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Heated tobacco products

Summary of research
and evidence of health impacts



World Health
Organization

Heated tobacco products: summary of research and evidence of health impacts

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Introduction

Heated tobacco products (HTPs) are a re-emerging class of consumer products that heat tobacco and deliver aerosolized nicotine to the user through the mouth for inhalation. In 1988, RJ Reynolds was the first company to sell HTPs to consumers, when it introduced Premier, a cigarette-like device heated by a carbon-tip element with a cigarette-like column consisting of aluminium capsules containing tobacco, onto test markets in the USA (Fig. 1). As this product was not a marketing success, Premier was withdrawn from the market in 1989. In 1996, RJ Reynolds again tried to market an HTP in the USA, with a product named Eclipse that had a carbon-tip element and a tobacco rod consisting of reconstituted tobacco. This product was withdrawn in 2007, but, in July 2018, the US Food and Drug Administration (FDA) allowed marketing of a slightly modified version because it was substantially equivalent to the previously marketed version of the product. In 1998, Philip Morris USA introduced Accord, a tobacco-heating system consisting of cigarette-like tobacco-containing components inserted into an external heating device. Accord was withdrawn from the US market in 2006. That same year, Philip Morris International (PMI) marketed Heatbar, a device similar to Accord, but withdrew this product from the market in 2008.

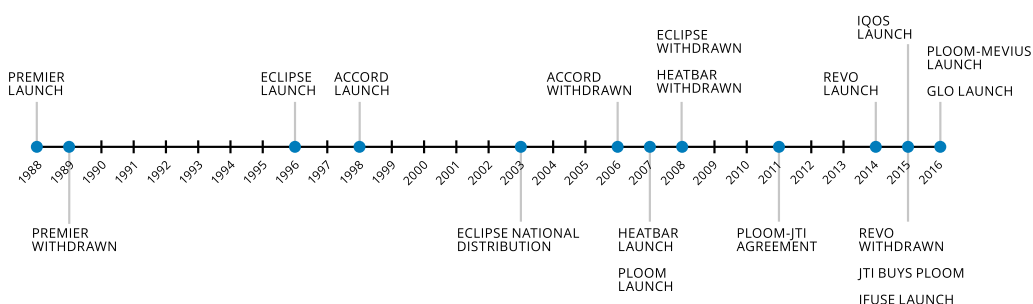


Fig. 1. Timeline of introduction of heated tobacco products, 1988–2016

Source: WHO (1).

A new generation of HTPs emerged with the launch of the Ploom, glo and IQOS brands. Ploom was a new HTP design with the same operating principle as Accord and was launched in the USA in 2007 by PAX Labs, a company with no direct ties to the tobacco industry but which was affiliated with Japan Tobacco International (JTI) in 2011 and was purchased outright by JTI in 2015. PMI launched IQOS onto various markets in 2015, and British-American Tobacco (BAT) introduced glo onto several markets in 2016.

HTPs: Definition, basic characteristics and design features

HTPs have two common components: an insert (such as a stick, capsule or pod) containing processed tobacco and a device to heat the tobacco. The heating source is usually electronic but may be a carbon tip. Tobacco inserts and devices are combined into an integrated tobacco product and are not intended to be used separately.

Manufacturers have used four basic design approaches to HTPs, depending on the mechanism for transferring heat to the tobacco and whether the tobacco material is combined with or separate from the heating element (Table 1).

Table 1. Classification of heated tobacco products (HTPs)

HTP type	Heating element	Tobacco	Example products
1	Device with a carbon tip that is lit	Tobacco provided by the device manufacturer in an adjacent chamber of the device	Premier, Eclipse, PMI "Platform 2" (TEEPS)
2	Device with a coil or blade resistance heated by electricity	Specially designed tobacco sticks provided separately by the device manufacturer	Accord, Heatbar, IQOS, glo
3	Device with a coil resistance heated by electricity that aerosolizes a liquid that passes through and warms the tobacco	Capsule containing tobacco and liquid provided separately by the device manufacturer	iFuse, PloomTech
4	Device with a mini oven heated by electricity	Loose tobacco not provided by the device manufacturer	Pax

HTPs release nicotine from tobacco by heating at a temperature lower than that of traditional cigarettes. The tobacco used is typically reconstituted, allowing manufacturers to manipulate the form and amount of nicotine. Humectants such as propylene glycol and glycerol are added to the tobacco to facilitate formation of

an aerosol (2). This aerosol, which is generated either separately (type 3) or during heating of the tobacco, serves as the vehicle to deliver nicotine to the user's lungs. Different HTP devices use various heating sources, including electric energy via a battery or a carbon tip that is ignited and smoulders. Eclipse (type 1) contains a pressed carbon cylinder and a tobacco rod in a single device. In PMI's IQOS (type 2), when the tobacco stick is introduced into the device, a blade enters the tobacco, so that, when electric power is applied to the blade by pressing a button, heat penetrates the tobacco (3). The heat generates an aerosol that passes through a hollow acetate tube and a polymer film filter to the user. BAT's HTP glo is similar to the previous Philip Morris product, Accord, in which a heating tube is activated by the user by pressing a button on the device (3). BAT's iFuse and JTI's Ploom Tech (type 3) are hybrid ENDS – tobacco products that generate an aerosol with ENDS technology and pass the aerosol over tobacco before delivery to the user (4). The iFuse e-liquid contains nicotine, whereas the Ploom Tech does not. Personal dry-herb vaporizers (type 4), such as Pax, are marketed to aerosolize the neurologically active chemicals in either cannabis or tobacco.

Marketing, including promotional strategies and impacts

Euromonitor International (5) predicts that the sales of HTPs worldwide will continue to rise, replacing much of the decrease in traditional cigarette sales. It is expected that global sales will continue to grow, from a global market value of US\$ 6.3 billion in 2018 to US\$ 22 billion by 2024 (6). This prediction approaches the market share expected to be gained by ENDS but is still dwarfed by the global market for cigarettes, which was valued at US\$ 888 billion in 2018 (7).

Three transnational tobacco companies, PMI, BAT and JTI, currently dominate the global HTP market. With Ploom HTP in 2013, JTI was the first transnational tobacco company to launch the new generation of HTPs, which have obtained a significant market share. Their Ploom HTPs (Ploom TECH, Ploom TECH+ and Ploom S) are available in Canada, Japan, Switzerland and the USA (8). PMI launched IQOS in 2014 in Japan, and this HTP was for sale on 57 markets as of June 2020. PMI estimated that, in 2020, there were 15.4 million IQOS users worldwide (9). BAT introduced iFuse in Romania in 2015 and then launched glo in Asia, which is now for sale on 17 markets. Korea Tobacco entered the HTP market in the fourth quarter of 2017 with the introduction of lil onto their domestic market.

The Asia–Pacific region currently reports the largest share of revenue from HTP sales, with use concentrated in the age group 18–39 years. Japan accounted for the largest share of that revenue and for 85% of the market in 2018 (10). HTPs have been widely used in Japan because electronic cigarettes with nicotine, which are used elsewhere, are prohibited under the Pharmaceutical Medical Device Act. HTP sales in the Republic of Korea, however, are increasing faster than in any other country (11). Other countries that have robust HTP markets now or are expected to see dramatic increases in sales of HTPs include Croatia, Czechia, Germany, Italy, Poland, Romania, the Russian Federation, Türkiye, Ukraine and the USA (12,13).

