdf/-char/en
2	"Chemical Analysis and Simulated Pyrolysis of Tobacco Heating System 2.2 Compared to Conventional Cigarettes" by Li et al.	A study conducted by a team of researchers of the China National Tobacco Quality Supervision and Test Centre (CNTQSTC)[4]. The study found that compared to the 3R4F reference cigarette, *IQOS* produced 90% lower levels of many of the harmful and potentially harmful substances found in cigarette smokes; and 50% to 80% lower levels of carbonyls, ammonia and NAB[5]. Members may wish to subscribe and read the full paper at https://academic.oup.com/ntr/advance-article-abstract/doi/10.1093/ntr/nty005/4793230?43directedFrom=fulltext

We hope the above would be of use to the honourable Members in reviewing and discussing HnB-related matters. Thank you.

Yours sincerely,



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[2] Japan's governmental research and training organization charged with improving public health in Japan.
[3] Tobacco-specific nitrosamines.
[4] CNTQSTC is a regulatory authority in China, as well as a member of the WHO Tobacco Laboratory Network.
[5] N'nitrosoanabasine.

PHILIP MORRIS
ASIA LIMITED

2018 年 5 月 14 日

香港《應貨稅品條例》下各類煙草產品之定義及 *Heatstick* 在國際市場上的應貨稅品分類

A. 香港《應貨稅品條例》下各類煙草產品之定義[1]

類別	定義
香煙	指任何並非雪茄的捲煙，本身已能為人吸用
雪茄	指任何捲煙，本身已能為人吸用，並：(a)外包一層天然煙草；或 (b)主要包含破碎或經研碎的煙葉，以再造煙草捆扎，外包一層螺旋式包捲的再造煙草
中國熟煙	用在中國種植的煙葉以中國傳統的方法製備的煙草
所有其他製成煙草	任何並未符合上述三類定義的煙草產品

由於 *Heatstick* (微司生產加熱煙草產品，利用加熱煙草系統 *IQOS* 加熱並使用)[2]本身並不能為人吸用，因此並不符合「香煙」的定義。加之 *Heatstick* 亦不符合「雪茄」及「中國熟煙」的定義，故此我們認為「所有其他製成煙草」是現行法例中最為適合 *Heatstick* 的分類。

B. *Heatstick* 在國際市場上的銷售稅分類

不少可合法買賣 *Heatstick* 的 OECD[3]市場均向 *Heatstick* 課以「其他製成煙草(Other manufactured tobacco)」或相似的類別的稅項。舉例而言，加拿大將 *Heatstick* 歸類為 "Manufactured tobacco other than cigarettes and tobacco sticks"；法國及荷蘭將 *Heatstick* 歸入 "Other smoking tobacco / pipe tobacco" 類別；德國及日本將 *Heatstick* 歸類為 "pipe tobacco"；英國將 *Heatstick* 歸入 "Other smoking tobacco and chewing tobacco"類別；西班牙將 *Heatstick* 歸類為 "Other smoking tobacco"；瑞士將 *Heatstick* 歸入 "Other manufactured tobacco"類別.

-完-

[1] https://www.elegislation.gov.hk/hk/cap109?xpid=ID_1438402562062_001
[2] https://www.pmi.com/glossary-section/glossary/heets-and-heatsticks
[3] OECD 即經濟合作暨發展組織，旨在協助 35 個成員國促進經濟增長和國際貿易。

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14th May, 2018

Definition of Tobacco Products under the Dutiable Commodities Ordinance (DCO) in Hong Kong versus Classification in International Jurisdictions

A. Definitions of Various Tobacco Products under DCO[1]

According to the DCO, tobacco products are categorized, defined and taxed in Hong Kong as follows:

