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Assessment of tobacco heating product THP1.0. Part 8: Study to determine puffing topography, mouth level exposure and consumption among Japanese users

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ABSTRACT

A four-arm study was undertaken in Japan to determine the puffing topography, mouth level exposure and average daily consumption by consumers of the tobacco heating products (THPs): the non-mentholated THP1.0(T), the mentholated THP1.0(M) and a tobacco heating system (THS). The extent of lip blocking of air inlet holes while using THP1.0(T) was also assessed. Groups 1, 2, and 4 included smokers, and group 3 included regular THP users. Smokers of 7–8 mg ISO nicotine free dry particulate matter (NFDPM) non-mentholated cigarettes took on average larger mean puff volumes from THPs than from conventional cigarettes, but puff numbers and durations were similar. Mouth level exposure to NFDPM and nicotine levels were significantly lower when using THPs than conventional cigarettes. Similar trends were observed among smokers of 7–8 mg ISO NFDPM mentholated cigarettes who used mentholated cigarettes and THP1.0(M). Regular users of commercial THS had similar puffing behaviours irrespective of whether they were using THS or THP1.0(T), except for mean puff volume which was lower with THP1.0(T). No smokers blocked the air inlet holes when using THP1.0(T). The puffing topography results support the machine puffing regime used to generate toxicant emissions data and *in vitro* toxicology testing.

1. Introduction

Cigarette smoking is one of the leading preventable causes of human diseases, such as cardiovascular disorders, chronic obstructive pulmonary disease and lung cancer (US DHHS, 2014). The cause of most smoking-related diseases is the inhalation of toxicants present in tobacco smoke (Farsalinos and Le Houezec, 2015), caused by the burning of tobacco in a cigarette, which produces more than 6500 compounds (Rodgman and Perfetti, 2013), of which around 150 are toxicants (Fowles and Dybing, 2003). As many of the toxicants are produced from combustion or pyrolysis of the tobacco (Baker, 2006) recent approaches to reducing the health risks related to tobacco use have concentrated on the heating rather than combustion of tobacco to reduce the level of combustion-derived toxicants in the inhalable aerosol (Forster et al., 2015; Gonzalez-Suarez et al., 2016; Schorp et al., 2012; Smith et al., 2016; Zenzen et al., 2012). Recently, British American Tobacco (BAT) developed a tobacco heating product (THP) THP1.0. This product heats rather than burns tobacco to release an aerosol with approximately 90% reduction in TobReg (9) toxicants than conventional cigarette smoke (Forster et al., 2017). THP1.0 comprises two functional parts: an electronic handheld device with a heating chamber, and a specially designed consumable to be inserted into the heating chamber (Eaton et al., 2017).

Murphy et al. (2015) and Murphy (2017) have proposed a new scientific framework to evaluate the reduced risk potential of tobacco and nicotine products. In the context of this framework, 'actual use' studies play a key part in determining whether

Abbreviations: THP, tobacco heating product; THS, tobacco heating system; ISO, International Organization for Standardization; NFDPM, nicotine-free dry particulate matter; BAT, British American Tobacco; FDA, Food and Drug Administration; MLE, mouth level exposure; TPM, total particulate matter; ADC, average daily consumption; SD, Standard Deviation; HCI, Health Canada intense.

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consumers will use the product in a manner that reduces their individual exposure or health risk compared with using other commercial tobacco and nicotine products. The US Food and Drug Administration (FDA) as part of the Modified Risk Tobacco Product Application guidelines recommend conducting 'actual use' studies where consumers interact freely with the products in their everyday environments, pre- and post-product launch (FDA, 2012).

'Actual use' studies provide an insight into consumer use behaviour such as the size and frequency of puffs taken, mouth level exposure (MLE) and number of interactions with the product per day. Studies reporting 'actual use' data for THPs are not widely available (Haziza et al., 2016; Lee et al., 2004; Lüdicke et al., 2017), likely due to the low numbers of commercially available devices, although several approaches to producing an aerosol by heating tobacco have been reported (Moennikes et al., 2008; Schorp et al., 2012; Stabbert et al., 2003). The commercially available THPs, Eclipse (R. J. Reynolds, Winston Salem, NC, USA), iQOS™ (Philip Morris International, New York, NY, USA), Ploom (Ploom, San Francisco, CA, USA), and glo™ (BAT; referred to as THP1.0 throughout), employ different methods of heating tobacco, with some of the more recent devices designed to control the heating profile (Eaton et al., 2017; Smith et al., 2016).

We report here a study with the objective of measuring puffing topography, MLE and average daily consumption (ADC) among Japanese smokers and THP users to characterise their use behaviour of non-mentholated and mentholated THPs [THP1.0(T) and THP1.0(M)] in comparison with commercially available combustible cigarettes (T189 and M322) and a tobacco heating system (THS). Study volunteers were smokers of non-mentholated and mentholated cigarettes who were naïve to the use of THPs and those who were regular users of the commercially available THP.