The marketing strategies used for HTPs are largely similar to those used for years by their parent tobacco companies to attract customers, primarily young people, and include:

- promoting these tobacco products as posing a lower health risk than conventional cigarettes (CCs) while allowing consumers to continue to enjoy the smoking experience;
- promoting these tobacco products as smokeless alternatives to cigarettes, thereby suggesting their use in places where smoking is prohibited;
- promoting the device separately from the tobacco inserts to avoid restrictions on tobacco advertising and promotion;
- design to appeal to the user’s social image;
- appealing to users’ desire for discretion and convenience by decreasing second-hand smoke, reducing odour, lengthening the battery life and rapid charging;
- opening dedicated retail stores for HTP brand demonstrations, sales and individual customer consideration;
- using strategies such as discount pricing of a base device, with recurrent sales of refills (e.g. HeatSticks);
- using marketing techniques that involve community activators and brand ambassadors, who promote HTPs through various channels, including social media marketing; and
- selling and marketing through multiple channels, including dedicated HTP retail establishments and e-commerce websites that emphasize the high-technology features of the products.

Robust peer-reviewed evidence of an association between HTP advertising and promotion and use is not yet available; however, research has identified youth-oriented aspects of HTP advertising, including high-tech and novel design features, claims that HTPs may be less harmful than combusted products, messaging as a more socially acceptable alternative to combusted products and use of young models in advertising (14,15). HTP advertising and promotional messaging and media should be closely monitored because of the appeal of HTPs and prevalence of use among youth and young adults.

Attractiveness

For consumers to initiate use of any product, they must first be attracted to that product. “Attractiveness” has been defined by WHO (16) as

factors such as taste, smell and other sensory attributes, ease of use, flexibility of the dosing system, cost, reputation or image, assumed risks and benefits, and other characteristics of a product designed to stimulate use.

Consumers rate the sensory properties of HTPs as less satisfying than those of conventional cigarettes, but they are willing to try them because of the suggestion of lower risk than CCs.

Participants in qualitative studies on HTPs reported that they were attracted by the reduced smoke odour but that the products felt unfamiliar, cumbersome and complicated to use (17). The price of devices may far exceed the price of the consumables (inserts containing processed tobacco); however, the unit price of consumables is generally close to that of CCs, and excise taxes on HTP consumables are generally lower than those on CCs. Although the price of the devices may be a barrier, it may contribute to the cachet of the product as luxurious and prestigious (18). HTPs marketed in futuristic flagship stores appeal strongly to youth and young adults, who are particularly enamoured of upscale high-tech devices. The innovative design and marketing build on the heightened interest of affluent young people in cell phones, video games and other electronic gadgets. Linking HTPs to popular cigarettes brands such as Marlboro, Camel or Kent can have a “halo effect” on current users of combusted cigarettes, easing the transition to use of a new product (19).

Tobacco companies use flavoured ingredients to reduce irritating sensations and provide organoleptic appeal to users and bystanders. The flavours used in tobacco products, however, appeal more to adolescents than to adults. Worldwide, HTPs are available in a variety of flavours, including tobacco, fruit, menthol and confectionary, but some focus group participants have also reported strange or unpleasant tastes or smells, milder taste, lower sensory cues and less throat discomfort (20). The variety of flavours is an attractive feature for non-smokers, including adolescents, and smokers who wish to change their current smoking experience. Young adults may become susceptible to using HTPs after viewing advertisements of fruit-, mint- and sweet-flavoured products. More research should be conducted to better understand the influence of flavours on HTP initiation and maintenance of use.

Perception

People's perception of products is largely influenced by what they are told about them and whether their subsequent use experience conflicts with the frame they were provided. Few studies are available on perceptions of HTPs among users and non-users, but there is a direct association between marketing and initiation of HTP use. In Japan, the largest volume of Internet searches for IQOS was seen during the week after a popular national television show that introduced IQOS (21), and sales and use of IQOS quickly accelerated thereafter. HTPs have been widely marketed as safer than CCs (22), and current and ever users of IQOS in the Republic of Korea indicated that the main reasons for using the products were perceptions that the product was less harmful or was useful in stopping smoking (23).

A qualitative study in the United Kingdom (24) identified several important factors related to consumers' perception of IQOS, which are likely to be similar in other countries:

- health (wanting to reduce or quit smoking and perceptions of reduced harm);
- cost (high start-up costs but cheaper continuing costs than smoking);
- some sensory experiences that influenced use, including discretion, cleanliness, less smell and tactile similarities to combustible cigarettes;

- ease of use (poor access, difficulty in maintaining or operating HTPs, which limits continuing use, whereas the possibility of using HTPs in smoke-free places increases use);
- use practices (similar rituals and routines, although new practices are developed to charge and clean; some liked “trailblazing” new technology); and
- social aspects (better social interactions when using IQOS instead of smoking, although some reported more limited sharing of social experiences).

Addictive potential

Addictive potential can be considered an indicator of a product’s abuse liability. Nicotine is the primary addictive component in all tobacco products, including HTP aerosol. If HTPs deliver nicotine to users and a maximum blood concentration similar to that with CCs is quickly attained, they are likely to have similar addiction potential. Tobacco product manufacturers design HTPs to deliver nicotine at rates and concentrations similar to CCs in order to encourage current smokers to initiate and continue use of HTPs. While substantial product development has gone into achieving this goal, manufacturers have had limited success, except for one brand. To date, 11 studies are available on nicotine delivery by HTPs, of which five were conducted or funded by HTP manufacturers. Many of these papers have been reviewed and are summarized below (25).

Investigators have reported that the nicotine content of IQOS Heatsticks (approximately 15.5 mg/g) is similar to that in CCs (15–20 mg/g) (26,27). Because Heatsticks are shorter, narrower and have higher levels of additives than CCs, they have less tobacco per stick than CCs. When IQOS are machine-smoked under the Canadian Intense smoking regimen, they deliver about 75% of the nicotine commonly delivered by traditional cigarettes. Uchiyama et al. (28) published the results of machine-smoking of several HTPs in both the ISO and the Canadian Intense smoking regimens. They found that IQOS delivers more nicotine per insert than glo, which delivers more nicotine than PloomTech.

In one study of nicotine pharmacokinetics in rats, 1.5–5 min of exposure to the aerosol from a single Heatstick in an IQOS yielded a 4.5-times higher post-exposure serum nicotine concentration than exposure to cigarette smoke (29). With briefer exposure, the serum nicotine concentrations were similar.

Both independent researchers and product manufacturers have studied the delivery of nicotine to human volunteers. In one independent study, the mean plasma cotinine (primary metabolite of nicotine) concentration increased from 34.4 ng/mL before using a CC to 65.5 ng/mL afterwards and from 30.4 ng/mL before using an IQOS to 61.0 ng/mL afterwards (30). In a similar study with a loose-leaf tobacco vaporizer HTP, Ploom, plasma nicotine levels increased by about 15 ng/mL with the HTP and by about 24 ng/mL with a traditional cigarette (31). The tobacco industry has reported nine studies of the human pharmacokinetics of nicotine after use of HTPs (25). In studies of use of the latest version of IQOS, similar maximum concentration and time to maximum concentration were found as with CCs, and the mean concentrations of nicotine and cotinine in plasma after extended use of IQOS were similar to those found when smoking cigarettes. In contrast, studies of users of glo indicated that the levels of biomarkers of nicotine were 59–74% those of cigarette smokers.

In six studies by the industry, the Questionnaire on Smoking Urges was used to evaluate the degree to which use of IQOS relieved craving (25). In these studies, use of IQOS was found to relieve craving similarly to CCs; however, one independent study found that IQOS was less effective than smoking. Studies conducted with the Modified Cigarette Evaluation Questionnaire by both independent and tobacco industry investigators found that IQOS was less reinforcing than smoking cigarettes.

Overall, the studies of the addiction potential of HTPs suggest that the most recent version of IQOS delivers a similar amount of nicotine and is as effective in reducing craving as CCs. Other HTPs may be less effective, but the data are limited. Future devices may achieve higher nicotine delivery.