Category	Definition
Cigarette	Any roll of tobacco capable of being smoked by itself not being a cigar
Cigar	Any roll of tobacco capable of being smoked by itself and which has an outer wrapper of natural tobacco, or predominately contains broken or threshed leaf and has a binder of reconstituted tobacco and an outer wrapper of reconstituted tobacco fitted spirally
Chinese Prepared Tobacco	Tobacco prepared in the traditional Chinese manner from tobacco leaf grown in China
All other manufactured tobacco	Tobacco product that does not fall within the above definition

Heatstick (the tobacco consumable to be used with our tobacco heating system *IQOS*)[2] does not fit into the definition of "cigarette" because that it is not "capable of being smoked by itself not being a cigar", and thus does not fall within the definition of cigarettes. It would seem most appropriate to classify *Heatstick* as **"other manufactured tobacco (OMT)"**, which is defined as a tobacco product that does not fall within the definitions of cigarettes, cigars and Chinese prepared tobacco.

B. Classification of *Heatstick* in International Jurisdictions

In a number of OECD[3] countries where *Heatstick* is legally available, it is taxed as **"other manufactured tobacco"** (or some other similar variants).

For example, in Canada, it is classified as "Manufactured tobacco other than cigarettes and tobacco sticks"; in France and the Netherlands, *Heatstick* is put into the "Other smoking tobacco / pipe tobacco" category; in Germany and Japan, *Heatstick* is classified as "pipe tobacco"; the United Kingdom classifies *Heatstick* as "Other smoking tobacco and chewing tobacco"; Spain classify *Heatstick* as "Other smoking tobacco" and "other tobacco" respectively; and Switzerland classifies *Heatstick* as "Other manufactured tobacco".

-End-

[1] https://www.elegislation.gov.hk/hk/cap109?xpid=ID_1438402562062_001
[2] https://www.pmi.com/glossary-section/glossary/heets-and-heatsticks
[3] The Organisation for Economic Co-operation and Development (OECD) is an intergovernmental economic organization with 35 member countries aimed at stimulating economic progress and world trade.

Committee on TOXICITY

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 Treasury[1], 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 cigarette[2]. 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 from part of any long-term strategy to minimise risk from tobacco use.

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

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COMMITTEES ON TOXICITY, CARCINOGENCITIY 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

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LETTER TO THE EDITOR, NEWS AND VIEWS

Levels of selected analytes in the emissions of "heat not burn" tobacco products that are relevant to assess human health risks

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Abstract

Consumers of combustible cigarettes are exposed to many different toxicologically relevant substances associated with negative health effects. Newly developed "heat not burn" (HNB) devices are able to contain lower levels of Harmful and Potentially Harmful Constituents (HPHCs) in their emissions compared to tobacco cigarettes. However, to develop toxicological risk assessment strategies, further independent and standardized investigations addressing HPHC reduction need to be done. Therefore, we generated emissions of a commercially available HNB product following the Health Canada Intense smoking regimen and analyzed total particulate matter (TPM), nicotine, water, aldehydes, and other volatile organic compounds (VOCs) that are major contributors to health risk. We show that nicotine yield is comparable to typical combustible cigarettes, and observe substantially reduced levels of aldehydes (approximately 80–95%) and VOCs (approximately 97–99%). Emissions of TPM and nicotine were found to be inconsistent during the smoking procedure. Our study confirms that levels of major carcinogens are markedly reduced in the emissions of the analyzed HNB product in relation to the conventional tobacco cigarettes and that monitoring these emissions using standardized machine smoking procedures generates reliable and reproducible data which provide a useful basis to assess exposure and human health risks.

