REVIEW PAPER

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NEW IDEAS, OLD PROBLEMS? HEATED TOBACCO PRODUCTS – A SYSTEMATIC REVIEW

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Abstract
Heated tobacco products (HTPs) are a form of nicotine delivery intended to provide an alternative to traditional cigarettes. The aim of this systematic review was to present the current state of knowledge on HTPs with an emphasis on the potential impact of HTP use on human health. During the preparation of this systematic review, the literature on HTPs available within Medline/PubMed, EMBASE, CINAHL, ScienceDirect, and Google Scholar was retrieved and examined. In the final review, 97 research papers were included. The authors specifically assessed the construction and operation of HTPs, as well as the chemical composition of HTP tobacco sticks and the generated aerosol, based on evidence from experimental animal and cellular studies, and human-based studies. Heated tobacco products were found to generate lower concentrations of chemical compounds compared to traditional cigarettes, except for water, propylene glycol, glycerol, and acetol. The nicotine levels delivered to the aerosol by HTPs were 70–80% as those of conventional combustion. The results of *in vitro* and *in vivo* assessments of HTP aerosols revealed reduced toxicity, but these were mainly based on studies sponsored by the tobacco industry. Independent human-based studies indicated that there was a potentially harmful impact of the active and passive HTP smoking on human health. Currently, a large body of knowledge on HTP exposures and health effects is provided by the tobacco industry (52% of identified studies). Based on the available evidence, HTPs produce lower levels of toxic chemicals, compared to conventional cigarettes, but they are still not risk-free. Int J Occup Med Environ Health. 2019;32(5):595–634

Key words:
smoking, systematic review, nicotine, tobacco industry, heat-not-burn tobacco products, heated tobacco products

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INTRODUCTION

Heated tobacco products (HTPs) are a form of nicotine delivery intended to provide an alternative to traditional cigarettes. These products were introduced for the first time in 1988, in the USA, as "Premier" from R.J. Reynolds [1]. As in the case of electronic cigarettes, this technology initially did not gain wide popularity and was discontinued shortly after its introduction. Recently, the tobacco industry has made another attempt to introduce HTPs to the market [2–6]. In 2014, a heated tobacco system from Philip Morris International (PMI), marketed as IQOS (I-Quit-Ordinary-Smoking), was introduced [3–6]. Other tobacco companies introduced their own HTPs in 2016. British American Tobacco (BAT) created an HTP called "glo" [6], while a heated tobacco and e-cigarette hybrid was developed by Japan Tobacco (JT) and marketed as "Ploom TECH" [6].

The heated tobacco smoking technology is based on a unique electronic method of heating to generate aerosols from tobacco sticks. Tobacco heating systems operate at lower temperatures (240–350°C) than conventional cigarettes (> 600°C) [7].

The IQOS tobacco heating system includes a "pen-shaped" electronically controlled heating element (holder) and a portable charger for recharging the holder [4,8]. The IQOS uses a metal blade to penetrate tobacco sticks (called "HEETS"), thus heating tobacco from inside the stick up to 350°C [8,9]. The heating holder supplies heat for 6 min and allows up to 14 puffs. After this time, the holder needs to be recharged [8]. Glo operates in a similar manner [9]. The device looks like a small simple box with an oval socket in the periphery on top, where the tobacco stick is placed. After pressing the button in the middle of the device, the tobacco stick (called "Kent Neostiks") is heated to 240°C through a metal heating element surrounding the tobacco stick [10,11]. A single charge lasts for up to 30 smoking sessions [11].

A slightly different heating technology is implemented by Ploom TECH [6,12]. In this case, the nicotine-containing aerosol is generated by heating an inhalation solution (containing propylene glycol or glycerol) which passes through a capsule made of granulated tobacco leaves [12,13].

Tobacco companies claim that HTPs are less harmful than traditional cigarettes [14–18]. However, the potential impact of HTP use on human health has not been fully investigated yet.

The prevalence of HTP use has been increasing, especially in highly developed countries such as Japan and Italy [2,3,5,6]. Based on the growth of the e-cigarette market in recent years, it is expected that the popularity of HTPs will continue to increase rapidly.

The aim of this systematic review is to examine the current state of knowledge on heated tobacco products. As a part of this process, the authors will:

- review the chemical composition of HTP tobacco sticks;
- review the chemical composition of the aerosol generated during HTP use;
- review evidence from experimental studies on animal and cellular models;
- review evidence from human-based studies;
- describe the prevalence of HTP use. In addition, they will also assess the marketing strategies of the tobacco industry as a way of considering the potential burden of the problem.

MATERIAL AND METHODS

The authors conducted a systematic review to complete the objectives outlined above. The search was carried out in Medline/PubMed, EMBASE, CINAHL, ScienceDirect, and Google Scholar. Combinations of the following key words: "IQOS," "glo," "Ploom TECH," "heat-not-burn," "heated tobacco," "novel tobacco products," with "aerosol," "chemical composition," "cells," "nicotine," "safety," "health effects," "toxicity," "secondhand exposure," "addiction," "frequency of use," "marketing" and "safety" were used. Potentially relevant articles were selected based on their titles and abstracts. If an article was considered potentially relevant, the full paper

was printed for review. Reference lists from the selected articles were checked for publications that may have been missed in the initial search. Manufacturer websites regarding data about the mode of use and all registration details were also reviewed. Finally, websites of leading health organizations were reviewed to identify their positions on HTPs. The final search was conducted on December 31, 2018.

Articles were eligible to be included in the review if they were original, peer-reviewed articles, published in English. There was no limit regarding the time that had passed since publication other than the final date being December 31, 2018. Review and personal opinion papers were excluded. Papers that focused on other forms of smoking, such as electronic cigarettes, smokeless tobacco such as chewing tobacco or snus, shisha, and hookah, were also excluded. The tobacco industry is also working on a new form of HTPs called carbon heated tobacco products (CHTPs) [19]. Due to the different mode of operation, the early phase of the products (no general product sales), and the limited amount of research related to these products, they were not analyzed in detail in this review. Nevertheless, carbon-covered tobacco products are an alternative form of nicotine delivery and will require close monitoring in the future.

The literature search and selection of articles were performed independently by 2 researchers. A comparison of the search results was made and, where there was a discrepancy, inclusion decisions were based on a consensus following discussion.

The search process that led to the identification of 289 potential articles is summarized in Figure 1. Of these, 138 were

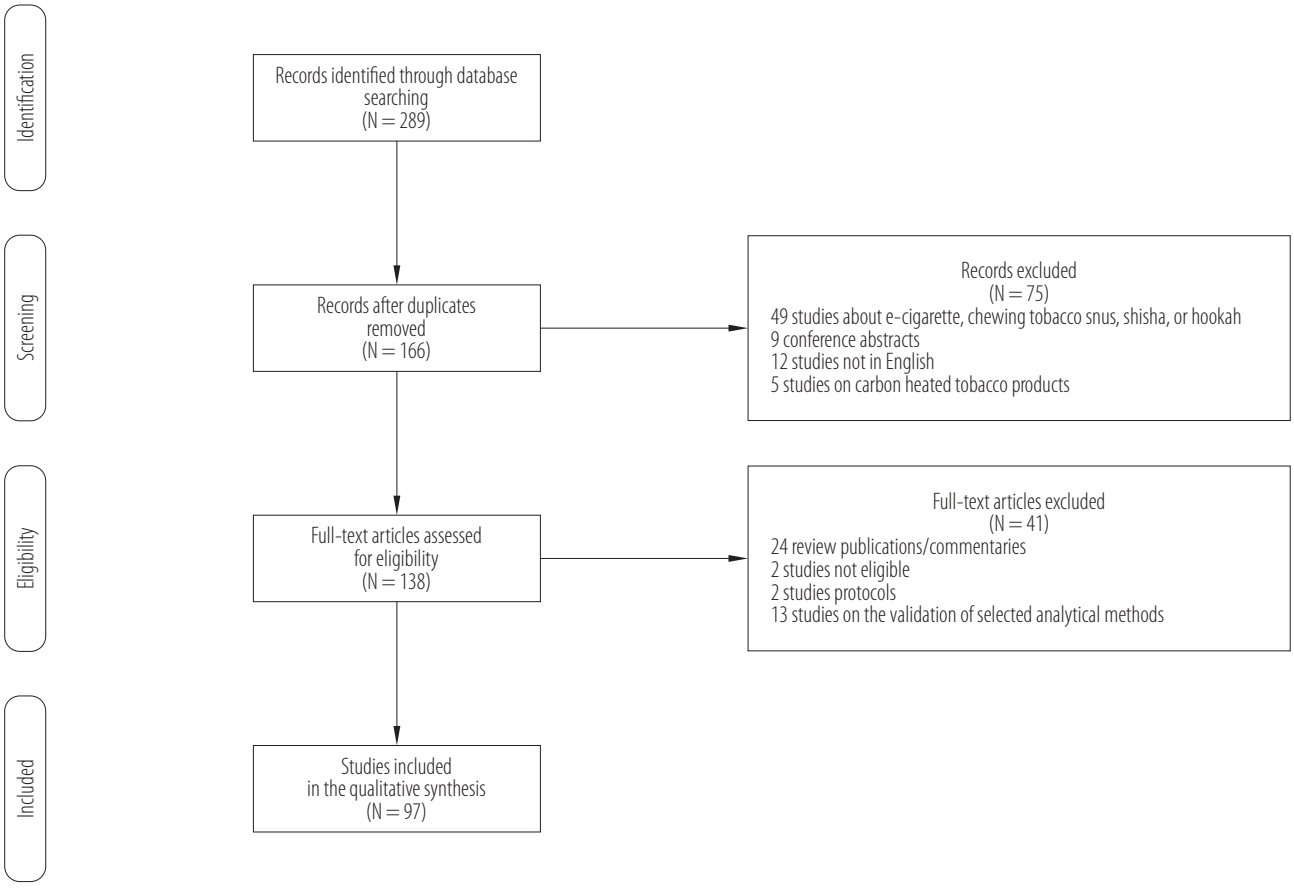

Figure 1. PRISMA Flow Diagram [105]

considered to be relevant after screening the titles and abstracts. After full-article review, 97 papers were considered eligible and included in this review. Review papers, commentaries and opinions as well as studies on the validation of selected analytical methods were excluded from the final analysis.

For each paper, the funding source and authors' conflict of interest declarations were analyzed. In this review, of the 97 identified papers, 50 (52%) had a potential conflict of interest. The presence of a conflict of interest in all papers regarding the toxicity of HTP aerosols may indicate a potential risk of bias. To help assess this phenomenon, tobacco industry sponsored papers were separated from independent studies and visibly marked in this review. The authors also completed a brief sensitivity analysis summarizing the results of the tobacco company funded studies and independently funded studies separately.

RESULTS

Chemical composition of tobacco sticks

Similar to conventional cigarettes, heated tobacco products use real tobacco. Tobacco sticks are available in multiple flavors [10,20]. Among the multiple HTP tobacco sticks available on the market, only IQOS tobacco sticks were tested in detail [8,9,21]. The chemical composition of HEETS tobacco sticks includes processed tobacco, water, glycerin, guar gum, cellulose fibers, a polymer-film filter, and a cellulose-acetate mouthpiece filter [22]. According to the manufacturer data, the IQOS tobacco stick contains smaller amounts of tobacco compared to conventional cigarettes [20]. Independent studies by Farsalinos et al. [9] and Bekki et al. [21] showed that IQOS sticks contained 70–80% of the nicotine concentration found in conventional cigarettes. Davis et al. evaluated the performance of the IQOS system under various conditions [8]. The use of 1 IQOS stick left a significant amount of debris, fluid, and fragments of cast-leaf in the device holder. Following the manufacturer recommendations, cleaning of the device after each 20 tobacco sticks seems to be crucial to provide proper thermal regulation [8]. Moreover, Davis et al. showed that the heat produced by the device was enough to cause charring of the tobacco plug via pyrolysis and melting of the polymer-film filter [8]. This independent observation is in contrast to the manufacturer's claim that pyrolysis is minimized during IQOS use. Detailed information on the chemical composition of HTP tobacco sticks is presented in Table 1.

Chemical composition of generated aerosol

The tobacco industry claims that during HTP use, emissions of toxic chemicals are reduced due to the lower working temperature of the devices [13–15,23,24]. The results of independent studies suggest that toxic compounds are not completely removed from the HTP aerosol and these products are still not risk-free (Table 1) [7,19,25–35].