A number of research groups have explored various approaches for using the materials trapped by the filter as an indicator of smoke exposure (Pauly et al., 2009; Shepperd et al., 2006; St. Charles et al., 2009; Watson et al., 2004). Due to the fundamental differences in the kinetics of formation, transfer and retention of aerosol constituents in the mouth end section of the THP consumable compared with a conventional cigarette, further research to understand the relationship between flow and retention efficiency of constituents is needed before MLE from THPs can be estimated with a filter- or mouth-piece-based approach. In this study, an optical obscuration technique based on that described by Slayford and Frost (2014) was used to estimate MLE to nicotine free dry particulate matter (NFDPM), nicotine and menthol from THPs and the cigarettes.

These MLE estimates derived using real-time optical obscuration were collected using the modified holder of the puffing topography device (SA7, developed by BAT in collaboration with C-Matic Limited, Crowborough, UK) described by Cunningham et al. (2016). The estimates were further reinforced by duplicating a subset of the puffing topography records in the laboratory.

Several studies have claimed that some smokers block or partially block the ventilation holes on cigarette filters with their lips, thereby increasing their MLE (Baker and Lewis, 1997; Kozlowski et al., 1980, 1982, 1988, 1996). According to the THP1.0(T) use instructions, the user is asked to insert the consumable into the device and hold the device while puffing on the mouth piece. The study included a fourth arm designed to investigate potential lip blocking of the air inlet holes of the specially designed consumable of THP1.0(T) during use. Saliva stains on the used consumables were visualised by treating the tipping paper with ninhydrin solution. The maximum mouth insertion depth was defined as the distance from the mouth end to the furthest point of the visible ninhydrin staining (Baker and Lewis, 1997; Porter and Dunn, 1998).

2. Methods

2.1. Study products

THP1.0, developed by BAT, was evaluated in this study. A full description of the design and thermophysical properties of THP1.0 is reported by Eaton et al. (2017). In brief, THP1.0 is a handheld electronic device with a heating chamber designed for a specific tobacco consumable that is inserted and heated to a maximum temperature of 240 °C ± 5 °C to produce an inhalable aerosol. THP1.0(T) comprises the glo™ heating device with Bright Tobacco Kent Neostiks™, and mentholated THP1.0(M) comprises the glo™ heating device with Intensely Fresh Kent Neostiks™. The devices and consumables were sourced from Japan. Participants were provided with study cigarettes according to their usual tobacco product type: either 7 mg ISO (International Organization for Standardization [ISO] 4387:2000) (ISO, 2000) NFDPM non-mentholated cigarettes based on Lucky Strike Regular (T189) or 7 mg ISO NFDPM mentholated cigarettes based on Lucky Strike Menthol (M322). The THS was the commercially available iQOS™ with Essence tobacco HeatStick™, also sourced from Japan. All products were provided by the study sponsor. Cigarettes were provided in unbranded white packaging and the THPs were provided in branded packaging.

2.2. Study participants

The study was conducted in Tokyo, Japan, during 2016. Four groups of study participants were recruited by a market research agency following the International Code on Market Opinion and Social Research and Data Analytics (ICC/ESOMAR, 2016). Adult Japanese tobacco users between the ages of 21 years and 7 months and 64 years were eligible for inclusion in the study. Group 1 and 4 participants (smokers of non-mentholated cigarettes) were eligible if they smoked five or more non-menthol 7–8 mg NFDPM (ISO yield) cigarettes per day and had been smoking for more than 6 months. Group 2 participants (smokers of mentholated cigarettes) were eligible if they smoked five or more menthol 7–8 mg NFDPM (ISO yield) cigarettes per day and had been smoking for more than 6 months. Group 3 participants (THS users) were eligible if they reported using THS for five or more sessions per day and had been a user for a minimum of 3 months, including those who smoked commercial cigarettes in addition to using THS (dual users). Females were excluded if they reported that there was a possibility that they were pregnant. All participants were screened using a written questionnaire and provided written informed consent prior to participating in the study. Participants were informed that they were free to withdraw from the study at any time and received remuneration for their participation in the study.

2.3. Study protocol

Participants in Groups 1, 2 and 3 were provided with study products to use in place of their regular tobacco products over a 4-day familiarisation period. Participants were provided with enough product to cover their self-reported average daily consumption rounded up to the nearest pack for each familiarisation period. The products relevant to each group were presented in a randomised order in consecutive product placements (Fig. 1). Group 1 were provided with three non-mentholated products, cigarette T189, THP1.0(T) and THS. Group 2 were provided with two mentholated products, cigarette M322 and THP1.0(M). Group 3 were provided with two THPs, THP1.0(T) and THS with tobacco consumables. All participants received instructions on how to operate the THP devices before the placement. Participants were asked to replace a