Keywords Heat not burn · Smoke chemistry · Nicotine · Non-cigarette tobacco products · Carcinogens

Abbreviations

FCTC	Framework convention on tobacco control
FDA	Food and Drug Administration
HNB	Heat not burn
HPHC	Harmful and Potentially Harmful Constituents
ISO	International Organization for Standardization
NFDPM	Nicotine-free-dried particulate matter
THS2.2	Tobacco Heating System 2.2
TPM	Total particulate matter
VOCs	Volatile organic compounds
WHO	World Health Organization

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Tobacco consumption remains one of today's major health hazards and was responsible for more than one in ten deaths in the year 2015 (GBD 2015 Tobacco Collaborators 2017). Consequently, tobacco control was strengthened by multiple measures in recent years, partly driven by implementation of the WHO Framework Convention on Tobacco Control (FCTC) (World Health Organization 2018). One strategy of tobacco companies to adapt to growing public and political pressure for further restrictions is the development of modified risk products or alternate tobacco products that are implied to be less hazardous. These claims are often based on reduced toxicant levels in the emissions, although these data cannot be directly translated into a health risk reduction. Notably, toxicant reduction strategies had also been proposed by WHO (World Health Organization 2014), opening discussions about feasibility of benefits for both smoking populations and individual smokers.

In principle, the conventional cigarettes are highly engineered products. A burning cigarette can be regarded as a connection of endo- and exothermic combustion systems (Baker et al. 2004). Yet, it gains complexity, since multiple mechanisms affect the generation of smoke (Muramatsu

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2005). Smoke constituents are generated according to a temperature gradient depending on exothermic combustion within the burning tip. During puffs, temperatures can reach up to 950 °C. The majority of compounds, however, are formed in endothermic reactions within the adjacent pyrolysis-distillation zone where temperatures decrease from approximately 600 to 200 °C (Baker et al. 2004). Cigarette smoke consists of approximately 4800 compounds (Rodgman and Green 2003). At least 69 carcinogens had been identified by the year 2000 (Hoffmann et al. 2001) with an update to 98 hazardous components in 2011 (Talhout et al. 2011). Fowles and Dybing proposed an approach for prioritization of tobacco smoke constituents by applying toxicological risk assessment methods. They identified 1,3-butadiene and other substances like acetaldehyde as major contributors to cancer risk and thus suggested that harm reduction efforts should set a special focus on volatile organic compounds (Fowles and Dybing 2003).

Attempts to reduce the toxicity of tobacco smoke can be traced back to the 1960s. The initial strategies aimed for the reduction of specific compounds with ambiguous effects on overall toxicant levels (Baker et al. 2004). Further strategies to reduce toxicant levels included filter tips, filter perforation, as well as technical features such as porosity of cigarette paper and tobacco processing (Hoffmann et al. 2001). Although nicotine and tar content have decreased by more than 60% since the 1950s, this trend could not be linked to a drop in mortality rates among smokers. Furthermore, proliferation of low-yield cigarettes became a highly controversial issue. Despite the lower tar and nicotine contents, toxicant exposure has even increased when smoking intensities and profiles of long-term smokers are considered (Hoffmann et al. 2001). Further means to reduce the toxicity of tobacco smoke are limited, because combustion and consequently pyrolysis and distillation cannot be avoided in the conventional cigarettes. Since most hazardous compounds in tobacco smoke are formed between 200 and 700 °C, lower temperatures would limit formation of noxious compounds. Although earlier "heat not burn" (HNB) devices failed to gain consumer acceptance (Caputi 2016), these systems provide some advantages in terms of toxicant reduction compared to the conventional cigarettes (Henkler and Luch 2015).

First, in contrast to low-yield cigarettes, reduction of tar and associated toxicants is not necessarily interlinked with lower nicotine levels. Therefore, an increased consumption aimed at compensating deficient nicotine delivery becomes unlikely. Second, the previous reports indicate that far lower levels of relevant carcinogens can be achieved in newly developed HNB devices. One novel product referred to as "Tobacco Heating System 2.2" (THS2.2) is currently marketed in more than twenty countries. The manufacturer has stated that the yield of harmful and potentially harmful constituents (HPHC) is reduced by about 90% compared to the 3R4F reference cigarette. Importantly, a reduction of more than 95% was reported for major carcinogens, including benzene and 1,3-butadiene, when emissions were generated using the Health Canada Intense smoking regimen (Schaller et al. 2016).