Uchiyama et al. compared the chemical composition of the aerosol from all 3 available heated tobacco products: IQOS with 4 different heat sticks, glo with 3 different heat sticks, and Ploom TECH with 3 different tobacco capsules, with smoke generated from 2 different reference cigarettes [7]. Water accounted for 75–85% of the total gaseous and particulate matter generated during IQOS and glo use, compared to 17–27% in the smoke from traditional cigarettes [7]. Heated tobacco products generated fewer chemical compounds compared to traditional cigarettes, except for water, propylene glycol, glycerol, and acetol, where the concentration in mainstream smoke was higher in heated tobacco than in traditional cigarettes [7,27].

Numerous studies, both independent and industry sponsored, have shown that the levels of nicotine contained in the aerosol released by HTPs (both regular and menthol versions) were 70–80% as those of conventional combustion cigarettes [15,27,29,33,36]. Farsalinos et al. reported that HTPs delivered nicotine to the aerosol at levels higher than e-cigarettes [9].

Table 1. Chemical composition of tobacco sticks and smoke generated during HTP use – a systematic review, 2015–2018

Study type and reference	Aim of the study	Study design	Summary
Independent studies			
Davis et al., USA (2018) [8]	to evaluate the performance of the IQOS system under various conditions; to test the effects of cleaning on performance and pyrolysis; and to determine the composition of, and the potential health risk from, the polymer-film filter of IQOS sticks	4 IQOS devices, IQOS sticks (strong menthol); 5 running conditions incorporating 2 different cleaning protocols; a visual and stereomicroscopic inspection of IQOS sticks pre-use and post-use to determine the extent of tobacco plug charring (from pyrolysis) and polymer-film filter melting, and to elucidate the effects of cleaning on charring; unused polymer-film filters were evaluated by gas chromatography-mass spectrometry headspace analysis to determine emissions of potential toxic chemicals during filter heating	– the use of 1 IQOS stick left a significant amount of debris, fluid and fragments of cast-leaf in the device holder – the implementation of manufacturer's cleaning instructions increased charring of the tobacco plug and melting of the polymer-film – the heat produced by the device was enough to cause charring of the tobacco plug via pyrolysis and melting of the polymer-film filter – formaldehyde cyanohydrin was released from the polymer-film filter at 90°C (which is well below the maximum temperature reached during normal usage) – device usage limitations (only operates for 6 min, max 14 puffs) may contribute to decreases in interpuff intervals, potentially increasing the intake of nicotine and other harmful chemicals
Farsalinos et al., Greece (2017) [9]	to measure the nicotine levels delivered during heated tobacco product (IQOS) use, compared to e-cigarettes and conventional cigarettes; to measure the amount of nicotine in unused IQOS sticks (both regular and menthol flavor)	2 types of IQOS sticks (menthol and regular), 3 different types of e-cigarettes (nicotine concentration 20 mg/ml), and commercially available cigarettes; all devices had fully charged batteries; the smoke and aerosols from all products were produced using the Health Canada Intense (HCI) puffing regime (55 mL puff volume, 27.5 mL/s puff flow rate, 2-s puff duration, 30-s interpuff interval); in the case of e-cigarettes and IQOS, the second puffing regime (55 ml puff volume, 13.75 mL/s puff flow rate, 4-s puff and 30-s interpuff interval) was used to assess the results of prolonged puffs on nicotine delivery	– IQOS sticks contained a comparable nicotine concentration to conventional cigarettes – the levels of nicotine delivered to the aerosol by regular and menthol IQOS sticks were comparable: 1.40±0.16 mg/12 puffs and 1.38±0.11 mg/12 puffs, respectively – an HTP delivers nicotine to the aerosol at levels higher (1.40±0.16 mg and 1.38±0.11 mg at 2s) than an e-cigarette (0.46±0.06 mg at 2 s) but lower than a conventional cigarette (1.99±0.20 mg/cigarette)

Table 1. Chemical composition of tobacco sticks and smoke generated during HTP use – a systematic review, 2015–2018 – cont.

Study type and reference	Aim of the study	Study design	Summary
Bekki et al., Japan (2017) [21]	to analyze the concentration levels of basic harmful components [nicotine, tar, carbon monoxide (CO) and tobacco-specific nitrosamines (TSNAs] in the mainstream smoke and IQOS sticks, and to compare their levels with those emitted during the use of conventional combustion cigarettes.	2 conventional combustion cigarettes (3R4F and 1R5F), and 2 IQOS sticks (regular and menthol); 4 samples (3R4F, 1R5F, menthol and regular IQOS sticks), each sample included 3 cigarettes or sticks; smoke and aerosols from all products were produced using the Health Canada Intense puffing regime (55 mL puff volume, 2-s puff duration, 30-s interpuff interval), puff number: 9 times for a cigarette and 11 times for an IQOS stick	– the concentrations of nicotine in IQOS sticks (regular: 15.7 mg/g; menthol: 17.1 mg/g) were almost the same as in conventional combustion cigarettes (3R4F: 19.7 mg/g, 1R5F: 15.9 mg/g) – the nicotine levels in the mainstream smoke of IQOS (regular: 1.1 mg/cig; menthol: 1.2 mg/cig) were lower compared to conventional combustion cigarettes (3R4F: 1.7 mg/cig; 1R5F: 1.0 mg/cig) – during IQOS use, the concentration of tobacco-specific nitrosamines was one-fifth and the concentration of CO was one-hundredth of those of conventional combustion cigarettes – toxic compounds are not completely removed from the mainstream smoke of IQOS
Protano et al., Italy (2016) [25] and (2017) [26]	to evaluate emissions of submicronic particles (SMPs) arising from the "real use" of a conventional cigarette, a hand-rolled cigarette, an e-cigarette, and IQOS, as well as to estimate the dose of SMPs deposited in the respiratory system of individuals (3 months to 21 years of age) exposed to secondhand smoke	4 adult smokers, aged 37–60; a model smoking room 52.7 m2, 3 smoking sessions (1 cigarette or IQOS stick each) with 1-h intervals for each smoking device; doses deposited in the respiratory system of passive smokers were estimated using a multiple-path particle dosimetry model	– both tested non-combustion devices (an e-cigarette and IQOS) emitted submicronic particles – particle emissions from IQOS were higher than from an e-cigarette – during IQOS use, 1-h interval between sessions, particle values were higher, compared to the baseline, during e-cigarette use, 1-h intervals between sessions were sufficient to allow particle decay to reach baseline values – an estimated uptake of passive smokers decreased with age; higher doses were estimated for traditional cigarettes compared to non-combustion devices – after all 3 smoking sessions, dosimetry estimates were 50–110% higher for IQOS than for an e-cigarette
Li et al., China (2018) [27]	– to evaluate the chemical substances emitted during the use of IQOS; – to simulate pyrolysis of IQOS sticks and to make comparisons with conventional cigarette	Tobacco Heating System 2.2 (THS2.2, marketed as IQOS) and the reference cigarettes (3R4F); the total particulate matter, water, tar, nicotine, propylene glycol, glycerin, carbon monoxide, volatile organic compounds, aromatic amines, hydrogen cyanide, ammonia, N-nitrosamines, phenol, and polycyclic aromatic hydrocarbon were analyzed under both the ISO and HCI regimes; THS2.2 and 3 other commercial tobacco	– the nicotine and tar levels emitted during the use of IQOS were almost identical to the reference cigarette (3R4F) – compared to a conventional cigarette, IQOS delivered > 90% fewer harmful and potentially harmful constituents, except for carbonyls, ammonia, and N-nitrosoanabasine, the levels of which were about 50–80% lower – using IQOS released much more water (1541.67% higher under the ISO regime, and 268.08% higher under the HCI regime) than 3R4F – a reduction of harmful constituents results from the lower temperature of HTPs during their use, rather than from the heating stick ingredients

		products were heated in the pyrolyzer; comprehensive gas chromatography-mass spectrometry was used to compare differences in emitted substances	
Pacitto et al., Italy (2018) [20]	– to characterize the emission of IQOS in terms of different aerosol metrics of sub-micron particles in – mainstream smoke; – to evaluate the effect of the IQOS stick flavor on the concentrations and size distributions of particles generated by IQOS; – to characterize the volatility of IQOS-emitted particles using a thermo-conditioning system; – to estimate the particle surface area doses in the human respiratory apparatus by means of a deposition model	measurements of the particle number concentration and distribution in the mainstream aerosol; 4 different IQOS sticks flavors (commercialized with the names "white," "orange," "blue" and "silver"); 4 different puff profiles (a new stick each) in order to include possible differences in the manufacturing of IQOS sticks; each puff profile: 5 puffs; length of 2 s, inter-puff time of 10 s (each test included a total of 20 puffs)	– the particle (including both volatile and non-volatile particles) number concentrations in the mainstream aerosols were $< 1 \times 10^8$ part. cm^{-3}, and lower than those characteristic of traditional cigarettes and e-cigarettes – the volatility analysis showed the high amount of volatile fraction of IQOS-generated particles – the particle number concentration does not statistically decrease at higher sampling temperatures
Farsalinos et al., Greece/USA (2018) [28]	to measure carbonyl emissions from an IQOS in comparison with an e-cigarette and a commercial cigarette	a laboratory-based analysis of the aerosol created during the use of: 1) regular and menthol IQOS, 2) an e-cigarette with 18 mg/ml nicotine, and 3) 1 widely available conventional cigarette, an IQOS device with sticks (regular), 1 popular brand of conventional cigarettes; a smoking device designed to capture the mainstream smoke; the ISO standards (35 ml) at 2 puffs/min were adapted; volatile organic compounds and nicotine levels were analyzed by gas chromatography coupled to a flame ionization detector; and polycyclic aromatic hydrocarbons were analyzed using high-performance liquid	– IQOS, compared with the conventional cigarette, emitted lower levels of formaldehyde (on average by 91.6%), acetaldehyde (on average by 84.9%), acrolein (on average by 90.6%), propionaldehyde (on average by 89.0%), and crotonaldehyde (on average by 95.3%) – IQOS use emitted substantially lower levels of carbonyls than a commercial tobacco cigarette but higher levels than an e-cigarette

Table 1. Chemical composition of tobacco sticks and smoke generated during HTP use – a systematic review, 2015–2018 – cont.

Study type and reference	Aim of the study	Study design	Summary
Auer et al., Switzerland (2017) [29], Letters to the editor [30–32]	to compare the contents of smoke generated during IQOS use with the contents of smoke from conventional cigarettes	chromatography coupled to a fluorescence detector; the temperature near the heater blade inside the IQOS holder was monitored	– volatile organic compounds, polycyclic aromatic hydrocarbons, and carbon monoxide were present in IQOS smoke – the smoke released by IQOS contains elements from pyrolysis and thermogenic degradation that are the same harmful constituents of conventional cigarette smoke – advertising slogans such as "heat-not-burn" are no substitute for science – IQOS smoke had 84% of the nicotine found in conventional cigarette smoke – the temperature of IQOS was lower (330°C) than that of the conventional cigarette (684°C)
Mallock et al., Germany (2018) [33]	chemical evaluation of smoke generated during IQOS use with the contents of smoke from conventional cigarettes	emission of a commercially available HTP (IQOS), following the HCI regime; analysis of the particulate matter (TPM), nicotine, water, aldehydes, and other volatile organic compounds (VOCs); a linear smoking machine, 12 puffs (4 intervals of 3 puffs each)	– nicotine yield was comparable to traditional combustible cigarettes – a substantial reduction in the levels of aldehydes (approx. 80–95%) and VOCs (approx. 97–99%) was observed – the levels of major carcinogens are markedly reduced in the emissions of the analyzed HTP in relation to a conventional cigarette – the water content in IQOS smoke was higher compared to that in a conventional cigarette – comparatively high levels of tar were found in both the HTP and cigarette smoke
Uchiyama et al., Japan (2018) [7]	to analyze smoke from heated tobacco products (IQOS, glo, Ploom TECH) and traditional cigarettes (3R4F and 1R5F)	3 HTP cigarette brands: IQOS with 4 types of IQOS sticks ("regular," "balanced regular," "mint" and "menthol"); glo with 3 types of glo sticks ("bright tobacco," "fresh mix" and "intensely fresh"); Ploom TECH with 3 types of liquid capsules ("Mevius Legular," "Cooler Green" and "Cooler Purple"); reference cigarettes (3R4F and 1R5F); smoke was collected using a GF-CX572 sorbent cartridge and a 9 mm glass-fiber filter	– no considerable difference in the total gaseous and particulate compounds were noted between HTPs and the traditional cigarette (total gaseous and particulate matter: 42 mg/IQOS stick; 29 mg/glo stick; 18 mg/Ploom TECH stick and 31 mg/traditional cigarette) – fewer chemical compounds were generated by HTPs than by traditional cigarettes, except for water, propylene glycol, glycerol, and acetol, the concentrations of which in mainstream smoke were higher in HTPs than in the traditional cigarette – water accounted for 75–85% of the total gaseous and particulate matter generated during the use of both IQOS and glo (vs. traditional tobacco: 17–27%) – the most abundant chemical compounds generated during HTP use were glycerol, menthol, nicotine, propylene glycol, and acetol