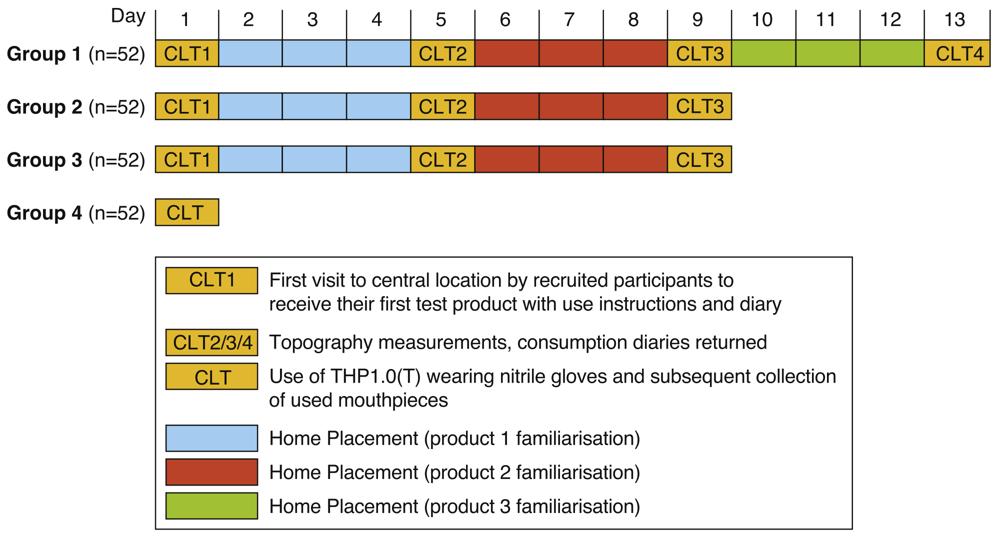

Fig. 1. Overview of the study design of 13-day product placement period.

minimum of five of their regular product-use sessions with the test product provided and to record their consumption of study and any non-study products in a diary provided. On day 5 of each product placement period, the participants attended a central location where their puffing topography was measured with the SA7 puffing topography device, using the modified holder previously described by Cunningham et al. (2016). Participants' puffing topography was measured and recorded in duplicate for each study product with a minimum of a 20 min break in between sessions.

Group 4 participants completed two product-use sessions at the central location using THP1.0(T), with a minimum of a 20 min break between sessions. During these sessions, participants were asked to wear nitrile gloves when handling and using the THP1.0(T) consumables to prevent the transfer of proteins from their hands to the consumable. At the end of each session, the tobacco portion of the used consumable was removed and disposed of, and the remainder placed in a labelled aluminium can for subsequent analysis of mouth insertion depth. An overview of the study design is shown in Fig. 1.

2.4. Analytical methods

2.4.1. Puffing topography

Puffing topography involved measurement and recording of puff volumes, puff durations, intervals between puffs and the number of puffs. Each participant was provided with two samples of the allocated study product and requested to use it through a puffing topography device, with an interval between each sample of at least 20 min. Puffing topography data were recorded using a proprietary SA7 portable topography analyser. The SA7 consists of a product holder connected to a data acquisition and transmission unit with two unidirectional pressure transducers connected to either side of an orifice. The pressure transducers detect a pressure change across the orifice (2 mm) in the holder, which is proportional to the flow rate squared (Slayford and Frost, 2014).

2.4.2. Mouth level exposure

MLE to NFDPM, nicotine and menthol was estimated using real-time measurement of optical obscuration of each individual puff. The optical obscuration technique is described in detail by Slayford and Frost (2014), but in brief works on the principle that light from an LED source within the topography head is obscured by the aerosol particles generated when puffing on either a cigarette or THP. The relationships between the extent of optical obscuration and the mainstream yields of NFDPM were determined using machine smoking across a number of smoking regimes judged to represent the expected spectrum of consumer use behaviour (Supplementary Table S1). The total particulate matter (TPM), nicotine, water and menthol in the mainstream aerosol were captured on a Cambridge filter pad using a PM1 smoking machine (Borgwaldt KC, Hamburg, Germany) and analysed by gas chromatography. The calculated NFDPM for each study product was used to determine the appropriate factors to allow the 'optical NFDPM' to be calculated, as previously described by Slayford and Frost (2014). Calibration graphs were also produced for each product to establish the relationship between the NFDPM and nicotine and between NFDPM and menthol for the mentholated products. These relationships were then used to estimate MLE to nicotine and menthol using 'optical NFDPM' in place of NFDPM. Mean MLE and ADC were used to calculate mean daily MLE.

2.4.3. Duplication

Verification of the use of optical obscuration as an appropriate measure of MLE was conducted by determining the agreement between NFDPM collected from mainstream aerosol and the measure of 'optical NFDPM' as the aerosol passes through the puffing topography head. The SA7 software suite allows the duplication of human puffing topography records on a laboratory smoke machine. A subset of puffing topography records for each of the study products were duplicated using a 4-port linear smoking machine (LM4X, Borgwaldt KC) in the laboratory with an SA7 in line to record optical obscuration. These puffing topography records were selected based on the total puff volume recorded, taking records with low (116–320 mL), medium (440–620 mL) and high (800–2750 mL) total puff volumes. The resulting mainstream aerosol was collected on a Cambridge filter pad and analysed by gas chromatography for water, nicotine and menthol. The correlation between the mainstream NFDPM measured using the gas chromatography methodology and that recorded using the optical obscuration approach was determined for each study product.