Use behaviour, including a potential role in initiating and quitting smoking

Even if a product is demonstrably associated with a lower risk than CCs, its potential impact on death and disease due to combusted tobacco use depends on its effectiveness in encouraging and sustaining complete switching from a higher-risk to a lower-risk product. Thus, use behaviour is a key to evaluating any benefits of these products to the current tobacco product harm landscape. Few studies are available on the impact of HTPs on use of other tobacco products. Most of the

available data are from studies conducted in Japan and from the “modified risk tobacco products” application submitted by PMI to the US FDA for marketing of IQOS in the USA (32).

Concurrent use of two (“dual use”) or more tobacco products (“polyuse”) involves a wide range of behaviours with different product use frequencies that may affect the health risk and the likelihood of further product use (complete switching, continued polyuse, complete quitting). If polyusers continue to smoke CCs at or at nearly the same frequency as exclusive CC smokers, they will not experience any health benefit from use of the reduced risk product, and this behaviour could increase risk.

Up to two thirds of HTP users in Japan and nearly all (96.2%) in the Republic of Korea also smoke cigarettes (22,33–36). Sutanto et al. (34) indicated that, in 2018, 63.2% of HTP users in Japan also smoked cigarettes, and, in 2019, 94.4% of dual users were smoking daily and only 0.5% were predominant HTP users (37). These data suggest that HTPs may not be adequate substitutes for cigarettes. Additionally, only about 10% of concurrent cigarette–HTP users planned to quit in the next 6 months. In Japan, concurrent cigarette–HTP users were younger than exclusive smokers, while studies of actual use in the USA showed greater interest among middle-aged smokers (37).

Tobacco industry investigators conducted a series of observational studies in Germany, Italy, Japan, the Republic of Korea, Switzerland and the USA to better understand the association between HTP use and product switching (32). When switching to IQOS was defined as > 70% of total tobacco product consumption being Heatsticks (IQOS inserts), about 15% of participants met this definition after being given IQOS for free for 4 weeks, whereas 22% consumed Heatsticks as 30–70% of their tobacco products. In a series of whole-offer tests with smokers, 10% of the study participants in Germany and 37% in the Republic of Korea had successfully switched to IQOS after 4 weeks. Data on the effectiveness of HTPs for quitting smoking of CC are very limited. One study in England of people who had stopped smoking in the 12 months before the survey indicated that 0.4% of the participants had used HTPs in quitting CCs.

The available data do not indicate that smokers who start using HTPs switch successfully to exclusive use of these products. Instead, most become dual users and do not substantially reduce their risk from tobacco products.

Chemical and physical processes undergone by the products during use, including characterization of emissions

Generation of chemical constituents in the aerosol to which users are exposed depends primarily on the heating temperature during product use. The type of tobacco, the chemical additives and the materials used in the device may add other constituents to the aerosol. The heat generated by HTPs is applied to the biomass of tobacco to aerosolize the nicotine and at the same time decompose the biomass. Therefore, the aerosol contains not only nicotine but also by-products of thermal decomposition of the biomass.

Biomass such as tobacco can be thermally decomposed by four different mechanisms: combustion, pyrolysis, gasification and liquefaction. **Combustion**, which occurs at high temperatures, is an exothermic reaction between oxygen and hydrocarbons and may be complete or incomplete. In complete combustion, an exothermic (energy-producing) reaction of oxygen and biomass leads to the formation of H₂O and carbon dioxide (CO₂). In contrast, during incomplete combustion, various other intermediate chemical products are formed. **Pyrolysis** occurs at relatively low temperature in either the absence or presence of a limited amount of oxygen and results in solid decomposition, the appearance of free radicals, formation of carbonyl groups and release of H₂O, carbon monoxide (CO) and CO₂. **Gasification** is an extension of pyrolysis in which gas, tar and solid residue react further to generate a mixture of low-molecular-weight hydrocarbons, CO, CO₂, H₂O vapour, nitrogen and ash. **Liquefaction** consists of decomposition of high-molecular-weight molecules into lower-molecular-weight molecules at relatively low temperature. Depending on the temperature, more than one of these processes may occur simultaneously in different locations in the product during generation of aerosol.

The claim by HTP manufacturers that their products heat and do not burn tobacco is based on their assertion of comparatively low operating temperatures that are sufficient to aerosolize nicotine. BAT's glo is stated to operate at a temperature < 250 °C and produces aerosols by evaporation and distillation (25). PMI claims that IQOS generates aerosols primarily by distillation and evaporation while operating at a temperature of < 350 °C (25). iFuse and Ploom Tech are reported to heat an e-liquid that then passes through and warms a tobacco plug at a temperature of < 35 °C (25), with evaporation and aerosolization to deliver

nicotine. Eclipse, which contains an integrated carbon fuel element for heating tobacco, has been described as operating at temperatures up to 160 °C, although the temperature depends strongly on use behaviour (38).

Differences in operating temperatures also influence biomass degradation and subsequent chemical reactions, which consequently alter the concentrations of harmful and potentially harmful constituents (HPHCs) measured in the aerosols emitted by the devices. Concentrations of CO in emissions from Eclipse due to the smouldering carbon fuel element used as the heat source were much higher (7.5 mg/stick) than those found in emissions from IQOS (0.5–0.6 mg/stick) (39).

Studies conducted to characterize the aerosol generated from HTPs suggest that the levels of HPHCs, including CO, tobacco-specific nitrosamines, carbonyls, volatile organic compounds, polycyclic aromatic hydrocarbons, reactive oxygen species and phenols, in aerosol are typically lower than those found in the smoke from CCs when machine-smoked with similar smoking regimens (25–28,31,40); however, many HPHCs, including known carcinogens (e.g., formaldehyde, tobacco-specific nitrosamines) are still present at quantifiable levels in HTP aerosol, perhaps because most volatile and semi-volatile organic compounds in CC smoke are formed at temperatures between 200 °C and 600 °C. In addition, the viscous liquid and solids that remain after pyrolysis condense in the low temperature zones of the device and may serve as sources for HPHCs during subsequent use of the product (42). Because of their design, Ploom TECH and iFuse may produce lower levels of HPHCs. Third-party products that have become available in Japan and new versions of previously marketed products may have higher power and thus operate at higher temperatures, increasing the concentrations of HPHCs in the aerosol. Studies of HPHCs generated by early-generation products may not be applicable to later-generation versions of the same products.

The aerosol of HTPs may contain additional chemicals of concern that are not typically measured in CC smoke. HTPs contain high levels of propylene glycol and glycerol, which are the principal constituents by volume of the aerosol. Thus, the aerosol will contain high levels of these compounds and also of carbonyls, which are a product of their breakdown (43). Forster et al. (44) identified seven chemical compounds (chromium, propylene glycol, glycidol, glycerol, *N*-nitrosodiethanolamine, acetoin and methylglyoxal) at higher concentrations in glo aerosol than in CCs. PMI reported a similar finding in their application for modified risk tobacco products to the US FDA (32).

Even if HTPs deliver lower concentrations of HPHCs in emissions than are found in CC smoke, there are still measurable levels of HPHCs and additional constituents that have not usually been assessed. Furthermore, changes to products over time could render previous measurements moot. It is not appropriate to draw general conclusions about the entire class of HTPs or other HTPs on the basis of data for one particular product. Regular surveillance and reporting of HPHCs delivered by HTPs are important for evaluating the impact of their use on public health.

Health impacts, including on non-users

The recent introduction of HTPs onto the market and the diversity of products make it difficult to assess adequately the long-term adverse health effects, particularly the carcinogenic risk, of use of the products. To date, most data have been generated by investigators who work for or are funded by the tobacco industry, which raises a conflict of interest. As virtually all the published and otherwise available studies have been conducted with type 2 HTPs, the discussion below refers only to those HTPs.

