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Original Research Article

Emissions, puffing topography, mouth level exposure and consumption among Japanese users of tobacco heated products

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ABSTRACT

Background: Tobacco heating products (THPs), which heat rather than burn tobacco, have been demonstrated by a number of studies to produce an aerosol with substantially lower levels of toxicants and reduced cytotoxicity relative to cigarette smoke. As they evolve in design and function, however, it is important to verify that variant THPs maintain sufficient equivalence to the original product if we are to leverage existing foundational datasets. Recent studies suggest that a bridging approach, in which a variant is shown to be comparable to the original product on which a large foundational dataset has been generated, might be used to ensure that the same product-related claims apply.
Methods: In this study, emissions and consumer behaviour were assessed for two variants of glo™ THPs: an extensively tested glo™ type 1 (glo 2.0), and glo™ type 3 (glo hyper) in base and boost modes. Emissions testing was conducted by measuring the percentage reduction of TobReg9 toxicants, relative to a 1R6F reference cigarette.
Results: Consumer behaviour, including puffing topography, average daily consumption (ADC) and mouth level exposure (MLE) to NFDPM and nicotine was measured among 63 regular glo™ users in Tokyo, Japan. Emissions testing showed a substantial reduction in TobReg9 toxicants compared to the reference cigarette (95.5-97.3%), whilst there were no substantial differences in the ADC, puffing behaviour or MLE among the three THPs.
Conclusions: Emissions analysis based on TobReg9 toxicants and consumer behaviour data provide evidence that the glo™ type 3 is comparable to glo™ type 1, indicating the possibility of using a bridging approach for the analysis of variant THPs based on use behaviour alone.

Keywords: THPs, glo™, User behaviour, Puffing topography, ADC, MLE, Emissions, Bridging

INTRODUCTION

Smoking is one of the leading causes of preventable death worldwide and a major risk factor in the development of cancer, cardiovascular disease, and pulmonary diseases.[1] However, the past 15 years have seen the commercialisation of a number of alternative nicotine products, such as electronic cigarettes, THPs and nicotine pouches, that have the potential to reduce the risk from cigarette smoking.[2,3]

THPs are electronic devices that heat, rather than burn, the tobacco stick, with temperatures typically lower than 350°C. The lack of combustion results in a simpler aerosol that has significantly fewer toxicants and reduced cytotoxicity relative to cigarette smoke, but still contains nicotine.[4-10] Smokers using THPs show reduced exposure to tobacco toxicants in both short-term (5-day) and mid-term (180 days) switching studies, and starting to show promise for health effects (improvement in respiratory symptoms, exercise tolerance, quality of life, and reduction in rate of disease exacerbations) in longer term (3-year) studies among smokers affected with COPD.[11-13]

To establish the reduced risk potential of novel tobacco and nicotine products, Murphy et al proposed a multi-

disciplinary assessment framework, comprising pre-clinical, clinical and population studies.[14] Berman et al, 2015, and Smith et al, 2016, have also proposed a similar approach.[15,16] Furthermore, Goodall et al, 2022, outlined how a comprehensive scientific weight of evidence evaluation of the risk profile allows the substantiation of any health-related claims, and the reduced-risk potential, when compared to a combustible cigarette (Figure 1).[17] The first commercially available THP system from British American Tobacco (BAT), glo™, was evaluated in alignment with this framework, which showed that this THP has potential for reduced health risks relative to cigarette smoking.[2]

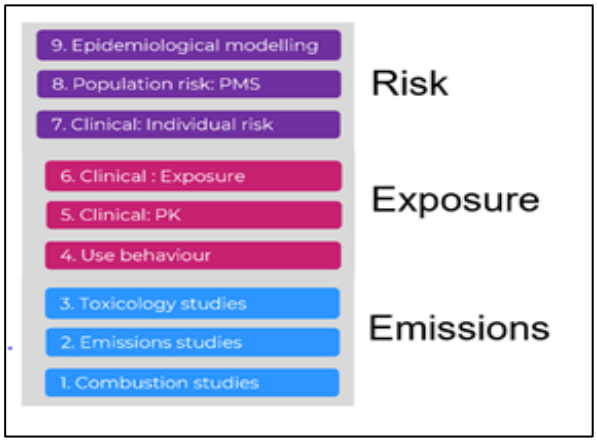

Figure 1: A risk assessment framework outlining a weight, evidence approach to assess reduced emissions exposure and risk of alternative nicotine products such as THPs when compared to conventional cigarettes.*

