

TOBACCO CONTROL

HEATED TOBACCO PRODUCTS

FROM
THE
HEALTH
EFFECTS
TO THE
POLITICS

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***Tobacco Control* aims to study the nature and consequences of tobacco use worldwide; tobacco's effects on population health, the economy, the environment and society; efforts to prevent and control the global tobacco epidemic through population level education and policy changes; the ethical dimensions of tobacco control policies; and the activities of the tobacco industry and its allies**

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Heated tobacco products: the example of IQOS

Stanton A Glantz

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Heated tobacco products (HTP) represent the latest in a long line of products tobacco companies have developed and marketed as less dangerous than conventional cigarettes, beginning with so-called 'safer cigarettes' in the 1960s.^{1,2} HTP (figure 1) heat tobacco to generate an inhaled nicotine aerosol and are marketed using messages that explicitly or implicitly claim they are safer than cigarettes.^{3–8}

In 2018, HTP were available in many countries (table 1). In the USA, before marketing new tobacco products, the Family Smoking Prevention and Tobacco Control Act⁹ (FSPTCA) requires premarket review by the Food and Drug Administration (FDA) to demonstrate that marketing them would be 'appropriate for the protection of the public health' (FSPTCA sections 910 and 905(j)). Additionally, to market any new tobacco product in the USA with claims of reduced risk or reduced exposure to toxins compared to other tobacco products ('Modified Risk Tobacco Product'; MRTP), the company must first obtain an MRTP marketing order from the FDA. In December 2016, Philip Morris International (PMI) submitted an application to market IQOS, one of its HTP, with MRTP claims.¹⁰ PMI's MRTP application included extensive details about the product, the chemistry of the aerosol it produces, related toxicology, effects on clinical measures in people, perceptions of the product and its packaging (including warning labels), and behavioural factors. This application sought FDA approval of PMI's claims that smokers who switched completely to IQOS would reduce their health risks or exposure to dangerous substances compared with smoking cigarettes.

As of November 2017, there were 31 studies of HTP published in the peer reviewed literature, 20 of which were affiliated with the tobacco industry.¹¹ The 11 independent studies focused on awareness, use, and secondhand emissions of HTP, while the industry affiliated papers examined nicotine delivery and mainstream emissions and exposures to selected toxicants. The fact that the literature has been dominated by industry is particularly concerning because tobacco companies have a record of publishing incomplete or manipulated information and presenting it to governments.^{12–16} For example, PMI^{17–20} and British American Tobacco^{21–23} (BAT) conducted and published studies arguing that additives did not increase cigarettes' toxicities. However, internal PMI documents and analysis of PMI's data done by people independent of the tobacco industry revealed that many toxicants increased when additives—notably menthol—were present.¹⁵

PMI's IQOS MRTP application (the 'application') provides an opportunity to analyse PMI's data. This supplement to *Tobacco Control* includes eight

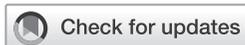
papers that present analyses of PMI's application by researchers independent of the tobacco industry and 12 papers that provide independent assessments of HTP effects, including their political and policy implications. Together, these papers provide insights into IQOS (and, in broad terms, other HTP) and support the January 2018 vote by the FDA Tobacco Product Scientific Advisory Committee that PMI's application did not demonstrate it reduced risk claims for IQOS²⁴ (online supplementary table S1). These papers also put HTP in the overall context of the tobacco companies' plans to maintain and grow their markets in the future and outline regulatory responses.

HEALTH EFFECTS

The fundamental justification for introducing HTP is the claim that they are substantially less dangerous than conventional cigarettes. PMI's application includes PMI's 3-month study of 24 non-cancer biomarkers of potential harm (BOPH) in humans using IQOS compared with conventional cigarettes. These biomarkers include measures of inflammation, oxidative stress, cholesterol and triglycerides, blood pressure, and lung function. (PMI did separate studies of biomarkers of exposure, several of which are carcinogens.) While PMI's application emphasises that these biomarkers generally changed in positive directions, Glantz's²⁵ examination of the data revealed no statistically detectable difference between IQOS and conventional cigarettes for 23 of the 24 BOPH in Americans and 10 of 13 in Japanese. Moreover, it is likely that the few significant differences were false positives. Thus, despite delivering lower levels of some toxicants, PMI's own data fail to show consistently lower risks of harm in humans using IQOS compared with conventional cigarettes.

In June, 2018 PMI issued a press release²⁶ announcing that a 6-month human study comparing IQOS with conventional cigarettes found eight biomarkers improved in those who switched to IQOS. PMI did not provide specific results. In contrast to the application, PMI's new study only examined six BOPH (plus two biomarkers of exposure). Further, PMI did not report the full range of biomarkers used in the earlier study although they can be measured in a blood sample or simple physiological test. This additional study raises questions about PMI manipulating the experimental design or data analysis as it and other companies have a history of doing.¹⁵

While HTP are presented as 'new', they are simply the latest incarnation of a technology tobacco companies have been developing for decades. Elias *et al*² analysed previously secret PMI documents, public communications and the



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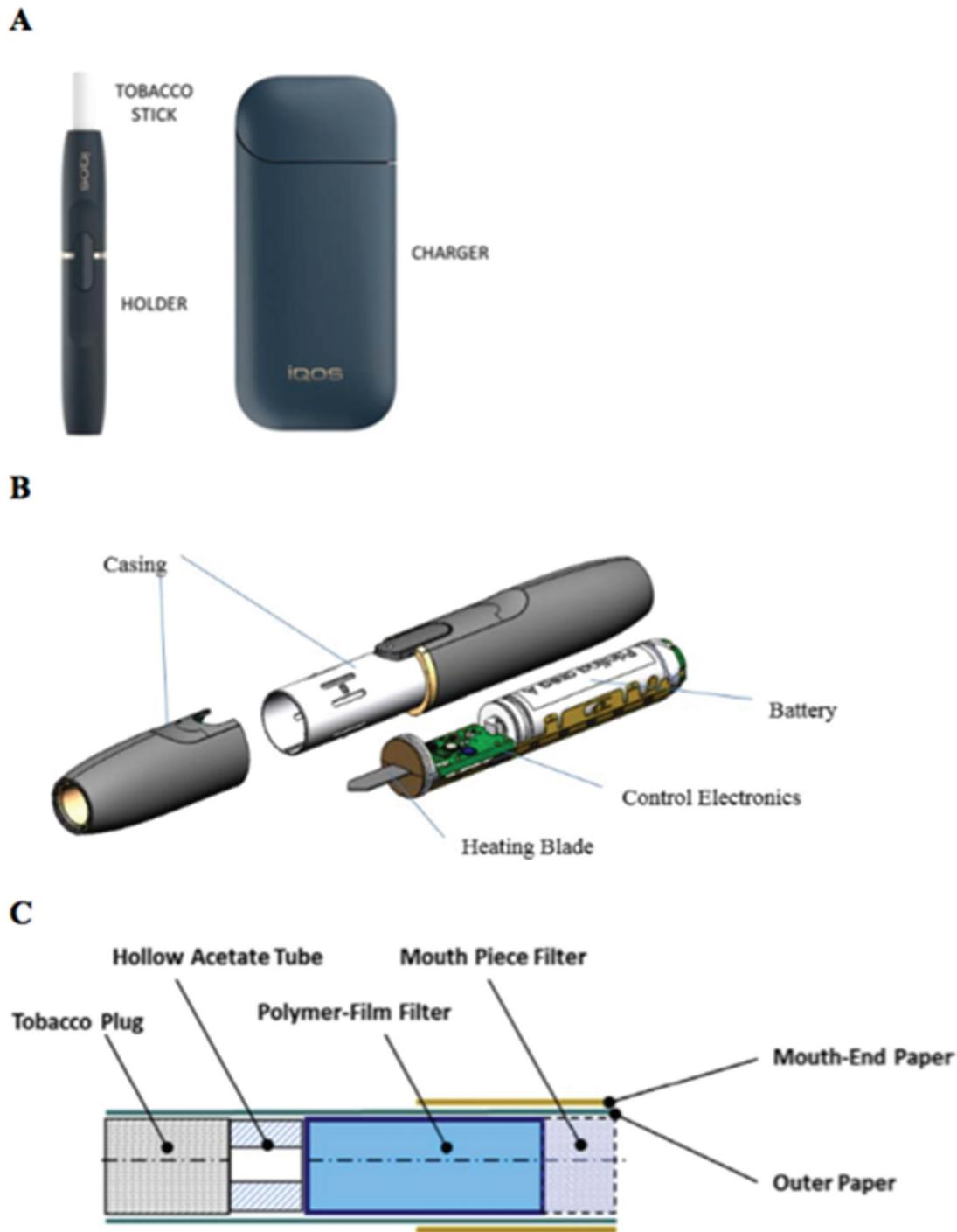


Figure 1 (A) The Philip Morris International IQOS charger, holder and HeetStick (tobacco stick). (B) Schematic drawing of holder. (C) Schematic of HeetStick tobacco stick.¹⁰

application to compare IQOS to Accord, an earlier HTP that PMI unsuccessfully marketed in the USA and Japan in 1998 and 2006, respectively. PMI's public statements seemed contradictory, claiming that Accord reduced exposure to harmful constituents while consistently emphasising that the reductions did not mean Accord was safer than conventional cigarettes. In terms of aerosol chemistry, Accord had lower levels than IQOS of some toxicants and higher levels of others. PMI appears to be capitalising on the MRTP process to make reduced exposure claims for IQOS despite the fact that overall toxicant exposures are not, on average, different than Accord.

Discussion of HTP (as well as e-cigarettes) has focused on cancer even though cardiovascular and metabolic disease kill about as many smokers as cancer.²⁷ Unlike cancer, the dose-response relationship for cardiovascular effects is highly non-linear, with large effects at low doses.²⁸ An important pathway through which tobacco use increases the risk of heart disease is by impairing the ability of arteries to enlarge when needed to accommodate increases in blood flow (flow mediated dilation, FMD). Nabavizadeh *et al*²⁹ tested whether exposure to IQOS aerosol impaired FMD in a well-established experimental model in which rats inhale IQOS aerosol from a single

Table 1 Availability of heated tobacco product by major cigarette company and country of availability (January 2018)

Company	Product	Year launched	Countries/comments
British American Tobacco	iFuse* glo	2015 2016	Romania, Japan, Switzerland, Canada, South Korea, Russia.
China National Tobacco Corporation/State Tobacco Monopoly Administration (STMA)	Not reported	Not launched	A few of the companies claim to have over 30 patents of HTP and continue to be engaged in research and development of these products. But none yet are in the market.
Imperial Brands	Not reported	Not launched	Focusing on e-cigarettes at the moment, claims to have options to launch when it deems that time is right.
Japan Tobacco International	Ploom TECH†	2016	Japan, Switzerland.
KT&G Corp	lil	2017	South Korea
Philip Morris International‡	IQOS TEEPS§	2014 Not yet launched	Canada, Guatemala, Colombia, Czech Republic, Denmark, France, Germany, Greece, Israel, Italy, Kazakhstan, Lithuania, Monaco, Netherlands, Poland, Portugal, Romania, Russia, Serbia, Slovak Republic, Slovenia, Spain, Switzerland, Ukraine, United Kingdom, South Africa, South Korea, Japan, New Zealand.

Source: Bialous and Glantz.⁴⁹

*It is unclear that iFuse will remain in the market in Romania, where glo was introduced in 2018.

†Ploom TECH is described as a hybrid between an HTP and a vaporiser. It is to be used with Mevius capsules. Mevius is one of JTI's best-selling cigarette brands. The capsules contain tobacco that are then heated by vapour.

‡PMI website states that it is developing a new heated nicotine delivery product that has no tobacco, STEEM, among other 'reduced risk' products.

§We do not know what TEEPS stands for, it is not included in the product's description (<https://www.pmi.com/smoke-free-products/teeps-carbon-heated-tobacco-product>).

HTP, heated tobacco product; JTI, Japan Tobacco International; PMI, Philip Morris International.

HeetStick (the IQOS tobacco stick), mainstream smoke from a single Marlboro Red cigarette, or clean air. In contrast with PMI's application claiming that IQOS causes less impairment than conventional cigarettes, Nabavizadeh *et al*²⁹ showed IQOS aerosol's acute effects impaired vascular endothelial function (measured with FMD) comparably with cigarette smoke.

Moazed *et al*³⁰ found data in PMI's application raising significant concerns about IQOS' pulmonary effects. Rats exposed to IQOS suffered pulmonary inflammation and immunomodulation. Although PMI did not report any direct measures of pulmonary inflammation in humans, they measured pulmonary function and found no evidence of improvement in cigarette smokers who switched to IQOS. PMI's application also ignores the effect of dual use and secondhand aerosol exposure.

Independent research confirmed adverse effects of IQOS aerosol on lung cells. Leigh *et al*³¹ exposed human bronchial epithelial cells in vitro to aerosols from three PMI products: IQOS (tobacco flavour), an e-cigarette (MarkTen, tobacco flavour) and a conventional cigarette (Marlboro Red) at comparable nicotine levels at the air-liquid interface. IQOS showed significantly higher cytotoxicity than e-cigarettes, but less than combustible cigarettes. These observations have important legal implications in the USA because to authorise marketing IQOS with reduced risk claims, the FDA would have to find that IQOS would benefit the public health and significantly reduce harm or reduce exposure to harmful substances 'compared to the similar types of tobacco products then on the market' (FSPTCA section 911(g)(2)(B)(ii)), and e-cigarettes were currently on the market at the time that PMI submitted its application.

Reinforcing the need to compare HTP to e-cigarettes rather than cigarettes, Leigh *et al*³² compared the levels of carcinogenic tobacco specific nitrosamines (TSNA) in IQOS aerosols to MarkTen e-cigarettes and Marlboro Red 100 conventional cigarettes at comparable nicotine delivery levels. TSNA yields per puff in IQOS aerosol was an order of magnitude lower than in Marlboro cigarette smoke, but an order of magnitude higher than in MarkTen e-cigarettes. In short, IQOS does not reduce exposure to these important carcinogens nearly as much as e-cigarettes.

Most discussion of the toxicants in non-cigarette tobacco products compare them to cigarettes on the assumption that if the non-cigarette products deliver lower levels of toxicants than cigarettes, the products would be less dangerous. However, St Helen *et al*³³ found that PMI's data only support its claim that IQOS reduces exposure to some (40 of 93) harmful and potentially harmful constituents (HPHCs) identified by the FDA. PMI's data also show significantly higher levels of many toxicants not on the FDA HPHC list in IQOS aerosol compared with cigarette smoke, with 22 over twice as high and 7 over 10 times higher. Therefore, it is important to expand chemical assessment of emissions from HTP and other new tobacco products beyond those found in cigarette smoke.

It is possible that HTP could cause some diseases not caused by conventional cigarettes. Chun *et al*³⁴ identified animal and human studies in PMI's application suggesting that IQOS may cause liver toxicity not observed in cigarette users. PMI compared liver toxicity in rats exposed to IQOS or cigarette smoke, and found that several measures of liver toxicity (liver weights, blood levels of alanine aminotransferase and hepatocellular vacuolisation) increased more in female (but not male) rats exposed to IQOS than cigarettes. PMI's human clinical data also suggested the possibility of increased liver injury in one of their studies: following 5 days of using IQOS, conventional cigarettes, or smoking abstinence, plasma bilirubin was higher in IQOS users than conventional smokers or abstainers. PMI Science posted a response to this paper on its website stating that "based on an analysis of our toxicological studies and clinical studies performed according to international standards of good practice, there is *no evidence* that IQOS use leads to hepatotoxicity [emphasis added]."³⁵ In contrast to this unequivocal statement, the point that Chun *et al* make is not that the data PMI submitted to the FDA prove hepatotoxicity, but that the combination of animal data and some of the human data constitute a pattern worth careful consideration, especially in light of the short duration of the studies and lack of additional potential insults to the liver including alcohol use and other drug use that is common in smokers.

IQOS (and likely HTP generally) are simply *different* from conventional cigarettes and deliver less of some toxicants and more of others, so that IQOS may pose lower, the same or higher health risks than cigarettes depending on the disease. IQOS emits more of several important toxins with more adverse health effects than e-cigarettes.

PERCEPTIONS OF THE PRODUCT AND WARNING LABELS

Despite the evidence discussed above, in 2018 IQOS and other HTP were being marketed around the world with claims that they are less harmful than cigarettes because they expose users to lower levels of some toxicants. Popova *et al*³⁶ examined the qualitative and quantitative Perception and Behavior Assessment Studies in PMI's application which revealed that consumers perceive even reduced exposure claims as reduced risk claims. Allowing PMI to promote IQOS with reduced exposure claims would amount to permitting the kind of 'light' and 'mild' fraud that the FSPTCA and WHO Framework Convention on Tobacco Control (FCTC) expressly prohibit for other tobacco products.

This misunderstanding of reduced exposure as reduced risk bears directly on how IQOS should be labelled so as not to mislead consumers. McKelvey *et al*³⁷ examined PMI's application focusing on the statements that switching completely from cigarettes to IQOS reduces risk. PMI failed to demonstrate that current smokers will understand what 'switching completely' means, and therefore failed to demonstrate that their IQOS will not decrease smokers' intentions to quit smoking, or that IQOS users will 'switch completely' (PMI's other studies showed most people use IQOS and cigarettes concurrently, so-called dual users.) Additionally, PMI's study design and measurement instruments suffered design flaws, and their reporting of associated findings is misleading. Experience with other products such as e-cigarettes suggests consumers will not understand that they must completely quit smoking cigarettes to achieve the claimed health benefits of IQOS. Rather, consumers will likely misunderstand unsupported claims of reduced risks to mean IQOS are risk-free.

Independently confirming PMI's results, El-Toukhy *et al*³⁸ examined the impact of reduced exposure and reduced harm MRTTP claims in a national sample of US adults and adolescents. They found that communicating lower risk in MRTTP claims led to lower perceived risk among adults and adolescents and increased the likelihood that adults would use the product. Reduced exposure claims led to lower perceived chemical quantity and lower perceived risk, but had no effect on likelihood of product use. Adults and adolescents misinterpreted reduced exposure claims as communicating lower risk, even when no explicit reduced risk claims were made. Because reduced exposure MRTTP claims are not permissible under US law if they mislead the public to believe the product presents less risk of harm, these studies demonstrate that reduced exposure claims for IQOS are impermissible.

These concerns are particularly acute for adolescents who are susceptible to using novel tobacco products. E-cigarettes provide a cautionary tale for any new tobacco product coming to market: e-cigarettes have attracted youth at low risk of initiating nicotine use with cigarettes,³⁹ many of whom then proceed to cigarettes.⁴⁰ McKelvey *et al*⁴¹ found that PMI's application failed to provide any evidence regarding the effect IQOS and its marketing will have on the likelihood that adolescents who are not tobacco users or who are former tobacco users will start nicotine use with IQOS. Instead, PMI conducted studies of adults that relied on 'behavioural intention' as a proxy to predict IQOS use, ignoring evidence that these models do not accurately predict tobacco

use. Of added concern, the IQOS name, packaging and retail shops resemble popular cell phones that attract youth.⁴² PMI's data and independent scientific studies regarding novel tobacco products (including e-cigarettes) marketing suggest IQOS will attract adolescent and young adult non-users to initiate tobacco use with IQOS and could also increase polyuse of different tobacco products.

Hair *et al*⁴³ examined IQOS marketing in Japan and Switzerland and studied consumer perceptions, attitudes and behaviours. Expert interviews and IQOS packaging and marketing analyses revealed that IQOS was marketed as a clean, chic and pure product which resonated in cultures that value cleanliness, exclusivity and high-tech appearances. Japanese consumers used IQOS for socialising with non-smokers. Focus group participants in both Japan and Switzerland reported lower levels of satisfaction with IQOS than cigarettes, although many found the packaging appealing. Few participants reported potential health benefits compared with cigarettes.

PMI introduced IQOS to Korea in May 2017. Three months later, Kim *et al*⁴⁴ conducted an online survey of young adults including current, ever and non-users. Rather than switching from conventional cigarettes to IQOS, all current IQOS users continued to use cigarettes or e-cigarettes. There were no IQOS-only users. Current users believed IQOS less harmful or useful to stop smoking. The observation that all the current IQOS users were dual users of conventional cigarettes or e-cigarettes contradicts PMI's assumption that cigarette smokers would switch to HTP.

As of July 2018, the FDA had not authorised HTP for sale in the USA, but awareness and use were increasing. Nyman *et al*⁴⁵ assessed awareness and use of HTP in the USA. From 2016 to 2017, adult awareness of HTP increased from 9.3% to 12.4%, ever use increased from 1.4% to 2.2% and current use doubled from 0.5% to 1.1%. Non-white adults, cigarette smokers, and both current and former users of e-cigarettes were more likely to use HTP.

POLICY, POLITICS AND LAW

Tobacco companies have promoted 'harm reduction' for decades. Although tobacco harm reduction proponents take British psychologist Michael Russell's 1976 idea that 'people smoke for nicotine but they die from the tar'⁴⁶ as an article of faith, he simply presented it as a 'hypothesis'. Elias and Ling⁴⁷ examined tobacco industry documents and found that Russell collaborated with BAT on two 'safer cigarette' studies and received £55 000 (£300 850 or \$398 000 in 2018) to study medium-nicotine low-tar cigarettes. The most prominent early HTP was RJ Reynolds' (RJR) Premier, introduced in the USA in 1988. Russell engaged extensively with RJR about Premier's 'positive aspects' and published an unsigned 1991 *Lancet* editorial⁴⁸ endorsing Premier as a 'near-perfect low tar cigarette' 2 years after RJR stopped marketing Premier without disclosing his conflict of interest. Although Premier failed, RJR saw future business opportunities for novel products if endorsed by health authorities, making conflicts of interest highly important considerations in assessing product endorsements, including those published by high-impact medical journals.

It is important to consider HTP in the context of multinational tobacco companies' product mix and response to the tightening regulatory environment promoted by FCTC. Bialous and Glantz⁴⁹ describe how HTP extend the industry's strategies to undermine government regulation by reframing tobacco companies from part of the problem to part of the solution. Under the 'harm reduction' moniker, companies are attempting

to rehabilitate their reputations to more effectively influence governments to roll back existing tobacco control policies or create exemptions for HTP. Where regulations are absent or loopholes exempt HTP from existing regulations, companies' market HTP to increase social acceptability for all their tobacco products. Governments must ensure that HTP are regulated or banned, and reject partnerships with tobacco companies to promote 'harm reduction'. Doing so requires governments in countries where HTP are not available to keep them out or, if allowed in the market, strictly regulate them under the FCTC.

Israel illustrates how PMI took advantage of regulatory ambiguity to implement an aggressive campaign promoting IQOS as safer than conventional cigarettes. Rosen and Kislev⁵⁰ describe how PMI promoted IQOS as part of its 'Smoke-Free Israel vision' after launching IQOS in December 2016. The campaign began with quiet pre-market meetings with government officials, followed by meetings in Israel's Parliament and an intense campaign in the printed press to promote harm reduction and PMI's 'Smoke-Free Israel vision'. The public campaign included digital and print marketing aimed at young people to promote PMI's 'Smoke-Free Israel vision' and harm reduction using the theme 'IQOS Changes Everything', that stressed IQOS was clean with less smell and no ash. PMI's campaign initially resulted in IQOS' exemption from tobacco regulations. These policies were later reversed after three petitions to the Supreme Court, pressure from health organisations and leading politicians, and wide press coverage of PMI's influence on Parliament's decision-making process. Israel's weak and poorly enforced advertising restrictions, however, have allowed PMI to continue its marketing claims.

In determining whether any new tobacco product may be sold, including HTP, the FDA must consider the product's overall population health impact. Importantly, in addition to any changes in specific toxicity for current smokers who switch from cigarettes to HTP, the availability of HTP affects nicotine and cigarette initiation and cessation. For products that have not been on the market to empirically answer these questions, modelling is an important element of the decision-making process. Max *et al*⁵¹ evaluated PMI's Population Health Impact Model (PHIM), as used in its application, in comparison with other available models. Although similar to many published models, PHIM includes assumptions likely to lead to a positive assessment of IQOS' population health impact. PHIM does not consider impacts on morbidity, underestimates mortality, does not include impacts on non-users, ignores the impact of IQOS on nicotine product initiation among never smokers and does not use the latest US data to set the model's parameters. Because PHIM systematically underestimates the impact of IQOS on the population as a whole, it cannot adequately justify marketing IQOS as 'appropriate to protect public health'.

The most important change in the policy environment since the tobacco companies were last actively promoting HTP in the 1980s and 1990s is the advent of formal regulatory regimes for tobacco products through the FSPTCA in the USA and the FCTC globally. Lempert and Glantz⁵² analysed laws and obligations that apply to the introduction, labelling and marketing of IQOS under FSPTCA and FCTC. PMI's premarket tobacco application and MRTP application for IQOS do not meet FSPTCA requirements on reduced harm or net public health benefit. The FDA can only authorise sale of new products through the new tobacco product pathway that are better for public health than products currently on the market, and e-cigarettes, currently sold in the USA, should probably be the comparator product. FCTC obligates parties to implement laws to reduce tobacco use

and nicotine addiction, and the introduction of any new tobacco product must be assessed against this goal. PMI's aggressive marketing techniques for IQOS using targeted customer interventions and sophisticated technologies to capture data and monitor use directly from the IQOS device via the internet⁵³ should concern privacy and public health advocates. Moreover, nothing in the US law or FCTC prevents authorities from prohibiting HTP. If not banned, all HTP components should be regulated as stringently as tobacco products, including restrictions on labelling, advertising, sales to minors, price and taxation policies, and smoke-free measures, and these laws should be aggressively enforced.

CONCLUSION

HTP are the latest effort by tobacco companies to adapt to a changing regulatory landscape to maintain and expand their customer base amid declining social acceptability of tobacco use and declining cigarette consumption. IQOS and other HTP are the newest in a long string of products designed to retain customers and protect tobacco companies' reputations and political influence. Because US law required PMI to provide detailed results of their IQOS research for its MRTP application, it was possible to independently assess their research. PMI's own data do not support its claims that IQOS is less dangerous than cigarettes. While IQOS may expose users to lower levels of some toxicants than cigarettes, they also expose users to higher levels of other toxicants. Likewise, IQOS likely exposes users to lower risks of some diseases and higher risks of others. PMI's research, confirmed by independent research, also highlights the fact that reduced exposure claims are misunderstood as reduced harm claims. These facts raise serious concerns that HTP and their marketing will harm youth and young adults and undermine cessation among smokers without providing health benefits to smokers who use them.

Fortunately, regulatory tools are in place to make rational, evidence-based decisions about these products. The question is whether public health advocates will ensure that policy-makers prioritise protecting public health and prevent tobacco companies from again using their extensive public relations and political resources to avoid regulation and protect profits. Policy makers should give greater weight to the advice provided by public health scientists than to submissions from industry when it comes to regulating tobacco products such as HTP.

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Heated tobacco products: things we do and do not know

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This Special Issue is focused on IQOS, electronic devices that offer yet another nicotine delivery alternative to smoking regular tobacco cigarettes. IQOS are designed to heat rather than burn tobacco, and represent somewhat of a hybrid of a regular cigarette and an electronic cigarette. Little is known about the toxicity and the public health impact of these products, relative to both the combustible cigarettes and other nicotine delivery products. Nevertheless, IQOS and other heated tobacco products (HTPs) are gaining popularity in some countries, caused in large part by the manufacturer's aggressive advertising and assertions that these devices are safe.

Most in the public health world would agree that the best evidence-based approaches should be applied to reduce death and illness due to tobacco use. Such approaches may include supporting addicted tobacco users to move to alternatives that are less harmful and truly reduce the population burden of tobacco diseases. It is important to bear in mind these two goals – alternative tobacco delivery devices may be less risky than combustible cigarettes for the individual smoker, but if they do not lead to a reduction in the prevalence of smoking there is no gain for public health.

What do we know about the safety of IQOS and the effect that introduction of these devices may have on smoking rates and the population burden of disease and premature mortality? Unfortunately information about IQOS and similar products is, at present, largely limited to industry reports. These include observations from marketing and data from product toxicity and human exposure studies. The papers in this Special Issue take a close look at the industry material, as well as the limited emerging academic literature on HTPs. The findings in broad terms are not terribly surprising. Data are scarce, and in particular, there are no long-term studies in human populations of the consequences of use of IQOS. Nevertheless an addictive product is being promoted by over-emphasising (or in some cases exaggerating) the limited evidence for its capacity to reduce harm, while minimising evidence on its potential toxicity. A sceptical view, conditioned by history, would be that this may be part of strategic efforts by the industry to retain existing consumers of tobacco products and generate new lifelong nicotine-dependent users. We offer some suggestions about what we do not know at present about IQOS, but need to understand to best inform tobacco control policies.

Research independent of the industry is required to inform product users, public health professionals, and regulatory agencies about the potential public health impact of IQOS and other HTPs. In addition, if reports of research studies are submitted by

the industry to regulatory agencies, there must be careful analysis of raw laboratory data to ensure the results are well tested and appropriately interpreted.

The chemical profile and toxicity of IQOS and other HTPs must be thoroughly investigated. It is critical to understand where these products are positioned along the continuum of risk relative not only to combustible cigarettes but also to other nicotine delivery devices that may have lower toxicity profile, such as e-cigarettes. Unlike e-cigarettes, HTPs do contain tobacco and therefore, even in the absence of combustion, are expected to deliver to their users thousands of chemicals that are present in the tobacco material. Moreover, some of the tobacco chemicals that would be partially or completely decomposed during the combustion process may be present in the emissions of HTPs. Thus, it is possible that HTPs deliver to their users a unique chemical mixture with a distinct toxicity profile. As the result, the benefits of reductions in exposure to some of the 'usual suspects', such as polycyclic aromatic hydrocarbons, may be attenuated by new health risks. Lastly, similar to e-cigarettes, IQOS and other HTPs contain substantial amounts of propylene glycol that is aerosolized when the device is in use. Oxidative stress and inflammation, some of which is most likely driven by exposures to the products of thermal decomposition of propylene glycol, are emerging as key concerns in assessing the long-term health consequences of e-cigarette use. It seems likely that users of HTPs will face similar risks, if these do indeed apply.

Characteristics of current and potential users of HTPs need to be taken into consideration while assessing the potential public health impact of these products. The concept of the continuum of harm often focuses on the toxicity profile of the product, as compared with cigarette smoke and isolated from the characteristics of the user. Similar to e-cigarettes, the relative harmfulness of HTPs may be greatly affected by whether or not a user is a former smoker, uses the product together with continued smoking of regular cigarettes, has significant co-morbidities (cardiovascular and lung diseases in particular), or a propensity to become a life-long nicotine-dependent user.

It is important to understand what HTPs will do to the prevalence of smoking. In the absence of substantial, reliable data, decisions about products such as IQOS are an exercise in risk management. On the one hand, there is the possibility of foregoing benefits (if there is a true, net reduction in harm), on the other the prospect of inflicting serious risks to health. How this balancing act is viewed will depend to some extent on context. Where the

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prevalence of smoking is already low and falling, a conservative approach to new tobacco products is understandable. Where prevalence is high, and in some population groups is hardly budging despite concerted effort, then there may be a greater willingness to explore alternatives to the combustible cigarette.

Finally, we note that current smokers who are concerned about their health risks and can afford electronic tobacco or nicotine delivery devices represent only a fraction of the tobacco industry's total consumer base. Regular tobacco cigarettes are still being aggressively marketed to low-income markets worldwide, contributing to sustained tobacco consumption and the narrative of demand-driven cigarette manufacturing and sales. Once again, a history-conditioned sceptical view would be that marketing of products like IQOS is just a new way to appeal to a wider variety

of nicotine consumers. Will the industry attempt to maintain their diverse consumer base by whatever means available? The most likely answer is yes, because this is what it takes to stay in the business of tobacco.

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PMI's own in vivo clinical data on biomarkers of potential harm in Americans show that IQOS is not detectably different from conventional cigarettes

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ABSTRACT

Introduction New 'heated tobacco products' are being marketed in several countries with claims that they expose users to lower levels of toxins than conventional cigarettes which could be read as being less likely to cause health problems than conventional cigarettes. In the USA, Philip Morris International (PMI) has submitted an application to the Food and Drug Administration for permission to market its heated tobacco product, IQOS, with reduced exposure and reduced risk claims.

Methods Analysis of detailed results on 24 biomarkers of potential harm in PMI studies of humans using IQOS compared with humans using conventional cigarettes.

Results Among American adults, there is no statistically detectable difference between IQOS and conventional cigarette users for 23 of the 24 biomarkers of potential harm in PMI's studies. In Japan, there were no significant differences between people using IQOS and conventional cigarettes in 10 of 13 biomarkers of potential harm. It is likely that some of the significant differences are false positives.

Conclusion Despite delivering lower levels of some toxins than conventional cigarettes, PMI's own data fail to show consistently lower risks of harm in humans using its heated tobacco product, IQOS, than conventional cigarettes.

In 2015, Philip Morris International (PMI) started test marketing its IQOS HTP outside the USA on the grounds that it is not as bad as a cigarette because 'the tobacco is heated and not burned, the levels of harmful chemicals are significantly reduced compared to cigarette smoke.'⁴

Because IQOS is a new tobacco product, PMI needs to obtain premarket authorisation from the US Food and Drug Administration (FDA) to sell it in the USA. In particular, PMI wants to market IQOS with reduced risk claims, what US law calls a 'modified risk tobacco product' (MRTP). To obtain authorisation to market IQOS with reduced risk claims, PMI submitted an application to the FDA in December 2016.⁵ As required by law, FDA has made most of the application available for the public to review. The application includes comparisons of the levels of 24 biomarkers of potential harm in human smokers, including comparisons with people who smoke conventional cigarettes. These biomarkers include measures of inflammation, oxidative stress, cholesterol and triglycerides, blood pressure and lung function. This paper uses information in the PMI application to evaluate this comparison and concludes that in people who actually use IQOS, the levels of these biomarkers of potential harm are not detectably different from conventional cigarettes.

INTRODUCTION

Nicotine is the addictive drug in tobacco. Burning the tobacco generates an aerosol of ultrafine particles that carries nicotine deep into smokers' lungs, where it is absorbed and rapidly reaches the brain. That burning yields toxic chemicals that cause disease. Ever since people started understanding in the 1950s that smoking kills, millions have struggled to stop smoking. The tobacco companies, desperate to keep and expand their customers, have been trying to make 'safer cigarettes' since the 1960s.¹ They have also developed products that avoided burning, including e-cigarettes,² nicotine replacement therapy,³ and products that heat the tobacco without setting it on fire. As of January 2018 all the major multinational tobacco companies had developed, or were in the process of developing, so-called 'heated tobacco products' (HTP; also called 'heat-not-burn' tobacco products). Because these devices generate their nicotine aerosols by heating a stick of ground tobacco and chemicals without setting the tobacco on fire, they generally produce fewer toxic chemicals than a conventional cigarette, which is promoted as meaning or implying that these products are not as dangerous as conventional cigarettes.

METHODS

The results analysed in this paper are from PMI's 'Three-month Reduced Exposure in a confined and ambulatory setting' studies (ZRHR-REXA-07-JP in Japan and ZRHM-REXA-08-US in the USA) that present human clinical studies of non-cancer biomarkers of potential harm presented in PMI's MRTP application's⁵ Executive Summary, Module 6: Summaries of All Research Findings, and Module 7.3.1: Scientific Studies and Analyses (Studies in Adult Human Studies: Clinical Studies), specifically the data on 24 biomarkers of potential harm *in human users* derived from two of their 'Reduced Exposure' studies: ZRHR-REXA-07-JP in Japan and ZRHM-REXA-08-US in the USA.

As described in Section 6.1.4.3.2 of the application, cigarette smokers were randomised, controlled, open-label, three-arm parallel group studies in which smokers were randomised to IQOS (menthol), continued smoking their current brand of cigarettes or smoking abstinence. Baseline data were collected on day 0 immediately before randomisation, people were held during a 5-day confinement period then released to the ambulatory setting and observed at 90 (± 3 (range)) days



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after randomisation. (Some variables were measured during confinement and before 90 days, but are not considered in this analysis.) During the confinement period, product use was directed and monitored by the study staff and participating smokers were controlled for product compliance. Subjects assigned to conventional cigarettes or IQOS used the products without restriction (ad libitum) during an extended daily time window (16 hours); dual use of conventional cigarettes and IQOS was not permitted. The 3-month ambulatory phase was designed to reflect a near real-world environment where dual use of IQOS and conventional cigarettes or other tobacco products could occur. PMI selected a 3-month extended ambulatory follow-up period so that the study would be long enough to assess the initial changes in some of the clinical risk endpoints that have been shown to be reversible within 2 weeks to 3 months.

The final sample (table 1) consisted of people who were adherent with their assigned study product and without major protocol deviations that impacted the validity of the evaluation of the study results. This sample was designed to assess the maximum exposure reduction achievable (what PMI characterised as the ‘optimal effect’) in subjects who were using IQOS ad libitum and exclusively or at least predominantly, rather than the effect in the full population representing a heterogeneous exposure (eg, as mixed product use, or non-use of the assigned product).

The point estimates and 95% confident intervals (CIs) at day 90 were computed using least squares means from an analysis of covariance with study arm as a factor adjusting for baseline value, sex and average daily conventional cigarette consumption over the last 4 weeks as reported during screening. (Thus, the width of the CIs for the differences between IQOS and conventional cigarette use in table 1 benefits from the information in the smoking abstinence group even though those subjects are not directly involved in the point estimates being compared.) Endpoints that were not normally distributed were log-transformed (base e) prior to analysis, then back-transformed to calculate least squares means ratios to compare IQOS with conventional cigarettes.

Both trials were registered with ClinTrials.gov.

Specific results are based on measures of inflammation in Section 6.1.4.4.2; cholesterol, triglycerides and physiological measures related to heart disease in Section 6.1.4.4.4; and lung function in Section 6.1.4.4.5.

RESULTS

Among American adults, there is no statistically detectable difference between IQOS and conventional cigarettes for 23 of the 24 biomarkers of potential harm in PMI’s studies (table 1). This is indicated by the fact that 23 of the 95% CIs include zero (ie, no statistically significant difference). Moreover, when using the conventional 95% confidence standard for statistical hypothesis testing, one would expect 5% of the tests to yield false positives. Five per cent of 24 tests is 1.2 tests, which means that one would expect one false positive result. PMI had one positive result (soluble intercellular adhesion molecule (ICAM)), which is what one would expect by chance.

PMI also reported the results on 13 biomarkers of potential harm among Japanese people (table 1). There were significant improvements in 4/13 of these biomarkers, 3 markers of inflammation (white cell count, prostaglandin F2 alpha and soluble ICAM) and 1 measure of cholesterol (high-density lipoprotein cholesterol). When using the conventional 95% confidence standard one would expect 0.65 positive tests, which means one would expect one false positive test.

Table 1 Summary of Philip Morris studies of changes in biomarkers in IQOS users compared with conventional cigarette smokers after 90 days of product use (95% CIs in parenthesis)

	Japan	USA
Inflammation (6.1.4.4.2**)		
White cell count	-0.57 GI/L (-1.04 to -0.10)	0.17 GI/L (-0.47 to 0.81)
C-reactive protein (CRP)	6.41% ↓ (-40.75 to 37.77)	16.23% ↓ (-21.69 to 42.33)
Soluble ICAM (sICAM-1)	8.72% ↓ (2.05 to 14.94)	10.59% ↓ (4.03 to 16.71)
Fibrinogen	5.42% ↓ (-1.80 to 12.13)	1.63% ↓ (-6.42 to 9.08)
Oxidative stress (6.1.4.4.3)		
Prostaglandin F2 alpha (8-epi-PGF2α)	12.71% ↓ (2.55 to 21.81)	13.46% ↓ (-1.95 to 23.61)
11-dehydrothromboxane B2 (11DTXB2)	5.42% ↓ (-1.80 to 12.13)	3.56% ↓ (-23.31 to 24.57)
Cholesterol and triglycerides (6.1.4.4.4)		
High-density lipoprotein cholesterol (HDL-C)	4.53 mg/dL (1.17 to 7.88)	1.4 mg/dL (-2.3 to 5.0)
Low-density lipoprotein cholesterol (LDL-C)	0.87 mg/dL (-6.55 to 8.30)	-3.3 mg/dL (-12.0 to 5.4)
Total cholesterol	2.00 mg/dL (-6.68 to 10.67)	-4.0 mg/dL (-13.3 to 5.2)
Triglycerides	-6.25 mg/dL (-21.20 to 8.69)	0.9 mg/dL (-12.8 to 14.6)
Apolipoprotein A1 (apoA1)	NA	3.1 mg/dL (-4.6 to 10.7)
Apolipoprotein B (apoB)	NA	-1.6 mg/dL (-7.24 to 4.03)
Physiological measures		
Systolic blood pressure	-0.59 mm Hg (-3.80 to 2.62)	-0.7 mm Hg (-4.5 to 3.1)
Diastolic blood pressure	-0.68 mm Hg (-3.04 to 1.69)	0.2 mm Hg (-3.7 to 4.0)
Lung function (6.1.4.4.5)		
Forced expiratory volume in 1 s (FEV ₁)	1.91 %Pred (-0.14 to 3.97)	0.53 %Pred (-2.09 to 3.00) 0.05 L (-0.06 to 0.15)
FEV ₁ /FVC (forced vital capacity)	NA	0.00 (-0.02 to 0.02)
Mid-expiratory flow (MEF 25–75) (L/s)	NA	-0.67 (-6.33 to 4.99)
Diffusion capacity for lung CO (DLCO) (mL/min/mm Hg)	NA	0.31 (-1.09 to 1.72)
Rate constant of CO (KCO) (mmol/min/kPa/L)	NA	0.05 (-0.02 to 0.12)
Total lung capacity (TLC) (L)	NA	0.09 (-0.25 to 0.43)
Functional residual volume (FRV) (L)	NA	-0.09 (-0.31 to 0.13)
Inspiratory capacity (IC) (L)	NA	0.21 (-0.08 to 0.51)
Vital capacity (VC) (L)	NA	0.10 (0.00 to 0.21)
Summary		
Number of biomarkers tested	13	24
Number significantly improved	3	1
Number expected by chance	1	1

Continued

Table 1 Continued

	Japan	USA
Sample sizes		
IQOS	70	47†
Conventional cigarettes	41	32‡
Smoking abstinence	37	9§

The results are either IQOS:CC or IQOS-CC (conventional cigarettes).

Bold results are statistically significant differences ($p < 0.05$).

*Section of Philip Morris International's Modified Risk Tobacco Product application.

† $n=45$ for fibrinogen, 8-epi-PGF2 α , 11DXTB2, systolic blood pressure, diastolic blood pressure, DCLO and KCO.

‡ $n=30$ for FEV $_1$, FEV $_1$ /FVC, MEF 25–75, DLCO, KCO, TLC, FRV, IC and VC.

§ $n=8$ for DLCO and 7 for KCO.

ICAM, intercellular adhesion molecule; NA, not applicable.

DISCUSSION

These human data are important information because they represent direct evidence on how IQOS affects people who use the product. They show that, despite the evidence that PMI submitted that the levels of some toxins in IQOS aerosol are lower than in conventional cigarettes,⁵ fewer toxic chemicals, however, do not necessarily translate into lower harm when people use the product.

In its MRTP application, PMI did not discuss the results of the conventional statistical tests described in the Results section, which are routine for such scientific analysis. Rather, they simply emphasise the direction of changes while ignoring the fact that these differences are within what would be expected based on simple randomness. No tobacco company would tolerate such assertions made by the FDA or other public health authorities.

The results reported in PMI's application (and in a published paper⁶) for Japan are slightly more positive for IQOS, with 4 of 13 biomarkers showing differences from conventional cigarettes (where one would expect one false positive by chance). These results are not strong enough to warrant drawing a conclusion of reduced risk. The conclusion of no significant difference on biomarkers of potential harm is based on taking PMI's results at face value despite the tobacco companies' (including Philip Morris) long record of manipulating the design, analysis and presentation of their published scientific studies <<ED: Citation should be "7-12" no "7-13".>>.^{7–13}

Like cigarettes (and e-cigarettes), IQOS uses an aerosol of ultra-fine particles to deliver the nicotine. These ultrafine particles cause heart and lung disease. The adverse health effects of these particles and many of the other toxins do not drop in proportion to reducing the dose, so even low levels of exposure can be dangerous.¹³ This effect is why smoke-free environment laws are followed by big drops in heart attacks and other diseases despite the fact that secondhand smokers breathe in much less smoke than the smokers.¹⁴ In addition, while the IQOS does not set the tobacco stick on fire, it heats it to 350°C (660°F), which is still hot enough to cause pyrolysis. There is already independent evidence that IQOS compromises functioning of arteries,¹⁵ a key risk factor for heart disease and heart attacks, as badly as a cigarette.

The clinical studies that PMI reported appropriately did not include cancer because carcinogenic effects take much longer to be manifest than cardiovascular and pulmonary effects. Even if the levels of carcinogens delivered by IQOS are lower than conventional cigarettes on a per-puff basis, these lower exposure levels may not yield proportionately lower cancer risks because both the intensity and duration of exposure impact cancer risk.^{16–18}

The purpose of this paper is to assess the data on biomarkers of potential harm of the Philip Morris IQOS HTP system in

people who were actually using the system compared with people who smoke conventional cigarettes based on the information submitted to the US FDA in PMI's MRTP application for IQOS. On 31 March 2018, the author conducted a PubMed search using the search term '(IQOS or 'heat not burn' or 'heated tobacco product') and (health or harm) and (human or clinical)'. This search returned 33 papers, none of which reported on comparisons of in vivo biomarkers of potential harm in people using IQOS (or any other HTP system) compared with conventional cigarettes. Thus, as of 9 July 2018, the data in the PMI MRTP application remained the only publicly available evidence on the in vivo human clinical effects of IQOS compared with conventional cigarettes.

While this analysis is limited to the data presented in PMI's IQOS MRTP application to the FDA, it is likely that the effects of other HTPs being developed by other tobacco companies will have similar effects because the fundamental principles behind all these products are the same.

On 15 June 2018, PMI issued a press release, 'Philip Morris (PM) Announces Positive Results from New Clinical Study on IQOS',¹⁹ that said, 'all eight of the primary clinical risk endpoints moved in the same direction as observed for smoking cessation in the group who switched to IQOS, with statistically significant changes in five of the eight endpoints compared with on-going smoking.' While PMI did not release any detailed results, examining the protocol (on ClinicalTrials.gov) revealed that this new study only examined six clinical measures, compared with the 24 in MRTP application (table 1). (The other two were biomarkers of exposure.) PMI did not say which of the changes were statistically significant, raising the possibility that the protocol and analysis were manipulated to achieve positive results.^{8,9} PMI increased the sample size from 88 in the original US study to 984. While bigger studies are better, the fact is that making the sample size big enough will increase the power to the point that almost any difference will reach statistical significance regardless of whether it is clinically significant or not. The true measure of reduced risk would be statistically significant changes that were large enough to be clinically significant in enough biomarkers of potential harm to be meaningful.

PMI's failure to show significant improvements in these biomarkers of potential harm is consistent with the data PMI reported on the levels of toxicants in IQOS mainstream aerosol compared with mainstream smoke of 3R4F reference cigarettes.²⁰ While many toxicants were lower in IQOS aerosol, 56 others were higher in IQOS emissions and 22 were more than twice as high, and 7 were more than an order of magnitude higher.

In short, PMI's results in humans failed to meet the legal requirement that IQOS 'as it is actually used by consumers, will significantly reduce harm and the risk of tobacco-related disease to individual users' that US law requires before the FDA can approve a reduced risk claim. In the USA, PMI wants to sell IQOS with claims that 'Scientific studies have shown that switching completely from cigarettes to the IQOS system can reduce the risks of tobacco-related diseases' and 'Switching completely to IQOS presents less risk of harm than continuing to smoke cigarettes';³ these claims are not substantiated by PMI's own data.

On 25 January 2018, based in part on the information in this paper (which had been submitted to FDA as a public comment) showing gaps in PMI's scientific evidence, the FDA's Tobacco Products Scientific Advisory Committee voted that PMI had failed to demonstrate that its proposed modified (reduced) risk labelling and advertising claims for IQOS were demonstrated by scientific evidence.²¹

Based on the data in the PMI MRTP application for IQOS, neither the US FDA nor comparable authorities elsewhere in

What this paper adds

- ▶ Heated tobacco products are being marketed in several countries with claims of reduced exposure to toxins compared with conventional cigarettes.
- ▶ Studies conducted in people using Philip Morris International's IQOS heated tobacco product did not reveal detectably better measures of biomarkers of potential harm than conventional cigarettes in human tests.
- ▶ These products should not be permitted to be marketed with claims that state or imply reduced risks compared with conventional cigarettes.

the world should permit such claims to be made. All companies wishing to market HTPs with reduced risk claims should be held to the same standard, and their claims independently verified.

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Data sharing statement All data are available in the PMI MRTP application on the FDA website.

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Vascular endothelial function is impaired by aerosol from a single IQOS HeatStick to the same extent as by cigarette smoke

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ABSTRACT

Background Heated tobacco products (also called 'heat-not-burn' products) heat tobacco at temperatures below that of combustion, causing nicotine and other compounds to aerosolise. One such product, IQOS from Philip Morris International, is being marketed internationally with claims of harm reduction. We sought to determine whether exposure to IQOS aerosol impairs arterial flow-mediated dilation (FMD), a measure of vascular endothelial function that is impaired by tobacco smoke.

Methods We exposed anaesthetised rats (n=8/group) via nose cone to IQOS aerosol from single HeatSticks, mainstream smoke from single Marlboro Red cigarettes or clean air for a series of consecutive 30 s cycles over 1.5–5 min. Each cycle consisted of 15 or 5 s of exposure followed by removal from the nose cone. We measured pre-exposure and postexposure FMD, and postexposure serum nicotine and cotinine.

Results FMD was impaired comparably by ten 15 s exposures and ten 5 s exposures to IQOS aerosol and to cigarette smoke, but not by clean air. Serum nicotine levels were similar to plasma levels after humans have smoked one cigarette, confirming that exposure conditions had real-world relevance. Postexposure nicotine levels were ~4.5-fold higher in rats exposed to IQOS than to cigarettes, despite nicotine being measured in the IQOS aerosol at ~63% the amount measured in smoke. When IQOS exposure was briefer, leading to comparable serum nicotine levels to the cigarette group, FMD was still comparably impaired.

Conclusions Acute exposures to IQOS aerosol impairs FMD in rats. IQOS use does not necessarily avoid the adverse cardiovascular effects of smoking cigarettes.

INTRODUCTION

Heated tobacco products (also called 'heat-not-burn' tobacco products) heat tobacco at temperatures that avoid combustion but cause the nicotine to aerosolise. Philip Morris International's (PMI's) heated tobacco product IQOS is now marketed in at least 30 non-US countries and has been considerably more successful than similar products introduced at various times over the last three decades.¹ In 2017, Philip Morris Products S.A. submitted modified-risk tobacco product (MRTP) applications to the FDA to market IQOS in the USA with reduced risk claims.²

IQOS is composed of three main parts: HeatStick, holder and pocket charger (figure 1). HeatSticks, which contain long strips of processed and

reformed tobacco packed together (figure 1), are inserted in the holder for use. The holder contains an electronic heating blade that is activated by pressing a side button on the holder and heats the mixture of tobacco and other compounds in the HeatSticks to 350°C. Aerosol is generated as the user inhales through the HeatStick/holder combination.

Despite harm reduction claims by the tobacco industry and the clinical and basic research reported by PMI researchers,^{3–23} the cardiovascular health effects of IQOS and similar products are incompletely understood. Notably, industry-supported studies of potential cardiovascular consequences of IQOS aerosol exposure published to date have not included some common measures of adverse effects of smoke exposure, such as vascular endothelial function tested *in vivo*. As IQOS has been marketed widely, it is important to study the health effects of this product so that regulatory agencies such as the FDA and consumers can make informed decisions.

Endothelial function assessed by arterial flow-mediated dilation (FMD) is a validated measure of cardiovascular health effects and is defined as the per cent by which the arteries vasodilate in response to an increase in blood flow.²⁴ Endothelial cells lining the vessel sense increases in flow and respond by producing nitric oxide, which triggers the artery to grow in diameter to accommodate the increased demand. In humans, FMD is determined by temporarily interrupting and restoring blood flow to the forearm, and using ultrasound to measure the increase in brachial artery diameter caused by the resulting sudden increase in flow. FMD is a clinical prognostic indicator of endothelial function and cardiovascular health.^{25–27} Acute and chronic exposures to secondhand smoke and active smoking impair FMD in humans.^{28–31} While such studies have typically focused on exposure to smoke, one group has reported that exposure to e-cigarette aerosol can impair FMD,³² raising the possibility that this effect is not limited to smoke from combustion and suggesting that inhalation of other non-combustible tobacco products may also have similar consequences.

We previously developed and validated an *in vivo* rat model for FMD measurements using high-resolution ultrasound and microsurgical techniques.³³ We showed that exposure of rats to sidestream smoke (from the smouldering tip; an accepted approximation of secondhand smoke) of cigarettes, little cigars and marijuana impairs FMD in an endothelium-dependent manner (endothelium-independent

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Figure 1 IQOS. IQOS is composed of three main parts: HeatStick, holder and pocket charger. HeatSticks are inserted in the holder, which contains an electronic heating blade to heat tobacco and release aerosol. HeatSticks contain strips of processed and reformed tobacco. Photos by MLS and PN.

vasodilation induced by nitroglycerin is not impaired).^{34–36} The consistent responses of humans and rats to smoke and non-combustion aerosols from multiple sources led us to hypothesise that IQOS aerosol can similarly cause endothelial dysfunction. We report here that exposure to IQOS aerosol impairs FMD to the same extent as mainstream cigarette smoke.