From the perspective of risk assessment, it is essential to verify levels of toxicants including nicotine that can be reliably achieved in novel or modified tobacco products. It needs to be clarified whether standardized machine smoking procedures and standardized analytical methods lead to reproducible data that can be used to compare devices and to define a standard to be met if reductions were recognized as relevant. This is also an important prerequisite to address the issue of putatively modified health risks or to provide a differentiated risk assessment according to product features and specifications. However, independent investigations are scarce and urgently required. We have, therefore, analyzed the mainstream smoke emitted by THS2.2 products using different variants of commercially available tobacco sticks. This study was focused on the group of carcinogenic volatile organic compounds and aldehydes in particular according to the prioritization framework proposed by Fowles and Dybing (2003). The acquired data provide an important basis to address health risks and potential benefits in terms of a potentially reduced exposure to toxicologically relevant constituents.

Four tobacco heating devices and two different tobacco stick variants were analyzed with an LM4E smoking machine (Borgwaldt, Hamburg, Germany) following the Health Canada Intense smoking regimen (Health Canada 2000). Detailed description of analytical procedure can be found in the Supplementary Material. An overview of the measured levels of analytes in the emissions of the two different tobacco stick variants is given in Table 1. The obtained values from all used devices were pooled. We compared our emission findings to levels in mainstream smoke of different combustible cigarettes, including low and high tar, slim, and reference cigarettes, that were published by Counts et al. (2005). We displayed the lowest and the highest yields per analyte that could stem from different brands and calculated the corresponding reductions of our findings as averages of both stick variants. The levels of nicotine in this study were lower compared to the data provided by the manufacturer (Schaller et al. 2016) and also lower but still in the same range compared to the conventional cigarettes (Counts et al. 2005). Total particulate matter (TPM) was comparable to the manufacturer's findings and higher than TPM from some combustible cigarettes. The yields of the carbonyl compounds formaldehyde, acetaldehyde, acrolein, and crotonaldehyde were, with a reduction of 80–96%, considerably lower when compared to combustible cigarettes (Table 1) and comparable to the published emissions observed by the

Table 1 Levels of analytes in the mainstream smoke of two different tobacco heating stick variants with "*n*" representing the number of replicates

Parameter	Unit	Stick variant 1		Stick variant 2		Combustible cigarettes (Counts et al. 2005)	Reduction
		Mean ± SD	*n*	Mean ± SD	*n*	Min–max (mean ± SD)	%
Puff count	Puff/stick	12 ± 0		12 ± 0		5.5 ± 0.3–13.6 ± 0.5	
TPM	mg/stick	52.6 ± 3.2	24	51.2 ± 3.2	24	27.5 ± 2.4–60.9 ± 3.3	
Nicotine	mg/stick	1.1 ± 0.1	24	1.1 ± 0.1	24	1.07 ± 0.06–2.70 ± 0.14	
Water	mg/stick	31.7 ± 5.5	24	28.5 ± 4.6	24	9.82 ± 1.42–21.35 ± 2.23	
NFDPM	mg/stick	19.8 ± 6.5	24	21.6 ± 5.9	24	16.3 ± 1.3–37.6 ± 2.1	
Acetaldehyde	µg/stick	179.4 ± 10.5	18	183.5 ± 10.1	14	930 ± 85–1540 ± 153	80.5–88.2
Acrolein	µg/stick	9.9 ± 1.2	18	8.9 ± 1.0	14	89.2 ± 7.3–154.1 ± 13.6	89.5–93.9
Formaldehyde	µg/stick	5.3 ± 0.4	18	4.7 ± 0.3	14	29.3 ± 3.8–130.3 ± 10.8	82.9–96.2
Crotonaldehyde	µg/stick	< 3.0	18	< 3.0	14	32.7 ± 1.5–70.8 ± 9.0	
1,3-Butadiene	µg/stick	0.22 ± 0.02	6	0.20 ± 0.02	6	77.0 ± 4.8–116.7 ± 14.3	99.7–99.8
Benzene	µg/stick	0.63 ± 0.07	6	0.54 ± 0.05	6	49.7 ± 7.7–98.3 ± 4.3	98.8–99.4
Isoprene	µg/stick	2.10 ± 0.35	6	1.82 ± 0.24	6	509 ± 41–1160 ± 65	99.6–99.8
Styrene	µg/stick	0.47 ± 0.06	6	0.49 ± 0.09	6	15.4 ± 0.8–33.3 ± 2.8	96.9–98.6
Toluene	µg/stick	2.15 ± 0.37	6	1.96 ± 0.23	6	86.2 ± 11.0–176.2 ± 15.7	97.6–98.8