PK: pharmacokinetic assessment, PMS: post market surveillance. Modified schematic adapted from Goodall et al.[17]

Since the first evaluation studies, glo™ THP has evolved with both "minor" changes in device materials and external appearance, and more recently "major" changes in the type of heating mechanism, heating profile and consumable format (Table 1). To verify that such innovations have not affected the original evaluation of the THP, a "bridging" strategy was proposed, whereby a subset of data can be used to confirm that the modified ("variant") product is equivalent to the original product.[14,17,18]

Bridging or read-across of partial data sets is well established in other industries to support product innovation, acceptance of natural product variation and informs efficient regulatory approvals.[18,19] This can be applied for THPs, if the principal of heat-not-burn is maintained and there is lack of tobacco combustion. A bridging data set covering emissions and exposure for a new THP variant could be used to demonstrate similarity to an original or established THP. The variant product should have a similar emissions yield and exposure profile to meet the criteria of equivalence.[20] An initial study comparing the original THP and variant THPs has demonstrated the equivalence of the products in terms of emissions and cytotoxicity, thereby supporting the feasibility of a bridging approach.[17,21]

Puffing topography and MLE studies play a key part in determining whether consumers use the product in a manner that reduces their individual exposure or health risk when compared to a conventional cigarette.[22,23] These studies provide a key insight into how consumers use the product, such as number of puffs taken, puff volume, puff duration, inter-puff interval, MLE to nicotine-free dry particulate matter (NFDPM) and nicotine and ADC, and therefore, will be a component in the dataset provided to bridge different variants of a given THP. A puffing topography and MLE study was previously conducted as part of the fundamental dataset for the original glo™ type 1 THP (Japan, 2018).[22]

In the present study, we have measured the puffing topography, MLE, ADC and emissions of TobReg9 toxicants (from the WHO study group on tobacco product regulation) between glo™ type 1 (glo™ 2.0) and glo™ type 3 (glo™ hyper), in order to assess whether a bridging approach can be applied to these THPs.[17,24]

METHODS

Study products

The glo™ THP (BAT, London, UK) is made up of two components: a cylindrical shaped tobacco consumable and an electronic heating device into which the consumable is inserted before use. The heating device comprises a rechargeable battery, an electrical element that heats the consumable, and electronic hardware that controls the warming up, heating temperature and heating period of the device. Two commercially available glo™ devices (Figure 2), in combination with two types of consumables and two heating profiles (Table 1), were used in this study. Product 1 is a type 1 glo™ product and consisted of the glo™ 2.0 device, which uses resistive heating, and a king size super slim tobacco stick ("neo stick", BAT). Products 2 and 3 are both type 3 glo™ products and consisted of the glo™ hyper device, which uses induction heating with a choice of standard (base) and boost heating modes, and a demi-slim neo stick. In this study, product 2 was locked to operate only in standard mode and product 3 to operate only in boost mode.

Figure 2: Neo sticks, glo™ type 1 device and glo™ type 3 device.

Table 1: Product and consumable information.

Products	Device	Heating mechanism	Heating profile	Consumable name	Format (tobacco weight)	Flavour
1[a]	glo™2.0 (Type 1)	Resistive	Standard[b]	Neo JP Fresh Plus	KSSS (280 mg)	Menthol
2	glo™ hyper (Type 3)	Induction	Base[c]	Neo JP Terracotta Tobacco	DS (340 mg)	Tobacco
3	glo™ hyper (Type 3)	Induction	Boost[d]	Neo JP Terracotta Tobacco	DS (340 mg)	Tobacco

KSSS, king size super slim; DS, demi-slim. a-Contained menthol capsule within the filter, in addition to menthol flavourings within the tobacco stick; b-45 seconds to first puff, 3.5-minute heating session at 240°C; c-20 seconds to first puff, 4-minute heating session at 250°C; d-15 seconds to first puff, 3-minute heating session at 260°C.