MATERIALS AND METHODS

Animals

We used male Sprague-Dawley rats (Charles River, MI) at 8–10 weeks of age with body weights of 200–250 g as has been the standard condition for our previous studies on smoke exposure. Rats were anaesthetised with intraperitoneal injection of ketamine (100 mg/kg)/xylazine (5 mg/kg) for these experiments. During all procedures, rats were kept on a heating pad to prevent hypothermia. Frequency and depth of respiration were closely monitored to ensure full anaesthesia and supplemental intraperitoneal (IP) anaesthetic was given if necessary.

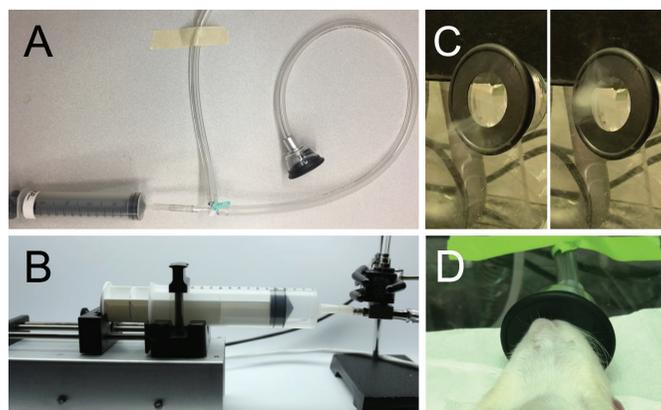


Figure 2 Aerosol generation and exposure systems. (A) Manual exposure system. (B) Analytical vaping machine made by Gram Research. (C) IQOS aerosol coming out of nose cone. (D) Rat's nose placed in the nose cone. Photos in A, C and D by PN; photo in B from Gram Research with permission.

Mainstream smoke/aerosol generation and exposure

Russian IQOS Parliament branded HeatSticks and an IQOS device from Ukraine were used for the first part of the project. Due to heating blade breaking incidences during cleaning, IQOS devices obtained from Japan and subsequently from South Korea were used for later exposures.

We exposed rats ($n=8/\text{group}$) via nose cone to IQOS aerosol, Marlboro cigarette mainstream smoke or clean air as control. The exposure regimen consisted of a series of consecutive 30 s cycles, each consisting of 15 or 5 s of exposure followed by removal of the nose cone for the rest of the 30 s interval. Each rat was exposed to either 10 cycles over 5 min or 3 cycles over 1.5 min, depending on the experiment, to approximate the consumption of a single IQOS HeatStick or less. To generate the aerosol and mainstream smoke, we used a manual syringe pump system for the initial experiment and then purchased a Gram Universal Vaping Machine version 5.0 (Gram Research, Oakland, California, USA) for the subsequent experiments (figure 2). The vaping machine contains an automatic syringe pump and has been shown to reproducibly generate aerosols from e-cigarettes under controlled conditions.³⁷ Both systems generated 35 mL of aerosol over 2 s and the vents on the side of the cigarette filters remained unoccluded. Separate sets of syringe pump, nose cone and connecting tubes and valves were used to avoid cross-contamination. The IQOS holder was fully cleaned and recharged after each use.

Endothelial function measurements

We used our previously established living rat model³³ to measure FMD before and after each exposure in individual animals.

We made a 1 cm incision on the rat's groin and surgically dissected around the common iliac artery. We then placed an arterial loop occluder consisting of a 5–0 Prolene filament under the artery and passed it through a 15 cm PE-90 tubing to enable transient occlusion of blood flow after suturing the skin. A series of diameter images of the femoral artery and accompanying Doppler blood flow images were recorded with a 35 MHz ultrasound transducer (Vevo660; VisualSonics, Toronto, Canada) before transient surgical occlusion at baseline. We induced a transient limb ischaemia for 5 min and obtained ultrasound imaging immediately after reperfusion, and then every 30 s for 5 min.

We used an automated program (Brachial Analyzer 5; Medical Imaging Applications, Coralville, Iowa, USA) to measure baseline artery diameter and peak postischaemia diameter during diastole. FMD was calculated as the per cent increase in the diameter of the artery after the transient ischaemia. FMD was measured before and after exposures to smoke or IQOS aerosol, as summarised schematically in figure 3A,B. The investigator was blinded to exposure conditions during FMD procedure, analysis of ultrasound images and subsequent calculations.

Serum nicotine and cotinine measurements

For measurement of nicotine and its metabolite cotinine, we collected blood immediately after exposure (from IQOS-exposed and cigarette-exposed rats not being used for FMD measurement; $n=5/\text{group}$) and 20 min later (from IQOS-exposed and cigarette-exposed rats after the final FMD measurement; $n=8/\text{group}$) via thoracotomy and cardiac puncture using a 23G blood collection set (BD Vacutainer) and untreated tubes. We centrifuged the blood samples at 800 rcf for 15 min and immediately

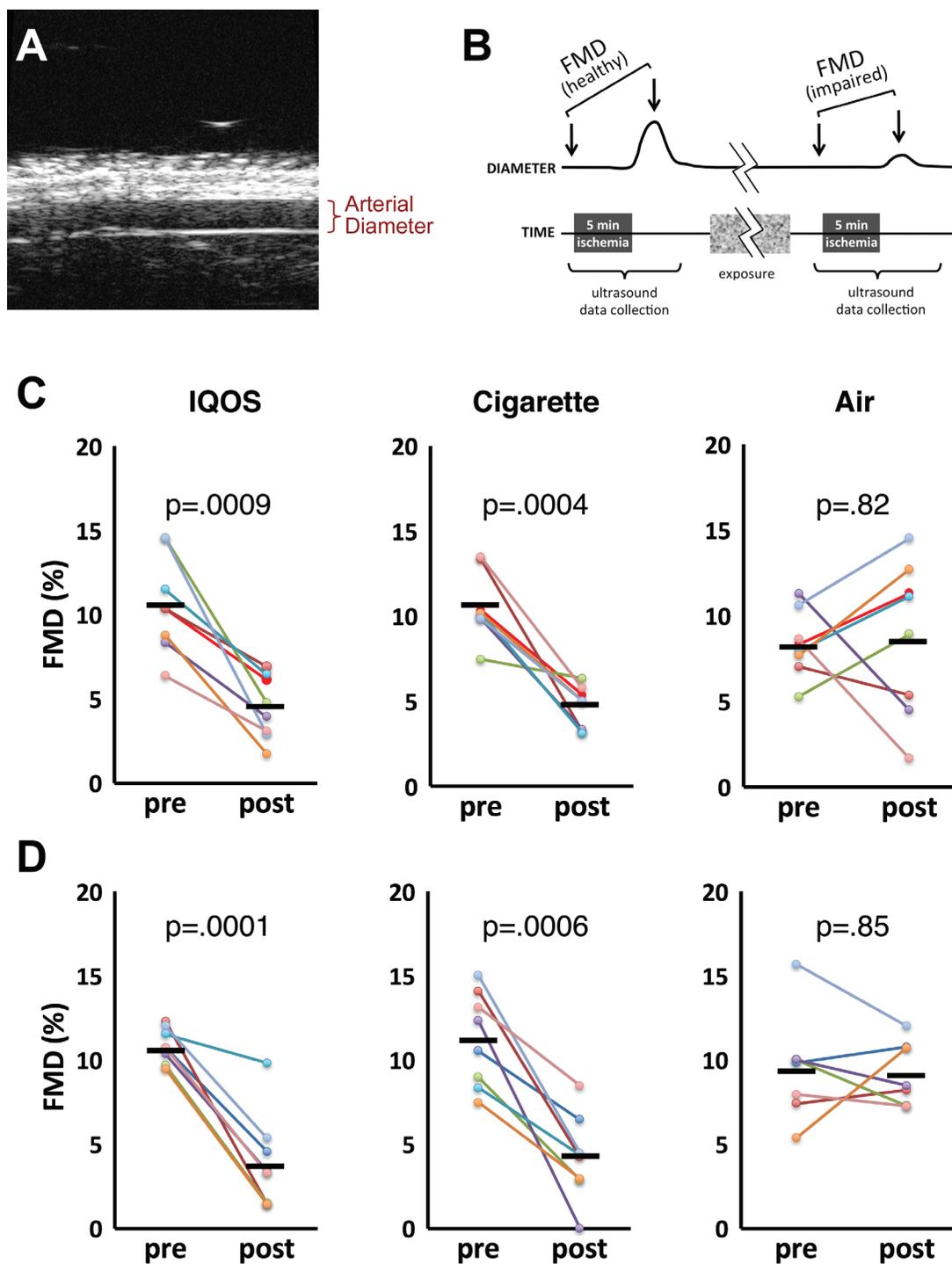


Figure 3 Arterial flow-mediated dilation was impaired by mainstream cigarette smoke and IQOS aerosol. (A) Ultrasound imaging of rat femoral artery. (B) FMD experimental design: FMD was measured pre-exposure and postexposure in each rat. (C) FMD after 10 cycles of 15 s exposure +15 s break. (D) FMD after 10 cycles of 5 s exposure +25 s break. Coloured lines denote individual rats pre-exposure and postexposure; bars denote group means; p values are derived from paired 2-tailed t-tests. FMD, flow-mediated dilation.

stored the serum samples at -80°C . Concentrations of nicotine and cotinine were determined by gas chromatography—tandem mass spectrometry.³⁸ The limits of quantitation were 1 ng/mL for nicotine and 10 ng/mL for cotinine.

Aerosol and mainstream smoke nicotine measurements

We measured nicotine in both gas and particle phases of the IQOS aerosol and mainstream smoke from Marlboro Red cigarettes and 1R6F research cigarettes using the method

described above. Particle phase nicotine was captured in mainstream aerosol and smoke on Cambridge filter pads placed downstream of the cigarette/IQOS filter, using modified ISO conditions of one 35 mL puff every 30 s for a total of 10 puffs ($n=3/\text{group}$). The filtered aerosol went through an impinger filled with 0.036 N HCl to trap the gas phase nicotine. We also analysed the postuse residual material in the HeatSticks as well as unused HeatSticks for nicotine levels. The filters and the contents of the HeatStick were

extracted with 20 mL of an extraction buffer containing 25% by volume of t-butanol, 0.5 M citric acid and 20 mM ascorbic acid by sonicating for 60 min at 60°C. The tubes were centrifuged at 3000 g for 5 min and aliquots of the supernatant were analysed. Liquid chromatography-tandem mass spectrometry³⁷ was used to measure the nicotine levels in the samples.

Statistics

We used paired t-tests to compare the FMD values in each group before and after exposures. Errors are presented in this report as SD. A two-way repeated measures analysis of variance (ANOVA) was run to examine the effect of type and duration of exposure on per cent FMD reduction. P value of <0.05 was considered statistically significant. Calculations were done using Stata V.13.1.

RESULTS

Comparable impairment of FMD by exposure to IQOS aerosol and cigarette mainstream smoke

Exposure in the first experiment (figure 3C) consisted of 10 cycles of 15 s exposure +15 s break (out of the nose cone). A subsequent experiment (figure 3D) used the more realistic regimen of 10 cycles of 5 s exposure +25 s break.

FMD was reduced comparably by ten 15 s exposures to IQOS aerosol ($10.6 \pm 2.9\%$ pre-exposure vs $4.5 \pm 1.9\%$ postexposure, $p=0.0009$) and cigarette smoke ($10.6 \pm 2.0\%$ pre-exposure vs $4.6 \pm 1.3\%$ postexposure, $p=0.0004$). FMD was not affected in the clean air control group ($8.3 \pm 1.9\%$ vs $8.8 \pm 4.5\%$, $p=0.82$).

FMD was also impaired comparably by ten 5 s exposures to IQOS aerosol and cigarette smoke ($10.8 \pm 1.0\%$ pre-exposure vs $3.8 \pm 2.6\%$ postexposure, $p=0.0001$; and $11.2 \pm 2.6\%$ pre-exposure vs $4.2 \pm 2.3\%$ postexposure, $p=0.0006$, respectively). FMD was not affected in the air control group ($9.5 \pm 3.0\%$ vs $8.1 \pm 1.8\%$, $p=0.85$).

A two-way repeated measures ANOVA revealed that there was not a significant interaction between type and duration of exposure on per cent FMD reduction, $F(2, 41)=0.30$, $p=0.73$. The per cent FMD impairment was not significantly different in groups exposed for 5 s compared with 15 s ($p=0.27$), which suggests that the endothelial response was saturated with a single HeatStick or cigarette.

Serum nicotine was comparable to that resulting from smoking by humans

To evaluate the accuracy of the exposure conditions in our rats and its relevance to real-world levels, we compared the post-cigarette exposure serum nicotine levels in rats to that reported for humans (figure 4). In rats subjected to the 10 x (5+25 s) regimen, mean nicotine levels in samples immediately after exposure were 70.3 ± 26.3 and 15.0 ± 7.7 ng/mL in the IQOS and cigarette groups, respectively. Average nicotine levels immediately after exposure in the cigarette group was similar to the levels in humans after smoking one cigarette (~ 10 – 50 ng/mL),^{39, 40} confirming that the exposure conditions were relevant to real-world smoking. In the serum samples taken 20 min after the exposure, mean nicotine levels were 39.7 ± 18.9 and 5.6 ± 2.5 ng/mL in IQOS and cigarette groups. Serum cotinine levels were 4.6 ± 1.9 and 6.5 ± 2.8 ng/mL in IQOS-exposed group immediately after exposure and 20 min later. In the cigarette-exposed group, cotinine was undetectable after exposure and 0.8 ± 1.4 ng/mL after 20 min.

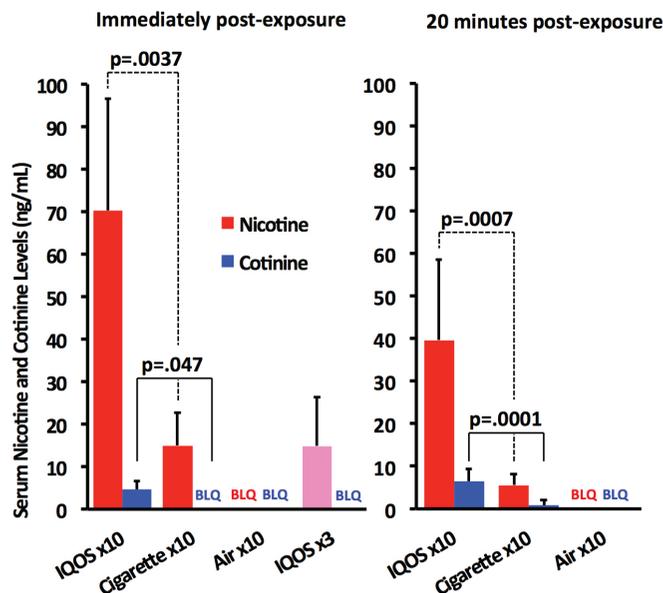


Figure 4 Serum nicotine and cotinine levels immediately and 20 min postexposure. Samples were taken after 10 cycles of 5 s exposure +25 s break. P values are derived from two-tailed Student's t-tests. IQOS x10, 10 IQOS exposure cycles; cigarette x10, 10 cigarette exposure cycles; air x10, 10 air exposure cycles; IQOS x3, three IQOS exposure cycles; BLQ, below level of quantification.

Serum nicotine and cotinine levels were significantly higher in the IQOS-exposed group compared with the cigarette-exposed group at all times. Nicotine and cotinine were not detected in the air groups.

Comparable FMD impairment from lower level IQOS exposure

Because the nicotine levels in IQOS group were substantially higher than that in the cigarette group, impairment of FMD in the IQOS group could potentially be attributed to excessive nicotine exposure. Therefore, we titrated the IQOS exposure timing down to conditions that led to serum nicotine comparable with the cigarette group (three 5+25 s cycles rather than 10 cycles led to 14.8 ± 11.6 ng/mL serum nicotine initially). Average FMD in a group of rats exposed to three cycles of IQOS aerosol decreased significantly from 11.0 ± 4.2 to 4.5 ± 1.5 ($p=0.0019$). A group of four air-exposed rats that was included for blinding purposes showed no significant change in FMD (figure 5).

Higher nicotine in Marlboro Red smoke than IQOS aerosol

To determine if the higher serum nicotine levels resulting from IQOS exposure than smoke exposure reflected higher nicotine concentrations in IQOS aerosol, we measured nicotine in both kinds of emissions, using both Marlboro Red cigarettes and 1R6F research cigarettes for comparison. Total nicotine levels in smoke from the Marlboro cigarettes were significantly higher than that in IQOS aerosol (1.07 ± 0.05 vs 0.67 ± 0.02 , $p=0.0006$). Nicotine levels in the 1R6F smoke were similar to IQOS aerosol levels (table 1).

Nicotine in the IQOS aerosol gas phase was below the detection limits. Analysis of HeatSticks before and after use also revealed that the nicotine in the aerosol is mainly in the particle phase.

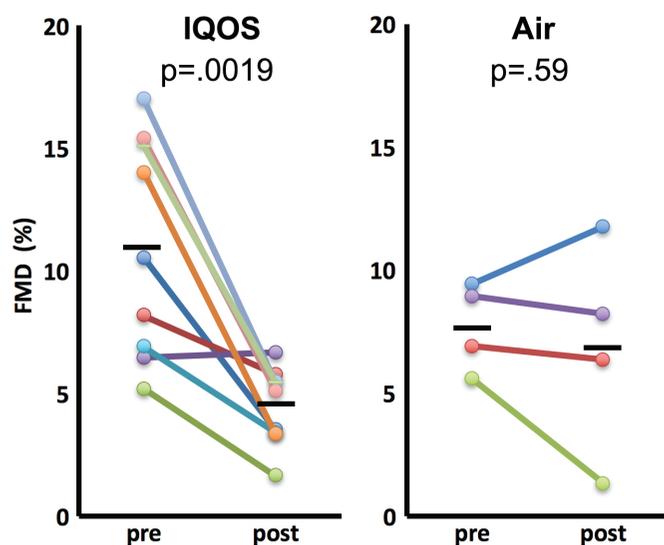


Figure 5 Reduced IQOS exposure to match nicotine absorption level of the cigarette group still impairs FMD to a comparable extent. Coloured lines denote individual rats pre-exposure and postexposure; bars denote group means; p values are derived from paired two-tailed t-tests. Exposure conditions were three cycles of 5 s exposure +25 s break. FMD, flow-mediated dilation.

DISCUSSION

Historically, the tobacco industry has made a major effort to introduce their so-called heat-not-burn tobacco products to consumers as reduced-risk products. Unlike earlier generation products such as R.J. Reynolds' Premier (1988), Eclipse (1996, 2003) and Revo (2015), and Philip Morris' Accord (1998) and Heatbar (2006), IQOS has been successfully marketed in at least 30 countries.^{1 41 42} Although IQOS is currently not available in the USA, industry analysts are making optimistic predictions regarding successful future US marketing of IQOS.^{41 43} Our aim was to study the vascular effects of exposure to IQOS aerosol before this product achieves more widespread use. To our knowledge, this is the first study of the effects of IQOS aerosol on vascular endothelial function in a physiological model.

PMI strongly implies in publications^{21 23 44} and in their MRTD applications⁴⁵ that IQOS causes less endothelial dysfunction than conventional cigarettes. Their conclusions were based only on cultured cell behaviour²¹ and circulating sICAM-1 protein²³ that indirectly reflect processes relevant to vascular function, but do not directly assess endothelial function physiologically.

Table 1 Nicotine concentration in IQOS aerosol, cigarette mainstream smoke and IQOS tobacco

Material	Total nicotine (mg) Mean±SD
IQOS aerosol (n=3)	
Particle phase	0.67±0.02*
Gas phase	BLQ
Marlboro Red MS (n=3)	
Particle phase	1.07±0.05*
1R6F MS (n=3)	
Particle phase	0.65±0.04
Used IQOS HeatStick (residual; n=3)	3.16±0.67
Unused IQOS HeatStick (n=4)	3.92±0.11

*P=0.0006 between starred values.

BLQ, below level of quantification; MS, mainstream smoke.

PMI's physiological cardiovascular studies were limited to the demonstration that long-term IQOS aerosol exposure led to less aortic plaque than cigarette smoke in transgenic mice predisposed to atherosclerosis.⁴⁴ In contrast, our direct evaluation of IQOS aerosol's acute effects showed that brief exposures to IQOS aerosol from a single HeatStick caused rapid impairment of vascular endothelial function in rats comparable with that caused by cigarette smoke. We assessed endothelial function with FMD, a validated measure of cardiovascular health effects²⁴⁻²⁷ that has been used by numerous groups to evaluate cardiovascular effects of smoke exposure in humans and animals.^{28-31 34-36} Therefore, our approach provides a robust readout of potential adverse effects of IQOS aerosol on endothelial function, and indicates that IQOS use is likely to have rapid adverse vascular effects comparable with those from cigarette smoking.

We chose to use a nose cone smoke/aerosol delivery system, rather than a whole-body exposure system, to prevent exposure via the ocular and oral routes and also to prevent subsequent oral exposure from licking fur and paws. Establishment of an exact relationship between our rat exposure conditions and human exposure is limited by differences in route of administration (rats are obligate nose breathers with complex nasal topography⁴⁶ while humans inhale cigarette smoke orally), differences between human intentional aerosol inhalation volume and anaesthetised rat tidal (inhalation) volumes,^{47 48} and differences in airway clearance rates.⁴⁹ Sophisticated models have been developed to convert inhalation dosimetry between rats and humans,⁴⁹ but smoke does not present a straightforward situation due to the combination of gas and highly heterogeneous particles that behave differently in such models. Therefore, to assess whether our exposure conditions were relevant to real-world smoking, we measured serum nicotine levels and confirmed that nicotine in the rats that were exposed to cigarette smoke for ten 5+25 s cycles were similar to the levels found in humans immediately after smoking one cigarette, validating our exposure model for cigarettes.

However, the serum nicotine level in the IQOS-exposed group under identical conditions was more than four times higher than in the cigarette group. This was surprising; our results revealed that the nicotine content in the IQOS aerosol in our generation system was much lower than that in the Marlboro mainstream smoke (table 1). Moreover, nicotine content in the filler and aerosol is reported in the literature to be roughly comparable for HeatSticks and cigarettes.^{50 51} The underlying reason for this remains unclear and deserves further investigation. One potential explanation for this difference could be particle size difference which determines to what extent the particles reach the respiratory zone. Nonetheless, reducing the number of IQOS exposure cycles from 10 to 3, to result in comparable serum nicotine concentrations to the cigarette group still led to impairment of FMD. Of note, the extents of FMD impairment in the three IQOS and cigarette groups were quite similar, indicating an extremely rapid saturation of the response to mainstream levels of smoke and IQOS aerosol.

A limitation of this study is that all functional measurements were obtained in anaesthetised rats which was necessary for the FMD procedure to be carried out. However, as in our previous reports using ketamine/xylazine,³⁴⁻³⁶ as well as our prior study unrelated to smoke in which isoflurane was used,⁵² negative control groups showed no significant alteration of FMD from preintervention to postintervention, and the relative responses of experimental and control groups have been consistent and reproducible. Moreover, prospective human exposure

experiments have shown similar impairment of FMD by smoke inhalation in conscious individuals.^{30,31,53}

Regarding potential variability between experiments, we used a manual syringe-pump-driven system to generate smoke and IQOS aerosol for our initial experiment, and a commercially available automatic vaping system for our subsequent experiments. The manual system was modelled after the automatic system; that is, the relevant volumes and aerosol paths were the same in all experiments. The volume of air drawn through the cigarettes and HeatSticks, and the time over which the syringe pump plunger was moved, were the same in all experiments, although slightly more accurate with the automatic system. Similarly, due to broken heating blades as described in the Materials and methods section, we used IQOS holders from three different countries over the course of the project. The characteristics of these electronic devices are presumably highly controlled and would not be expected to vary greatly by country. We did not perform comparative analyses of aerosols generated from the three devices. When it was necessary to switch from a broken device to a new one, rats in both experimental and control groups were exposed to aerosol from the new device.

We conclude that mainstream IQOS aerosol from a single HeatStick can rapidly and substantially impair endothelial function in rats comparably to smoke from a cigarette. While these findings do not prove that inhalation of IQOS aerosol causes endothelial dysfunction in humans, the results underscore that integrative physiological assays of function can reveal adverse health effects not noted in PMI's biomarker and cell culture studies,² and suggest that at least some of the adverse health effects of cigarettes may not be avoided by using IQOS.

What this paper adds

- ▶ IQOS is a new heated tobacco product from Philip Morris International that has been marketed in 30 countries and has been portrayed to consumers and regulatory agencies as modified-risk tobacco product.
- ▶ Brief exposures to IQOS aerosol cause endothelial dysfunction, a well-established physiological measure of cardiovascular risk that is also caused by exposure to cigarette smoke, to the same extent as cigarette smoke in rats.
- ▶ Acute exposure to IQOS aerosol impairs flow-mediated dilation in rats.
- ▶ Use of IQOS does not necessarily avoid the adverse cardiovascular effects of cigarette smoking.

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Contributors PN, JL, CMH, SI and RD performed experiments and collected/analysed data. PN, CMH, PJ and MLS designed experiments, PN and MLS conceived of the project and wrote the paper.

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Assessment of industry data on pulmonary and immunosuppressive effects of IQOS

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ABSTRACT

Introduction Heated tobacco products are being touted as novel reduced-harm tobacco products by tobacco companies. In the USA, Philip Morris International submitted a modified risk tobacco product (MRTP) application to the US Food and Drug Administration in 2016 in which it purports that its heated tobacco product, I-Quit-Ordinary-Smoking (IQOS), is associated with reduced harm compared with conventional cigarettes.

Methods We reviewed Philip Morris International's MRTP application to assess the pulmonary and immune toxicities associated with IQOS use in both animal and human studies.

Results Among rats exposed to IQOS, there was evidence of pulmonary inflammation and immunomodulation. In human users, there was no evidence of improvement in pulmonary inflammation or pulmonary function in cigarette smokers who were switched to IQOS.

Conclusion IQOS is associated with significant pulmonary and immunomodulatory toxicities with no detectable differences between conventional cigarette smokers and those who were switched to IQOS in Philip Morris International's studies. Philip Morris International also failed to consider how dual use and secondhand aerosol exposure may further impact, and likely increase, the harms associated with these products.

lower temperatures and the subsequent lack of combustion generated by these products, tobacco companies have argued that these products are healthier than conventional cigarettes and represent a harm reduction tool that could aid conventional cigarette smokers. However, to date, there has been little data that support HTPs as less harmful compared with conventional cigarettes.

On 5 December 2016, Philip Morris International (PMI) submitted an application to the US Food and Drug Administration (FDA) to market its HTP, I-Quit-Ordinary-Smoking (IQOS), as a 'modified risk tobacco product' (MRTP) in the USA. Section 911 of the Family Smoking Prevention and Tobacco Control Act requires the FDA to enforce rigorous standards that tobacco companies must meet before marketing a product as an MRTP. Section 911(g) mandates that the FDA may issue an MRTP order only if the applicant has demonstrated by substantial and objective scientific evidence that its product, as it is actually used by consumers, will '(A) significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and (B) benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products'. These standards place the burden on the applicant to demonstrate that their product results in decreased harm, rather than merely equivalence. Such standards may often require a variety of studies, including invasive and/or longitudinal testing, in both animal and human models to provide evidence of reduced harm. This paper uses information and data from the publicly available PMI MRTP application to compare IQOS and conventional cigarettes in animal and human studies of pulmonary health and evaluate PMI's claim of harm reduction related to pulmonary health.

METHODS

In order to conduct this study, we searched PMI's publicly available MRTP application for data relevant to the pulmonary and immune toxicity of IQOS. In addition, when identified, publicly available raw data were downloaded from the FDA MRTP application to conduct independent statistical analyses.

Preclinical studies

Our analysis of PMI's preclinical studies focuses on data presented by Wong and colleagues,¹¹ which was published in Regulatory Toxicology and Pharmacology in 2016, and included in Module 7.2: Preclinical Studies of PMI's MRTP application. In order to compare the effects of IQOS emissions to

INTRODUCTION

Conventional cigarettes have long been known to have numerous pulmonary toxicities. Cigarettes generate inflammation in the lung; over time, chronic inflammation contributes directly to the development of significant respiratory diseases including chronic obstructive pulmonary disease (COPD) and lung cancer.¹⁻³ In addition, cigarette smoke directly impacts immunity in the lung⁴ and smoking is associated with an increased risk of respiratory infection,⁵⁻⁷ a leading cause of mortality worldwide.^{8,9} Driven by decades of data indicating the harms of cigarettes, public health campaigns have decreased the prevalence of cigarette smoking worldwide.¹⁰

In the setting of public awareness of the dangers of cigarettes and declining cigarette smoking in many parts of the world, tobacco companies have repeatedly attempted to develop 'safer cigarettes', including 'low-tar' cigarettes, electronic cigarettes and heated tobacco products (HTPs). HTPs heat tobacco to temperatures (~600°F) below the temperatures observed in conventional cigarettes (>900°F) to avoid combustion and produce a nicotine aerosol that is inhaled by the user. Given these

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conventional cigarette smoke, PMI conducted a 90-day inhalation study in 10-week-old male and female Sprague-Dawley rats. Outcomes included markers of inflammation, histopathology, transcriptomics and standard toxicological endpoints, with comparisons of sham-exposed rats and rats exposed to the aerosol of IQOS and 3R4F research cigarettes. The IQOS product tested in these studies was the Tobacco Heated Systems (THS) V.2.2 tobacco stick which uses the FR1 tobacco blend. Rats were nose-exposed in flow-pass inhalation chambers for 6 hours per day to aerosols that were diluted with filtered air to obtain targeted nicotine concentrations ranging from 15 to 50 µg per litre aerosol. Unless otherwise stated, we focused on the highest level of aerosol nicotine for each product. Toxicants were measured at the breathing zone of the rats in the inhalation chambers and reported in ppm (carbon monoxide) or µg/litre (acetaldehyde, acrolein, formaldehyde).

Human studies

Our analyses of human clinical studies are based on the data presented in PMI's MRTP application's Executive Summary, Module 6: Summaries of all research findings, and Module 7.3.1: Scientific Studies and analyses (Studies in Adult Human Studies: Clinical Studies). The human data within these sections draw from two primary studies: ZRHR-REXA-07-JP, performed in Japan and ZRHM-REXA-08-US, performed in the USA. Briefly, both studies enrolled otherwise healthy adults who smoked at least 10 conventional cigarettes per day for the prior 3 years and randomised them into one of three groups: (1) those who smoked menthol conventional cigarettes, (2) those who quit completely and (3) those who switched to IQOS with menthol heatsticks. Participants were initially followed in confinement for 5 days of usage and then in the ambulatory setting for a total of 90 days. The goal of the 90-day ambulatory study period was to examine changes in biomarkers of exposure and clinical harm related to IQOS in near-real-world conditions. During the ambulatory study period, participants were discouraged from dual use. All participants kept a usage diary that documented their tobacco product usage. At the day 90-study visit, several clinical risk points were assessed including plasma white blood cell count (WBC), C reactive protein (CRP) and pulmonary function testing (PFT). Clinical risk endpoints were then compared between participants who continued smoking conventional cigarettes and those that were switched to HTPs.

Statistical analyses

PMI's main analyses included analysis of variance testing with baseline value, product exposure, sex and baseline cigarette consumption as fixed effect factors. We conducted independent analysis of publicly available raw data from PMI's MRTP application. We used Student's *t* test, analysis of variance testing and Pearson's χ^2 test to compare normally distributed variables. Non-normally distributed variables were compared using the Mann-Whitney Wilcoxon U-test or Kruskal-Wallis test. A *p* value ≤ 0.05 was considered statistically significant. Statistical analyses were performed with STATA V.15.0 (StataCorp).

RESULTS

Preclinical studies

A comparison of the toxicant profiles of IQOS, 3R4F cigarettes and sham exposure conditions revealed that, while containing generally lower toxicant levels than 3R4F smoke, IQOS emissions contain significant levels of volatile organic compounds, including known toxicants such as acrolein, acetaldehyde and

Table 1 Summary of preclinical pulmonary findings for I-Quit-Ordinary-Smoking (IQOS) compared with sham and 3R4F research cigarette groups

Parameter	Sham (n=10)	IQOS (n=8-10)	3R4F (n=9)
Lung weight (normalised to body weight)	35.8 (1.4)	40.3 (1.0)*	50.6 (1.4)*†
BAL cell count# ($\times 10^5$ /lung)	22.9 (3.4)	42.5 (7.1)*	116.4 (13.4)*†
BAL inflammatory markers MIP-1 β , MCP-3, MPO, PAI-1		†*	††*
Respiratory epithelial hyperplasia and metaplasia		†*	††*

Unless otherwise specified, results signify those from male rats at the highest nicotine exposure levels for each group.

*Significantly increased compared with sham.

†Significantly increased compared with IQOS.

#Female rats at targeted nicotine 23 µg/L.

BAL, bronchoalveolar lavage; MCP, monocyte chemoattractant protein; MIP, macrophage inflammatory protein; MPO, myeloperoxidase; PAI, plasminogen activator inhibitor.

formaldehyde. IQOS-exposed rats had impaired weight gain during the 90-day exposure compared with sham, but greater weight gain compared with animals exposed to 3R4F smoke. Similarly, IQOS-exposed rats had a trend towards increased numbers of inflammatory cells in bronchoalveolar lavage (BAL), but significantly less BAL cellularity than 3R4F-exposed rats (table 1). Respiratory histopathology demonstrated that IQOS caused significant epithelial hyperplasia and metaplasia compared with sham, though to a lesser extent than was observed following 3R4F exposure. Taken together, these data suggest that IQOS induces a significant inflammatory injury, but less severe than that observed with intense cigarette smoke exposure.

PMI's data indicate that IQOS exposure may be associated with substantial immunomodulatory effects (table 2). Animals exposed to IQOS developed systemic neutrophilia that trended nearly 75% higher than that observed in rats exposed to 3R4F smoke. Notably, blood neutrophil counts in female rats remained elevated compared with both sham and 3R4F exposed animals following a 6-week recovery period. Furthermore, IQOS-exposed animals had higher levels of thymic atrophy (by gross organ weight and histology) than both sham and 3R4F-exposed groups. Although functional immunological assays were not reported, thymic atrophy has previously been associated with decreases in host memory T cell populations¹² and reductions in the speed and sensitivity of host immune function.¹³

Table 2 Summary of preclinical systemic immune effects of I-Quit-Ordinary-Smoking (IQOS) compared with sham and 3R4F research cigarettes

Parameter	Sham (n=8-10)	IQOS (n=7-9)	3R4F (n=9-10)
Blood neutrophil count (10^9 /L)	1.3 (0.3)	4.8 (2.1)*	2.7 (0.4)*
Thymus weight	4.0 (0.4)	2.6 (0.6)*	2.5 (0.3)*
Histological thymic atrophy score	0.1 (0.1)	1.8 (0.4)*	1.1 (0.4)*

Unless otherwise specified, results signify those from male rats at the highest nicotine exposure levels for each group.

*Significantly different compared with sham; statistical comparisons between IQOS and 3R4F were not reported for blood neutrophil count or thymic atrophy score.

Table 3 Participant demographics and baseline data for Japan-based (ZRHR-REXA-07-JP) and US-based (ZRHM-REXA-08-US) studies

Japan-based study ZRHR-REXA-07-JP				
Measurement	Conventional cigarettes (n=41)	Abstinence (n=37)	IQOS (n=70)	P values
Age	38±11	38±10	38±11	0.99
Male (%)	24 (59%)	22 (59%)	39 (56%)	0.92
Smoking history				
10–19 cig/day	23 (56%)	20 (54%)	36 (51%)	0.92
>19 cig/day	18 (44%)	17 (46%)	34 (49%)	
FEV1 (% predicted)	94±9	93±10	94±8	0.69
FEV1/FVC	0.81±0.05	0.81±0.06	0.82±0.07	0.73
WBC (GI/L)	5.8±1.4	6.4±1.9	5.9±1.2	0.12
CRP (mg/L)	0.1 (0.1–0.26)	0.1 (0.1–0.45)	0.1 (0.1–0.45)	0.81
US-based study ZRHM-REXA-08-US				
Measurement	Conventional cigarettes (n=32)	Smoking abstinence (n=9)	IQOS (n=47)	P values
Age (years)	34±10	41±11	37±13	0.27
Male	20 (63%)	7 (78%)	28 (60%)	0.59
Smoking history				
10–19 cig/day	19 (59%)	6 (67%)	21 (45%)	0.29
>19 cig/day	13 (41%)	3 (33%)	26 (55%)	
FEV1 (% predicted)	97±14	96±11	93±13	0.46
FEV1/FVC	0.79±0.07	0.78±0.04	0.80±0.05	0.74
WBC (GI/L)	8.3±1.8	6.9±2.2	8.3±1.7	0.08
CRP (mg/L)	0.1 (0.1–0.2)	0.1 (0.03–0.2)	0.1 (0.1–0.3)	0.11

IQOS, I-Quit-Ordinary-Smoking; CRP, C reactive protein; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; WBC, white blood cell count.

Human studies

Japan-based study

The Japan-based study randomised 231 participants between two study sites. However, only one of these sites collected participant data at 90 days. After limiting the sample to participants who had samples drawn at 90 days (n=160), and excluding those who were lost to follow-up (n=12), 148 participants remained. At the day 0 baseline visit, we found no difference in age or sex between groups (table 3). We did not detect a difference between groups in baseline pulmonary function, CRP or WBC, although there was a trend towards increased levels of WBC in the smoking abstinence group.

At the 90-day study visit, PMI reported decreased plasma WBC in IQOS users compared with conventional cigarette smokers (6.14 GI/L vs 5.57 GI/L, difference: -0.57 GI/L, 95% CI: -1.04 to -0.10). Given that WBC had also been measured at the day 0 baseline visit, we compared the change in WBC from baseline to 90 days between groups, rather than only comparing the level at 90 days. We found that compared with cigarette smokers, participants using IQOS had a decrease in plasma WBC (difference: -0.63 GI/L, 95% CI: -1.1 to -0.2, p=0.006). There was no significant difference in the change in WBC between the IQOS and smoking abstinence group. PMI did not detect a difference in CRP levels at 90 days between cigarette smokers and IQOS users (95% CI for difference between groups: -40.75 to 37.77). In our analyses, we did not detect a significant difference in the change in CRP from baseline to 90 days between IQOS users (median:

Table 4 Difference (95% CI) in 90-day pulmonary function testing between I-Quit-Ordinary-Smoking users and conventional cigarette smokers as presented by Philip Morris International

Clinical endpoint	US-based study ZRHM-REXA-08-US* (n=77)	Japan-based study ZRHR-REXA-07-JP† (n=111)
FEV1 (% predicted)	0.53 (-2.09 to 3.00)	1.91 (-0.14 to 3.97)
FEV1/FVC	0.00 (-0.02 to 0.02)	N/A
MEF 25–75 (L/s)	-0.67 (-6.33 to 4.99)	N/A
DLCO (mL/min/mm Hg)	0.31 (-1.09 to 1.72)	N/A
KCO (mmol/min/kPa/L)	0.05 (-0.02 to 0.12)	N/A
TLC (L)	0.09 (-0.25 to 0.43)	N/A
FRV (L)	-0.09 (-0.31 to 0.13)	N/A
IC (L)	0.21 (-0.08 to 0.51)	N/A
VC (L)	0.10 (0.00 to 0.21)	N/A

*Without bronchodilator.

†With bronchodilator.

DLCO, diffusion capacity of lung for carbon monoxide; IC, inspiratory capacity; FEV1, forced expiratory volume in 1 s; FRV, functional residual volume; FVC, forced vital capacity; KCO, rate constant of carbon monoxide; MEF, mid expiratory flow; N/A, not conducted or reported by PMI; TLC, total lung capacity; VC, vital capacity.

0 mg/L) and either cigarette smokers (median: 0 mg/L, p=1.0) or the smoking abstinence group (median: 0 mg/L, p=0.74).

PMI also reported on forced expiratory volume in 1 s (FEV1) without bronchodilator administration and found no difference in FEV1 at 90 days between cigarette smokers and IQOS users (table 4). We independently studied the change in FEV1 from day 0 baseline to 90 days. We found no difference between the three groups in the change in FEV1 (cigarette smoking group: -0.3 % predicted, 95% CI: -2.3 to -1.7; smoking abstinence group: 1.5 % predicted, 95% CI: -0.3 to 3.3; IQOS group: 1.5 % predicted, 95% CI: 0.3 to 2.6, p=0.2).

US-based study

In the US-based study, 88 participants underwent testing at 90 days. At the day 0 baseline visit, we did not detect a difference between the three arms in age, sex, pulmonary function, WBC or CRP, although there was a trend towards increased CRP in the IQOS group and decreased WBC in the smoking abstinence group (table 3).

In the US-based study, PMI reported no difference in plasma WBC at 90 days between participants who continued to smoke conventional cigarettes and those who were randomised to IQOS (7.09 GI/L vs 7.26 GI/L, difference: 0.17 GI/L, 95% CI: -0.47 to 0.81). Similarly, PMI reported no difference in CRP levels between conventional cigarette smokers and IQOS users (95% CI for difference between groups: -21.69 to 42.33). In our independent analyses, we did not detect a difference in the change in WBC from baseline to 90-day visit between the IQOS arm and either the conventional cigarette arm (difference: -0.06 mg/L, 95% CI: -0.8 to 0.7, p=0.87) or the smoking abstinence arm (difference: -0.5 mg/L, 95% CI: -1.6 to 0.7, p=0.43). Similarly, we did not detect a difference in change in CRP from baseline to day 90 visit between the IQOS group and either the conventional cigarette group (p=0.30) or the smoking abstinence group (p=0.50).

The US-based study conducted more extensive PFTs than the Japan-based study and notably these tests were performed following bronchodilator administration, which differed from the Japan-based study. At 90 days, PMI did not report a significant difference between the IQOS and conventional cigarette

Table 5 Changes in pulmonary function testing from day 0 to day 90 in the US-based study (ZRHM-REXA-08-US)

Clinical endpoint	Conventional cigarettes (n=30)	IQOS (n=47)	Smoking abstinence (n=9)	P values
FEV1 (% predicted)	-3.1 (-5.6 to -1.7)	-2.3 (-4.6 to -0.04)	-2.9 (-11.3 to 5.6)	0.72
FVC (% predicted)	-2.6 (-4.4 to 0.9)	-1.8 (-3.4 to -0.05)	-0.6 (-4.5 to 3.4)	0.57
FEV1/FVC	0.01 (-0.004 to 0.02)	-0.004 (-0.02 to 0.01)	0.04 (0.002 to 0.08)	0.01
MEF 25-75 (L/s)	-0.1 (-0.3 to 0.2)	-0.1 (-0.3 to 0.05)	0.2 (-0.8 to 1.1)	0.57
DLCO (mL/min/mm Hg)	0.2 (-1.0 to 1.3)	0.2 (-0.8 to 1.2)	-1.5 (-5.1 to 2.2)	0.40
TLC (L)	-0.3 (-0.6 to 0.1)	-0.02 (-0.3 to 0.2)	-0.6 (2.0 to 0.7)	0.15

DLCO, diffusion capacity of lung for carbon monoxide; FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; MEF, mid expiratory flow; TLC, total lung capacity.

group for any of the pulmonary function tests that were assessed. We conducted independent analyses of the change in pulmonary function from baseline day 0 to 90-day visits between groups. We did not detect a difference in changes in pulmonary function over time between the three groups except for FEV1/FVC, which increased slightly in the smoking abstinence group relative to both the conventional cigarette group and the IQOS group (table 5). There were no other differences detected between the IQOS group and either the conventional cigarette or smoking abstinence groups.

DISCUSSION

The FDA requires that MRTP applicants demonstrate that their products, as actually used by consumers, will reduce harm in individuals and benefit the health of the public overall. PMI's data are incomplete as they lack adequate endpoints to specifically assess subclinical pulmonary toxicity in humans and do not incorporate enough longitudinal measures for the tests they do include. Additionally, PMI fails to account for real-world usage patterns and secondhand aerosol exposures that may negatively impact both individual and public health. However, even the data that are presented by PMI suggest that IQOS has significant potential to induce adverse pulmonary health effects in humans.

Data from PMI's MRTP application indicate that compared with conventional cigarettes, emissions from IQOS have lower levels of volatile organic compounds and are associated with decreased levels of pulmonary inflammation in rats after 90 days of exposure. However, compared with sham controls, IQOS induces significant changes in the respiratory epithelium and airspaces that are consistent with inflammatory injury. Furthermore, the two clinical studies of real-world usage cited by PMI do not definitively show evidence of reduced inflammation in IQOS users compared with conventional cigarette smokers. Although a very small reduction in plasma WBC was observed in IQOS users in the Japan-based study, there was no difference in plasma WBC in the US-based study. In addition, there was no difference in CRP levels between conventional smokers and IQOS users in either study.

While inflammation is an important toxic mediator in a number of respiratory diseases that have been linked to cigarette smoking, plasma WBC and CRP are not direct measures of pulmonary inflammation but rather non-specific measures of systemic inflammation. There was no difference in levels of these biomarkers at 90 days between conventional cigarette smokers and those who quit smoking, suggesting that these are poorly sensitive markers, particularly when measured over such a short period of time. There are several more specific measures that can assess pulmonary inflammation in humans, including studies of inflammatory biomarkers in sputum, airway tissue or BAL fluid.^{14 15} Such tests directly sample lung tissue and thus more accurately reflect processes in the lung. However, despite presenting no human data directly from the lung, PMI concludes

that 'human clinical studies have confirmed that clinical markers of ... inflammation show positive changes, similar to those seen following smoking abstinence' (PMI MRTP Application, Section 2.7, Executive Summary, p. 106) and that these changes indicate that 'smokers who switch to [IQOS] would have a lower risk of COPD compared with continued smoking' (PMI MRTP Application, Section 2.7, Executive Summary, p. 107). Thus, PMI not only fails to accurately assess pulmonary inflammation in their human studies, but also misleadingly concludes that their IQOS product reduces inflammation and the risk of COPD in humans, a claim that is simply not supported by their data.

Neither PMI's Japanese nor American ambulatory human clinical study shows any statistically significant improvement in any measure of PFT. In fact, after 3 months of usage, smokers who have transitioned to IQOS use have the same pulmonary function as those who continued to smoke conventional cigarettes. Notably, PMI reports several cases of worsening pulmonary function in IQOS users in their adverse event reports (Appendix A6.1.5.4 in the PMI MRTP application). However, PMI concludes that 'in the Japanese study (ZRHM-REXA-07-JP), smokers who switched to THS had an increase of 1.91 percent of predicted value (%Pred) in their FEV1 as compared with smokers who continued to smoke cigarettes' (PMI MRTP Application, Section 2.7, Executive Summary, p. 92) and that 'in the US study (ZRHM-REXA-08-US), the difference in FEV1 values between smokers who switched to THS and those who continued to smoke was smaller in magnitude as compared with in the Japanese study. Nonetheless, the results were consistent and trended in the expected direction following smoking abstinence' (PMI MRTP Application, Section 2.7, Executive Summary, p. 93). These conclusions are simply not supported by PMI's own actual data, which shows no statistically significant difference in pulmonary function between IQOS users and conventional smokers. Furthermore, the relatively short period of follow-up fails to address longer term effects of IQOS on pulmonary function. While prior studies have shown that there are small improvements in pulmonary function in the first year of smoking cessation,¹⁶ a significant benefit arises from a slowing in the decline of lung function over many years.^{16 17} A 90-day study period is simply not long enough to detect any meaningful changes in lung function, as evidenced by the lack of difference detected in pulmonary function between the smoking abstinence group and the conventional cigarette or IQOS groups for almost all tests of pulmonary function measured. Thus, the short follow-up period in PMI's studies is unable to assess the important clinical question of the long-term effects on IQOS on pulmonary health compared with both conventional cigarettes and complete smoking cessation.

Conventional cigarettes are known to directly impact immunity and are associated with increased rates of respiratory infection.⁵⁻⁷ PMI's animal data suggest that IQOS may impact immunity, inducing thymic atrophy in exposed rats. Given that respiratory

infection represents a leading cause of morbidity and mortality worldwide,^{8,9} this finding raises alarm that IQOS could increase the risk of infection in users and indicates that further studies of the immunomodulatory effects of IQOS are needed, including animal models of respiratory infection. Notably, PMI reports several cases of infection associated with human IQOS use in their adverse data reports (Appendix A6.1.5.4), which adds to the concern that these products may adversely affect immunity and predispose users to developing infection. The omission of additional studies on the immune effects of IQOS from PMI's MRTP application is significant and further clouds the picture on the true health risks of IQOS.

PMI's analyses focus on studying the harms associated with exclusive IQOS use. However, there is significant data that dual or poly use, the use of two or more tobacco products, will be a significant usage pattern among IQOS users. In PMI's US-based study, nearly one in four participants was still using conventional cigarettes after being switched to IQOS. Internationally, per PMI's own reports, it is estimated that up to 30% of IQOS users also use an additional tobacco product, including conventional cigarettes.¹⁸ However, despite significant evidence of the potential for dual use among IQOS users,¹⁹ PMI has failed to simulate dual use in their animal studies. Furthermore, in their human studies, PMI strictly prevented dual use during confinement study periods and strongly discouraged, although somewhat unsuccessfully, dual use in the ambulatory setting, resulting in less validity to their claims that it mimicked a 'real world' setting. In addition, no analyses are performed on the effects of dual use that was known to occur. Given that dual use is likely to impact any potential for harm reduction for individual users, its omission from PMI's study design and analyses on harm reduction potential is a glaring one.

Finally, PMI studies fail to account for the pulmonary health effects of secondhand aerosol exposure. A prior study of HTPs found that they do generate sidestream aerosol, the primary component of secondhand smoke exposure,²⁰ which comprises a large number of volatile organic compounds, polycyclic aromatic hydrocarbons and ultrafine particles.^{21,22} Furthermore, a recent study found that people exposed to secondhand IQOS emissions experienced symptoms, including sore throat (20.6%), eye pain (22.3%) and feeling ill (25.1%).¹⁹ Given that a number of public health organisations, including WHO, have deemed that no level of sidestream exposure is safe or acceptable,²³ these findings are clearly concerning and merit further study, which PMI has either failed to conduct or present.

In conclusion, PMI's IQOS MRTP application raises significant concerns about the pulmonary safety of IQOS. PMI ignores the effect of dual use and secondhand aerosol exposure in both study design and analyses; furthermore, no measurements of inflammation specific to the lung were made in any of the human studies presented, and the duration of follow-up does not allow for any meaningful study of pulmonary function. Any future studies of these products must include measurements specific to the lung, such as in sputum or BAL fluid, as well as additional longitudinal follow-up to more accurately assess the acute and chronic toxicities of these products. In addition, given that dual use is expected to be the predominant usage pattern, it is critical that future studies take into account dual use when assessing the public health impact of these products. However, even if these significant gaps were ignored, PMI's own data show that IQOS is associated with significant pulmonary and immune toxicity that does not appear to be significantly different from cigarette smoking in real-world human users.

What this paper adds

- ▶ Heated tobacco products are being touted as reduced harm tobacco products by tobacco companies across the world despite limited scientific evidence supporting this claim.
- ▶ Philip Morris's modified risk tobacco product (MRTP) application for I-Quit-Ordinary-Smoking (IQOS) shows that IQOS generates significant pulmonary and immunomodulatory harm, most notably in human studies.
- ▶ With regards to pulmonary and immunomodulatory harm, based on the limited available data to date, IQOS use does not appear to significantly differ from conventional cigarettes.

Contributors All authors contributed to the study design/concept, interpretation of the data and drafting/revisions of the manuscript. All authors give final approval and agree to be accountable for all aspects of the work.

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Cytotoxic effects of heated tobacco products (HTP) on human bronchial epithelial cells

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ABSTRACT

Background Heated tobacco product(s) (HTP), also called heat-not-burn products, are a re-emerging class of tobacco products that purport to reduce health risk compared with smoking combustible tobacco products. This study examined the potential toxic effects of inhaling emissions from an HTP in comparison with electronic and combustible tobacco cigarettes.

Methods Inhalation toxicity of HTP (IQOS; tobacco flavour), e-cigarette (MarkTen; tobacco flavour) and tobacco cigarette (Marlboro Red) was examined in vitro using an air-liquid interface with human bronchial epithelial cells (H292). Cells were exposed directly to 55 puffs from the e-cigarette, 12 puffs from the HTP and 8 puffs from the tobacco cigarette to equilibrate nicotine delivery to the cells across products. Cytotoxicity was measured using neutral red uptake and trypan blue assays. Cytotoxic effects of each tested product (HTP, e-cigarette and tobacco cigarette) were compared with an air control. Release of inflammatory markers (cytokines) was measured using ELISA.

Results The HTP showed higher cytotoxicity compared with the air controls using the neutral red assay. The HTP also showed higher cytotoxicity than the e-cigarette, but lower cytotoxicity than the combustible cigarettes using the same assay. A significant increase in cytokines levels, compared with air controls, was observed postexposure to tobacco smoke but not to emissions from HTP or e-cigarette aerosol.

Discussion Using limited cytotoxic measures, the HTP showed reduced cytotoxicity relative to a combustible cigarette but higher toxicity than an e-cigarette. More comprehensive testing is needed to determine long-term effects of inhaling emissions from HTP.

