TOX/2017/42

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COT)

Toxicological evaluation of novel heat-not-burn tobacco products: preliminary review of literature from sources not associated with product manufacturers and developers.

Introduction

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

2. The Committees have considered scoping papers on the topic at the COT meetings in December 2016 and February 2017 (papers TOX/2016/42 and TOX/2017/09), the COM meeting in February 2017 (MUT/2017/01) and the COC meeting in March 2017 (COC/2017/07).

3. To date, two novel HNB tobacco products have been notified to PHE in accordance with the Tobacco and Related Products Regulations 2016. At the COT meeting in May 2017, the manufacturers of these two HNB products presented their data to address a list of data requirements compiled based on the comments provided by each Committee.

4. In addition to the manufacturer data, the Committees also requested a review of the literature on HNB tobacco products published by sources that are independent of the developers/manufacturers of these products. Literature searches were performed and the publications identified are reported in this paper.

Question for the Committee

i. Is there any information in the independent literature summarised in this paper which should be incorporated in the second draft statement?

Abbreviations

AEP	Acute eosinophilic pneumonia
CC	Conventional cigarette
CO	Carbon monoxide
ISO	International Organization for Standardization
IQOS	I quit ordinary smoking
HCI	Health Canada Intense
HNB	Heat-not-burn
LHC	Less harmful cigarettes
MRTP	Modified risk tobacco products
PAH	Polycyclic aromatic hydrocarbon
PMI	Philip Morris International
PREP	Potential reduced exposure products
SMP	Submicronic particle
VOC	Volatile organic compound

What are novel heat-not-burn tobacco products?

5. Novel tobacco products are defined in The Tobacco and Related Products Regulations 2016, as a tobacco product which 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 is first supplied by the producer after 19th May 2014.

6. In HNB tobacco products, processed tobacco is heated instead of being burnt as is the case for conventional tobacco products. A range of HNB tobacco products exists, whereby processed tobacco is either heated directly to produce vapour, heated in a vaporiser, or vapour is produced from a non-tobacco source and then flavoured by being passed over processed tobacco. The temperature at which the tobacco is heated varies considerably between products, which may result in differences in the thermogenic degradation, combustion and pyrolysis products and hence potential health outcomes, as Industry states that harmful components of tobacco cigarette smoke are the products of the incomplete combustion. For example, one product where the tobacco is heated directly reported a maximum heating temperature of up to 350 °C, while for another product in which the tobacco is heated by a vapour; the maximum heating temperature is less than 50 °C. For comparison, when tobacco in cigarettes is burnt it reaches temperatures of at least 400 °C.

Details of the literature searches

7. A literature search was performed by Imperial College London under contract to PHE on 01/06/2017, with the aim of identifying reports relating to HNB products that were not conducted or sponsored by developers or manufacturers of these products. The details of the search are described in Annex A. In total ten papers were identified. From these, five citations were identified as being independent publications on HNB tobacco products. These comprise two investigative reports (Auer *et al.,* 2017; Protano *et al.,* 2016), one clinical case report (Kamada *et al.,* 2016), one literature review (Kleinstreuer & Feng, 2013) and one commentary (Caputi, 2016). Details of these reports are described in paragraphs 9 to 13, below. The remaining papers were in some way associated with the tobacco industry and therefore were excluded from further consideration. The recent publication by Farsalinos *et al.,* (2017), identified by PHE after the literature search that was carried out in June 2017, was excluded as authors were associated with AEMSA (a Federation of e-cigarette manufacturers) and Tennessee Smoke Free Association (a not-for-profit corporation comprising consumers, retail vendors, manufacturers and supporters), hence considered not to be an independent source.

8. A further literature search was performed by National Centre for Environmental Toxicology at WRc (NCET at WRc) and IEH-Consulting (IEH-C) (NCET at WRc/IEH-C) under contract to PHE on 01/08/2017 using additional search terms and additional literature databases. The details of this search are described in Annex B. Four further publications were identified as probably relating to HNB

products and possibly from independent sources. Due to time constraints, these publications have not yet been reviewed. These four citations are listed in Annex B.