Emissions analysis

Emissions analysis was conducted by Labstat, Kitchener, ON, Canada (SH1318-H) to determine the concentration of key analytes in the glo™ aerosol and the percentage reduction of TobReg9 toxicants, relative to smoke from a certified 1R6F reference cigarette [Center for tobacco reference products, university of Kentucky, Lexington, KY, USA].

Before testing, all neo sticks and reference cigarettes were environmentally conditioned as specified in ISO 3402.[25]

THP aerosol was generated using a modified Health Canada intense (m-HCI) machine-puffing regime of puff volume 55±0.5 ml, puff duration 2.0±0.1 s, puff interval 30±1 s, bell-shaped profile and 0% blocking of the perforations.[26] Ten puffs were taken per consumable for product 1, nine puffs per consumable for product 2 and eight puffs per consumable for Product 3, to reflect differences in heating times of the device (Table 1).

1R6F reference cigarette was machine-smoked using HCI regime, without modification. glo™ aerosol and cigarette smoke were collected by certified and established methods set out in accordance with international organization for standardization ISO 3308:12.

Topography study

Participants

The randomised controlled, open-label crossover puffing topography and MLE study was conducted in Tokyo, Japan, in 2021 to 2022. Sixty-four regular glo™ users were recruited by an independent market research agency (Kantar, Japan) in accordance with the international code on market opinion and social research and data analytics.[27] Potential participants were selected based on their nicotine product use history, a review of their self-reported glo™ use status and history, and their general eligibility check. The inclusion criteria were age 21-64 years, regular glo™ user for at least 6 months, using a minimum of five neo sticks or conventional cigarettes per day and willing to use both mentholated and non-mentholated products. Due to the coronavirus pandemic, participants were also required to have had at least two COVID-19 vaccinations, to lower the risk of participants contracting COVID-19. Women who were pregnant or breastfeeding, individuals with a pacemaker or other imbedded electronic medical devices and those trying to quit or planning to quit during the course of the study were excluded.

All participants read and signed an informed consent form (ICF) prior to enrolment and were each given a unique volunteer ID code to identify them throughout the study. They were informed that they were able to withdraw from the study at any time and received pro-rata remuneration for their involvement in the study. The study protocol and ICF were approved by an independent ethics committee (IEC) in accordance with the ethical principles outlined in the declaration of Helsinki and other relevant guidelines.

Protocol

Following screening the recruited participants were randomised and provided with the first test product, including the device and a one-week supply of the associated consumable (equivalent to 120% of their self-declared consumption at recruitment), and a daily consumption diary. Participants were instructed to use the allocated product instead of their normal product at home for 5-7 consecutive days and to record the number of neo sticks used per day (and any other nicotine or tobacco products used) in the daily consumption diary.

After each home placement, participants attended a central location facility, where they used the same product in two sessions separated by a 20-minute interval. They were asked to abstain from nicotine or tobacco use for 1-hour prior to participating in the product session. In each session, participants used the product, as they would normally, through a puffing analyser device (SA7), comprising a unique product holder and a data acquisition transmission (DAT) unit, which measured their puffing topography.[22,23,28] A disposable plastic mouthpiece was attached to the product

holder at the beginning of each session (to avoid cross-contamination between participants). During the 20-minute interval between sessions, participants completed a sensory questionnaire on draw effort, intensity, aerosol delivery, amount of aerosol filling the mouth, irritation and taste. These attributes were scored on a magnitude scale ranging from 1 (low) to 5 (high).

After completing the two puffing topography sessions, participants were given their next allocated study product according to the randomisation procedure, to use at home for the following 5-7 days, before returning to the central location facility for further puffing topography measurements. This process was repeated until all participants had used all three products.