			– the mean heating temperatures were 210°C for IQOS; 170°C for glo; 23°C for Ploom TECH; and 460°C for traditional cigarettes – the levels of generated chemical compounds depended on the temperature of tobacco sticks in HTPs
Ruprecht et al., Italy/ USA/Hong Kong (2017) [34, 35]	to compare the environmental pollution generated by e-cigarettes, IQOS, and traditional cigarettes, in a standard indoor environment	the characterization of black carbon, metal particles, organic compounds, and the size-segregated particle mass, and the concentrations emitted from IQOS; a room 48 m^2; 13 smoking/ vaping sessions: an e-cigarette (16 mg/ml nicotine, 1 puff every min for 7 min, followed by 3 min pause), IQOS (with 10 menthol and 14 without menthol IQOS sticks, 3-h smoking session, average smoking time – 7 min, followed by a short 3-min pause), conventional cigarette (9 cigarette per each session, average smoking time – 7 min, followed by a short 3-min pause)	– the IQOS side-stream smoke indicated that the particulate emission of organic matter from these devices is significantly different, depending on the organic compound – IQOS smoke was mostly free from aromatic hydrocarbons (PAHs) – IQOS use still emitted substantial levels (up to 2–6 mg/h during a regular smoking regimen) of certain n-alkanes, organic acids (such as suberic acid, azelaic acid, and n-alkanoic acids with carbon numbers 10–19) and levoglucosan – compared to both e-cigarettes and conventional cigarettes, metal emissions were reduced in IQOS smoke, and these emissions were mostly similar to the background levels – carcinogenic aldehyde compounds, including formaldehyde, acetaldehyde, and acrolein, where present in IQOS smoke (but their levels were substantially lower compared to conventional cigarettes) – although IQOS smoke has substantially lower emissions of the most toxic compounds, compared to traditional cigarettes, they are still not risk-free
Leigh et al., USA (2018) [37]	to determine tobacco-specific nitrosamine (TSNA) yields in the aerosol emitted from HTPs in comparison to the e-cigarettes and tobacco cigarettes	IQOS (Amber, tobacco flavor), an e-cigarette (3.5% nicotine, tobacco flavored) and a widely available tobacco cigarette; a smoking machine was used to generate puffs: IQOS (12 puffs), an e-cigarette (55 puffs) and a single tobacco cigarette (8 puffs), the average TSNA yields were calculated per puff and per puffing session	– IQOS use emits substantial levels of tobacco-specific carcinogenic substances – IQOS emits 8–22 lower amounts of TSNA (ng/puff) than combustible cigarettes, but significantly higher than e-cigarettes

Table 1. Chemical composition of tobacco sticks and smoke generated during HTP use – a systematic review, 2015–2018 – cont.

Study type and reference	Aim of the study	Study design	Summary
Salman et al., Lebanon/USA (2018) [38]	to investigate the toxicity and nicotine delivery potential of IQOS	IQOS and a widely available tobacco cigarette; smoke/aerosol was generated under 2 regimes: HCI and ISO, using a smoking machine; reactive oxygen species, carbonyl compounds, free-base and protonated nicotine emissions were measured	– IQOS emits significant levels of reactive oxygen species (6.26±2.72 nmol H_2O_2/session) and carbonyl compounds (472±19 μg/session), but they are 85% and 77% lower than the levels emitted by combustible cigarettes – IQOS emits harmful constituents that are linked to cancer, pulmonary diseases, and addiction in cigarette smokers – IQOS delivers similar levels and free-base fractions of nicotine at the mouthpiece as combustible cigarettes
Studies with a potential conflict of interest			
Pratte et al., Switzerland (2017) [23] PMI	to compare the solid particles levels in the mainstream aerosol from THS2.2 and the mainstream smoke of the reference cigarette (3R4F)	IQOS (THS2.2), the reference cigarette (3R4F), a commercially available thermodenuder operating at 300°C, coupled to a 2-stage impactor, was used to trap solid particles; any collected particles were subsequently analyzed by electron microscope scanning and an electron dispersive X-ray	– the mainstream aerosol from THS2.2 was free from solid carbon particles, which confirms the thesis that no combustion process takes place during THS2.2 use
Buratto et al., Switzerland (2018) [24] PMI	to analyze the concentration of 8 carbonyl compounds in THS2.2 aerosols	3R4F cigarettes and THS2.2; smoke/aerosol was generated under the HCI regime conditions, using a 30-port carousel smoking machine;	– in THS2.2 aerosols, carbonyl concentrations (formaldehyde, acetaldehyde, acetone, acrolein, propionaldehyde, crotonaldehyde, methyl-ethyl-ketone, and butyraldehyde) were lower compared to those measured in cigarette smoke
Mitova et al., Switzerland (2016) [14] PMI	to assess the impact of THS2.2 use on indoor air quality	THS2.2 and a widely available tobacco cigarette, an environmentally controlled room, 3 scenarios: "Office," "Residential" and "Hospitality;" selected indoor air constituents were measured	– the concentrations of respirable suspended particles, ultraviolet particulate matter, fluorescent particulate matter, solanesol, 3-ethenylpyridine, formaldehyde, acrolein, crotonaldehyde, acrylonitrile, benzene, 1,3-butadiene, isoprene, toluene, CO, NO and NO_x after the use of THS2.2 under 3 environmental conditions were equivalent to the concentrations found in background indoor air – THS2.2 use resulted in increased acetaldehyde and nicotine concentrations in indoor air, but these concentrations were considerably lower than those found in conventional cigarettes

Jaccard et al., Switzerland (2017) [15] PMI	to compare the chemical composition and toxicity of THS2.2 aerosols with smoke from the reference cigarette (3R4F)	THS2.2, the reference cigarette (3R4F); a smoking machine; analyses of the constituents of mainstream smoke from the reference cigarette (3R4F) and the aerosol of THS2.2 under the HCI regime	– except for nicotine, harmful and potentially harmful constituents were reduced by 90% in the THS2.2 aerosol in comparison with the reference cigarette (3R4F) smoke
Ichitsubo et al., Japan (2018) [13] Japan Tobacco	to analyze the impact of using a novel tobacco vapor product (the Ploom TECH prototype) on indoor air quality	the Ploom TECH prototype; an environmentally controlled chamber; 3 environments: 2 non-smoking areas and 1 smoking area; indoor air quality was evaluated by: 1) measuring the constituents in mainstream emissions, 2) by determining the classic environmental tobacco smoke and 3) by representative air quality markers	– the mainstream emissions of vapor from Ploom TECH were chemically simpler than those of cigarette smoke – environmental tobacco smoke markers, volatile organic compound (toluene), carbon monoxide, propylene glycol, glycerol, and triacetin were below the limit of detection, or the limit of quantification, in both the non-smoking and smoking environments after using the Ploom TECH – no significant increase in the levels of formaldehyde, acetone or ammonia in the exhaled air were observed following Ploom TECH use – Ploom TECH had no measurable effect on the indoor air quality

CO – carbon monoxide; HCI – Health Canada Intense; HTPs – heated tobacco products; ISO – International Organization for Standardization; SMPs – submicronic particles; THS2.2 – tobacco heating system 2.2 (IQOS); TSNA – tobacco-specific nitrosamines; PMI – Philip Morris International; VOCs – volatile organic compounds; 3R4F – reference cigarette.

The tobacco industry claims that the aerosol formed during the heating process has around 90–95% lower levels of toxicants than conventional cigarette smoke [13–15,23,24]. This was partially confirmed by independent studies [27,28]. Li et al. reported that, compared to conventional cigarettes, IQOS delivered a > 90% lower concentration of harmful and potentially harmful constituents (HPHCs) except for carbonyls, ammonia, and N-nitrosoanabasine, where the levels were about 50–80% lower [27]. Farsalinos et al. showed that IQOS use emitted substantially lower levels of carbonyls than a commercial cigarette but higher levels than an e-cigarette [28]. Mallock et al. observed substantially lower levels of aldehydes (approx. 80–95%) and volatile organic compounds (approx. 97–99%) in the IQOS aerosol compared to cigarette smoke [33]. Pacitto et al. also showed lower volatile and non-volatile particle concentrations in the mainstream IQOS aerosols compared to traditional cigarette smoke [20].

Protano et al. compared the emission of submicronic particles (SMPs) from IQOS and e-cigarettes [25,26]. Both devices emitted SMPs but the particle emissions from IQOS were higher than those from e-cigarettes. Ruprecht et al. noted that the IQOS aerosol was free from metal emissions, in contrast to cigarette and e-cigarette aerosols [34,35]. However, toxic compounds were not completely removed from the heated tobacco aerosol [15]. Li et al. and Mallock et al. showed that IQOS emitted comparable levels of tar to the reference cigarette [27,33]. Bekki et al. observed that the concentration of tobacco-specific nitrosamines were one-fifth of those of conventional cigarettes [21]. Leigh et al. also observed that IQOS emitted lower amounts of tobacco-specific nitrosamines than combustible cigarettes, but a significantly higher amount than e-cigarettes [37]. Salman et al. reported that the use of IQOS emitted significant levels of reactive oxygen species and carbonyl compounds, but these were still 85% and 77% lower than the levels emitted by combustible cigarettes [38].

Controversial results were presented by Auer et al. who showed that in the IQOS aerosol, volatile organic compounds, polycyclic aromatic hydrocarbons, and carbon monoxide were detected [29]. Moreover, the smoke released during the use of IQOS contained elements from pyrolysis and thermogenic degradation, similar to the harmful constituents of conventional cigarette smoke [29]. These findings significantly differed from those presented by the tobacco industry and gave rise to heated discussions among the experts [30–33]. Independent experts [31] and industry representatives [32] concluded that the results presented by Auer et al. could be misinterpreted due to the absence of a standardized protocol for emission generation and specifically validated analytical measurements.

Some authors suggest that, even without such combustion as in the case of traditional cigarettes, HTPs still release harmful compounds which can then expose bystanders [25,26,34,35]. Ruprecht et al. showed that IQOS emitted detectable and substantial levels (up to 2–6 mg/h during a regular smoking regimen) of several organic compounds, including n-alkanes, organic acids, and aldehyde species such as formaldehyde, acetaldehyde, and acrolein [34,35]. Protano et al. estimated the dose of submicronic particles deposited in the respiratory system of individuals exposed to secondhand smoke from a combustible cigarette, an e-cigarette, and IQOS [25,26]. The highest doses were reported to originate from combustible cigarettes compared to non-combustion devices. However, the dosimetry estimates were 50–110% higher for IQOS than for e-cigarettes [25,26]. Although the IQOS aerosol has substantially lower emissions of toxic compounds compared to traditional cigarettes, it is still a source of passive exposure [25,26].

Based on evidence from studies not sponsored by the tobacco company, in general, the results have shown that HTP use releases lower levels of most toxic chemicals and harmful substances compared to conventional cigarettes. However, toxic compounds are not completely removed from the HTP aerosol. Moreover, some independent studies have suggested that pyrolysis processes can still be present during HTP use. On the one hand, the levels of some toxicants can be reduced during HTP use but, on the other hand, HTP users can be exposed to higher levels of other toxic chemical and harmful substances compared to tobacco smoke.

Evidence from the experimental animal and cellular studies

The tobacco industry has performed multiple [22,37–70] *in vitro* studies on human bronchial epithelial cells, coronary arterial endothelial cells, a 3-D nasal culture model, gingival epithelial organotypic cultures, monocytic cells, and *in vivo* mouse models (Table 2). The results of these studies have indicated that the aerosol from HTPs has lower toxicity and no new hazards compared to cigarette smoke [10,11,22,39–68].

The aqueous aerosol extract from IQOS has reduced effects on the adhesion of monocytic cells to human coronary endothelial cells compared to the aqueous reference cigarette smoke extract [55]. The aerosol extracts from IQOS were also found to induce less inflammation and migration, and to be less cytotoxic than those from burning conventional cigarettes [56]. The IQOS aerosol exerted a weaker biological impact on human organotypic bronchial epithelial cells than cigarette smoke at similar nicotine concentrations [57]. Compared to cigarette smoke, there was a substantially lower impact of the IQOS aerosol in terms of alterations in tissue morphology, secretion of pro-inflammatory mediators, impaired ciliary function, increased perturbed transcriptomes, and miRNA expression profiles [58]. Exposure to IQOS aerosols had a lower impact on the pathophysiology of human gingival organotypic cultures than conventional cigarette smoke [59]. Cigarette smoke caused significant discoloration of dental composite resins [60] while this effect was minimized during IQOS use [60].