BACKGROUND

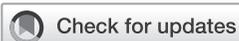
In conventional cigarettes, once tobacco is heated above 600°C, combustion occurs, and smoke containing harmful chemicals is released.¹ Heated tobacco product(s) (HTP) release nicotine-containing emissions without burning tobacco. These products heat rather than burn tobacco, using an electronically controlled heating element. Hypothetically, by reducing the formation temperature, HTP products may emit lower levels of tobacco combustion byproducts and show reduced toxicity compared with combustible tobacco cigarettes. Some early models of HTP products were developed in the late 1980s; however, they did not reach a significant number of consumers and were withdrawn from the market.¹ The HTP IQOS device was developed by Philip Morris International (PMI) and launched in international markets in mid-2014. According to manufacturer data, IQOS devices heat

tobacco to temperatures up to 350°C, avoiding combustion.²

In December 2016, PMI submitted an application to the US Food and Drug Administration for their HTP IQOS to be authorised as a modified risk tobacco product. Claims of lowered risk of IQOS (non-combustible tobacco product) compared with conventional cigarettes (combustible cigarettes) are based almost exclusively on industry-funded research, and reliable independent research is not available to support these claims as of early 2018. A PMI-funded study reported a 90% reduction in cytotoxicity, determined by the neutral red uptake assay and the mutagenic potency in the mouse lymphoma assay, between HTP versus combustible tobacco cigarettes.³ Results showed only minor histopathological alterations and minimal cytotoxicity on HTP emission exposure compared with combustible cigarette smoke (1% for HTP vs 30% for tobacco cigarette). Among the 14 proinflammatory mediators analysed, only five exhibited significant shifts with HTP exposure compared with 11 on combustible cigarette smoke exposure.⁴ Transcriptomic and metabolomic analysis indicated a general reduction of the impact in HTP emission-exposed samples with respect to tobacco smoke-exposed controls (~79% lower biological impact compared with tobacco smoke).⁴ In the 90-day inhalation exposure study, PMI examined microRNA (miRNA) levels in the bronchoalveolar lavage fluid from lungs of Sprague Dawley rats exposed to HTP compared with tobacco smoke.⁵ Transcriptomic and metabolomics study performed on Sprague Dawley rats exposed to tobacco smoke or HTP emissions showed that only tobacco smoke caused global miRNA downregulation in nasal epithelium and lung parenchyma. Upregulation of specific miRNA species indicated that they were causal elements in the inflammatory response in tobacco smoke-exposed lungs, but they were reduced after HTP emission exposure.⁶

Although all of above-cited studies evaluated relative effects of IQOS to combustible cigarettes, none of the studies cited above compared toxicity of IQOS to e-cigarettes. Independent research is therefore urgently needed to provide a balanced view on absolute potential health impact of HTP and the relative effects compared with other potential reduced-risk products like e-cigarettes.

Since there is a critical knowledge gap in the potential impact of HTP emissions on respiratory health, this study examined the potential cytotoxic effects of inhaling emissions from an HTP in comparison with the electronic and combustible cigarettes using an in-vitro model.



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MATERIALS AND METHODS

Products

Three nicotine-containing products made by PMI were used in this study: (1) HTP (IQOS; with the PMI Amber HeatSticks (HEETS), (2) e-cigarettes (MarkTen brand; 3.5% nicotine, tobacco flavoured) and (3) tobacco cigarette (Marlboro Red 85 mm). The HTP was purchased in Florence, Italy, and the electronic and tobacco cigarettes were purchased in Buffalo, USA.

Generation of emissions from tested products

Emissions from tested products were generated using a Borgwaldt LX-1 (Richmond, Virginia, USA) single-port, piston-operated smoking machine. The Health Canada Intense puffing protocol was used with the following conditions: 2 s puff duration, every 30 s, with a 55 mL puff volume. The number of puffs varied, depending on the product tested, to represent one smoking session. This was accomplished by using one tobacco cigarette and one HTP HEETS, and then matching nicotine delivery from one HTP HEETS to an e-cigarette. In our previous smoking-machine study using the Health Canada Intense puffing protocol,⁷ we found that one tobacco cigarette delivered 2.1 mg/cigarette in 8 puffs, the HTP delivered 1.4 mg/HEETS in 12 puffs and the e-cigarette delivered a similar amount of nicotine as the HTP 1.3 mg/session with 55 puffs.⁷ Air exposures (control), 55 puffs over a total of 30 min, were run during each experiment.

Cell exposure conditions

Cells were acutely exposed, on three separate days, to emissions (both gas phase and particulates), aerosol or smoke from tobacco products using an air-liquid interface (ALI) interface. The NCI-H292 human bronchial epithelial cell line (ATCC) was plated on 0.4 μ m permeable supports (PS) 24 hours prior to experimentation under previously described conditions.⁸ Immediately prior to exposure, the media were removed from the apical side of the PS, and cell-containing inserts (n=3) were placed in the ALI chamber. While the apical side of the cells were directly exposed to either: (1) an air control, (2) emissions from HTP, (3) aerosol from e-cigarettes or (4) smoke from tobacco cigarettes, fresh media were cycled over the basal side of the PS at a flow rate of 5 mL/min. After exposure, the apical side was resubmerged with complete or neutral red media until assay measurements 2.5 hours later. The ALI chamber was cleaned with methanol and distilled water between each of the four exposure conditions. A detailed description of this exposure system can be found in our previous study⁸ and online supplementary materials.

Toxicity assays

After 2.5 hours, cytotoxicity of exposed H292 cells was measured using two assays: neutral red uptake and trypan blue assays. The neutral red uptake assay provides a quantitative estimation of the number of metabolically active cells attached to the PS, based on the ability of viable cells to incorporate and bind the supravital dye neutral red into lysosomes.⁹ The trypan blue assay, a cell viability assay, is based on the principle that live cells possess intact cell membranes that exclude certain dyes, such as trypan blue, whereas dead cells do not.¹⁰ This assay measured the number of live cells attached to the PS (removed by trypsin) and the number of dead cells in the fresh apical media. Cytokines released into the fresh apical media were measured as an indicator of cell inflammatory response. Six cytokines (interleukin (IL)-1 β , IL-6, IL-10, CXCL1, CXCL2 and CXCL10) were measured using commercially available ELISA kits (Abcam and

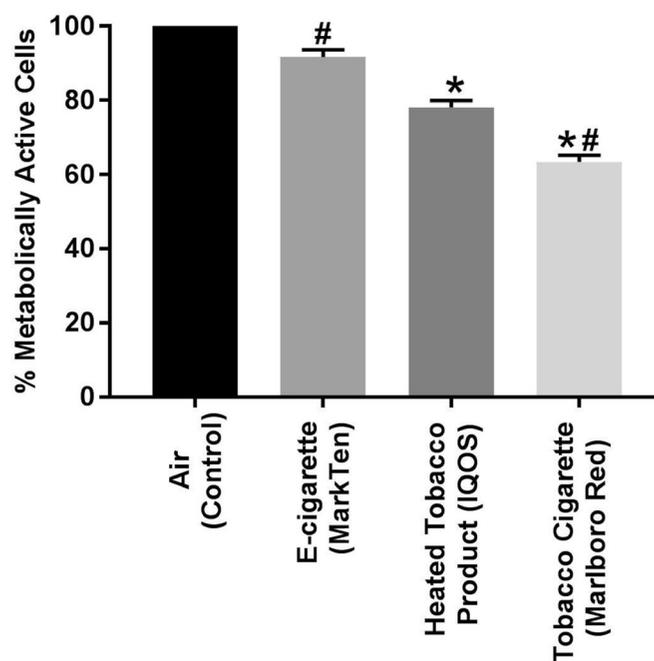


Figure 1 Metabolic activity (neutral red assay) from H292 bronchial epithelial cells directly exposed using an air-liquid interface to emissions from heated tobacco product (HTP), e-cigarette, combustible tobacco cigarette and air (controls). Emissions were generated from a MarkTen electronic cigarette (55 puffs), IQOS HTP (12 puffs/heatstick) and Marlboro Red combustible cigarette (eight puffs/cigarette). *Significant difference compared with the air control ($p < 0.05$). #Significant difference compared with IQOS product ($p < 0.05$).

R&D System) following the manufacturers' protocols. These cytokines were chosen as a panel of inflammatory markers commonly used in in-vitro, in-vivo and clinical human studies. Changes in those markers have been shown to correlate with several clinically relevant outcomes and diseases.¹¹⁻¹⁵ A detailed description of these assays can be found in our previous study⁸ and online supplementary materials.

Statistical analysis

Statistical analysis was performed using Prism V.6.07 (GraphPad). Kruskal-Wallis non-parametric tests and Dunn multiple comparison tests were performed for each study outcome to compare: (1) each product versus air controls, (2) combustible cigarettes versus HTP and (3) e-cigarettes versus HTP. All experiments were performed in triplicate, with each outcome measured three times per experiment (three wells per chamber).

RESULTS

Metabolic activity of H292 cells decreased significantly after exposure to HTP emissions compared with the air control ($p = 0.002$, figure 1). Exposure to combustible tobacco smoke but not to e-cigarette aerosols also resulted in decreased cell viability ($p < 0.001$, online supplementary figure 1) and metabolic activity ($p < 0.001$, figure 1), compared with the air controls. The neutral red assay, but not the trypan blue assay, revealed that IQOS emissions were significantly more toxic compared with e-cigarette aerosol ($p = 0.044$, figure 1 and online supplementary figure 1).

We were only able to detect IL-1 β and IL-6 released to media after exposure to all tested products; all other cytokine levels were below the limit of quantitation. There was no statistically significant differences between cytokines levels released

postexposure to HTP emissions compared with air controls (IL-1 β : 13.7 \pm 5.1 vs 13.5 \pm 6.4; IL-6: 6.9 \pm 2.1 vs 11.8 \pm 3.2 pg/10⁷ cells; mean \pm SD; all p >0.05, online supplementary figures 2 and 3). HTP showed reduced release of cytokines compared with combustible cigarettes (IL-1 β : 13.7 \pm 5.1 vs 133.6 \pm 41.9; IL-6: 6.9 \pm 2.1 vs 65.5 \pm 21.7 pg/10⁷ cells; all p <0.05, online supplementary figures 2 and 3). Levels of cytokines measured postexposure to HTP did not differ statistically from levels detected postexposure e-cigarettes (IL-1 β : 13.7 \pm 5.1 vs 12.9 \pm 4.7; IL-6: 6.9 \pm 2.1 vs 12.2 \pm 2.7 pg/10⁷ cells; all p <0.05, online supplementary figures 2 and 3). Smoke generated from tobacco cigarettes increased cytokine levels compared with air controls, as well as the two other products (p <0.05).

DISCUSSION

This pilot study used an established ALI system to examine the cytotoxic and inflammatory effects of an HTP. Our results show that emissions from HTP caused damage to human bronchial epithelial cells relative to air controls. At the same time, HTP emissions showed lower toxicity compared with combustible cigarettes but higher toxicity compared with e-cigarettes. Our data suggest that use of IQOS products may lead to increased risk of respiratory health impairment, and although this risk may be reduced compared with smoking tobacco cigarettes, it is likely to be higher than risk from vaping e-cigarettes.¹⁶ However, it is important to note that the data presented have shown the relative effects of acute exposure to three different tobacco products and that further research is needed to determine the long-term health effects of the HTP product use.

In addition to the cytotoxicity results, we measured two important markers of inflammatory response. Cytokine IL-1 β is involved in a variety of cellular activities, including cell proliferation, differentiation and apoptosis. Cytokine IL-6 is primarily produced at sites of acute and chronic inflammation and has been implicated in a wide variety of inflammation-associated disease states. In summary, we found that bronchial epithelial cells exposed to HTP emissions released less IL-1 β and IL-6 than cells exposed to cigarette smoke. Additionally, no differences in cytokine concentrations were found between the e-cigarette and the HTP. The rapid death of cells exposed to tobacco smoke may have resulted in low levels of cytokines measured in our study since the proinflammatory activity of dead cells decays over time, presumably as the active cell components are degraded. While it is possible that in some situations intracellular stores of proinflammatory cytokines might be released on cell disintegration and cause inflammation, most of these mediators have restricted expression in cells and therefore cannot account for how the cells induce inflammation on death.¹⁷

An important limitation of our study is that we have used a single type of immortalised cell line to examine cytotoxicity. Although the ALI exposure provides a novel and specific exposure approach for performing the biological study on health effects related to inhalation of emerging tobacco products, extrapolating data from in-vitro studies to human risks remains hypothetical.¹⁸ This model may not recapitulate how these products affect tissues and do not aim to estimate any harmful effects in IQOS users. Future in-vitro studies with organotypic models as well as in-vivo animal studies are needed to confirm our findings. When real-life data on IQOS users' behaviours and puffing topography are available, future studies should adopt an appropriate exposure protocol that reflects real-life product use conditions.¹⁹ Finally, since our study focused on the acute toxic

effects of HTP, our observations require verification in chronic exposure models, more relevant to regular use of HTP.

What this paper adds

- ▶ The extent to which heated tobacco product(s) (HTP) impact respiratory health is currently not defined.
- ▶ We tested cytotoxicity of HTP using cell viability and metabolic activity assays and examined the release of inflammatory cytokines in bronchial epithelial cells. These cells were exposed in vitro directly to HTP emissions and the results were compared with the observed effects after exposure to air (controls), e-cigarette aerosols and smoke from combustible tobacco cigarettes.
- ▶ We found that emissions from HTP damaged bronchial epithelial cells, and their cytotoxic effect was higher compared with e-cigarettes but lower compared with combustible tobacco cigarettes.

Contributors MLG contributed to the conception of the work. MLG and NJL contributed to data analysis. MLG, NJL and RJO drafted the manuscript. NJL and PLT ran all experiments. All authors approved the final version of the manuscript. MLG has full access to all study data and takes responsibility for the integrity of the data and accuracy of the data analysis.

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Competing interests MLG reports grants from and served as an advisory board member to pharmaceutical companies that manufacture smoking cessation drugs. RJO was a member of the FDA Tobacco Products Scientific Advisory Committee which considered Philip Morris International's modified risk application for IQOS in January 2018. Other authors declare no conflict of interest.

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IQOS: examination of Philip Morris International's claim of reduced exposure

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ABSTRACT

Background New electronic heated tobacco products are being introduced in the global market and are gaining popularity. In 2016, Philip Morris International, Inc. (PMI) submitted a modified risk tobacco product (MRTP) application to the Food and Drug Administration (FDA) to market IQOS in the USA with claims of reduced exposure and reduced risk.

Methods We examined PMI's MRTP application, specifically sections on aerosol chemistry and human exposure assessment, to assess the validity of PMI's claims of reduced exposure and risk.

Findings PMI reported levels for only 40 of 93 harmful and potentially harmful constituents (HPHCs) on FDA's HPHC list in IQOS mainstream aerosol. All substances in PMI's list of 58 constituents (PMI-58) were lower in IQOS emissions compared with mainstream smoke of 3R4F reference cigarettes. However, levels of 56 other constituents, which are not included in the PMI-58 list or FDA's list of HPHCs, were higher in IQOS emissions; 22 were >200% higher and seven were >1000% higher than in 3R4F reference cigarette smoke. PMI's studies also show significantly lower systemic exposure to some HPHCs from use of IQOS compared with smoking combustible cigarettes.

Conclusion PMI's data appear to support PMI's claim that IQOS reduces exposure to HPHCs. However, PMI's data also show significantly higher levels of several substances that are not recognised as HPHCs by the FDA in IQOS emissions compared with combustible cigarette smoke. The impact of these substances on the overall toxicity or harm of IQOS is not known.

INTRODUCTION

Many alternative tobacco products have entered the USA market in the last three decades. These include electronic cigarettes that heat a nicotine solution¹ as well as products that heat tobacco without combustion called heated tobacco products (HTPs) or heat-not-burn (HNB) products. A 2000 internal R J Reynolds document gave the rationale for the pursuit of an acceptable HTP:

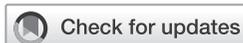
Given that no particular agent or group of agents can be definitely assigned the carcinogenic risk associated with cigarettes, the most effective strategy for reducing lung cancer risk in the smoking population is an overall reduction in both the number and concentration of particulate and vapor phase components. This strategy can be achieved by primarily heating, rather than burning, tobacco to form cigarette smoke aerosol.²

R J Reynolds first released Premier in 1988,³ which was followed by Eclipse, a paper-encased tobacco plug heated by a carbon element.⁴

Independent studies showed that use of Eclipse decreased tobacco cigarette consumption without causing withdrawal symptoms, maintained blood nicotine concentrations and decreased exposure to the carcinogenic tobacco-specific nitrosamine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butane, but increased exposure to carbon monoxide (CO).⁵⁻⁷ Other HTPs included Philip Morris' Accord, which was a combination of a handheld device that heated specially constructed cigarettes. One independent study showed that use of Accord suppressed withdrawal symptoms and reduced CO exposure.⁸ Each iteration of HTPs was commercially unsuccessful, and most products were discontinued shortly after their introduction.⁹

Despite repeated failures at producing a commercially viable HTP, tobacco companies continue to research and develop these products. R J Reynolds launched a revamped Eclipse, rebranded as 'Revo', in November 2014. Revo was briefly test marketed in Wisconsin but pulled off the market.¹⁰ Other current HTPs include British American Tobacco's Glo iFuse, a hybrid of HTP and e-cigarettes. It consists of a heating element, a liquid tank (like e-cigarettes) and a tobacco cavity through which the e-cigarette-like aerosol passes and is infused with tobacco flavour.¹¹ Japan Tobacco's Ploom Tech, which entered the Japanese market in 2016,¹² consists of a liquid cartridge and a capsule of granulated tobacco leaves that the vapour passes through.

Philip Morris Products S.A., a subsidiary of Philip Morris International, Inc. (PMI), developed IQOS ('I Quit Ordinary Smoking') as an HTP.^{9 10} IQOS consists of a tobacco stick (HeatStick) and a battery-powered tobacco heating device.¹³ As of May 2018, IQOS is currently sold in over 37 countries, including Japan, the UK and Canada.¹⁴ Philip Morris Products S.A. filed a modified risk tobacco product (MRTP) application with the US Food and Drug Administration (FDA) in December 2016^{15 16} to market IQOS in the USA with reduced exposure and reduced risk claims. The FDA's Tobacco Products Scientific Advisory Committee (TPSAC) reviewed the MRTP application in January 2018. The TPSAC committee approved, in an 8 to 1 vote, PMI's statement '*Scientific studies have shown that switching completely from cigarettes to the IQOS system significantly reduces your body's exposure to harmful or potentially harmful chemicals[HPHCs]*' was true.¹⁷ Of the eight committee members who agreed with PMI's claim that IQOS significantly reduced exposure to HPHCs, a majority (five of eight) voted that PMI has not '*demonstrated that the reductions in exposure are reasonably likely to translate to a measurable and substantial reduction in morbidity and/or mortality*'.¹⁷



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Examination of PMI's studies, results and interpretation of data to support claims of reduced exposure and risk is critically important before FDA approval in order to protect public health, particularly as PMI's MRTP application and approval may set the precedent for other MRTP applications of similar products. This paper examines PMI's reported studies on IQOS aerosol chemistry and human exposure assessment, and we assessed whether they support PMI's claims of reduced exposure.

METHODS

We examined studies presented in PMI's MRTP application,¹⁶ namely those in Module 6.1.1: *Aerosol Chemistry*; Module 6.1.3.1: *Justification of Selection of Biomarkers of Exposure*; and Module 6.1.3.2: *Summary of Biomarkers of Exposure Assessments*. We also reviewed data presented in the document, *Addendum to FDA Briefing Document: January 24–25, 2018*,¹⁸ which was prepared by FDA's Center for Tobacco Products for the TPSAC meeting on IQOS held on 24 and 25 January 2018.

To examine the aerosol chemistry of IQOS, mainstream aerosol from IQOS HeatSticks (regular and menthol) and smoke from 3R4F reference cigarettes were generated according to the Health Canada Intense machine-smoking regimen on a Borgwaldt linear smoking machine type LM20X (Borgwaldt KC GmbH, Hamburg, Germany) for most analytes and Burghart rotary smoking machine type RMB 20 (Burghart Tabaktechnik GmbH, Wedel, Germany) for elements.¹⁹ Methods for chemical analyses have been described previously.¹⁹

PMI conducted four clinical studies to examine whether human exposure to harmful substances are statistically significantly reduced with IQOS (Module 6.1.3.2).¹⁶ All studies were randomised, controlled, open-label, three-arm, parallel group, single-centre studies. Studies ZRHR-REXC-03-EU (conducted in Poland) and ZRHR-REXC-04-JP (conducted in Japan) were conducted over 5 days in confinement. Each study included 160 combustible cigarette smokers who were randomly assigned to one of three arms, namely, IQOS with regular HeatSticks, commercially available combustible cigarettes or smoking abstinence. Use of IQOS or combustible cigarettes was from 06:30 to 23:00 and was ad libitum. Studies ZRHM-REXA-07-JP (conducted in Japan) and ZRHM-REXA-08-US (conducted in the USA) were conducted over 3 months, during which 160 participants were randomised to one of three arms in each study, namely, IQOS with menthol HeatSticks, commercially available menthol combustible cigarettes or smoking abstinence. These two studies included 5 days in confinement followed by 85 or 86 days, respectively, in an ambulatory setting. Participants in the IQOS or combustible cigarettes arms used each product ad libitum in confinement (06:30–23:00) and in the ambulatory setting. Compliance with study protocol could not be enforced during the ambulatory phase.

For the two 5-day confinement studies, it was evaluated whether reductions of 50% or more in 24 hours urine concentrations of mercapturic acid metabolites of 1,3-butadiene, acrolein and benzene and carboxyhaemoglobin in blood were observed in smokers assigned to IQOS compared with smokers who continued smoking combustible cigarettes. Levels of selected biomarkers of exposure over the 5-day exposure period were also compared between smokers who switched to IQOS and those who continued smoking and the maximum reduction in biomarker levels in abstinent smokers was assessed. For the two 3-month studies, they examined whether the geometric mean levels of biomarkers of exposure for IQOS (menthol) were lower relative to combustible cigarette (menthol) use. Differences in

mercapturic acid metabolites of 1,3-butadiene, acrolein and benzene and carboxyhaemoglobin in blood were tested on day 5 and total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol on day 90.

RESULTS

PMI reported the levels of 58 constituents (which PMI refers to as 'PMI-58') in mainstream aerosol generated from IQOS and 3R4F reference cigarettes (Module 6.1.1).¹⁶ The PMI-58 list includes 40 (43%) out of the 93 harmful or potentially harmful constituents (HPHCs) on FDA's list of HPHCs.²⁰ The PMI-58 list included 18 additional constituents that do not appear on FDA's list of HPHCs, including water, total particulate matter, pyrene and nitrogen oxides. PMI concluded that the levels of HPHCs on the PMI-58 list were reduced by >92% on a stick basis and >89% on a normalised for nicotine basis for the regular tobacco stick, and >93% on a stick basis and >88% on a normalised for nicotine basis for the mentholated tobacco stick compared to 3R4F reference cigarette (Module 6.1.1, p. 45).¹⁶

Importantly, the addendum to the briefing document for the 24 and 25 January 2018 TPSAC meeting, prepared by FDA's Center for Tobacco Products,¹⁸ presented additional data from PMI studies that showed higher levels of many substances in IQOS emissions compared with 3R4F cigarette smoke (table 1). The addendum consisted of data from Module 3.3.2 and section 6.1.1.3.4 of the MRTP application and appendix A of an amendment to the MRTP application. The addendum reported levels of 113 constituents, including 56 of the 58 constituents on the PMI-58 list (total particulate matter and nicotine-free dry particulate matter were the two exclusions) and 57 constituents that do not appear on the PMI-58 list. Fifty-six of the 57 non-PMI-58 constituents were higher in IQOS emission than in 3R4F smoke (median, 154% higher; range, undefined to 13 650% higher in IQOS aerosol vs 3R4F mainstream smoke); tar was the exception. Twenty-two of the non-PMI-58 constituents were at least 200% higher while seven were at least 1000% higher in IQOS emission compared with 3R4F mainstream smoke (table 1).

PMI characterised the droplet size distribution of IQOS aerosol by measuring the mass median aerodynamic diameter (MMAD) (the diameter at which 50% of the particles by mass are larger and 50% are smaller) and geometric standard deviation (presented in Module 6.1.1).¹⁶ The MMAD for the various IQOS products tested (regular and menthol) ranged between 0.54 μm to 0.75 μm and fell within the respirability region, based on the respirability upper threshold defined at 2.5 μm . The range of MMAD for IQOS appears slightly larger than those of e-cigarettes and conventional tobacco cigarettes, which one report showed were about 0.15 μm and 0.17 μm , respectively.²¹

Regarding the human exposure studies, 11 of the 17 HPHCs measured are included in a list of 18 HPHCs that FDA recommends to be measured and reported in users of tobacco products.²⁰ PMI assessed systemic exposure to pyrene, which is not included in FDA's list of HPHCs, as a proxy for exposure to polycyclic aromatic hydrocarbons (PAHs) using 1-hydroxypyrene. PMI did not assess systemic exposure to inorganic compounds, phenols and metals.

Biomarkers of HPHCs measured were statistically significantly lower with IQOS use compared with combustible cigarette use (Module 6.1.3.2).¹⁶ Reductions of at least 50% in levels of biomarkers of exposure to HPHCs were reported when smokers switched from combustible cigarettes to IQOS during 5 days of confinement; these reductions were sustained during the 85/86 days in ambulatory settings (Module 6.1.3.2, p. 145).

Table 1 Compounds in mainstream aerosol of Marlboro HeatSticks compared with 3R4F reference cigarette

PMI product	Unit	PMI-58	IQOS HeatStick	3R4F	Change (%) with 3R4F on stick basis
1,2,3-Propanetriol, diacetate (diacetyl)	µg/stick	No	1.23	0.381	↑ 223
1,2-Propanediol, 3-chloro	µg/stick	No	9.94	5.93	↑ 68
1,4-Dioxane, 2-ethyl-5-methyl-	µg/stick	No	0.055	0.0004	↑ 13 650
12,14-Labdadiene-7,8-diol, (8a,12E)	µg/stick	No	1.43	0.064	↑ 2134
1 hour-Indene, 2,3-dihydro-1,1,5,6-tetramethyl-	µg/stick	No	0.026	0.014	↑ 86
1-Hydroxy-2-butanone	µg/stick	No	0.947	0.465	↑ 104
1-Hydroxy-2-propanone(1,2-Propenediol)	µg/stick	No	162	96.8	↑ 67
2 (5H)-Furanone	µg/stick	No	5.32	1.99	↑ 167
2,3-Dihydro-5-hydroxy-6-methyl-4 hour-pyran-4-one	µg/stick	No	0.231	0.135	↑ 71
2,4-Dimethylcyclopent-4-ene-1,3-dione	µg/stick	No	0.333	0.193	↑ 73
2-Cyclopentene-1,4-dione	µg/stick	No	3.8	0.764	↑ 397
2-Formyl-1-methylpyrrole	µg/stick	No	0.128	0.064	↑ 100
2-Furancarboxaldehyde,5-methyl-	µg/stick	No	11.1	2.94	↑ 278
2-Furanmethanol	µg/stick	No	39.2	7	↑ 460
2-Furanmethanol, 5-methyl-	µg/stick	No	0.123	0.029	↑ 324
2 hour-Pyran-2-one,tetrahydro-5-hydroxy	µg/stick	No	4.45	3.11	↑ 43
2-Methylcyclobutane-1,3-dione	µg/stick	No	2.78	0.71	↑ 292
2-Propanone, 1-(acetyloxy)-	µg/stick	No	16.9	8.01	↑ 111
3 (2H)-Furanone, dihydro-2-methyl-	µg/stick	No	0.326	0.119	↑ 174
3-Methylvaleric acid	µg/stick	No	5.1	3.63	↑ 40
4(H)-Pyridine, N-acetyl-	µg/stick	No	0.296	0.112	↑ 164
5-Methylfurfural	µg/stick	No	0.995	0.632	↑ 57
Anhydro linalool oxide	µg/stick	No	0.457	0.291	↑ 57
Benzene, 1,2,3,4-tetramethyl-4-(1-methylethenyl)-	µg/stick	No	0.006	0.005	↑ 20
Benzenemethanol, 4-hydroxy-	µg/stick	No	0.011	0	↑
Benzoic acid, 2,5-dihydroxy-methyl	µg/stick	No	4.55	2.18	↑ 109
Butylated hydroxytoluene	µg/stick	No	0.132	0.007	↑ 1786
Butyrolactone	µg/stick	No	4.08	0.728	↑ 460
Cis-sesquisabinene hydrate	µg/stick	No	0.061	0	↑
Cyclohexane, 1,2-dioxo-	µg/stick	No	0.083	0.046	↑ 80
Cyclohexane-1,2-dione, 3-methyl-	µg/stick	No	0.101	0.073	↑ 38
Eicosane, 2-methyl-	µg/stick	No	0.05	0.014	↑ 257
Ergosterol	µg/stick	No	3.18	1.58	↑ 101
Ethyl 2,4-dioxohexanoate	µg/stick	No	6.73	3.57	↑ 89
Ethyl dodecanoate (ethyl laurate)	µg/stick	No	0.023	0	↑
Ethyl linoleate	µg/stick	No	0.135	0.008	↑ 1588
Ethyl linolenate	µg/stick	No	0.614	0.153	↑ 301
Furfural	µg/stick	No	31.1	25.9	↑ 20
Glycerol	mg/stick	No	5.02	2.08	↑ 141
Glycidol	µg/stick	No	5.71	1.76	↑ 224
Heneicosane, 2-methyl-	µg/stick	No	0.063	0.021	↑ 200
Hexadecanoic acid, ethyl ester	µg/stick	No	0.491	0.008	↑ 6038
Isolinderanolid	µg/stick	No	4.99	1.85	↑ 170
Isoquinoline, 3-methyl	µg/stick	No	6.29	4.99	↑ 26
Labdane-8,15-diol, (13S)	µg/stick	No	0.143	0.015	↑ 853
Lanost-8-en-3-ol, 24-methylene-, (3beta)	µg/stick	No	6.3	1.61	↑ 291
Maltoxazine	µg/stick	No	0.077	0.038	↑ 103
Methyl furoate	µg/stick	No	0.147	0.029	↑ 407
Phenylacetaldehyde	µg/stick	No	1.41	0.529	↑ 167
p-Menthan-3-ol	µg/stick	No	0.786	0.322	↑ 144
Propylene glycol	µg/stick	No	175	23.7	↑ 638
Pyranone	µg/stick	No	6.54	5.07	↑ 29
Pyranone	µg/stick	No	9.26	5.84	↑ 59
Pyridoxin	µg/stick	No	0.699	0.526	↑ 33
Stearate, ethyl-	µg/stick	No	0.074	0.003	↑ 2367

Continued

Table 1 Continued

PMI product	Unit	PMI-58	IQOS HeatStick	3R4F	Change (%) with 3R4F on stick basis
Tar	mg/stick	No	19.4	25	↓ 22
Trans-4-hydroxymethyl-2-methyl-1,3-dioxolane	µg/stick	No	2.09	0.044	↑ 4650
1,3-Butadiene	µg/stick	Yes	0.21	89.2	↓ 99.8
1-Aminonaphthalene	ng/stick	Yes	0.043	20.9	↓ 99.8
2-Aminonaphthalene	ng/stick	Yes	0.022	17.5	↓ 99.9
3-Aminobiphenyl	ng/stick	Yes	0.007	4.6	↓ 99.8
4-Aminobiphenyl	ng/stick	Yes	0.009	3.21	↓ 99.7
Acetaldehyde	µg/stick	Yes	192	1602	↓ 88
Acetamide	µg/stick	Yes	2.96	13	↓ 77
Acetone	µg/stick	Yes	30.7	653	↓ 95
Acrolein	µg/stick	Yes	8.32	158	↓ 95
Acrylamide	µg/stick	Yes	1.58	4.5	↓ 65
Acrylonitrile	µg/stick	Yes	0.145	21.2	↓ 99.3
Ammonia	µg/stick	Yes	12.2	33.2	↓ 63
Arsenic	ng/stick	Yes	<0.36	<7.49	NA
Benz[a]anthracene	ng/stick	Yes	2.65	28.4	↓ 91
Benzene	µg/stick	Yes	0.45	77.3	↓ 99.4
Benzo[a]pyrene	ng/stick	Yes	0.736	13.3	↓ 94
Butyraldehyde	µg/stick	Yes	20.7	81.3	↓ 74
Cadmium	ng/stick	Yes	<0.28	89.2	↓ >99.7
Carbon monoxide	mg/stick	Yes	0.35	29.4	↓ 99
Catechol	µg/stick	Yes	14	84.1	↓ 83
Chromium	ng/stick	Yes	<11.0	<11.9	NA
Crotonaldehyde	µg/stick	Yes	<3.29	49.3	↓ >93
Dibenz[a,h] anthracene	ng/stick	Yes	<0.124	<0.689	NA
Ethylene oxide	µg/stick	Yes	<0.119	16	↓ >99.3
Formaldehyde	µg/stick	Yes	14.1	79.4	↓ 82
Hydrogen cyanide	µg/stick	Yes	<1.75	329	↓ >99.5
Hydroquinone	µg/stick	Yes	6.55	94.5	↓ 93
Isoprene	µg/stick	Yes	1.51	891	↓ 99.8
Lead	ng/stick	Yes	2.23	31.2	↓ 93
m-Cresol	µg/stick	Yes	0.042	4.24	↓ 99
Mercury	ng/stick	Yes	1.38	3.68	↓ 63
Methyl-ethyl-ketone	µg/stick	Yes	10.1	183	↓ 94
Nickel	ng/stick	Yes	<15.9	<12.9	NA
Nicotine	mg/stick	Yes	1.29	1.74	↓ 26
Nitric oxide	µg/stick	Yes	12.6	484	↓ 97
Nitro benzene	µg/stick	Yes	<0.011	<0.038	NA
Nitrogen oxides	µg/stick	Yes	14.2	538	↓ 97
N-nitrosoanabasine	ng/stick	Yes	2.35	29	↓ 92
N-nitrosoanatabine	ng/stick	Yes	14.7	254	↓ 94
NNK	ng/stick	Yes	7.8	244.7	↓ 97
NNN	ng/stick	Yes	10.1	271	↓ 96
o-Cresol	µg/stick	Yes	0.078	4.81	↓ 98
o-Toluidine	ng/stick	Yes	1.1	96.2	↓ 99
p-Cresol	µg/stick	Yes	0.071	9.6	↓ 99
Phenol	µg/stick	Yes	1.47	15.6	↓ 91
Propionaldehyde	µg/stick	Yes	10.8	109	↓ 90
Propylene oxide	ng/stick	Yes	142.3	896	↓ 84
Pyrene	ng/stick	Yes	8.2	79.2	↓ 90
Pyridine	µg/stick	Yes	6.58	30.9	↓ 79
Quinoline	µg/stick	Yes	<0.011	0.43	↓ >98
Resorcinol	µg/stick	Yes	<0.055	1.72	↓ >97
Selenium	ng/stick	Yes	1.27	<4.42	NA
Styrene	µg/stick	Yes	0.58	13.9	↓ 96

Continued

Table 1 Continued

PMI product	Unit	PMI-58	IQOS HeatStick	3R4F	Change (%) with 3R4F on stick basis
Toluene	µg/stick	Yes	1.42	129	↓ 99
Vinyl chloride	ng/stick	Yes	<0.657	93.4	↓ >99
Water	mg/stick	Yes	30.2	14.7	↑ 105

Notes: presented in table 1 of *Addendum to FDA Briefing Document, January 24-25, 2018*, Meeting of the Tobacco Products Scientific Advisory Committee; data source: section 3.3.2 and section 6.1.1.3.4 of the Modified Risk Tobacco Product application (MRTPAs) and appendix A of an amendment to the MRTPAs submitted on 8 December 2017. Total particulate matter and nicotine-free dry particulate matter, two constituents on the PMI-58 list were not reported by PMI in this table.

↑, higher in IQOS; ↓, lower in IQOS.

PMI, Philip Morris International; PMI-58, PMI's list of 58 constituents.

DISCUSSION

According to FDA's draft guidance, an MRTP is 'any tobacco product that is sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products'.²² FDA may issue an order allowing a product to be marketed as a modified risk product if it is demonstrated that the product: (A) significantly reduces harm and the risk of tobacco-related disease to individual tobacco users; and (B) benefits the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products. PMI's data show that IQOS significantly reduces emissions and exposure to several HPHCs compared with combustible cigarettes. However, PMI's data also show that IQOS emissions contain higher levels of many other substances compared with combustible cigarettes. The impact of these substances on IQOS toxicity and harm are not known.

Over 7000 distinct substances have been identified in tobacco smoke, many of which are toxic or carcinogenic.²³ HPHCs in tobacco or tobacco smoke have been proposed by several public health authorities, such as the FDA,²⁰ as possible causes of tobacco-related morbidity and mortality. Elimination or reduction of exposure to these HPHCs may potentially reduce health risks, which is the premise of HTP technology. Schaller and colleagues¹⁹ described five criteria used by PMI to select HPHCs to measure in IQOS aerosol for comparison with 3R4F reference cigarette. Criterion 1 includes smoke constituents determined by International Organization for Standardization (ISO) methods, such as total particulate matter, nicotine and CO. Criterion 2 includes priority toxicants in tobacco smoke selected from the lists issued by regulatory bodies or proposed by cognizant authorities, such as volatile organic compounds like acrylonitrile, 1,3-butadiene and benzene. Criterion 3 includes toxicants for which there is an established biomarker of exposure. Criterion 4 includes toxicants that are predominantly formed below 400°C and that are not included under 'Criterion 2', such as acrylamide and acetamide. Criterion 5 includes toxicants that are predominantly formed above 400°C and that are not included under 'Criterion 1' and 'Criterion 2', such as dibenz[a,h]anthracene and benz[a]anthracene.

PMI's conclusion that IQOS reduces exposure to HPHCs, which TPSAC agreed with,¹⁷ is based, in part, on evidence of lower levels of PMI-58 substances in IQOS emissions compared with 3R4F reference cigarette smoke. However, the PMI-58 list is selective (based on PMI's criteria described before); PMI did not report levels of 53 HPHCs on FDA's list of 93 HPHCs. Of the 53 FDA HPHCs not measured, 50 are carcinogenic (eg, 2,6-dimethylaniline, benz[j]aceanthrylene, ethylbenzene and furan).²⁰ In addition to the PMI-58 substances, PMI measured levels of 57 other substances in IQOS emissions (non-PMI-58 substances). Importantly, 56 of these 57 non-PMI-58 substances were higher in IQOS aerosol compared with 3R4F mainstream

cigarette smoke. It appears that IQOS reduces exposure to some toxicants but elevates exposure to other substances.

Given the elevated levels of the non-PMI-58 substances in IQOS aerosol compared with reference cigarette smoke, their inherent toxicities could play a role in the overall harm of IQOS. A number of these substances, including several that were more than 50% higher in IQOS aerosol, belong to chemical classes that are known to have significant toxicity, such as α,β -unsaturated carbonyl compounds (eg, 2-cyclopentene-1,4-dione),²⁴ 1,2-dicarbonyl compounds (eg, cyclohexane, 1,2-dioxo-),²⁵ furans (eg, 2 (5H)-furanone)²⁶ and epoxides (eg, anhydro linalool oxide).²⁷ There is limited information on the toxicity of many of the non-PMI-58 substances. We speculate that some of these substances are components of flavour additives in IQOS or thermal degradation compounds. For example, anhydro linalool oxide is listed among flavouring ingredients that are generally regarded as safe (for oral ingestion) by the Flavor and Extract Manufacturers' Association.²⁸ (5H)-Furanone is a food additive that suppresses appetite and/or food intake and has been shown to induce cellular DNA damage *in vitro*.^{29,30} 2-Furanmethanol is a flavouring agent with a flavour profile of burnt, caramel or cooked.³¹ 2-Furanmethanol also causes eye, nose, throat and skin irritation and has central nervous system effects.³¹ 2-Cyclopentene-1,4-dione is likely generated from thermal breakdown of sugars.³² 1-Hydroxy-2-butanone, a flavouring ingredient found in coffee and coffee products, is also a degradation product of polysaccharides.³³ Some compounds appear to be contaminants. 3-Chloro-1,2-propanediol (or 1,2-propanediol, 3-chloro), a food contaminant,³⁴ has not been shown to be genotoxic *in vivo*,³⁵ but mutagenic effects were observed at high concentrations *in vitro* experiments.³⁶ A 2-year study found increased incidence for the development of tumours in kidney and testis in male rats exposed to 3-chloro-1,2-propanediol.³⁷ 1,2,3-Propanetriol, diacetate (diacetin) is a solvent used for decaffeinating coffee.

PMI's MRTP application fails to address the important question of whether the aerosol generation process for IQOS produces toxic substances not found in the smoke of combustible cigarettes, which could have been answered through non-targeted chemical analysis. Combustible tobacco cigarettes reach about 900°C during a puff and smoulder at about 400°C between puffs.²³ The burning process, substances emitted and their levels vary at different temperatures.³⁸ Distillation, the process during which nicotine and aromas are transferred from tobacco to smoke, occurs below 300°C; pyrolysis occurs at about 300°C–700°C, entails the decomposition of biopolymers, proteins, and other organic materials and generates the majority of substances emitted in smoke; and combustion occurs above 750°C and results in the generation of carbon dioxide, CO and water.³⁸ HeatSticks are heated to a maximum of 350°C,¹⁹ a temperature sufficient to enable pyrolytic decomposition of some organic materials. Formation of toxic volatile organic

compounds, including formaldehyde, acetaldehyde and acrolein, via dehydration and oxidation of the humectants, propylene glycol and glycerin, have been reported in e-cigarette aerosols at similar temperatures as IQOS.^{39–42} In addition, flavouring chemicals in e-cigarettes undergo thermal degradation and contribute significantly to levels of toxic aldehydes emitted in e-cigarette aerosol.⁴³ Since the constituents of HeatSticks may be different from that of combustible cigarettes, including flavourants and additives, it is plausible that the IQOS aerosol may contain substances not present in tobacco smoke.

A study by Klupinski and colleagues⁴⁴ reported that unique substances, such as ambrox, 3-methylbutanenitrile and 4-methylimidazole, were found in little cigar smoke that were not found in cigarette smoke, indicating that different tobacco products can have different chemical fingerprints and lead to different exposure and toxicological profiles. The study by Klupinski and colleagues describes methodology for ‘non-targeted’ analysis of tobacco smoke aerosol, and the authors suggest that ‘the same approach could also be applied to other samples to characterize constituents associated with tobacco product classes or specific tobacco products of interest’. FDA should recommend that manufacturers of HTPs undertake ‘non-targeted’ analyses (along with targeted analysis), comparing HTP aerosol with smoke from combustible tobacco products to identify potentially toxic chemicals in HTP emissions that may not be present in tobacco smoke.

Although smoking machine studies are appropriate for examining the relative differences in emissions between products, they do not predict use patterns and systemic exposure to toxicants. PMI reported systemic exposure to 17 HPHCs in its human exposure studies. PMI did not assess systemic exposure to any inorganic compounds, phenols and metals, possibly due to the fact that there are no valid biomarkers for some substances or that the time course of the biomarkers may not be optimal for studies of the duration used by PMI. PMI used 1-hydroxypyrene, a metabolite of pyrene (a PAH) as a biomarker of PAHs. Pyrene is not included as an HPHC on FDA’s list. We have previously demonstrated that 1-hydroxypyrene is not a selective measure of tobacco-related PAH exposure and is weakly related to nicotine intake and tobacco-specific nitrosamine exposure.⁴⁵ Instead, we found that monohydroxylated metabolites of fluorene (particularly 1-hydroxyfluorene) and 2-naphthol (a naphthalene metabolite) were more selective of tobacco smoke exposure. In characterising PAH exposure from HNB products, manufacturers should include biomarkers with relatively high selectivity for tobacco.

In conclusion, PMI’s data show that IQOS emissions have significantly lower levels of several HPHCs compared with combustible cigarettes. Furthermore, PMI’s data from human studies show that use of IQOS is associated with significantly lower systemic exposure to some HPHCs compared with smoking combustible cigarettes. These data appear to support PMI’s claim that IQOS is a reduced exposure product. However, PMI’s data also show significantly higher levels of other substances in IQOS emissions compared with combustible cigarette smoke. The impact of these substances on the overall toxicity or harm of IQOS is not known.

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What this paper adds

- ▶ Studies conducted by Philip Morris International, Inc. (PMI) show that IQOS emissions contain lower levels of many harmful or potentially harmful constituents (HPHCs) compared with combustible tobacco smoke.
- ▶ PMI’s studies show that use of IQOS results in significantly lower systemic exposure to several HPHCs compared with combustible cigarette smoking.
- ▶ PMI’s own data also show that IQOS emissions contain many other substances, some of which are potentially toxic, at higher levels than in combustible cigarette smoke.

Disclaimer The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health, the Food and Drug Administration or TRDRP. The funding agencies played no role in design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript.

Competing interests NLB has served on smoking cessation advisory boards for Pfizer and has been an occasional consultant to McNeil and Achieve Life Sciences and has served as a paid expert witness in litigation against tobacco companies.

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Tobacco-specific nitrosamines (TSNA) in heated tobacco product IQOS

BACKGROUND

Heated tobacco products (HTP) have an electrical heating component, like e-cigarettes, that heats processed tobacco to 350°C releasing volatile components that often are not detectable in e-cigarettes.¹ Although many combustion by-products may be eliminated in HTP devices, nitrosamines are generated in the process of tobacco curing rather than during combustion, and may be transferred from the HTP into the aerosol that it generates.²⁻⁴ We hypothesised that HTP may be a significant source of tobacco-specific nitrosamines (TSNA). This pilot study determined TSNA yields in aerosol emitted from HTP in comparison to the electronic and tobacco cigarettes.

METHODS

HTP (IQOS; Amber, tobacco flavour), e-cigarettes (MarkTen; 3.5% nicotine, tobacco flavoured) and tobacco cigarettes (Marlboro Red 100) were tested using a Borgwaldt LX-1 smoking machine following the Health Canada Intense protocol (55 mL puff volume, 2 s duration, 30 s interval). Using this puffing protocol, we generated aerosol from a single HTP HeatStick (12 puffs), single tobacco

cigarette (8 puffs) and from e-cigarette (55 puffs). We used different number of puffs for each product to achieve a comparable nicotine delivery across all tested products. Cambridge filters (44 mm) were used to capture the total particulate matter from all tested products. The control samples (blanks) were generated by passing 55 puffs of air through the filter. Cambridge filters were spiked with deuterated internal standards and extracted using 20 mL 100 mM ammonium acetate. The following TSNAs were measured using liquid chromatography-tandem mass spectrometry: N'-nitrosoanabasine, N'-nitrosoanatabine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and N'-nitrosornicotine (Toronto Research Chemicals; Canada).⁵ A limit of quantitation for each compound was 0.5 ng/filter. Nicotine was measured using gas chromatography with nitrogen-phosphorous detector (GC-NPD) method as described previously.⁶ Each product was tested in triplicate. The average TSNA yields for each product were calculated per single puff and per puffing session. We used analysis of variance to test for statistical differences between the three tested products and t-tests to compare TSNA yields from HTP with yields detected in e-cigarettes and combustible cigarettes.

RESULTS

All four TSNA compounds analysed were detected in the HTP. The yields of individual TSNA per puff in the HTP aerosols were 8–22 times lower than in tobacco cigarette smoke (figure 1; all $p < 0.05$). HTP delivered 1.4 ± 0.2 mg nicotine from a single HeatStick (12 puffs); e-cigarette 1.3 ± 0.2 mg per 55 puffs; and a single combustible cigarette 2.1 ± 0.1 mg (8 puffs). TSNA yields normalised per nicotine delivery were also significantly higher in the HTP than those found in e-cigarettes and significantly lower than those found in tobacco cigarettes, except for NNK ($p < 0.05$). TSNA yields in a single tobacco cigarette were between 7 and 17 times higher than TSNA yields in a single HTP HeatStick. No TSNAs were detected in the air control samples.

CONCLUSIONS

Like combustible products, HTPs emit substantial levels of carcinogenic TSNA. Although HTP emits lower amounts of TSNA than combustible cigarettes, the amounts are significantly higher than from e-cigarettes. Our findings are consistent with prior

reports.³⁻⁷ One limitation of this study is that one puffing protocol was used for all devices. While this was helpful in comparing TSNA and nicotine delivery between devices, machine-based measurements are not representative of human smoking patterns or constitute intake.^{8,9} The tested HTP does not reduce emissions of an important class of tobacco carcinogens to the same degree as other commercially available technologies.

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Contributors MLG contributed to the conception of the work. MLG and NJL contributed to data analysis. AMM, MNP, MLG, NJL and RJO drafted the manuscript. AMM, MNP and NJL ran all experiments. All authors approved the final version of the manuscript. MLG has full access to all study data and takes responsibility for the integrity of the data and accuracy of the data analysis.

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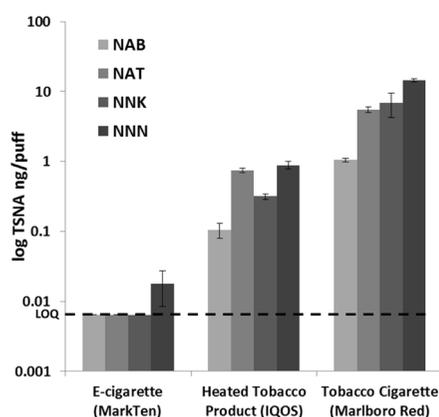
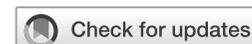


Figure 1 Yields of tobacco-specific nitrosamines (TSNA) (per puff) in aerosols generated from IQOS heated tobacco product (12 puffs/HeatStick), MarkTen e-cigarette (55 puffs) and smoke from Marlboro Red 100 combustible cigarettes (8 puffs/cigarette). The data presented are log transformed. LOQ, limit of quantitation; NAB, N'-nitrosoanabasine; NAT, N'-nitrosoanatabine; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNN, N'-nitrosornicotine.

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Possible hepatotoxicity of IQOS

On 25 January 2018, the Food and Drug Administration (FDA) Tobacco Scientific Advisory Committee unanimously voted (with one abstention) that Phillip Morris International (PMI) could not claim their heated tobacco product (HTP) IQOS (I-Quit-Ordinary-Smoking) would reduce the risk of tobacco-related diseases. Regardless, IQOS is already available in over 30 countries, and thus merits scrutiny from the scientific and medical communities. The preclinical and clinical data PMI submitted to FDA indicate that IQOS exposure may be associated with unexpected liver toxicity. We reviewed preclinical studies conducted by PMI scientists¹ and clinical studies of 5 and 90 days of exposure to IQOS and IQOS menthol²⁻⁵ included in PMI's Modified Risk Tobacco Product application submitted to the US FDA.

Wong and colleagues¹ exposed 92 male and 92 female Sprague Dawley rats to up to 90 days of mainstream aerosol from IQOS, mainstream smoke from 3R4F research cigarettes, or room air (sham). After 90 days of exposure, liver weights and blood levels of alanine aminotransferase (ALT) were measured. ALT is an enzyme released into the blood by hepatocytes during hepatocellular injury⁶ and liver weight is a sensitive measure of hepatocellular hypertrophy.⁷ After 90 days, ALT levels and liver weights were significantly higher with IQOS than with conventional cigarettes in female animals (table 1). Hepatocellular vacuolisation, a sign of acute liver injury,⁷ was significantly increased in IQOS-exposed female rats, an effect not seen in cigarette-exposed animals (table 1).

The human clinical data PMI submitted to FDA provide further cause for concern. Increased plasma bilirubin may signify cholestatic liver injury with impaired hepatic bile flow, accelerated red blood cell destruction, or decreased bilirubin metabolism.⁷ Following 5 days of exposure to

IQOS, conventional cigarettes or smoking abstinence, plasma bilirubin was elevated in 8.8% of IQOS subjects compared with 0% of cigarette smokers and 2.6% in abstainers.² In another 5-day study, the mean increase in ALT was higher with IQOS than with conventional cigarettes or smoking abstinence (4.5, 2.9 and 1.6 IU/L, respectively).³ In a 90-day study of exposure to mentholated IQOS, mentholated cigarettes or smoking abstinence, the only subject experiencing a grade 2 (moderate) increase in ALT was in the IQOS group.⁴ In another study, the rate of grade 1 (mild) increases in ALT after 60 days of exposure was highest with IQOS at 6.3% compared with 0% for conventional cigarettes and 2.6% with smoking abstinence.⁵

Hepatotoxicity constitutes a broad spectrum of injuries to the liver, with consequences ranging from asymptomatic lab abnormalities to hepatic failure and death.^{6,7} Notably, there is some evidence that smoking cessation may be associated with a small increase in the unconjugated fraction of bilirubin over the next 1–4 weeks, averaging 0.06 mg/dL.⁸ However, in the 5-day exposure study cited above, the rate of elevated bilirubin (>1.0 mg/dL) in IQOS users was over three times higher than that observed with smoking abstinence (8.8% vs 2.6%), and the mean increase above baseline was 0.05 mg/dL with IQOS compared with -0.07 mg/dL with smoking abstinence.² We can find no evidence in the literature that smoking cessation is associated with an increase in ALT.

Taken together, PMI's preclinical and clinical data constitute a concerning pattern of possible hepatotoxicity, especially considering the short period of exposure. These findings indicate IQOS may have unexpected organ toxicity that has not been associated with cigarettes. Although IQOS exposes users to lower levels of many toxins than conventional cigarettes, it exposes users to higher levels of other toxins (St Helen *et al*, submitted manuscript). Given the potential for synergistic hepatotoxicity with other medications (eg, acetaminophen), alcohol^{9,10}

and herbal supplements, the public health community should focus intense scrutiny on possible liver injury in users of IQOS and other HTPs. A broader implication of this finding is that health assessments of IQOS and other non-cigarette tobacco products should consider possible toxicities not associated with conventional cigarettes.

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Contributors LC, FM, CC, MM and JG drafted the manuscript. LC, FM, CC, MM and JG edited and revised the manuscript. LC, FM, CC, MM and JG prepared the tables. LC, FM, CC, MM and JG approved the final version of the manuscript.