When using product 1, which contained a menthol capsule in addition to menthol flavourings within the neo stick, participants were given the option to crush the capsule for the duration of the home placement. If participants reported crushing the capsule during the home placement, then the capsule was crushed during both puffing topography measurements.

Puffing topography measurements

Puffing topography measurements, including number of puffs taken, puff volume, puff duration, inter-puff interval, session duration, pressure drop, effort and optical obscuration of aerosol, were recorded using the SA7 desktop puffing analyser device (Figure 3). The SA7 was originally developed to measure smoking topography, and subsequently modified for use with products containing higher levels of humectants, such as e-cigarettes and THPs.[22,23,28,29] It comprises of a product holder attached to a data acquisition transmission unit. Two tubes on either side of a 2 mm diameter orifice within the product holder detect the change in pressure during puffing, which is proportional to flow rate squared.[28]

Figure 3: Image of glo™ attached to SA7 topography device.

Mouth level exposure

MLE to nicotine-free dry particulate matter (NFDPM) and nicotine were estimated using the optical obscuration methodology as described previously.[22,23,28] In brief, an LED within the SA7 product holder measures the amount of light obscured by the aerosol as it passes through the holder during puffing. The extent of the obscuration is correlated against the mainstream NFDPM yield generated for each product from a series of 13 pre-set machine puffing regimes using a PM1 smoking machine (Borgwaldt KC, Hamburg, Germany). Total particulate matter (TPM) generated from the THP aerosol for each puffing regime was captured on a 44mm Cambridge filter pad. The amount of water and nicotine in the TPM was determined by GC as previously described and subsequently used to calculate weight of NFDPM generated by each puffing regime (NFDPM=TPM-nicotine-water).[23] The NFDPM weights were then used to determine the most appropriate calculation factors to estimate "optical NFDPM" when the products were used by participants.[28] MLE to nicotine was estimated based on the relationship to NFDPM, generated from calibration graphs, using optical NFDPM in place of actual NFDPM. Mean MLE and ADC, based on participant's daily consumption diary were used to calculate mean MLE per day.

Data analysis

Emissions data for the three study products were analysed and reported as a percentage reduction relative to the 1R6F reference cigarette. For each TobReg9 toxicant, the percentage reduction was calculated from the mean stick value as follows:

$$\%\ Reduction = 100 - \left(\frac{THP}{1R6F}\right) * 100$$

Where toxicants were reported as below detection level (BDL), the mean was reported as half of the level of detection (LOD). Where toxicants were reported as not quantifiable (NQ) the mean was reported as the midpoint between the LOD and level of quantification (LOQ).

A linear mixed model ANOVA (Proc Mixed) was used to analyse for differences in puffing topography, ADC, MLE and sensory perception responses among the three study products. Where a significant difference was found ($p<0.05$) between mean values, a Tukey's post-hoc test was used to identify the source of the difference. Records/data relating to participants who did not produce a complete data set were excluded from the statistical analysis, resulting in a total of 63 out of 64 participants being included. All statistical analyses were carried out using SAS v. 9.4 statistical analysis software.

RESULTS

Emissions data

To assess the possibility of using bridging data to establish the equivalence of an updated THP to the original tested product, we first analysed emissions of the

TobReg9 toxicants among the three study products in relation to a 1R6F reference cigarette.[17] In this study, product 1 is a type 1 glo™ product, on which a large set of safety and regulatory data has been amassed.[2,17] In products 2 and 3, both type 3 products, the glo™ device has been updated with "major" changes to the heating mechanism, heating profile and the neo stick format.

TobReg9 toxicants were significantly reduced in all three products relative to the reference cigarette (85.03-99.98% reduction), whilst there was almost no difference among the three products in the percentage reduction of 1,3-butadiene, acrolein, benzene and CO, with a reduction of close to 100% (Table 2). Some small changes in the percentage reductions of acetaldehyde, benzo(a)pyrene, formaldehyde, NNN and NNK were observed, which is likely due to the increase in tobacco weight for the neo sticks used for products 2 and 3 (demi-slim, 340 mg) in comparison to the neo sticks used for product 1 (king size super-slim, 280 mg). However, no differences were observed in overall TobReg9 reductions across products.