Table 2. Evidence from the experimental animal and cellular studies – a systematic review, 2015–2018

Study type and reference	Aim of the study	Study design	Summary
Independent studies			
Nabavizadeh et al., USA (2018) [71]	to determine the potential impact of exposure to the IQOS aerosol on arterial flow-mediated dilation	8 male rats; anaesthetized rats were exposed to the IQOS aerosol from single HeatSticks, mainstream smoke from single cigarettes or clean air for a series of consecutive 30-s cycles over 1.5–5 min; each cycle – 15 or 5 s of exposure, followed by removal from the nose cone; measurement: pre-exposure and post-exposure flow-mediated dilation, and post-exposure serum nicotine and cotinine	– acute exposures to the IQOS aerosol impair the flow-mediated dilation in rats – the mainstream IQOS aerosol from a single HeatStick can rapidly and substantially impair the endothelial function in rats, comparably to cigarette smoke – the post-exposure serum nicotine levels were 4.5-fold higher in the rats exposed to IQOS than in those exposed to cigarettes
Leigh et al., USA (2018) [72]	to examine the potential cytotoxic effects of inhaling emissions from an HTP, in comparison with the electronic and combustible cigarettes.	human bronchial epithelial cells exposed directly to 1) 55 puffs from an e-cigarette, 2) 12 puffs from an HTP, and 3) 8 puffs from a conventional cigarette; neutral red uptake and trypan blue assays were used to measure cytotoxicity	– emissions from the HTP damaged bronchial epithelial cells; however, the HTP showed reduced cytotoxicity relative to a combustible cigarette but higher toxicity than an e-cigarette – compared with air controls, a significant increase in cytokines levels was observed post-exposure to tobacco smoke but not to the HTP or e-cigarette aerosols
Chun et al., USA (2018) [70]	to assess the possible hepatotoxicity of IQOS	an independent revision of preclinical and clinical data on IQOS submitted by PMI to FDA, in order to identify the potential relationship between IQOS exposure and unexpected liver toxicity	– a combination of animal data and human-based data reveals a pattern of IQOS hepatotoxicity which is worth careful consideration – PMI's preclinical and clinical data constitute a concerning pattern of possible hepatotoxicity, especially considering the short period of exposure – IQOS may have unexpected organ toxicity that has not been associated with cigarettes

Table 2. Evidence from the experimental animal and cellular studies – a systematic review, 2015–2018 – cont.

Study type and reference	Aim of the study	Study design	Summary
Studies with a potential conflict of interest			
a cycle of 9 tobacco industry publications about Tobacco Heating System 2.2 (THS2.2, marketed as IQOS) in Regular Toxicol Pharmacol [22,39–47], Switzerland (2016) PMI	to assess the potential for THS2.2 to be a candidate modified risk tobacco product	8 laboratory experimental investigations or chemical analyses, and 1 early clinical investigation on THS2.2; comparison to the results observed after the reference cigarette (3R4F) use	– *in vitro* and *in vivo* assessments of THS2.2 smoke revealed reduced toxicity and no new hazards compared to cigarette smoke, as well as a reduced impact on smoking-related disease networks – smokers who had switched to THS2.2 presented reduced exposure to harmful and potentially harmful constituents (HPHCs) – the cytotoxicity of THS2.2 aerosols was reduced by > 90% compared with the reference cigarette smoke, the THS2.2 aerosol fraction was not mutagenic in the Ames mutagenicity assay – there was no change in the HPHC yields or *in vitro* toxicology findings for the different tobacco blends used in IQOS tobacco sticks; the aerosols produced by tobacco blends in the THS2.2 contained significantly lower concentrations of HPHCs than the 3R4F mainstream smoke – a 90-day nose-only inhalation study in rats showed that there were no apparent new toxicity effects in the THS2.2 aerosol, compared with the reference cigarette (3R4F) smoke – after 90-day exposure the alanine aminotransferase levels and liver weights were significantly higher in female animals exposed to IQOS than in the case of conventional cigarettes – hepatocellular vacuolization was significantly increased in IQOS-exposed female rats, an effect not seen in cigarette-exposed animals – the THS2.2 aerosol in contrary to the 3R4F cigarette smoke, did not cause global miRNA downregulation – a 90-day nose-only inhalation study in rats showed that systemic toxicity and alterations in the respiratory tract were significantly lower in the rats exposed to the mentholated variant of THS2.2 than in the groups exposed to traditional (3R4F) and mentholated reference cigarettes – cigarette smoke induced an inflammatory response, triggered cellular stress responses, and affected sphingolipid metabolism while these effects were reduced or absent during exposure to the THS2.2 aerosol (the mentholated variant)

			– in a 5-day controlled open-label clinical study (N = 160 adults) all biomarkers of HPHC exposure (except for nicotine) were significantly reduced in THS2.2 users, compared to cigarette smokers, and approached the levels observed in the smoking abstinence group – the tested signature of 11 genes on the blood transcriptome of the subjects enrolled in the clinical study showed a reduced exposure response in the subjects who stopped smoking or switched to THS2.2, compared to those who continued traditional cigarette smoking
a cycle of 9 tobacco industry publications about Tobacco Heating Product 1.0 (THP1.0, marketed as glo) in Regular Toxicol Pharmacol [10,11,48–54], United Kingdom (2018) BAT	to assess the potential for THP1.0 to be a candidate modified risk tobacco product	7 pre-clinical studies on the safety and toxicological assessment of THP1.0; 2 types of tobacco sticks (regular tobacco and menthol flavors); comparison to the results observed after the reference cigarette (3R4F) use	– aerosol formed during the heating process had around 90–95% fewer toxicants than the smoke of conventional cigarettes – during THP1.0 use, the aerosol was generated in a mechanism of distillation or evaporation; there was very little or no combustion during THP1.0 use – in the aerosol of THP1.0, the levels of toxicants were substantially lower than in 3R4F smoke: a reduction of 96.1% on average for 9 substances prioritized for lowering in cigarettes, and 96.8% for 18 substances prioritized by the FDA – the levels of nicotine, acetaldehyde, formaldehyde and particulate matter emitted during THP1.0 use exceeded ambient air measurements, but were > 90% reduced relative to cigarette smoke, markers of tobacco combustion were not observed; the residual tobacco smoke odor was significantly lower from THP1.0 than from a conventional cigarette – THP1.0 demonstrated significantly reduced cytotoxicity compared to the reference cigarette exposure – THP1.0 showed reduced activity (little or no activity) in all 10 different toxicity and oxidative-stress endpoints, assessed using normal human bronchial epithelial cells, compared to the reference cigarette – THPs demonstrated significantly reduced *in vitro* toxicological activity compared to the reference cigarette – the puffing behaviors for naive and regular HTP users were similar (the mean puff duration was 1.8 s; the mean puff interval was 7.4–9.9 s) – THP1.0 showed substantially reduced responses in pre-clinical tests, in comparison to cigarettes, so the authors concluded that THP1.0 could have the potential to be a reduced risk product compared to cigarettes

Table 2. Evidence from the experimental animal and cellular studies – a systematic review, 2015–2018 – cont.

Study type and reference	Aim of the study	Study design	Summary
Poussin et al., Switzerland (2016) [55] PMI	to assess the effects of aqueous extracts from THS2.2 aerosols, and the reference cigarette (3R4F) smoke on the adhesion of monocytic cells to human coronary arterial endothelial cells	human coronary arterial endothelial cells; human monocytic cells; a direct and indirect exposition to the aqueous 3R4F smoke or the THS2.2 aerosol extract	– the aqueous aerosol extract from THS2.2 had reduced effects on the adhesion of monocytic cells to human coronary endothelial cells, compared to the aqueous cigarette (3R4F) smoke extract – the authors suggested that THS2.2 had a potential to reduce the risk for cardiovascular diseases compared to combustible cigarettes
van der Toorn et al., Switzerland (2015) [56] PMI	to investigate the effect from THS 2.2 on the migratory behavior of monocytes, in comparison with the reference cigarettes (3R4F)	the aerosol extract from THS2.2 and the smoke extract from 3R4F; the monocytic cell line and human coronary arterial endothelial cells were used to analyze chemotaxis and transendothelial migration; flow cytometry and ELISA assays	– the inhibitory effects of the THS2.2 extract for chemotaxis were approx. 18 times less effective compared to the 3R4F extract – extracts from THS2.2 induced less inflammation and migration, and were less cytotoxic than those from burning conventional cigarettes (3R4F) – heated tobacco products (THS2.2) have a potential to reduce the risk for cardiovascular diseases compared to combustible cigarettes
Iskandar et al., Switzerland (2017) [57] PMI	to perform a comparative assessment of the biological impact of the THS2.2 aerosol and the reference cigarette smoke	THS2.2, the reference cigarette (3R4F); human organotypic bronchial epithelial cultures exposed to an aerosol from THS2.2 or cigarette smoke at similar nicotine concentrations; the assessment included culture histology, cytotoxicity, secreted pro-inflammatory mediators, ciliary beating, and genome-wide mRNA/miRNA profiles	– the THS2.2 aerosol exerted a weaker biological impact than cigarette smoke at similar nicotine concentrations – no morphological change was observed following exposure to the THS2.2 aerosol – exposure to the THS2.2 aerosol evoked lower levels of secreted mediators and fewer miRNA alterations than the reference cigarette (3R4F) smoke
Iskandar et al., Switzerland (2017) [58] PMI	to investigate the application of *in vitro* human 3-D nasal epithelial culture models for the toxicological assessment of inhalation exposure	THS2.2, the reference cigarette (3R4F); a human 3-D nasal culture model; a systems toxicology approach was implemented, a series of 5 experimental repetitions, for each repetition 3 independent exposure runs, were performed (28-min continuous exposure to the smoke/aerosol each)	– the reference cigarette (3R4F) smoke was substantially greater than that of the THS2.2 aerosol in terms of cytotoxicity levels, alterations in tissue morphology, secretion of pro-inflammatory mediators, impaired ciliary function, and increased perturbed transcriptomes and miRNA expression profiles

Zanetti et al., Switzerland/ USA/ Germany (2017) [59] PMI	to compare the exposure effects of the reference cigarette (3R4F) and THS2.2 on human gingival epithelial organotypic cultures using a systems toxicology approach	a human gingival epithelial organotypic culture model; a smoking machine; 10 3R4F cigarettes (10–11 puffs each) and 10 THS2.2 sticks (up to 12 puffs each); the study design in accordance with the Health Canada smoking regime; repeated exposure (3 days) for 28 min at 2 matching concentrations of the reference cigarette (3R4F) smoke or the THS2.2 aerosol	– exposure to the THS2.2 aerosol had a lower impact on the pathophysiology of human gingival organotypic cultures than cigarette smoke – the THS2.2 aerosol caused minor histopathological alterations and minimal cytotoxicity compared to cigarette smoke (1% for the THS2.2 aerosol vs. 30% for cigarette smoke, at a high concentration) – THS2.2 had a reduced impact on the release of proinflammatory mediators: THS2.2 exposure caused significant alterations in 5 of 14 proinflammatory mediators analyzed, cigarette use altered 11 of 14 proinflammatory mediators
Zhao et al., USA/ China/ Switzerland (2017) [60] PMI	to evaluate the effects of cigarette smoke on the discoloration of dental resin composite compared with the aerosol from a heated tobacco product (THS2.2)	60 discs from 3 commercial resin composites; 20 discs of each composite were divided into 2 groups and exposed to cigarette smoke from 20 reference cigarettes (3R4F) or the aerosol from 20 IQOS tobacco sticks per day for 3 weeks; the color, gloss and surface roughness of the composite discs were measured at baseline and after exposure and brushing with a toothpaste in 3 consecutive weeks	– color differences relative to the baseline (ΔE) were on average 27.1 (±3.6) in the 3R4F group and 3.9 (±1.5) in the THS2.2 group after 3 weeks of exposure ($p < 0.0001$) – the reference cigarette (3R4F) smoke caused significant discoloration of dental composite resins while this effect was minimized during the use of THS2.2 (IQOS)
Malinska et al., Poland/Switzerland (2018) [61] PMI	to evaluate the mitochondrial function and oxidative stress after exposure to HTP and cigarette smoke	human bronchial epithelial cells, following 1- and 12-week exposures to the total particulate matter from the TSH2.2 and reference cigarette (3R4F) aerosol	– the total particulate matter from THS2.2 had a lower effect on oxidative phosphorylation, gene expression and proteins involved in oxidative stress than the total particulate matter from the reference cigarette
van der Toom et al., Switzerland (2018) [62] PMI	to evaluate functional and molecular changes in human bronchial epithelial cells following a 12-week exposure to the total particulate matter from THS2.2 compared to the reference cigarette (3R4F)	THS2.2, the reference cigarette (3R4F); human bronchial epithelial cell line, 12-week exposure, the assessment of endpoints linked to lung carcinogenesis	– long-term exposure to the total particulate matter from the THS2.2 had a lower biological impact on human bronchial epithelial cells compared with the total particulate matter from the reference cigarette smoke – short-term exposure to the total particulate matter from the reference cigarette resulted in cellular crisis and epithelial-mesenchymal transition – long-term exposure to the total particulate matter from the reference cigarette resulted in cellular transformation

Table 2. Evidence from the experimental animal and cellular studies – a systematic review, 2015–2018 – cont.