Independent publications on HNB tobacco products (to 01/06/2017)

Study reports

9. Auer *et al.* (2017) raised concerns over the characterisation of I Quit Ordinary Smoking (IQOS)[1] devices that produces an 'aerosol' rather than 'smoke'. To support this assertion, the authors carried out a comparative analysis of the aerosol produced by IQOS Heets Marlboro brand variant and the contents of smoke produced by a conventional 'light' cigarette (CC) (Lucky strike Blue Lights). A smoking device designed and tested in their laboratory according to standardised procedures (for cigarettes/e-cigarettes) and operated under International Organization for Standardization (ISO) smoking conditions was used to capture mainstream aerosol. Volatile organic compounds (VOCs) and nicotine from IQOS and CC were analysed by gas chromatography coupled to a flame ionisation detector. Polycyclic aromatic hydrocarbons (PAHs) from IQOS collected on a glass filter were analysed by HPLC coupled to a fluorescence detector and compared with mean values for CC abstracted from another study (Vu *et al.,* 2015). The authors concluded that IQOS aerosol contains some of the same harmful constituents (VOCs, PAHs and carbon monoxide – see Table 1 below) as CC smoke, representing markers of pyrolysis and thermogenic degradation. The IQOS aerosol contained 84% of the nicotine found in CC smoke. A temperature of 330°C was measured near the heater blade of the IQOS holder compared to 684°C at the core of the CC. The authors called for independent studies that further evaluate the health effects of the IQOS product and recommended that all HNB products should fall under the same indoor-smoking bans as CC.

[1] Tobacco heating system from Philip Morris International: the three main components comprise a heated tobacco unit (HEETS or HeatSticks), an IQOS holder, and a charger.

Table 1. Concentrations of chemicals in mainstream aerosol of HNB IQOS cigarettes and conventional cigarettes (adapted from Auer *et al.,* 2017)

Analysed Compound	**HNB cigarette**		**Conventional cigarette**		**Percentage of the chemical in HNB compared with conventional cigarettes, %**
	Amount, mean (SD)	**No. replications for each assay**	**Amount, mean (SD)**	**No. replications for each assay**	
Volatile organic compounds, μg per cigarette[a]					
Acetaldehyde	133 (35)	5	610[b]	1	22
Acetone	12.0 (12.9)	5	95.5 (13.5)	2	13
Acrolein	0.9 (0.6)	2	1.1	1	82
Benzaldehyde	1.2 (1.4)	5	2.4 (2.6)	2	50
Crotonaldehyde	0.7 (0.9)	5	17.4	1	4
Formaldehyde	3.2 (2.7)	5	4.3 (0.4)	2	74
Isovaleraldehyde	3.5 (3.1)	5	8.5 (10.8)	2	41
Propionaldehyde	7.8 (4.3)	5	29.6 (36.6)	2	26
Polycyclic aromatic hydrocarbons, ng per cigarette[c]					
Naphthalene	1.6 (0.5)	4	1105 (269)	7	0.1
Acenaphthylene	1.9 (0.6)	4	235 (39)	7	0.8
Acenaphthene	145 (54)	4	49 (9)	7	295
Fluorene	1.5 (0.6)	4	371 (56)	7	0.4
Anthracene	0.3 (0.1)	4	130 (18)	7	0.2
Phenanthrene	2.0 (0.2)	4	292 (44)	7	0.7
Fluoranthene	7.3 (1.1)	4	123 (18)	7	6
Pyrene	6.4 (1.1)	4	89 (15)	7	7
Benz[a]anthracene	1.8 (0.4)	4	33 (4.2	7	6
Chrysene	1.5 (0.3)	4	48 (6.2)	7	3
Benzo[b]fluoranthene	0.5 (0.2)	4	24 (2.9)	7	2
Benzo[k]fluoranthene	0.4 (0.2)	4	4.3 (2.8)	7	9
Benzo[a]pyrene	0.8 (0.1)	4	20 (2.9)	7	4
Indeno[1,2,3-cd]pyrene	ND	4	NA	NA	NA
Benzo[ghi]perylene	ND	4	NA	NA	NA
Dibenzo[a,h]anthracene	ND	4	NA	NA	NA
Inorganics, ppm in the mainstream smoke[d]					
Carbon dioxide	3057 (532)	5	>9000	3	NA
Carbon monoxide	328 (76)	5	>2000	3	NA
Nitric oxide	5.5 (1.5)	5	89.4 (71.6)	3	6
Other measures					
Nicotine, μg per cigarette	301 (213)	4	361	1	84
Temperature, °C	330 (10)	2	684 (197)	1	NA
Puff total count	12.6 (2.4)	32	13.3 (3.1)	6	NA