Table 2: Percent reduction in TobReg9 toxicants in THP aerosol relative to cigarette smoke[a].

TobReg9 toxicant	Product 1	Product 2	Product 3
1,3-Butadiene	99.98	99.93	99.93
Acetaldehyde	93.89	91.80	90.87
Acrolein	98.78	98.22	97.88
Benzene	99.92	99.87	99.87
Benzo(a)pyrene	98.23	96.63	98.23
CO	99.45	99.45	99.39
Formaldehyde	96.86	95.47	94.82
NNK	97.55	93.19	94.76
NNN	91.23	85.03	87.67
Overall reduction	97.32	95.51	95.94

a-Percent reduction (%) compared to 1R6F reference cigarette. Machine smoked using a modified health Canada intense (m-HCI) puffing regime of volume 55±0.5 ml, duration 2.0±0.1 s, interval 30±1 s, bell-shaped profile and 0% blocking of the perforations. Ten puffs taken per consumable for product 1, nine puffs per consumable for product 2 and eight puffs per consumable for product 3.

Table 3: Comparison of other aerosol constituents among the study products[a].

Smoke constituent	Product 1	Product 2	Product 3
NO [µg/100cm^3]	2.08	3.23	2.15
NOx [µg/ 100cm^3]	2.32	3.57	2.38
Nicotine [mg/stick]	0.57	0.81	0.81
NFDPM [mg/stick]	12.6	17.6	18.0
TPM [mg/stick]	28.7	40.1	40.6

a-Machine smoked using a modified health Canada intense (m-HCI) puffing regime of volume 55±0.5 ml, duration 2.0±0.1 s, interval 30±1 s, bell-shaped profile and 0% blocking of the perforations. Ten puffs taken per consumable for product 1, nine puffs per consumable for product 2 and eight puffs per consumable for product 3.

Similarly, there were differences in the content of other aerosol constituents (NO, NO_x, NFDPM, Nicotine and TPM), whereby these constituents were higher in products 2 and 3 compared with product 1 (Table 3), due to the difference in the tobacco weight of the KSSS and DS consumables. The British standardisation institute (BSI) suggest that for a product to be accepted as a THP it should have emissions levels of NO less than 4 µg per 100 cm^3 and NO_x less than 5 µg per 100 cm^3 under standard analytical testing conditions.[4] We have shown that NO and NO_x for the type 1 and Type 3 glo™ fall within this acceptance criteria.

Topography data

Study participants

In total 64 participants were recruited for the puffing topography study. Of these, 63 (98%) completed all puffing topography measurements, daily consumption diaries and sensory questionnaires, and were included in the analyses. Among the participants, 44 (69.8%) were male, 19 (30.2%) were female and the age range was 21-64 years. When using Product 1, 38 participants (60.3%) crushed the menthol capsule and 20 (31.7%) did not crush the capsule. The capsule status (crushed/not crushed) was undetermined for the remaining 5 participants. No significant differences were observed in any of the reported puffing topography, ADC or MLE attributes between those that crushed the capsule compared to those that did not crush the capsule, and therefore this data is not displayed.

Puffing topography

The mean and standard deviation of the puffing topography attributes, including number of puffs, puff volume, puff duration, inter-puff interval, session

duration, pressure drop, and effort expended, are summarised in Table 4. Overall, larger puff volumes were taken for products 2 and 3 compared with product 1 (68.8-80.8 vs 56.7 ml), while the pressure drop experienced by the user during puffing was lower for products 2 and 3 compared with product 1 (11.3-12.1 vs 19.1 cmWG). Similarly, the effort expended into puffing was lower for products 2 and 3 compared with product 1 (288-328 vs 554 cmWGs). These differences may be attributed to the difference in consumable format, whereby the smaller diameter KSSS consumable used with product 1 results in a higher open pressure drop relative to the DS consumable used with products 2 and 3 (70 vs 45 mmWG at constant flow of 17.5 ml/s), and may therefore restrict the range of flow rates, and hence puff volumes, that may be taken when using product 1.