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Competing interests None declared.

Patient consent Not required.

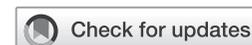
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Table 1 Liver parameters in Sprague Dawley rats after 90 days of exposure

	Female			Male		
	Sham	IQOS	3R4F	Sham	IQOS	3R4F
ALT levels (IU/L)	51.0±4.4	73.0±3.2**,****	54.0±2.6	57.0±6.5	75.0±6.7*	68.0±5.8
Liver weight†	339.6±6.6	442.6±10.2***,****	386.7±15.1*	329.3±5.1	381.7±13.2**	373.0±7.9***
Hepatocellular vacuolisation	0.7±0.4	1.5±0.2*	1.2±0.3	1.4±0.3	0.8±0.4	1.8±0.8

Data are from Wong *et al*¹ and are presented as mean±SEM.

*P<0.05 relative to sham; **P<0.01 relative to sham; ***P<0.001 relative to sham; ****P<0.01 relative to 3R4F.

†Normalised to body weight and reported as ×10⁻⁴.

ALT, alanine aminotransferase.

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Heated tobacco products likely appeal to adolescents and young adults

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ABSTRACT

Background Beginning in the 1960s in the USA and globally since 1998, tobacco companies have been aggressively promoting heated tobacco products (HTP). In 2016, Philip Morris International (PMI) applied to the US Food and Drug Administration (FDA) seeking authorisation to market their IQOS HTP system and flavoured 'HeatSticks' in the USA as a modified-risk tobacco product (MRTP).

Methods We systematically evaluated the publicly available data PMI submitted to FDA in its MRTP application to determine whether PMI's IQOS product meets the US Tobacco Control Act's standard for MRTP claims. We examined whether PMI provided sufficient data showing tobacco users will not initiate with IQOS, that youth will not misperceive the MRTP-related claims being made concerning IQOS, and how youth perceive health risks associated with IQOS.

Results PMI's own studies failed to provide evidence that youth, including non-users and former users, will not find IQOS appealing, will not initiate use of IQOS and will not perceive these products as risk-free. Further, PMI did not refer to independent studies conducted among adolescents which could influence their conclusions. Finally, their studies suffered from design and implementation flaws and cannot be relied on to support the proffered claims.

Conclusion PMI's own data and available evidence from scientific studies conducted independent of the tobacco industry regarding how novel tobacco products are currently being marketed suggest that introduction of IQOS will result in adolescent and young adult non-users initiating tobacco use with IQOS and could also increase poly-use of IQOS along with other tobacco products.

your body's exposure to harmful and potentially harmful chemicals.

In accordance with the Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act),³ when considering whether a new tobacco product such as HTPs should be introduced into the US market, the FDA must consider what impact the new products and its related marketing will have on adolescents (ages 10–17) and young adults (ages 18–25), including providing clear evidence about the effect the HTP and related marketing will have on adolescents and young adults (AYA) who are not using tobacco (including never and former tobacco users); whether the new product and related marketing will influence initiation; how AYA consumers *actually use* the HTP; evaluation of consumers' understanding and perceptions of the HTP, including its MRTP claims, labelling, marketing and advertising; and consumers' beliefs about the health risks of using the HTP relative to other tobacco products.

In this paper, we systematically evaluate the publicly available data that PMI submitted to the FDA in its MRTP application to determine whether PMI's IQOS meets the US Tobacco Control Act's standard for making their MRTP claims. In particular, we examine whether PMI provided sufficient data to show whether AYA who are not using tobacco (including never and former tobacco users) will initiate tobacco use with the new IQOS HTP product, whether HTP use among AYA consumers results in reduced levels of harm based on how they actually use the product, and whether AYA correctly understand the risks of HTP relative to other tobacco products.⁴

Because PMI studies provide no evidence on adolescents, we brought in evidence from other tobacco products, particularly e-cigarettes. Unlike regular combustible cigarettes, HTP heat sticks use an electronic heat source to create nicotine-containing aerosols to be inhaled by the user. The resemblance of the HTP device and process is similar to that of e-cigarettes which heat nicotine-containing liquids to generate aerosols. As such, HTPs are considered a form of e-cigarettes in Japan,⁵ Korea¹ and Italy.⁶ PMI, in their own studies on perceptions, used e-cigarettes for comparison with IQOS (and showed the products were rated similarly).⁴ These similarities in consumer perceptions are particularly important because the subjective perceptions and beliefs are what primarily drives consumer behaviour, rather than the physical product features, particularly among adolescents.

INTRODUCTION

Beginning in the 1960s in the USA and globally since 1998, tobacco companies have been developing heated tobacco products (HTP)^{1,2}; in 2017, tobacco companies began aggressive worldwide promotion of HTPs. In December 2016, Philip Morris International (PMI) submitted an application seeking the US Food and Drug Administration's (FDA) authorisation to market their IQOS HTP system and flavoured 'HeatSticks' in the USA as a modified-risk tobacco product (MRTP). In the application, PMI sought to make three claims in consumer marketing: (1) switching completely from cigarettes to the IQOS system can reduce the risks of tobacco-related diseases, (2) switching completely to IQOS presents less risk of harm than continuing to smoke cigarettes and (3) switching completely from cigarettes to the IQOS system significantly reduces



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Table 1 Systematic evaluation of evidence required by the Tobacco Control Act and evidence provided by PMI vs extant evidence to support or refute MRTP claims

Evidence required by Tobacco Control Act	PMI's evidence	Extant evidence as of 1 June 2018
Will IQOS and its marketing increase the likelihood that AYA non-users (including never users and former tobacco products users) will start using the product?	PMI did not provide this evidence. PMI claimed that in a premarket setting, the effect of IQOS on initiation among non-users could not be assessed. Instead, PMI used 'behavioural intentions' among adults as a proxy for behaviour.	Large proportions of non-users are using IQOS and other non-cigarette tobacco products. Studies have found evidence of gateway from e-cigarettes to combusted tobacco products. Intentions are not a suitable proxy for actual behaviour, especially for adolescents. ^{10-13 48 55-57 77 96}
Does IQOS expose consumers to the claimed reduced level of harm considering how consumers actually use IQOS, including concurrent use of multiple nicotine or tobacco products?	Given that dual and poly use were the prevailing patterns in the PMI studies, PMI did not demonstrate that IQOS, as actually used by consumers, reduced levels of harm.	Epidemiological evidence suggests that for other non-cigarette tobacco products, switching completely has not been the most common outcome. ^{48 77}
Does IQOS advertising or labelling enable the public to comprehend the information concerning modified risk in the context of total health and in relation to all of the diseases and health-related conditions associated with the use of tobacco products and cessation aids?	PMI's application did not include information from studies with adolescents younger than 18. In PMI's studies, adult never-smokers had higher perceived risks of IQOS use compared with current or former smokers. They perceived risks of IQOS as lower than those of combusted cigarettes, but similar to health risks of e-cigarettes.	Extensive literature on adolescents conducted independently of the industry that PMI could have, but did not, present on current, former and non-users of cigarettes demonstrates the need to consider both perceptions of risks and benefits. ¹⁵ The actual marketing of IQOS to date in countries other than the USA demonstrates that PMI has not adequately protected against use by non-smokers and suggests that the product's name, physical appearance, flavours and retail environment will appeal to young people. ^{11 13 14 16-25 68 97}

AYA, adolescents and young adults; MRTP, modified-risk tobacco product; PMI, Philip Morris International.

Finally, given that PMI's MRTP application and their referenced data come mostly from the USA and that PMI is asking permission to market IQOS in the USA, our study largely focuses on US data. However, this study can help inform regulation of other HTP products globally, including whether new HTP products should be approved for sale under explicit or implicit reduced risk claims and marketing in light of how reduced-risk claims are perceived by the public.

METHODS

As part of the public comment process for all FDA MRTP applications submitted from 24 May 2017 to 24 January 2018, the FDA made the majority of PMI's MRTP application materials for HTP available online on a rolling basis.⁴ We analysed the MRTP application materials and researched the available literature to determine whether PMI's claims concerning IQOS could be supported. The following sections of the PMI MRTP application were analysed in whole or in part: (1) Executive Summary; (2) Module 3: Product Description and Formulation; (3) Module 4: Labels, Labeling, and Advertising; (4) Module 6: Summaries of All Research Findings and (5) Module 7: Scientific Studies and Analyses, including product analyses (7.1), preclinical studies (7.2), studies in adult human subjects (7.3), populations health impact model (7.4) and mechanistic and systems toxicology studies.⁴ Considered outside the scope of the present investigation were Module 1 (cover letters), Module 2 (table of contents) and Module 5 (environmental impact), as none contained data germane to the questions addressed in this study.

RESULTS

Table 1 summarises the evidence required by the Tobacco Control Act³ to make modified risk claims and the evidence provided by PMI in support thereof, including (1) the effect of IQOS marketing on non-users; (2) actual use of the IQOS product and (3) consumer and potential consumer perceptions of IQOS. Table 1 also provides extant evidence on these issues from the literature. For more details on the evidence required

and provided by PMI, please see the expanded table in the online supplementary appendix.

PMI's application did not provide any scientific evidence regarding the effect that IQOS and its marketing could have on the likelihood that adolescents who are currently non-tobacco users or who are former tobacco users will start using IQOS (table 1). Instead, PMI claimed that they could not conduct studies on the actual use of IQOS among adolescents, and thereby conducted studies of adults that relied on 'behavioural intention', defined as 'a person's perceived likelihood or subjective probability that he or she will engage in a given behavior,' as a proxy to predict MRTP use behaviours. While many decision-making theories such as Social Cognitive Theory,⁷ the Health Belief Model,⁸ The Theory of Reasoned Action⁹ and The Theory of Planned Behavior⁹ have argued that people's behaviours are largely shaped by their intentions to engage in that behaviour, more recent studies¹⁰⁻¹³ have shown that these models do not accurately or fully predict adolescent behaviour, including tobacco use.

Further, there is concern regarding the packaging of IQOS and its potential impact on AYA use. IQOS packaging resembles iPhones and other high-end smartphones, where the device and parts are neatly placed in moulded plastic trays inside a glossy white box (figure 1). Piper Jaffray's 11 October 2017 'Taking Stock with Teens' survey of 6100 US teens showed that Apple's iPhone continues to rise in popularity among teens, with 78% of US teens saying they owned an iPhone, and 82% of teens saying their next smartphone will be an iPhone.¹⁴ Adding to these concerns, the IQOS flagship stores in Seoul, Korea, visited in June 2017, look remarkably similar to high-end technology brand stores such as Apple or Microsoft stores in the USA (figures 2 and 3).¹ There is concern that this similarity in appearance to popular personal electronic devices could increase appeal among AYA (the most frequent users of such tech-based devices) and especially since as marketed the IQOS device itself is more similar to a (familiar and low risk) mobile electronic device than a (harmful) tobacco product such as cigarettes. That



Figure 1 Packaging of IQOS (top: picture taken by Minji Kim) resembles that of a high-end smartphone (bottom: Apple iPhone 7; source: www.phonearena.com).

said, the HeatSticks themselves bear the Marlboro brand and are clearly identifiable as a tobacco product. Packaging and marketing IQOS similarly to non-tobacco products could reduce perceptions of harm. The global experience with e-cigarette marketing demonstrates that perceptions of reduced harm are an important selling point of new products.^{11 13 15–27} Another



Figure 2 IQOS Flagship store in Seoul, Korea, June 2017 (photos by Minji Kim).



Figure 3 IQOS Flagship store in Amsterdam, Netherlands, September 2017 (photo by Minji Kim).

example is JUUL, a pod-based e-cigarette which looks like a USB stick.^{28 29} The similarity with a popular consumer technology (USB stick) is another reason for JUUL popularity among adolescents, who are able to ‘stealth vape’ in school without teachers noticing.^{30–32}

PMI also did not demonstrate that IQOS, as actually used by consumers, would ‘benefit the health of the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products,’ of whom AYA are a major group (table 1). For example, it is widely established that AYA are most likely to use flavoured tobacco products, as we have seen with e-cigarettes, little cigars, smokeless tobacco, and hookah.^{19 22 33–41} IQOS HeatSticks currently come in three flavours, Marlboro HeatSticks, Marlboro Smooth Menthol HeatSticks and Marlboro Fresh Menthol HeatSticks. PMI was negligent in their review of the existing literature which shows that exposure to flavour-focused tobacco marketing and reduced risk claims attract AYA never-smokers to initiate tobacco use.^{19 22 33–42} While PMI’s application is silent on whether or not there will be more flavours of IQOS in the future, tobacco companies have considerable and well-documented experience developing and using flavours to increase the appeal of cigarettes, e-cigarettes, cigars, and smokeless tobacco to young people.^{39 41 43–47} Given this history,^{39 41 43–47} knowing that the flavoured and menthol products appeal to AYA <<PLEASE ADD REFS 19, 22, 33–41 HERE >>, it is highly likely that PMI will apply this expertise to IQOS <<PLEASE DELETE THESE REFS HERE>> .^{11 13 15–27 33 35–42 48}

Finally, PMI did not provide sufficient evidence concerning perceptions of HTP products, including potential adolescent, young adult and adult consumers’ beliefs about the MRTP claims, health risks, and cessation claims. There is an extensive literature showing that whether or not there is evidence of a product (most notably e-cigarettes) being safer than combustible cigarettes, if adolescents believe a product is safer (i.e., in the absence of clear evidence and consistent warnings), they are more likely to try and use the product which is an undesired population-level outcome (table 1).^{15 18 25 49} <<PLEASE ALSO ADD REF 48 TO THIS LIST>> For example, many e-cigarette users (including AYA who have not smoked conventional cigarettes and those who are at low risk of smoking cigarettes) started using e-cigarettes

because they perceived them as less harmful (i.e., 'reduced risk') compared with cigarettes.^{15 16 18 21 49 50} This could be explained, at least in part, by how e-cigarettes were marketed online.^{26 51} Websites that compared cigarettes with e-cigarettes stated that e-cigarettes were cleaner (95% of the websites), cheaper (93% of the websites), could be used to circumvent indoor clear air policies (71% of the websites), and could aid in smoking cessation (64% of the websites).⁵² These data suggest that marketing strategies for IQOS that could reduce perceptions of harm are likely to increase appeal to AYA. In fact, PMI in their 'IQOS Brand Voice Guidelines' is already marketing HTP as cleaner than cigarettes and states as an 'upside' to using their product: 'It produces less of a smell and no ash, so it's less invasive'. In Japan and Switzerland, the marketing was focused more on cleanliness and 'Clinical purity,' rather than direct claims on health benefits or reduced health risks.⁵³ In Canada,⁵⁴ PMI is promoting IQOS on their own cigarette packs saying 'Why burn tobacco when you can heat it? Real tobacco. Free of Smoke & Ash.'

DISCUSSION

PMI's application to the FDA to market IQOS as a MRTP in the USA ignores the likely effects IQOS and its marketing may have on AYA. PMI fails to provide a sufficiently comprehensive view of how marketing IQOS would benefit the health of the population as a whole and would significantly reduce harm and the risk of tobacco-related disease. PMI failed to provide adequate evidence concerning the effect that IQOS and its marketing will have on the likelihood that *non-users* (including never users and former tobacco products users) will start using the product bearing the proposed marketing claims. There are several problems with the evidence that was presented in PMI's application.

Behavioural intentions are a poor proxy for actual tobacco use behaviour among AYA

PMI used behavioural intentions as a proxy to predict MRTP use behaviours, claiming that the effect of IQOS on initiation among non-users could not be assessed in a premarket setting. However, the literature clearly shows that intentions are a poor proxy for actual behaviour, especially among adolescents.^{8-12 55 56} While adolescents may not have an active plan or intention to use tobacco, they often find themselves in situations in which they would consider using even though they were originally committed to avoiding tobacco. Such willingness to use tobacco is a much better predictor of tobacco use than intentions and should be used in studies examining whether and why an adolescent would use any tobacco product.^{12 55 57} Hence, not only is it incorrect to claim the impact of marketing cannot be assessed, especially considering PMI is already engaged in marketing IQOS around the world,^{1 58} it is also incorrect to assume intentions are the primary drivers of behaviour, especially for adolescents.

Existing independent research studies on other tobacco products should have been presented

Companies are expected to provide evidence of population-level harms and benefits that could result from their MRTP application being reviewed by the FDA. Because those under age 18 are part of the population (and usually their initiation of the product results from actions requested in applications such as the instant MRTP application by PMI) and would be affected by population-level harms, the FDA unquestionably needs information on how those under 18 could be affected by any action resulting from an MRTP application.

Still, PMI cited no studies conducted among adolescents younger than 18, effectively ignoring the fact that most tobacco product use begins before age 18.⁵⁰ There is no reason to expect that initiating IQOS would be any different, particularly in light of the fact that levels of other tobacco product use, including e-cigarettes, are highest among AYA.^{42 59-63} While neither PMI nor any other tobacco company should be permitted to conduct research on youth below the legal age for tobacco use (21 to be conservative) because the companies could use the information to design marketing campaigns to attract them to their products, it is not credible for PMI to argue that it does not know about or has not reviewed the literature on adolescents' use of other tobacco products, including e-cigarettes. Instead, PMI could conduct and present findings from a comprehensive literature review to inform their conclusions. There is a rich evidence-base of studies conducted among adolescents, independent of the tobacco industry, that PMI failed to review, including data on current, former and non-users of cigarettes.^{11 13 15-18 21-27 33-42 57} That will help us understand adolescents' intentions and willingness to use novel, non-cigarette tobacco products analogous to IQOS.

Appeal to adolescents of devices with flavours and high-tech look should have been addressed

Adolescents' decisions to adopt use of any tobacco product are based on several considerations, including whether the product appeals to them; the product's flavour, smell and taste; the product's perceived harm or reduced harm; and the ease and location of use.^{15 16 18 25 29 64-66} Just as e-cigarettes, particularly the JUUL-style, promoted with a modern, high-tech image and harm reduction and 'smokeless' messages, appeal to adolescents, it is likely that IQOS, marketed in a similar manner, will also appeal to adolescents. It is especially concerning that the IQOS packaging and retail stores as shown in figures 1-3 closely mimic Apple's iPhone and other savvy, high-tech electronic products which might increase appeal to AYA never-smokers.

Flavour or 'taste' is one of the most commonly used marketing techniques to entice AYA to use a product.⁶⁷ In particular, sweet and salty flavours are used to promote food (mostly candy and snacks) to children and exposure to flavoured products and ads for such products is positively associated with AYA consumption.^{40 68 69} Research on other products such as cigars,^{70 71} e-cigarettes,^{16 34 38} smokeless tobacco^{50 72} and waterpipe^{73 74} comports with these findings.^{36 68 70} Flavours are frequently used in online e-cigarette marketing and boost user interaction and positive emotion.^{23 75} Further, compared with ads for unflavoured tobacco products, flavoured e-cigarette advertisements elicit greater appeal and interest in buying and trying e-cigarettes.⁴⁰ The appeal of ads for flavours has been linked to rapid and persistent adoption of e-cigarettes among AYA; and 75% of US AYA stated they would not use e-cigarettes without flavours.⁷⁶ Questions regarding the appeal of IQOS flavours to AYA who have never used a tobacco product were left unanswered in PMI's MRTP application.

Concept of 'switching completely' poorly understood

PMI's proposed marketing claims are contingent on the phrase 'switching completely from cigarettes to IQOS' which is incongruent with PMI's own evidence regarding how consumers will *actually use* IQOS, as well as existing epidemiological evidence for related products. Epidemiological evidence suggests that for other non-cigarette tobacco products, switching completely has been an uncommon occurrence. Among US adults who use

e-cigarettes, 75%–82% use it in combination with at least one other form of combustible tobacco.^{48–77} Similarly, AYA smokers who use novel tobacco products often use two or more kinds of tobacco products concurrently.^{42 63 78–82}

Evidence of AYA understanding and perceptions should have been presented

PMI failed to provide evidence concerning AYA understanding and perceptions of HTP products, including labelling, marketing, advertising, MRTP claims, health risks, and cessation. Tobacco use studies among AYA show perceptions that e-cigarettes present less risk than cigarettes predicts e-cigarette use, even among non-smokers.^{15–18 34 42 60 83–93} Adolescents report believing that e-cigarettes are safer than cigarettes, can help people quit smoking conventional cigarettes and contain no or just limited amounts of nicotine.^{15–18 34 42 60 83–93} Adolescents also consider e-cigarettes to be trendier, more prevalent and more acceptable than conventional cigarettes.^{15–18 34 42 60 83–93}

<<PLEASE JUST INCLUDE REFS 15-18 HERE; DELETE THE OTHERS FOR THIS LIST ONLUY>> The lowest perceptions of harm and the most positive attitudes regarding e-cigarettes have been reported among adolescents who have used e-cigarettes.^{10 16 25 64 88 94 95}

Given the similarities between IQOS and e-cigarettes, including the newer JUUL-style (electronic, hi-tech and claims of reduced harm, a better alternative to cigarettes, no ‘smoke’), it is reasonable to hypothesise that IQOS will be popular among AYA because they will make similar assumptions about the risks associated with IQOS, and will be willing to initiate and use IQOS. Perceptions of IQOS and e-cigarettes might be very different due to the differences in products; however, at least from risk perception perspective, IQOS studies themselves show similar levels of perceived risk for e-cigarettes and HTP.

Finally, with any reduced risk claims made by the tobacco industry, it is important to consider whether the evidence is from *independent studies*, versus studies conducted by the industry or influenced or paid for by that industry. Independent studies, as well as an accurate assessment of the extant literature, will better inform whether HTP products will influence tobacco use and misperceptions, with the ultimate goal of improving public health.

LIMITATIONS

In the absence of a research base for IQOS in the USA, we relied on analogous data from e-cigarette research. While an imperfect analogy, we feel the global regulatory atmosphere that largely treats HTP and e-cigarettes similarly, the parallels in devices such that both HTP and e-cigarettes heat and aerosolise tobacco or tobacco components and/or flavours for inhalation by the user, and the similar marketing techniques for HTP and e-cigarettes allow for reasonable analogies to be made and conclusions to be reached.

CONCLUSION

When evaluating whether IQOS or any HTP or new tobacco product should be allowed to come to market, one must consider that adolescents who otherwise would not have used any tobacco product might find the new product appealing, and thus likely will initiate tobacco use with this tobacco product. This is especially likely given AYA's attraction to flavoured tobacco products, the appeal of novel and technology-centric products among adolescents and the tendency for the public at large, including AYA, to misinterpret reduced harm claims. PMI completely ignored all the evidence that flavoured products attract AYA and

that they will find the IQOS flavours appealing and therefore will be more likely to use them. The tobacco industry could and should use data available from experiences with other tobacco products, such as with e-cigarettes, that have been collected completely independently of the tobacco industry, to draw reasonable inferences about how the HTP product would affect AYA. No regulatory authority throughout the world should allow any new tobacco product to come to market without solid, independent evidence clearly showing that the new product will not appeal to AYA, misinform AYA about risks or encourage use of multiple tobacco products. Failing to account for these effects make it possible that the overall population impact of introducing new HTP (and other new tobacco products) would be negative even if they pose lower individual risks compared with smoking a cigarette.

What this paper adds

- ▶ This is the first independent analysis examining whether Philip Morris International's (PMI) proposed marketing of their new IQOS heated tobacco products (HTP) in the USA will appeal to adolescents.
- ▶ PMI's own studies failed to provide evidence that reduced risk perception among youth will not lead to increased use of these products.
- ▶ PMI did not refer to an important body of existing, independent research that could influence their conclusions.
- ▶ Based on PMI's research and evidence from other non-cigarette tobacco products (e.g., e-cigarettes), HTPs should not be labelled or sold as a modified-risk tobacco product.

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IQOS labelling will mislead consumers

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ABSTRACT

Background Philip Morris International (PMI) continually expands and diversifies their nicotine product portfolio, which includes IQOS, a heated tobacco product. In December 2016, PMI filed a modified risk tobacco product (MRTP) application with the US Food and Drug Administration (FDA), seeking authorisation to market IQOS in USA with three claims of reduced harm: 'switching completely from conventional cigarettes to the IQOS system...' (1) 'can reduce the risks of tobacco-related diseases;' (2) 'significantly reduce[s] your body's exposure to harmful or potentially harmful chemicals;' and (3) 'presents less risk of harm than continuing to smoke cigarettes.' Consumers may misunderstand what is meant by 'switching completely'.

Methods We critically reviewed study reports submitted to FDA by PMI in support of proposed marketing claims in its MRTP application for IQOS and focused on the statement that switching completely to IQOS reduces risk.

Results We found deficiencies with evidence provided by PMI supporting their assertions that: current smokers will understand what is meant by the phrase 'switching completely'; the proposed claims will not decrease smokers' intentions to quit; and IQOS users will in fact 'switch completely' from smoking cigarettes to using IQOS. The studies and measurement instruments employed by PMI suffer from design flaws and their reporting of associated findings is misleading.

Conclusion Consumers will not understand the condition of the claims—that they must quit using cigarettes completely to achieve the inferred health benefits of IQOS. Rather, they are likely to misunderstand the unsupported claims of reduced risks to mean IQOS are harm-free.

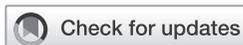
INTRODUCTION

As tobacco companies increasingly expand and diversify their nicotine product portfolio,¹ new heated tobacco products (HTPs), also known as heat-not-burn products, that heat modified cigarettes to produce an aerosol for inhalation have been introduced worldwide,²⁻⁴ including Philip Morris International's (PMI's) IQOS.²⁻⁵ As of February 2018, PMI's marketing in several countries claims that because IQOS heats tobacco sticks, not burns them, it poses lower risks than regular combustible cigarettes. These claims have already been made explicitly on PMI's website and in interviews with the media.^{6,7} In December 2016, PMI filed a modified risk tobacco product (MRTP) application with the US Food and Drug Administration (FDA), seeking authorisation to market IQOS in USA with three claims, each addressing a particular section

of FDA regulation for MRTP applications (see table 1)—two focused on claims of reduced risk, and one focused on the claim of reduced exposure. These claims are provided to participants by PMI in its studies as 'Available Evidence to Date' to discern consumer perceptions of the proposed claims in light of 'warnings' also provided by PMI.

Tobacco companies' history of manipulating scientific studies and interpretation of findings makes it imperative that independent scientists examine the study designs, underlying data and conclusions from all tobacco industry-drive studies, including those involving IQOS and MRTP claims.⁸ It is also necessary to bring in research from other fields or with other tobacco products to help inform the regulatory agencies on the potential effects of the new tobacco products and proposed marketing claims. For example, to help inform its decision regarding IQOS, FDA would be well served to consider the recent and well-documented experience with e-cigarettes. In particular, exposure to electronic cigarette ('e-cigarette') advertisements has been shown to cause increases in smoking urges among adult former and current smokers, reduce adolescent never-smokers' perceived risks of regular cigarettes, and to be associated with increased odds of e-cigarette and cigarette use in both cross-sectional and longitudinal studies.⁹⁻¹⁰

In USA, FDA may issue a *risk modification order* permitting an MRTP to be commercially marketed only if the applicant has demonstrated that the product, as it is actually used by consumers, will: (1) Significantly reduce harm and the risk of tobacco-related disease to individual tobacco users. (2) Benefit the health of the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco (Tobacco Control Act section 911(g)(1)). If scientific evidence is not currently available to meet these standards, FDA may issue an *exposure modification order* permitting the marketing of an MRTP that claims to reduce or eliminate exposure to a substance if reduced morbidity or mortality is likely to be demonstrated in future studies and it would 'promote the public health' (Tobacco Control Act section 911(g)(2)). The labelling claims made for MRTPs seeking an exposure modification order must be limited to an explicit or implicit representation that: (1) The tobacco product or its smoke does not contain a substance. (2) The product or its smoke contains a reduced level of a substance. (3) The product presents reduced exposure to a substance in tobacco smoke (Tobacco Control Act section 911(g)(2)(A)(ii)). (See supplementary appendix A for details).



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Table 1 Summary of the text provided to participants in Phillip Morris International's (PMI's) studies conducted to evaluate consumer understanding and associated behavioural effects of proposed claims for the IQOS heated tobacco product

Study: THS-PBA-05-RRC-US ¹⁷ (n=2255)	Study: THS-PBA-05-RRC2-US ¹⁸ (n=2247)	Study: THS-PBA-05-REC-US ¹⁹ (n=2272)
Available evidence to date: claim 1* <ul style="list-style-type: none"> ▶ The iQOS system heats tobacco but does not burn it. ▶ This significantly reduces the production of harmful and potentially harmful chemicals. ▶ Scientific studies have shown that switching completely from conventional cigarettes to the iQOS system can reduce the risks of tobacco-related diseases. 	Available evidence to date: claim 2* <ul style="list-style-type: none"> ▶ Switching completely to iQOS presents less risk of harm than continuing to smoke cigarettes. 	Available evidence to date: claim 3* <ul style="list-style-type: none"> ▶ The iQOS system heats tobacco but does not burn it. ▶ This significantly reduces the production of harmful and potentially harmful chemicals. ▶ Scientific studies have shown that switching completely from cigarettes to the iQOS system significantly reduces your body's exposure to harmful or potentially harmful chemicals.
Important warning:† <ul style="list-style-type: none"> ▶ Reduced risk does not mean no risk. The best way to reduce your risk of tobacco-related diseases is to completely quit tobacco use. ▶ HeatSticks contain nicotine, which is addictive. ▶ Using the iQOS system can harm your health. 	Important warning:† <ul style="list-style-type: none"> ▶ Less risk of harm does not mean no risk of harm. The best way to reduce your risk of tobacco-related diseases is to completely quit tobacco use. ▶ HeatSticks contain nicotine, which is addictive. 	Important warning:† <ul style="list-style-type: none"> ▶ It has not been demonstrated that switching to the iQOS system reduces the risk of developing tobacco-related diseases compared with smoking cigarettes. ▶ HeatSticks contain nicotine, which is addictive. ▶ Using the iQOS system can harm your health.

Source, PMI Research and Development. 6.4 *Consumer Understanding and Perceptions*. 2015. Available at: https://www.accessdata.fda.gov/Static/widgets/tobacco/MRTP/PMI/PMP_MRTPA_FDA-2017.zip

*'Available evidence to Date'. Term used by PMI to refer to 'caveats on disease risk and addiction included in PMI Warnings'⁶

†'Important Warning'. Term used to refer to proposed warnings developed by PMI.

In making the determination of whether to issue either a risk modification or an exposure modification order, FDA must take into account the net 'benefit to the health of the population as a whole', considering 'the increased or decreased likelihood that existing users of tobacco products who would otherwise stop using such products will switch to the tobacco product that is the subject of the application' and 'the increased or decreased likelihood that persons who do not use tobacco products will start using the tobacco product that is the subject of the application' (Tobacco Control Act section 911(g)(4)). For an exposure modification order, the applicant must also demonstrate that actual consumer perception tests show that, 'as the applicant proposes to label and market the product, consumers will not be misled into believing that the product – (I) is or has been demonstrated to be less harmful; or (II) presents or has been demonstrated to present less of a risk of disease than one or more other commercially marketed tobacco products' (Tobacco Control Act section 911(g)(2)(B)(iii)).

Therefore, to obtain a risk modification order under US law allowing PMI to market IQOS with its proposed labelling and advertising claims, PMI must present scientific data demonstrating that switching completely from conventional cigarettes to IQOS significantly reduces harm and the risk of tobacco-related diseases. To obtain an exposure modification order allowing PMI to market IQOS with its proposed labelling and advertising claim, PMI must demonstrate that switching completely from cigarettes to IQOS significantly reduces consumers' exposure to harmful substances, and that actual consumer perception studies show that consumers understand that the product has *not* been demonstrated to be less harmful or present less risk of disease.

The goal of this paper is to critically review the reports on the studies PMI submitted as part of its MRTP application for IQOS to support their proposed marketing claims, with a particular focus on the statements that switching completely to IQOS reduces risk.¹¹

METHODS

Beginning in May 2017, the FDA made most of PMI's MRTP application materials for their HTP available online on a rolling basis for public comment. Most of the materials, including PMI's actual studies, were not publicly available until November 2017. We reviewed and analysed PMI's IQOS MRTP application

materials and researched the relevant available literature to evaluate the evidence to support PMI's claims. We reviewed sections in the application that are pertinent to the product advertisements, warning labels and PMI's reports of relevant studies. We examined these application documents to establish what PMI provided as evidence in support of their MRTP application and sought to determine whether such evidence was sufficient. To determine sufficiency, we reviewed study designs, reported study limitations, and determined whether conclusions were supported by the data. Methods used by PMI in their studies are discussed below within the context of the MRTP application claims.

We examined PMI's studies for evidence that tobacco consumers and non-consumers will accurately understand the risks of IQOS as conveyed by PMI's proposed claims and understand what is meant by 'switching completely'; that IQOS claims will not affect combustible tobacco users' intentions to quit; and that combustible tobacco users will completely switch to IQOS (see table 2 for overview of PMI studies).

RESULTS

PMI did not provide sufficient evidence of consumer understanding of the concept of switching completely

PMI conducted quantitative studies to test comprehension of and risk perceptions associated with their proposed modified risk claims (section 6.4).¹¹ Table 1 delineates PMI's designated study numbers, PMI's claims and what PMI termed 'available evidence' that were shown to participants. Studies were conducted among US adult consumers (n=6774 total for the three studies), who were stratified into five groups: smokers with no intention to quit, smokers with an intention to quit, former smokers, never smokers and never smokers from the legal smoking age to age 25 years. Participants were then randomised by stratum and exposed to different combinations of PMI proposed claims and warnings or to the current Surgeon General's warnings mandated for cigarettes: (1) 'Smoking causes lung cancer, heart disease, emphysema, and may complicate pregnancy;' (2) 'Quitting smoking now greatly reduces serious risks to your health;' (3) 'Smoking by pregnant women may result in fetal injury, premature birth, and low birth weight;' and (4) 'Cigarette smoke contains carbon monoxide'. Table 3 presents outcome measures used in these studies.

Table 2 Overview of studies conducted by Philip Morris International (PMI) in support of its MRTP application

Study name	Methodology	Study year	Stated study goal
THS-PBA-01-US	Qualitative and quantitative	December 2012–June 2014	Development and validation of psychometric instruments for 'Risk Perception' and 'Intent to Use for tobacco products'
THS-PBA-02-US	Qualitative	October–December 2013	Testing 9* potential 'plain text'† messages
THS-PBA-03-US	Quantitative	October–December 2014	Testing three potential 'plain text' messages selected from THS-PBA-02-US
THS-PBA-04-US	Qualitative	December 2014	Testing five potential branded‡ communication materials with claims selected from THS-PBA-02-US
THS-PBA-05-RRC-US	Quantitative	July 2015	Testing three branded communication materials with claim #1 'Reduced risks of tobacco-related diseases'
THS-PBA-05-RRC2-US	Quantitative	September 2015	Testing three branded communication materials with the claim #2 'Reduced risk of harm'
THS-PBA-05-REC-US	Quantitative	December 2015	Testing three branded communication materials with the claim #3 'Reduced body's exposure to harmful and potentially harmful chemicals'

*The table in the PMI document mentions 9 messages, but there were actually 13 different messages for phase I because there are two versions of some (A1, A2, B, C1, C2, D and so on). Phase II of the study tested seven messages.

†'Plain text' message describes the information communicated on the product.

‡Branded communication materials were brochure, pack, and direct mail piece with the IQOS commercial name and the Tobacco Sticks as HeatSticks with the Marlboro Brand.

MRTP, modified risk tobacco product.

While PMI emphasised that the majority of participants were able to select the 'correct' statement (indicating that the risk of tobacco-related diseases can be reduced by completely switching from cigarettes to IQOS), PMI did not test whether participants understood what 'switching completely' meant. PMI reported that after seeing the proposed claims, 62%–78% of all participants were able to identify the 'correct' statement, which indicated that the risk of tobacco-related diseases can be reduced by completely switching from cigarettes to IQOS. However, this question did not measure whether participants understood the phrase 'completely switching', rather it tested recognition of the terms 'reduced' and 'eliminates'; all response options included the phrase 'completely switch'. Still, PMI interpreted this finding to indicate participants understood the 'reduced' risks of IQOS compared with regular cigarettes. Further, to assess perceptions of their claims and the IQOS product, PMI created and used a new 18-item Perceived Health Risk Scale, a 7-item Perceived Addiction Risk Scale and a 2-item Perceived Harm to Others Scale. PMI reported that HTP was on average '8 and 22 points lower than conventional cigarettes on the 0 to 100 perceived health risk scale'.¹² Hence, PMI failed to demonstrate at least two important factors that FDA deemed critically important to its review of MRTP applications: (1) Whether consumers fully 'understand the modified risk claims and the significance of the information in the context of one's health'. (2) Whether consumers truly understand 'the health risks of using the product.'

PMI's studies of whether smokers will completely switch from cigarettes to IQOS

Premarket human behaviour studies (design and results)

PMI's proposed marketing claims were all contingent on the phrase 'switching completely' from cigarettes. PMI's application drew evidence from two groups of premarket studies in which adult daily cigarette smokers were provided with IQOS *HeatSticks* and asked to record their tobacco use over time. The 'Whole Offer Test' (WOT) studies were conducted in five countries (Japan, Italy, Germany, Switzerland and South Korea) and the study THS-PBA-07-US took place in USA (table 4).

Participants were instructed to record each instance of using IQOS or smoking a cigarette in an electronic (THS-PBA-07-US) or pencil-and-paper (WOT) diary. The WOT studies ran for 4 weeks; THS-PBA-07-US ran for 6 weeks. Participants were given access to IQOS free of charge and, presumably, purchased any cigarettes at their own expense.

The studies examined several behavioural patterns, based (presumably, but not explicitly) on the percentage of diary entries made for use of a cigarette or IQOS. There was no category for 'switching completely' from cigarettes to IQOS. The 'exclusive' IQOS category included individuals at 95%–100% IQOS use, not necessarily completely switched, and not counting tobacco products other than IQOS and cigarettes. Behaviours beyond 6 weeks, when *HeatSticks* were no longer available for free, were not examined.

In these PMI studies, switching from cigarettes to 'exclusive' (ie, 95%–100%) IQOS use was rare (table 5). In THS-PBA-07-US, among adult daily cigarette smokers who completed the 6-week follow-up period, only 6% (58/968) of participants achieved 'exclusive' IQOS use, defined by PMI as using IQOS ≥ 100 times during the study and having *HeatSticks* comprise $\geq 95\%$ of total recorded amount of cigarettes smoked and *HeatSticks* used in week 6 (table 4). Only 3% (15/465) of study completers who also kept valid diaries throughout achieved exclusive use (per-protocol analysis), and among all completers who reported using IQOS ≥ 100 times, just 16% become exclusive users. Occurrence of exclusive IQOS use among study completers was similarly uncommon in other settings: Japan (13%), Italy (5%), Germany (8%), Switzerland (4%) and South Korea (15%).

Premarket human behaviour studies (limitations)

The WOT and THS-PBA-07-US studies did not provide sufficient evidence that a substantial portion of adult cigarette smokers will completely switch to IQOS, first and foremost because the outcome 'switching completely' (ie, 100% IQOS use) was not reported. Additional limitations deserve mention. For example, participants were given access to IQOS *HeatSticks* free of charge but, presumably, purchased cigarettes, giving an economic advantage to IQOS over cigarettes that would not be present in a real world setting.

No efforts to validate the accuracy of the self-reports were described. There was no comparison group to evaluate how keeping a daily tobacco diary, regardless of access to IQOS, would affect cigarette consumption. Such validation is important, as it is well documented that individuals change their behaviour when asked to keep a running log, such as food diaries.^{13 14} Given that approximately half the sample did not use the diaries to document tobacco use for the duration of the study, the validity of estimates based on the full sample is questionable.

PMI reported that the proportion of participants switching back to cigarettes from exclusive IQOS use was 'very low'. However, participants were not classified as switching back to

Table 3 Outcome measures in quantitative studies

Construct	Instrument	Example questions
Intent to use	The Intent to Use Questionnaire (ITUQ) ▶ Intention to try (ie, to sample at least once; two items) ▶ Intention to use (ie, for continued usage; two items) (Answers on a 6-point scale from 'Definitely Not' to 'Definitely')	Based on what you know about IQOS, how likely or unlikely are you to try IQOS? If you try IQOS and like it, and taking into consideration the prices that are shown on the material, how likely or unlikely are you to use IQOS regularly?
Change in intention to quit smoking	Yes/no questions based on Prochaska and DiClemente's Stages of Change model ³¹ measured before and after exposure to IQOS message to determine change in intention to quit smoking (four items—two for smoking, two for all tobacco products)	Are you seriously considering quitting smoking within the next 6 months? Are you planning to quit smoking in the next 30 days?
Comprehension	1. 'Global comprehension': overall comprehension of the IQOS message on exposure to harmful chemicals and risk of tobacco-related diseases of using IQOS. 2. 'Specific comprehension': comprehension of three specific parts of the IQOS message: the Intended Users Statement, Evidence Statement and Warning Statement. Both types of comprehension were assessed with multiple-choice questions, five response options were presented, with one correct option, three incorrect options and an option for 'don't know'.	Next, thinking about all of the information on the IQOS material, completely switching from conventional cigarettes to IQOS: a. Can increase the risk of tobacco-related diseases. b. Can reduce the risk of tobacco-related diseases (correct). c. Has the same risk of tobacco-related diseases. d. Can eliminate the risk of tobacco-related diseases. e. Don't know. What happens to tobacco when IQOS is used? a. It is burned. b. It remains at room temperature. c. It is cooled. d. It is heated but not burned (correct). e. Don't know.
Risk perception	The Perceived Risk Instrument-Personal Risk (PRI-P) comprised of two domains, each measured by a unidimensional scale: 1. Perceived Health Risk 18-item Scale 2. Perceived Addiction Risk 7-item Scale 3. Perceived Harm to Others (two separate questions) Answers were no risk, low risk, moderate risk, high risk, very high risk and don't know, and were later converted into a 0 to 100 scale (0=no risk and 100=very high risk)	If you were to start using IQOS, what do you think would be the risk, if any, to you personally of getting the following (sometime during your lifetime) because you use IQOS...losing some sense of taste, having heart disease, an earlier death, having sores of the mouth or throat, and so on. If you were to start using IQOS, what do you think would be the risk, if any, to you personally of experiencing the following because you use IQOS... being unable to quit cigarettes, feeling like you have to smoke cigarettes, and so on. If you were to start using IQOS, what do you think would be the risk, if any, to others because you use IQOS... harming others through your secondhand smoke, harming unborn baby.

Source, Adopted from Table 17 in the Executive Summary, p. 121.¹⁵

smoking (cigarettes) unless cigarettes comprised 70% of products used, and participants first had to be classified as 'exclusive' IQOS users, leaving only a fraction of the observation period remaining to switch back. Nonetheless, PMI concluded that IQOS 'has the potential to completely 'switch' a sizeable proportion of participants',¹⁵ despite the fact that in these PMI studies, an unknown percentage (but no more than 3%–15%) of adult cigarette smokers with access to IQOS free of charge switched completely. Together, the potentially misleading and arbitrary product use definitions, non-validated measurement methods, lack of a comparison group, and differential financial cost between IQOS and cigarettes cast doubt on the real world relevance of these PMI behavioural studies, even had the occurrence of switching completely been more common.

PMI summary reports misrepresent their own data on the effects of message exposure on changing intentions to quit smoking

The executive summary of the MRTP application, referring to the results stated in the executive summary of PMI's MRTP application, reported the effect of the proposed claims on smokers' intentions to quit smoking cigarettes, stating that: 'most smokers did not change their intentions to quit, maintaining positive responses to quitting in a range of 83% to 97% across all arms of the study'. However, the study tables showed that PMI designated participants who lowered their intentions to quit from planning to quit in the 'next 30 days' to planning to quit within 'next 6 months' as 'did not change their intentions to quit'.¹⁶ The disaggregated data show that among those who had

intentions to quit in the next 30 days at baseline, between 7% and 24% reduced their intentions to 'quit within next 6 months' and an additional 3%–10% said they no longer plan to quit. Among those who planned to quit in the next 6 months at baseline, 5%–17% indicated they no longer had intentions to quit (see tables 4 and 6 for detailed findings). Similarly, the executive summary for studies THS-PBA-05-RRC, THS-PBA-05-RRC2 and THS-PBA-05-REC stated that smokers with intentions to quit 'did not appreciably change their stated intentions to quit smoking...' and listed proportions of participants who 'stated a change in intentions' between 3.2% for increased intentions and 11.8% for decreased intentions.^{17–19} The detailed data in the tables show that among smokers who planned to quit within 30 days, after exposure 3%–24% deferred quitting to the next 6 months, and an additional 0%–10% changed to stating they never planned to quit. Further, detailed study results found in PMI results tables show much greater reductions in intentions to quit following exposure to IQOS messaging when compared with the results PMI emphasised in the executive summary.

PMI's perceived risk measures were flawed and incomplete

PMI's perceived risk instrument was flawed and the choice of their risk perception questions was seemingly guided by tobacco companies' goals rather than measures of validity.⁸ In their Instrument, PMI measured absolute perceptions of risk for each product (separately for cigarettes, e-cigarettes and IQOS; for example, 'If you were to start [smoking/using e-cigarettes/using IQOS], what do you think would be the risk, if any, to you personally of experiencing the following because you [smoke

Table 4 Premarket human behaviour studies

	Duration	Participants started	Participants completed	Switch to 'Exclusive' IQOS use*	IQOS use category in the final study week (completed participants)				
					Exclusive† IQOS use	Predominant‡ IQOS use	Combined§ IQOS+cigarettes	Predominant¶ cigarette use	Exclusive** cigarette use
THS-PBA-07-US									
Analytical sample††	6 weeks	1106	968	6.0%	7.5%	7.0%	22.4%	28.2%	34.5%
On-protocol sample‡‡	6 weeks	1106	465	3.2%	6.5%	5.2%	20.8%	32.9%	34.6%
WOT - Japan									
Included sample§§	4 weeks	718	638	13.2%	13.6%	16.1%	32.3%	27.7%	10.2%
WOT - Italy									
Included sample§§	4 weeks	571	535	4.7%	5.2%	6.9%	37.9%	39.3%	10.7%
WOT - Germany									
Included sample§§	4 weeks	443	377	7.7%	8.5%	11.4%	27.3%	24.7%	28.1%
WOT - Switzerland									
Included sample§§	4 weeks	516	416	3.8%	4.3%	5.5%	39.4%	30.5%	20.2%
WOT - South Korea									
Included sample§§	4 weeks	936	843	15.3%	15.7%	21.5%	36.3%	17.3%	9.3%

*Recorded use of ≥100 *HeatSticks* during the study and *HeatSticks* comprised ≥95% of total cigarettes and *HeatSticks* recorded in the final week.
 †Of cigarettes and *HeatSticks* recorded, *HeatSticks* comprised ≥95% of total.
 ‡Of cigarettes and *HeatSticks* recorded, *HeatSticks* comprised ≥70% but <95% of the total.
 §Of cigarettes and *HeatSticks* recorded, *HeatSticks* comprised ≥30% but <70% of the total.
 ¶Of cigarettes and *HeatSticks* recorded, *HeatSticks* comprised ≥5% but <30% of the total.
 **Of cigarettes and *HeatSticks* recorded, *HeatSticks* comprised <5% of the total.
 ††Analytical sample restricted to a subset of enrolled participants who met inclusion criteria and recorded ≥1 cigarette use during the 1-week baseline run-in period and ≥1 IQOS *HeatStick* use during the 6-week observation period (excludes 262 of 1368 initially enrolled participants).
 ‡‡Per-protocol sample restricted to participants who also documented tobacco use 39 days of the 42-day observation period and did not report IQOS use exceeding number of *HeatSticks* supplied by >5% or 20 units.
 §§Sample restricted to participants who completed 26 of the 28 daily tobacco use diary entries (ranges from 81% to 93% of participants who were eligible to begin the 4-week studies based on willingness to use IQOS).
 n/a=not applicable; nr, not reported; WOT, whole offer test.

cigarettes/use e-cigarettes/use IQOS]...'), rather than asking direct comparative questions (eg, 'Are (IQOS products) less harmful/equally as harmful/more harmful than (cigarettes)?'). A better approach would have been to use both types of questions. Not doing so unavoidably biased results. Further, PMI did not provide any information on how a particularly relevant population—youth—will perceive these claims.

PMI failed to include a control group in studies testing effects of claims and marketing materials

PMI's designs to assess perceptions and intentions to quit did not include a control group. A control group with no exposure to IQOS information or to marketing material without any modified risk claim but with a strong health-related warning would have allowed PMI to draw conclusions on the effects of the

messages on perceptions of risk of IQOS, and on intent to use and intent to quit smoking. Without a control group it is impossible to tell whether the messages had an effect on intentions to quit, if the effect was a result of repeated testing, or if using messages without modified risk claims may have prevented or otherwise altered the reported reduction in intentions to quit smoking.

DISCUSSION

We found deficiencies with the evidence provided by PMI in support of their assertions that current smokers will understand what is meant by the phrase 'switching completely'; that IQOS users will not in fact 'switch completely' from smoking cigarettes to using IQOS and may become 'dual users' of IQOS and cigarettes; and that their proposed claims will not decrease smokers' intentions to quit smoking. Further, the studies and measurement instruments employed by PMI suffer from design flaws and their reporting of associated findings is misleading.^{16 20 21}

In their MRTP application, PMI included three proposed claims of reduced harm, risk and exposure that assert 'switching completely' from cigarettes to IQOS bestows health benefits.¹¹ According to the Tobacco Control Act section 911(g)(2)(B)(iii), in MRTP applications for exposure modification orders, the applicant is required to demonstrate that consumers will not be misled by claims in labels or advertising. In their MRTP application materials, PMI failed to provide evidence that current smokers will understand what is meant by the phrase 'switching completely'.

PMI did not provide adequate evidence of how and if people understood the phrase 'completely switching', as used in their claims. Instead, their research only tested recognition of the terms 'reduced' versus 'eliminates', because the questionnaire

Table 5 Postexposure intentions to quit among smokers who intend to quit within the next 6 months at baseline

Row #	Study	Next 6 months	No intention	Increased intentions to quit (next 30 days)
1	PBA-03	79%–90%	5%–17%	0%–5%
2	PBA-05-RRC	80%–89%	7%–18%	0%–6%
3	PBA-05-RRC2	74%–98%	0%–21%	2%–6%
4	PBA-05-REC	76%–92%	7%–19%	0%–5%
5	Overall	74%–98%	0%–21%	0%–6%

Note. Showing proportion of respondents among those who originally reported intention to quit within the next 6 months (100%) and then chose each answer postexposure to PMI proposed claims. The range indicates the lowest and highest numbers among the different messages/arms used in each study. PMI reports data separately for each arm of the study, rather than presenting the average for the whole study.

Table 6 Postexposure Intentions to quit among smokers who intend to quit within the next 30 days at baseline

Row #	Study	Plan to quit in the next 30 days	Plan to quit in the next 6 months	No intention to quit	Total reduction
1	PBA-03	67%–90%	7%–24%	3%–10%	10%–33%
2	PBA-05-RRC	83%–95%	3%–18%	0%–3%	5%–17%
3	PBA-05-RRC2	73%–95%	3%–24%	2%–6%	5%–27%
4	PBA-05-REC	83%–97%	3%–15%	0%–7%	3%–17%
5	Overall	67%–97%	3%–24%	0%–10%	3%–33%

Note. Showing proportion of respondents among those who originally reported intention to quit within the next 30 days (100%) and then chose each answer postexposure to PMI proposed claims. The range indicates the lowest and highest number among the different messages/arms used in each study. PMI reports data separately for each arm of the study, rather than presenting the average for the whole study.

asked, after reading the warning labels of IQOS, whether the respondents think ‘completely switching from conventional cigarettes to IQOS’ results in (1) ‘increase the risk of tobacco-related diseases’, (2) ‘reduce the risk of tobacco-related diseases’, (3) ‘the same risk of tobacco-related diseases’, (4) ‘eliminate the risk of tobacco-related diseases’ (underlines added). There remains considerable concern that IQOS consumers and potential IQOS consumers will not fully understand there is a contingency to PMI’s claim of modified risk—namely, that one must ‘completely switch’ from cigarettes to IQOS to benefit their health.

PMI also failed to test whether people understood that ‘switching completely’ refers to switching away from cigarettes; thus, there is concern that e-cigarette users could interpret the claim to mean switching away from any tobacco product, including e-cigarettes, to a HTP would reduce harm, despite there being no evidence that IQOS are less harmful to health than e-cigarettes.

The claim that switching completely to IQOS could reduce harm and tobacco-related diseases assumes that people who attempt to switch will be successful at cigarette smoking cessation. However, available data suggest that cigarette smokers who try to switch from cigarettes to other tobacco products or who use other tobacco products for smoking cessation are more likely to be nicotine-dependent and experience difficulty with smoking cessation compared with people who do not use these alternative tobacco products.²² Further, PMI ignores evidence that smokers who use novel tobacco products such as e-cigarettes often use two or more tobacco products in combination instead of switching entirely. Indeed, PMI’s own data on IQOS show substantial levels of combined use in their test populations, and epidemiological evidence demonstrates that for other non-cigarette tobacco products, switching completely is not the most common outcome. Among US adults who use electronic cigarettes, 75% to 82% use e-cigarettes in combination with at least one other form of combustible tobacco, and only 20% of e-cigarette users report switching completely from combustible cigarettes. Finally, PMI’s proposed warnings do not specifically inform consumers that continuing to smoke while using IQOS could reduce the likelihood of quitting smoking.^{23 24} As such, PMI’s data do not support their MRTP claim, and instead both data presented by PMI and in the literature base support the idea that introducing any HTP product (including IQOS) will likely be harmful to population health.