2.4.4. Mouth insertion depth

The potential blocking of the air inlet zone in the THP consumable was assessed using a ninhydrin staining technique, as previously applied to smoked cigarette filters (Baker and Dixon, 1998; Hu et al., 2003; Porter and Dunn, 1998). The incidence of in-use blocking the air inlet holes of the THP1.0(T) consumable by the Group 4 participants was assessed by the application of a ninhydrin solution to the used consumable mouthpieces. Each mouthpiece sample was sprayed until evenly coated with a solution of 5% ninhydrin in ethanol, and allowed to dry. After the development of the stain pattern, the sample was cut lengthways, flattened and the mouth insertion depths were measured. Maximum mouth insertion depth was defined as the point furthest from the mouth end of the mouthpiece where staining was visible. Blocking of the air inlet zone was considered to have occurred where any part of the mouth insertion profile covered the air inlet holes on the filter. Observations of any occurrences of blocking were recorded.

2.5. Statistical analysis

SAS version 9.4 statistical software (SAS Institute Inc., Cary, NC, USA) was used to conduct statistical analysis. As the data collected were skewed, they were log transformed to fit normal distributions. ADC, MLE and puffing topography data are presented as mean ± standard deviation (SD). The data presented in the summary tables are arithmetic means and standard deviations, irrespective of whether the data were transformed to perform statistical analysis. Analysis of variance using a linear mixed model (Proc Mixed) was used to compare ADC, MLE and puffing topography data for products within user groups. Where a significant difference between the means was found, Tukey's post-hoc test was applied to investigate the source of the difference. Where the same product was used by different groups, between-group differences were also analysed using the same approach.

3. Results

3.1. Study participants

Demographic characteristics of study participants were similar between user groups except for Group 3, which had a greater number of participants (48%) in the 21–29 year age range compared with the other groups ((19–27%) Table S2, supplementary). In each group, male and female participants were recruited to the study in approximately equal numbers. Members of Group 1 and 2 were smokers of regular and mentholated cigarettes and none reported using THS in the previous 30 days.

3.2. Puffing topography

Mean values for total puff volume, mean puff volume, puff duration, puff number and interval between puffs per product and by user group are shown in Table 1.

Group 1 participants took significantly larger total volumes when using THP1.0(T) and larger mean puff volumes when using THP1.0(T) and THS than when using cigarette T189. Puff intervals were significantly shorter for THPs than for cigarettes, but there were no differences between number of puffs per use or the mean puff durations for any of the study products within this group.

Group 2 participants displayed similar behaviour to Group 1, with respect to a significantly higher mean puff volume and shorter puff interval for THP1.0(M) than the cigarette M322. No differences were observed for total volume, number of puffs and mean puff durations.

In Group 3 no differences between THS and THP1.0(T) were observed in puffing behaviour except for mean puff volume, which was significantly lower for THS.

A comparison of Groups 1 and 3 showed there were no differences between THP1.0(T) and THS in puffing behaviour except for mean puff volume for THS, which was significantly greater for Group 1 (Table 2).

3.3. Average daily cigarette consumption

For Groups 1 and 2, ADC of cigarettes was higher than consumption of the tobacco heating products (Table 3). In Group 1 the cigarette ADC was similar to that reported at screening, whereas in Group 2 ADC was higher than that reported at screening. Consumption of THPs was lower than self-reported cigarette consumption at recruitment for participants in Groups 1 and 2. Group 3 reported significantly higher ADC when using THS than when using THP1.0(T); the ADC of THS was comparable to the self-reported ADC. In all groups, the total ADC was greater than that of the study product, indicating some use of non-study products during the home placement periods.

3.4. Mouth level exposure

MLE data are reported per product for each Group in Table 4. MLEs to NFDPM and nicotine were significantly lower for the THPs than for the cigarettes in Group 1. The ranking for MLE per stick and per day was T189 > THS > THP1.0(T) for both NFDPM and nicotine. Group 2 obtained significantly lower amounts of NFDPM and nicotine MLE per stick and per day from THP1.0(M) than from mentholated cigarettes (M322). Average reductions in MLE per stick compared with cigarettes were 61% for NFDPM and 77% for nicotine for THP1.0(T) (vs. T189), 58% for NFDPM and 77% for nicotine for THP1.0(M) (vs. M322) and 38% for NFDPM and 23% for nicotine for THS (vs. T189). No differences were observed in MLE to

Table 1
Comparison of puffing topography within user groups.