More puffs were taken when using product 2 (20.6 puffs), compared with product 1 (17.5 puffs) and product 3 (17.0 puffs), while the session duration was longest when using product 2 (179 s) compared with product 3 (146 s). These observations are consistent with the differences in the tobacco heating time of the device, (which was 4 min for product 2, 3.5 min for product 1 and 3 min for product 3).

ADC and MLE

The mean and standard deviation of the ADC and MLE to NFDPM and nicotine (per stick and per day) are tabulated (Table 5).

Although the ADC among the three products was found to be significantly higher for products 1 and 3 compared to product 2 (10.0-10.2 vs 9.6 sticks per day), this difference is less than half a neo stick and is therefore not a meaningful difference.

MLE to NFDPM per stick and per day was higher when using products 2 and 3 compared to product 1 (18.8-19.9 vs 12.5 mg per stick and 207-208 vs 132 mg per day). Similarly, MLE to nicotine per stick and per day was higher

for products 2 and 3 compared to product 1 (1.53-1.68 vs 0.81 mg per stick and 17.2-17.5 vs 8.6 mg per day). Observed differences in MLE reflect differences in NFDPM and nicotine yields generated under standard machine puffing conditions of volume 55 ml, duration 2.0s, and frequency 30s with bell-shape profile (Table 3).

Table 4: Comparison of puffing topography attributes among the three study products. Mean±SD and Tukey's ranking[a], (n=63).

Parameters	Product 1		Product 2		Product 3	
	Mean±SD	Tukey's ranking	Mean±SD	Tukey's ranking	Mean±SD	Tukey's ranking
Puff number	17.5±6.9	A	20.6±9.6	A	17.0±7.1	B
Puff volume (ml)	56.7±24.3	B	80.8±67.5	A	68.8±33.6	A
Puff duration (s)	1.89±1.00	A	1.80±1.03	AB	1.59±0.65	B
Inter-Puff Interval (s)	8.9±3.8	A	8.9±4.4	A	8.6±3.8	A
Session duration (s)	163±57	B	179±68	A	146±45	C
Pressure drop (cmWG)	19.1±7.7	A	11.3±6.0	B	12.1±6.0	B
Effort (cmWGs)	554±291	A	328±209	B	288±176	B

a-Analysed using a linear mixed model ANOVA (Proc Mixed), followed by Tukey's post-hoc test. For a given parameter, values sharing the same alphabet letter are not significantly different ($p>0.05$); values not sharing the same alphabet letter are significantly different ($p<0.05$). Values are the mean from 63 participants, with two measurements per participant (averaged).

Table 5: Comparison of ADC and MLE (per stick and per day) among the three study products. Mean±SD and Tukey's ranking[a], (n=63).

Parameters	Product 1		Product 2		Product 3	
	Mean (±SD)	Tukey's ranking	Mean (±SD)	Tukey's ranking	Mean (±SD)	Tukey's ranking
ADC (sticks per day)	10.0±4.5	A	9.6±4.9	B	10.2±4.9	A
MLE						
NFDPM (mg/stick)	12.5±5.8	B	19.9±11.9	A	18.8±9.0	A
NFDPM (mg/day)	132.0±90.5	B	208.4±183.6	A	207±162.1	A
Nicotine (mg/stick)	0.81±0.41	B	1.68±1.12	A	1.53±0.86	A
Nicotine (mg/day)	8.59±6.0	B	17.54±16.2	A	17.15±14.47	A

a-Analysed using a linear mixed model ANOVA (Proc Mixed), followed by Tukey's post-hoc test. For a given parameter, values sharing the same alphabet letter are not significantly different ($p>0.05$); values not sharing the same alphabet letter are significantly different ($p<0.05$). Values are the mean from 63 participants, with two measurements per participant (averaged).