Research on e-cigarettes indicates that some dual users of e-cigarettes and combustible cigarettes viewed reduction in smoking as equivalent to quitting, not recognising the need to switch completely.²³ The evidence base showing adult tobacco users have difficulty understanding modified risk ‘warnings’ such as ‘light’ or ‘low tar’ cigarettes is well known, widely accepted and was relied on in formulating the Tobacco Control Act of 2009. Moreover, such messages are also shown to be misinterpreted

by youth.^{25–27} When individuals do not adequately understand warning messages or receive vague messages, they often make assumptions that the tobacco product is safe and are therefore more likely to initiate and/or continue using the product.^{26 28} In fact, the Tobacco Control Act, Section 2, Finding 40 states:

The dangers of products sold or distributed as modified risk tobacco products that do not in fact reduce risk are so high that there is a compelling governmental interest in ensuring that statements about modified risk tobacco products are complete, accurate, and relate to the overall disease risk of the product.

PMI’s studies failed to offer findings that users and potential users of IQOS will not harbour similar misperceptions as has been seen with e-cigarettes and other tobacco products.

PMI also failed to provide evidence that their proposed claims will not decrease smokers’ intentions to quit smoking or that IQOS users will in fact ‘switch completely’ from smoking cigarettes to using IQOS.¹⁵ Instead, the evidence provided by PMI showed that use of both cigarettes and IQOS would be the predominant pattern, rather than switching completely from smoking cigarettes to using the IQOS. The detailed reports for PMI’s studies on the effect of exposure to their proposed warnings on intentions to quit did not present information separately for smokers who had intentions to quit in the next 30 days and those with intentions to quit in the next 6 months at baseline. Rather, they obfuscated findings that actually showed that post-exposure to their proposed warnings, up to nearly a quarter of smokers who planned to quit in the next 30 days at baseline switched to planning to quit within the next 6 months, and up to an additional 10% no longer intended to quit. Similarly, up to 24% of smokers who had planned to quit within the next 6 months at baseline said they were never planning to quit postexposure. In multiple instances, PMI’s MRTP application departs from standard practices in scientific reporting, leaving out important methodological details, using non-standard, non-validated measurement tools and definitions, and summarising findings in misleading ways. For example, in examining whether non-smokers would be interested in using IQOS, PMI inappropriately characterised data from limited qualitative studies as representative of consumer perceptions. In their Perceived Risk Instrument, PMI measured absolute perceptions of risk for each product (separately for cigarettes, e-cigarettes and IQOS), rather than asking direct comparative questions. Past research has found that when risks are measured for products separately, a greater proportion of people perceive alternative tobacco products as less harmful.²⁹ When comparative risk is measured with a direct question, a greater portion of participants respond that alternative tobacco products are equally as harmful as cigarettes.^{29 30} Use of both types of measures is necessary to demonstrate their findings are not simply an artefact of their carefully designed measurement tool.

CONCLUSION

PMI failed to demonstrate that the proposed IQOS claims within their MRTP application, and especially statements regarding 'switching completely' (1) Will be interpreted as meaning that the potential health benefits of IQOS are contingent on one completely quitting cigarettes. (2) Will not result in widespread misperceptions that the IQOS product is a harm-free alternative to combustible cigarettes. (3) Will not lead to substantial product appeal (and subsequent use) among youth, non-smoking adults and former smokers. (4) Are consistent with the scientific evidence of actual harm and exposure. (5) Are consistent with how those marketing claims will be interpreted and perceived by potential consumers. (6) Will not mislead consumers, especially adolescents and young adults, about the health risks of IQOS and the relative risks compared with not using any tobacco product. FDA should deny PMI's MRTP application because it does not include sufficient evidence to address these points.

What this paper adds

- ▶ This study is among the first to critically review data submitted by Philip Morris International (PMI) as part of their modified risk tobacco product (MRTP) application to the Food and Drug Administration (FDA).
- ▶ PMI's studies did not provide sufficient evidence that heated tobacco products (HTP) users will completely switch from cigarettes to HTP or that consumers understand the proposed claims regarding exposure, harm and 'switching completely'.
- ▶ PMI's MRTP application does not satisfy FDA requirements that consumers will not be misled; therefore, HTP should not be allowed to be marketed with reduced risk claims.

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Awareness and use of heated tobacco products among US adults, 2016–2017

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ABSTRACT

Introduction Although heated tobacco products (HTP) have been on and off the commercial market for the past three decades (eg, Premier, Eclipse and Accord), they have not received widespread consumer acceptance as an alternative to combustible cigarettes. This may change with recent product innovations, shifts in consumer preferences and the tobacco market landscape and a US regulatory environment that may permit an internationally available HTP to be sold in the USA, possibly with a reduced exposure or risk statement. This study examined the extent of awareness and use of HTP in the USA and assessed the characteristics of those aware of and using these products.

Methods Data came from the 2016 and 2017 Tobacco Products and Risk Perceptions Surveys of national probability samples of US adults, conducted online during September–October 2016 (n=6014) and August–September 2017 (n=5992). Weighted χ^2 tests and regression analyses examined changes in awareness and use of HTP between 2016 and 2017 and characteristics associated with awareness and use.

Results From 2016 to 2017, awareness of HTP among US 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 two fold, from 0.5% to 1.1% ($p=0.004$). Men and adults under age 45 years had higher rates of awareness than women and those 45 and older, respectively. Non-white adults, cigarette smokers and both current and former users of electronic nicotine delivery systems were more likely to be using HTP.

Conclusions Awareness and use of HTP in the USA are increasing. These products are more familiar to men and younger adults and may be being used disproportionately by racial/ethnic minorities. With increases in HTP availability and the potential for reduced-risk claims ahead, surveillance of patterns and consequences of use by both smokers and non-smokers is needed.

INTRODUCTION

Heated tobacco products (HTP), also called ‘heat-not-burn’ tobacco products, contain tobacco that manufacturers claim is heated to temperatures that are below the level of combustion,¹ even though recent research has called this into question.² Users inhale a nicotine-containing aerosol created by heating the tobacco materials, instead of smoke from combustion,³ thereby reducing the intake of chemicals previously identified by Food and Drug Administration (FDA) as harmful or potentially harmful but increasing the levels of certain other constituents.^{4–7}

HTP have been manufactured and commercially available in the USA since the 1980s but have not experienced widespread commercial success. However, the historically lacklustre consumer adoption and market failures may give way to increased appeal and consumer acceptance owing to recent product innovations, shifts in consumer preferences and the tobacco market landscape and a US regulatory environment that might soon permit an internationally available HTP to be sold in the USA, and possibly with a reduced exposure or reduced risk statement. Although many electronic nicotine delivery systems (ENDS), which typically contain no tobacco, have held promise as less-toxic substitutes for cigarettes,⁸ many smokers have rejected them as unsatisfying and not similar enough in feel to cigarettes.^{9–10} In contrast, HTP have a taste and nicotine delivery profile similar to combustible cigarettes.⁹ Some HTP, such as TEEPS by Philip Morris International (PMI), which uses an ignited heat source, also have an appearance and feel similar to cigarettes that may make them more appealing to smokers as substitutes for the combustible cigarette. However, some early independent research found that smokers did not perceive IQOS, another HTP from PMI that uses an electronically (battery) powered heat source, as delivering the same taste and nicotine intensity as cigarettes.¹¹

Currently sold in markets in at least 30 countries,¹² the IQOS HTP by PMI has generated considerable consumer and market interest, as well as concerns among tobacco control proponents and policy makers.¹³ In South Korea, where IQOS has been available since May 2017, and in numerous other locations, PMI has sold the products in spacious, sleek stores resembling those for other high tech devices and employed sophisticated marketing strategies to engage potential users.^{14–15} Few studies of prevalence of the IQOS or other HTP awareness and use have been conducted. A 2017 survey of respondents ages 15 years and older in Italy, where IQOS has been available since 2014, found 19.5% of respondents were aware of IQOS and 1.4% have tried it.¹⁶ In Japan, where IQOS has been available since November 2014 and is now sold nationally along with competing HTP from Japan Tobacco and British American Tobacco (but no nicotine-containing ENDS),¹⁷ prevalence of current IQOS use increased dramatically (from 0.3% in 2015 to 3.6% in 2017) following publicity on a popular television show in April 2016.^{12–18} Japanese Google searches for HTP have also increased substantially since 2015.¹⁹

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In the USA, PMI has applied to the FDA for IQOS to make claims as a Modified Risk Tobacco Product (MRTP).^{1,20} MRTPs are those tobacco products that are 'sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products'.²¹ Between May and November 2017, the FDA made the PMI MRTP application materials available online, and they were still accepting public comments on the application as of April 2018.²⁰ Studies conducted by PMI affiliates have claimed that IQOS produces fewer harmful constituents than combustible cigarettes,²² though other studies have demonstrated that these products still contain and produce toxic constituents,^{1,23} some of which may be present in even greater amounts in IQOS⁷ and that users are not necessarily at lower levels of risk.²⁴ A meeting of the FDA's Tobacco Products Scientific Advisory Committee was held on 24 and 25 January 2018, during which PMI's MRTP application was debated. The ensuing discussion by the committee focused on concerns that the evidence presented by PMI was not adequate to support making modified risk or exposure claims. Unlike new tobacco product authorisation, modified risk authorisation restricts the use of modified risk claims to a limited time period, following which the applicant must demonstrate that the product and the modified risk claims continue to meet the statutory standard.

Given the popularity of HTP in Japan and elsewhere, it is expected that the commercial introduction of these products in the USA will impact consumers of nicotine and tobacco products.⁹ To our knowledge, there have not yet been any published studies of the prevalence of awareness and use of HTP in the USA. Early understanding of the characteristics of HTP users in the USA may indicate the trajectory these products are likely to take in the future. Of particular importance is smoker interest in HTP and whether HTP might replace ENDS as a preferred substitute (or complement) for combustible cigarettes. Also worthy of investigation are the demographic characteristics of the earliest adopters of HTP. Our data serve to provide a baseline view of HTP use and trends against which to compare subsequent use following market shifts and regulatory actions.

METHODS

Study sample and procedures

Data come from the 2016 and 2017 Tobacco Products and Risk Perceptions Surveys, annual, cross-sectional surveys of a probability sample with oversample of current cigarette smokers drawn from GfK's KnowledgePanel. Survey participants were adults ages 18 years and older and were selected with probabilities proportional to size after application of the panel demographic poststratification weight. At the sampling stage, the 2017 sample excluded anyone who completed the 2016 Tobacco Products and Risk Perceptions Survey. Data collection occurred during September and October of 2016 and during August and September of 2017. Computers with internet access were provided for those recruited panellists who did not have them. All participants received a cash equivalent of \$5 for their participation.

In 2016, 8125 KnowledgePanel members were invited to participate in the survey: 7157 members from the general population sample, of which 76.2% completed the screener and 5445 qualified for the survey and 968 members from the smoker oversample, of which 73.6% completed the screener and 616 qualified for the main survey by confirming their current smoking status. Of the 6061 qualified completers, 47 cases were excluded

due to refusing to answer more than half of the survey questions, yielding an analytic sample of 6014 cases. A final stage completion rate of 74.0% was obtained for the 2016 sample.

In 2017, 8229 KnowledgePanel members were invited to participate in the 2017 survey: 7270 members from the general population sample, of which 75.1% completed the screener and 5455 qualified for the survey and 959 members from the smoker oversample, of which 68.1% completed the screener and 578 qualified for the main survey by confirming their current smoking status. Of the 6033 qualified completers, 22 cases were excluded due to refusing to answer more than half the survey questions and 19 were removed due to low duration or being flagged twice for highly improbable or incompatible responses, yielding an analytic sample of 5992 cases. A final stage completion rate of 72.8% was obtained for the 2017 sample.

A study-specific poststratification weight was computed using an iterative proportional fitting (raking) procedure to adjust for survey non-response as well as for oversampling of smokers. Demographic and geographic distributions from the most recent Current Population Survey were employed as benchmarks for adjustment, and included sex, age, race/ethnicity, education, household income, census region and metropolitan area.

Measures

Awareness and use of HTP

In both the 2016 and 2017 surveys, all participants were shown images of Revo and IQOS HTP, chosen as examples of some types of HTP, along with the following description: 'Heat-not-burn' uses leaf tobacco like traditional cigarettes. However, these products heat the tobacco to a lower temperature than traditional cigarettes to avoid burning the tobacco. When heated, they produce aerosol with nicotine, similar to electronic cigarettes. Depending on the specific product, the tobacco is heated by either a flame (with a lighter or match) or a battery. Some brands are Eclipse, Accord, Premier, Ploom, Revo and IQOS with Marlboro Heat Sticks. Participants were then asked if they had ever seen or heard of any HTP before this study. Those who reported being aware of the products were next asked if they had ever used HTP, even one or two puffs. If they answered affirmatively, they were asked if they now use it 'every day', 'some days', 'rarely' or 'not at all'. Those who reported using HTP 'every day', 'some days' or 'rarely' were classified as current users, while those who had ever used HTP, but now use it 'not at all', were classified as former users.²⁵

Cigarette smoking

Participants who reported smoking at least 100 cigarettes in their lifetime were asked, 'Do you currently smoke cigarettes every day, some days, or not at all?'. Current smokers were those who responded 'every day' or 'some days', and former smokers were those who responded 'not at all'. Those who reported that they had not smoked at least 100 cigarettes in their lifetime were considered never smokers.

ENDS use

Participants who were aware of ENDS were asked if they had ever used ENDS, even one or two times. Ever users of ENDS were then asked if they now use them 'every day', 'some days', 'rarely' or 'not at all'. Those who responded 'not at all' were classified as 'former ENDS users' while those who responded 'every day', 'some days', or 'rarely' were classified as 'current ENDS users'.

Quit status and quit intentions

We created a three-level quit status variable consisting of former smokers, unsuccessful quitters and those who have never tried to quit. Current smokers were asked, 'In the past, have you ever made a serious attempt to quit smoking? That is, have you stopped smoking for at least one day or longer because you were trying to quit?'. Those who answered 'yes' were classified as unsuccessful quitters, while those who answered 'no' were classified as those who have never tried to quit. Current smokers were also asked to select the statement that best describes when and if they plan to quit smoking. Responses were then grouped into four categories, 'intend to quit in the next month', 'intend to quit in the next 6 months', 'intend to quit sometime in the future, but not in the next 6 months' and 'never plan to quit' to form a four-level quit intentions variable.

Early adopter propensity

Participants were asked to select whether they agreed 'not at all', 'somewhat', 'a lot' or 'completely' with each of three statements: 'I usually try new products before other people do', 'When I shop, I look for what is new' and 'I like to be the first among my friends and family to try something new'. The composite measure ranged from a low score of 3 (responding 'not at all' to all three statements) to a high score of 12 (responding 'completely' to all three statements).

Participant sociodemographics

Participant sociodemographics used in analyses included sex, age, education level, race/ethnicity and annual household income and were obtained from profile surveys administered by GfK to KnowledgePanel members.

Statistical analysis

Where temporal change was not being examined or patterns of associations did not differ, data from the 2016 and 2017 surveys were pooled to improve statistical precision and power. Analyses were conducted using IBM SPSS with Complex Samples module (V.25) to obtain weighted point estimates and 95% CIs for sample sociodemographics, awareness and use of HTP, overall and by sample characteristics, quitting status and quitting intentions. Associations among awareness and use of HTP, sample characteristics, quitting status and quitting intentions were measured by weighted multivariable logistic regression models and Rao-Scott χ^2 tests.

RESULTS

Estimates of the population sociodemographic characteristics, smoking status and ENDS use for 2016 and 2017 are shown in table 1. In 2017, there was a significantly greater proportion of adults who currently smoked cigarettes ($p=0.003$) and who currently used ENDS ($p<0.001$) than in 2016. Adults in 2017 also reported greater propensity to be an early adopter of new products ($p=0.001$) than in 2016.

Table 2 compares awareness and use of HTP between 2016 and 2017. In 2017, 12.4% of all adults had heard of them, 2.2% had ever used them and 1.1% reported current use of HTP. Among all adults, awareness ($p<0.001$), ever use ($p=0.005$) and current use ($p=0.004$) increased significantly between 2016 and 2017.

Shown in table 3 are the proportions of awareness, ever use and current use of HTP by sample characteristics, as well as the adjusted ORs for sample characteristics and HTP awareness and use, for the 2016 and 2017 data combined. Adjusting for all other factors, men and those younger than age 45

years had greater odds of awareness of HTP than women and those 45 years and older, respectively. Non-white participants had greater odds of ever and current use of HTP, compared with white participants. Current cigarette smokers were nearly twice as likely to have ever used HTP as never smokers. Both former and current users of ENDS were more likely to be aware of, have ever used or be current users of HTP than those who have never used ENDS. Similarly, early adopters of new products had greater odds of awareness, ever use and current use of HTP.

Table 4 displays associations between quit status and quit intentions with awareness, ever use and current use of HTP, for the 2016 and 2017 samples. Former smokers in 2016 had lower odds of ever or current use of HTP compared with smokers who had never tried to quit. In 2017, smokers who had made quit attempts had increased odds of ever using HTP compared with smokers who had never tried to quit. Among current smokers in 2016, those who had plans to quit either in the next month or next 6 months were more than twice as likely to be aware of HTP than smokers with no plans to quit. Smokers in 2016 with plans to quit in the next 6 months also had greatly increased odds of currently using HTP compared with those with no plans to quit. There were no significant differences in awareness or use of HTP by quit intentions in 2017.

DISCUSSION

Though HTP products have not yet achieved widespread use, the number of US adults who are aware of and using these products is rapidly increasing. In 2017, ever and current use were still uncommon, 2.2% and 1.1%, respectively, though the proportion for current use had more than doubled since 2016. These numbers correspond to over 7 million people in the USA ever trying and over 3.5 million currently using HTP. If patterns of usage follow those occurring in Japan, we can expect these numbers to increase substantially following commercial introduction of IQOS. Analysts predict rapid sales growth in the USA, similar to that of Japan, over the next few years.⁹⁻¹⁴ Caution should be used when extrapolating from the Japan example; however, as there are notable ways in which the Japanese market is different from the US market. Commercially available ENDS in Japan do not contain nicotine,¹² making ENDS less competitive with other tobacco and nicotine-containing products. Government regulations are also less stringent in Japan.¹⁷

PMI's MRTP application to the FDA outlines the 'considerations (that) will ensure that the product benefits the health of the population as a whole'.²⁰ Included are the stipulations that 'an MRTP should not increase initiation among non-users of tobacco products, and hence should not appeal to former users and never users' and 'an MRTP should not have a significant impact on the decision of a smoker who would otherwise quit smoking'.²⁰ PMI then cites studies that purport to show that IQOS is not attractive to adult never smokers and 'minimally attractive' to adult former smokers.²⁰ While our data do show that current smokers have thus far had significantly greater odds of using HTP, there are small numbers of never and former smokers who have tried and are currently using these products. In Italy, while current cigarette smokers and current ENDS users have the highest rates of HTP (IQOS) use, a small proportion of non-smokers have tried the products as well.¹⁶ Though the number of both the Italian and US survey participants who have used HTP is small, roughly half of the Italian sample who used IQOS and just under half of the US sample who ever used any HTP are either never or former cigarette smokers. We do not know

Table 1 Participant sociodemographics

	2016		2017		P values*
	Unweighted n	Weighted %/mean (95% CI)	Unweighted n	Weighted %/mean (95% CI)	
Total	6014	–	5992	–	
Sex					
Male	3013	48.0 (46.5 to 49.6)	2987	48.1 (46.6 to 49.6)	0.923
Female	3001	52.0 (50.4 to 53.5)	3005	51.9 (50.4 to 53.4)	
Age (years)					
18–29	981	20.8 (19.5 to 22.3)	1092	20.8 (19.5 to 22.1)	0.992
30–44	1213	24.8 (23.5 to 26.2)	1183	24.9 (23.6 to 26.4)	
45+	3820	54.3 (52.8 to 55.9)	3717	54.3 (52.7 to 55.8)	
Education					
Less than high school	297	10.8 (9.6 to 12.1)	326	10.8 (9.7 to 12.1)	0.961
High school	1781	29.3 (27.9 to 30.6)	1345	28.9 (27.5 to 30.4)	
Some college	1876	28.8 (27.5 to 30.2)	2014	28.6 (27.4 to 29.9)	
College graduate or more	2060	31.1 (29.8 to 32.5)	2307	31.6 (30.3 to 33.0)	
Race/ethnicity					
White, NH	4434	65.1 (63.5 to 66.6)	4365	64.3 (62.8 to 65.9)	0.919
Black, NH	547	11.8 (10.8 to 12.9)	600	11.8 (10.8 to 12.8)	
Hispanic	672	15.3 (14.1 to 16.6)	639	15.8 (14.6 to 17.2)	
Other, NH	361	7.8 (6.9 to 8.9)	388	8.0 (7.1 to 9.1)	
Income					
Less than \$30 000	1486	20.7 (19.6 to 22.0)	1290	19.1 (18.0 to 20.3)	0.067
\$30 000–\$99 900	3144	47.4 (45.9 to 49.0)	2961	47.0 (45.6 to 48.5)	
\$100 000+	1384	31.8 (30.3 to 33.4)	1741	33.9 (32.4 to 35.3)	
Cigarette smoking status					
Never	3107	59.7 (58.2 to 61.2)	3061	56.4 (54.9 to 57.8)	0.003
Former	1619	27.1 (25.8 to 28.4)	1660	28.7 (27.3 to 30.0)	
Current	1288	13.2 (12.3 to 14.1)	1271	15.0 (14.0 to 16.0)	
ENDS use status					
Never	4821	83.9 (82.7 to 85.0)	4664	79.7 (78.5 to 80.9)	0.000
Former	792	10.7 (9.8 to 11.7)	786	11.8 (10.8 to 12.8)	
Current	390	5.4 (4.8 to 6.1)	542	8.5 (7.7 to 9.4)	
Early adopter propensity†	4832	5.11 (5.03 to 5.19)	5612	5.28 (5.22 to 5.35)	0.001

* χ^2 test.

†Range from 3 to 12.

ENDS, electronic nicotine delivery systems; NH, non-Hispanic.

whether the former smokers who have used HTP did so before or after they stopped smoking.

PMI also claims that their test communications about the products had no significant impact on the intention of adult smokers to quit smoking.²⁰ However, because their experimental studies did not include a control group, they cannot make causal claims on whether the messages had any impact on cessation.²⁶

Furthermore, between 3% and 33% of participants who had intentions to quit before exposure to the messages reported lower intentions to quit after they saw the messages about IQOS with modified risk claims.²⁶ It is possible that using messages without modified risk claims or combining the claims with stronger warnings (such as pictorial warning labels) might have prevented this decline in intentions to quit smoking.

Table 2 Awareness and use of HTP among US adults

	2016 n=6014		2017 n=5992		P values*
	Unweighted n	Weighted % (95% CI)	Unweighted n	Weighted % (95% CI)	
Aware of HTP	560	9.3 (8.4 to 10.2)	730	12.4 (11.4 to 13.4)	<0.001
Ever used HTP	88		142		
Among all US adults		1.4 (1.1 to 1.8)		2.2 (1.8 to 2.7)	0.005
Among those aware of HTP		14.8 (11.6 to 18.8)		17.8 (14.6 to 21.5)	0.243
Currently use HTP	36		61		
Among all US adults		0.5 (0.4 to 0.7)		1.1 (0.8 to 1.5)	0.004
Among those aware of HTP		5.6 (3.8 to 8.0)		8.6 (6.3 to 11.7)	0.076

* χ^2 test.

HTP, heated tobacco product.

Table 3 Characteristics associated with HTP product awareness and use, among US adults, 2016 and 2017

	n	Aware of HTP		Ever used HTP		Currently use HTP	
		%/Mean (95% CI)	AOR† (95% CI)	%/Mean (95% CI)	AOR† (95% CI)	%/Mean (95% CI)	AOR† (95% CI)
Sex							
Male	5998	13.4 (12.3 to 14.5)	1.67 (1.42 to 1.95)***	2.0 (1.6 to 2.6)	1.34 (0.92 to 1.96)	0.8 (0.6 to 1.2)	1.13 (0.63 to 2.04)
Female	5999	8.5 (7.7 to 9.3)	REF	1.6 (1.3 to 2.0)	REF	0.8 (0.5 to 1.0)	REF
Age (years)							
18–29	2069	13.9 (12.1 to 15.9)	1.58 (1.26 to 1.97)***	3.0 (2.3 to 4.1)	1.57 (0.92 to 2.66)	1.5 (1.0 to 2.4)	1.89 (0.89 to 4.00)
30–44	2394	13.4 (11.9 to 15.1)	1.50 (1.24 to 1.81)***	2.6 (2.0 to 3.4)	1.34 (0.84 to 2.15)	1.2 (0.8 to 1.8)	1.16 (0.59 to 2.29)
45+	7534	8.5 (7.8 to 9.2)	REF	0.9 (0.7 to 1.2)	REF	0.3 (0.2 to 0.5)	REF
Education							
<High school	622	12.6 (9.9 to 15.9)	1.15 (0.79 to 1.66)	3.6 (2.4 to 5.4)	1.51 (0.72 to 3.17)	1.6 (0.8 to 3.0)	1.50 (0.46 to 4.93)
High school	3121	10.7 (9.4 to 12.1)	1.09 (0.86 to 1.39)	1.8 (1.3 to 2.5)	1.22 (0.64 to 2.34)	0.9 (0.5 to 1.4)	1.64 (0.61 to 4.43)
Some college	3888	10.3 (9.2 to 11.5)	0.95 (0.78 to 1.15)	1.9 (1.4 to 2.4)	1.21 (0.68 to 2.15)	0.8 (0.5 to 1.1)	0.99 (0.44 to 2.21)
College graduate or more	4366	10.9 (9.9 to 12.0)	REF	1.1 (0.8 to 1.5)	REF	0.5 (0.3 to 0.8)	REF
Race/ethnicity							
White, NH	8794	10.2 (9.4 to 10.9)	REF	1.3 (1.0 to 1.5)	REF	0.4 (0.3 to 0.6)	REF
Black, NH	1143	11.1 (9.2 to 13.4)	1.08 (0.84 to 1.39)	2.0 (1.3 to 3.0)	1.39 (0.83 to 2.32)	1.2 (0.7 to 1.9)	2.54 (1.24 to 5.21)*
Hispanic	1311	13.6 (11.5 to 15.9)	1.09 (0.87 to 1.38)	3.4 (2.4 to 4.8)	2.09 (1.29 to 3.37)**	1.6 (0.9 to 2.7)	2.82 (1.36 to 5.86)**
Other, NH	749	10.5 (7.9 to 13.7)	1.00 (0.70 to 1.41)	2.7 (1.5 to 4.8)	2.57 (1.23 to 5.35)*	1.5 (0.6 to 3.3)	3.95 (1.29 to 12.07)*
Income							
Less than \$30 000	2770	12.7 (11.1 to 14.4)	1.14 (0.88 to 1.48)	3.2 (2.5 to 4.2)	1.71 (0.92 to 3.19)	1.5 (1.0 to 2.3)	1.13 (0.50 to 2.57)
\$30 000–\$99 900	6102	10.3 (9.4 to 11.2)	0.92 (0.75 to 1.13)	1.8 (1.4 to 2.3)	1.32 (0.73 to 2.41)	0.7 (0.5 to 1.1)	0.84 (0.40 to 1.79)
\$100 000+	3125	10.5 (9.3 to 11.8)	REF	0.9 (0.6 to 1.4)	REF	0.4 (0.3 to 0.8)	REF
Cigarette smoking							
Never	6161	9.6 (8.7 to 10.6)	REF	0.8 (0.5 to 1.1)	REF	0.3 (0.2 to 0.6)	REF
Former	3278	10.8 (9.6 to 12.1)	1.21 (1.00 to 1.47)	1.3 (0.9 to 1.9)	1.20 (0.64 to 2.25)	0.5 (0.3 to 1.1)	1.25 (0.51 to 3.04)
Current	2558	15.9 (14.1 to 17.9)	1.16 (0.91 to 1.47)	7.0 (5.7 to 8.5)	1.96 (1.14 to 3.37)*	3.1 (2.3 to 4.2)	1.57 (0.81 to 3.04)
ENDS use							
Never	9485	9.3 (8.6 to 10.1)	REF	0.4 (0.3 to 0.6)	REF	0.2 (0.1 to 0.3)	REF
Former	1578	15.0 (12.8 to 17.5)	1.45 (1.14 to 1.85)**	6.4 (4.9 to 8.2)	11.51 (6.20 to 21.36)***	0.8 (0.4 to 1.6)	4.04 (1.28 to 12.75)*
Current	932	21.5 (18.3 to 25.0)	1.78 (1.36 to 2.33)***	10.9 (8.6 to 13.7)	14.87 (7.84 to 28.19)***	8.1 (6.1 to 10.7)	35.97 (13.55 to 95.50)***
Early adopter propensity‡	10 437	5.72 (5.56 to 5.88)	1.08 (1.04 to 1.12)***	6.56 (6.15 to 6.98)	1.13 (1.04 to 1.22)**	6.97 (6.35 to 7.59)	1.14 (1.02 to 1.28)*

***P<0.001; **p<0.01; *p<0.05.

†Adjusted OR for sex, age, education, race/ethnicity, income, cigarette smoking, ENDS use and early adopter propensity.

‡Range from 3 to 12.

ENDS, electronic nicotine delivery systems; HTP, heated tobacco product; NH, non-Hispanic.

Smokers with concrete plans to quit were more likely to be aware of HTP than those with no plans to quit in 2016, but not in 2017, possibly indicating that media coverage of HTP may have contributed to expanding awareness beyond only those with intentions to quit smoking. Smokers in 2017 who had unsuccessfully tried to quit were more than twice as likely as those who have never tried to quit to have used HTP, which may indicate that HTP are increasingly being explored as quit aids among smokers who were unsuccessful with other cessation tools. We do not yet know the patterns in which HTP are being used by these groups; specifically, whether these products will be used only temporarily as smokers are trying to quit, if they will continue to be used as a substitution for quitting tobacco products entirely, or if they will be used concurrently with cigarettes, indefinitely. Careful monitoring of product uptake among non-smokers and of use among smokers trying to quit will be essential.

It is not surprising that current smokers in the USA are more likely to be aware of and using these products than those who have never smoked. More strikingly, those who have used ENDS, and current ENDS users, particularly, have much higher odds of having used HTP than never users of ENDS. It remains to be seen whether dual users of ENDS and HTP will find one product more satisfying and switch completely to that. It is also possible that smokers who have never tried (or who have tried but rejected) ENDS may consider trying HTP.

PMI's and our study did not evaluate the appeal of IQOS to youth, to whom these products should not appeal. Given the experience with ENDS in the USA, it is reasonable to assume that HTP would be appealing to youth and young adult newer smokers²⁷ ENDS are similar to HTP in that both are alternatives to cigarettes promoted by emphasising lack of smoke and reduced harm. As rates of ENDS use have been increasing rapidly in the USA since they were first introduced

Table 4 Awareness and use of HTP by quit status and quit intentions among current and former smokers, among US adults, 2016 and 2017

	n	Aware of HTP		Ever used HTP		Currently use HTP	
		% (95% CI)	AOR† (95% CI)	% (95% CI)	AOR† (95% CI)	% (95% CI)	AOR† (95% CI)
2016	6014						
Among current and former smokers (n=2904):							
Quit status							
Former smokers	1619	9.5 (8.0 to 11.3)	1.06 (0.63 to 1.77)	1.0 (0.6 to 1.7)	0.24 (0.10 to 0.56)**	0.2 (0.1 to 0.5)	0.14 (0.03 to 0.60)**
Unsuccessful quitters	895	13.9 (11.2 to 17.1)	1.54 (0.90 to 2.64)	5.1 (3.5 to 7.3)	0.95 (0.44 to 2.04)	2.7 (1.6 to 4.5)	1.49 (0.48 to 4.63)
Never tried to quit	390	9.7 (6.3 to 14.7)	REF	5.4 (2.9 to 10.0)	REF	1.9 (0.6 to 5.5)	REF
Among current smokers (n=1279):							
Quit intentions							
In next month	207	15.3 (9.7 to 23.3)	2.53 (1.05 to 6.08)*	9.2 (4.6 to 17.4)	4.29 (0.87 to 21.12)	3.3 (1.2 to 8.7)	7.05 (0.91 to 54.80)
In next 6 months	210	14.7 (9.4 to 22.2)	2.38 (1.00 to 5.67)*	8.1 (4.6 to 14.1)	3.85 (0.84 to 17.67)	6.0 (2.9 to 12.0)	15.85 (2.45 to 102.38)**
Future but not next 6 months	672	12.6 (9.7 to 16.3)	1.97 (0.95 to 4.09)	4.0 (2.3 to 6.6)	1.62 (0.40 to 6.53)	1.6 (0.7 to 3.8)	3.49 (0.52 to 23.41)
Never plan to quit	190	6.5 (3.6 to 11.5)	REF	2.3 (0.7 to 7.1)	REF	0.5 (0.1 to 2.2)	REF
2017	5992						
Among current and former smokers (n=2928)							
Quit status							
Former smokers	1660	12.0 (10.2 to 13.9)	0.95 (0.60 to 1.51)	1.7 (1.0 to 2.6)	0.48 (0.20 to 1.15)	0.9 (0.4 to 1.9)	0.58 (0.15 to 2.22)
Unsuccessful quitters	931	20.1 (16.9 to 23.8)	1.54 (0.99 to 2.41)	9.8 (7.4 to 12.7)	2.46 (1.24 to 4.87)*	4.1 (2.6 to 6.4)	2.25 (0.81 to 6.25)
Never tried to quit	337	17.0 (12.4 to 22.9)	REF	6.1 (3.4 to 10.7)	REF	2.8 (1.3 to 6.3)	REF
Among current smokers (n=1266)							
Quit intentions							
In next month	231	20.3 (13.9 to 28.6)	1.02 (0.53 to 1.96)	9.9 (5.6 to 17.0)	1.72 (0.62 to 4.79)	5.2 (2.1 to 12.4)	1.51 (0.40 to 5.69)
In next 6 months	219	18.5 (13.0 to 25.7)	0.94 (0.49 to 1.78)	7.8 (4.5 to 13.2)	1.45 (0.52 to 4.02)	4.2 (1.9 to 9.0)	1.25 (0.37 to 4.22)
Future but not next 6 months	645	18.2 (14.6 to 22.6)	0.83 (0.48 to 1.42)	8.9 (6.3 to 12.4)	1.40 (0.58 to 3.41)	3.1 (1.7 to 5.6)	0.83 (0.26 to 2.62)
Never plan to quit	171	21.1 (14.5 to 29.7)	REF	6.5 (3.0 to 13.2)	REF	3.2 (1.3 to 7.8)	REF

***P<0.001; **p<0.01; *p<0.05.

†Adjusted OR, adjusted for sex, age, education, race and income.
HTP, heated tobacco products.

into the market, so it is likely that HTP will enjoy the same popularity.

Our data show that minority adults in the USA are significantly more likely than non-Hispanic white adults to have ever used and to be current users of HTP, even when controlling for other demographic characteristics. These findings have no precedent in the literature, as prevalence studies of these products in other countries presumably used more racially homogeneous samples. As HTP are introduced in the USA and gain popularity, it will be important to monitor this trend. The Japanese study from 2015 found that use of HTP was higher among younger people,¹⁸ and our current data appear to uphold that pattern, at least for awareness of these products. This is not surprising, as younger people are more likely to be aware of and interested in new or innovative technology, and this extends to innovative tobacco products as well.²⁸ A separate Japanese study of education level and HTP use found no clear associations, though a larger sample size of HTP users may have produced different results.²⁹ Usage trends among racial and ethnic minorities, younger people and those with varying levels of education could amplify tobacco-related health disparities and should be monitored as use of HTP products becomes more widespread in the USA.

Limitations

Our study is not without limitations. Our measures of HTP awareness and use featured images and descriptions of only

some types and brands of HTP, and some of these products are no longer available. It is possible that some participants who were aware of or had used or were currently using HTP did not reply in the affirmative because they did not see their particular brand or recognise that the product they used fit within this definition. This measure is not specific enough to capture awareness and use of any one brand or type of HTP, but rather only of HTP generally. HTP have also been used for consuming marijuana, and though our survey description of HTP refers to use with tobacco, it is possible that some respondents reported on their use of HTP with marijuana. Our survey also did not explore where the products are being purchased (eg, online vs in stores, within the USA vs outside the USA). We did not measure risk perceptions, reasons for use, duration or intensity of use or satisfaction with HTP. Additionally, although our total sample size was large, the low prevalence of HTP use may have limited statistical power for some analyses and did not permit a finer-grain description of the sociodemographics and tobacco use characteristics of HTP users.

CONCLUSIONS

Based on current international experience, the latest generation of HTP could have a substantial impact on the US tobacco market. Significant increases in awareness and use are already apparent, with evidence that awareness is highest among men and young adults and that these products are being used in greater proportions by racial minorities.

Cigarette smokers and ENDS users also have higher odds of both awareness and use than non-users. Continued surveillance is needed, including further exploration of the perceptions and other characteristics associated with use, and the effects of HTP use on patterns of use of other nicotine and tobacco products.

What this paper adds

- ▶ Heated tobacco products (HTP) are being marketed aggressively and gaining popularity in many countries, and Philip Morris International is seeking Food and Drug Administration authorisation to market its IQOS HTP as a modified risk product in the USA.
- ▶ Little is known about current levels of awareness and use of HTP among US adults or the characteristics of those using these products.
- ▶ Our nationally representative survey data from 2016 and 2017 show that awareness and use of HTP are low, but increasing, among US adults.
- ▶ Awareness is higher among men, younger adults, smokers and users of electronic nicotine delivery systems (ENDS), while racial and ethnic minorities, cigarette smokers and ENDS users currently have the greatest odds of using HTP in the USA. Continuing surveillance is needed, in order to monitor potential patterns and purposes associated with HTP use.

Contributors All authors conceptualised the study and approved the final version of the manuscript. ALN ran the analyses, wrote the first draft of the manuscript and revised subsequent drafts. SRW and JH provided statistical guidance, interpretation of results and contributed to writing, reviewing and revising drafts of the manuscript. LP, TFP, and DLA contributed to interpretation of results, writing, reviewing and revising drafts of the manuscript. MPE oversaw design of the parent study, reviewed manuscript drafts and provided feedback on analyses and revisions.

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Impact of modified risk tobacco product claims on beliefs of US adults and adolescents

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ABSTRACT

Objective Under US law, tobacco product marketing may claim lower exposure to chemicals, or lower risk of health harms, only if these claims do not mislead the public. We sought to examine the impact of such marketing claims about potential modified risk tobacco products (MRTPs).

Methods Participants were national samples of 4797 adults and 969 adolescent US smokers and non-smokers. We provided information about a potential MRTP (heated tobacco product, electronic cigarette or snus). Experiment 1 stated that the MRTP was as harmful as cigarettes or less harmful (lower risk claim). Experiment 2 stated that the MRTP exposed users to a similar quantity of harmful chemicals as cigarettes or to fewer chemicals (lower exposure claim).

Results Claiming lower risk led to lower perceived quantity of chemicals and lower perceived risk among adults and adolescents (all $p < 0.05$, Experiment 1). Among adults, this claim led to higher susceptibility to using the MRTP ($p < 0.05$). Claiming lower exposure led to lower perceived chemical quantity and lower perceived risk (all $p < 0.05$), but had no effect on use susceptibility (Experiment 2). Participants thought that snus exposed users to more chemicals and was less safe to use than heated tobacco products or electronic cigarette MRTPs (Experiments 1 and 2).

Discussion Risk and exposure claims acted similarly on MRTP beliefs. Lower exposure claims misled the public to perceive lower perceived risk even though no lower risk claim was explicitly made, which is impermissible under US law.

INTRODUCTION

Attempts to market products as safer alternatives to conventional cigarettes or as smoking cessation tools date back to the 1950s. The tobacco industry aimed to appeal to health-conscious consumers¹ and respond to declining cigarette smoking rates^{2,3} attributable to tobacco control efforts (eg, smoke-free laws, media campaigns, taxation)⁴ and growing antismoking norms.⁵ Some tobacco companies made claims that their tobacco products cause less harm or deliver lower levels of chemicals than conventional cigarettes. For example in the early 2000s, Brown & Williamson advertised their Advance Lights as 'A step in the right direction. All of the taste ... Less of the toxins'⁶ and Vector claimed their Omni cigarettes to be 'The only cigarette to significantly reduce carcinogens that are among the major causes of lung cancer'.⁷ More recently, electronic cigarette (e-cigarette) marketing has often claimed e-cigarettes to be safer than combusted

cigarettes.^{8–10} Such advertising claims of reduced exposure to harmful chemicals and reduced risk of harm lower public perceptions of harm and increase willingness to try these products.^{11–17}

After decades of misleading reduced risk claims,¹⁸ the 2009 US Family Smoking Prevention and Tobacco Control Act (Tobacco Control Act) provided a regulatory framework in which tobacco companies could introduce and market tobacco products with lower exposure or risk claims only after a review and obtaining a marketing order from the US Food and Drug Administration (FDA).¹⁹ Under the law, products with these claims are 'modified risk tobacco products' (MRTPs), defined as products 'sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products'.²⁰

According to US law, applicants for MRTP status can qualify through one of two legal pathways.²¹ For the first pathway, a manufacturer can qualify by demonstrating that the product, as used by consumers, lowers harm or risk of tobacco-related diseases compared with other tobacco products (modified risk pathway, Section 911(g)(1)).^{22, 23} Alternatively, for the second pathway, a manufacturer can qualify by demonstrating that the product or its smoke is free of or contains reduced levels of harmful chemicals, but only if such claims do not mislead the public to believe the product poses less harm than other commercially available products (modified exposure pathway, Section 911(g)(2)).^{22, 23} In 2014, Swedish Match North America filed the first MRTP application for 10 of their General snus products.²⁴ The FDA did not grant the Swedish Match request for MRTP status.^{24, 25} In 2016, Philip Morris International filed an MRTP application for its IQOS heated tobacco product.²⁶ In January 2018, FDA's Tobacco Product Scientific Advisory Committee voted that Philip Morris International's application did not demonstrate reduced risks of disease. The FDA is also reviewing an MRTP application by Reynolds American for its Camel Snus.²⁷ E-cigarettes are another tobacco product for which future modified-risk applications are likely.

The purpose of our study was to examine the impact of marketing claims about exposure and risk for potential MRTPs. We hypothesised that modified risk claims would lower perceptions of chemical quantity and health harm, and increase susceptibility to use an MRTP. Similarly, we hypothesised that modified exposure claims would lower perceptions of chemical quantity, lower perceived

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risk of health harm and increase use susceptibility. Of particular importance would be whether exposure claims lower perceived risk in the absence of explicit claims of lower risk, which would prevent a product from gaining an MRTP status under US law.

METHODS

Participants

Participants were national samples of US adults and adolescents. The Carolina Survey Research Laboratory (CSRL) used sampling frames with coverage for 96% of US households, oversampling geographical areas, households and individuals to ensure adequate representation of smokers. CSRL recruited 4964 adults aged 18 years or older using both random digit dialling (of landlines and cell phones) and respondent-driven sampling approaches from August 2016 to May 2017. Separately, CSRL recruited 975 adolescents aged 13–17 years using random digit dial and list-assisted sampling frames from August 2016 to May 2017. The response rate was 39% for adults and 33% for adolescents. Adults provided consent verbally; adolescents' parents or guardians provided consent verbally on behalf of their adolescents, who provided their assent verbally. The analytical sample comprised the 4797 adults and 969 adolescents who were correctly randomised and responded to all outcomes. Additional details about the survey methodology are available elsewhere.^{28 29}

Procedures

We conducted two between-subjects factorial experiments. In Experiment 1, we randomised 2352 adults and 480 adolescents to receive one message that varied by (a) risk claim (less harmful than cigarettes, as harmful as cigarettes, no statement (control)) and (b) potential MRTP type (IQOS heated tobacco product, Apollo e-cigarette, Swedish snus), which we also refer to as product type. For example, a message about snus read, 'I am going to describe a new type of moist tobacco called Swedish snus. It comes in a small pouch that goes under your lip. Suppose the FDA approves a label saying that Swedish snus is less harmful than cigarettes.'

In Experiment 2, we randomised 2445 adults and 489 adolescents to receive one message that varied by (a) exposure claim (20% less than cigarettes, 90% less than cigarettes, similar to cigarettes (control)) and (b) potential MRTP type (same as in Experiment 1). To increase the generalisability of the findings, the scenarios used one of three randomly selected chemicals (arsenic, carbon monoxide, formaldehyde). An example message about IQOS was, 'I am going to describe a new type of cigarette called IQOS. It makes less smoke because it warms the tobacco without burning it. Suppose the FDA approves a label saying that IQOS exposes you to 90% less arsenic than cigarettes.'

Measures

We adapted survey items from previous studies, or for new items, cognitively tested them.³⁰ The survey measured perceived chemical quantity with the following item, 'Do you think that using [product] would expose you to...' The 4-point response scale ranged from 'almost no harmful chemicals' (coded as 1) to 'a lot of harmful chemicals' (coded as 4). The survey assessed perceived risk of health harm using the following item, 'If you used [product] regularly for the next 10 years, how likely do you think it is that you would eventually develop serious health problems?' The 4-point response scale ranged from 'not at all likely' (1) to 'extremely likely' (4). This item includes the four components required to accurately gauge perceived risk: who

is at risk, for what hazard, over what period of time, given a person's behaviour.³¹ The survey measured susceptibility to use the potential MRTP, 'If one of your best friends was to offer you [product], would you try it?' The 4-point response scale ranged from 'definitely not' (1) to 'definitely yes' (4).

The survey also collected demographic data including education (for adolescents, maternal education). The survey assessed numeracy (ability to understand and use numeric information) using the item: 'In general, which of these numbers shows the biggest risk of getting disease?' Response options were: 1 in 10, 1 in 100 or 1 in 1000.³² We categorised adults as current smokers if they had smoked 100 or more cigarettes in their lifetime and currently smoke some days or every day.³³ We categorised adolescents as current smokers if they had smoked at least 1 day in the past 30 days.³⁴

Data analysis

We analysed the data using R (V3.4.3).³⁵ All statistical tests were two tailed and used a critical alpha of 0.05. In randomisation checks, only 25 associations of 80 models were significant ($p < 0.05$) confirming that demographics, numeracy and smoking status were equally distributed across experimental conditions.

We conducted 2×3 between-subjects analyses of variance. Analyses combined categories for risk claim (less harmful than cigarettes vs as harmful as cigarettes or no statement) in Experiment 1 and exposure claim (similar to cigarettes vs 20% less or 90% less) in Experiment 2 because the combined categories showed the same pattern of results. We further examined statistically significant main effects of potential MRTPs with post hoc t-tests comparing IQOS and the e-cigarette to Swedish snus, using Bonferroni adjustments. Finally, we used linear regression models to examine whether perceived quantity and perceived risk mediated the relationship between independent variables and susceptibility to use MRTPs as a dependent variable. Analyses bootstrapped total, direct and mediated effects with 1000 iterations.

RESULTS

The samples were 55% female, 67% white, 91% non-Hispanic and 70% non-smokers (table 1). Less than one-third had a high school diploma or equivalent or earned US\$25 000 or less in annual income. Mean age for adults was 46 (SD=17) years and 45 (SD=17) years in Experiments 1 and 2, respectively. Mean age for adolescents was 15 (SD=1) years in both Experiments 1 and 2.

Experiment 1: lower risk claim

Perceived chemical quantity. Among adults, claims that an MRTP was less harmful than cigarettes led to lower perceived chemical quantity compared with claims that an MRTP was as harmful as cigarettes or when there was no statement ($p < 0.001$) (table 2; figure 1). Perceived chemical quantity differed among the products ($p < 0.001$); post hoc t-tests showed higher perceived chemical quantity for Swedish snus than for IQOS ($p < 0.001$) and the e-cigarette ($p < 0.001$) (figure 2). Adolescents showed the same pattern of results for the experimental manipulations.

Perceived risk of health harm. Lower risk claims led to lower perceived risk of harm among adults ($p < 0.001$). Perceived risk differed among the products ($p < 0.001$); post hoc t-tests showed Swedish snus elicited higher perceived risk of harm than IQOS ($p < 0.001$) and the e-cigarette ($p < 0.001$). Adolescents again showed the same pattern of results as adults except that snus and IQOS did not differ.

Table 1 Sample characteristics

	Experiment 1		Experiment 2	
	Adults (n=2352)	Adolescents (n=480)	Adults (n=2445)	Adolescents (n=489)
	%	%	%	%
Age (years)				
13–17	–	100	–	100
18–25	15.2	–	17.5	–
26–34	14.5	–	16.0	–
35–44	16.7	–	16.2	–
45–54	18.2	–	17.3	–
55–64	21.6	–	19.4	–
65+	13.7	–	13.6	–
Male	45.0	50.0	45.5	49.0
Race				
White	67.1	79.2	67.2	82.4
Black or African-American	21.6	14.0	22.3	11.5
American Indian or Alaska native	3.9	1.3	3.6	1.0
Asian or Pacific islander	2.4	2.0	2.3	0.6
Other	5.0	3.5	4.6	4.5
Hispanic	8.7	6.7	8.1	5.7
Education				
<High school	12.0	4.8	9.6	5.1
High school diploma or equivalent	26.2	18.8	25.7	17.5
Some college	20.3	12.4	21.7	11.2
Associate degree	10.4	11.0	10.6	12.1
Bachelor's degree	19.1	33.0	19.8	34.0
Master's degree	9.3	15.8	9.1	15.4
Professional or doctorate degree	2.7	4.3	3.5	4.7
Low numeracy	31.8	24.2	29.7	21.4
Income per year				
US\$0–US\$24 999	31.0	–	29.8	–
US\$25 000–US\$49 999	24.6	–	26.5	–
US\$50 000–US\$74 999	17.9	–	18.5	–
US\$75 000–US\$100 000	11.5	–	10.5	–
>US\$100 000	15.0	–	14.7	–
Current smoker	26.7	3.5	25.7	2.0

Among adults, missing data for income and education were 5% in Experiments 1 and 2. Among adolescents, missing data were less than 5% for age in Experiment 2 and 9% and 8% for mother's education in Experiments 1 and 2, respectively. Missing data for other characteristics were minimal.

Susceptibility to use potential MRT. Lower risk claims elicited higher susceptibility to use the product among adults ($p < 0.001$). Use susceptibility differed among the products ($p < 0.001$); post hoc t-tests showed use susceptibility was lower for Swedish

snus than for IQOS ($p < 0.001$) and the e-cigarette ($p < 0.001$). Among adolescents, risk claims and product type had no effect on use susceptibility. Interactions with smoking status were not statistically significant.

Table 2 Impact of lower risk and lower exposure claims

	df	Perceived quantity		Perceived risk		Use susceptibility	
		Adults	Adolescents	Adults	Adolescents	Adults	Adolescents
		F	F	F	F	F	F
Experiment 1							
Risk claim	1	31.8**	21.5**	12.9**	10.1*	14.1**	0.4
Product	2	50.0**	10.6**	19.7**	8.6**	31.4**	0.5
Risk claim×product	2	1.6	0.7	0.3	1.5	0.2	1.2
Experiment 2							
Exposure claim	1	82.6**	35.3**	21.6**	5.2*	3.1	0.0
Product	2	8.4**	5.5*	8.9*	2.9	30.6**	1.3
Exposure claim×product	2	1.9	0.4	2.1	0.7	0.6	1.9

Experiment 1: n=2352 adults and 480 adolescents. Experiment 2: n=2445 adults and 489 adolescents. df=degrees of freedom.

* $P < 0.05$, ** $P < 0.001$.

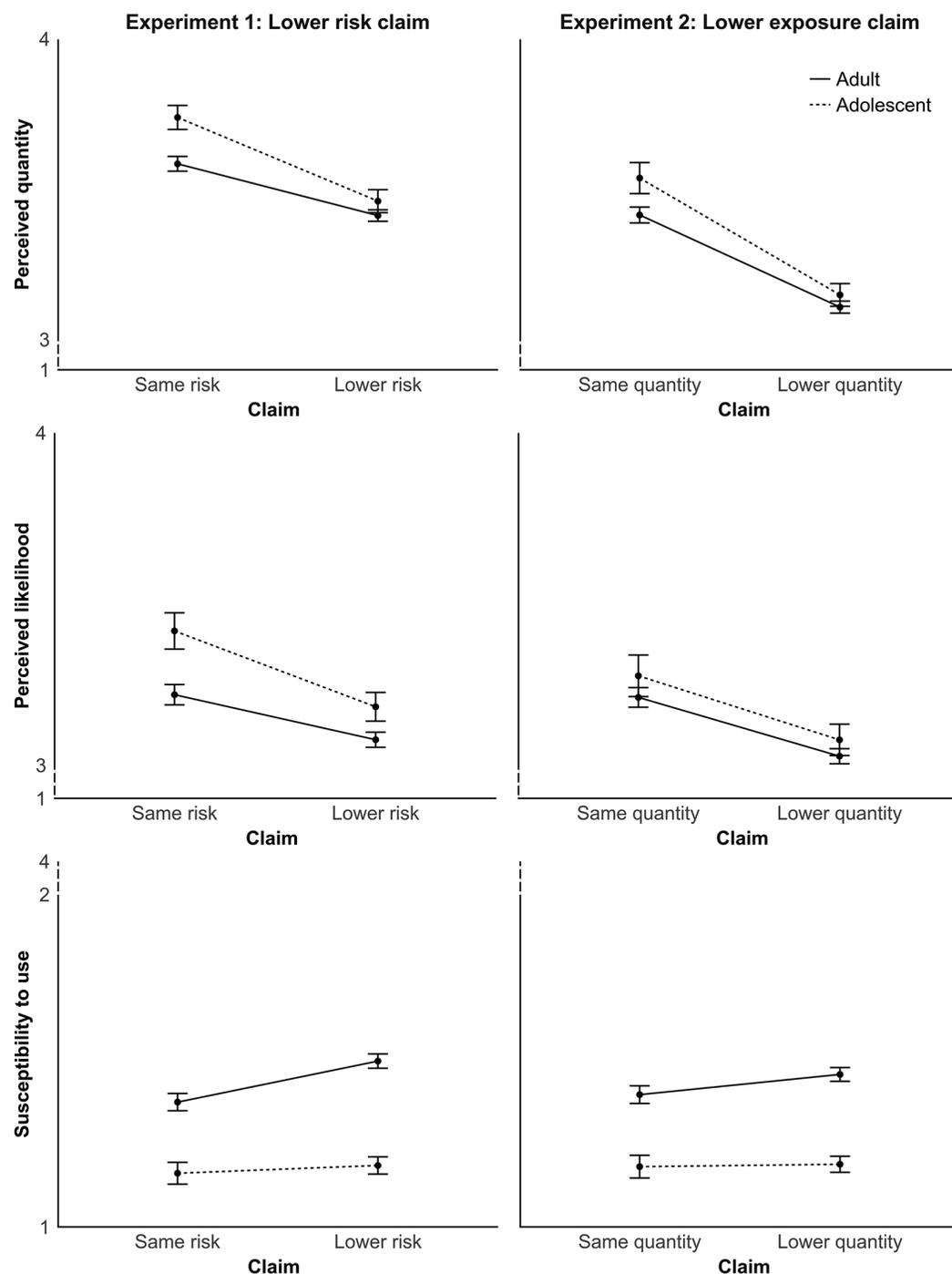


Figure 1 Impact of lower risk claim (Experiment 1) and lower exposure claim (Experiment 2). Error bars show standard errors.