HNB, heat-not-burn; NA, not analysed; ND, not detected. a Methods described previously in Varlet *et al.* (2016; Sci Rep. 2016;6:25599). were applied; b Because there was only 1 replication, no SD can be computed. c Values reported from Vu *et al.* (Chem Res Toxicol. 2015;28(8):1616-1626.) for the ISO smoking regimen and for a mean of the 35 top-selling US cigarette brands are presented. d Carbon dioxide was measured with a Testo 535 (Testo), and carbon monoxide and nitric oxide were measured with a Pac 7000 that detected carbon monoxide (Draeger). The apparatus measured the smoke when it was released from the syringe pump.

10. Two comments on Auer et al. (2017) are listed on PubMed Commons[2].

11. Manuel Peitsch, an employee of Philip Morris International (PMI), notes that there are several differences between the results presented by Auer et al. (2017) and the peer-reviewed data that have been published by PMI. This commentator suggests that differences in methodologies may account for these differing results and questions whether some of the methods and mode of reporting used by Auer *et al*. are sufficiently rigorous to allow robust comparisons to be made, both between the IQOS and CC results presented by Auer *et al*. and more generally with published data from other sources. A 12-point list is presented, detailing points considered to be of importance in this context.

12. Valerio Cozzani, Professor of Chemical Engineering at the University of Bologna, Italy, discusses the Auer *et al*. (2017) report in the context of the technical definition of 'smoke' (physical aspects and chemical components). This commentator argues that the aerosol produced from a recently developed PMI HNB tobacco product is very different in chemical composition from general or CC-derived smoke and that its classification as smoke is not appropriate, for reasons including: 1- absence of combustion processes in the PMI HNB product; 2- aerosols produced by vaporisation; and 3- very limited low temperature pyrolysis in the HNB product during operation (at temperatures < 350 °C).

13. Protano *et al.* (2016) evaluated levels of submicronic particles (SMPs) in indoor air to simulate exposure to second-hand smoke from conventional tobacco cigarettes, HNB products and e-cigarettes. For each test, carried out in triplicate, a current smoker in a sealed room (approx. 53 m^2), smoked a CC (Pall Mall San Francisco), hand-rolled CC (Golden Virginia tobacco + Rizla Blue Regular Rolling Paper), 12 puffs of an e-cigarette (Smooke E-SMART (L) e-cigarette filled with Smooke Light e-liquid containing nicotine at 9 mg/mL) or one IQOS stick. An air sampler (Fast Mobility Particle Sizer spectrometer) placed 2 metres from the smoker and 1.5 metres above the floor measured SMP levels (nominal diameter ranging between 5.6-560 nm) present during a period of 1 hour following ignition. The theoretical SMP deposition (instant dose) in the respiratory tree of a 'normal nose-breathing adult male at rest' was calculated using a multiple path particle dosimetry model. The predicted level of SMPs deposited in the airway of the passive smoker (Figure 1) during the immediate usage period was four-fold higher for CC/hand-rolled CC compared with e-cigarette/IQOS. Values remained high after smoking CC/hand-rolled CC (six-fold background), but returned quickly to background levels after using e-cigarette/IQOS. The authors suggested, from size distribution calculations, that around half of all SMPs produced were small enough to enter the alveolar region of a passively exposed subject.