Table 6: Comparison of the sensory perception responses. Mean±SD and Tukey's Ranking[a]., (n=63).

Sensory aspect	Product 1		Product 2		Product 3	
	Mean (±SD)	Tukey's ranking	Mean (±SD)	Tukey's ranking	Mean (±SD)	Tukey's ranking
Draw effort	2.1±1.0	A	2.7±1.2	A	2.8±1.3	A
Aerosol delivery	2.8±0.8	A	3.1±0.9	A	3.1±1.0	A
Impact	2.8±1.0	A	3.5±1.1	A	3.6±1.1	A
Irritation	2.6±1.2	A	3.2±1.3	A	3.4±1.3	A
Mouth drying	2.8±1.0	A	3.3±1.3	A	3.5±1.1	A
Mouthful	2.8±0.8	A	3.2±0.9	A	3.1±1.1	A
Natural taste	2.8±1.2	A	2.9±1.1	A	2.6±1.1	A
Pleasantness of taste	4.1±0.9	A	3.3±1.2	A	3.1±1.2	A
Strength of aftertaste	3.3±1.1	A	3.3±1.1	A	3.4±1.1	A
Taste amount	3.3±0.8	A	3.4±1.0	A	3.6±1.0	A

a-Analysed using a linear mixed model ANOVA (Proc Mixed), followed by Tukey's post-hoc test. For a given parameter, values sharing the same alphabet letter are not significantly different ($p>0.05$); values not sharing the same alphabet letter are significantly different ($p<0.05$). Values are the mean score from 63 participants, with 1 measure per participant (recorded between puffing topography sessions 1 and 2).

Sensory questionnaire

Between the two puffing topography sessions, participants were asked to rate their perception of different sensory aspects of the products, such as draw effort, aerosol delivery and taste, among others, on a magnitude scale of 1 (low) to 5 (high). The scores for all aspects ranged from 2.1 to 4.1. Apart from pleasantness of taste, which was higher for menthol flavoured product 1, mean sensory scores marginally higher for products 2 and 3; however, differences were not significant (Table 6).

DISCUSSION

The present study has explored the feasibility of a bridging approach to evaluate glo™ type 3 (glo™ hyper) in relation to glo™ type 1 (glo™ 2.0). Regarding the emissions data, the overall reduction in the content of TobReg9 toxicants in the THP aerosol relative to smoke from the reference cigarette was similar between the glo™ type 1 (Product 1, 97.3%) and the two variants of glo™ type 3 (Products 2 and 3, 95.5% and 96.0%, respectively), in support of a bridging approach. These values are very similar to the overall average reduction of 97.1% in TobReg9 toxicants noted for the original glo™ type 1, suggesting the equivalence of the THPs.[4] A recent *in vitro* study on the feasibility of bridging also found comparable chemical reductions (94–97%) among glo™ type 1 and five variants.[21] Notably, the variants in that study had minor changes in aesthetics and tobacco flavour in contrast to the major changes between glo™ type 1 and glo™ type 3 in the present study, indicating that fairly substantial adaptations may be made to the device while maintaining equivalence.

Regarding puffing topography, there was a range in puff volume (56.7-80.8 ml) reported for the three products in the present study, compared to 60.9-66.7 ml in the original puffing topography study of glo™ type 1 (Japan, 2018).[22] The puff duration was fairly consistent among the three products (1.59-1.89 s) and similar to the original study (1.80 s).

At 9.6-10.2 sticks/day, the ADC of the THPs used in this study was similar to that reported in the original study (8.6-11.2 sticks/day), but significantly lower than a recent clinical study of biomarkers of potential harm, which reported an average ADC of 22 sticks/day among smokers switching to exclusive use of a similar type 1 glo™ product.[12,22] MLE to nicotine was 0.3 mg/stick in the original study, as compared with 0.81-1.68 in the present study.[22] Similarly, MLE to NFDPM was 5.0-5.2 mg/stick in the original study, as compared with 12.5-19.9 mg/stick in this study.[22] The higher MLE to NFDPM and nicotine observed in the present study is likely due to larger numbers of puffs taken (17.0-20.6 puffs), compared with the original study (10.9-12.3 puffs).