Mediation. Claims that an MRTP was less harmful than cigarettes elicited lower perceived chemical quantity, which in turn, was associated with greater use susceptibility among adults (mediated effect = 0.07, $p < 0.001$; table 3). Similarly, the claims elicited lower perceived risk, which was associated with greater use susceptibility (mediated effect = 0.05, $p < 0.001$). The two constructs also mediated the effect of product type on susceptibility among adults. Although risk claims and product type did not change adolescents' susceptibility to use, analyses showed the same pattern of mediation as among adults. The correlation between the mediators, perceived chemical quantity and

perceived risk, was $r = 0.53$ among adults and $r = 0.54$ among adolescents (both p values < 0.001).

Experiment 2: lower exposure claim

Perceived chemical quantity. Among adults, claims that an MRTP exposed users to fewer chemicals led to lower perceived chemical quantity compared with the claim that an MRTP had chemical quantities similar to cigarettes ($p < 0.001$) (table 2; figure 1). Perceived chemical quantity differed among the products ($p < 0.001$); post hoc t -tests showed higher perceived chemical quantity for use of Swedish snus than IQOS ($p = 0.002$) and

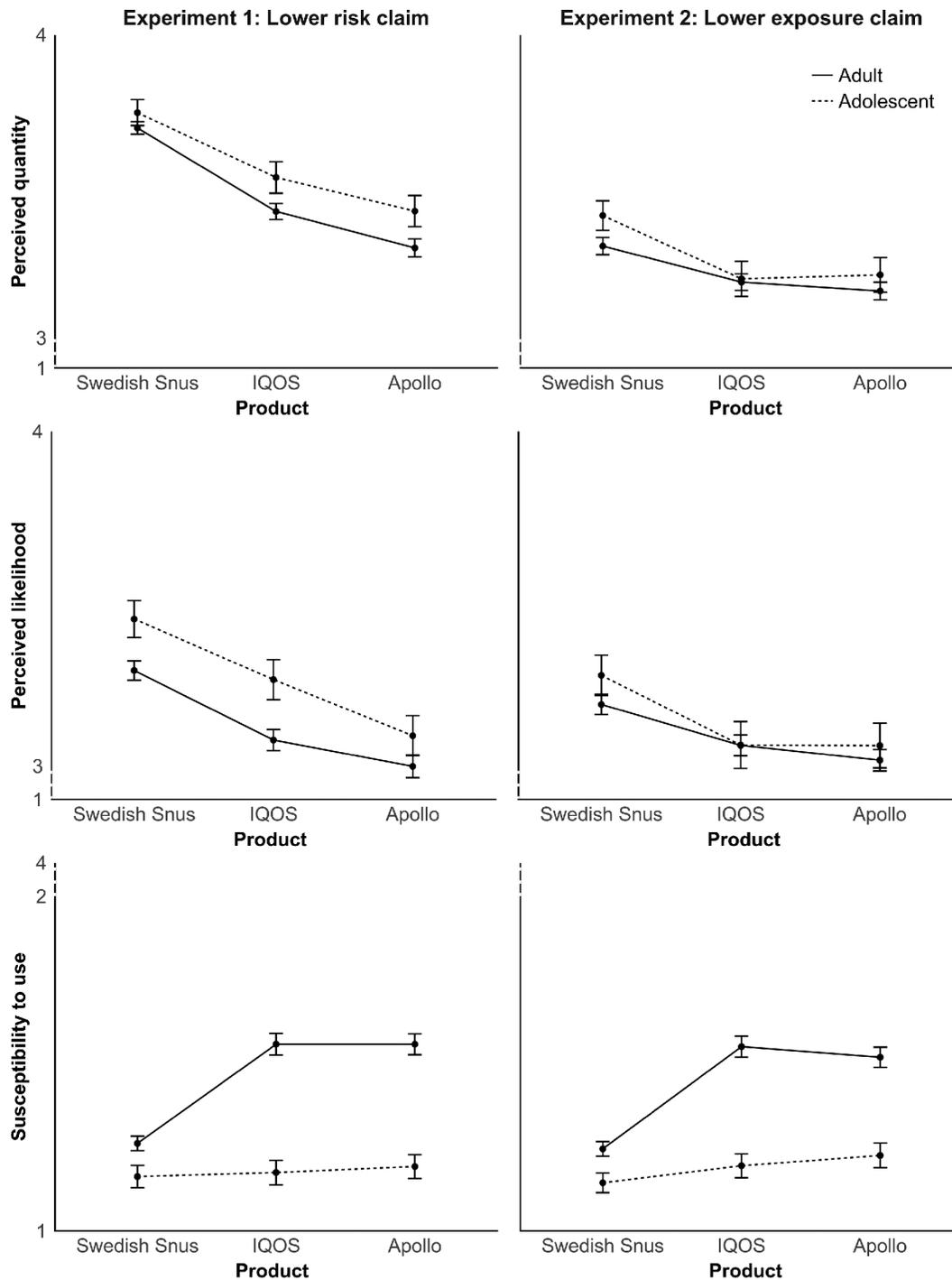


Figure 2 Impact of potential modified risk tobacco product. Error bars show standard errors.

the e-cigarette ($p < 0.001$). Adolescents showed the same pattern of results as adults.

Perceived risk of health harm. Claims that an MRTP exposed users to less chemicals lowered adults' perceived risk of health harm ($p < 0.001$). Perceived risk differed among the products ($p < 0.001$); post hoc t-tests showed perceived risk was higher for use of Swedish snus than IQOS ($p = 0.005$) and e-cigarettes ($p < 0.001$). Exposure claims had a similar effect on adolescents, but product type had no effect.

Susceptibility to use potential MRTP. Exposure claims did not change use susceptibility among adults or adolescents. Among adults, use susceptibility differed among the products ($p < 0.001$); post hoc t-tests showed lower susceptibility

to use Swedish snus than IQOS ($p < 0.001$) or the e-cigarette ($p < 0.001$). Among adolescents, use susceptibility did not vary among the products. Interactions with smoking status were not statistically significant.

Mediation. Although claims of lower exposure did not change adults' susceptibility to use an MRTP, the claims led to lower perceived chemical quantity, which was associated with greater use susceptibility (mediated effect = 0.09, $p < 0.001$; table 3). Similarly, claims of lower exposure led to lower perceived risk, which was associated with greater use susceptibility (mediated effect = 0.06, $p < 0.001$). The two constructs also mediated the effect of product type on use susceptibility among adults. While risk claims and product type did

Table 3 Path coefficients from mediation analysis for the effects of lower risk and lower exposure claims on susceptibility to use MRTPs

	Perceived quantity				Mediated effect	Perceived risk				Mediated effect
	a	b	c	c'		a	b	c	c'	
EXPERIMENT 1										
Adults (n=2352)										
Risk claim	-0.17**	-0.41**	0.12*	0.05	0.07**	-0.14**	-0.34**	0.12**	0.08*	0.5**
IQOS versus snus	-0.28**	-0.40**	0.30**	0.19**	0.11**	-0.21**	-0.33**	0.30**	0.23**	0.07**
E-cigarettes versus snus	-0.40**	-0.40**	0.30**	0.14**	0.16**	-0.29**	-0.33**	0.30**	0.20**	0.09**
Adolescents (n=480)										
Risk claim	0.28**	-0.17**	-0.02	-0.02	0.05**	-0.23*	-0.20**	0.02	-0.02	0.05*
IQOS versus snus	-0.21*	-0.17**	-0.01	-0.02	0.04**	-0.18*	-0.20**	0.01	-0.02	0.04*
E-cigarettes versus snus	-0.33**	-0.17**	-0.03	-0.03	0.06**	-0.35**	-0.20**	0.03	-0.04	0.07**
EXPERIMENT 2										
Adults (n=2445)										
Exposure claim	-0.31**	-0.29**	0.06	-0.03	0.09**	-0.18**	-0.31**	0.06	0.01	0.06**
IQOS versus snus	-0.12*	-0.27**	0.31**	-0.27**	0.03**	-0.12*	-0.30**	0.31**	0.27**	0.04*
E-cigarettes versus snus	-0.15**	-0.27**	0.27**	-0.23**	0.04**	-0.17**	-0.30**	0.27**	0.22**	0.05**
Adolescents (n=489)										
Exposure claim	-0.39**	0.19**	0.01	-0.07	0.07**	-0.19*	-0.18**	0.01	-0.03	0.04*
IQOS versus snus	-0.21*	0.17**	0.05	0.01	0.04*	-0.21*	-0.18**	0.05	0.01	0.04*
E-cigarettes versus snus	-0.20*	0.17**	0.08	0.05	0.03*	-0.21*	-0.18**	0.08	0.04	0.04*

a=path from independent variable to mediator. b=path from mediator to dependent variable. c=path from independent variable to dependent variable (total effect). c'=c-path adjusted for mediator (direct effect).

*P<0.05, **P<0.001.

MRTPs, modified risk tobacco products.

not change adolescents' susceptibility to use, lower exposure claims and product type showed similar mediation effects as among adults. The correlation between perceived chemical quantity and perceived risk was $r=0.47$ among adults and $r=0.49$ among adolescents (both p values<0.001).

DISCUSSION

Tobacco product claims about reduced exposure to harmful chemicals and health risk had similar impact on the beliefs of four diverse samples of US adults and adolescents. A key finding was that claims of lower exposure led to lower perceived risk of harm from MRTP use, even in the absence of an explicit claim of reduced risk. This linkage makes it extremely unlikely that, absent actual evidence of reduced risk, reduced exposure claims can be allowed under the Tobacco Control Act without misleading consumers. Adults' susceptibility to use MRTPs increased in response to lower risk claims but not in response to lower exposure claims whereas adolescents were not affected by either claim, suggesting some impact of claims on behaviour.

With respect to policy, a modified exposure claim would probably not satisfy US regulations for MRTP marketing.²³ The intent of the law is to proactively ensure 'that statements about MRTPs are complete, accurate and relate to the overall disease risk of the product' because the 'dangers of products sold or distributed as MRTPs that do not in fact reduce risk are so high.'³⁶ National samples of adults and adolescents misinterpreted modified exposure claims as showing reduced risk. Accordingly, the modified exposure pathway (section 911(g)(2)) is not likely to be a viable legal mechanism to introduce and market MRTPs that reduce exposure without actually reducing risk. In contrast, in our studies the public interpreted modified risk claims as intended, which suggests a modified risk claim for a product that truly does reduce risk compared with other products would appear to satisfy

US regulatory requirements with respect to public understanding.²³ In addition, per the law, applications would need to back up the risk claim with clear evidence of reduction in health harms to support an issuance of a risk modification order under section 911(g)(1).²³ Finally, our findings about use susceptibility suggest that, should the FDA issue a risk or exposure modification order, the agency should first require measures to minimise initiation among non-users and multiple tobacco product use among current users.

Several risk perception findings in our studies are likely to be generalisable beyond the context of MRTPs. First, the public infers that both risk and exposure are lower when they hear that either one is lower. Our participants perceived lower risk claims for MRTPs as indicating lower quantities of harmful chemicals and less health harm, consistent with previous studies.^{11 13 16} Our findings and previous studies also show claims of reduced quantities of chemicals are associated with lower perceived harm.^{12-14 17} Perceived risk and perceived chemical quantity were also highly correlated in our studies. Second, perceived risk is surprisingly responsive to claims about products and chemical amounts even in the absence of explicit reduced risk claims. Perceived risk is fairly insensitive to pictorial warnings and many other persuasion approaches.^{37 38} Yet, perceived risk changed in response to our experimental manipulations of exposure and risk claims, and MRTP type. It is reasonable for the public to think of lower exposure claims to be relevant to and influence the assessment of MRTP harm.³⁹ Third, the public is quite susceptible to being misled about tobacco products. Exposure claims were misleading to our study participants. Tobacco companies have successfully misled the public on many topics for decades.^{12 13 16} Disclaimers are unlikely to remedy these misperceptions as evidenced by industry-sponsored studies²⁶ and by external scientists.⁴⁰

Exposure and risk beliefs mediated all pathways to susceptibility to use MRTPs in both experiments and age groups,

which is broadly consistent with our hypotheses. However, only risk claims changed use susceptibility and only among adults. Nonetheless, the results raise some concerns about uptake of MRTPs given that susceptibility is a risk factor for tobacco use behaviour.⁴¹ This is concerning given the detrimental health effects of multiple (vs single) tobacco product use⁴² and those of any tobacco use compared with non-use.⁴³ Among current tobacco users, MRTP marketing claims might encourage multiple tobacco product use. Previous studies show that users of non-cigarette tobacco products are less likely to quit⁴⁴ and are more likely to progress to smoke cigarettes in addition to or instead of these alternative tobacco products.^{45–46} Among non-users, MRTP marketing claims might encourage initiation of tobacco use. This is particularly relevant to youth and their perceptions of potential MRTPs such as IQOS and e-cigarettes. Existing evidence on e-cigarettes shows that they appeal to youth because of their trendiness, youth-oriented flavours and social appeal.⁴⁷ Literature on adolescents' tobacco use shows that experimentation with non-cigarette tobacco products is a predictor of future cigarette smoking⁴⁸ and multiple tobacco product use,⁴⁹ and that adolescents who initiate tobacco use are more likely to continue using tobacco in their adulthood and experience its negative health effects over a longer period.⁵⁰

Our studies' strengths include national samples, inclusion of adults and adolescents, use of experimental designs, and replication of many of our findings across the samples. Limitations include the use of brief descriptions of the products, some of which may have been new to participants, and not examining actual product use. Using three tobacco products currently on the market increases the relevance of our results. Additional research is needed to replicate our findings with other candidate MRTPs, both existing and proposed.

CONCLUSION

Accuracy of claims and public comprehension of health risks associated with MRTPs are a requirement of US law.¹⁹ At long last, the Tobacco Control Act shifts the burden to tobacco manufacturers to demonstrate with scientific evidence that the issuance of an MRTP order under the Tobacco Control Act section 911 would be appropriate for the protection of the public health. Our national samples of adults and adolescents understood modified risk claims as intended. However, they misinterpreted modified exposure claims as communicating lower risk even when there was no explicit claim of lower risk, suggesting that this may not be a viable pathway under the law.

What this paper adds

- ▶ The US Tobacco Control Act allows marketing of tobacco products as causing less exposure to harmful chemicals only if this claim does not mislead the public into believing the product presents reduced risk of health harm.
- ▶ Claims of lower exposure and lower risk acted similarly, with both leading to lower perceived quantity of harmful chemicals and lower perceived risk of health harm.
- ▶ Absent concurrent evidence of reduced risk, claims of lower exposure are intrinsically misleading.
- ▶ Claims of lower exposure do not satisfy US legal requirements for modified risk tobacco products.

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Examining perceptions about IQOS heated tobacco product: consumer studies in Japan and Switzerland

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ABSTRACT

Objective To examine consumer perceptions, attitudes and behaviours regarding the heated tobacco product, IQOS, as well as to document the product's marketing strategies to determine its potential for appealing to youth and young adults.

Method Truth Initiative, in collaboration with Flamingo, collected qualitative data via: (1) expert interviews, (2) semiotic analysis of IQOS packing and marketing materials, and (3) 12 focus groups with adults in Switzerland (ages 19–44 years; June 6–9, 2016) and Japan (ages 20–39 years; June 22–24, 2016) (n=68 for both groups).

Results Expert interviews and IQOS packing and marketing analyses revealed the product is being marketed as a clean, chic and pure product, which resonated very well in Japan given the strong cultural values of order, cleanliness, quality and respect for others. Focus groups results indicated Japanese IQOS users used the product for socialising with non-smokers. Focus group participants in both Japan and Switzerland reported lower levels of satisfaction with the product relative to combustible cigarettes, although many found the product packaging to be appealing. While participants identified several benefits and barriers related to IQOS, few reported any potential health benefits of use compared with combustible tobacco products.

Conclusion IQOS was marketed as a sophisticated, high tech and aspirational product. Because youth and young adults are more interested in such product positioning, this approach raises some concern about youth appeal. This research shows cultural factors appeared to affect the appeal of this messaging, indicating that prevalence and uptake data will likely not be similar from country to country.

INTRODUCTION

The heated tobacco product (HTP), IQOS, is a battery-powered, pen-like device that delivers nicotine to users by heating tobacco. This device was developed by Phillip Morris International (PMI) and released to the market in 2014. Users operate it by inserting a 'HeatStick', a rod of tobacco that is electrically heated to a high temperature without igniting and combusting like a traditional combustible cigarette. According to PMI, nicotine is delivered to the user through this heating process with a taste similar to a traditional combustible cigarette.¹ These devices are entering markets at a time when e-cigarette popularity is beginning to wane, and research suggests e-cigarette users are dissatisfied with the lack of rapid nicotine delivery and

'throat-hit' that come from combustible tobacco use.² The use of real tobacco in IQOS may make this new device a more appealing alternative to those looking for a seemingly less harmful alternative to combustible tobacco. Tobacco executives appear to be aware of this opportunity and prepared to take advantage of it, with PMI CEO reportedly stating HTPs are the 'greatest growth opportunity in the years to come, which we believe has the very real potential to transform the industry'.³

IQOS is marketed as a clean alternative to cigarettes using online promotional materials that present the device as sophisticated, high tech and providing all the benefits of smoking but less ash and odour.¹ IQOS products were first test-marketed in Japan and Italy in 2014 and are now being test-marketed in 30 countries around the world, including Switzerland.⁴ Japan, however, remains the only country that has seen a national roll-out of IQOS. A longitudinal online survey of youth and adults in Japan found less than 1% of respondents had ever used an IQOS device from January to March 2015. However, that percentage doubled in 2016 and reached 3.6% by February 2017, with an estimated 3 million people in Japan using IQOS.⁴ Analysis of Google search data revealed dramatic increases in searches for HTPs between 2014 and 2017 in Japan, a further indication of the rapid growth in interest and popularity of the products.⁵ Surveys of Italian youth and adults revealed that almost 20% were aware of IQOS, and 2.3% reported intentions to try the device in the future.⁶ Another indication of the growing popularity of IQOS is its increasing share of the tobacco product market, reaching over 13% of the market share of all tobacco products in Japan by October 2017.⁷

In 2016, PMI filed an application to the US Food and Drug Administration (FDA) for IQOS to be marketed as a modified risk tobacco product in the USA. To date, FDA continues to accept comments to the PMI application.⁸ In January 2018, the FDA Center for Tobacco Products, Tobacco Products Scientific Advisory Committee rejected PMI's claim that IQOS is less harmful than cigarettes. However, the committee did concede that evidence suggests that 'switching completely from cigarettes to the IQOS system significantly reduces your body's exposure to harmful or potentially harmful chemicals'.⁹ Given the ongoing review of PMI's application, and the product's growing popularity and expansion into worldwide markets,¹⁰ the current study was designed to explore knowledge, attitudes, beliefs and marketing strategies related to IQOS use in Japan and Switzerland.



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METHODS

Original data were gathered by Truth Initiative, a US-based non-profit public health organisation focused on tobacco prevention, and Flamingo, an insight and brand consultancy firm based in the UK, via expert interviews, product and marketing analyses and focus groups.

Expert interviews

Expert interviews were conducted with professionals working in youth culture and youth and young adult tobacco and electronic nicotine delivery system use in order to gain insight into how IQOS might translate into markets. Experts were identified via desk research and included an ethnographer specialising in e-cigarettes and young adult smoking and an editor at Vice.com who specialises in youth culture. These experts were selected to ensure both an academic and a cultural lens on smoking and were financially incentivised for their time. Questions asked via a structured discussion guide encouraged experts to explain their understanding of youth smoking culture to unpack the differences between what cigarettes and e-cigarettes represent in culture. Experts were also asked to hypothesise how IQOS might fit into cultures and markets, based on their understanding of tobacco and e-cigarettes. This process provided key information to better understand how IQOS's marketing fits into broader cultural landscapes. Questions covered areas such as, 'what attracts young people to smoking and vaping today?' and 'where do you see the future of smoking – what will keep it relevant for young people?'

Interviews were audio-recorded and transcribed. Transcripts were analysed by two Flamingo semioticians who specialise in connecting product attributes with broader cultural trends. The two researchers performing the analyses differed in their level of involvement with the project (ie, one was closely involved in the design and implementation of the study, while the other was not) in order to check the reliability of study findings. A thematic analysis approach was used to place interview findings into cultural contexts, informed by additional research on youth websites, such as Vice.

Product and marketing analysis

An analysis of IQOS packaging (font, colour scheme, pack and product shape and claims) and advertisements (claims, colours, font and visuals) was also conducted to document the brand positioning and use of terminology. Field workers visited IQOS stores in Tokyo and Zurich, the majority of which were located within close proximity to train stations to ensure high volume of foot traffic and collected print marketing materials and photographs of point-of-sale marketing. The stores visited represented a convenience sample of IQOS retailers in the two cities.

Focus groups

Results of the expert interviews and IQOS product and marketing analyses were used to inform the focus group guides. Twelve focus groups (six in each country) were conducted in Japan and Switzerland during June 2016. These were stratified according to age (18–19 years, 20–25 years and 26–44 years in Lausanne and Zurich, Switzerland; 20–24 years, 25–29 years and 30–39 years in Nagoya, Japan) and segmented by attitudes to IQOS. A total of 68 participants from both countries were recruited through social media posts, telephone lists and at retail venues that sold IQOS. The cities of Lausanne and Zurich were selected as they were the first cities in Switzerland where IQOS was available, and Nagoya was selected because it was the location

IQOS was initially launched. Recruitment criteria included age (segmented as described above), smoking habits, attitudes to smoking and willingness to talk freely on the subject in a group setting. Participants were recruited to fit within the following smoking categories: (1) those who had fully converted to IQOS use from cigarettes, (2) dual users of both IQOS and cigarettes, (3) those who had tried and rejected IQOS and (4) those who were aware of IQOS but had never tried it. Focus groups included a set of open-ended questions related to respondents' combustible tobacco smoking habits (eg, 'What occasions do you smoke? Who with? What? Why? Do you smoke other things on different occasions? Why/Why not?') and IQOS perceptions (eg, 'How did you discover it? What were your initial impressions? How has your opinion changed?'), usage (eg, 'What moments do you use IQOS? Any moments where you'd be less likely to use it? Why? Why not?') and behaviours (eg, 'How does it compare using IQOS versus regular cigarettes? Has it changed your routine at all? How do you find it to hold?'). Questions also examined receptivity to IQOS marketing and promotional message themes (eg, 'What (if any) communications have you seen for the product? What stands out in your mind? Why? Have you attended any IQOS events? If so, describe the event to me. How did it make you feel?').

Focus groups were audio-recorded and transcribed. Transcriptions were analysed by Flamingo through the four thematic lenses that resulted from the semiotic packaging analysis and expert interviews: cleanliness, customisation, next generation smoking and sociability (see Results section for more details). The analysis team at Flamingo consisted of three qualitative researchers in the UK (at different levels of closeness to the project to maintain objectivity), two semiotics team members (also at different levels of closeness to the project) and two qualitative research/semiotics hybrids in Japan (who had conducted the Japanese interviews). Analysis methods included recurring sentiment and attitudinal analysis, through which patterns in participants' emotional reactions to the four themes were analysed across markets, and examination of linguistic themes, through which emotive language used was explored in detail in order to identify additional themes.

RESULTS

Expert interviews

The expert interviews helped define and examine the intersection of smoking and youth culture, unearthing insights such as: technology's most important role for young people is as an emotional facilitator, and today's youth are more wedded to technology than any previous generation, across all aspects of their lives. One expert stated, 'My younger siblings grew up with Facebook and Snapchat and they grew up not knowing anything else [...] I feel like they don't understand offline etiquette'. Two key spaces emerged from these expert interview discussions around youth culture: freedom and control—a tension between using technology as freedom of expression, to pursue emotional desires, and set yourself apart, but also to control your body, organise your life and uncover the processes behind the goods they consume. The expert interviews suggested that vaping speaks to the freedom space (rebellion, smoke, 'hackable' nature of the device and no clear rules), while IQOS would likely sit more in the control space (clean lines, official branding, not 'hackable' or flexible in terms of flavour).

Product and marketing analysis results

Analysis of marketing strategies revealed a comprehensive effort to promote IQOS as a sophisticated and aspirational product in

both Japan and Switzerland. IQOS promotional efforts centred around presenting the product in a clean, controlled, minimalist environment during invitation-only pop-up events in dedicated spaces. These events introduced the product by employing brand ambassadors to showcase the product and answer questions with free samples. These brand representatives highlighted the sleek, exclusive 'iPhone' style and quality of IQOS products, as well as the benefits of reduced ash and odour. An analysis of the product's marketing and advertising in both countries identified four key message themes: cleanliness, customisation, comparisons with combustible smoking and sociability. The overarching message architecture focused on the concept of modernising traditional smoking by promoting themes of control and freedom from the negative aspects of combustible tobacco smoking. Analysis of the product packaging revealed eight additional themes, specific to the device: clinical purity, a closed system, premium design, sensory invitations, nostalgia for combustible tobacco smoking, stability, familiar technology and normalisation. For example, the product's 'clinical purity' allowed smokers to control offensive factors like smoke and ash, distinguishing the product from combustible cigarettes. At the time of data collection, any potential health benefits associated with IQOS use were not included on the product packaging or marketing materials in either country. Some marketing materials in Switzerland contained the health message, 'This tobacco product can harm your health and is addictive'.

IQOS marketing efforts in both countries were also found to highlight product factors that are similar to traditional combustible cigarettes in an effort to invoke familiarity and nostalgia for smoking. Marketing materials highlight the similarity of the product's taste and behavioural process to combustible cigarettes, the similarity between the size of HeatSticks and combustible cigarettes and the charging mechanism to an old-fashioned cigarette lighter. Additionally, IQOS products are occasionally displayed next to combustible cigarettes in stores.

Focus group results

Focus group participants in Japan consistently reported IQOS as a clean, chic and pure product, indicating the effectiveness of the marketing strategy. Respondents primarily reported using IQOS when socialising with groups of non-smokers where the use of combustible cigarettes could infringe on smoke-free social situations. One respondent commented, 'Most of my friends have little kids and I started feeling uncomfortable smoking around them. So now I am only using IQOS'. Participants also reported using the product in places where smoking combustible cigarettes may leave an unwanted residue in an area. One participant stated, 'I like smoking IQOS while watching the TV with my family at home. IQOS is the best for smoking in the house because it creates no ash or odour'. Japanese participants also commented on the cumbersome process of using IQOS. For these respondents, taking along the charger and HeatSticks can be bulky and burdensome. Nonetheless, Japanese focus group participants found the packaging of the product to be appealing. Even non-users unimpressed by descriptions of the device were intrigued when presented with the actual product, indicating that the product's sleek appearance blended well with existing tech devices. Younger non-users commented that price could be a potential barrier, but after analysis of the focus group conversations, this in fact served to contribute to the overall cache of the product as luxurious and prestigious.

In Switzerland, the product's promise of freedom was subverted by the realities of using an HTP. Swiss respondents

complained about the charging and cleaning of IQOS. Focus group results suggested a view of smoking combustible cigarettes as a tool for self-expression, and it appeared that the IQOS's promotional efforts failed to resonate in this culture. In reference to smoking combustible cigarettes, one young adult participant stated, 'I guess it's the time where you have that sense of freedom, you're doing something the teachers don't want you to do'. Many focus group participants reported initiating smoking combustible tobacco products to impress friends, rebel against authority figures (eg, teachers and parents) or set a trend. Several participants reported that the product did not provide the same level of intensity as smoking combustible cigarettes, and thus, comparisons with combustible cigarettes made by IQOS were not deemed credible. Swiss participants also cited the milder taste and reduced sensory cues as barriers to continued use. One Swiss participant commented, 'There's just something about that after-work drink, I need a proper cigarette with it. Same with coffee; cigarettes just "go" with coffee'.

Focus group participants in both countries identified several benefits of IQOS use, including less throat discomfort, appealing packaging, cleanliness, lack of ash and smoke and more social acceptability. Participants commented on the novelty of the product as both an advantageous 'conversation starter' for some, as well as 'ostentatious' by others. Participants in both locations also identified several barriers to using the device, including a strange or unpleasant taste and smell, unfamiliar appearance, high maintenance and high cost. Some who had previously smoked combustible cigarettes noted that the product was cumbersome because it could not be held like a traditional combustible cigarette. Among participants in both countries, few identified any potential health benefits of IQOS use compared with combustible tobacco products, and many expressed that the product still felt unfamiliar and complicated to use.

DISCUSSION

Findings from this exploratory study suggest HTPs, like IQOS, may appeal to consumers, particularly within cultures that value cleanliness, exclusivity and high tech appearances. Others who perceive combustible tobacco use as an expression of freedom, and individualism may be deterred by the price of the product, its cumbersome utility, high maintenance and unfamiliar taste, smell and appearance. The consumer research presented here suggests consumer reception of IQOS may differ depending on culture. Similar cultural differences have been observed in the acceptance and use of snus as a harm reduction tool. While evidence suggests snus may be an effective harm reduction method among Swedish smokers, the same has not been found in the USA.^{11 12}

Consistent with the current study, PMI's research that was presented in their modified risk tobacco product application to the US FDA suggested there is more interest in IQOS in Asian markets compared with European markets.¹³ This suggests usage patterns and IQOS acceptance are likely to significantly vary from country to country. However, the popularity of e-cigarettes in the USA and the potential for HTPs to become a more appealing alternative to current e-cigarette users highlights the need to further monitor the launch of novel HTPs, like IQOS, in US markets.

Evidence from tobacco industry executives suggests a strong desire and interest in heavily promoting HTPs in order to take advantage of the declining consumer interest in combustible tobacco products and e-cigarettes.² As was historically

done with combustible cigarette promotions,¹⁴ the marketing strategies used by PMI for HTPs may seek to capitalise on the products' potential among youth and young adults in the USA—a group for whom combustible cigarette use continues to decline.¹⁵ Marketing efforts to portray HTPs as sleek, exclusive items akin to iPhones could find success among American teens and young adults, and researchers are already warning of growing interest and potential demand within new markets.^{5 16}

What this paper adds

- ▶ To our knowledge, this is the first study of IQOS conducted independent of a tobacco company to provide a brief overview of the marketing and promotional efforts, as well as consumer responses related to the heated tobacco product (HTP), IQOS, in Japan and Switzerland.
- ▶ Tobacco industry executives have indicated significant interest in developing and promoting novel HTPs, like IQOS. Given the probable increasing effort by the industry to promote HTPs, and the pending application for IQOS to be marketed as a modified risk tobacco product in the USA, findings are key in understanding how this product may be promoted and how to counter these efforts for at-risk groups, particularly youth and young adults.

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Awareness, experience and prevalence of heated tobacco product, IQOS, among young Korean adults

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ABSTRACT

Introduction Philip Morris International introduced 'IQOS' to the Korean market in June 2017. To monitor the use of IQOS among young Korean adults, we identified their awareness, experience and current use of IQOS.

Methods Three months after the introduction of IQOS in Korea, we conducted an online survey with 228 general young adults, aged 19–24 years.

Results 87 participants (38.1%) were aware of IQOS, 13 (5.7%) were IQOS ever users and 8 (3.5%) were current IQOS users. All the current IQOS users were triple users of conventional cigarettes and electronic cigarettes (e-cigarettes). There were no IQOS-only users and one IQOS ever user was a non-cigarette smoker. Among the eight current IQOS users who smoked 9.1 conventional cigarettes a day on average, four smoked 10–20 HEETS sticks a day. The current IQOS users decided to use IQOS because they believed it was less harmful or to stop smoking. The current conventional cigarette smokers were much more likely to be aware of IQOS (OR 4.496; 95% CI 2.185 to 9.250) and to be IQOS ever users (OR 11.649; 95% CI 1.024 to 132.564).

Conclusion Awareness, experience and use of IQOS among young Korean adults were relatively higher than among their Japanese counterparts. Current IQOS users were more likely to smoke conventional cigarettes and/or e-cigarettes, which contradicts the tobacco industry's claims that conventional cigarette smokers will switch to heated tobacco products. Until obtaining robust evidence concerning heated tobacco products, the government should regulate the tobacco industry's marketing tactics and health claims.

INTRODUCTION

Philip Morris International (PMI) introduced its heated tobacco product, IQOS, to the Korean market in June 2017. After their market success in Japan, the company penetrated the Korean market by establishing two flagship stores in Seoul and signing a contract with CU—Korea's largest convenience store chain with 1654 locations in the capital city and 7946 nationwide—to sell IQOS and packs of modified cigarettes, named HEETS.¹

PMI offered discount coupons to customers who registered on their IQOS website (www.myIQOS.com). With these coupons, the price of a device can be discounted by 20% and the warranty period can be extended from 6 to 12 months.¹ The company has marketed their heated tobacco product as a harm reduction product and it advertised that IQOS reduces harmful substances by approximately 90% on average compared with conventional cigarettes which are sold in the Korean market (figure 1).²

This assumes that Korean smokers' behaviour reflects these marketing tactics.³ It is not hard to find IQOS users on the streets of Korea.

Korea has been successful in enforcing tobacco control policies. Tobacco tax increased in 2015 and pictorial health warnings were introduced on cigarette packages in 2016. The smoking prevalence among adult men decreased to 40.7% in 2016 from 66.3% in 2001.⁴ However, the introduction of new types of tobacco products, such as heated tobacco products, to the Korean market can threaten this achievement. Although there are many current smokers who can quit and be free from nicotine addiction with existing tobacco control policies and programmes, the tobacco industry claims that they developed alternative products, such as heated tobacco products, to continue cigarette smoking. The industry tries to hold on to their customers with 'harm reduction' strategies.⁵

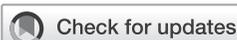
Three months after the introduction of IQOS in the Korean market, the government and Congress were confused about IQOS while preparing to define the product and impose taxes on it. Due to this situation, the public has been exposed to marketing messages generated by the tobacco company. There is an urgent need to collect data related to IQOS to develop effective policies regarding heated tobacco products.

The purpose of this study was to identify awareness, experience and current use of the heated tobacco product, IQOS, among Korean adults aged 19–24 years. The results of this study can contribute to helping the government to prepare appropriate regulations to control such products.

METHODS

In September 2017, three months after the introduction of IQOS in Korea, we carried out an online survey to identify the awareness, experience and prevalence of the new product, IQOS, among young Koreans. We recruited 228 general adults aged 19–24 years, which included 114 men and 114 women, from an online survey panel, which was managed by a survey company, EMBRAIN (<http://www.embrain.com/eng/>). The study participants were defined by age and gender. The online survey consisted of 24 questions and only took 10–15 min to complete. If there were questions that were not answered, participants could not complete the survey. The survey company, EMBRAIN, provided online points, which can be exchanged for cash or gifts, to participants who completed the survey.

Conventional cigarette smoking questions were: 'Have you ever smoked in your life?' (none/less than 100 cigarettes/more than 100 cigarettes) and 'Do you currently smoke?' (yes/no). Electronic



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Figure 1 The IQOS ad on top of the shelf in a convenience store claims, 'IQOS reduces harmful substances by approximately 90% on average compared to conventional cigarettes which are sold in the Korean market' (photo taken by Dr Jinyoung Kim).

cigarette (e-cigarette) use questions were: 'Have you ever used e-cigarettes?' (yes/no) and 'Have you used e-cigarettes in the past 30 days?' (yes/no). IQOS use questions were 'Have you ever used IQOS?' (yes/no) and 'Have you used IQOS in the past 30 days?' (yes/no). The IQOS awareness question was 'Are you aware of IQOS?'

We included several demographic variables because these variables could be associated with IQOS use: age, education level (using the question, 'What is the highest *educational* qualification that you have completed?') and monthly allowance (using the question, 'How much money do you spend a month?'). Response options for educational level were 'high school', '2 year college degree' and '4 year college degree'. Response options for monthly allowance were 'none', 'less than 50 000 won' (equivalent to approximately US\$50), '50 000 to 99 999 won', '100 000 to 149 999 won' and 'more than 150 000 won'. We also asked about the amount of IQOS daily use and the reason that current IQOS users decided to use it.

Data analyses were performed using SPSS software, V.21.0 for Windows (SPSS).

RESULTS

Among the participants, those aged 23 years old were the largest group with 27.2%, followed by those aged 24 years old with 21.5%, and those aged 22 years old with 20.6%. The mean age and SD of the male participants and female participants were 22.3 years old (± 1.4) and 22.0 years old (± 1.5), respectively. A total of 53.1% of all participants were university students and 16.2% of participants were college students. The remaining 70 participants' (30.7%) education level was a high school degree. More than half of participants (57.9%) lived in Seoul, the capital city, or Gyeonggi Province. Almost one-third (30.7%) of participants spent between 50 000 and 99 999 won a month. 18.0% and 19.7% spent 100 000–149 999 won or more than 150 000 won, respectively. The number of current conventional cigarette smokers in this study sample was 38

(33.3%) among men and 39 (34.2%) among women. Among the participants, 20 men (17.5%) and 14 women (12.3%) were current e-cigarette users.

Table 1 shows the awareness, experience and current use of IQOS among the study group.

Eighty-seven participants (38.1%) were aware of IQOS. More men (52.9%) were aware of IQOS than women (47.1%), but the difference was not statistically significant ($p=0.495$). IQOS awareness was significantly higher for conventional cigarette smokers (57.5% vs 42.5% for non-cigarette smokers; $p<0.0001$). Among participants who were aware of IQOS, 25 (28.7%) were current e-cigarette users, while 62 (71.3%) did not use e-cigarettes ($p<0.0001$).

Thirteen participants (5.7%) had tried IQOS; nine of these were men and four were women. Almost every IQOS ever user (12 out of 13) was also a current conventional cigarette smoker and the one non-current cigarette smoker was a never smoker. In addition, 10 of the 13 IQOS ever users were current e-cigarette users. There were eight current IQOS users (3.5%) among all the participants and all current IQOS users were triple users of conventional cigarettes and e-cigarettes.

Although the current IQOS users were few, we analysed their daily IQOS use and reasons for IQOS use. Among the eight current IQOS users, four participants smoked less than 10 HEETS sticks a day, but the other four participants smoked 10–20 HEETS sticks a day. Six current IQOS users decided to use the product because they believed that heated tobacco products were less harmful and less smelly compared with conventional cigarettes. Two out of eight current IQOS users used it to stop smoking. They believed that IQOS was a smoking cessation aid.

Multivariable logistic regression analysis indicated that current conventional cigarette smokers were much more likely to be aware of IQOS (OR 4.496; 95% CI 2.185 to 9.250) and to be IQOS ever users (OR 11.649; 95% CI 1.024 to 132.564) than non-smokers. Men, older participants and those with a high monthly allowance and higher education levels were more likely to be aware of IQOS and to become IQOS ever users, although the differences were not significant. In addition, the OR for being IQOS ever users among current e-cigarette users was 9.647 (95% CI 1.632 to 57.013).

DISCUSSION

In 2014, PMI introduced IQOS in Japan. Compared with Ploom, which is another type of heated tobacco product manufactured by Japan Tobacco International, the growth of IQOS in Japan was relatively very rapid. After a big success in Japan, PMI accessed the Korean market in 2017 with similar marketing tactics to that used in Japan. Once the product was marketed in Korea, the media focused on IQOS and introduced it as the equivalent of the 'iPhone' in the field of the tobacco business.

A previous study found that 48% of Japanese people were aware of IQOS, 6.6% had ever used it and 1.3% had used it in the last 30 days in 2015, one year after its introduction in the Japanese market.⁶ Later research conducted in 2017 found that 3.6% of Japanese people were current IQOS users.⁷ The prevalence of IQOS use in Japan has increased almost threefold in the last 2 or 3 years. The study also found that 4.7% of Japanese people used at least one type of heated tobacco product or e-cigarettes; of these, 72% smoked conventional cigarettes.⁷ Unlike the tobacco industry's claim that current cigarette smokers can switch from conventional cigarettes to heated tobacco products, it was found that most IQOS users were triple or dual users of conventional cigarettes and/or e-cigarettes.

Table 1 Awareness, experience and prevalence of IQOS among the Korean young adults and multivariable association of IQOS awareness and ever use

Factor	Category	n (228)	Univariate association between IQOS awareness/ever use/current use and sociodemographic characteristic and smoking behaviour						Multivariable association of IQOS awareness and ever use	
			IQOS awareness (n=87)		IQOS ever use (n=13)		Current IQOS use (n=8)		IQOS awareness OR (95% CI)	IQOS ever use OR (95% CI)
			n (%)	P values	n (%)	P values	n (%)	P values		
Gender	Female	114	46 (52.9)	0.495	9 (69.2)	0.153	6 (75.0)	0.569	Ref	Ref
	Male	114	41 (47.1)		4 (30.8)		2 (25.0)		1.10 (0.59 to 2.05)	3.11 (0.67 to 14.30)
Age (mean±SD)		228	22.31±1.43	0.279	21.92±1.12	0.526	21.50±0.93	0.082	1.12 (0.89 to 1.40)	0.80 (0.46 to 1.37)
Education level	High school	121	27 (31.0)	0.497	4 (30.8)	0.770	2 (25.0)	0.850	Ref	Ref
	2-year college degree	37	11 (12.6)		3 (23.1)		2 (25.0)		0.70 (0.25 to 1.96)	0.84 (0.10 to 6.78)
	4-year college degree	70	49 (56.3)		6 (46.2)		4 (50.0)		1.51 (0.71 to 3.20)	1.22 (0.22 to 6.68)
Monthly allowance (KRW)	None	49	14 (16.1)	0.076	1 (7.7)	0.028	0 (0.0)	0.386	Ref	Ref
	Less than 50 000 won	39	13 (14.9)		1 (7.7)		1 (12.5)		1.65 (0.59 to 4.61)	1.72 (0.06 to 50.87)
	50 000–99 999 won	54	17 (19.5)		3 (23.1)		1 (12.5)		1.28 (0.49 to 3.29)	3.63 (0.23 to 57.01)
	100 000–149 999 won	41	20 (23.0)		1 (7.7)		1 (12.5)		1.59 (0.60 to 4.27)	0.37 (0.02 to 9.47)
	More than 150 000 won	45	23 (26.4)		7 (53.8)		5 (62.5)		1.00 (0.36 to 2.80)	1.95 (0.17 to 22.78)
Conventional cigarette smoking	Never smoker	151	37 (42.5)	0.000	1 (7.7)	0.000	0 (0.0)	0.188	Ref	Ref
	Current smoker	77	50 (57.5)		12 (92.3)		8 (100.0)		4.50** (2.19 to 9.25)	11.65* (1.02 to 132.56)
E-cigarette use	Never e-cigarette user	194	65 (71.3)	0.000	3 (23.1)	0.000	0 (0.0)	0.012	Ref	Ref
	Current e-cigarette user	34	25 (28.7)		10 (76.9)		8 (100.0)		2.99* (1.11 to 8.07)	9.65* (1.63 to 57.01)

KRW is South Korea's currency, the won (1000 won=US\$1).

*P<0.05; **P<0.0001.

Korea has experienced a similar situation to that of Japan. Compared with a Japanese study,⁶ which was carried out 1 year after the introduction of IQOS in the Japanese market, awareness of IQOS (48% in Japan vs 38.1% in Korea) and ever-use of IQOS (6.6% in Japan vs 5.7% in Korea) were slightly lower. However, since there were similar percentages of current IQOS users in Korea (3.6% in Japan vs 3.5% in Korea), urgent action is needed to tackle the rapid growth of heated tobacco product use in Korea.

Given that the sample size of the present study was relatively smaller than previous studies in Japan, there is a limitation in directly comparing the results. However, if we consider that our study was carried out just 3 months after the introduction of IQOS in the Korean market, we could assume the IQOS growth in Korea has been much faster compared with its growth in Japan. According to the announcement of the Ministry of Finance, the market share of heated tobacco products, including IQOS, British American Tobacco's Glo, and KT&G's (the largest tobacco company in Korea) lil, reached 9.1% of the total sale of tobacco products in Korea.⁸

Importantly, our study found that none of the IQOS current users had switched from conventional cigarettes to IQOS. In addition, among 13 IQOS ever users, one ever user smoked neither conventional cigarettes nor e-cigarettes. This can be explained in that IQOS might possibly be a gateway product for tobacco use among never smokers. Similarly, a recent study describing the Italian experience of heated tobacco products reported that nearly half (45%) of Italian IQOS current users

and over half (51%) of Italian people who were interested in IQOS were never smokers.⁹

In our sample, there were many conventional female cigarette smokers, although the smoking prevalence among Korean female adults was low. This might affect the finding that there was no significant difference in awareness of IQOS between men and women.

Not surprisingly, we found that all current IQOS users in the sample were current conventional cigarette and e-cigarette users. This is similar to the finding of a Japanese study.⁷ In addition, four out of eight current IQOS users consumed 10–20 HEETS sticks a day, while they smoked 9.1 conventional cigarettes a day on average. Considering that Korean adult smokers aged 19–29 years old smoke 10.8 cigarettes a day on average,⁴ dual users of conventional cigarettes and IQOS in our study sample were exposed to more nicotine and other tobacco-related toxic substances. Although six out of eight decided to replace their tobacco products with heated tobacco products with the faith that IQOS was less harmful and can be used as a smoking cessation aid, these triple users' total nicotine absorption and toxic exposure from conventional cigarettes, e-cigarettes and IQOS can be really high and cause serious adverse effects to their health.

This study has a limitation in that the sample was small, and thus the findings should be interpreted carefully. Nevertheless, this study is likely to remain valuable because it analysed the early influence of IQOS on young Korean adults.

CONCLUSIONS

Due to aggressive marketing activities by the tobacco industry, awareness, experience and use of heated tobacco products, particularly among young adults, have rapidly increased. Additionally, smokers readily believe that heated tobacco products are less harmful and would help them quit smoking. Current IQOS users are more likely to smoke conventional cigarettes and/or e-cigarettes, which contradicts the tobacco industry's claims that conventional cigarette smokers will switch to heated tobacco products.

What this paper adds

- ▶ Awareness, experience and use of IQOS among young Korean adults were relatively higher than among their Japanese counterparts.
- ▶ IQOS users decided to use the product because they believed it was less harmful and would help them quit smoking. All the current IQOS users were triple users of conventional cigarettes and electronic cigarettes, which contradicts the tobacco industry's claims that conventional cigarette smokers would switch to heated tobacco products.

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IQOS campaign in Israel

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INTRODUCTION

At present, IQOS, Philip Morris's (PM's) heated tobacco product, is being test-marketed in 30 countries worldwide.¹ Similarly to electronic cigarettes,² regulation varies widely by country. In the USA, for example, sales and marketing of IQOS are currently prohibited by the Food and Drug Administration's (FDA's) premarket approval structure, pending a decision by the FDA.³ Canada allows marketing, and has been termed a 'dark market' due to its strong tobacco advertising ban in combination with its categorisation of IQOS as a tobacco product.⁴ Italy, by contrast, has exempted IQOS from its comprehensive ban on cigarette advertising and also from the graphic warnings which are required on cigarettes.⁵

This paper describes the entry of IQOS into Israel, and its marketing campaign (see Figure 1). In 2016, when the IQOS campaign began, the adult smoking prevalence was 21.6%.⁶ Israel was a signatory to the Framework Convention on Tobacco Control (FCTC), had a governmentally approved tobacco control plan, national legislation for smoke-free public indoor and outdoor places and high levels of taxation.⁷ A partial advertising ban was in place which prohibited advertisement of tobacco products on television and radio, and in print press publications directed at youth.⁷ No premarket regulatory mechanism existed for any tobacco or nicotine product, and Israel did not have any distinct category for emerging tobacco and nicotine products.

During the first half of 2016, PM communicated directly with officials from the Ministries of Health and Finance via high-level meetings and letters prior to marketing of IQOS to the public.⁶ This is consistent with PM's global strategy.⁸ Following these meetings, the Ministry of Health (MOH) sent a letter to the Tax Authority defining IQOS as a new product which did not fall under existing tobacco regulation.⁹ PM began advertising IQOS online in December 2016. In January 2017, online sales began, and in February 2017, retail sales began. Initially, the cost was about US\$100 for IQOS plus 10 packs of HEETS (HEETS, or Heat Sticks, are the cigarette-like product inserted into the IQOS holder).

The classification of IQOS as a product not subject to existing tobacco legislation was challenged in the Supreme Court with three petitions. The first petition, filed on 12 March 2017 by Dubek, a local tobacco company, demanded that IQOS be defined as a tobacco product, with taxation equal to that on cigarettes.¹⁰ The second petition was filed on 19 March 2017 by the Israel Association for Progressive Democracy, and also demanded that IQOS be defined as a tobacco product, subject to existing regulations on tobacco

products.¹¹ The Supreme Court then requested clarification from the MOH regarding IQOS's status. On 2 April 2017, the MOH responded that IQOS should be regulated under existing tobacco legislation, as requested by the petitioners. The third petition was filed on 15 November 2017 by two advocacy organisations: The Israel Association for a Progressive Democracy and the National Initiative to Eradicate Smoking (Smoke Free Israel). They demanded that the Minister of Finance sign the bill to tax IQOS.¹² On 17 January 2018, the Minister of Finance signed the tax order for IQOS, and on 13 March 2018, following an 83–0 vote in the plenary of the Knesset, IQOS was taxed at the same rate as cigarettes.¹³

THE IQOS MARKETING CAMPAIGN

We observed five distinct advertising elements which were used in two separate campaigns, one for policy-makers, and another for the public. Examples of the advertisements are shown in figure 2A–F.

The five campaign elements

1. *PM's 'Smoke-free Israel Vision'* embodied the main concept of the entire campaign and was part of PM's global campaign for a Smoke-Free World.¹⁴ It framed the emerging tobacco and nicotine products as being fundamentally different from the combusted cigarette and promoted the idea that PM was taking a global leadership role in pursuing a world without smoke (figure 2A).
2. *The harm-reduction* element focused on transitioning smokers from combustible to non-combustible products. The claim that non-combustible products were risk-reduced compared with cigarettes appeared as part of this element. PM referred to the harmful chemicals in cigarette smoke as the main cause of tobacco-attributable illness, proposed alternatives and quoted from the FDA and the WHO (figure 2B). The advertisements did not state that the original WHO and FDA statements did not endorse any particular product, type of product or company in their original statements.
3. *IQOS status*: PM proposed that non-combustible products should enjoy a different status for the purpose of regulation due to the harm reduction (figure 2C).
4. *Taxation policy*: The content of messages regarding taxation policy were specific to Israel policy, though not specific to IQOS (figure 2C).
5. *The classic product element* was aimed at the public, and was similar to IQOS marketing elsewhere. Messages included: 'IQOS: This changes everything' (in English), TRUE (tobacco taste),



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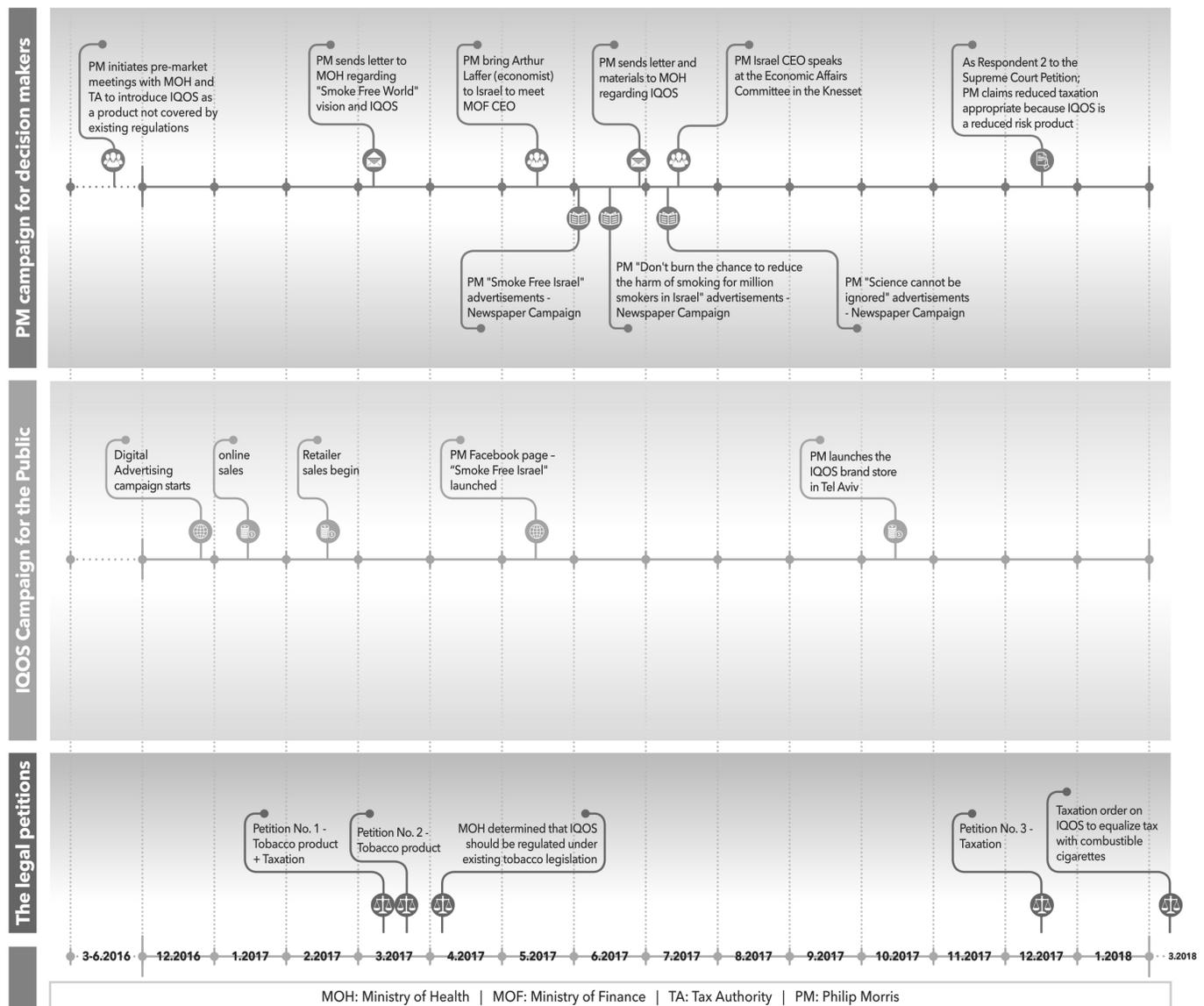


Figure 1 Timeline of IQOS campaign in Israel.