Yields are compared to lowest and highest levels found by Counts et al. in combustible cigarettes

All levels were generated using HCI smoking regime

TPM total particulate matter, *NFDPM* nicotine-free-dried particulate matter

manufacturer (Schaller et al. 2016). Similar to the carbonyl compounds, the emissions of the volatile and semi-volatile compounds benzene, 1,3-butadiene, isoprene, styrene, and toluene were with a reduction of 97 to over 99% markedly lower when compared to combustible cigarettes (Table 1). The range of values found is again similar to the manufacturer's data (Schaller et al. 2016). To address consistency of nicotine and TPM release during the smoking procedure, the 12 puffs of the smoking protocol were divided into four intervals of three puffs each and analyzed separately. The nicotine and TPM release was shown to be inconsistent with lower yields in the beginning. More detailed information can be found in the Supplementary Material.

For a profound assessment of health risks and putative benefits, independent studies by different laboratories are needed. Furthermore, our intention was not only to reassess emissions of HPHC and compare to other studies, but also to use standardized methods as used by surveillance authorities and establish them for this particular application. More HNB products from different manufacturers are expected to appear on a wider market in the future with claims of reduced toxicant levels. Therefore, surveillance authorities will require standardized methods for routine analysis of HNB products to verify claims and to protect consumers from being misled.

In this study, we applied methods that are based on international standards to investigate emissions of a novel HNB product. We have used a commercially available linear smoking machine that was initially developed for electronic cigarettes. Thus, the procedure can be easily transferred. Our data are in good agreement with some recent investigations. In their recent study, Li et al. analyzed a set of HPHCs, including aldehydes and VOCs, in the emissions of the same HNB product using ISO and HCI smoking regimen (Li et al. 2018). The data presented in our study support their findings and conclusions. Farsalinos et al. analyzed the nicotine delivery in the preceding HNB model of the same manufacturer (Farsalinos et al. 2017). They found a higher nicotine yield as compared with the currently marketed THS2.2 that was analyzed here. Another study that used a custom instrument and custom smoking regimen reported similar findings for aldehydes but not for nicotine (Auer et al. 2017). A recent study by Bekki et al., that used the preceding HNB model as well, focused on tobacco-specific nitrosamines (Bekki et al. 2017). Their determined levels for nicotine, TPM, and water are comparable to ours. Another group developed a headspace solid-phase microextraction-based method for semi-quantitative assessment of VOCs emitted by HNB products (Savareear et al. 2017). The issue of toxicant reduction is complex, since these calculations depend on the reference product. Importantly, our data confirm absolute values for selected toxicants in the emissions of the analyzed HNB that are in agreement with data published by the manufacturer (Schaller et al. 2016). Furthermore, our study is in agreement with the currently published FDA Tobacco Products Scientific Advisory Committee (TPSAC) briefing document (Food and Drug Administration 2018).

Another interesting point to show was that emissions of particulate matter and nicotine were not consistent during the smoking procedure. Unlike electronic cigarettes, in the European Union conventional cigarettes are not regulated to

provide consistent nicotine delivery. Although HNB products are likewise not regulated in terms of consistency of nicotine delivery, the observed inconsistent delivery may influence consumer satisfaction, nicotine blood levels, and adaptations of smoking behavior, and needs to be investigated further.