Despite this, the MLE to NFDPM observed in this study is similar to the NFDPM yield generated under standard machine puffing conditions of volume 55 mL, duration 2.0 s, and frequency 30 s with a bell-shape profile (12.6-18.0 mg/stick, Table 3), suggesting that this machine puffing regime is broadly representative of human behaviour and that the percentage reduction in TobReg9 toxicants (Table 2) is relevant to actual human use.

The studies on the original glo™ type 1 (Product 1) discussed here have shown a strong consistency in the large differences between this THP and that of conventional cigarettes for chemical emissions, biological activity in toxicological tests and long-term toxicant exposure in clinical studies.[4,12] The glo™ aerosol emissions were similar among the three products despite 'major' changes in device and consumable design, including increased operating temperature, change of heating mechanism, consumable blend, flavour changes and increased tobacco weight. The similarity between the

findings of glo™ type 1 and 3 suggests that if the toxicant emissions (compared to reference cigarette) is within the range established in this study, then it is possible to inform consumer behaviour.

The amount of data required to bridge between product versions will depend on the change made to the new products compared to the original type 1 glo™ product. A minimal change that does not impact on the pathway or process of aerosol formation, such as a change in material to the external surfaces of the device, should not require additional data. Substantial modifications that may require additional data collection include changes in heating profile that cause temperatures greater than those set for non-combustion; the use of a novel tobacco substrate with properties that could change the toxicant profile; and the use of technologies that might increase nicotine delivery to levels above those delivered by a cigarette. The data required in these cases to see if bridging to the original foundational data set is possible would include consumer behavioural studies and analytical chemical studies in the first instance, supported by robust toxicological risk assessments of THP materials and ingredients.[34] If the data values produced on the new variant was outside of the range of data collected for the original THP variant, discussed in this paper, then further studies, including additional toxicological testing and clinical studies may be required.

However, this general observation should be qualified. It assumes that any new features of subsequent versions of the device or the consumable are unlikely to affect consumption behaviour and that these changes do not affect toxicant profile of the THP system. In this study, emissions testing indicates that the percentage reductions in the selected toxicants versus the reference combustible cigarette are maintained. Data presented demonstrated the similarity of aerosol composition across the glo™ products tested. This is further supported by little to no change in puffing behaviour and ADC (sticks/day) despite higher NFDPM and nicotine exposure.

A recent long-term 180-day ambulatory clinical study, using a similar type 1 glo™ product to that used in the present study, reported an average ADC of 22 sticks per day.[12] This is 120% higher than the ADC observed in the present study for the type 1 glo™ product (10 sticks per day), and can be used as a threshold for equivalence. In the present study, the MLE for the type 3 glo™ (Table 5) was approximately 58% higher for NFDPM and 104% higher for nicotine, compared to the type 1 glo™ product. The increase in NFDPM and nicotine for the Type 3 glo™ compared to the type 1 glo™ are below the 120% threshold for equivalence based on the clinical study and are therefore bridgeable.

Limitations

The glo™ consumables for the emissions and topography study differed slightly, where the consumables used for the emissions data had no capsule. Previous studies suggest that the presence of a capsule has no impact on the TobReg9 emissions. There were no other differences between consumables used for emissions and topography.

CONCLUSION

The similarities between the reference and product variants' emissions and consumer behaviour data suggest that the toxicant profile and use behaviour were similar between glo™ type 1 (glo 2.0), and a glo™ type 3 (glo hyper). ADC for all glo™ products are significantly lower than previously seen in the 180-day clinical study. The change in the type of THP device heating mechanism (resistive vs inductive), heating modes (base vs boost) and change in consumable format (KSSS to DS) across the product variants tested are deemed 'bridgeable' to the original glo™ type 1 product.

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