

**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 19<sup>th</sup> 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<sup>1</sup>, 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 16<sup>th</sup> 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.

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<sup>1</sup> 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<sup>2</sup>. 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.

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

## **Epidemiological data**

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

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

## **Committees' discussion**

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

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

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

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

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

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

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

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

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

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

### **Committees conclusions and recommendations**

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

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

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

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

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

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

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

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

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

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

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

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

## **References**

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

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**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