In our study, we found comparatively high levels of tar. For the conventional cigarettes, "tar" is defined as particulate matter subtracted by nicotine and water (ISO 4387:2000), and is limited to 10 mg tar per cigarette as determined with the ISO smoking regimen (ISO 3308:2012) according to European regulations (EU 2014). Importantly, the water content in the smoke of the HNB product is high compared to the conventional cigarettes, thus affecting the NFDPM calculation more than in the conventional cigarettes. The manufacturer applied a special instrumental set-up to avoid the loss of water (Ghosh and Jeannet 2014). This special equipment is neither standardized nor applicable for surveillance authorities. Therefore, we decided to use the extraction and titration method which is already applied in routine analysis.

Although the NFDPM value for HNB products can be formally calculated as for the conventional cigarettes, direct comparisons would be misleading. TPM of the conventional cigarettes, which is defined as the portion that is trapped on the filter (ISO 4387:2000), contains typical toxicants that were confirmed to be strongly reduced in the analyzed HNB product. In contrast, the proportion of humectants in NFDPM of HNB products is markedly higher compared to the conventional tobacco cigarettes.

The strongly reduced HPHC levels in the emissions of the analyzed HNB device are likely to reduce toxicant exposure. Nevertheless, it should be noted that machine smoking protocols are standardized methods aimed to monitor reliable emissions, but not accurate models for human exposure or smoking behavior. Further studies are required to address the magnitude of exposure reduction. However, the herein confirmed reductions of relevant toxicants by about 80–99% are substantial, leading to the relevant question of putatively reduced health risks. Risk assessment models need to be established that could take advantage of the framework for prioritization of carcinogens in cigarette smoke as proposed by Fowles and Dybing (2003). Mainstream smoke constituents were prioritized according to their concentrations and their cancer potency factors. A recent study performed calculations with one data set of THS2.2 and provisionally concluded cancer potencies of HNB products to be more than 10% lower than the conventional cigarettes (Stephens 2018). We could confirm a highly substantial reduction of prioritized major carcinogens, such as 1,3-butadiene, acetaldehyde, and benzene. Several studies addressed lowered health risks due to reduced smoking of tobacco cigarettes and substantial data are available (Inoue-Choi et al. 2018; Law et al. 1997; Pesch et al. 2012). It is still uncertain whether these data are applicable to model reduced exposure in relation to HNB products. Although modified health risks are expected, it is difficult to provide an estimate for both populations and individual smokers.

HNB products are a novelty to the market and more manufacturers are expected to launch new versions in this product category. Therefore, it is essential to define criteria that should be met by new products. Analytical assessment of HPHC contents in mainstream smoke can help to define these standards. Regarding a risk–benefit analysis that is required for novel tobacco products in Europe (2014/40/EU) (EU 2014), substantial reductions of toxicant levels might be regarded as a discrete benefit compared to combustible cigarette consumption, even if potential consequences for human health still need to be explored. This is consistent with the previous approaches proposed for the conventional cigarettes by WHO (World Health Organization 2014).

We propose that new HNB products need to show comparable or lower HPHC levels in the emissions as the analyzed device to confirm a benefit in the context of an overall risk assessment. The applicable values for toxicant levels should be continuously minimized and reassessed when refined products and technologies become available. By contrast, it should be considered insufficient to show only a minor decrease of HPHC levels in comparison to the conventional cigarettes. Furthermore, it should be assessed whether other levels of toxicologically relevant substances are elevated in return as already discussed for propylene glycol, glycerol, glycidol, and acetol (Food and Drug Administration 2018). Therefore, further studies need to be conducted: first, more independent assessments of toxicant yields need to be published by using standardized methods for the above discussed reasons. Second, it should be examined whether HNB products lead to other toxicants and health hazards that have been neglected so far. Finally, the long-term impact on public health needs to be assessed in the future.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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