Product manufacturers have published numerous studies on the cytotoxicity and mutagenicity of HTP aerosol derived using the ISO 3308 standard smoking regimen. The studies show that HTP aerosol causes substantially less ($\leq 40\%$) cytotoxicity and mutagenicity ($\leq 90\%$) than CC smoke when expressed as total particulate matter (45–47). Similar reductions were reported for precursors of IQOS tested in Canadian intense smoking regimens (39,48). Greater smoking intensity that more closely reflected actual human topography resulted in increased cytotoxicity and mutagenicity, indicating an association between delivery and effect (49). Studies by independent researchers generally confirm the lower cytotoxicity of HTP aerosol than of CC smoke but show greater cytotoxicity than air controls.

Tobacco industry researchers also studied tumorigenicity and inhalation toxicity in animal models and generally reported substantially less toxicity and carcinogenicity than CC smoke. These studies also, however, showed more adverse outcomes in animals exposed to HTP aerosol than in those exposed to CC smoke. A recent independent study indicated that exposure of rats to IQOS aerosol impaired vascular flow-mediated dilation to an extent similar to CC smoke, despite a lower concentration of nicotine in the aerosol than in the CC smoke (29).

Investigators in the transnational tobacco companies have published several studies of biomarkers of exposure and effect in users of HTPs and reported marked reductions in biomarkers of exposure when CC smokers stop smoking CC entirely and switch exclusively to HTPs (50,51). Urinary mutagenicity is also reduced under these conditions. In several studies, biomarkers of cardiovascular health did not change after switching, but other studies indicated reductions in some biomarkers of effect. More intense puffing by switchers to HTPs than before they switched indicates that long-term studies should be conducted of smoking topography and to indicate the smoking regimens that should be used to assess these products. No studies of biomarkers of exposure in polyusers of HTPs and CCs have been conducted. Given the wide prevalence of polyuse described above and the findings from polyuse of ENDS and cigarettes, this is a significant knowledge gap.

Independent researchers have carried out several studies of passive exposure to HPHCs from HTP use. These studies have shown that use of HTPs exposes bystanders to substantially lower concentrations of HPHCs than from CC smoke but higher concentrations than from ENDS use, suggesting that second-hand exposure from HTPs is not negligible (52).

Overall, while limited, the available data on health effects resulting from exclusive HTP use indicate that:

- exposure to major carcinogens found in CC smoke may be reduced; however, limited data are available on effects on health risks; and
- the nicotine delivered by HTPs may have detrimental effects on reproduction and be harmful to the developing brains of youth and young adults.

Claims of reduced harm

“Harm reduction” suggests that combusted tobacco product users who are unwilling or unable to quit altogether can reduce their risk by switching completely from a more harmful product, typically CCs, to a less harmful alternative. Product manufacturers have used this concept to market HTPs with claims of “reduced risk”, as a “cleaner alternative to CCs” and as a “smoke-free alternative to smoking”. Manufacturers of HTPs have used the results of assays in vitro, studies in animals, studies of human biomarkers and population modelling to support claims of reduced risk. In these studies, the likely health outcomes of exclusive use of the product under question in place of CCs by healthy individuals is estimated.

Typically, investigators funded by the tobacco industry do not evaluate effects in smokers who already have compromised health, although this is the group that is most concerned about their health and are likely to seek a safer alternative, or effects in polyusers, which is the most common use behaviour of smokers who initiate use of an alternative, potentially lower-risk product.

Models used by the tobacco industry to estimate the health benefits of uptake of HTPs have suggested significant reductions in morbidity and mortality. Independent researchers have also developed probabilistic methods to model carcinogenic risks (53), which indicate that consumption of IQOS instead of CCs would be associated with a substantial increase in life expectancy in respect to cancer. This preliminary conclusion was based on analysis of eight carcinogens that are representative toxicants in CC smoke.

Decision-makers must properly review these assessments, because aerosols from HTPs can contain compounds that have not yet been characterized. For example, PMI's IQOS application to the US FDA for a modified risk product indicated significantly lower concentrations of a substantial number of HPHCs in HTP emissions than in CC smoke (54). This evaluation did not, however, account for 80 other constituents that either occurred at higher concentrations in HTP emissions or were not present in CC smoke (32,54). As the toxicity of many of these additional constituents is unknown, the overall projection of risk is indefinite. Toxicity studies in animals reported in the application also indicated several adverse outcomes (increases in liver weight and blood levels of alanine aminotransferase and hepatocellular vacuolization) that are not seen after use of CCs. These models must be carefully evaluated, as some of those provided by the industry exclude or underestimate important outcomes and factors, including morbidity, mortality, tobacco products other than CCs and effects on non-users and other population groups (55). The US FDA authorized marketing of IQOS in the USA and the claim of modified exposure in spite of the data limitations described above. According to this agency, the decision was based largely on the

substantial reduction across the constituents on US FDA's HPHC list, which demonstrates that, on the whole, as compared to combusted cigarette smoke, the process used to heat tobacco in the IQOS system significantly reduces the production of harmful and potentially harmful chemicals compared to cigarette smoke. The applicant also demonstrated

that the magnitude of differences in biomarkers of exposure to 15 HPHCs when smokers switch completely to IQOS is substantial.

The US FDA nevertheless expressed concern that: dual use is the predominant use behaviour, dual use will result in meaningful reductions in exposure, dual use is unlikely to provide a benefit over smoking, and consumers will understand the difference between exclusive and dual use. Therefore, the US FDA required PMI to conduct studies of use behaviour over time (56).

Availability, applicability and adaptability to HTPs of current standard operating procedures for contents and emissions

In 2008, the WHO Study Group on Tobacco Product Regulation (TobReg) evaluated lists of chemicals identified as being of “adverse health concern” in CCs and recommended a list for regulation and monitoring (57). In 2015, TobReg recommended that the constituents on the list be measured in other combusted tobacco products, although it recognized that the list of constituents might differ by product (58). In 2005, WHO established the WHO Tobacco Laboratory Network (TobLabNet), a global network of independent non-tobacco-industry-influenced laboratories, with a primary objective of developing, validating and disseminating methods for measuring chemicals in tobacco products. WHO TobLabNet has developed and validated testing methods for 12 of the 39 chemicals identified by TobReg, as occurring in emissions, acetaldehyde, acrolein, formaldehyde, benzene, 1,3-butadiene, carbon monoxide, benzo[*a*]pyrene, nicotine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and *N*'-nitrosonornicotine (NNN), and for contents: nicotine, humectants and ammonia. Standard operating procedures for these methods are available at https://www.who.int/tobacco/publications/prod_regulation/en/.

The principles of the methods developed and validated by TobLabNet for analysing the contents of CC tobacco filler for the substances listed above are generally directly applicable to analysing the tobacco in HTPs. Nevertheless, attention must be paid to the limitations of transferring the performance characteristics of methods validated for CC tobacco filler to HTPs because of potential differences in matrix effects and concentration ranges. As the nicotine levels in HTP tobaccos are similar to those in CC tobacco filler, WHO TobLabNet

Official Method SOP04 should be directly transferrable to HTPs. Official Method SOP06 for measuring humectants in tobacco has already been proven to be applicable for analysis of waterpipe tobacco, which contains high concentrations of these constituents, like many HTPs. This suggests that the method principle is also directly transferrable, with possible restrictions in the working range of the method. As data on levels of ammonia in the tobacco used in HTPs are limited, it is premature to reach a conclusion on the applicability of Official Method SOP07 to HTPs.