Study type and reference	Aim of the study	Study design	Summary
Haswell et al., United Kingdom (2018) [16] BAT	to compare the transcriptomic perturbations following an acute exposure of a 3D airway tissue to the aerosols from 2 commercial THPs and the reference cigarette (3R4F)	2 Tobacco Heating Products (THP and THP1.0), the reference cigarette (3R4F), a 3D airway cell model and RNA-sequencing were used to assess transcriptomic perturbations after exposure	– THPs had a reduced impact on gene expression compared to 3R4F – there was no pro-inflammatory effect observed after THP use
Crooks et al., United Kingdom (2018) [17] BAT	to determine whether the inclusion of potential flavorings in the THP would add to the levels of toxicants in the emissions or alter *in vitro* responses	glo, tobacco glo sticks (Neostik), both flavored and unflavored, a comparison with the reference cigarette (3R4F) smoke	– the levels of measured toxicants were similar in the flavored and unflavored tobacco sticks (Neostik) emissions, and significantly lower than in the emissions from the reference cigarette (3R4F) – the THP aerosol was not mutagenic in the Ames mutagenicity assay or in the mouse lymphoma assay – weak genotoxic responses in the *in vitro* micronucleus test were observed, using Chinese hamster lung fibroblasts, from both flavored and unflavored Neostiks, and these were weaker than for the reference cigarette
Ishikawa et al., Japan (2018) [18] Japan Tobacco	to analyze the biological effects of aerosols from the reference cigarette (3R4F) and a novel tobacco vapor product (the Ploom TECH prototype)	the Ploom TECH prototype, the reference cigarette (3R4F), MucilAir organotypic bronchial epithelial cultures; a direct aerosol exposure system, 5 exposure conditions for cigarette smoke and 3 for Ploom TECH	– the reference cigarette (3R4F) smoke increased cytotoxicity, cytokine secretion, and differential gene expression, depending on the exposure dose – no changes were observed in any of the analyzed endpoints following the Ploom TECH vapor exposure – the authors concluded that the biological effects of Ploom TECH vapor were lower than those of conventional combustible cigarettes
Takahashi et al., Japan/Switzerland (2018) [63] Japan Tobacco	to examine the emission levels for selected cigarette smoke constituents, and *in vitro* toxicity of the aerosol from a novel tobacco vapor product (the Ploom TECH prototype) and to compare them to the reference cigarette (3R4F) smoke	the Ploom TECH prototype, the reference cigarette (3R4F); "Hoffmann analytes" were conducted, the Ames assay and the *in vitro* Micronucleus Assay were performed to assess cyto- and genotoxicity	– a chemical analysis of the Ploom TECH prototype aerosol demonstrated that the Hoffmann analyte levels were substantially lower than in the 3R4F smoke and that they were mostly below quantifiable levels – no measurable genotoxicity or cytotoxicity features were observed during Ploom TECH prototype use

Szostak et al., Switzerland (2017) [64] PMI	to evaluate the impact of exposure to cigarette smoke and the THS2.2 aerosol on mice heart tissues	the reference cigarette (3R4F), a THS2.2 heated tobacco system (IQOS); female Apoe$^{-/-}$ mice; exposure to cigarette smoke or the THS2.2 aerosol for up to 8 months	– the cigarette smoke exposure induced the downregulation of genes involved in the cytoskeleton organization and the contractile function of the heart (mainly genes that encode β-actin, actinin-α-4, and filamin-C) and downregulate genes related to the inflammatory response – these effects were not observed in the group exposed to the THS2.2 aerosol
Lo Sasso et al., Switzerland/ Singapore/ Germany (2016) [65] PMI	to investigate the effects of exposure to the THS2.2 aerosol, the reference cigarette smoke or filtered air on the livers of Apoe$^{-/-}$ mice	an 8-month inhalation study with Apoe$^{-/-}$ mice, exposure to 1) the THS2.2 aerosol, 2) the reference cigarette (3R4F) smoke, or 3) filtered air; after 2 months some mice exposed to cigarette smoke were switched to THS2.2 or filtered air exposure	– signs of overt hepatotoxicity were absent in all 3 groups – compared with cigarette smoke, the THS2.2 aerosol had reduced biological effects on the livers of Apoe$^{-/-}$ mice – the livers of the Apoe$^{-/-}$ mice exposed to cigarette smoke did exhibit molecular responses (such as dysregulation of lipid, xenobiotic and possibly iron homeostasis) which were much less affected in the THS2.2, cessation and switching groups
Phillips et al., Singapore/ Switzerland/ Germany (2016) [66,67] PMI	to investigate features of chronic obstructive pulmonary disease (COPD) and cardiovascular disease (CVD) among the apolipoprotein E-deficient (Apoe$^{-/-}$) mice exposed to cigarette smoke or the THS2.2 aerosol for up to 8 months	(Apoe$^{-/-}$) mice exposed to cigarette smoke (3R4F) or the aerosol from THS2.2 for up to 8 months; some groups exposed to cigarette smoke were either switched to the THS2.2 aerosol or underwent cessation after 2 months; the exposure effects were investigated using physiology and histology, combined with transcriptomics, lipidomics, and proteomics	– cigarette smoke induced nasal epithelial hyperplasia and metaplasia, lung inflammation, and emphysematous changes (impaired pulmonary function and alveolar damage) – cigarette smoke exposure had an atherogenic effect including altered lipid profiles and aortic plaque formation – exposure to the THS2.2 aerosol neither induced lung inflammation or emphysema, nor consistently changed the lipid profile or enhanced plaque formation – cessation or switching to THS2.2 reversed the inflammatory responses and halted the progression of initial emphysematous changes and the aortic plaque area
Titz et al., Switzerland/ Singapore/Finland (2016) [68] PMI	to investigate the THS2.2 exposure effects on lung lipid metabolism in an apolipoprotein E-deficient (Apoe$^{-/-}$) mouse study	mice exposed to high concentrations of the reference cigarette (3R4F) smoke, the aerosol from THS2.2 or filtered air, for up to 8 months; some groups exposed to cigarette smoke were either switched to the THS2.2 aerosol or underwent cessation after 2 months	– the reference cigarette (3R4F) smoke induced a coordinated lipid response controlled by transcription regulators (such as SREBP proteins) and supported by other metabolic adaptations; most of these changes were absent in the mice during exposure to THS2.2, in the cessation group, and the in switching group – the Apoe$^{-/-}$ mice exposed to THS2.2 for 3 months showed some downregulation of several sphingolipids, a response opposite to that observed in the group exposed to the reference cigarette (3R4F) smoke

Apoe$^{-/-}$ mouse – apolipoprotein E-deficient mouse; BAT – British American Tobacco; ELISA – enzyme-linked immunosorbent assay; FDA – Food and Drug Administration; HPHCs – harmful and potentially harmful constituents; HTPs – heated tobacco products; miRNA – micro ribonucleic acid; PMI – Philip Morris International; THP1.0 – tobacco heating product (glo); THS2.2 – tobacco heating system 2.2 (IQOS); 3R4F – reference cigarette.

The total particulate matter from IQOS had a lower effect on oxidative phosphorylation, gene expression, and proteins involved in oxidative stress, compared to the total particulate matter from the reference cigarette [61]. Long-term exposure to the total particulate matter from IQOS had a lower biological impact on the human bronchial epithelial cells line compared to the total particulate matter from cigarette smoke [62].

The aerosol from glo also demonstrated significantly reduced *in vitro* toxicological activity compared to conventional cigarettes [16,17]. There was no pro-inflammatory effect observed after the use of glo [16]. The glo aerosol was not mutagenic in the Ames mutagenicity assay or in the mouse lymphoma [17]. Similarly, no measurable genotoxicity or cytotoxicity features were observed after Ploom TECH use [63], and the biological effects of the Ploom TECH aerosol were also lower than those of conventional cigarette smoke [18].

Most *in vivo* studies were performed on apolipoprotein E-deficient ($Apoe^{-/-}$) mouse models exposed to cigarette smoke or the IQOS aerosol for 8 months (Table 2). In contrast to traditional cigarette smoke, IQOS aerosols did not affect the downregulation of genes involved in the cytoskeleton organization, contractile function of the heart, or genes related to the inflammatory responses [64]. The IQOS aerosol had reduced biological effects on the livers of the $Apoe^{-/-}$ mice [65]. However, Wong et al. observed a significant increase in alanine aminotransferase (ALT), liver weights, and hepatocellular vacuolization in female rats exposed to IQOS. These effects were lower or absent in the case of cigarette-exposed rats [42]. Exposure to the IQOS aerosol did not induce lung inflammation or emphysema, nor did it consistently change the lipid profile or enhance the aortic plaque formation [66,67]. There was no relevant IQOS aerosol exposure effect on lung lipid metabolism either [68].

All the studies presented above were performed or sponsored by the tobacco industry. Moreover, most of them were published in 1 journal that had a history of concealed pro-industry bias [69].

An independent review of industry sponsored preclinical and clinical data on IQOS, performed by Chun et al., points to the potential hepatotoxic effects of IQOS use [70]. A combination of animal data and human-based data reveals a concerning pattern of possible hepatotoxicity, especially considering the short period of exposure. Chun et al. suggested that IQOS might have unexpected organ toxicity, not observed during cigarette smoking.

Independent experimental animal and cellular studies on HTPs are very limited. Nabavizadeh et al. showed that the mainstream IQOS aerosol from a single tobacco stick might rapidly and substantially impair the endothelial function in rats, comparable to smoke from a cigarette. The use of IQOS does not necessarily avoid the adverse cardiovascular effects of cigarette smoking [71]. Leigh et al. reported that the aerosol emitted from IQOS damaged human bronchial epithelial cells; however, IQOS cytotoxicity was lower compared to that of a combustible cigarette, but it exhibited higher toxicity than an e-cigarette, which was consistent with tobacco industry data [72].

Potential impact of heated tobacco on human health

Based on studies sponsored by the tobacco industry (Table 3), among healthy Japanese adult smokers, the results have shown that HTPs effectively deliver nicotine and achieve similar pharmacokinetic profiles to combustible cigarettes [12,36,73]. Brossard et al. showed that the nicotine pharmacokinetic profile of IQOS was close to that of conventional cigarettes with similar urge-to-smoke levels [36]. The use of IQOS or glo reduced the exposure to smoke toxicants in a manner comparable to quitting tobacco use [74,75]. After switching from conventional cigarettes to HTPs (IQOS or glo), a significant reduction in the levels of biomarkers of exposure to harmful and potentially harmful constituents was observed [76–78].