Product	User group	Total puff volume (mL)		Mean puff volume (mL)		Puff number (n)		Mean puff Duration (s)		Mean puff interval (s)	
		Mean ± SD	Tukey's ranking[a]	Mean ± SD	Tukey's ranking[a]	Mean ± SD	Tukey's ranking[a]	Mean ± SD	Tukey's ranking[a]	Mean ± SD	Tukey's ranking[a]
T189	1	489.0 ± 177.7	b	48.9 ± 14.8	b	10.7 ± 5.0	a	1.8 ± 0.6	a	9.7 ± 3.4	a
THP1.0(T)		736.4 ± 415.8	a	66.7 ± 23.7	a	10.9 ± 5.6	a	1.8 ± 0.6	a	7.4 ± 2.7	b
THS		668.1 ± 322.6	ab	63.5 ± 20.3	a	10.3. ± 3.6	a	1.8 ± 0.6	a	8.3 ± 3.0	b
M322	2	493.7 ± 192.4	a	51.1 ± 16.0	b	10.0 ± 3.7	a	2.0 ± 0.5	a	9.9 ± 3.4	a
THP1.0(M)		618.2 ± 389.6	a	62.2 ± 32.8	a	10.0 ± 4.5	a	1.8 ± 0.5	a	8.1 ± 3.0	b
THP1.0(T)	3	773.5 ± 545.7	a	60.9 ± 24.8	a	12.3 ± 7.3	a	1.8 ± 0.7	a	7.7 ± 3.9	a
THS		588.0 ± 360.0	a	55.1 ± 23.9	b	10.8 ± 5.1	a	1.8 ± 0.7	a	8.6 ± 3.1	a

Abbreviations: SD = standard deviation; THP = tobacco heating product; THS = tobacco heating system.
[a] Same letter within a group indicates no statistical difference (p > 0.05).

Table 2
Comparison of puffing behaviour by product type.

Product	User group	Total puff volume (mL)		Mean puff volume (mL)		Puff number (n)		Mean puff duration (s)		Mean puff interval (s)	
		Mean ± SD	Tukey's ranking[a]	Mean ± SD	Tukey's ranking[a]	Mean ± SD	Tukey's ranking[a]	Mean ± SD	Tukey's ranking[a]	Mean ± SD	Tukey's ranking[a]
THP1.0(T)	1	736.4 ± 415.8	a	66.7 ± 23.7	a	10.9 ± 5.6	a	1.8 ± 0.6	a	7.4 ± 2.7	a
	3	773.5 ± 545.7	a	60.9 ± 24.8	a	12.3 ± 7.3	a	1.8 ± 0.7	a	7.7 ± 3.9	a
THS	1	668.1 ± 322.6	a	63.5 ± 20.3	a	10.3 ± 3.6	a	1.8 ± 0.6	a	8.3 ± 3.0	a
	3	588.0 ± 360.0	a	55.1 ± 23.9	b	10.8 ± 5.1	a	1.8 ± 0.7	a	8.6 ± 3.1	a

Abbreviations: SD = standard deviation; THP = tobacco heating product; THS = tobacco heating system.
[a] Same letter within a group indicates no statistical difference (p > 0.05).

Table 3
Participants' average daily consumption of study products.

Product	User group	Self-reported average daily consumption at screening	Average daily consumption of study product recorded in diary		Total average daily consumption recorded in diary	
			Mean ± SD	Tukey's ranking[a]	Mean ± SD	Tukey's ranking[a]
T189	1	15.3 ± 5.0	16.0 ± 8.1	a	16.3 ± 7.9	a
THP1.0(T)			10.3 ± 5.5	c	12.1 ± 5.5	c
THS			12.2 ± 6.2	b	13.7 ± 5.6	b
M322	2	12.9 ± 4.8	15.3 ± 6.9	a	15.6 ± 6.9	a
THP1.0(M)			11.4 ± 5.7	b	13.1 ± 6.0	b
THP1.0(T)	3	12.9 ± 5.9[b] (11.1 ± 7.5)[c]	8.6 ± 4.6	b	11.2 ± 6.2	b
THS			12.4 ± 7.8	a	13.4 ± 7.8	a

Abbreviations: SD = standard deviation; THP = tobacco heating product; THS = tobacco heating system.
[a] Same letter within a group indicates no statistical difference (p > 0.05).
[b] Self-reported average daily consumption of cigarettes and commercial heated tobacco consumables for dual users (n = 37).
[c] Self-reported average daily consumption of THS tobacco consumables (n = 52).

Table 4
MLE to NFDPM, nicotine and menthol within user groups.