Because of the differences in operating principles and the chemical nature of the emissions, different equipment, smoking regimens and other procedures may be necessary for collecting aerosols from HTPs. For example, HTPs often have a button that must be pressed to activate the device. In addition, there is a significant lag between pressing the button and attainment of the operating temperature of the device, and this must be programmed into the operation timing. Furthermore, the puff topography of HTP users affects the delivery of aerosol and is likely to differ from the way in which cigarettes are smoked. Studies should be conducted to determine appropriate smoking regimens for testing these products and to determine whether the methods should be adjusted to account for the differences. The characteristics of different types of HTPs, such as the maximum number of puffs or the maximum heating time, should be addressed in defining suitable puffing regimes. The humectant concentration of HTP aerosol is higher than that in CC smoke, and methods for measuring the constituents of HTP emissions should therefore be evaluated to ensure that the higher concentration does not affect extraction efficiency or result in analytical interference.

When aerosol samples are collected onto Cambridge filters or into solutions with impingers, as is done for CC smoke, the procedures developed and validated by TobLabNet should generally be transferrable to the aerosol generated by use of HTPs. As the concentration of nicotine in HTP aerosol should be similar to that in CC smoke, SOP10 should be directly transferrable to HTP aerosol, with the caveats explained previously. The analytical principles for determining nitrosamines according to SOP03, benzo[*a*]pyrene according to SOP05, carbonyls according to SOP08 and volatile organic compounds according to SOP09 in mainstream cigarette smoke should be applicable to HTP aerosols. As the concentrations in HTP emissions are likely to be lower than those in CC smoke, however, the suitability of the analytical procedures mandated in the SOPs must be validated or modified if required. Some relevant analytes might be present at higher concentrations in HTP aerosols than in mainstream CC smoke.

Suitable methods for measuring the contents and emissions of HTPs

As discussed above, the principles of the methods developed and validated by TobLabNet for CC filler and mainstream CC smoke are likely to be transferrable to HTPs. Nevertheless, the methods were not originally developed and validated to evaluate the delivery of HPHCs by HTPs. As indicated above, while HTPs may emit lower concentrations of certain chemical species targeted in CCs, their different design and ingredients suggest that other constituents in emissions might appropriately be analysed. St Helen et al. (54) identified 22 HPHCs that occurred at concentrations more than 200% and seven HPHCs at concentrations more than 1000% higher in emissions from IQOS than in CC smoke from a reference cigarette. The health implications of higher concentration of HPHCs are currently unknown, and studies should be conducted to determine whether they present a significant risk to human health. Their findings also suggest that additional, untargeted analytical methods should be used to evaluate each type of HTP. Quantitative methods might have to be developed and validated for constituents that are not usually measured in CC smoke but are of concern in the emissions of HTPs.

The complexity of HTP product design presents new challenges for testing protocols, similar to those that arise with testing of ENDS and roll-your-own tobacco, as the products are not single entities but comprise multiple, integrated components. As shown in Table 1, many current HTPs consist of a separate heating device and a source of tobacco such as a stick or cartridge. Most manufacturers of these products provide a tobacco component that is intended exclusively for use with their device; however, invariably, third parties manufacture and sell compatible tobacco-containing components that may differ in design and ingredients from the originals, and substitution with third-party components may change the HPHC profile in the generated emissions. Regulatory bodies must consider this added complexity when developing protocols for testing and regulating HTPs. The full range of risks arising from combinations of different components might have to be addressed.

In order to control the exposure of users, many HTPs have a fixed limit on the number of puffs allowed before the device powers down. For example, IQOS (PMI) allows up to 14 puffs or 6 min of use, whereas glo (BAT) allows as many puffs as possible within the 3.5 min that the heating element is warm. As delivery may not be the same from early and late puffs in the sequence, use of a standard

number of puffs from the device with the fewest allowed puffs or time limit may not accurately characterize delivery of HPHCs or provide data appropriate for comparison. Regulations must include evaluation and use of the testing protocol that most appropriately reflects differences among products.

The emissions from HTPs when used under different conditions should be evaluated. Unlike cigarettes, which are consumed when burnt, the heating device in an HTP is reused and the tobacco is not consumed. This adds complexity to the use of machine testing for understanding possible health risks from use of these products. For example, char and other residue can build up in the device after multiple uses if the device is not adequately cleaned. Manufacturers provide instructions for cleaning, but the annoyance of cleaning the device may discourage consumers from following the manufacturers' instructions. The build-up of char in a device due to insufficient cleaning is likely to change its operating characteristics and, in turn, the concentrations of HPHCs in the emissions. The devices may also operate differently under full or partial charge and should be tested under all conditions of use.

All these factors introduce additional questions, which must be addressed to ensure that testing procedures are as accurate as possible in characterizing the delivery of HPHCs from HTPs according to user experience. Otherwise, manufacturers will test their products under the most favourable conditions and the results will not appropriately inform policy-makers, regulators or consumers.

Further, the incentives for testing must be strengthened. Initial tests have been performed to characterize exposure and health risks associated with use of CCs and other tobacco products. In the future, individual brands of HTP devices could be compared. As the product spectrum grows, differences in constituents and emissions are likely to increase. Performance standards should be defined in parallel with the development or adoption of testing methods.

Regulatory experience and monitoring of Parties

As of January 2020, HTPs had been sold legally in over 50 countries in all six WHO regions and traded illegally in some countries where they are banned. The Eighth Session of the Conference of the Parties to the WHO FCTC recognized HTPs as tobacco products in Decision FCTC/COP8(22) on novel and emerging tobacco products, and WHO recommends that Member States classify HTPs as tobacco

products (59). The novelty of HTPs, differences in regulatory legislation among countries and marketing strategies have, however, led to disparate approaches to their classification and of traditional tobacco control measures to these products. Regulators have classified HTPs as tobacco products, heated tobacco products, smokeless tobacco products, novel, emerging or new tobacco products, next-generation products or e-cigarettes. In some countries, HTPs may fall into hybrid or exempt categories. Some regulatory authorities classify the device and the inserts in different product classes, further adding to the complexity.

Current tobacco control regulations apply in countries in which HTPs are classified as tobacco products, while different regulations or no regulations may apply when they are classified otherwise. In Australia, HTPs are not classified as such, but nicotine is regulated as a Schedule 7 poison, making its sale and possession illegal. Several countries (e.g. Mexico, Thailand) categorize HTPs as e-cigarettes and have used this designation to ban the sale or importation of the entire category of products. Others use designation of HTPs as e-cigarettes to impose specific restrictions. Under the European Union's Tobacco Product Directive, HTPs are considered novel tobacco products, which imposes several regulatory requirements, including before marketing a product. The extent of these requirements depends, however, on whether a product is defined as a smokeless tobacco product or a tobacco product for smoking. Some countries (e.g., New Zealand and several European Union Member States, such as The Netherlands) classify heat sticks as smokeless tobacco products.

Overall, classification of HTPs affects their availability, use and the applicability of regulations, including taxation; restrictions on advertising, promotion and sponsorship; use of products in smoke-free areas; and packaging and labelling requirements, including health warnings. For example, in most countries, flavour regulation and health warnings for alternative or novel products are less strict than for cigarettes. In some countries, health warnings may be required only for tobacco-containing inserts and not for the electronic device. Many countries impose sales restrictions on HTPs, including prohibition of sales to minors. Few countries limit the concentration of nicotine in HTPs or ban the use of flavours in these products, which is likely to increase their attractiveness to young people and circumvents the regulation on use of flavours in traditional tobacco products. Differences among regulatory authorities should be considered when making recommendations for defining or classifying HTPs.

Lack of understanding of and misinformation about HTPs and gaps in legislation have led to suboptimal application of tobacco product regulation to these products in some countries. Tobacco industry representatives have sought designations that are advantageous to the marketing of these products and exemption from applicable laws and have challenged the applicability of regulations in court.