[2] https://www.ncbi.nlm.nih.gov/pubmed/28531246/#comments

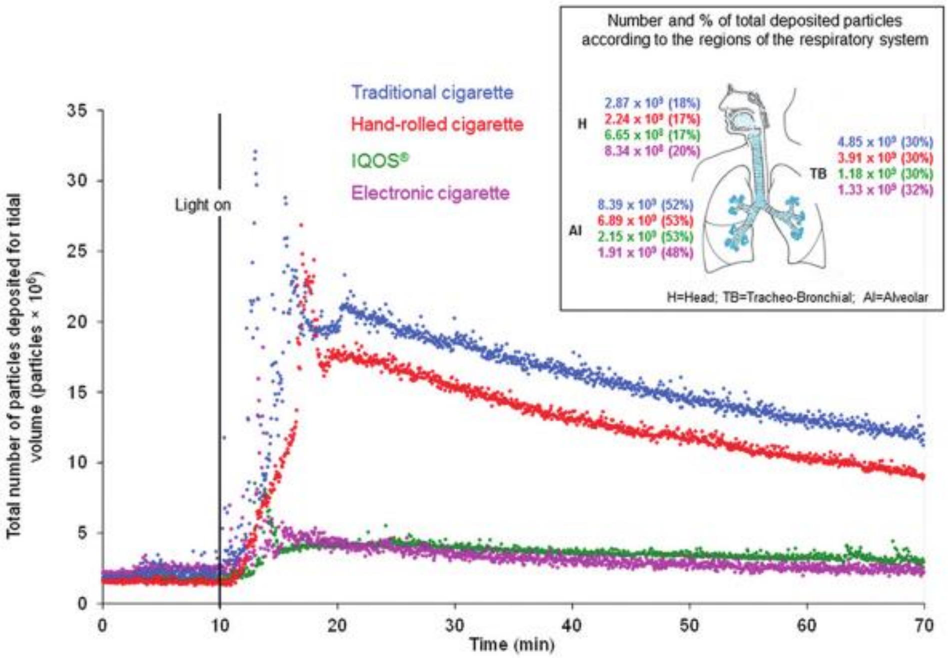

Figure 1. Calculated SMPs with a nominal diameter in the range 5.6-560 nm (mean values of three replicates): instant doses (graph) and size distribution (%) in different respiratory regions (box) for a normal nose-breathing adult male in rest condition. Reproduced from Protano *et al.* (2016).

Clinical case reports

14. Kamada *et al.* (2016) reported a case of acute eosinophilic pneumonia (AEP) associated with smoking HNB cigarettes assumed to be in Japan. AEP is a rare disorder characterised by hypoxaemia, pulmonary infiltrates and pulmonary eosinophilia, which occurs secondary to drug exposure or hypersensitivity reaction to an inhaled antigen. Although the exact aetiology of AEP is not known, recent alterations in tobacco-smoking habits are described as a common factor. In this case, a 20-year-old man was admitted with acute respiratory failure. He had started smoking 20 HNB cigarettes per day 6 months previously, then purchased a second device for smoking HNB to increase smoking to 40 cigarettes per day, 2 weeks before hospitalisation. AEP was diagnosed based on medical history, chest high-resolution computed tomographic findings, and bronchoalveolar lavage fluid eosinophilia. Complete recovery was achieved with prednisolone treatment, with no relapse on cessation of treatment. The authors recommended that, as for CCs, HNB cigarettes should be recognised as a potential cause of AEP.

Reviews/commentaries

15. Kleinstreuer & Feng (2013) provided an overview of studies published between 2009 and 2013 that evaluated the potential health risks of toxicants in inhaled toxic aerosols, and also highlighted challenges and future directions. This review discusses tobacco products and manufacturing approaches, as well as their potential health risks to humans, especially to the most vulnerable population groups