Table 3. Human-based studies – a systematic review, 2015–2018

Study type and reference	Aim of the study	Study design	Summary
Independent studies			
Adriaens et al., Belgium (2018) [79]	to investigate the effect of using an IQOS on the exhaled CO, acute cigarette craving, withdrawal symptoms, and subjective positive and negative experiences after overnight smoking abstinence, compared to using an e-cigarette or a regular cigarette	30 participants (aged 22±3.09 years; 67% male), 3 consecutive measurement days after being overnight smoking abstinent; 3 different products: a conventional cigarette, an e-cigarette, IQOS; during each session 1 product was used for 5 min; the exhaled CO measurements and dedicated questionnaires were administered throughout each session	– cigarette smoking for 5 min resulted in a significant increase in the exhaled CO, whereas using IQOS resulted in a small but reliable increase (0.3 ppm) – cigarette craving was reduced significantly after the product use, with the decline being stronger for tobacco smoking than for e-cigarettes or IQOS – a short-term use of IQOS can be effective to momentarily reduce the acute cigarette craving and withdrawal symptoms – IQOS is more popular with novice users than an e-cigarette
Tabuchi et al., Japan (2017) [5]	to assess the symptoms induced by secondhand exposure to the HTP (IQOS, Ploom or glo) tobacco aerosol in Japan	a follow-up 3-year longitudinal Internet survey of 8240 subjects (aged 15–69 years in 2015; 49.6% male) to evaluate the prevalence of HTP use and symptoms induced by secondhand exposure to the HTP tobacco aerosol	– 997 (12%) of subjects reported secondhand exposure to HTP smoke – among all people exposed to secondhand smoke, 37% experienced at least 1 health symptom of exposure to passive HTP smoking, most of them reported feeling ill (25%), eye pain (22.3%), and sore throat (20.6%)
Stephens, United Kingdom (2017) [80]	to compare cancer potencies of various nicotine delivering aerosols	the cancer potencies of various nicotine delivering products (cigarettes, e-cigarettes, a nicotine inhaler, the HTP prototype) aerosols were modeled using published chemical analyses of emissions and their associated inhalation unit risks; the smoke and vapor were expressed in common units; the lifetime cancer risks were calculated from these potencies using daily consumption estimates	– heated tobacco devices had lower cancer potencies than traditional tobacco smoke by at least 1 order of magnitude, but higher potencies than most e-cigarettes – the mean lifetime cancer risks declined in the sequence: combustible cigarettes > heated tobacco products > e-cigarettes ≥ nicotine inhaler
Kamada et al., Japan (2016) [81]	to report the first case of acute eosinophilic pneumonia caused by smoking IQOS	a case report; a 20-year-old man who had smoked 20 IQOS sticks daily for 6 months, and doubled stick consumption 2 weeks before the hospitalization	– heated tobacco cigarette use caused acute eosinophilic pneumonia in an adult male smoker

Table 3. Human-based studies – a systematic review, 2015–2018 – cont.

Study type and reference	Aim of the study	Study design	Summary
Aokage et al., Japan (2018) [82]	to report the case study of fulminant acute eosinophilic pneumonia caused by HTPs	a case report; a 16-year-old man with a history of crustacea allergy and bronchial asthma in childhood, who had started HTP use 2 weeks before the hospitalization and subsequently suffered from shortness of breath that gradually worsened	– HTP use induced fulminant acute eosinophilic pneumonia – the patient was successfully treated with venovenous extracorporeal membrane oxygenation for severe respiratory failure
Studies with a potential conflict of interest			
Yuki et al., Japan (2017) [12] Japan Tobacco	to investigate the pharmacokinetics of nicotine following the use of a prototype novel tobacco vapor product (the Ploom TECH prototype) in comparison to a conventional cigarette	24 subjects (aged 21–63 years; 100% male), the Ploom TECH prototype, a conventional cigarette; healthy Japanese adult male smokers; the plasma nicotine concentrations in blood samples and the nicotine intake were estimated based on the mouth level exposure	– the pharmacokinetics of nicotine, following the Ploom TECH prototype use, were not markedly different from those following the conventional cigarette use, while the Ploom TECH prototype provided less nicotine following a controlled single use – the estimated nicotine mouth level exposure, following the Ploom TECH prototype use, was approximately two-thirds of that obtained following the conventional cigarette smoking
Brossard et al., Switzerland (2017) [36] PMI	to investigate the single-use nicotine pharmacokinetic profile of THS2.2, combustible cigarettes and nicotine replacement therapy (a gum)	62 healthy adult Japanese smokers (aged 23–65 years; 52.5–55% male); THS2.2 (the regular and menthol variant), a commercially available brand of cigarettes, and nicotine replacement therapy (gum); the plasma nicotine concentrations were measured in 16 blood samples collected over 24 h after a single use	– THS2.2 delivered nicotine as effectively as combustible cigarettes and faster than the nicotine gum – the urge-to-smoke total scores were comparable between THS2.2 and combustible cigarettes – THS2.2 can satisfy smokers and be an alternative to combustible cigarettes for adult smokers who do not want to quit smoking
Picavet et al., Switzerland (2016) [73] PMI	to compare the pharmacokinetics of nicotine THS2.1 and combustible cigarettes	28 healthy smokers (aged 23–65 years); THS2.1 (the prototype of IQOS) and a commercially available brand of cigarettes; the assessment of the pharmacokinetics of nicotine after a single and *ad libitum* use of THS2.1 or the reference cigarette; a 7-day confinement period; blood samples were drawn for pharmacokinetic analysis	– the nicotine delivery rate was similar for THS2.1 and the combustible cigarette after a single and *ad libitum* use – THS2.1 effectively delivers nicotine and achieves similar pharmacokinetic profiles to combustible cigarettes – THS2.1 reduces the urge to smoke in a manner similar to combustible cigarettes

Lüdicke et al., Switzerland (2018) [74,75] PMI	to examine the impact of switching to menthol THS2.2 on the biomarkers of exposure to Harmful and Potentially Harmful Constituents (HPHCs), and the clinically relevant risk markers of smoking-related diseases, relative to menthol combustive cigarettes and smoking abstinence	160 Japanese adult smokers (aged 23–65 years; 57.5% male): 78 used menthol THS2.2, 42 smoked menthol cigarettes, 40 were classified to the smoking abstinence group; 5 days of use in confinement and 85 days in ambulatory settings, follow up on day 90	– switching from menthol combustible cigarettes to menthol THS2.2 significantly reduced HPHC exposure, with concentrations similar to those observed following smoking abstinence – switching from menthol combustible cigarettes to menthol THS2.2 resulted in reduced biomarkers of exposure to cigarette smoke, and changes were observed in clinically relevant biomarkers of oxidative stress (8-epi-prostaglandin F2α), platelet activity (11-dehydro-thromboxane B2), endothelial function (soluble intracellular adhesion molecule-1), lipid metabolism (high-density lipoprotein cholesterol) and lung function (forced expiratory volume in 1 s), similar to the smoking abstinence group – the authors suggest that switching to THS2.2 has the potential to reduce the adverse health effects of smoking-related diseases
Lüdicke et al., Switzerland (2017) [76] PMI	to assess the patterns of THS2.1 use, as well as to evaluate the biomarkers of exposure to tobacco smoke toxicants among adult smokers	40 smokers (aged 24–56 years; 45% male) using the prototype of IQOS – THS2.1 (N = 20) or their own brand of commercially available cigarettes (N = 20) for 5 days; the biomarkers of exposure were measured at baseline and on day 1 through day 5; puffing topography was observed	– the biomarkers of exposure to tobacco smoke toxicants were significantly reduced with THS2.1 use compared to cigarette smoking – THS2.1 was perceived as less rewarding in terms of sensory and physical effects than conventional cigarettes – THS2.1 users adapted their puffing behavior initially through longer puff duration and more puffs; however, on day 5 the total puff volume returned to baseline levels – the use of THS tobacco sticks increased by 27% over the study period
Haziza et al., Switzerland (2016) [77] PMI	to demonstrate reduced exposure to harmful and potentially harmful constituents among the subjects who switched from cigarettes to THS2.2, as compared to continued cigarette smoking and smoking abstinence for 5 days	160 healthy adult Japanese smokers (aged 23–65 years; 50% male): THS2.2 users (N = 80); cigarette smokers (N = 40), abstain from smoking (N = 40); 5-day exposure; each day 24-h urine was collected	– the levels of biomarkers of exposure to harmful and potentially harmful constituents were significantly reduced in the participants switching to THS2.2 compared to conventional cigarette smokers – THS2.2 reduced the urge to smoke in a manner similar to combustible cigarettes – THS2.2 was slightly less satisfactory than conventional cigarettes

Table 3. Human-based studies – a systematic review, 2015–2018 – cont.

Study type and reference	Aim of the study	Study design	Summary
Gale et al., United Kingdom/Switzerland (2018) [78] BAT	to evaluate changes in the biomarkers of toxicant exposure on switching from conventional cigarettes to HTPs	180 Japanese adult smokers (aged 33 ± 9.0 years; 50% male); THP1.0 (glo), THS2.2 (IQOS), a combustible cigarette; the smokers smoked combustible cigarettes for 2 days; after this period, they were switched to the following groups: 1) continue smoking, 2) switch to the mentholated or non-mentholated variant of glo, 3) switch to non-mentholated IQOS, or 4) quit nicotine and tobacco product use; each group used their dedicated products for 5 days; the baseline and post-randomization 24-h urine samples were collected, carbon monoxide in exhaled breath was measured daily	– glo or IQOS use for 5 days reduced the exposure to smoke toxicants in a manner comparable to quitting tobacco use – on day 5 after switching, the urinary biomarkers of toxicants (except the nicotine) and exhaled CO levels were significantly reduced by medians 21–92%, compared with the baseline in all groups using glo or IQOS, or quitting tobacco use

BAT – British American Tobacco; CO – carbon monoxide; ppm – parts per million; HPHCs – harmful and potentially harmful constituents; HTPs – heated tobacco products; PMI – Philip Morris International; THP1.0 – tobacco heating product (glo); THS2.1 – tobacco heating system 2.1 (the prototype of IQOS); THS2.2 – tobacco heating system 2.2 (IQOS); 3R4F – reference cigarette.

Independent studies performed with the aim of assessing the health impact of HTP use are very limited (Table 3). Adriaens et al. showed that 5 min of IQOS use resulted in a small but reliable increase (0.3 ppm) in the exhaled CO level [79]. Stephens et al. compared cancer potencies of various nicotine delivering aerosols [80]. Performed estimations revealed that HTPs had lower cancer potencies than traditional cigarettes, but higher potencies than most e-cigarettes [80].

Tabuchi et al. showed that among 8240 subjects who participated in a 3-year longitudinal survey, 12% (N = 997) reported secondhand exposure to heated tobacco aerosols [6]. Among all people exposed to secondhand smoke, 37% had experienced at least 1 health symptom. The most common reported symptoms after secondhand exposure to IQOS smoke were: feeling ill (25%), eye pain (22.3%) and sore throat (20.6%) [6]. The highest prevalence of symptoms caused by secondhand exposure to HTP smoke was observed among never-users of any tobacco products [6].

Researchers from Japan reported 2 cases of acute eosinophilic pneumonia following HTP use [81,82]. The first case of acute eosinophilic pneumonia was diagnosed in a 20-year-old man who had smoked 20 IQOS sticks daily for 6 months and doubled stick consumption 2 weeks before the hospitalization [81]. The second case of fulminant acute eosinophilic pneumonia was diagnosed in 16-year-old man with bronchial asthma in childhood, who had used HTPs for 2 weeks [82]. There were no available human-based studies assessing the potential impact of HTP use on lung physiology.

Moazed et al. reviewed the PMI modified risk tobacco product (MRTP) application to the U.S. Food and Drug Administration in 2016 [83]. An assessment of industry data revealed that IQOS use was associated with significant pulmonary and immunomodulatory toxicities, with no detectable differences between cigarette smokers and those who were switched to IQOS [83]. Furthermore, the analysis of the same PMI MTRP application by Glantz [84] suggested that, in human testing, IQOS did not reveal detectably better measures of the biomarkers of potential

harm than traditional cigarettes. Glantz pointed out that there were no statistically significant differences in the biomarkers of potential harm between IQOS and conventional cigarette users among American adults (for 23 of the 24 biomarkers) and Japanese adults (for 10 of the 13 biomarkers) [84].

Although tobacco industry sponsored studies have mostly shown health benefits of switching from conventional cigarette use to HTP use, independent studies indicate some potentially harmful consequences of exposure to HTP aerosols. Currently there is no evidence regarding the long-term health effects of HTP use. The potential role of HTPs as a tool in smoking cessation is also unknown.

The frequency of using heated tobacco products

Heated tobacco products have been widely available for only a few years. The data on the frequency of use of these products are mainly from Japan and Italy, the test markets where these products were first introduced (Table 4). Tabuchi et al. reported that the number of current IQOS users in Japan was consistently increasing, from 0.3% in 2015 to 0.6% in 2016, and up to 3.6% in 2017 [5,6]. The prevalence of Ploom TECH use in 2015–2017 increased 4-fold (from 0.3% to 1.2%) [5,6]. Among 8240 surveyed subjects, 0.8% declared the current use of glo [5,6]. Face-to-face interviews with 3086 Italians aged ≥ 15 years showed that 19.5% of respondents were aware of heated tobacco products [2,3]. Ever use of HTPs was reported by 1.4% of subjects and 2.3% of subjects intended to try HTPs in the near future.