Impact on tobacco control

The existing evidence:

- indicates that HTPs are probably not harmless to users and bystanders and that, while smokers who switch completely from CCs to HTPs may reduce their exposure to some HPHCs, they do not reduce their exposure to all of them;
- is inconclusive about whether smokers who switch completely from CCs to HTPs are exposed to less harm from tobacco-related diseases than smokers who continue to use CCs; and
- is inconclusive about whether HTPs overall help to transition smokers from CCs either partially or entirely.

Claims of reduced harm or reduced risk relative to CCs are, however, the basis of the marketing narrative for HTPs and are combined with exploiting the passion for technology of primarily young people, disregarding appropriate protection for bystanders. Therefore, the introduction of HTPs onto the market presents unique challenges for tobacco product regulation in the context of tobacco control, as mandated by the WHO FCTC. Tobacco control has been successful internationally in decreasing the prevalence of tobacco smoking, and it is unclear how the introduction onto the market of a wide variety of HTPs with substantially different characteristics and user behaviour will alter the current landscape. Nevertheless, national authorities should be reminded that HTPs are an integrated product, as they always require the combination of a source of nicotine with a device. A separate marketing regulation of the device as a non-tobacco product is therefore not warranted. In addition, marketing of HTP consumables at a price lower than CCs undermines the progress made in reducing use that was accomplished by making products more expensive.

Until evidence shows clearly that HTPs help smokers to switch completely from CCs and that they decrease the harm of tobacco-related diseases experienced by continuing smokers, these products should be taxed at a rate similar to that of CCs. Finally, countries should continue to monitor all tobacco use and enact policies to protect public health.

Research gaps

HTPs were first marketed in 1988, at which time they did not attain a significant market share, and only limited research was published about these products at that time. The resurgence of these products since 2014 and the substantial sales in certain countries underline the importance of understanding their impact on public health. Because of their recent restricted availability, research by independent scientists on the factors that influence their impact on public health has been limited. Additional studies that should be conducted to inform regulatory decisions include those listed below.

Surveillance and monitoring

- Global surveillance of all HTPs, including new and modified products, because of their rapid evolution
- Monitoring of HTP advertising and promotional messaging, particularly claims of lower risk

Regulatory mapping

- Comprehensive, regularly updated regulatory mapping of HTP legislation and its implementation

Product appeal

- The role of flavours in the attractiveness of HTPs, particularly to youth and nonusers
- Perceptions of HTPs and how they influence consumer's decisions to initiate use, poly-use, exclusive use or rejection of these products

Addictive potential and user behaviour

- The addiction potential of HTPs, particularly those other than IQOS, which have been inadequately studied
- HTP use behaviour, including puffing topography, to inform risk assessment and the laboratory regimens appropriate for testing
- Dual use and transitions between no use, poly- and exclusive use, including the impact on biomarkers of exposure and effect
- Effects of product misuse, including failure to follow use and cleaning instructions, on emissions and exposure
- Relief of cravings and their potential as complete substitutes for smoking

Laboratory analyses and investigations

- Validation of application of current TobLabNet methods to HTPs
- Emissions of all HTPs under different product use conditions, including the underlying chemical and physical processes
- Surveillance of emissions of products marketed in different countries
- Development and validation of methods and evaluation of risk from HPHCs in HTP emissions as compared with non-use and cigarette smoke

Characterization of products and untargeted analysis of HTP contents and emissions

- Investigation and characterization of compounds potentially generated by thermal degradation of propylene glycol, glycerol and other additives in the reconstituted tobacco, the paper wrapping of tobacco and filters
- Untargeted analysis to identify new, potentially important toxicants
- Studies of chronic exposure in animal models
- Studies of the health outcomes of users

Legal obligations and policy options

In decision FCTC/COP8(22) (59), Parties to the WHO FCTC recognized HTPs as tobacco products and were reminded of their commitments under the Convention for addressing the challenges posed by novel and emerging tobacco products such as HTPs. In regulating products such as HTPs, the focus must be maintained on wider tobacco control. Parties and other WHO Member States should consider the following regulatory objectives:

- prevent initiation of use by non-smokers and youth, with special attention to vulnerable groups;
- minimize as far as possible potential health risks to users, and protect non-users from exposure to emissions;
- prevent unproven claims from being made about these products, including health claims, comparative claims, smoking cessation claims, ingredients and emissions claims, comparisons and reduction of disease risk claims; and
- protect tobacco-control activities from all commercial and other vested interests of the tobacco and related industries.

Further to these objectives and in light of design and marketing strategies for HTPs, both the device and the tobacco insert should be considered tobacco products for the purposes of domestic tobacco control laws. As devices and tobacco inserts are always used together, they should be considered integrated products, even when sold or marketed separately. Consequently, policy-makers should apply existing national regulations on tobacco products to HTPs (including the device) or strengthen them to provide the highest standards for the protection of public health, even in countries in which HTPs are currently not legally available.

Regulators should not allow themselves to be distracted by tobacco and related industry tactics or the aggressive promotion of these products. Tobacco control policies must therefore be forcefully protected from the influence of nicotine and tobacco industries, in line with Article 5.3 of the WHO FCTC and its guidelines for implementation. In this regard, policy-makers must base their decisions on sound science, promote independent research, require clarification of the source of research funding in order to identify undue influence and verify the industry's research. Furthermore, they should seek full disclosure of product information to regulators.

The following policy options may be considered to achieve the objectives and measures outlined in decision FCTC/COP8(22):

- a. Until more is known about the harms and relative risks of HTPs and given the relative homogeneity of the tobacco inserts in HTPs, these products should be taxed at the same rate as CCs to achieve parity with the average CC tax rates in a country. In the case of a specific tax, the base should be per unit (Article 6).

- b.** Ban the use of HTPs where smoking is prohibited, ensuring that legislation on smoke-free environments complies with all the recommendations of WHO FCTC Article 8 Guidelines.
- c.** Regulation of product content and disclosure (Articles 9 and 10):
 - i.** Monitor priority harmful compounds in HTP emissions, such as nicotine, aldehydes and carbon monoxide, and reduce them as appropriate, according to WHO recommendations and the national context.
 - ii.** Consider using the methods developed by WHO TobLabNet to measure priority toxicants in HTP contents and emissions.
 - iii.** Regulate the contents, emissions and design features of HTPs and require disclosure of their contents in accordance with Articles 9 and 10 of the WHO FCTC, including restriction of the use of flavours that appeal to minors and prohibition of the addition of pharmacologically active substances (in jurisdictions in which they are legal).
- d.** Require large graphic health warnings and plain packaging on HTP inserts and device packs as for any other smoked tobacco product (Article 11).
- e.** Ensure that the public is well informed about the risks associated with use of HTPs, including the risks of dual-use with CCs and other tobacco products, and stress that reduced exposure does not necessarily mean reduced harm (Article 12).
- f.** Apply existing bans on tobacco advertising, promotion and sponsorship to tobacco inserts and devices. Where this is not currently possible, strengthen the law to ban all forms of advertising, promotion and sponsorship of HTP inserts and devices (Article 13).
- g.** In taking effective measures to promote cessation of tobacco use and adequate treatment for tobacco dependence, HTPs should be considered tobacco products, as such measures are applicable to all tobacco use (Article 14).
- h.** Ban sale of HTPs to and by minors (Article 16).
- i.** Strengthen national and international monitoring and surveillance of trends in HTP use, sales and marketing strategies, with particular attention to social media (Article 20).