User Group	Product	MLE to NFDPM				MLE to Nicotine				MLE to Menthol			
		Mean ± SD (mg/stick)	Tukey's ranking*	Mean ± SD (mg/day)	Tukey's ranking*	Mean ± SD (mg/stick)	Tukey's ranking*	Mean ± SD (mg/day)	Tukey's ranking*	Mean ± SD (mg/stick)	Tukey's ranking*	Mean ± SD (mg/day)	Tukey's ranking*
1	T189	13.5 ± 6.2	a	224.1 ± 154.9	a	1.3 ± 0.5	a	22.2 ± 14.1	a	–	–	–	–
	THP1.0(T)	5.2 ± 3.4	c	58.0 ± 56.4	c	0.3 ± 0.2	c	3.3 ± 2.8	c	–		–	
	THS	8.4 ± 4.5	b	110.4 ± 109.1	b	1.0 ± 0.5	b	13.1 ± 12.9	b	–		–	
2	M322	14.8 ± 7.4	a	232.6 ± 156.2	a	1.3 ± 0.6	a	20.4 ± 13.0	a	1.2 ± 0.5	a	18.5 ± 11.8	a
	THP1.0(M)	6.2 ± 3.8	b	77.1 ± 72.9	b	0.3 ± 0.2	b	3.5 ± 3.4	b	1.4 ± 0.8	a	17.7 ± 16.0	a
3	THP1.0(T)	5.0 ± 3.1	b	42.5 ± 30.1	b	0.3 ± 0.1	b	2.5 ± 1.6	b	–	–	–	–
	THS	7.0 ± 3.3	a	90.6 ± 74.7	a	0.8 ± 0.4	a	10.7 ± 8.8	a	–		–	

Abbreviations: MLE = mouth level exposure; NFDPM = nicotine free dry particulate matter; SD = standard deviation; THP = tobacco heating product; THS = tobacco heating system.
* Same letter within a group indicates no statistical difference (p > 0.05).

menthol between THP1.0(M) and M322. In Group 3, MLEs to NFDPM and nicotine were significantly lower for THP1.0(T) than for THS. A comparison across Groups 1 and 3 showed no differences in MLEs to NFDPM and nicotine between THP1.0(T) and THS (Table 5).

3.5. Duplication

There was a strong positive correlation observed between optical NFDPM and NFDPM determined from duplication smoking of participant records, with r^2 values of 96.7% and 97.9% for cigarettes (Fig. S1, supplementary) and 82.7–88% for THPs (Fig. S2, supplementary). The mean difference between optical NFDPM and NFDPM for the study products ranged from −1.9 to 0.4 mg/stick for THPs and 2.7–3.4 mg/cig for cigarettes (Table 6). There was evidence of increasing difference between the two methods for cigarettes with increasing yield resulting in higher estimates of MLE by use of optical NFDPM than from use of NFDPM collected on a Cambridge filter pad.

3.6. Mouth insertion depth

All used THP1.0(T) mouthpieces collected from Group 4 were analysed by the application of a ninhydrin solution (examples shown in Supplementary Fig. S3). A total of 104 mouthpieces were collected, of these, three samples did not develop a staining profile and were marked inconclusive. The air inlet zone on Bright Tobacco Kent Neostiks™ were positioned 18 mm from the mouth end. The mean maximum mouth insertion depth was 7.7 mm ± 3.4 mm (Fig. 2). The maximum mouth insertion depth observed from all samples analysed was 17 mm and none of the samples analysed showed evidence of blocking of the air inlet holes of the tobacco consumable used with THP1.0(T).

4. Discussion

Recent innovations in tobacco products have focused on the heating of tobacco rather than tobacco combustion, with the aim of reducing the health risks associated with tobacco use. The results of

Table 5
Between-group comparison of MLE to NFDPM and nicotine by product type.

Product	User Group	MLE to NFDPM (mg/cig)		MLE to Nicotine (mg/cig)	
		Mean ± SD	Tukey's ranking*	Mean ± SD	Tukey's ranking*
THP1.0(T)	1	5.2 ± 3.4	a	0.3 ± 0.2	a
	3	5.0 ± 3.1	a	0.3 ± 0.1	a
THS	1	8.4 ± 4.5	a	1.0 ± 0.5	a
	3	7.0 ± 3.3	a	0.8 ± 0.4	a

Abbreviations: MLE = mouth level exposure; NFDPM = nicotine free dry particulate matter; SD = standard deviation; THP = tobacco heating product; THS = tobacco heating system.
* Same letter indicates no statistical difference between groups ($p > 0.05$).

Table 6
Mean differences in optical NFDPM and NFDPM generated from duplication smoking.

Product	Mean ± SD difference (mg/stick) (optical NFDPM−NFDPM)
T189	2.7 ± 2.3
M322	3.4 ± 3.8
THP1.0(T)	0.4 ± 1.8
THP1.0(M)	−0.3 ± 1.2
THS	−1.9 ± 1.8

Abbreviations: NFDPM = nicotine free dry particulate matter; SD = standard deviation; THP = tobacco heating product; THS = tobacco heating system.

this study indicate a significant reduction in MLE to NFDPM and nicotine (58–61% and 77%, respectively) from 'actual use' of THP1.0(T) or THP1.0(M), compared with 7 mg ISO NFDPM non-mentholated and mentholated cigarettes among Japanese smokers. Reductions in MLE to NFDPM were higher for THP1.0(T) and THP1.0(M) than those observed for the commercially available THS. Additionally, it should be noted that the composition of NFDPM from THP1.0 is very different from that collected from cigarettes (Forster et al., 2017).