Brose et al. estimated the awareness and prevalence of HTP use in Great Britain [85]. Among 12 696 adult participants, 9.3% were aware of heated tobacco products. Ever use of HTPs was declared by 1.7% of respondents and 0.8% were current users [85]. Kim et al. reported that among 228 young Korean adults, more than one-third (38.1%) were aware of IQOS [86]. The current IQOS use was declared by 3.5% of respondents, wherein all current IQOS users were triple users of conventional cigarettes and e-cigarettes, as well as HTPs [86]. HTPs have also gained popularity in the USA [87,88]. From 2016 to 2017, the awareness of HTPs among U.S. adults increased from 9.3% to 12.4%, ever use increased from 1.4% to 2.2%, and the current use doubled, from 0.5% to 1.1%, among U.S. adults [87]. In the USA, the highest awareness of HTPs was observed among current smokers as well as younger adults, under the age of 30 [88].

Tabuchi et al. pointed to the power of mass media and TV broadcasting as a tool to promote the use of IQOS [6]. The highest prevalence of ever IQOS use was observed among people who had seen a TV program where Japanese comedians discussed their IQOS use, compared to those who had not seen it. The willingness to use IQOS was significantly higher among current tobacco smokers with the intention to quit than among those with no intention to quit [6]. Experience with electronic cigarette use indicates that most smokers who reach for an e-cigarette to quit traditional cigarettes are dual users who ultimately use both forms of cigarettes [89]. A risk of dual use exists also in the case of heated tobacco products. Miyazaki et al. indicated a higher tendency (but not statistically significant) to ever use heated tobacco products among former smokers with lower education levels [89].

The study from Italy by Liu et al. also revealed that the highest prevalence of ever HTP users was among current e-cigarette users and current cigarette smokers [2,3]. Only 1% of those who had never smoked cigarettes and 1.2% of those who were never e-cigarette users had tried IQOS [2]. These findings were supported by a study from Great Britain, conducted by Brose et al [85]. Current e-cigarette users were more likely to use HTPs (6.2%) compared to subjects who had never used e-cigarettes (0.3%, $p < 0.05$). Ever e-cigarette users were also more likely to be aware of HTPs [85]. In Korea and the USA, the highest awareness and ever or current use of HTPs were also observed among current smokers or e-cigarette users [86,87].

Table 4. The frequency of using heated tobacco products – a systematic review, 2015–2018

Study type and reference	Aim of the study	Study design	Summary
Independent studies			
Tabuchi et al., Japan (2016) [5]	to estimate the awareness and use of e-cigarettes and HTPs in the Japanese population	an Internet survey, including 8240 respondents (aged 15–69 years) in the final analysis, the study performed in 2015	– as many as 6.6% of respondents ever used e-cigarettes or HTPs – among the 554 subjects who ever used e-cigarettes or heat-not-burn (HNB) tobacco, 7.8% ever tried Ploom TECH, and 8.4% ever used IQOS
Tabuchi et al., Japan/ Italy/USA (2017) [6]	to assess the prevalence, predictors of use and symptoms of secondhand exposure to HTP (IQOS, Ploom TECH or glo) tobacco aerosols in Japan	2 data sources: Google search query data to assess the population's interest in HTPs a follow-up 3-year longitudinal Internet survey of 8240 subjects (aged 15–69 years in 2015) to evaluate the prevalence of the current HNB tobacco use	– the number of current IQOS users was constantly increasing, from 0.3% in January–February 2015 to 0.6% in 2016, and up to 3.6% in 2017 – the highest prevalence of ever IQOS use was among people who had seen a television program (10.3%) promoting IQOS, compared to the people who had not seen it (2.7%) – the prevalence of Ploom TECH for 2 years increased 4 times (from 0.3% in 2015 to 1.2% in 2017) – in 2017 0.8% of subjects were current glo users – the willingness to use IQOS was significantly higher among current smokers with an intention to quit than among those with no intention to quit (AOR: 13.3 vs. 6.7, respectively)
Liu et al., Italy (2018) [2,3]	to investigate the awareness and use of HTPs in Italy	a face-to-face survey of 3086 subjects, from a representative population aged ≥ 15 years	– as many as 19.5% of respondents were aware of HTPs – as many as 1.4% of respondents had ever used HTPs, and 2.3% intended to try HTPs – the highest prevalence of ever HTP users was among current e-cigarette smokers (7.7%), and current cigarette smokers (3.1%); only 1% of the respondents who had never smoked cigarettes and 1.2% of never e-cigarette users had tried IQOS
Brose et al., United Kingdom (2018) [85]	to estimate the awareness and use of HTPs in Great Britain	a cross-sectional online survey, February–March 2017, involving 12 696 adults	– as many as 9.3% of respondents were aware of HTPs – as many as 1.7% of respondents had ever used HTPs, of whom 0.8% were current users – never e-cigarette users were more likely to be unaware of HTPs – current e-cigarette users were more likely to use HTPs (6.24%) compared to the subjects who had never used e-cigarettes (0.33%, $p < 0.05$) – among the 173 subjects who had ever tried HTPs, 38.7% had tried them up to 2 times, 17.3% used them weekly, and 12.7% were daily HTP users

Kim et al., Republic of Korea (2018) [86]	to investigate the awareness, experience and current use of IQOS among young Korean adults	228 young adults, aged 19–24 years, an online survey performed 3 months after the introduction of IQOS to the Korean market	– as many as 38.1% of respondents were aware of IQOS, wherein the IQOS awareness was significantly higher for conventional cigarette smokers (57.5%) compared to non-cigarette smokers (42.5%) – as many as 5.7% of respondents had tried IQOS – the current use of IQOS was declared by 3.5% of respondents, wherein all current IQOS users were triple users of conventional cigarettes and e-cigarettes – current cigarette smokers were much more likely to be aware of IQOS (OR = 4.49) and to ever be IQOS users (OR = 11.64) than non-smokers
Nyman et al., USA (2018) [87]	to investigate the awareness and use of HTPs in the USA	a national probability sample of U.S. adults, online Products and Risk Perceptions Surveys, data from 2016 (N = 6014) and 2017 (N = 5992)	– in 2016–2017 the awareness of HTPs among U.S. adults increased from 9.3% to 12.4% ($p < 0.001$), ever use increased from 1.4% to 2.2% ($p = 0.005$) and current use increased 2-fold, from 0.5% to 1.1% ($p = 0.004$) – the highest awareness of HTPs was among men and younger adults – former and current e-cigarette users were more likely to be aware of, to have ever used or to be current users of HTPs than those who had never used e-cigarettes
Marynak et al., USA (2018) [88]	to assess the awareness and ever use of heated tobacco products among U.S. adults	an Internet survey conducted in June–July 2017 among U.S. adults aged ≥18 years (N = 4107)	– as many as 5.2% of U.S. adults were aware of HTPs, including 9.9% of current cigarette smokers – as many as 0.7% of U.S. adults, including 2.7% of current smokers, had ever used HTPs – current smokers were more likely to be aware of HTPs (aOR = 6.18) than never smokers, and younger adults (aged < 30 years [aOR = 3.35]) were more likely to be aware of HTPs than those aged ≥ 30 years
Miyazaki et al., Japan (2018) [89]	to analyze the relationship between educational attainment and e-cigarette and HTP use	7338 respondents (randomly sampled, a national representative sample) aged 18–69 years in 2015 (3706 women);	– the association between educational attainment and ever use of HTPs was not statistically significant – former smokers with a lower educational level indicated the tendency to higher ORs (but not statistically significant) for both e-cigarette and HTPs ever use

Table 4. The frequency of using heated tobacco products – a systematic review, 2015–2018 – cont.

Study type and reference	Aim of the study	Study design	Summary
Caputi et al., Japan/ USA (2017) [1,90]	to describe trends in the popularity of HTPs in their Japanese test market, and to compare these trends with historical trends for e-cigarettes to understand the growth potential of this new product globally	monthly Google query trends monitoring (from 1.01.2010 through 13.09.2017); all queries including HNB tobacco and/or the most popular brands in Japan; a comparison of the Japanese HTPs search trends against searches for e-cigarettes in the United States	– searches for HNB products have increased substantially – average monthly searches rose by 1,426% (95% CI: 746±3,574) between the first (2015) and second (2016) complete years since HTPs were marketed – queries for HTPs continued to grow in 2016–2017 (to September): an additional 100% (95% CI: 60±173) – queries for HNB products in Japan occur more frequently than queries for e-cigarettes in the USA – the change in average monthly queries for HTPs in Japan in 2015–2017 was 399 (95% CI: 184±1,490) times larger than the change in the average monthly queries for e-cigarettes in the USA over the same time period
Studies with a potential conflict of interest none available			

AOR – adjusted odds ratio; CI – confidence interval; HTPs – heated tobacco products; OR – odds ratio.

Given the consistent growth and development of the e-cigarette market, it is expected that the popularity of HTPs will also increase rapidly. The 10-fold increase in the frequency of IQOS use in Japan, observed within 3 years, indicates the rapidly growing magnitude of the problem [6]. Caputi et al., assessing the growth potential of heated tobacco products, compared trends in the popularity of HTPs with historical trends for e-cigarette use in Japan [1,90]. The monthly Google query trends monitoring revealed that the average monthly searches for HTPs rose by 1,426% between 2015 and 2016 [90]. Moreover, the change in the average monthly queries for HTPs in Japan in 2015–2017 was approx. 399 times larger than the change in the average monthly queries for e-cigarettes in the USA over the same time period [90].

Due to the increase in the frequency of HTP use and the growing number of countries where these products are being introduced, the prevalence of heated tobacco use requires constant monitoring.

Marketing strategies of HTP promotion

In many countries, heated tobacco products are under different laws and jurisdiction than conventional cigarettes, which has implications on the marketing strategies and promotion of these products (Table 5). In Japan, heated tobacco products are sold as tobacco products and regulated by the Tobacco Industries Act [5]. In South Korea, heated tobacco products are regulated as a variant of e-cigarettes [4]. In the EU, advertising for IQOS and other heated tobacco devices (except for the tobacco stick) is not regulated under the European Union Tobacco Products Directive (2014/40/EU) [3]. Elias et al. analyzed internal PMI documents [91]. After a comparison of the product design, exposure data, and safety claims, the authors concluded that IQOS appeared to be a variant of Accord without consistent improvements in exposure to aerosol toxic compounds [91]. Elias et al. suggested that the industry's reduced risk claim was an effect of the marketing

Table 5. HTP marketing strategies and product promotion – a systematic review, 2015–2018

Study type and reference	Aim of the study	Study design	Summary
Independent studies			
Kim, USA (2017) [4]	to describe PMI's marketing of IQOS in South Korea	news monitoring, direct observation – study visits by the author to the 2 flagship stores in Seoul (June 2017) and the purchase of an IQOS device from 1 store	– the manufacturer encourages customers to register on a dedicated website to obtain a limited-time discount for their first device purchase and to extend the warranty from 6 to 12 months – a professional presentation by an "IQOS coach": all store customers take part in a 15-min information session before buying their fist IQOS device – designs of the store, device and packaging, and the product purchasing process give an impression that IQOS is a high-demand, upscale product for tech-savvy users – due to the Korean IQOS regulation (as a variant of e-cigarettes) IQOS sticks packs have only labels warnings about nicotine addiction, without showing various negative consequences of smoking – the tax on IQOS sticks is only half of that on regular cigarettes – the price of IQOS sticks is similar to regular cigarettes
Mathers et al., Canada (2018) [92]	to describe PMI's marketing of IQOS in Canada	data on IQOS promotion in 49 retail outlets, interviews with clerks and observations outside an IQOS store	– the dominant marketing channel was visible availability of IQOS in a large number of tobacco retail outlets (1029 across Ontario) – IQOS boutique stores were the locus of aggressive promotion, including exchanging a pack of sticks or a lighter for an IQOS device, launch parties, "meet and greet" launches and after-hours events – the prominent IQOS signs and a sandwich board sign reading "Building a Smoke-Free Future" were widely available outside the stores – sales representatives regularly using IQOS made a significant contribution to the direct promotion of that product – IQOS users were invited to register as customers on a dedicated website, where they received customer support, dedicated marketing campaigns and a map of retail locations – registered IQOS users were regularly invited to complete surveys about IQOS use, for which they were compensated with an opportunity to win prizes

Table 5. HTP marketing strategies and product promotion – a systematic review, 2015–2018 – cont.