References

1. Heated tobacco products (HTPs): Market monitoring information sheet. Geneva: World Health Organization; 2018 (<https://apps.who.int/iris/bitstream/handle/10665/272875/WHO-NMH-PND-17.6-eng.pdf?ua=1>).
2. Eaton D, Jakaj B, Forster M, Nicol J, Mavropolou E, Scott K et al. Assessment of tobacco heating product THP1.0. Part 2: Product design, operation and thermophysical characterisation. *Regul Toxicol Pharmacol* .2018;93:4–13.
3. Smith MR, Clark B, Lüdicke F, Schaller JP, Vanscheeuwijck P, Hoeng J et al. Evaluation of the Tobacco Heating System 2.2. Part 1: Description of the system and the scientific assessment program. *Regul Toxicol Pharmacol* .2016;81:S17–26.
4. Poynton S, Sutton J, Goodall S, Margham J, Forster M, Scott K et al. A novel hybrid tobacco product that delivers a tobacco flavour note with vapour aerosol (Part 1): Product operation and preliminary aerosol chemistry assessment. *Food Chem Toxicol* .2017;106:522–32.
5. Cigarettes to record US\$7.7 billion loss by 2021 as heated tobacco grows 691 percent. *Euromonitor Int*. 24 June 2017 (<https://blog.euromonitor.com/cigarettes-record-loss-heated-tobacco-grows-691-percent/>, accessed 6 August 2020).
6. Heat not burn tobacco products market – Forecasts from 2019 to 2024. *Research and Markets*; 2019 (<https://www.researchandmarkets.com/reports/4849645/heat-not-burn-tobacco-products-market-forecasts>, accessed 6 August 2020).
7. Electronic cigarette – Global market outlook (2017–2026). *Research and Markets*; 2019 (https://www.researchandmarkets.com/reports/4827644/electronic-cigarette-global-market-outlook?utm_source=CI&utm_medium=PressRelease&utm_code=jxtpcf&utm_campaign=1292644+-+Global+Electronic+Cigarette+Market+Outlook+Report+2017-2019+%26+2026&utm_exec=chdo54, accessed on 6 August 2020).
8. Japan Tobacco International annual report. Japan Tobacco International; 2018 (www.jti.com/sites/default/files/global-files/documents/jti-annual-reports/jt-annual-report-2018.pdf, accessed 6 August 2020).
9. Tobacco meets technology. Philip Morris International; 2021 (<https://www.pmi.com/smoke-free-products/iqos-our-tobacco-heating-system>, accessed 6 August 2020).
10. Uranaka T, Ando R. Philip Morris aims to revive Japan sales with cheaper heat-not-burn tobacco. *Reuters*, 23 October 2018 (<https://www.reuters.com/article/us-pmi-japan/philip-morris-aim-to-%0Arevive-japan-sales-with-cheaper-heat-not-burn-tobacco-idUSKCN1MX06E>, accessed 6 August 2020).
11. Heated tobacco products. Tobacco Tactics, University of Bath (<https://tobaccotactics.org>, accessed 10 June 2020).

12. Asia Pacific heat-not-burn tobacco product market (2019–2025): Market forecast by product type, by demography, by sales channels, by countries, and competitive landscape. Research and Markets; 2019 ([https://www.researchandmarkets.com/reports/4911922/asia-pacific-heat-not-burn-tobacco-product-market?utm_source=dynamic&utm_medium=GNOM&utm_code=j59rvm&utm_campaign=1345174+-+Asia-Pacific+Heat-not-Burn+\(HnB\)+Tobacco+Products+Industry+Analysis%2C+2015-2025](https://www.researchandmarkets.com/reports/4911922/asia-pacific-heat-not-burn-tobacco-product-market?utm_source=dynamic&utm_medium=GNOM&utm_code=j59rvm&utm_campaign=1345174+-+Asia-Pacific+Heat-not-Burn+(HnB)+Tobacco+Products+Industry+Analysis%2C+2015-2025), accessed 6 August 2020).
13. MacGuill S, Genov I. Emerging and next generation nicotine products (webinar). London: Euromonitor International; 2017 (<http://go.euromonitor.com/rs/805-KOK-719/images/Emerging-and-Next-Generation-Nicotine-Products-Euromonitor.pdf>, accessed 6 December 2020).
14. Kang H, Cho S. Heated tobacco product use among Korean adolescents. *Tob Control*. 2019;0:1–3 (doi:10.1136/tobaccocontrol-2019-054949).
15. McKelvey K, Popova L, Kim M, Chaffee BW, Vijayaraghavan M, Ling P et al. Heated tobacco products likely appeal to adolescents and young adults. *Tob Control*. 2018;27:s41–7.
16. Partial guidelines for implementation of Articles 9 and 10 of the WHO Framework Convention on Tobacco Control. Geneva: World Health Organization; 2012 (<https://fctc.who.int/publications/m/item/regulation-of-the-contents-of-tobacco-products-and-regulation-of-tobacco-product-disclosures>, accessed 6 August 2020).
17. Lee J, Lee S. Korean-made heated tobacco product, “lil”. *Tob Control*. 2019;28:e156–7.
18. Liber AC. Heated tobacco products and combusted cigarettes: Comparing global prices and taxes. *Tob Control*. 2019;28:689–91.
19. Lee JGL, Blanchflower TM, O’Brien KF, Averett PE, Cofie LE, Gregory KR. Evolving IQOS packaging designs change perceptions of product appeal, uniqueness, quality and safety: A randomised experiment, 2018, USA. *Tob Control*. 2019;28(e1):e52–5.
20. Hair EC, Bennett M, Sheen E, Cantrell J, Briggs J, Fenn Z et al. Examining perceptions about IQOS heated tobacco product: Consumer studies in Japan and Switzerland. *Tob Control*. 2018;27:s70–3.
21. Tabuchi T, Gallus S, Shinozaki T, Nakaya T, Kunugita N, Colwell B. Heat-not-burn tobacco product use in Japan: Its prevalence, predictors and perceived symptoms from exposure to second-hand heat-not-burn tobacco aerosol. *Tob Control*. 2018;27:e25–33.
22. Bialous SA, Glantz SA. Heated tobacco products: Another tobacco industry global strategy to slow progress in tobacco control. *Tob Control*. 2018;27:s111–7.
23. Kim J, Yu H, Lee S, Paek YJ. Awareness, experience and prevalence of heated tobacco product, IQOS, among young Korean adults. *Tob Control*. 2018;27:s74–7.
24. Tompkins CNE, Burnley A, McNeill A, Hitchman SC. Factors that influence smokers’ and ex-smokers’ use of IQOS: A qualitative study of IQOS users and ex-users in the UK. *Tob Control*. 2020;30(1):16–23 (doi: 10.1136/tobaccocontrol-2019-055306).