REAL (tobacco experience), 'No fire/No smoke/No ash/Less smell/Unlike cigarettes/CLEAN' (figure 2D,E,F).

The two campaigns

We observed two distinct campaigns.

The *Policy Makers Campaign* began with contacts between PM and governmental officials prior to advertisement or sales of IQOS to the Israeli public, and continued postmarketing. On 5 March 2017, these actions were complimented by a letter sent by PM to the MOH regarding their 'Smoke-Free World Vision' and IQOS.¹⁵ Advertisements in the print press were a key element of the campaign: these were publicised in the weekend editions of papers over many weeks, often in full or half-page advertisements. The earliest advertisements featured the Smoke-Free Israel Vision (figure 2A), often with text only, without pictures and without any mention of IQOS at all. In the Smoke-Free Vision ads, the PM logo was present, but not prominently. At the bottom of the advertisements were black boxed warnings. The warnings provided at the time of IQOS's launch in Israel were placed voluntarily by PM, with messages such as 'Medical researches suggest that cigarettes cause addiction' (figure 2A,D).

These advertisements used the identical style and font as governmentally required tobacco product warnings, but did not use the governmentally approved set of warnings and did not attribute them to the MOH. After IQOS's status had changed to that of a tobacco product, the black boxes included MOH-approved warnings for cigarettes and were attributed to the MOH.

Further actions in the campaign for decision-makers were reactive to the Supreme Court petitions and decisions. In March 2017, following the two first petitions by Dubek and the Israel Association for Progressive Democracy, PM placed large advertisements in the printed press demanding that the MOH 'review our science' and 'inform Israeli adult smokers about the findings in an objective and transparent manner' (figure 2B). Once IQOS was defined as a tobacco product, the battle for preferential taxation, on the basis of PM's risk-reduction argument, ensued. PM sent world-famous economist Arthur Laffer to meet with officials in the Ministry of Finance regarding taxation.¹⁶ PM further addressed the issue in well-funded print press campaigns, made possible, even after definition of IQOS as a tobacco product, by the lack of a tobacco advertising ban in the print press. The 'Don't burn the chance to reduce the harm of smoking'

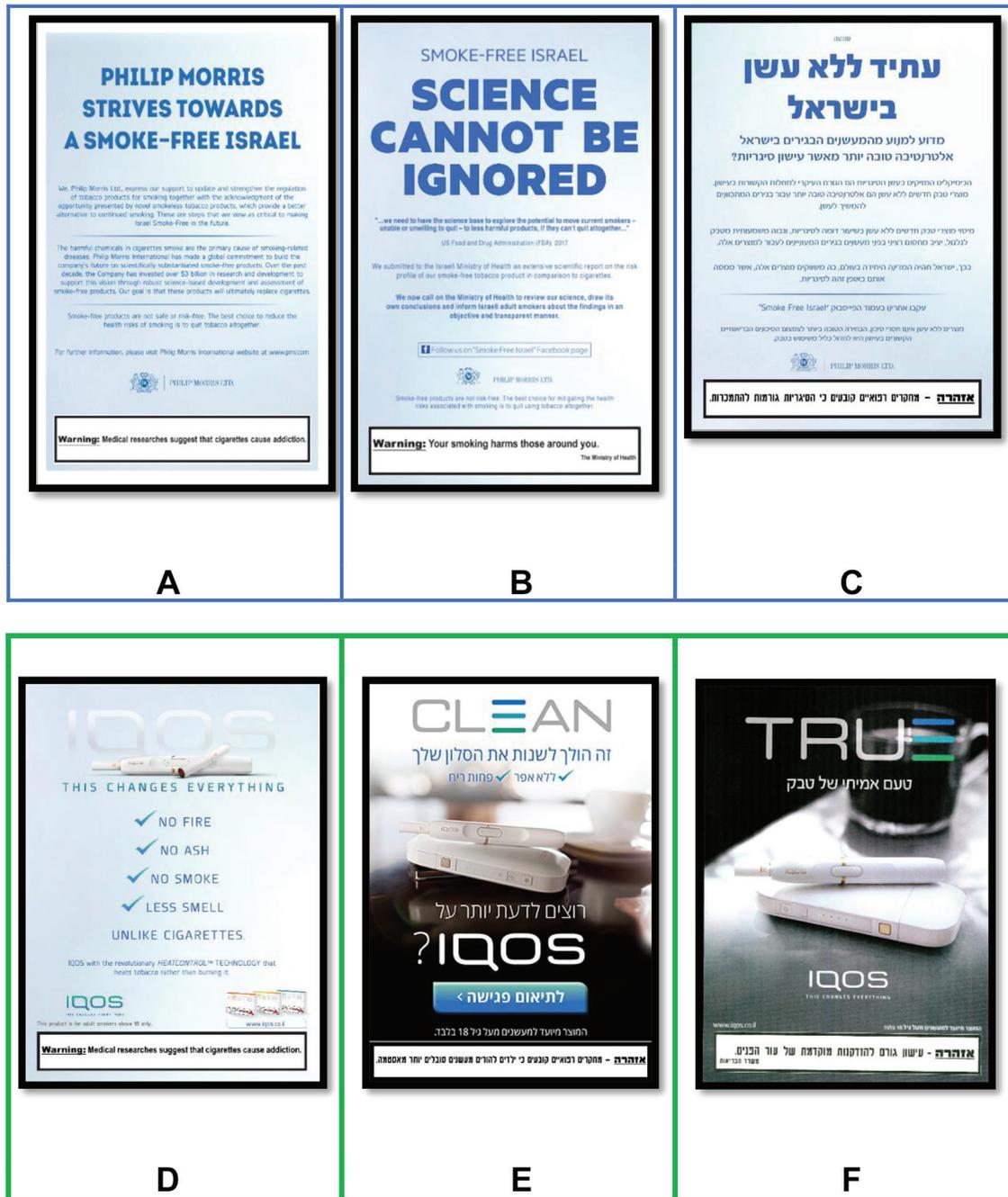


Figure 2 (A) Advertisement in English (B) Advertisement in English (C) Translation of Hebrew to English: A future without smoke in Israel. Why prevent adult smokers in Israel from having better alternatives to smoking cigarettes? The harmful chemicals in cigarette smoke are the primary cause of disease due to smoking. New smokeless tobacco products are better alternatives for smokers who plan to continue smoking. Taxation of new smokeless tobacco products at the same rate as cigarettes, at rates substantially higher than taxes on roll-your-own cigarettes, will be a serious impediment to those smokers who want to switch to these products. If this is done, Israel will be the only country in the world where these products are sold which tax them equally with cigarettes. Smoke-free products are not risk free. The best way to reduce health risks from smoking is to stop using tobacco altogether. Follow us on Facebook page Smoke Free Israel. In black box: WARNING: Medical researches suggest that cigarettes cause addiction. (D) Advertisement in English (E) Translation of Hebrew to English: This is going to change your living room. No ash. Less smell. Want to know more? To schedule an appointment, press here. This product is for adult smokers >18 only (F) Translation of Hebrew to English: True tobacco taste. This product is for adult smokers > 18 only. Warning: Smoking causes premature ageing of facial skin. The Ministry of Health.

advertisement, which appeared as full page ads, argued in favour of lower taxation. As the battle intensified, PM presented data in the advertisements about taxation policies in other countries, suggesting that if Israel did move to equalise taxation, it would be the only country in the world with equal taxation (figure 2C).

The Public Campaign, which began with the IQOS launch, started with a widely disseminated digital marketing campaign¹⁷ which included photos of the product and short text messages. The word IQOS and the phrase ‘This changes everything’ appeared, in English only, on many advertisements. This differed

from the other terms which were in Hebrew (except in advertisements in the English press, some of which are presented here). Pop-ups appeared regularly on internet sites and as people opened their smartphones or popular news websites. This was later complemented by print press advertising with similar types of messages. Other components of the campaign included a unique Facebook page under the slogan 'Smoke Free Israel' and cars with advertising messages. Package inserts advertising IQOS appeared in cigarette packages. Journalists were flown to Switzerland by PM. As an example of coverage, the report in a local English paper by a reporter flown by PM to Switzerland mentioned the words 'harm reduced' or 'less harm' 12 times in a single article, described reduced exposure to toxicants and quoted PM executives extensively.¹⁸ IQOS was also distributed to celebrities.¹⁹ ²⁰ A flagship IQOS store, closely resembling Apple iPhone stores, was opened in Tel Aviv on October 2017.

IMPLICATIONS

1. In countries such as Israel, which neither require premarket approval nor have clear product definitions for emerging products, the following types of industry behaviour may occur:
 - a. The entry of IQOS and/or other non-combustible tobacco or nicotine products may be accompanied by campaigns aimed at both policy-makers and the public.
 - b. Prior to market entry, the tobacco industry may try to define emerging products as belonging to a new type of product not covered by existing tobacco laws, even if the product label clearly states that it is a tobacco product. This is particularly important if the terminology used in local laws is based on use of the term 'smoking' which PM claims is distinct from 'vaping'.
 - c. PM may focus on its 'smoke-free vision' which is not specific to a single product or type of product, or it may emphasise a particular product.
 - d. If the product is not defined as a tobacco product subject to tobacco warnings under local laws, PM may voluntarily place warnings on the product and use the identical style and font as for locally required warnings, but with messages which would not necessarily be approved by local authorities. For example, the warning stating that 'research suggests that cigarettes cause addiction' (figure 2A,D), which was used during the IQOS campaign, may cause people to doubt the well-established evidence regarding the addictiveness of cigarettes. Introducing doubt into the public debate is consistent with the tobacco industry's previous behaviour.²¹
 - e. PM may 'change gears' during the course of the campaign, in response to regulatory proposals, in its efforts to obtain advantageous policies.
 - f. In countries where FCTC Article 5.3 is adhered to but there is a lack of a complete advertising ban, PM will be able to communicate directly with policy-makers through the media, even if IQOS is defined as a tobacco product.
 - g. In its promotional strategy, PM may selectively cite favourable policies in other countries, as well as statements made by major health organisations.
2. Because only a small minority of countries in the world have complete implementation of FCTC obligations,²² and even fewer have premarket regulation of tobacco and nicotine

products, there is worldwide vulnerability to poorly regulated industry marketing, advertisement and promotion of non-combustible tobacco and nicotine products. The absence of comprehensive, enforced marketing bans on all tobacco and nicotine products, which include digital and social media, and restrictions on health claims, are specific areas of vulnerability.

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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

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ABSTRACT

Objectives We review the Population Health Impact Model (PHIM) developed by Philip Morris International and used in its application to the US Food and Drug Administration (FDA) to market its heated tobacco product (HTP), IQOS, as a modified-risk tobacco product (MRTP). We assess the model against FDA guidelines for MRTP applications and consider more general criteria for evaluating reduced-risk tobacco products.

Methods In assessing the PHIM against FDA guidelines, we consider two key components of the model: the assumptions implicit in the model (outcomes included, relative harm of the new product vs cigarettes, tobacco-related diseases considered, whether dual or polyuse of the new product is modelled, and what other tobacco products are included) and data used to estimate and validate model parameters (transition rates between non-smoking, cigarette-only smoking, dual use of cigarettes and MRTP, and MRTP-only use; and starting tobacco use prevalence).

Results The PHIM is a dynamic state transition model which models the impact of cigarette and MRTP use on mortality from four tobacco-attributable diseases. The PHIM excludes morbidity, underestimates mortality, excludes tobacco products other than cigarettes, does not include FDA-recommended impacts on non-users and underestimates the impact on other population groups.

Conclusion The PHIM underestimates the health impact of HTP products and cannot be used to justify an MRTP claim. An assessment of the impact of a potential MRTP on population health should include a comprehensive measure of health impacts, consideration of all groups impacted, and documented and justifiable assumptions regarding model parameters.

INTRODUCTION

Philip Morris International (PMI) submitted an application to the Food and Drug Administration (FDA) to market its heated tobacco product (HTP), IQOS, as a modified-risk tobacco product (MRTP) in the USA, arguing that because the product does not actually burn tobacco, it will have a reduced impact on health compared with cigarettes. PMI used a computational model they developed, the Population Health Impact Model (PHIM),¹ to estimate the potential impact of this IQOS marketing on public health. While the application was denied by the FDA, the proliferation of purported reduced harm products suggests the need for an

understanding of how to assess the impact on population health of new tobacco products.

No models specifically consider the health impact of IQOS, but several simulation models analyse the impact of two tobacco products on population health. These models evaluate the impact of a reduced-risk tobacco product on population health by comparing a factual scenario (considering cigarette use only) with a counterfactual scenario, in which the new product is introduced. None of the models consider the impact of other tobacco products. Details of the models, the assumptions they are based on and their findings are summarised in online supplement 1 and online supplement table 1. Four models compared the health effects of cigarettes with e-cigarettes (or a vaporised nicotine product), measuring health effects either as an index² or as mortality.^{3–6} Two of these models reported a net positive impact on health^{3 4 6} while two reported net population harm.^{2 5} All four research teams assumed that e-cigarettes were safer than cigarettes by factors ranging from 5% to 30%, but they differed in their assumptions about the impact of e-cigarettes on cigarette smoking initiation and cessation. Three studies analysed the impact of introducing a non-specified MRTP on cigarette smoking and mortality. Each study reported a potential reduction in mortality,^{7–9} though one study indicated that mortality could increase if the MRTP were 50% as risky as cigarettes and 50% of initiates were never smokers.⁸ One study¹⁰ evaluated the impact of promoting use of the smokeless product snus on a health index, and concluded that promoting snus as a safer product than cigarettes is not likely to result in population health benefits.

These models illustrate how different assumptions about what is included in the model as well as the data sources for estimating transition rates and tobacco use prevalence lead to varying conclusions about the net impact of a new product. These model characteristics will be reviewed for the PHIM.

PMI's multiple tobacco product model, the PHIM, was refined for its application for IQOS. This paper reviews the FDA guidelines for MRTP applications and assesses whether the PHIM as used in the IQOS MRTP application meets the criteria the FDA has developed to determine whether or not the impact of IQOS on population health justifies the introduction of the product as an MRTP. We also consider more generally the criteria for

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assessing the impact of a new tobacco product on population health.

METHODS

We evaluate the PHIM as published^{1 11} and as submitted for marketing IQOS as a MRTP^{12 13} against FDA guidelines for MRTP applications.¹⁴ In our evaluation, we consider two key components of the model: the assumptions implicit in the model (outcomes included, relative harm of the new product vs cigarettes, tobacco-related diseases considered, whether dual or polyuse of the new product is modelled, and what other tobacco products are included) and data used to estimate and validate model parameters (transition rates between non-smoking, cigarette-only smoking, dual use of cigarettes and MRTP, and MRTP-only use; and starting tobacco use prevalence).

The FDA issued draft guidelines for MRTP applications in March 2012.¹⁴ The guidelines specify that 'scientific studies submitted by the applicant "should contain an overall assessment of the potential effect that the marketing of the product as proposed may have on tobacco-related morbidity and mortality". (p21)¹⁴ The guidelines further recommend that the potential impact on mortality and morbidity be assessed for seven population groups and exposure patterns.(p22)¹⁴

RESULTS

The PMI PHIM

The PHIM, developed by PMI researchers and their collaborators, is described briefly here and in more detail in online supplement 2. The PHIM is a dynamic state transition model which models the impact of cigarette and MRTP use on mortality. It follows a cohort aged 15 and older for 20 years. The PHIM consists of a prevalence component ('P-component') and an epidemiological risk component ('E-component').¹ The P-component models changes in the distribution of cigarette and/or MRTP use occurring in a hypothetical population over a defined period. The model compared a null (ie, no MRTP) scenario and an MRTP scenario.(p88)¹ For each scenario, transition probabilities for initiation, reinitiation and cessation of smoking and of product switching (including dual cigarette/MRTP use) are estimated from historical cigarette smoking prevalence data, and premarket Perception and Behavioral Assessment studies conducted by PMI.¹² The E-component uses the tobacco use patterns from the P-component along with estimates of the relative risk (RR) of death for lung cancer, ischaemic heart disease (IHD), stroke and chronic obstructive pulmonary disease (COPD) to estimate mortality using published estimates of RR for smoking and assumptions about how much less risky MRTP use is compared with smoking.

Sensitivity analyses vary assumptions about initiation and reinitiation of tobacco use; transition rates between smoking, MRTP and dual use; time frames; and the RR of the MRTP versus cigarettes.

Comparison of IQOS MRTP application with FDA guidelines

Impact of IQOS on morbidity

The PHIM does not include any measure of morbidity, such as incident or prevalent cases of tobacco-related illness. One way of quantifying the impact of morbidity is through healthcare costs which incorporate the severity and time course of illness, and would include hospitalisations, outpatient care, medications and other services. No estimates of healthcare costs are made in the PHIM.

Impact of IQOS on mortality

The PHIM considers mortality from four diseases caused by smoking—lung cancer, IHD, stroke and COPD.

The base case in the IQOS MRTP application assumes that compared with cigarettes, sole MRTP use is 80% less risky and dual use of MRTP and cigarettes is 40% less risky than cigarette smoking alone. The RR of death for dual use of cigarettes and IQOS is assumed to be the midpoint of the risk of cigarette smoking and the risk of IQOS use.(p19)¹² To simulate the mortality impact on the US population, the model uses smoking prevalence from 1990 projected through 2010.

Impact of IQOS on different types of individuals

We next assess how the PHIM treats the seven population groups and exposure patterns recommended for consideration by the FDA.(p22)¹⁴ More detailed descriptions are contained in online supplement table 2.

1. *Tobacco users who switch from other commercially marketed tobacco products to the proposed product.* The PHIM considers switching only from cigarettes. PMI acknowledges that other tobacco products are not considered in their model, arguing that there is no evidence to indicate that IQOS users will switch from other tobacco products.(p7)¹²
2. *Tobacco users and non-users who, after adopting the proposed product, switch to or switch back to other tobacco products that may present higher levels of individual health risk.* The PHIM assumes that each month 0.1% of IQOS users will switch to cigarette smoking, but that after a year of IQOS use virtually no users will become cigarette smokers or dual users. They also assume that 10% of dual IQOS/cigarette smokers will become sole cigarette smokers each month (p14)¹² (online supplement table 4).
3. *Tobacco users who opt to use the proposed product rather than cease tobacco use altogether.* PMI indicates that this group was 'considered by a specific analysis in which current conventional cigarette smokers who would otherwise have switched to MRTP or to dual use, quit instead'.(p5, Module 7.4)¹³ PMI indicates that 'here, the reduction in deaths associated with MRTP introduction was estimated to be about 11 times greater in males and about 13 times greater in females than that for the basic analysis'.(p5, Module 7.4)¹³
4. *Tobacco users who opt to use the proposed product rather than an FDA-approved tobacco cessation medication.* PMI indicates that this is 'outside the present scope of the model'. (p5, Module 7.4)¹³
5. *Non-users who initiate tobacco use with the proposed product, such as youth, never users, former users.* The PHIM assumes that uptake of the IQOS HTP will be limited among youth because of the relatively high cost. It assumes that the per cent of never-smokers who will initiate tobacco use with IQOS each month ranges from 0.05% to 0.08% (after 25 years), and that the rate drops with age, with no one initiating use after age 35 (p13, Module 6.5)¹² (online supplement table 3). The model assumes that reinitiation rates of former smokers with IQOS range from 0.01% for youth aged 15–19 years to 0.08% for older adults (aged 75–79 years) after more than 25 years (p13, Module 6.5)¹² (online supplement table 3).
6. *Tobacco users who use the product in conjunction with other tobacco products.* The PHIM assumes that few smokers or IQOS users will become dual users (p14, Module 6.5)¹² (online supplement table 4) and that fewer than 0.02% of never tobacco users and fewer than 0.04% of former smokers will

become dual users (p13, Module 6.5)¹² (online supplement table 3).

7. *Non-users who experience health risks from the product.* Risk to non-users is not considered in the PHIM.

DISCUSSION

The PHIM is similar in structure to many of the published models reviewed which are all dynamic in nature and model state transitions in tobacco use over time, with the exception of one steady state model.² The PHIM focuses on mortality as the outcome measure as do all but two models which included a health effects index.^{2 10} The PHIM models the population aged 15 and older, an improvement over some of the models which focus on a subgroup of the population. It follows the population for 20 years which is reasonable for MRTP application purposes, and is in line with the published models which use varying time horizons from 10 to 84 years.

However, the PHIM analysis of IQOS has some important limitations that are apparent in reviewing the model against FDA recommendations. Morbidity-related outcomes are omitted, mortality is underestimated, transition rates used in the model are based on PMI perception studies and the model uses data for the USA in 1990 as a starting point. The role of other tobacco products such as e-cigarettes and impact on non-users are not considered. Thus, the analysis of IQOS does not fully satisfy FDA guidelines for MRTP applications, and results in an overestimation of the benefit of IQOS on population health.

Morbidity is ignored

The PHIM does not include any measures of morbidity, such as tobacco-related disease incidence or tobacco-attributable health-care costs, though this is an FDA requirement. Morbidity costs are more than half of total costs of cigarette smoking for high-income countries,¹⁵ so this omission is potentially serious.

Mortality is underestimated

The clinical results presented for US adults to justify the lower RR of mortality for IQOS versus cigarette use do not show statistically significant improvements in the biomarkers of harm that PMI assessed in actual people who used HTP (with a single exception).¹⁶ This contradicts the assertion of reduced harm, and does not justify the 70%–90% reductions in risk assumed in the PHIM. The RR of mortality for IQOS compared with cigarettes is a critical parameter in the model and a smaller reduction in harm should be used in the analyses.

The RRs of mortality from smoking used in the PHIM are based on multicountry studies rather than those published by the 2014 US Surgeon General and based on US cohorts.¹⁷ PMI's sensitivity analyses indicate that the proportion of smoking-attributable deaths from the four causes for men would increase 15% (2005–2009) if based on the RRs from the Surgeon General report,¹¹ with less of a change for women. The Surgeon General estimates, which are more current and vetted through a more thorough process of independent peer review than the PHIM estimates, are more appropriate and should be used in these analyses.

The PHIM assumes that the RR of dual use of IQOS and cigarettes is the midpoint of the two RRs. However, there is some evidence that dual users of cigarettes and e-cigarettes have greater risks of negative health outcomes than sole cigarette users,¹⁸ suggesting that there could be greater risks for dual users of IQOS and cigarettes and that the PHIM model may underestimate the number of deaths attributable to dual use.

The inclusion of only four smoking-attributable diseases in the PHIM further reduces the estimates of mortality from IQOS versus cigarette use. At least 22 causes of death for adults¹⁹ and 4 causes of death for infants²⁰ have been causally linked to cigarette smoking. PMI acknowledges that the 'overall estimates of deaths saved due to the introduction of IQOS would have to be increased about 50% to give an estimate for all smoking-related diseases combined'.(p41)¹²

Given that mortality is the main measure of population health used in the PHIM, the use of low RRs and the inclusion of only four causes of death will result in an overestimate of the benefit of IQOS introduction as an MRTP which will greatly impact the results.

Assumptions about transition rates are not well justified

The PHIM uses transition probabilities for smoking dating back to 1986 for 12 countries. PMI does report an adjustment for poor model forecast performance through 2005 but does not report the methodology or provide documentation of the model predictions against historical data. Other models use more recent data, document the methodology and report the predictive performance against historical data. For example, Warner and Mendez⁶ validate their model to US data through 2015, and Levy *et al*³ calibrate their model using US data through 2010. The absence of an explanation of methodology and documentation for the PHIM predictive performance is a serious weakness because poor forecasts of status quo and alternative scenarios may bias the results.

Transition probabilities for IQOS initiation, reinitiation, cessation and product switching are based on PMI perception surveys. The only empirical data available are from Italy, but these data report on ever use and are thus not comparable with the PHIM estimates.²¹ Youth have initiated tobacco use with e-cigarettes at high rates,²² and may find the IQOS product to be similarly appealing. Flavours, electronic features and perceptions of harm are factors that are important determinants of adolescent decisions regarding tobacco use, and IQOS is likely to appeal to them on all these characteristics.²³ The PHIM assumption that youth uptake will be limited because of the relatively high cost ignores the use of coupons to reduce prices, a common tobacco industry pricing strategy, and also ignores shared use among users. Recent estimates suggest that the prevalence of sharing e-cigarette devices among adolescents over the previous 30 days exceeds 70%.²⁴

The PHIM makes optimistic assumptions about cigarette smoking cessation rates associated with IQOS use, assuming that 0.4%–1.5% of smokers will quit smoking each month due to IQOS use,(Module 6.5)¹² (online supplement table 3) a relatively high rate in light of evidence that many IQOS users continue to smoke cigarettes, including PMI's own finding that 36% of Japanese IQOS users use another tobacco product.²⁵ Recent research has produced evidence for the USA that, with the current regulatory environment and smoking behaviours, e-cigarettes do not increase smoking cessation in the general population greater than what would have occurred without them.²⁶ Furthermore, the potential effectiveness of e-cigarettes in aiding smoking cessation may depend greatly on the level of the smoker's nicotine dependence.²⁷ This is also likely to impact the effectiveness of IQOS in cessation, but is not acknowledged in the PHIM.

The potential gateway effect of IQOS is not fully considered. There is evidence for youth and young adults that e-cigarette use increases subsequent uptake of cigarette smoking.²⁸ PMI

indicates in its application that IQOS mimics cigarette smoking better than e-cigarettes or vaping because of more rapid nicotine delivery, suggesting that IQOS may be much more effective at addicting youth and young adults to nicotine as well as increasing transitions to cigarette smoking. A net increase in nicotine addiction and cigarette uptake among adolescents and young adults is a realistic possibility that the PHIM does not consider.

Transition rates are one of the key parameters in the model, and their correct estimation is critical to the results.

The model uses the 1990 US population and smoking prevalence as the starting point for the simulations

The PHIM simulates the health impact on the population starting with a baseline population and smoking prevalence representative of the USA in 1990. (Module 6.5.2.2)¹² It is not clear why 1990 data was used, when smoking prevalence was much greater than in more recent years; data for 2015 were readily available at the time of the analyses. Other published models use more recent prevalence data from 2000,⁸ 2006,¹⁰ 2011⁶ and 2016.³ The use of 1990 prevalence is likely to lead to higher than actual smoking-attributable costs and higher expected benefits from IQOS.

The PHIM ignores other tobacco products, such as e-cigarettes

The population health results would be different if the PHIM comparison were between IQOS and a lower-risk product such as e-cigarettes. There are reasons to expect that e-cigarette users may find IQOS to be a tempting and attractive product, and ignoring the role of e-cigarette use in a model of the population health impact of IQOS will lead to an incomplete analysis.

The PHIM assumes very low rates of transition to dual use, contrary to empirical evidence from other countries showing that many of those individuals who use IQOS will continue to use their previous product. In Japan, where IQOS products are now available, over one-third of IQOS users are polyusers, most of whom also smoke cigarettes.²⁵ Dual use of electronic tobacco products (HTP products including IQOS, Glo and Ploom Tech, or non-nicotine e-cigarettes) and combustible cigarettes was reported by 3.4% of Japanese internet survey respondents in 2017.²⁹ Thus, actual evidence of dual IQOS and cigarette use indicates that the assumptions of dual use rates in the PHIM are too low.

Impact of IQOS on non-users is not considered

Ignoring the impact on non-users who experience health risks from IQOS is not reasonable. Empirical evidence already exists for second-hand exposure from HTP aerosol. A Greek study found that nicotine levels for IQOS aerosol were greater than those in e-cigarettes at low puff duration, though lower than tobacco cigarettes.³⁰ Another study using an animal model that exposed rats to cigarette smoke and IQOS aerosol at levels that were relevant to real-world human exposure levels found that both exposures resulted in similar vascular impairment.³¹ There is also direct evidence of negative health impacts from exposing human non-users to HTP aerosol. In Japan, 49% of never-tobacco users and 41% of former tobacco users exposed to second-hand HTP aerosol reported symptoms including general illness, eye discomfort or a sore throat.²⁹

Children are particularly likely to be impacted by exposure to HTP products. They may suffer negative health effects when exposed to their parents' second-hand aerosol, as they are when exposed to second-hand cigarette smoke.³²⁻³⁴ A Canadian study

found that children suffered respiratory effects from exposure and digestive effects of ingestion of e-cigarettes.³⁵ Women who use IQOS while pregnant may cause lifelong health impacts for their children, as is the case for women who smoke cigarettes or use snuff while pregnant.^{20 36 37} Another potential risk from IQOS use is fires and explosions, such as those that occur with e-cigarettes. Ignoring the health impact of IQOS on non-users overestimates the benefit of IQOS as an MRTP. While this impact may be of a smaller magnitude than the impact on users of IQOS or cigarettes, the impact on non-users is recommended by the FDA for consideration.

CONCLUSION

The PHIM has a structure not unlike other simulation models reviewed. However, because it is used to justify the marketing of a tobacco product as a MRTP, it must satisfy FDA guidelines that other models are not subject to. The FDA is likely to receive a number of applications for MRTP orders in the coming years, and it is important that reasonable criteria be established for reviewing them. Future analyses of the impact of new tobacco products used for social decision-making such as regulatory actions should consider all relevant and substantial social effects. This includes both morbidity and mortality that arise from a comprehensive list of tobacco-attributable diseases. Model-based estimates need to carefully document methods for estimating key parameters such as transition rates and to validate model's predictive performance. Also, the effects of policy on all populations that will be affected should be included in the analyses, including non-tobacco users who will suffer health effects. These recommendations are relevant for the evaluation of new tobacco products as well as potential harm-reduction products more generally.

PMI, through its analysis of IQOS using the PHIM, has not shown that this product would 'significantly reduce harm and the risk of tobacco-related disease to individual tobacco users;

What this paper adds

- ▶ Heated tobacco products (HTP), also referred to as heat-not-burn products, are not currently marketed in the USA and their impact on the health of the US population is not known.
- ▶ Philip Morris International developed a Population Health Impact Model that they used to estimate the potential impact of marketing an HTP, IQOS, as a modified-risk tobacco product (MRTP) in the USA.
- ▶ Because the model is used to support an MRTP application, the Food and Drug Administration guidelines indicate that it should include the impact of the new product on morbidity and mortality, and the impact on seven population groups and exposure patterns. However, the model underestimates mortality, omits morbidity measures, excludes impacts on non-users and underestimates the impact on other groups. Therefore, the model underestimates the potential impact of IQOS on the population as a whole and does not justify marketing the product as an MRTP.
- ▶ An assessment of the impact of a new tobacco product on population health should include a comprehensive measure of health impacts, consideration of all groups impacted, and documented and justifiable assumptions regarding model parameters such as the relative harm of the new product compared with existing products and transition rates between tobacco use categories.

and benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products'. (p3)¹⁴ As new tobacco products are introduced into US and worldwide markets, particularly those that purport to be less harmful than currently used products, models of population health impacts will play an important role. The PMI PHIM as applied to the marketing of IQOS as a MRTP illustrates some of the potential pitfalls of analysis that should be avoided.

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Light and mild redux: heated tobacco products' reduced exposure claims are likely to be misunderstood as reduced risk claims

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ABSTRACT

Introduction Heated tobacco products (HTPs) are being marketed in several countries around the world with claims that they are less harmful than combusted cigarettes, based on assertions that they expose users to lower levels of toxicants. In the USA, Philip Morris International (PMI) has submitted an application to the Food and Drug Administration (FDA) in 2016 seeking authorisation to market its HTPs, IQOS, with reduced risk and reduced exposure claims.

Methods We examined the PMI's Perception and Behavior Assessment Studies evaluating perceptions of reduced risk claims that were submitted to the FDA and made publicly available.

Results Qualitative and quantitative studies conducted by PMI demonstrate that adult consumers in the USA perceive reduced exposure claims as reduced risk claims.

Conclusion The data in the PMI modified risk tobacco product IQOS application do not support reduced risk claims and the reduced exposure claims are perceived as reduced risk claims, which is explicitly prohibited by the FDA. Allowing PMI to promote IQOS as reduced exposure would amount to a legally sanctioned repeat of the 'light' and 'mild' fraud which, for conventional cigarettes, is prohibited by the US law and the WHO Framework Convention on Tobacco Control.

INTRODUCTION

Heated tobacco products (HTPs), also called heat-not-burn products, are tobacco products that heat tobacco to temperatures that avoid combustion and produce a nicotine aerosol that is inhaled by smokers and may also generate side-stream emissions.¹ As of February 2018, HTP entrants into the global market included Philip Morris International's (PMI)'s 'IQOS', British American Tobacco's 'Glo', Japan Tobacco's 'Ploom Tech' and RJ Reynolds' revamped 'Eclipse'. Because of the growing evidence of severe negative health effects of smoking and smokers' concerns about their health, tobacco companies have been motivated to create 'safer cigarettes' since the 1960s, and in 1988 they first introduced HTPs, marketing them as less harmful than combusted cigarettes. While HTPs produce different toxic chemicals than combusted cigarettes,² the human health effects of HTPs are not completely understood and the evidence that PMI submitted to the US Food and Drug Administration (FDA) revealed that, in terms of the clinical biomarkers of disease³ or pulmonary and immune toxicity,⁴ IQOS was not significantly different from cigarettes.

As of February 2018, the new HTPs, like PMI's IQOS, were being sold in multiple countries around the world in minimalist high-tech looking stores that resemble Apple stores.⁵⁻⁷ Advertisements and marketing materials for IQOS emphasise both its superiority over combustible cigarettes (in terms of cleanliness and customisability) and similarity to them (in terms of product's taste, size and providing similar behavioural experience).⁶ Claims about health benefits or lower risks of IQOS are not emphasised in the marketing materials and some of the materials carry minimal health warnings, such as 'This tobacco product can harm your health and is addictive'⁶ or it is 'not risk-free or a safe alternative to cigarettes but it is a much better choice than smoking.'⁷ Before IQOS is introduced into the US market, PMI needs the FDA's permission. The 2009 Family Smoking Prevention and Tobacco Control Act⁸ (FSPTCA) assigns the FDA authority to regulate the manufacturing, marketing and distribution of tobacco products in the USA. Tobacco manufacturers may seek authorisation from FDA to market products with claims that they reduce risks of tobacco-related diseases compared with other tobacco products currently on the market.

To obtain FDA authorisation to market a product as a 'modified risk tobacco product' (MRTP), a company must submit an MRTP application to FDA. FDA may issue one of two types of orders permitting such marketing: (1) a 'risk modification order' or (2) an 'exposure modification order'.^{9,10} For a *risk modification* order, a company must provide scientific evidence that the product 'as actually used by consumers will (1) significantly reduce harm and the risk of tobacco-related disease to individual users and (2) benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products.'¹⁰ When such scientific evidence is not available and cannot be obtained without long-term epidemiological studies, an *exposure modification* order can be issued if the company demonstrates that such an order would be appropriate for promoting public health (once again taking into account both users and non-users) and that lower levels of harmful chemicals in the product will likely result in reduced death and disease among individual tobacco users. Under the exposure modification order, the marketing claim can only state that the product has lower levels of or is free of a certain substance. Furthermore, a company needs to demonstrate that "consumers will not be misled into believing that the product is [...] less harmful or presents [...] less of a risk of disease than



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one or more other commercially marketed tobacco products.”⁹ The FSPTCA puts the burden on the MRTP applicant, not the FDA, to demonstrate that the product presents reduced risk or reduced exposure and to demonstrate that consumers do not perceive reduced exposure claims as reduced risk claims.

Long before the MRTP process was enacted in 2009, tobacco companies had been misleading the public with reduced exposure claims since the 1950s, asserting that filtered and low-tar cigarettes¹¹ gave smokers ‘less tar and nicotine’,¹² a reduced exposure claim. ‘Light’ and ‘mild’ cigarettes have been marketed to smokers concerned about their health and positioned as an alternative to quitting smoking.^{13–15} Even though advertisements for light and mild cigarettes almost never explicitly stated that they would reduce risk of tobacco-related disease, people who saw these advertisements with reduced exposure claims perceived these cigarettes to have lower health risks than regular cigarettes.^{16–17}

Furthermore, these cigarettes did not result in lower levels of exposure to harmful chemicals for users. Tobacco companies created them with microscopic ventilation holes in the filters to draw in air and reduce machine-measured tar and nicotine, which gave the appearance that these products delivered lower emissions to the user.^{18–19} However, the cigarette companies designed these products so that smokers would compensate for dilution of the smoke by blocking ventilation holes with their lips, taking larger puffs or taking more frequent puffs.^{20–23}

This inherently deceptive nature of reduced exposure and reduced risk (‘light’ and ‘mild’) marketing claims was at the core of the US Department of Justice’s Racketeer Influenced and Corrupt Organization (RICO) Act lawsuit against the major cigarette companies for defrauding the public about the dangers of smoking and which essentially became the basis of the FSPTCA’s MRTP provisions. In August 2006, Federal Judge Gladys Kessler held²⁴ that the tobacco companies, including Philip Morris, violated RICO by fraudulently covering up the health risks associated with smoking and for marketing their products to children. Judge Kessler found that the companies “have engaged in and executed – and *continue to engage in and execute* -- a massive 50-year scheme to defraud the public, including consumers of cigarettes, in violation of RICO [emphasis added].” In her 1683-page opinion with extensive Findings of Fact, Judge Kessler found, among other fraudulent acts, that Philip Morris and other tobacco companies deceptively marketed cigarettes characterised as ‘light’ or ‘low tar’, while knowing that those cigarettes were at least as hazardous as ‘full flavoured’ cigarettes; misled smokers, former smokers and non-smokers to believe that these cigarettes were safer and deliberately targeted the youth market (see table 1 for examples of relevant findings). Importantly, the court found that there was a reasonable likelihood that defendants would continue to violate RICO in future.

Following the 2006 RICO decision, in 2009, Congress recognised and described the tobacco companies’ use of reduced exposure claims to mislead the public and Judge Kessler’s findings in 14 of the 49 Findings for the FSPTCA.¹⁰ Of particular relevance, Congressional Finding 40 states: “The dangers of products sold or distributed as modified risk tobacco products that do not in fact reduce risk are so high that there is a compelling governmental interest in ensuring that statements about modified risk tobacco products are complete, accurate, and relate to the overall disease risk of the product.”

Given the long history of the tobacco industry using reduced exposure claims to mislead consumers into believing that the products in question have reduced risk, most notably through the use of ‘light’ and ‘mild’ cigarette claims, it is important to

Table 1 Relevant findings from Racketeer Influenced and Corrupt Organization case

“According to [Brand Manager of Marlboro from 1969 to 1972, James] Morgan, Philip Morris made a calculated decision to use the phrase ‘lower tar and nicotine’ even though its own marketing research indicated that consumers interpreted that phrase as meaning that the cigarettes not only contained comparatively less tar and nicotine, but also that they were a healthier option.”	²⁴ Para 2402, p. 888
“Morgan, who later became CEO of Philip Morris, further explained in 2002 that rather than relying on the tar and nicotine numbers from the FTC Method, ‘the major influence in people’s perceptions in the tar of a cigarette would have come from the marketing positioning of a brand as opposed to people literally reading the FTC [tar and nicotine figures].’”	²⁴ Para 2403, p. 888
Philip Morris and the other tobacco companies knew that “many smokers who were concerned and anxious about the health risks from smoking would rely on the health claims made for low tar cigarettes as a reason, or excuse, for not quitting smoking”	²⁴ Para 2627, p. 971

evaluate to what extent the modified risk claims for the new HTP products are based on scientific evidence and whether reduced exposure claims are perceived by consumers as reduced risk claims. This paper uses the materials in the PMI MRTP application made public by the FDA to evaluate these claims.

METHODS

We examined the materials in the PMI MRTP applications to FDA²⁵ for its HTP IQOS system and Heatstick products (PMI also refers to IQOS as Tobacco Heating System (THS) 2.2 in these materials). On 5 December 2016, PMI submitted its MRTP applications asking the FDA to authorise marketing of IQOS with reduced risk and reduced exposure claims. Our analysis is based on the Executive Summary²⁶ and Module 7: Scientific Studies and Analyses,²⁷ specifically Section 7.3 Studies in Adult Human Subject (7.3.2 Perception and Behavior Assessment (PBA) Studies), studies THS-PBA-02-US, THS-PBA-03-US, THS-PBA-04-US and THS-PBA-05-REC-US. We report PMI’s findings on the consumer perceptions of reduced exposure claims.

RESULTS

To develop and evaluate marketing messages and materials with reduced risks and reduced exposure claims, PMI conducted Consumer PBA Studies (table 2). Participants were recruited by phone from proprietary databases maintained by local research agencies, which include people interested in participating in market research. Participants’ smoking status was based on self-report.

Qualitative studies

PMI’s qualitative studies (THS-PBA-02-US and THS-PBA-04-US) were conducted by TNS Qualitative. Focus groups and individual interviews were conducted in person, in facilities with one-way mirrors with PMI representatives observing the studies. They followed discussion guides and employed ‘visual aids’ to position products on relative risk and interest to use scales. Focus groups lasted 2.5 hours, while individual interviews took 1.5 hours. Participants evaluated various messages containing either reduced exposure or reduced risk claims. In THS-PBA-02-US, they evaluated 13 messages in focus groups in Phase 1 (Online Supplementary 1), which were subsequently modified

Table 2 Philip Morris International's (PMI)'s Consumer Perception and Behavior Assessment (PBA) Studies in the USA

Study name	Methodology	Location	Study year	Participants	Age	Materials
THS-PBA-02-US	Qualitative 20 focus groups (n=113) 37 individual interviews	Boston, MA Chicago, IL Charlotte, NC Phoenix, AZ	Oct–Dec 2013	S-NITQ, S-ITQ, FS, NS*	21+	Nine potential 'plain text'† messages‡
THS-PBA-03-US	Quantitative (n=1713)	Chicago, IL Marlton, NJ Phoenix, AZ Atlanta, GA	Oct–Dec 2014	S-NITQ, S-ITQ, FS, NS	LA+	Three potential 'plain text'† messages selected from THS-PBA-02-US
THS-PBA-04-US	Qualitative 28 individual interviews	Chicago, IL Phoenix, AZ	Dec 2014	AS, FS, NS	18+	Five potential branded§ communication materials with claims selected from THS-PBA-02-US
THS-PBA-05-RRC-US	Quantitative (n=2255)	Paramus, NJ Dallas, TX St Louis, MO Los Angeles, CA	Jul 2015	S-NITQ, S-ITQ, FS, NS	LA+	Three branded§ communication materials with claim #1 'Reduced risks of tobacco-related diseases'
THS-PBA-05-RRC2-US	Quantitative (n=2247)	Marlton, NJ Chicago, IL Tampa, FL Denver, CO	Sep 2015	S-NITQ, S-ITQ, FS, NS	LA+	Three branded§ communication materials with the claim #2—'Reduced risk of harm'
THS-PBA-05-REC-US	Quantitative (n=2272)	Framingham, MA San Diego, CA St Louis, MO Baltimore, MD	Dec 2015	S-NITQ, S-ITQ, FS, NS	LA+	Three branded§ communication materials with the claim #3 'Reduced body's exposure to harmful and potentially harmful chemicals'

*Never smokers participated only in Phase 2 of THS-PBA-02-US.

†'Plain text' message describes the information communicated on the product.

‡The table in the PMI document says nine messages, but the file (Online Supplementary 1) for Phase 1 shows 13 messages because there are two versions of some (A1, A2, B, C1, C2, D and so on). Phase 2 tested seven messages (Online Supplementary 2).

§The branded communication materials were brochure, pack and direct mail piece with iQOS commercial name and the Tobacco Sticks as HeatSticks with the Marlboro Brand. AS, adult smokers; FS, adult former smokers; LA, legal smoking age; NS, adult never smokers; S-ITQ, adult smokers with the Intention to quit; S-NITQ, adult smokers with no intention to quit.

Source: adapted from table 1 Overview of the Studies from PMI Research and Development⁵¹ (p. 7).

into seven messages for testing with individual interviews in Phase 2 (Online Supplementary 2).

Participants frequently equated reduced exposure claims with reduced risk, conflating the reduction in chemicals with lower chances of developing tobacco-related health issues. For example, female smoker (21–34 years old, Phoenix) stated: "It reduces your body's exposure to the chemicals... that would be my biggest take-away... it suggests that it is better for you than a traditional cigarette." When asked to clarify: (Better—In what way?), she specified: "It's the lesser of two evils; it's a better bad choice... It reduces harmful chemicals which is likely to reduce your chances of getting a tobacco-related disease."

While the PMI's claims that reduced exposure does not mean reduced harm tried to address this issue, some people found this juxtaposition of a claim of reduced exposure and no reduced harm confusing and hard to believe, which reduced credibility of the message source. Female smoker (21–35 years old, Boston) explained: "It says to me that if you smoke this or if you use this thing, you're still at risk of getting all those diseases that they claim it reduces your exposure to... The way it's worded... I'm not buying into it. It's kind of doubletalk... [...] It's flip flopping, saying it will reduce but you still might get it, or ... It's just weird, it doesn't make me want to use it at all, now that I'm reading this... This makes me less likely to use it, because I'm... almost mad that it tries to claim that it... has benefits, but it really doesn't."

The THS-PBA-02-US Study report concludes that all messages (both reduced risk and reduced exposure claims) were perceived by participants as statements about lower harm. In Phase 2, three out of seven messages were reduced exposure claims. For all three reduced exposure messages, the PMI's report stated that

participants perceived IQOS to be a lower risk than conventional cigarettes because the tobacco is heated, not burned, which results in reduced 'exposure to harmful chemicals' (pp. 31, 34) and 'the absence of smoke and second-hand smoke' (p. 37).²⁸ For the four reduced risk messages, the report similarly concluded that the product was 'perceived to be a lower risk than conventional cigarettes' (pp. 40, 42, 44, 46) by 'reducing the production of harmful chemicals found in cigarette smoke and providing a possible chance of reducing the risk of tobacco-related diseases' (pp. 44, 46).²⁸

The fact that PMI's report does not distinguish perception of reduced risk and reduced exposure provides additional evidence that reduced exposure claims are viewed as reduced risk claims.

The findings from the second qualitative study (THS-PBA-04-US) that assessed reduced risk and reduced exposure claims in the context of marketing materials (brochure, pack and direct mail) portray a similar picture. The study report concludes that "There is a clear recognition that this is an innovative product that heats, rather than burns, the tobacco using electronic technology combining the tobacco taste satisfaction of CC's [conventional cigarettes] with hygiene benefits (less odor, no ash, less mess) and the potential to reduce the risk to health compared to smoking conventional cigarettes."²⁹ Also, "Understanding is generally consistent across all label, labeling and marketing material and subject groups."²⁹

In this second qualitative study, reduced exposure claims in combination with the information that IQOS does not reduce risk of tobacco-related disease (presented as 'Important Warning') were also perceived as confusing and contradictory, but still made participants rate the risk as moderate, below the

risk of conventional cigarettes. Some participants were able to articulate that reduced exposure does not mean reduced risk:

“It’s still as risky as smoking a cigarette. It does not mean a reduction in the risk of developing tobacco related diseases... Tobacco related diseases are what you get from smoking cigarettes. It’s telling me that even though it scientifically reduces my body’s exposure to these chemicals, I have the exact same risk of developing a tobacco-related disease.” (female adult smoker, 26–35 years old, Chicago).

Yet others were still very optimistic about the product that offers reduced risk, particularly appreciating the implications of reduced exposure as the ability to use HTPs in smoke-free places:

“There’s still a risk, so we all know we can’t get anywhere besides- you can’t get anywhere, you can’t even hide from that, so there’s going to be risk. But it’s just a better way of smoking a cigarette. It gives you a better option. ‘Real tobacco, no fire, tobacco heating system’, so obviously trying to make it a better way of smoking, make it better for you to smoke at your workplace, school, anywhere. So yeah, that’s what I get from it. Well, they give you the less odor, no fire. It even tells you-it gives you a little hint that it will be better for the people that’s around you worrying about affecting them, so that’s good.” (male adult smoker, 18–25 years old, Phoenix).

In summary, PMI’s qualitative studies demonstrate that US adults understand reduced exposure claim to mean that the lower levels of harmful chemicals in the product means reduced risk of health harms.

Quantitative studies

PMI reports results of two quantitative studies (THS-PBA-03-US and THS-PBA-05-REC-US, see table 2 for details) that were conducted by Covance Market Access Service. Quantitative studies were five-arm parallel group experiments, where each arm corresponded to the different message condition tested in the study. Studies used computer-assisted self-interviews (with computer-assisted personal interviews for more in-depth questions in THS-PBA-03-US) and lasted 45 min on average. The outcome measures used in these studies are presented in table 3. For the purpose of our study, we focus on the measures PMI used to assess global comprehension and risk perceptions because they indicate to what extent reduced exposure claims are perceived as reduced risk claims.

In THS-PBA-03-US, five different text-based messages were evaluated: four contained reduced exposure claims and one had a reduced risk claim (figure 1). Participants were randomised into five groups, where each group saw one of the messages. For the measure of global comprehension, the proportion selecting the answer ‘Reduces the risk of tobacco-related diseases’ was 18% for reduced exposure Message 3, 28% (Message 2), 32% (Message 1) and 35% (Message 4). For all perceived risk measures (health risk to self (figure 3), addiction risk and risk to others), participants rated IQOS lower in risk than cigarettes for all messages, whether it was a reduced exposure message or a reduced risk message.

In THS-PBA-05-REC-US, participants evaluated marketing materials with a reduced exposure warning: a brochure, a pack

Table 3 Outcome measures in quantitative studies

Construct	Instrument	Example question
Intent to Use	The Intent to Use Questionnaire <ul style="list-style-type: none"> ▶ Intention to Try (ie, to sample at least once; two items) ▶ Intention to Use (ie, for continued usage; two items) (Answers on 6-point scale from ‘Definitely Not’ to ‘Definitely’).	Based on what you know about IQOS, how likely or unlikely are you to try IQOS? If you try IQOS and like it, and taking into consideration the prices that are shown on the material, how likely or unlikely are you to use IQOS regularly?
Change in Intention to Quit Smoking	Yes/No questions based on Prochaska and DiClemente’s Stages of Change model (Prochaska and DiClemente 1982) measured before and after exposure to THS 2.2 message to determine change in Intention to Quit Smoking (four items).	Are you seriously considering quitting smoking within the next 6 months?
Comprehension	1. ‘Global comprehension’: overall comprehension of the THS 2.2 message on exposure to harmful chemicals and risk of tobacco-related diseases of using THS 2.2. 2. ‘Specific comprehension’: comprehension of three specific parts of the THS 2.2 message: the Intended Users Statement, Evidence Statement and Warning Statement. Both types of comprehension were assessed with multiple choice questions; five response options were presented, with one correct option, three incorrect options and an option for ‘don’t know’.	1. Thinking about all of the information on the card, would you say that compared with cigarettes, using THS 2.2: a. Has a greater risk of tobacco-related diseases b. Reduces the risk of tobacco-related diseases c. Has not been demonstrated to reduce the risk of tobacco-related diseases (correct) d. Eliminates the risk of tobacco-related diseases e. Don’t know 2. What happens to tobacco when IQOS is used? a. It is burned b. It remains at room temperature c. It is cooled d. It is heated but not burned (correct) e. Don’t know
Risk Perception	The Perceived Risk Instrument-Personal Risk comprised of two domains, each measured by a unidimensional scale: 1. Perceived Health Risk 18-item scale 2. Perceived Addiction Risk 7-item scale 3. Perceived Harm to Others (two separate questions) Answers were no risk, low risk, moderate risk, high risk, very high risk and don’t know and were later converted into a 0–100 scale (0=no risk and 100=very high risk).	1. If you were to start using IQOS, what do you think would be the risk, if any, to you personally of getting the following (sometime during your lifetime) because you use IQOS... losing some sense of taste, having heart disease, an earlier death, having sores of the mouth or throat and so on. 2. If you were to start using IQOS, what do you think would be the risk, if any, to you personally of experiencing the following because you use IQOS... being unable to quit cigarettes, feeling like you have to smoke cigarettes and so on. 3. If you were to start using IQOS, what do you think would be the risk, if any, to others because you use IQOS... harming others through your secondhand smoke, harming unborn baby.