Study type and reference	Aim of the study	Study design	Summary
Hair et al., USA/ United Kingdom (2018) [93]	to examine consumer perceptions, attitudes and behaviors regarding the heated tobacco product (IQOS); to document the product marketing strategies to determine its potential for appealing to young adults in Japan and Switzerland	expert interviews; a semiotic analysis of the IQOS packing and marketing materials; 12 focus groups with adults in Switzerland and Japan (N = 68 for both groups)	– IQOS users from Japan and Switzerland reported lower levels of satisfaction with the product relative to combustible cigarettes – Japanese IQOS users used the product for socializing with non-smokers – brand ambassadors were employed to showcase the product and answer questions with free samples – the product marketing exhibited 4 key messages: cleanliness, customization, comparisons with combustible smoking, and sociability
Rosen et al., Israel (2018) [94]	to describe the entry of IQOS to Israel, and its marketing campaign	data on IQOS entry to Israel	– 2 distinct campaigns: the Policy Makers Campaign (the lobbying of intended legal regulations) and the Public Campaign (a digital marketing campaign, photos of the product and short text messages to promote the product in public) – 5 campaign elements: PMI's "Smoke-free Israel Vision," the harm-reduction claim, proposing different regulations for "non-combustible products," attempting to tax IQOS at a different rate than cigarettes; advertising slogans (e.g., No fire/No smoke/No ash)
Kreitzberg et al., USA (2018) [96]	to describe HTP marketing strategies on Instagram	the Instagram programming interface was used to examine the image content of HTP posts, general textual topics and larger themes related to these textual topics, public health relevant topics, and different types of Instagram users who posted HTPs; IQOS related hashtags (e.g., #IQOS, #IQOSFamily, #IQOSFriends) were used to identify HTP content	– there were 12 774 posts and comments related to IQOS identified – posts associated HTPs with #luxury, #fashion, and #superiority – posts compared heated tobacco devices with cigarettes and suggested their use for smoking cessation – HTP users customized their IQOS cases, tips, and skins, and the framing of these devices, as fashion accessories – Instagram may increase the social acceptance of tobacco use
Studies with a potential conflict of interest none available			

HTPs – heated tobacco products; PMI – Philip Morris International.

strategy focused on the social and regulatory landscape rather than the result of toxicological differences between IQOS and its precursor, Accord [91].

According to Italian law, advertising and promotions of heated tobacco products are not banned [3]. Dedicated shops called an "IQOS embassy" or an "IQOS boutique" are present in several strategic Italian cites [3]. Similar shops are present in Japan, South Korea, and Canada [4,92]. In these fancy concept stores (designed similar to electronics stores), people can try IQOS for free [3,4]. Mathers et al. noted that sales representatives in Canada, by regularly using IQOS, made a significant contribution to the direct promotion of this product [92]. A similar marketing strategy was launched in Japan where "brand ambassadors" were employed to showcase the products and answer questions with free samples [93]. In South Korea, each IQOS-store customer takes part in a 15-min professional presentation by an "IQOS coach" before buying their first IQOS device [4]. Rosen et al. identified 5 elements of a marketing campaign of IQOS in Israel, including the following: 1) Philip Morris's "Smoke-free Israel Vision"; 2) the harm-reduction claim; 3) the proposition of a different regulation for "non-combustible products"; 4) attempts to tax IQOS at a different rate from that applicable to cigarettes; and 5) catchy advertising slogans (e.g., No fire/No smoke/No ash) [94].

Liber reported that, in most of the countries where HTPs were sold, these products had received tax advantages and its tax rates were lower than those of conventional cigarettes [95]. The differences between regulations for traditional cigarettes and HTPs can also be seen in the packaging of these products. For example, in Italy, health warnings are required to cover only 30% of the HTP packing in contrast to the traditional cigarette packing where warnings are required to cover 65% of cigarette packs [3]. In South Korea, the IQOS tobacco stick packs only have labels warning about nicotine addiction, without showing various negative consequences of smoking [4]. Moreover, the IQOS classification as a variant of e-cigarettes implies taxation and, in Korea, taxes on IQOS tobacco sticks are only half of that of traditional cigarettes [4]. In Israel, IQOS is taxed at the same rate as cigarettes [94].

Kreitzberg et al. identified 12 774 posts and comments related to IQOS on Instagram (a photo and video-sharing social networking service) [96]. The analysis of the IQOS users' behavior in social media has shown that they are customizing IQOS devices and accessories dedicated to HTPs [96]. Sharing content related to the use of IQOS in social media, such as Instagram (photos when using the device or photos of customized devices), is used to build a community identified by such hashtags as #IQOSFamily or #IQOSFriends. Kreitzberg et al. suggested that Instagram might increase the social acceptability of tobacco use and, due to this fact, there should be an age restriction on the content promoting HTPs [96].

Furthermore, in many countries, heated tobacco products may be used in public places, in contrast to traditional cigarettes. All these activities have the potential to change social norms and attitudes towards tobacco use, and suggest to the public that HTPs are a safe form of tobacco use. Elias and Ling emphasized the key role of respected health leaders in shaping public attitudes towards novel tobacco products and their impact on the commercial fate of HTPs [97]. The authors encouraged public health experts to carefully formulate opinions, bearing in mind the past experience with the industry-backed "safer tobacco products," such as filtered and low-tar cigarettes, which served to undermine and delay the global tobacco control efforts [97]. Lempert and Glantz pointed out legal uncertainties regarding HTPs, especially electronic devices used to heat up tobacco sticks [98]. The authors concluded that in the USA and parties to the WHO Framework Convention on Tobacco Control (FCTC) all components of HTPs should be regulated at least as stringently as tobacco products and should be subject to all tobacco control laws that apply to other tobacco products [98].

DISCUSSION

The heated tobacco smoking technology has become increasingly popular [6,79]. The most popular HTP product – IQOS from PMI – is widely available in 33 countries worldwide, including 21 European countries [93]. Other popular HTPs – glo and Ploom TECH – are also gaining new markets [6]. The source of the aerosol is a tobacco stick made of processed tobacco [12,13]. Tobacco sticks are available in multiple flavors [10,20]. The variety of flavors, and especially the introduction of sweet fruit variants of tobacco sticks, may encourage young people to reach for HTPs because of their attractive taste. The chemical composition of HTP tobacco sticks differs from traditional cigarettes [22]. However, both of them have a comparable nicotine concentration [9,21]. Therefore, the levels of nicotine contained in the HTP aerosol have been 70–80% as those of conventional combustion cigarettes [15,27,29,33], based on the results of both independent and industry studies. This finding may suggest that HTPs were launched in response to the dissatisfaction with the lack of rapid nicotine delivery by e-cigarettes. However, further research is needed to describe the profile and characteristics of HTP users.

According to the tobacco industry data, aerosols formed during the heating process have around 90–95% lower levels of toxicants than conventional cigarette smoke [13–15,23,24]. Independent studies have confirmed that the concentration of chemical compounds generated by HTPs is lower than that generated by traditional cigarettes [27,28,33]. However, toxic compounds are not completely removed from the HTP aerosol [7,19,25–35]. The results of independent studies have shown that IQOS emit substantially lower levels of carbonyls and submicronic particles than a commercial cigarette but higher levels than an e-cigarette [25,26,28]. The emission of reactive oxygen species during IQOS use points to potentially harmful effects of IQOS use, such as cancer or pulmonary diseases [38]. Moreover, an independent review of preclinical and clinical data on IQOS has revealed the possible hepatotoxicity associated with IQOS use [70]. Chun et al. suggested that HTP use might have unexpected organ toxicity not observed when smoking traditional cigarettes [70].

Following the manufacturer recommendations, especially proper cleaning of the device after each 20 tobacco sticks seems to be crucial to provide proper thermal regulation and reduce emissions of harmful substances. Most of the research regarding the chemical composition of generated aerosol was carried out on brand new, never used devices [39–54]. Independent researchers showed that the use of 1 IQOS tobacco stick left a significant amount of debris, fluid, and fragments of cast-leaf in the device holder [8]. It can be assumed that the lack of proper cleaning can lead to the accumulation of undesirable substances in the holder, influencing the heating conditions and chemical composition of the generated aerosol.

The tobacco industry has performed multiple studies regarding health consequences of HTP use. The results of *in vitro* and *in vivo* studies indicate that HTP aerosols have lower toxicity and no new hazards compared to conventional cigarette smoke [39–54]. The results of human-based studies also suggest that switching from conventional cigarettes to IQOS or glo leads to reductions in exposure to smoke toxicants in a manner comparable to quitting tobacco use [74–78]. However, there have been no independent studies regarding short-term and long-term health consequences of HTP use.

Data provided by the tobacco industry did not convince the leading health organizations to recognize HTPs as "reduced risk products" [99–101]. In December 2016, PMI applied to the FDA (U.S. Food and Drug Administration) to consider IQOS as a modified risk tobacco product [83]. In January 2018, the FDA Tobacco Products Scientific Advisory Committee concluded that there was no conclusive scientific evidence that IQOS use was less risky than continuing tobacco smoking and PMI should not claim that IQOS use cut the risk of tobacco-related diseases [86,102]. Furthermore, the FDA experts were not convinced that

smokers would use IQOS alone and stated that there was a high to medium risk of dual use of IQOS and conventional cigarettes [86,102].

According to the World Health Organization (WHO) statement, there is no evidence that HTPs are less harmful than conventional cigarettes [99]. The WHO has also emphasized that conclusions about the HTP ability to assist with quitting smoking cannot yet be drawn. The WHO has concluded that all forms of tobacco use are harmful and new tobacco products should be regulated under the WHO Framework Convention on Tobacco Control (FCTC) [99].

The European Respiratory Society (ERS) has stated that, as with regular tobacco smoking, heated tobacco products are addictive and carcinogenic to humans [100]. According to the ERS statement, there is no evidence that heated tobacco products are efficient tools to aid in smoking cessation. Moreover, the ERS cites some strong evidence suggesting that studies performed or sponsored by tobacco industry companies cannot be trusted [100]. The ERS has concluded that it cannot recommend any products which can be harmful to the lungs and human health [100].

A more liberal position is presented by Public Health England (PHE) [101]. This organization has concluded that available evidence suggests that heated tobacco products may be considerably less harmful than conventional cigarettes, but more harmful than e-cigarettes [101]. Despite this fact, PHE emphasizes the urgent need to provide more research independent of commercial interests [101].

The prevalence of HTP use is constantly growing, especially among current cigarette or e-cigarette smokers [6]. Such a high interest in HTPs among current smokers may pose a risk of dual use in this group. In many countries, the advertising and promotion of HTPs are not banned [3,98]. The marketing strategies and promotion of these products, such as fancy concept stores, brand ambassadors, and free samples testing, can support the increase in the number of HTP users [4,92,93]. Like e-cigarettes [103,104], HTPs are advertised via the Internet and social media [92–94]. Tobacco companies use dedicated hashtags and advertising slogans to promote HTPs on their websites [96]. The use of social media for the promotion of HTPs can make it more difficult to monitor the marketing activities which may contradict the WHO Framework Convention on Tobacco Control.

Current knowledge on HTP exposures and health effects is often based on data provided by the tobacco industry (52% of identified studies). There is a need for future independent research, especially human-based studies assessing short-term as well as long-term health effects of HTP use. Future studies will provide more information about passive HTP smoking and the impact of HTP secondhand smoke on bystanders, which will be crucial to implement proper regulations regarding HTPs, especially HTP use in public places. Currently, there is no evidence that HTPs can be used as an effective tool for smoking cessation. This topic also needs further investigation.

There are a few limitations to this study. This review was restricted to peer-reviewed articles available in English. Most of them focused only on data from 5 countries, which limits the external validity of this research. There was also substantial variation in the study designs of *in vitro* and *in vivo* studies, especially the conditions of exposure and the length of follow up. Sample sizes also varied substantially between studies. Nevertheless, this study is the most up-to-date systematic review regarding heated tobacco products and addresses several different aspects of HTP use.

CONCLUSIONS

Heated tobacco products are gradually gaining in popularity. A chemical analysis of aerosols has revealed that heated tobacco products release lower levels of toxic chemicals compared to conventional cigarettes. However, toxic compounds are not completely removed from the HTP aerosol and these products are still not risk-free. The nicotine levels delivered to the aerosol by heated tobacco products were almost the same as those of conventional combustion. Health consequences of HTPs as well as their role in

smoking aid are unknown. Among the currently available data on HTPs, most papers (52%) have been sponsored by the tobacco industry. There is a need for the future independent and standardized investigations of the potential health effects associated with heated tobacco use and HTP potential in smoking cessation aid.

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