(e.g. children and seniors). The tobacco products reviewed include the less harmful cigarettes (LHCs) or potential reduced exposure products (PREPs), or modified risk tobacco products (MRTP) grouped as being: (i) non-burning cigarettes. e.g. Reynolds Tobacco Premier® and Eclipse® (where a tobacco pellet is heated instead of being burnt using lit charcoal acting as an air heater), (ii) electrically heated cigarettes, e.g. PMI's Accord (IQOS predecessor) (where a tobacco mat surrounds a conventional cigarette tobacco filter, smoked with a specifically designed lighter), and (iii) e-cigarettes (a battery powered device which delivers nicotine as a vaporized solution). The review also reports studies suggesting that LHCs may be more harmful than CCs due to variations in puffing or post-puffing behaviour of users, differences in physical and chemical characteristics of the inhaled toxic aerosols, and longer exposure conditions. The authors urge scientists, engineers and manufacturers to undertake laboratory experiments, clinical investigations, and develop predictive numerical models for tracking the intake and deposition of toxicants of both MRTPs and CCs. The authors also draw attention to the value of determining the physical mechanisms and parameters that have significant impacts on droplet/vapour transport and deposition (e.g. droplet coagulation, hygroscopic growth, condensation and evaporation, vapour formation and changes in composition) for evaluating the association between inhaled toxicants and lung and other diseases. Study recommendations are provided on the impact assessment of different puffing behaviours, smoke inlet conditions, droplet geometries, and mass transfer of deposited material into systemic regions.

16. Caputi (2016) commented on the tobacco industry's activities and strategies governing HNB market penetrance. Several previously and currently available HNB products are discussed. HNB products were first unsuccessfully introduced into the market in 1988 and only began to thrive following the introduction and ready availability of e-cigarettes. Although there was an initial rapid growth in sales of e-cigarettes, a slower rate of increase in growth is now being reported in US. Caputi suggested that the decelerated growth may be unrelated to potential health concerns, but rather be due to taste issues associated with consuming a vaporised, nicotine-infused liquid, the inability of e-cigarettes to deliver nicotine into the bloodstream as quickly as CCs, and the absence of a 'throat hit' that CCs offer. Caputi proposed that the growth in HNB products may be related to a transfer of the perception of low risk relating to e-cigarettes to HNB products.

Summary

17. A literature search was carried out on 01/06/2017 to identify literature on heat-not-burn (HNB) tobacco products published by sources independent of the developers/manufacturers of these products. Five publications were identified. These comprise two investigative reports, one clinical case report, one literature review and one commentary.

18. Two studies evaluated substances released into the aerosol or to ambient air by 'puffing' the IQOS cigarette. Auer *et al.* (2017) reported that VOCs, PAHs and CO

were detectable in the vapour produced from puffing IQOS, although at lower levels than those detected in smoke puffed from a conventional cigarette (CC). The study by Protano *et al.* (2016) focussed on the release of submicronic particles (SMPs) into ambient air: SMPs were present in air sampled in a room during either the smoking of a CC, use of an e-cigarette or an IQOS product, but did not persist in the air once use of the IQOS or e-cigarette had ceased. One clinical case report described the development of acute eosinophilic pneumonia (AEP) in a young adult male who had smoked 40 HNB cigarettes per day (brand not specified) for the preceding 2-week period. The authors noted that HNB products should be recognised as a potential aetiological factor for AEP (Kamada *et al.,* 2016), as are CCs. A review by Kleinstreuer & Feng (2016) summarised the literature on 'less harmful cigarettes' (LHC) (including e-cigarettes and HNB products) published from 2009-2013. The authors noted the importance of appropriate modelling of vapour/particle deposition in the airways, including the incorporation of different puffing patterns. Caputi *et al.* (2016) commented on how the perception of a low associated risk may positively influence the choice of consumers to use HNB products over alternatives.

19. The findings and authors' conclusions of identified literature are summarised in Table 2, below.

Table 2. Literature on heat-not-burn tobacco published by independent sources.