25. Simonavicius E, McNeill A, Shahab L, Brose LS. Heat-not-burn tobacco products: a systematic literature review. *Tob Control*. 2019;28:582–94.
26. Bekki K, Inaba Y, Uchiyama S, Kunugita N. Comparison of chemicals in mainstream smoke in heat-not-burn tobacco and combustion cigarettes. *J UOEH*. 2017;39:201–7.
27. Farsalinos KE, Yannovits N, Sarri T, Voudris V, Poulas K. Nicotine delivery to the aerosol of a heat-not-burn tobacco product: Comparison with a tobacco cigarette and e-cigarettes. *Nicotine Tob Res*. 2018;20:1004–9.
28. Uchiyama S, Noguchi M, Takagi N, Hayashida H, Inaba Y, Ogura H et al. Simple determination of gaseous and particulate compounds generated from heated tobacco products. *Chem Res Toxicol*. 2018;31:585–93.
29. Nabavizadeh P, Liu J, Havel CM, Ibrahim S, Derakhshandeh R, Jacob P III et al. Vascular endothelial function is impaired by aerosol from a single IQOS HeatStick to the same extent as by cigarette smoke. *Tob Control*. 2018;27:s13–9.
30. Biondi-Zoccai G, Sciarretta S, Bullen C, Nocella C, Violi F, Loffredo L et al. Acute effects of heat-not-burn, electronic vaping, and traditional tobacco combustion cigarettes: The Sapienza University of Rome-Vascular Assessment of Proatherosclerotic Effects of Smoking (SUR-VAPES) 2 randomized trial. *J Am Heart Assoc*. 2019;8:e010455.
31. Lopez AA, Hiler M, Maloney S, Eissenberg T, Breland AB. Expanding clinical laboratory tobacco product evaluation methods to loose-leaf tobacco vaporizers. *Drug Alcohol Depend*. 2016;169:33–40.
32. PMTA coversheet: Technical project lead review (TPL). Silver Spring (MD): US Food and Drug Administration; 2017 (<https://www.fda.gov/media/124247/download>, accessed 6 August 2020).
33. Hwang JH, Ryu DH, Park SW. Heated tobacco products: Cigarette complements, not substitutes. *Drug Alcohol Depend*. 2019;204:107576.
34. Sutanto E, Miller C, Smith DM, O'Connor RJ, Quah ACK, Cummings KM et al. Prevalence, use behaviors, and preferences among users of heated tobacco products: Findings from the 2018 ITC Japan Survey. *Int J Environ Res Public Health*. 2019;16:4630
35. Tabuchi T, Kiyohara K, Hoshino T, Bekki K, Inaba Y, Kunugita N. Awareness and use of electronic cigarettes and heat-not-burn tobacco products in Japan. *Addiction*. 2016;111:706–13.
36. Tabuchi T, Shinozaki T, Kunugita N, Nakamura M, Tsuji I. Study profile: The Japan “Society and New Tobacco” Internet Survey (JASTIS): A longitudinal internet cohort study of heat-not-burn tobacco products, electronic cigarettes, and conventional tobacco products in Japan. *J Epidemiol*. 2019;29:444–50.
37. Roulet S, Chrea C, Kanitscheider C, Kallischnigg G, Magnani P, Weitkunat R. Potential predictors of adoption of the Tobacco Heating System by US adult smokers: An actual use study. *F1000Res*. 2019;8:214.

38. Slade J, Connolly GN, Lympers D. Eclipse: Does it live up to its health claims? *Tob Control*. 2002;11:ii64–70.
39. Schaller JP, Pijnenburg JP, Ajithkumar A, Tricker AR. Evaluation of the Tobacco Heating System 2.2. Part 3: Influence of the tobacco blend on the formation of harmful and potentially harmful constituents of the Tobacco Heating System 2.2 aerosol. *Regul Toxicol Pharmacol*. 2016;81:S48–58.
40. Jankowski M, Brozek GM, Lawson J, Skoczynski S, Majek P, Zejda JE. New ideas, old problems? Heated tobacco products – A systematic review. *Int J Occup Med Environ Health*. 2019;32:595–634.
41. Mallock N, Boss L, Burk R, Danziger M, Welsch T, Hahn H et al. Levels of selected analytes in the emissions of “heat not burn” tobacco products that are relevant to assess human health risks. *Arch Toxicol*. 2018;92:2145–9.
42. Davis B, Williams M, Talbot P. iQOS: evidence of pyrolysis and release of a toxicant from plastic. *Tob Control*. 2019;28:34–41.
43. Gasparyan H, Mariner D, Wright C, Nicol J, Murphy J, Liu C et al. Accurate measurement of main aerosol constituents from heated tobacco products (HTPs): Implications for a fundamentally different aerosol. *Regul Toxicol Pharmacol*. 2018;99:131–41.
44. Forster M, Fiebelkorn S, Yurteri C, Mariner D, Liu C, Wright C et al. Assessment of novel tobacco heating product THP1.0. Part 3: Comprehensive chemical characterisation of harmful and potentially harmful aerosol emissions. *Regul Toxicol Pharmacol*. 2017;93:14–33.
45. Roemer E, Stabbert R, Veltel D, Müller BP, Meisgen T, Schramke H et al. Reduced toxicological activity of cigarette smoke by the addition of ammonium magnesium phosphate to the paper of an electrically heated cigarette: Smoke chemistry and in vitro cytotoxicity and genotoxicity. *Toxicol In Vitro*. 2008;22:671–81.
46. Tewes FJ, Meisgen TJ, Veltel DJ, Roemer E, Patskan G. Toxicological evaluation of an electrically heated cigarette. Part 3: Genotoxicity and cytotoxicity of mainstream smoke. *J Appl Toxicol*. 2003;23:341–8.
47. Werley MS, Freelin SA, Wrenn SE, Gerstenberg B, Roemer E, Schramke H et al. Smoke chemistry, in vitro and in vivo toxicology evaluations of the electrically heated cigarette smoking system series K. *Regul Toxicol Pharmacol*. 2008;52:122–39.
48. Zenzen V, Diekmann J, Gerstenberg B, Weber S, Wittke S, Schorp MK. Reduced exposure evaluation of an electrically heated cigarette smoking system. Part 2: Smoke chemistry and in vitro toxicological evaluation using smoking regimens reflecting human puffing behavior. *Regul Toxicol Pharmacol*. 2012;64:S11–34.
49. Jaunky T, Adamson J, Santopietro S, Terry A, Thome D, Breheny D et al. Assessment of tobacco heating product THP1.0. Part 5: In vitro dosimetric and cytotoxic assessment. *Regul Toxicol*

- Pharmacol. 2018;93:52–61.
50. Tricker AR, Stewart AJ, Leroy CM, Lindner D, Schorp MK, Dempsey R. Reduced exposure evaluation of an electrically heated cigarette smoking system. Part 3: Eight-day randomized clinical trial in the UK. *Regul Toxicol Pharmacol.* 2012;64:S35–44.
 51. Tricker AR, Jang IJ, Martin Leroy C, Lindner D, Dempsey R. Reduced exposure evaluation of an electrically heated cigarette smoking system. Part 4: Eight-day randomized clinical trial in Korea. *Regul Toxicol Pharmacol.* 2012;64:S45–53.
 52. Protano C, Manigrasso M, Avino P, Vitali M. Second-hand smoke generated by combustion and electronic smoking devices used in real scenarios: Ultrafine particle pollution and age-related dose assessment. *Environ Int.* 2017;107:190–5.
 53. Slob W, Soeteman-Hernández LG, Bil W, Staal YCM, Stephens WE, Talhout R. A method for comparing the impact on carcinogenicity of tobacco products: A case study on heated tobacco versus cigarettes. *Risk Anal.* 2020;40:1355–66.
 54. St Helen G, Jacob P III, Nardone N, Benowitz NL. IQOS: examination of Philip Morris International's claim of reduced exposure. *Tob Control.* 2018;27:s30–6.
 55. Max WB, Sung HY, Lightwood J, Wang Y, Yao T. Modelling the impact of a new tobacco product: Review of Philip Morris International's Population Health Impact Model as applied to the IQOS heated tobacco product. *Tob Control.* 2018;27:s82–6.
 56. Scientific review of modified risk tobacco product application (MRTPA) under section 911(d) of the FD&C Act – Technical project lead. Silver Spring (MD): Food and Drug Administration; 2016 (<https://www.fda.gov/media/139796/download>, accessed 10 June 2020).
 57. The scientific basis of tobacco product regulation: Second report of a WHO study group (WHO Technical Report Series, No. 951). Geneva: World Health Organization; 2008.
 58. The scientific basis of tobacco product regulation: Fifth Report of a WHO study group (WHO Technical Report Series, No. 989). Geneva: World Health Organization; 2015.
 59. Decision FCTC/COP8(22). Novel and emerging tobacco products. Geneva: World Health Organization; 2018 ([https://fctc.who.int/who-fctc/governance/conference-of-the-parties/eight-session-of-the-conference-of-the-parties/decisions/fctc-cop8\(22\)-novel-and-emerging-tobacco-products](https://fctc.who.int/who-fctc/governance/conference-of-the-parties/eight-session-of-the-conference-of-the-parties/decisions/fctc-cop8(22)-novel-and-emerging-tobacco-products)).



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