In general, measurement of puffing topography demonstrated that both total and mean puff volumes were larger for THPs than for cigarettes, giving the rankings THP1.0(T) > THS > T189 and THP1.0(M) > M322. Conversely, puff intervals were shortest for THP1.0 devices, with the ranking being T189 > THS > THP1.0(T) and M322 > THP1.0(M). Although the total puff volumes for THPs were higher than for cigarettes, the mean MLE to NFDPM and nicotine were lower, which is likely to be a result of their relatively low mainstream yields compared with cigarettes (Table S1, supplementary).

MLEs to NFDPM and nicotine when using THP1.0(T) and THS were observed to be similar for smokers who were naïve to THPs and regular users of THS, although the mean puff volumes was larger among THP-naïve smokers than among regular users. No difference in puff volume was seen between THP-naïve smokers and among regular users of THS when they were using THP1.0(T). The general lack of difference in puffing behaviour between naïve and experienced THP users suggests a familiarisation period of 4 days is sufficient to reflect representative behaviour of experienced users.

Mean ADC per group for the THPs were lower for smokers of non-mentholated and mentholated cigarettes than the mean self-reported ADCs when they smoked their regular products. The study participants reported minimal usage of non-study products during the study period (on average one to two cigarettes). The regular users of the commercial THPs were generally dual users of THPs and cigarettes, and during the study they recorded ADCs similar to their self-reported regular consumption for both the THS and cigarettes. There were clear differences between the daily MLE to each study product for both NFDPM and nicotine for all groups,

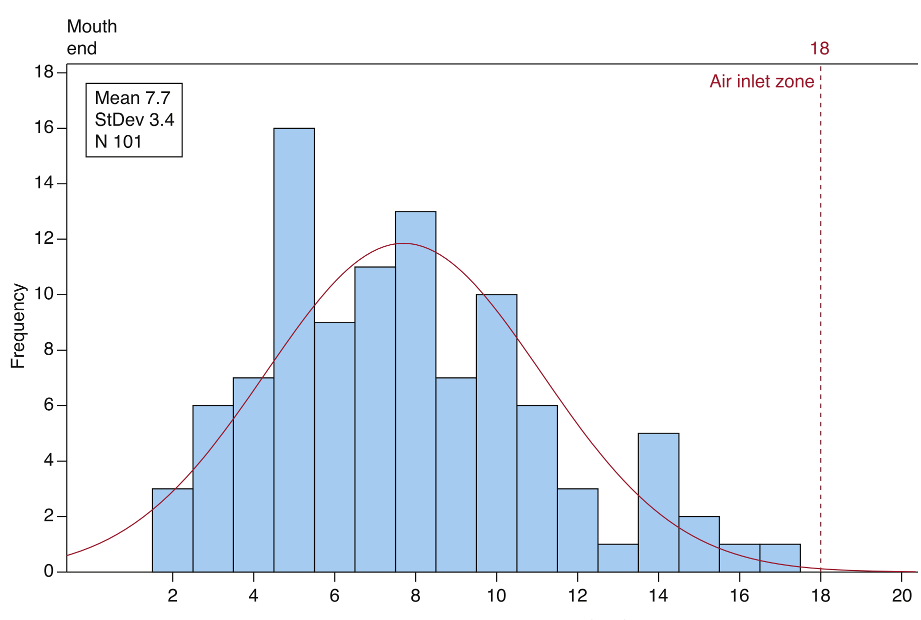

Fig. 2. Distribution of mouth insertion depths.

with the following trends being observed T189 > THS > THP1.0(T) for Group 1, M322 > THP1.0(M) for Group 2 and THS > THP1.0(T) for Group 3. The total daily MLE to NFDPM when using THP1.0(T) and THP1.0(M) was less than half that with cigarettes. Group 1 and 2 smokers reported consuming an average of one to two non-study cigarettes during THP1.0(T) and THP1.0(M) placement periods, indicating that compliance with the study protocol was high for the majority of participants.