Ref.	**Report type**	**Products discussed / compared**	**Smoking (puffing) regime tested**	**Results**	**Author conclusions / commentary**
Auer *et al.* (2017)	Research letter (study report)	IQOS; CC	International Organization for Standardization (ISO)	VOCs, PAHs and CO detected in IQOS and CC smoke; Core temperature 330ºC (IQOS), 684ºC (CC); Nicotine level IQOS 84% (IQOS vs. CC)	The aerosol produced by IQOS contains typical products of pyrolysis and thermogenic degradation, as found in the smoke of CCs, and should be included under the same indoor-smoking regulations as CCs
Protano *et al.* (2016)	Short paper (study report)	IQOS; CC; CC (hand-rolled); e-cigarette	A current smoker smoked 1 unit of the product (e.g. a single cigarette)	The predicted level of SMPs deposited in the airway of a passive smoker during the immediate smoking period was four-fold higher for CCs/hand-rolled CCs compared with e-cigarette/IQOS. Values remained high after smoking CC/hand-rolled cigarettes, but returned quickly to background levels after smoking e-cigarette/IQOS	Around half of all SMPs produced are small enough to enter the alveolar region of a passively exposed subject. One hour of exposure to SMPs generated by CC, hand-rolled CC, e-cigarette, and IQOS would be equivalent to spending 49, 39, 12 and 10 minutes, respectively, in a heavy traffic area
Kamada *et al.* (2016)	Clinical case report	HNB cigarettes (product not specified)	-	A 20-year-old man developed acute eosinophilic pneumonia (AEP). He had smoked 20 and 40 HNB cigarettes per day for the previous 6 months and 2 weeks, respectively. Upon 2-week treatment with prednisolone, he recovered completely, without subsequent relapse	HNB cigarettes should be recognized as a potential cause of AEP
Kleinstreuer & Feng (2013)	Review article	LHCs; CCs	-	Review of the literature on LHCs (non-burning cigarettes, electrically heated cigarettes, and	An important aspect for future studies is the modelling of vapour/particle deposition in the

				e-cigarettes), published from 2009 to 2013. Discusses factors influencing transport and deposition of toxins and carcinogens in the airways	airways, including modelling different puffing patterns
Caputi (2016)	Commentary	Previously and currently available HNB devices	-	Commentary on the marketing and consumer uptake of HNB products	The appeal of HNB products to the consumer may be related to the perception of low risk of associated adverse health effects

20. An updated literature search was performed on 01/08/2017. Four additional citations were identified as potentially relevant but require further review.

Question for the Committee

i. Is there any information in the independent literature summarised in this paper which should be incorporated in the second draft statement?

NCET at WRc/IEH-C under contract supporting the PHE COT Secretariat
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References

Auer R, Concha-Lozano N, Jacot-Sadowski I *et al.* (2017). Heat-Not-Burn Tobacco Cigarettes: Smoke by Any Other Name. JAMA Int. Med., 177, 1050-1052.

Caputi TL (2016). Heat-not-burn tobacco products are about to reach their boiling point. Tob. Control DOI: 10.1136/tobaccocontrol-2016-053264.

Farsalinos MD, Yannovitos N, Sarri T *et al.* (2017). Nicotine delivery to the aerosol of a heat-not-burn tobacco product: Comparison with a tobacco cigarette and E-cigarettes. Nic. & Tobacco Res., 00, 1-6.

Kamada T, Yamashita Y, Tomioka H (2016). Acute eosinophilic pneumonia following heat-not-burn cigarette smoking. Respirol. Case Rep., 4 (6) 1-3 (e00190).

Kleinstreuer C, Feng Y (2013). Lung Deposition Analyses of Inhaled Toxic Aerosols in Conventional and Less Harmful Cigarette Smoke: A Review. Int. J. Environ. Res. Public Health, 10, 4454-4485.

Protano C, Manigrasso M, Avino P *et al.* (2016). Second-hand smoke exposure generated by new electronic devices (IQOS® and e-cigs) and traditional cigarettes: submicron particle behaviour in human respiratory system. Ann. Ig., 28, 109-112.

Vu A, Taylor KM, Holman MR *et al.* (2015). Polycyclic aromatic hydrocarbons in the mainstream smoke of popular US cigarettes. Chem. Res.Toxicol., 28(8), 1616-1626.

COMMITTEE ON TOXICITY OF CHEMICALS IN FOOD, CONSUMER PRODUCTS AND THE ENVIRONMENT (COT)

Toxicological evaluation of novel heat-not-burn tobacco products: preliminary review of literature from sources not associated with product manufacturers and developers.

Details of literature search carried out

A literature search was performed by Imperial College London under contract to PHE on 01/06/17 using the following search terms in PubMed:

- Neopod, iFuse, Heatstick, Heet*, Electrically + heated + tobacco + product, EHTP, “heat-not-burn”, IQOS, THS + PMI, “tobacco heating system”, “electrically heated” + tobacco, “modified risk tobacco product”, Mrtp, “British American Tobacco” + rtp, “British American Tobacco” + prototype

Search terms that were related to British American Tobacco (BAT) and Philip Morris International (PMI) were removed, leaving the following search terms:

- “heat-not-burn”, “electrically heated” + tobacco, “modified risk tobacco product”, Mrtp

Nine papers were provided by PHE to WRc for consideration. In addition, a paper by Farsalinos *et al.,* 2017 was included which was published subsequent to the literature search in June.

Exclusion criteria

Papers that had any connection to a tobacco industry were excluded from further consideration (Table A1).

Table A1. Exclusion criteria

Ref.	**Reason for exclusion**
Bombick *et al.* (1998)	Published by RJ Reynolds Tobacco Company
Dayan (2016)	Associated with Philip Morris International
Farsalinos *et al.* (2017)	Associated with AEMSA (a Federation of e-cigarette manufactures) and Tennessee Smoke Free Association (a not-for-profit corporation comprised of consumers, retail vendors, manufacturers and supporters)
Fields *et al.* (2017)	Associated with RJ Reynolds Tobacco Company, American Snuff Co. and Santa Fe Natural Tobacco Company
Scherer *et al.* (2010)	Authored by the tobacco company, Altria Client Services (parent company of Philip Morris International)

Five papers were published by independent sources and hence were included in the evaluation.

NCET at WRc/IEH-C under contract supporting the PHE COT Secretariat
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Toxicological evaluation of novel heat-not-burn tobacco products: preliminary review of literature from sources not associated with product manufacturers and developers.

Details of Literature search carried out by NCET at WRc/IEH-C

The subsequent literature search was performed by NCET at WRc/IEH-C under contract to PHE on 01/08/17 using the following search terms in PubMed, Scopus and Web of Science. Terms related to tobacco manufacturers were not included.

- "heat not burn" OR "modified risk tobacco" OR "heat* tobacco" OR "electrically heat* cigarette" OR "electrically heat* tobacco"

Total no. of papers retrieved (for screening) = 95

Exclusion criteria

Papers that had any connection to a tobacco industry were excluded from further consideration and those that were not relevant to the study question, i.e. papers referring to test methodologies, regulatory aspects, growing of tobacco plants. Papers for which only abstracts or conference proceedings were available were also excluded from further evaluation.

From the 95 papers retrieved, 27 were deemed appropriate for further consideration based on the titles. Twelve papers were excluded as they were not independent from the tobacco industry. Six papers were excluded as only abstract or conference proceedings were available and all were associated with PMI. The nine remaining papers were obtained and reviewed, five of which were excluded as they were covered e-cigarettes, smokeless tobacco, conventional cigarettes (CC) or were not independent. The remaining four papers were included in the review.

Total no. of papers for further evaluation = 4.

List of papers for further consideration

- Buchhalter AR & Eissenberg T (2000). Preliminary Evaluation of a Novel Smoking System: Effects on Subjective and Physiological Measures and on Smoking Behavior. Nicotine and Tobacco Research, 2(1), 39-43.

- Committee on Scientific Standards for Studies on Modified Risk Tobacco Products, Board on Population Health and Public Health Practice & Institute, o. M. (2012). Scientific Standards for Studies on Modified Risk Tobacco Products.

- Ruprecht AA, De Marco C, Saffari A, et al. (2017). Environmental Pollution and Emission Factors of Electronic Cigarettes, Heat-Not-Burn Tobacco Products, and Conventional Cigarettes. Aerosol Science and Technology, 51(6), 674-684.

- Vassallo R, Wang L, Hirano Y, et al. (2015). Extracts from Presumed "Reduced Harm" Cigarettes Induce Equivalent Or Greater Toxicity in Antigen-Presenting Cells. Toxicology, 335, 46-54.

The above mentioned papers will be tabled for the committee meeting.

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