Although MLE for cigarettes is often estimated using part-filter analysis (St. Charles et al., 2009), early investigations into the application of this methodology for use with THP1.0(T) proved unsuccessful, most likely due to the differences in the kinetics of formation and transfer of constituents of the THP1.0(T) aerosol to the mouthpiece. Poget et al. (2017) extended the filter assay approach to estimating MLE for use with mouthpieces of the THS consumable. Relationships between the nicotine retained in the mouthpiece and harmful and potentially harmful constituents in the aerosol generated by machine smoking were investigated. Many of the relationships were determined to be polynomial rather than linear, as has been observed for cigarettes. This approach to regression modelling of the relationships between constituents retained in the mouthpiece of THPs and the mainstream aerosol merits further investigation. The use of optical obscuration to produce estimates of MLE for smokers has been reported previously by Slayford and Frost (2014). In this study, the method was extended to produce estimates of MLE to NFDPM, nicotine and menthol for THPs. The suitability of this approach for use with THPs was examined by comparison of the agreement between the optical NFDPM and NFDPM produced from duplicated human records. The mean differences between the measurements of optical NFDPM and NFDPM of −1.9 to 0.4 mg/stick for the THP products are reasonable considering that the accepted variability in the measurement of the NFDPM is ±1 mg or 15%, whichever is the greater (ISO 8243:2013) (ISO, 2013) when measured according to ISO 4387:2000 (ISO, 2000). The difference between the two methodologies was greater for the cigarettes (between 2.7 mg and 3.4 mg) than for the THPs. This difference is greater than that of ±1.3 mg per cigarette over the range of 1–23 mg yields reported by Slayford and Frost (2014). This difference is likely due to the increase in the repeatability limit in the measurement of the NFDPM with higher yields, which is reported as 1.19 mg/cig at a mean yield of 17.40 mg NFDPM per cig (ISO 4387:2000). Cigarettes in this study had a higher ISO NFDPM yield than those used in the Slayford and Frost study, with resultant yields of up to 37.8 mg NFDPM observed in duplication smoking. Further investigations to improve the agreement between the two methodologies at higher NFDPM are needed to understand the sources of variation. The novel approach of using real-time optical obscuration offers a cost-effective approach to estimating consumers' MLE to NFDPM, nicotine and menthol from aerosols generated by combustible cigarettes and THPs.

Compared with cigarettes, there are few published data on 'actual use' of THPs. Haziza et al. (2016) reported results from a clinical study conducted in Poland that included the *ad libitum* use of a THP in confined conditions. The average puff volumes of 52.9 mL and average puff durations of 2.1 s differ from those recorded for users of THPs in this study (55.1–66.7 mL and 1.8 s). The differences in study population, products and methodology may have contributed to the behavioural differences observed.

Puffing topography data from actual consumer use allows laboratory-based evaluations of products to be conducted in a manner that is reflective of actual behaviour. To date, most laboratory evaluation of THPs has focussed on the use of the puffing parameters from the standard Health Canada intense (HCI) regime (Health Canada, 1999) for machine puffing. The results from this study and that conducted by Haziza et al. (2016) support the continued use of the HCI puffing parameters in the evaluation of THPs. Although the range of mean THP puff volumes (55.1–66.7 mL) measured in this study were higher than the 55 mL puffing-volume parameter of the HCI, they are similar to the range normally observed with cigarettes for which the HCI puffing parameters were established. It should be noted that puffing analysers preclude the possibility of vent blocking and, therefore, all puffing parameters measured are with ventilation holes open. Therefore, even though puff volumes for cigarettes approached the HCI puff volumes and exceeded them for the THS or THP1.0 devices, they were obtained with ventilation holes open.

The mean puff duration (1.8 s) reported in this study for THP use is similar to the 2 s puff duration of the HCI regime. The range of mean puff intervals determined for all products in this study was 7.4–9.9 s, and resulted in a puff frequency much higher than one puff every 30 s as used in the HCI regime. At the central location, although the participants were allowed to use the cigarettes and THPs *ad libitum*, their normal behaviour may have been altered by the need to use the smoking behaviour analyser and the presence of investigators, both of which are likely to have resulted in more intense behaviour. Although these puffing parameters could be duplicated on a specific smoking/puffing machine designed for the purpose, they cannot be reproduced on the machines used for routine toxicant measurements owing to design limitations. Consequently, the standard HCI puff frequency of one puff every 30 s was considered to be acceptable for evaluation of THPs.

Furthermore, studies published in the literature have assessed the potential for smokers to block filter ventilation holes during smoking of cigarettes and consequently increase exposure to mainstream yields of smoke constituents (Baker and Lewis, 1997, 2001; Djordjevic et al., 2000; Kozlowski et al.,1980, 1982, 1988, 1996). The HCI regime takes this behaviour into account by applying 100% ventilation blocking for cigarettes. In this study, the user mean mouth insertion depth for the THP1.0(T) consumable was determined to be 7.7 mm (Fig. 2), which was among THP-naïve users, although differences might be observed in experienced users or different user groups. However, the THP1.0(T) consumable was designed with air inlet holes positioned just outside the heating device, making it difficult for a user to block the air inlet zone. None of the analysed consumables showed any evidence of air inlet blocking, and, therefore, it is appropriate that the air inlet zone is not blocked during laboratory evaluation of THP1.0(T) and THP1.0(M). Thus, overall the puffing topography results from the study support the use of a modified HCI puffing regime of 55 ml puff volume, 2 s puff duration every 30 s but no ventilation blocking for THP1.0(T) to generate emissions (Forster et al., 2017) and *in vitro* toxicology assessments (Jaunky et al., 2017; Taylor et al., 2017; Thorne et al., 2017).

Conflict of interest statement

This work was funded by British American Tobacco (BAT), all authors are full time employees except Jodie Gee who is a former employee of BAT.

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Appendix A. Supplementary data

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Transparency document

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