Source: adapted from table 17 in the Executive Summary, p. 121.²⁶

Message 1	Message 2	Message 3	Message 4	Message 5
Evidence Statement 1 (reduced exposure) <ul style="list-style-type: none"> • When tobacco is burned, it produces many harmful or potentially harmful chemicals. • THS 2.2 heats tobacco but does not burn it • With the exception of nicotine, with THS 2.2 there is a significant reduction in the production of harmful or potentially harmful chemicals 	Evidence Statement 1 (reduced exposure) <ul style="list-style-type: none"> • When tobacco is burned, it produces many harmful or potentially harmful chemicals. • THS 2.2 heats tobacco but does not burn it • With the exception of nicotine, with THS 2.2 there is a significant reduction in the production of harmful or potentially harmful chemicals 	Evidence Statement 2 (reduced exposure) <ul style="list-style-type: none"> • THS 2.2 heats tobacco but does not burn it • This significantly reduces the production of harmful or potentially harmful chemicals • Scientific studies have shown that switching completely from cigarettes to THS 2.2 significantly reduces your body's exposure to harmful or potentially harmful chemicals 	Evidence Statement 2 (reduced exposure) <ul style="list-style-type: none"> • THS 2.2 heats tobacco but does not burn it • This significantly reduces the production of harmful or potentially harmful chemicals • Scientific studies have shown that switching completely from cigarettes to THS 2.2 significantly reduces your body's exposure to harmful or potentially harmful chemicals 	Evidence Statement 3 (reduced risk) <ul style="list-style-type: none"> • THS 2.2 heats tobacco but does not burn it • This significantly reduces the production of harmful or potentially harmful chemicals • Scientific studies have shown that switching completely from cigarettes to THS 2.2 can reduce the risks of tobacco-related diseases
WARNING A <ul style="list-style-type: none"> • <u>It has not been demonstrated</u> that switching to THS 2.2 reduces the risk of developing tobacco-related diseases compared to smoking cigarettes • THS 2.2 tobacco sticks contain nicotine which is addictive • Using THS 2.2 can harm your health 	Warning B1 <ul style="list-style-type: none"> • A significant reduction in the production of harmful chemicals, compared to cigarettes, <u>does not mean a reduction in the risk of tobacco-related diseases</u> • THS 2.2 tobacco sticks contain nicotine which is addictive • Using THS 2.2 can harm your health 	WARNING A <ul style="list-style-type: none"> • <u>It has not been demonstrated</u> that switching to THS 2.2 reduces the risk of • developing tobacco-related diseases compared to smoking cigarettes • THS 2.2 tobacco sticks contain nicotine which is addictive • Using THS 2.2 can harm your health 	Warning B2 <ul style="list-style-type: none"> • A significant reduction in the your body's exposure to harmful chemicals compared to cigarettes, <u>does not mean a reduction in the risk of tobacco-related diseases</u> • THS 2.2 tobacco sticks contain nicotine which is addictive • Using THS 2.2 can harm your health 	Warning C <ul style="list-style-type: none"> • Reduced risk <u>does not mean no risk</u>. The best way to reduce your risk of tobacco-related diseases is to completely quit tobacco use • THS 2.2 tobacco sticks contain nicotine which is addictive • Using THS 2.2 can harm your health

Figure 1 Reduced exposure and reduced risk messages used in study THS-PBA-03-US. Note: same messages are indicated by the same colour. PBA, Perception and Behavior Assessment.

and a direct mail piece (figure 2). In this study, all materials had a reduced exposure claim, but it was paired with either a Surgeon General (SG) warning for cigarettes or a PMI-developed warning for IQOS communicating that reduced exposure does not mean reduced risk, that IQOS contains addictive nicotine and that IQOS can be harmful ('PMI Important Warning' in figure 2). Participants were randomised into five groups: (1) brochure with SG warning, (2) brochure with PMI warning, (3) pack with the SG warning, (4) pack with PMI warning and (5) direct mail piece with PMI warning.

Between 26% of participants (brochure with a PMI warning) and 58% (pack with SG warning) selected an answer that using IQOS reduces the risk of tobacco-related diseases for the global comprehension measure. An additional 0.8–2.6% answered that it 'eliminates the risk of tobacco-related diseases.' The proportion of participants who answered 'don't know' was 3.1–12.3%. In sum, a large proportion of participants who saw the reduced exposure messages selected answers indicating that tobacco-related disease risk is reduced by switching from cigarettes to IQOS.

For the measures of perceived risk to self, IQOS was rated lower than cigarettes. IQOS was rated similar in perceived risks to e-cigarettes for all measures of perceived risk (figure 3).

Participants also consistently rated IQOS as lower in perceived risk of addiction than combusted cigarettes, even though the marketing brochure did not contain any information on how IQOS compared with cigarettes in terms of addiction risk. PMI's report speculated that participants might be inferring lower

perceived addiction risk for IQOS based on the information about reduced exposure to harmful chemicals.³⁰

PMI's study report³¹ concluded, "In general, reduced exposure messages may present a greater challenge than reduced risk messages on comprehension of disease risk" (p. 74). "It appears likely that consumers will typically infer a degree of reduced disease risk, even where such inferences are explicitly contradicted by warning statements" (p. 76).³¹ The report suggested that reduced exposure claims for IQOS "may present an apparent contradiction between (1) reductions in HPHCs [harmful or potentially harmful chemicals identified by the FDA in conventional cigarettes] and (2) a lack of reduced risk for disease" where participants have a hard time reconciling these claims. The report referred the FDA MRTP Draft Guidance, which also acknowledged that "there may be challenges to constructing appropriate claim language that conveys the potential benefits of the product to tobacco users and does not convey that the product is less harmful than other tobacco products." In summary, PMI's quantitative studies corroborated the findings from qualitative studies that US adults perceive reduced exposure claims as reduced risk claims.

DISCUSSION

PMI proposed to market IQOS with reduced exposure and reduced risk claims in the USA. PMI's own qualitative and quantitative studies consistently show that reduced exposure claims are likely to be perceived as reduced risk claims and will,

Reduced Exposure Claim (REC) and associated Warnings (Tested in study THS-PBA-05-REC-US)

AVAILABLE EVIDENCE TO DATE:

- The *iQOS* system heats tobacco but does not burn it.
- This significantly reduces the production of harmful and potentially harmful chemicals.
- Scientific studies have shown that switching completely from cigarettes to the *iQOS* system significantly reduces your body’s exposure to harmful or potentially harmful chemicals.

SURGEON GENERAL’S WARNINGS:

- Smoking Causes Lung Cancer, Heart Disease, Emphysema, And May Complicate Pregnancy.
- Quitting Smoking Now Greatly Reduces Serious Risks to Your Health.
- Smoking By Pregnant Women May Result in Fetal Injury, Premature Birth, And Low Birth Weight.
- Cigarette Smoke Contains Carbon Monoxide.

PMI IMPORTANT WARNING:

- It has not been demonstrated that switching to the *iQOS* system reduces the risk of developing tobacco-related diseases compared to smoking cigarettes.
- *HeatSticks* contain nicotine, which is addictive.
- Using the *iQOS* system can harm your health.



Figure 2 Reduced exposure message and an example of marketing materials from study THS-PBA-05-REC-US. In study THS-PBA-05-REC-US, all marketing materials carried a reduced exposure claim. PBA, Perception and Behavior Assessment; PMI, Philip Morris International.

therefore, mislead the public. While few studies outside the tobacco industry evaluated consumer perceptions of reduced risk or reduced exposure claims for non-cigarette tobacco products,³²⁻³⁴ the results were similar. El-Toukhy *et al*³⁴ found that modified exposure claims reduced perceived risks of snus and e-cigarette products among adults and adolescents. These results indicate that perceptions of exposure and risk are highly correlated and communication about one— either lower risk or lower exposure—reduces perceptions of both risk and chemical exposure.

The conclusion that consumers interpret reduced exposure information as reduced harm seems to hold across different contexts and tobacco products. The tobacco industry’s ‘reduced exposure’ claims are perceived as indicators of lower harm, as demonstrated by the PMI’s studies reviewed here and by research on ‘light’ and ‘mild’ descriptors.^{16 17} Furthermore, studies on different ways to communicate amounts of harmful chemicals in cigarettes consistently show that consumers misinterpret quantities of harmful chemicals as indicators of health risks.^{35 36} This

misperception holds regardless of the way the information on reduced exposure is presented: graphically, numbers only, or numbers with additional information, such as common use of these chemicals.³⁷

The tobacco industry has a long history of using reduced exposure claims to mislead consumers into believing that the products in question have reduced risk, most notably through the use of ‘light’ and ‘mild’ cigarette claims.²⁴ Therefore, it is particularly important that the FDA and comparable authorities elsewhere in the world take care not to give legal sanction for PMI or other tobacco companies to market their IQOS or other similar products to mislead the public in the same way that it and other tobacco companies have done with earlier products. In particular, IQOS and other HTPs should not be permitted to be marketed with labelling or advertising that claims or implies modified exposure because the PMI’s own studies demonstrate that consumers perceive reduced exposure claims as reduced risk claims. Both US law (FSPTCA, 911(g) and 903)¹⁰ and the Framework Convention on Tobacco Control³⁸ (FCTC) and FCTC’s

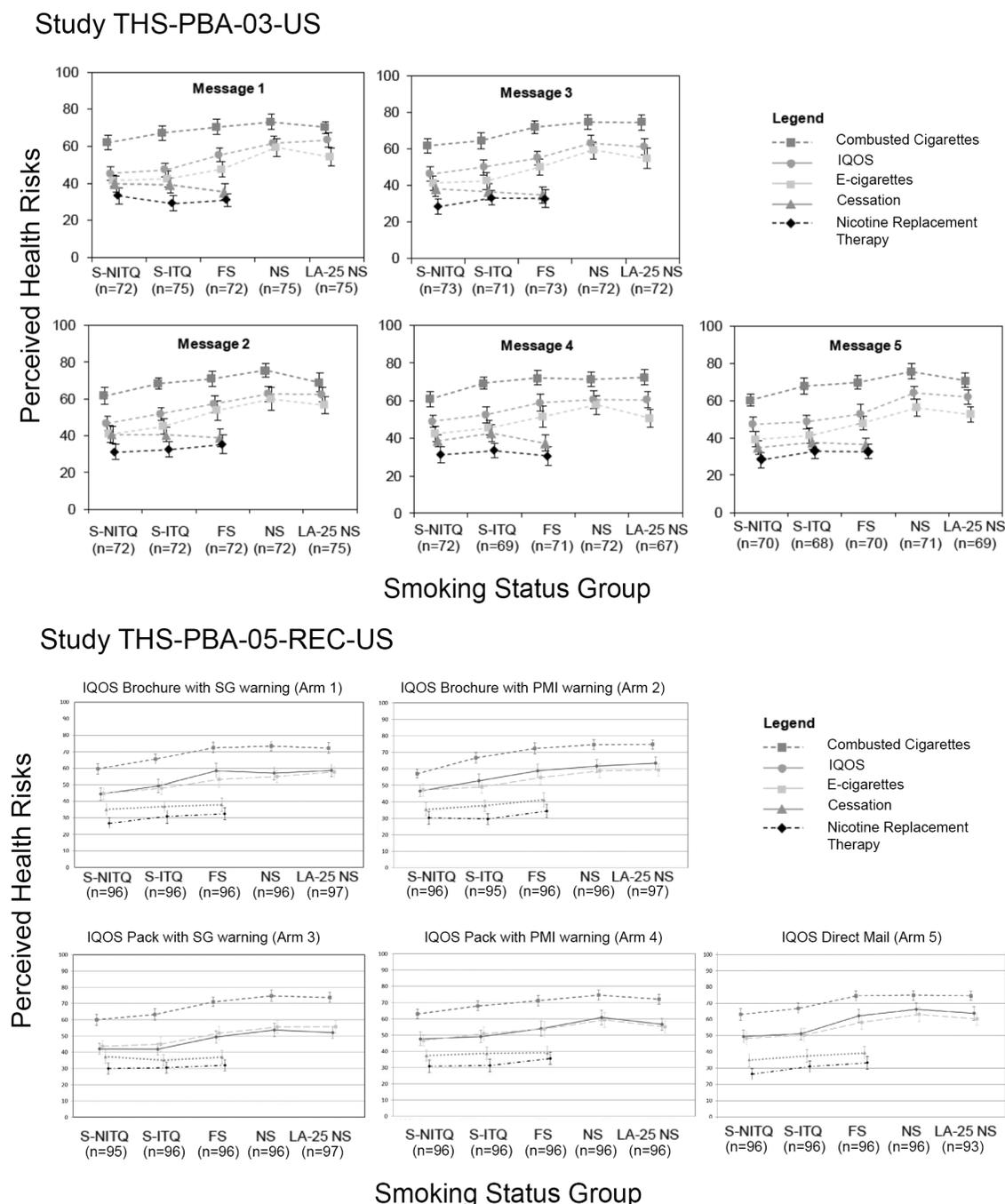


Figure 3 Participants in a quantitative study (THS-PBA-03-US, top panel) perceived health risk of IQOS to be significantly lower than health risks of combusted cigarettes, regardless of whether they saw a reduced exposure claim (Messages 1–4) or a reduced risk claim (Message 5)³¹ (p. 68). Similarly, participants in THS-PBA-05-REC-US (bottom panel) rated perceived health risks of IQOS lower than combusted cigarettes for all marketing materials with reduced exposure claim³⁰ (pp. 56, 72, 86). Note: answers were no risk, low risk, moderate risk, high risk, very high risk and don't know and were later converted into a 0–100 scale (0=no risk and 100=very high risk). Error bars represent 95% CIs from the mean. Connecting lines are only to highlight clustering of outcomes for each comparator along the y-axis across IQOS messages. Abbreviations for Smoking Status Group: FS, adult former smokers; LA-25 NS, adult never smokers aged between their state legal smoking age (18 or 21) to 25 years; NS, adult never smokers; PBA, Perception and Behavior Assessment; PMI, Philip Morris International; SG, Surgeon General; S-ITQ, adult smokers with the intention to quit combusted cigarettes; S-NITQ, adult smokers with no intention to quit combusted cigarettes.

Guidelines for Implementation³⁹ prohibit tobacco product labeling that is false or misleading, especially labelling that would mislead consumers to believe that the product is less harmful than other products.⁴⁰

Even though tobacco companies almost never marketed light and mild cigarettes with explicit claims of reduced health risks, promotions focused on reduced exposure (lower tar and nicotine) made smokers believe they were reducing their health risks

by switching to light cigarettes.^{13–17} Later, tobacco companies went further to promote light and mild cigarettes with aspirational messages, linking light cigarettes to highly desirable places and situations, such as style, relaxation and sophistication.⁴¹ PMI is using the same playbook in marketing IQOS around the world by promoting IQOS as sophisticated and aspirational,⁷ emphasising the themes of cleanliness, customisation and sociability.⁶ Based on what we have learnt from marketing of light cigarettes and natural tobacco,^{42–44} as well as the results of PMI's own research, it is likely that these claims will also be understood by consumers as reduced risk claims.³⁴

Limitations and directions for future research

We report findings from PMI's qualitative and quantitative studies, relying primarily on the summary reports for each study rather than re-analysing the raw data. Our study is limited by the shortcomings of the original studies. For example, it is possible that participants in the qualitative studies perceived reduced exposure claims as reduced risk claims in part because they were exposed to all claims during their focus groups or interviews. These studies focused on more intensive message processing under conditions of participants paying attention to the messages. In the real world, these claims might be processed differently, and the resultant perceptions might be different. Future research should investigate how understanding of reduced exposure and reduced risk claims varies under situations of limited attention and unmotivated processing. Combining reduced risk/exposure claims with warning information that comes from a different source (such as the government) might result in differential processing by various people and more studies need to be done with warnings attributed to various sources to evaluate whether the findings were the artefacts of these specific claims.

Another area worth examining is the role of the source of modified risk information. The PMI's studies do not report on who the consumers attributed the claims to; however, given what we know, understanding whether consumers think this information comes from FDA or from tobacco companies would play an important role. Past research found that consumers (including tobacco users) generally trust FDA and generally distrust tobacco companies.⁴⁵ Furthermore, attributing reduced risk claims to FDA might make consumers mistakenly believe that the government endorsed these products and further reduce their risk perceptions, resulting in less informed decision making in the marketplace.³³

CONCLUSION

PMI's MRTP application for IQOS makes reduced risk claims about IQOS that, like its earlier 'light' and 'mild' claims that were deemed fraudulent in the RICO case, are not substantiated by PMI's own internal research reported in its application.^{2–4} Several of the other papers in this supplement indicate that IQOS is not significantly less harmful than combusted cigarettes^{2–4 46 47} and that while IQOS had lower levels of pulmonary cytotoxicity⁴⁸ and carcinogens⁴⁹ than combusted cigarettes, they were higher than those of e-cigarettes. Therefore, the limited evidence on the health risks of HTPs does not support the much lower levels of perceived harm that PMI's consumer studies found. Even the evidence for the reduced exposure claim is questionable because PMI's data show *higher* levels of exposure than conventional cigarettes to some toxins.²

In the MRTP application, PMI makes an argument that the 'reduction in exposure to toxicants provides the foundation

for the reduced harm rationale for this product as an MRTP', which further indicates that they do not currently have evidence aside from the data on reduced emissions to demonstrate effects on health. However, this is exactly what FDA says is not sufficient to show reduced risk, that is, to demonstrate that IQOS 'significantly reduce[s] harm and the risk of tobacco-related disease to individual users.' On 25 January 2018, the FDA Tobacco Products Scientific Advisory Committee (TPSAC) voted not to accept Philip Morris' claims that IQOS is less harmful than cigarettes (with 8 'No's and 1 'Abstain'). The TPSAC found (on an 8 to 1 vote) that the evidence presented by PMI demonstrated its reduced exposure claim, but unanimously rejected the idea that PMI demonstrated that consumers accurately understand the risks of IQOS. The important point is that the evidence from consumer studies clearly indicates that even a reduced exposure claim does not meet the regulatory criteria because consumers will understand such a claim as a reduced risk claim.

PMI's reduced exposure claims in its labelling and marketing for IQOS and similar claims for HTPs made by other companies are likely to be misunderstood as reduced risk claims. Therefore, FDA and other regulatory agencies in other countries should not permit PMI or any other tobacco company to market IQOS with reduced exposure claims. If PMI and other tobacco companies are allowed to make confusing (if not deliberately deceptive) claims in its labelling and/or advertising, it is likely to result in consumers being misled into believing HTPs are endorsed by regulatory agencies or into misunderstanding HTP's harmfulness.⁵⁰ In short, despite PMI's contradictory statements,²⁶ the actual reports, transcripts and data submitted by PMI to FDA provide substantial evidence that consumers perceive reduced exposure claims as reduced risk claims. Allowing PMI to promote IQOS as reduced exposure would amount to a legally sanctioned repeat of the 'light' and 'mild' fraud which, for conventional cigarettes, is prohibited by the US law and the FTC.

What this paper adds

- ▶ The US Food and Drug Administration can authorise marketing of tobacco products as causing less exposure to harmful chemicals or lowering health risks. The law requires that claims of lower exposure do not mislead the public into believing the product presents reduced risk of health harm.
- ▶ The evidence in Philip Morris International's qualitative and quantitative studies submitted as part of its modified risk tobacco product application reveals that adult consumers in the USA perceive reduced exposure claims as reduced risk claims.
- ▶ Without evidence of reduced risk, claims of lower exposure are inherently misleading because they will be interpreted as reduced risk claims even if they do not explicitly make reduced risk claims.

Contributors All authors conceptualised the study, contributed to the writing and revision and approved the final version of the manuscript. LP and LKL analysed the data.

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Invisible smoke: third-party endorsement and the resurrection of heat-not-burn tobacco products

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ABSTRACT

Background Tobacco companies are introducing new 'heat-not-burn' cigarettes in dozens of countries. Historically, these products failed commercially, and independent researchers contested their health claims. The most prominent early heat-not-burn cigarette was RJ Reynolds's (RJR's) Premier, introduced in the USA in 1988. Curiously, *The Lancet* endorsed Premier as a 'near-perfect low tar cigarette' in a 1991 editorial, 2 years after Premier had been removed from the market. We examined the context of this endorsement.

Methods To ascertain what RJR knew about this endorsement, we systematically searched and analysed previously secret RJR documents in public archives and triangulated the industry document data with other published work.

Results RJR had a long-standing interest in collaborating with outside scientists to endorse potentially reduced harm cigarettes. The author of *The Lancet* editorial had previously corresponded with RJR regarding Premier's health effects and market potential. Internally, RJR regarded *The Lancet's* editorial, its stance on novel tobacco products, and its endorsement of Premier as major successes. While the editorial came too late to save Premier, RJR saw future business opportunities for novel products if endorsed by health authorities.

Conclusions Endorsement by high-impact medical journals and health authorities may be critical in helping heat-not-burn' products succeed where previous attempts have failed. Conflicts of interest influenced these endorsements in the past. Health leaders and academic journals should consider both conflicts of interest and the ethics of endorsing tobacco product substitution, as tobacco companies simultaneously work to promote cigarette smoking and undermine tobacco control globally.

BACKGROUND

Since the 1960s, the tobacco industry has developed 'safer' products to attract health-conscious smokers and improve its public image.¹ Major tobacco companies have recently expanded their product portfolios to include alternative nicotine products, such as electronic cigarettes (e-cigarettes) and 'heat-not-burn' cigarettes.² In 2015, Philip Morris International (PMI), British American Tobacco (BAT), RJ Reynolds (RJR; now owned by BAT) and Japan Tobacco International (JTI) all launched heat-not-burn products in dozens of countries.

Heat-not-burn cigarettes have a near 30-year record of dismal market performance.^{3,4} RJR introduced the first heat-not-burn product—Premier 'smokeless' cigarettes—in the USA in 1988. RJR

internally hoped Premier would 'address the growing pressures cigarette smokers face on the subjects of smoking and health, environmental tobacco smoke, and other issues related to the social acceptability of smoking'.⁵ In an internal memo to employees, RJR's President of Development Richard Kempe described Premier as 'one of the most important projects any of us will be involved in during our professional lives...because the success of this project could easily result in a tremendous long-term competitive advantage to RJR and would clearly have a substantial impact on the industry as we know it'.⁶ Smokers nonetheless widely rejected the product's taste, smell and difficulty of use. Having invested \$300 million (\$635 million inflation-adjusted to 2018), RJR removed Premier from test markets after only 6 months.

In 1991, 2 years after Premier's failure, *The Lancet* published an editorial praising Premier's ability to deliver nicotine with fewer carcinogens.⁷ The editorial called for health authorities, particularly in the UK, to promote cigarettes that delivered nicotine with as little accompanying tar as possible. As one of the earliest examples of an influential journal promoting a novel tobacco product, *The Lancet's* endorsement of Premier provides important context for the tobacco industry's current pursuit of health authority endorsements for its new products.⁸ Though the 1991 editorial appeared after Premier's demise, RJR viewed *The Lancet's* position as promising evidence that some health authorities would support novel tobacco products, and that with such endorsements, consumers might accept future products.

METHODS

We analysed previously secret internal tobacco industry documents available through the Truth Tobacco Industry Document Library (<https://industrydocuments.library.ucsf.edu/tobacco/>) between January 2016 and February 2017. In seeking to identify why *The Lancet* endorsed Premier in 1991, we combined qualitative analytical methods with iterative search strategies.^{9–11} Initial keyword searches included: 'Lancet' AND 'Premier'; 'Nicotine use after the year 2000'; 'editorial' AND 'Premier' and 'Chemical and Biological Studies of a Cigarette that Heats Rather than Burns Tobacco'. On learning that two historians attributed the anonymous editorial to Michael Russell,^{2,12} we conducted further searches with keywords including: 'Michael Russell', 'MAH Russell' and 'Russell' AND 'Premier'. We conducted snowball searches to locate related documents using reference (Bates) numbers, file locations, dates and individuals mentioned in pertinent documents. Triangulation with online search engines and



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news coverage (eg, Google News) generated data that helped resolve and contextualise questions raised by the documents. We repeated iterative searches until keywords and documents yielded only previously viewed documents, suggesting saturation. This analysis is based on a final set of 196 documents.

RESULTS

In a 1988 internal memo, RJR insisted that in its marketing of Premier, the company was:

[N]ot claim[ing] that the cigarette is 'safe' or 'safer'... [instead] we have used the word 'cleaner'... This is not a therapeutic claim... Premier's tobacco-heating technology is a breakthrough that 'changes the very composition of the smoke – substantially reducing many of the controversial compounds found in smoke of tobacco-burning cigarettes.'¹³

RJR President and CEO for West Germany, Peter Fischer, stressed that, when meeting with policy makers, RJR's scientific representatives should 'concentrate on "tar"/condensate related scientific aspects of [Premier] thereby avoiding to address [sic] the remaining nicotine and CO issues'¹⁴ which, if independently interrogated, might lead scientists to refute Premier's implicit health claims as 'cleaner'.

Legally restricted from making health claims, RJR depended on the scientific community and media to make those claims on its behalf. Proctor notes that Premier's marketing campaign included 'one-on-one briefings with university presidents, medical school deans, science writers, and medical organizations, along with politicians and "opinion leaders" throughout the world'.¹ In a confidential 1987 planning document, Fischer discussed strategy to 'insure [sic] a successful product launch' for Premier, recommending RJR 'build strong support for the product concept among scientific, regulatory and political constituencies'.¹⁴

In 1990, to garner scientific and public support for Premier, Donald deBethizy, a senior toxicologist and Vice President of Research and Development at RJR, published a paper with nine other RJR scientists that compared the nicotine absorption, urine mutagenicity and carcinogens in mainstream smoke from Premier to a conventional cigarette.¹⁵ According to the paper—entitled "Chemical and Biological Studies of a Cigarette that Heats Rather than Burns Tobacco"—all chemical and carcinogen levels, save formaldehyde, were lower among Premier smokers.¹⁶ The authors attributed these reductions to Premier's smoke, reported as consisting of more than 90% water, glycerol and propylene glycol.¹⁵

The Lancet endorses Premier

Before its publication in the *Journal of Clinical Pharmacology*, deBethizy's paper was rejected by the *Journal of the American Medical Association*¹⁷ and the *New England Journal of Medicine*.¹⁸ In October 1989, deBethizy submitted the paper to *The Lancet*, hoping for 'better luck in England',¹⁹ despite the product already having been pulled from US shelves 8 months earlier.²⁰ *The Lancet* also rejected the paper on the grounds that its printing in the journal was 'not justifiable'.²¹ In the rejection letter, *The Lancet* editor David Sharp nonetheless called the paper 'a substantial study... [that] deserves to be published in full'.²¹ Sharp proposed a future editorial about Premier should a different journal publish the article.²¹ Over a year later, deBethizy notified *The Lancet* of the paper's publication in the *Journal of Clinical Pharmacology* and requested the editorial.¹⁶

In this follow-up letter, deBethizy argued that Premier 'speak[s] directly to the call by the Froggett (sic) Committee in

Great Britain for reduced "tar" to nicotine ratio cigarettes'¹⁶ The Froggett Committee was, since Peter Froggett's appointment as chair, the informal name of the Independent Scientific Committee on Smoking and Health (ISCSH; earlier known as the Hunter Committee). The ISCSH served as the UK government's chief scientific advisory body on the issue of smoking and health through the 1970s and 1980s and was openly advised by major British tobacco manufacturers.²² Effectively, deBethizy, an RJR scientist, used the authority of the ISCSH, which was under industry influence, to stress to *The Lancet* the importance of RJR-funded findings on Premier (an RJR product). In his letter, deBethizy set Premier in a framework promoting tobacco product substitution:

The public health community in the US has not been receptive to these prototypes, taking the position that prohibition of smoking is the only avenue that should be pursued. We believe that this is a short-sighted approach which ignores the projections that by the year 2000, forty million Americans and an even greater number worldwide will choose to smoke.... We feel that cigarettes that heat tobacco will provide an alternative to smokers who choose to smoke despite warnings that adverse health effects may arise from smoking.¹⁶

While we found no return correspondence from *The Lancet*, the journal published the editorial 6 months later.⁷ Historians Virginia Berridge and Mark Elam^{2 12} attribute this editorial's authorship to Michael Russell, one of Britain's most prominent tobacco scientists during the second half of the 20th century. We found no evidence of collaboration between RJR and Michael Russell regarding the content of this editorial.

Michael Russell

Michael Russell is oft-quoted as stating, 'people smoke for nicotine but they die from the tar'.²³ A psychiatrist by training, Russell is today widely regarded^{24 25} as influential in British health organisations²⁶⁻²⁸ and authorities^{29 30} promotion of e-cigarettes for long-term nicotine maintenance and cessation purposes. One of the first researchers to identify nicotine as the primary reason for which smokers became addicted, Russell was an early developer of and advocate for nicotine replacement therapy.³¹ Among other proposals, Russell promoted medium and high nicotine, low tar cigarettes so as to avoid smokers' 'compensation', a phenomenon in which low-tar cigarette smokers inhale more deeply to obtain nicotine, thereby ingesting as much, if not more tar and negating any 'health' benefits of low-tar cigarettes.²³

In the late 1970s, Russell collaborated with BAT on two 'safer' cigarette studies³² and received £55,000 (£300,850 inflation adjusted to 2018) in funding to conduct a third joint study, testing medium nicotine, low tar cigarettes.³³⁻³⁶ Russell acknowledged this 'strong relationship with BAT' and their 'help with some funding' in a 2004 interview with *Addiction*, commenting that maintaining relationships with tobacco companies was common practice among researchers at the time.³⁷ Russell also engaged extensively with RJR about Premier's 'positive aspects',³⁸ both prior to the product's release and following its failure (box 1).

In August 1988, Russell requested 3000 Premier cigarettes from RJR to conduct a study measuring 'nicotine, cotinine and carboxyhemoglobin levels in persons smoking Premier'.³⁹ On RJR's approval of his study in October 1988, Russell stated that the 'publication of results in an English Medical Journal', showing Premier to have fewer carcinogens than regular cigarettes, 'could go a long way to raising interest here [i.e. in the UK] and casting a favorable light on things'.⁴⁰ The first time RJR attempted to send Premier cigarettes to Russell, however, British customs

Box 1 Events prior to *The Lancet* editorial favouring Premier

August 1988: Michael Russell writes to RJ Reynolds (RJR) requesting 3000 Premier cigarettes for 'a week-long study with 10–12 male smokers... [to] monitor plasma, nicotine, cotinine and carboxyhemoglobin levels in persons smoking Premier'.³⁹ Jack Blanchard, Director of Scientific Relations at RJ Reynolds, saw this correspondence as a 'result of discussions that Dr. Russell had with several of us on this topic...last month'.⁴¹ Blanchard suggests to Wallace Hayes, Vice President of Research at RJR, that research scientist Donald J. deBethizy interact with Russell to facilitate these studies.⁴¹

October 1988: On RJR's approval of his study, Russell states that the 'publication of results in an English Medical Journal', showing Premier to be healthier than regular cigarettes, 'could go a long way to raising interest here and casting a favorable light on things'.⁴⁰

November 1988: Premier introduced to American test markets.
February 1989: Premier withdrawn from American test markets.

February 1989: deBethizy *et al* manuscript sent to Martin Cline at UCLA for comment; Cline suggests RJR to submit the paper to the *New England Journal of Medicine*, and failing that the *Journal of the American Medical Association (JAMA)*.⁷¹

February 1989: deBethizy paper submitted to the *JAMA*, which rejects it.¹⁷

July 1989: deBethizy paper submitted to *New England Journal of Medicine*, which rejects it.¹⁸

August 1989: Wallace Hayes, coauthor and Vice President of Research at RJR, sends a copy of the paper and recent articles on Premier to Michael Russell, whom he thanks in a letter for his 'encouragement regarding Premier'.⁷²

October 1989: deBethizy submits paper to *The Lancet*.¹⁹

November 1989: *The Lancet* rejects the paper, but editor David Sharp proposes a future editorial on Premier should the article be published elsewhere.²¹

January 1990: deBethizy submits paper to *Journal of Clinical Pharmacology*, on recommendation by Eliot Vessel.⁷³

August 1990: deBethizy paper published in *Journal of Clinical Pharmacology*.⁷³

December 1990: deBethizy alerts *The Lancet* to the article's publication, hoping the journal will follow up on its initial interest in writing an editorial about Premier.¹⁶

January 1991: Russell writes to RJR proposing future tests on Premier that he could lead were funding from RJR granted.^{42 74}

May 1991: Editorial praising Premier (attributed to Russell) appears in *The Lancet*.⁷

detained them. Russell consequently proposed to Wallace Hayes, RJR Vice President of Research and Development that RJR send the cigarettes to Russell directly, the associated fees for which Russell could pay, and for which RJR could later reimburse him. Russell suggested he could then "lose" records of this [reimbursement] such that no 'note would be kept in the Heathrow customs that could eventually be traced to your company'.⁴⁰ We were unable to determine if Russell ever received the cigarettes or conducted the study. While RJR internally planned to coordinate discussions between Russell and deBethizy,⁴¹ we found no evidence of subsequent discussions between the two.

In January 1991, Russell met with RJR executives again, to whom he proposed additional studies on Premier, which 'would of course need to be funded, and we [i.e. Russell's research team]

would be interested to consider this when the time is ripe from your [i.e. RJR's] point of view'.⁴² Russell noted that it would not even be necessary for these studies to demonstrate 'that harmfulness is reduced in any direct way' but that it would be 'sufficient initially to simply show that when people switched [to Premier] their blood nicotine levels are if anything lower'.⁴² In that letter, Russell also mentioned having done a 'preliminary study with [Premier] cigarettes that we purchased ourselves'.⁴² This preliminary study may have been the basis for a 1993 paper that Russell coauthored in *Thorax*, showing lower average nicotine, carbon monoxide and tar intake among Premier smokers.⁴³

Four months after this January 1991 correspondence, the anonymous editorial, 'Nicotine Use After the Year 2000', appeared in *The Lancet*, praising Premier as a 'near-perfect low tar cigarette'.⁷ In the tradition of newspapers, *The Lancet* publishes unsigned editorials, occasionally from outside authors whose opinion reflects the journal's editorial board and represents the position of *The Lancet*. Russell's editorial urged the British government to promote the long-term, recreational and even addictive use of nicotine as a cessation therapy provided the nicotine could be delivered alongside as little tar as consumers found acceptable.⁷ Such products should then be made 'as acceptable and palatable as possible, advertised, actively promoted with health authority endorsement, and given tax advantages over tobacco'.⁷ In the same month, Russell published an article in the *British Journal of Addiction*, in which he promoted a nasal nicotine spray and nicotine lozenge as potential 'long-term alternatives to tobacco that makes the virtual elimination of tobacco a realistic target'.⁴⁴ Using near-identical wording to that employed in *The Lancet* editorial, Russell argued that such products should be made as palatable and acceptable as possible and actively promoted on the open market to enable competition with conventional cigarettes. He stated the products would also need health authority endorsement, tax advantages and support from the anti-smoking movement if tobacco use is to be gradually phased out altogether.⁴⁴

Russell also advised RJR in correspondence to seek advice about introducing Premier into the UK market from Peter Froggatt, Chairman of the ISCSH.⁴² Initially receptive, Froggatt ultimately decided to neither endorse Premier nor lobby for its entrance into the UK market.⁴⁵ Premier was never marketed in the UK.

RJR reacts

A month after *The Lancet* editorial appeared, deBethizy sent an interoffice memo stressing to colleagues that:

[T]he position on nicotine advocated in this editorial is a major departure from the position taken by the public health community in the US...[indicating] a willingness on the part of some prominent physicians to propose tobacco product modification as an essential component to a realistic public health policy on smoking and health.⁴⁶

deBethizy saw this difference between American and British attitudes towards potentially reduced harm tobacco products as a major business opportunity. In September 1991, deBethizy and one of his coauthors, David Doolittle, cited *The Lancet's* endorsement of Premier in a letter to RJR President James Johnston. deBethizy and Doolittle advocated that the company should continue to market products that specifically respond to consumers' increasing 'health consciousness,' in order to 'stabiliz[e] or revers[e] market decline'.⁴⁷ As health concerns around smoking intensified, the two scientists argued that the 'long-term vitality' of RJR would depend on repositioning cigarettes to

address these concerns. The letter stated, 'one can only imagine the market share' that such products, 'uniquely perceived...as less hazardous', stood to secure.⁴⁷

RJR executives again acknowledged the importance of third-party endorsements after Premier was removed from the market. In 1993, Russell wrote to Carl Ehmann, RJR's Research Director, arguing that RJR should not abandon Premier or similar potentially reduced harm products.⁴⁸ Ehmann responded that RJR was confident it could redress Premier's shortcomings and introduce a similar product that smokers would accept.⁴⁹ Nonetheless, Ehmann stated that the company's

ability to market such a product [in the future] will be dependent upon more rational scientists, like yourself, speaking up and encouraging such concepts. Otherwise, we will be at the mercy of anti-smoking zealots who mistakenly believe they can engineer a smoke-free society and therefore have no interest in products which address the very issues about which they are concerned.⁴⁹

DISCUSSION

A major UK medical journal's endorsement of a defunct American tobacco product was aided by an enthusiastic scientist's cooperation with RJR tobacco company. This scientist's conflict of interest with the maker of Premier should have been, at the very least, disclosed by both Russell and *The Lancet*. Russell's conduct (eg, soliciting funding from RJR and stating *a priori* that publication of the study results in an English journal could go a long way to 'casting a favorable light on things';⁴⁰ offering to 'lose' records' of reimbursement from RJR,⁴⁰ and suggesting RJR pay him to undertake research on a product he later anonymously endorsed while representing *The Lancet*⁴²) raises serious questions of integrity. It is unclear whether these conflicts of interest were disclosed to the journal, or why the journal offered to write the editorial for a paper they deemed 'not justifiable' for publication in *The Lancet*. Current industry communications attribute new products' public health impact to consumer acceptance,⁵⁰ framed publicly more simplistically than their internal research,⁵¹ as the product of nicotine, taste and the user's associated 'ritual'.⁵² Our analysis, however, suggests that health-authority backing will also be central in determining whether the next generation of heat-not-burn devices succeeds where previous attempts have failed.

The industry document database consists mainly of documents produced during litigation and is not a complete archive. As such, we may have missed relevant information, particularly information contained in documents that the industry has withheld on the grounds of trade secrets or client/lawyer privilege.⁵³ Nonetheless, the documents we have analysed provide a window into prominent RJR scientists' and executives' candid discussions of a potentially reduced harm product. These insights may help public health professionals craft policy that anticipates reiterations of the tobacco industry's promotional strategies for its newest crop of products.

While Premier was a commercial failure, the industry has continued to pursue potentially reduced risk tobacco products.⁵⁴ The major tobacco companies have adopted 'harm reduction' language to promote their product portfolios.⁵⁵ In 2014, PMI introduced its heat-not-burn product IQOS in Italy and Japan, before expanding to 30 other markets within 2 years. In 2015, BAT and JTI launched heat-not-burn products in Japan. In December 2016, PMI filed an application to the Food and Drug Administration so that it may market IQOS as a modified risk tobacco product in the USA.⁵⁶ PMI now claims that its 'vision... is that these [reduced-harm] products will one day replace

cigarettes',⁵⁷ and in September 2017 announced it would commit \$1 billion to the establishment of the 'Foundation for a Smoke-Free World'.⁵⁸ Wells Fargo analyst Bonnie Herzog has predicted that heat-not-burn products could displace 'up to 30 percent of the combustible cigarette industry in developed markets by 2025',⁵⁹ although sales for IQOS, the current industry leader, began to plateau in the first quarter of 2018.⁶⁰

The industry has also continued courting public health endorsement of its new products. PMI's 'Foundation for a Smoke-Free World' claims to want to combat cigarette smoking via public health partnerships and the promotion of new products.⁵⁸ Part of the foundation's launch included publication of an article in *The Lancet*,⁸ penned by Derek Yach, a former WHO official who previously worked in tobacco control. While many oppose the Foundation,⁶¹ and *The Lancet* also published a comment by public health advocates voicing concerns,⁶² *The Lancet* editorial board failed to support the WHO's strong stance against industry cooperation in their accompanying editorial.⁶³

Nearly 1000 peer-reviewed papers based on tobacco industry documents, as well as the US District Court's ruling that the tobacco companies violated the Racketeer Influenced Corrupt Organizations Act⁶⁴ demonstrate the folly of partnership with the tobacco industry. August public health organisations, authorities and journals that believe 'the best science must lead to better lives'⁶⁵ should consider the ethics of endorsing tobacco industry attempts to preserve profits⁶⁶ with products claimed to be, but not yet demonstrated as reduced risk,⁶⁷ while simultaneously continuing to both aggressively promote cigarettes and undermine tobacco control worldwide.⁶⁸ Public health practitioners should also bear in mind past experience with industry-backed 'safer' cigarettes (eg, filtered and low-tar) that served to undermine and delay tobacco control efforts.^{69,70} Endorsements from health leaders and regulatory authorities may be the key factor in determining current heat-not-burn products' commercial

What this paper adds

What is already known on this subject

- ▶ The tobacco industry has long viewed the endorsement of external authorities as necessary to the success of its potentially reduced harm products.
- ▶ In 1991, *The Lancet* endorsed RJ Reynolds' (RJR) heat-not-burn cigarette, Premier, as a safer alternative to traditional cigarettes.
- ▶ While Premier failed commercially, the support of potentially reduced harm tobacco products as substitutes continues among some public health organisations and authorities, and is aggressively promoted by tobacco and electronic cigarette manufacturers.

What this paper adds

- ▶ The author of *The Lancet's* editorial had previously collaborated with and advised RJR on Premier.
- ▶ While the editorial appeared after Premier was removed from the market, RJR internally regarded *The Lancet's* stance on Premier as both opening a critical business opportunity for harm-reduced products and as an important departure from health authorities in the USA.
- ▶ Endorsements by respected health leaders are likely to play a critical role in determining new heat-not-burn tobacco products' commercial fate and may help the newest crop of modified tobacco products succeed where previous attempts have failed.

success, as well as the tobacco industry's future legitimacy as it promotes new products.

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OPEN ACCESS

Revolution or redux? Assessing IQOS through a precursor product

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ABSTRACT

Background Philip Morris International (PMI) currently claims that its heated tobacco product, IQOS, reduces health risk by reducing users' exposure to harmful and potentially harmful constituents present in tobacco smoke. Given the tobacco industry's long history of misrepresenting and obfuscating research, independent assessment of PMI's claims is important. Analysis of Accord, a failed but strikingly similar precursor to IQOS, may help contextualise PMI's claims in its Modified Risk Tobacco Product (MRTP) application.

Methods We analysed previously secret internal Philip Morris (PM) and PMI documents, public communications and MRTP application.

Results PM marketed Accord as a 'cleaner' tobacco product in an attempt to address smokers' growing health concerns without making explicit health claims. While PM communications asserted that Accord reduced users' exposure to harmful constituents, company scientists and executives consistently stressed to both regulators and the public that such reductions did not render Accord safer. IQOS's design and marketing are similar to Accord's. On the basis of aerosol chemistry data, IQOS reduces user exposure to some compounds compared with Accord but raises them for others.

Discussion IQOS appears to be a variant of Accord without consistent improvements in exposure to aerosol toxic compounds. In contrast to PM's past claims for Accord, PMI now claims in its MRTP application that IQOS reduces health risk. This shift in stance is likely not the result of any toxicological difference between Accord and IQOS, but rather a change in the social and regulatory landscape permitting these claims.

BACKGROUND

The tobacco industry has developed heated tobacco products since the 1960s.¹ When these 'safer' offerings have been marketed, consumers have generally rejected the products' poor taste, smell and user experience.² As of May 2018, however, a heated tobacco product from Philip Morris International (PMI), IQOS, had won at least moderate consumer acceptance in several of the 31 countries in which it was available.³ By early 2018, IQOS had captured nearly 15% of the national tobacco market share in Japan, 2 years after its introduction.⁴ Despite the continued predominance of conventional cigarettes to company profit,³ PMI publicly frames IQOS as presaging the company's supposed departure from the cigarette business altogether.⁵

In promoting IQOS, PMI has attempted to foster a perception of the product as reduced risk. The company's public communications and warning label statements claim that switching completely to

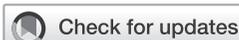
IQOS is a safer alternative to smoking cigarettes.⁶ In an attempt to court favourable regulation, taxation and exemptions from smoke-free ordinances for IQOS, PMI has begun promoting the product's purported benefits in meetings with national health authorities.⁷ In December 2016, PMI submitted a multi-million page Modified Risk Tobacco Products (MRTP) application to the US Food and Drug Administration (FDA).⁸ If approved, PMI will be able to market IQOS in the USA as a reduced risk alternative to conventional cigarettes.

Given the tobacco industry's well-documented history of misrepresenting and obfuscating its research,² independent assessment of PMI's claims is important. While PMI's internal data and business strategy on IQOS are largely unknown, internal Philip Morris (PM) documents discussing Accord—a failed, but similar heat-not-burn precursor to IQOS—are available in public archives. We compared available documents detailing product design, exposure data and safety claims PM made for Accord to data and claims submitted as part of the IQOS MRTP application. Our aims were to compare product design characteristics; determine if IQOS exposure levels were demonstrably and consistently improved compared with Accord; and learn how PM understood the extent to which reductions in exposure to harmful constituents reduced harm to users.

METHODS

Between October 2013 and January 2016, we searched industry documents (available through the Truth Tobacco Industry Document Library; <https://industrydocuments.library.ucsf.edu/tobacco/>) detailing tobacco companies' development of various heat-not-burn tobacco product prototypes. Between January 2017 and May 2018, this dataset was expanded with additional iterative searches^{9–11} focused specifically on Accord, with initial keyword searches including "Accord market*," "Accord research," "Accord consumer," "Accord science," and related terms drawn from earlier searches, such as "electrically heated cigarette smoking system" (EHCSS) and "EHCSS." We then conducted snowball searches to locate related documents using reference (Bates) numbers, file locations, dates and individuals mentioned in pertinent documents, and by refining subsequent searches with Boolean operators and year and publication type filters. Iterative searches were repeated until keywords and documents yielded only previously viewed documents, suggesting saturation.

To ensure documents' internal consistency, all documents were organised thematically and chronologically, and relevant documents were



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compared with relevant sections of PMI's MRTP application available on the FDA's website.⁸ Triangulation with online search engines, news coverage, public statements made by PMI (most often found at <http://www.pmi.com>) and internal PMI documents obtained by Reuters (accessible at https://www.documentcloud.org/public/search/projectid:_2033738) generated data that helped resolve and contextualise questions raised by the documents. Having reviewed over 1,000 documents, this analysis is based on a final collection of 200 documents.

RESULTS

Accord origins and specifications

Through the late 1980s and early 1990s, public health consensus on the negative health effects and addictiveness of smoking led to smoke-free policies and the broader social denormalisation of smoking.¹² In response to these pressures, RJ Reynolds introduced its 'clean smoke' heated tobacco product, Premier, in 1988.¹³ Although similar to a conventional cigarette, Premier heated tobacco, instead of burning (combusting) it, producing an aerosol for inhalation.^{14 15} Industry scientists hypothesised that

such products presented a lower health risk to users: because tobacco was not combusted, smokers might be exposed to fewer respiratory irritants and carcinogens.¹ Marketed as a 'smokeless', 'cleaner' cigarette, Premier was widely rejected by consumers and pulled from shelves within 4 months of its release.

In response to Premier, PM began developing reduced-risk tobacco products of its own.^{2 13 16} A 1990 presentation introduced Project Beta, a battery-operated device that would heat rather than burn tobacco.¹⁷ Through Project Beta, PM developed the heat-not-burn product, Accord (internally referred to as an electrically heated smoking system (EHCSS)).¹⁸ Accord comprised a short, low-tar cigarette (in 3 and 6 mg tar versions) and a battery-powered lighter into which the user inserted the short cigarette. On the user's puffing, the tobacco in the cigarette would heat, generating a tobacco-flavoured aerosol for inhalation. Retailing at US\$77 (inflation-adjusted to 2018), Accord was packaged for sale as part of a kit that included Accord's special cigarettes (sold at prices comparable to regular cigarettes), the product's heating device and an instructional video (table 1).¹⁶

Table 1 Component comparison: Accord and IQOS

	Accord	IQOS
Product description	'... [Accord is] an electrically heated cigarette smoking system, comprised of a lighter/heater, which supplies power to the system, and a cigarette designed to be used only with the lighter/heater ... activation occurs as the smoker takes a puff. The flow of the puff is detected by a sensor, which then activates the blade-heating cycle. The electronic system in the lighter/heater synchronizes puffing and energy to the blades. The result is that the cigarette delivers eight puffs to the smoker on demand, one for each blade.' ³⁶	'To operate ... the user inserts a Tobacco Stick into the holder and turns on the device by means of a switch. This initiates the heating of the tobacco via the heating blade inserted into the tobacco plug. The tobacco neither ignites nor burns. The electronically controlled heating, in combination with the uniquely processed tobacco, prevents combustion from occurring. The holder supplies heat to the Tobacco Stick through the heating blade for a fixed period of approximately six min and allows up to fourteen puffs to be taken during that time.' ⁶¹
Health claims	'The Accord product has not been proven to be safer. Substantial reductions in certain harmful compounds have not been proven to lead to a reduction in smoking-related diseases.' ⁴¹	'[IQOS] heats tobacco but does not burn it. This significantly reduces the production of harmful and potentially harmful chemicals. Scientific studies have shown that switching completely from cigarettes to [IQOS] can reduce the risks of tobacco-related diseases.' ⁶¹
Tobacco material	Tobacco, glycerol, water, ammonium magnesium phosphate, pectin, beta-cyclodextrin	Tobacco, glycerol, water, guar gum, cellulose, and propylene glycol
Cigarette configuration	62 mm (overall length) 32 mm (tobacco plug)	45 mm (overall length) 12 mm (tobacco plug)
Tobacco weight (mg/cig)	407.6	314
Tar (mg/cig)	3.0	19.4
Nicotine (mg/cig)	0.2	1.29
Filters	A low-efficiency filter (30 mm), containing a segment of activated carbon-in-paper	A polylactic acid filter (18 mm) and a low-density cellulose acetate mouthpiece filter similar to the filter of a conventional cigarette
Tube	Hollow acetate tube	Hollow acetate tube
Paper	Outer paper Tipping paper	Outer paper Tipping paper
Retail price	US\$77 (inflation adjusted to 2018)	US\$110
Heater description	'The heater is equipped with an array of eight blades made from an iron-aluminide alloy, one blade for each of the eight possible puffs per cigarette ... activation occurs as the smoker takes a puff. The flow of the puff is detected by a sensor, which then activates the blade-heating cycle.' ¹⁸	'The Holder heats the tobacco using a ceramic blade, which is pushed into the tobacco plug [upon insertion]. The Holder has a small battery, which stores enough energy for a single experience (ie, complete use of one Tobacco Stick). The power to the heating element is controlled by an embedded electronic system, which ensures that the temperature follows a pre-defined heating profile for each puff regardless of the user's puffing behaviors. The Holder needs to be recharged prior to each Tobacco Stick use. The Holder is activated by a simple button and its status is conveyed through an interface that includes a colored LED.' ⁶¹
Peak temperature (°C)	500	310–350
Heating blade thickness (mm)	8	0.36
Puffs per charge	13 cigarettes (eight puffs each)	14 puffs per cigarette or 6 minutes of use (whichever comes first), after which the Holder must be recharged in the portable case before a new tobacco stick can be used. Portable case can charge Holder 20 times before needing re-charge.

Accord marketing

In October 1998, PM introduced Accord in 16–20 stores in Richmond, Virginia (the location of a major PM manufacturing facility), expanding to 120 stores within 3 months.¹⁹ In the same year, PM released Accord in Osaka, Japan, under the name ‘Oasis’. The tobacco industry has long marketed its ‘cleaner’ (eg, low-tar) products in Japan due to perceptions that Japanese smokers value cleanliness and are more willing than consumers in other countries to embrace new technologies.^{13 20} During Accord’s first three years on the market, consumer awareness remained limited, and sales and retention were low.²¹ Dual use of Accord with conventional cigarettes was also high: 86% of those who smoked Accord used the product for between one-quarter and one-half of their tobacco use; and only 9% of Accord users used the product for 75% or more of their tobacco use.²² PM attributed this ‘situationa[l]/occasiona[l]’ use to the

product’s poor taste, higher price than conventional cigarettes, unfamiliar operating system and unconventional appearance.^{21 22}

PM characterised Accord smokers as favouring product characteristics related to ‘hygiene or consideration of others,²³ and attributed the little success that Accord enjoyed to its perception as a ‘cleaner’ product that would not irritate others.²¹ To attract hygiene-conscious consumers, one Accord advertisement read, ‘Less smoke around you. Virtually no lingering odor. And no ashes’, all of which rendered Accord ‘a whole new way to smoke’.²⁴ Another ad (figure 1) showed a couple sitting together on the same lounge chair while the man holds an Accord device, the woman seemingly unperturbed by any foul smell or smoke.

While PM emphasised Accord’s ‘cleanliness’ in consumer communications,²⁵ the company also went to great lengths to clarify that such ‘cleanliness’ did not render the product safer than conventional cigarettes. In an advertisement accompanying

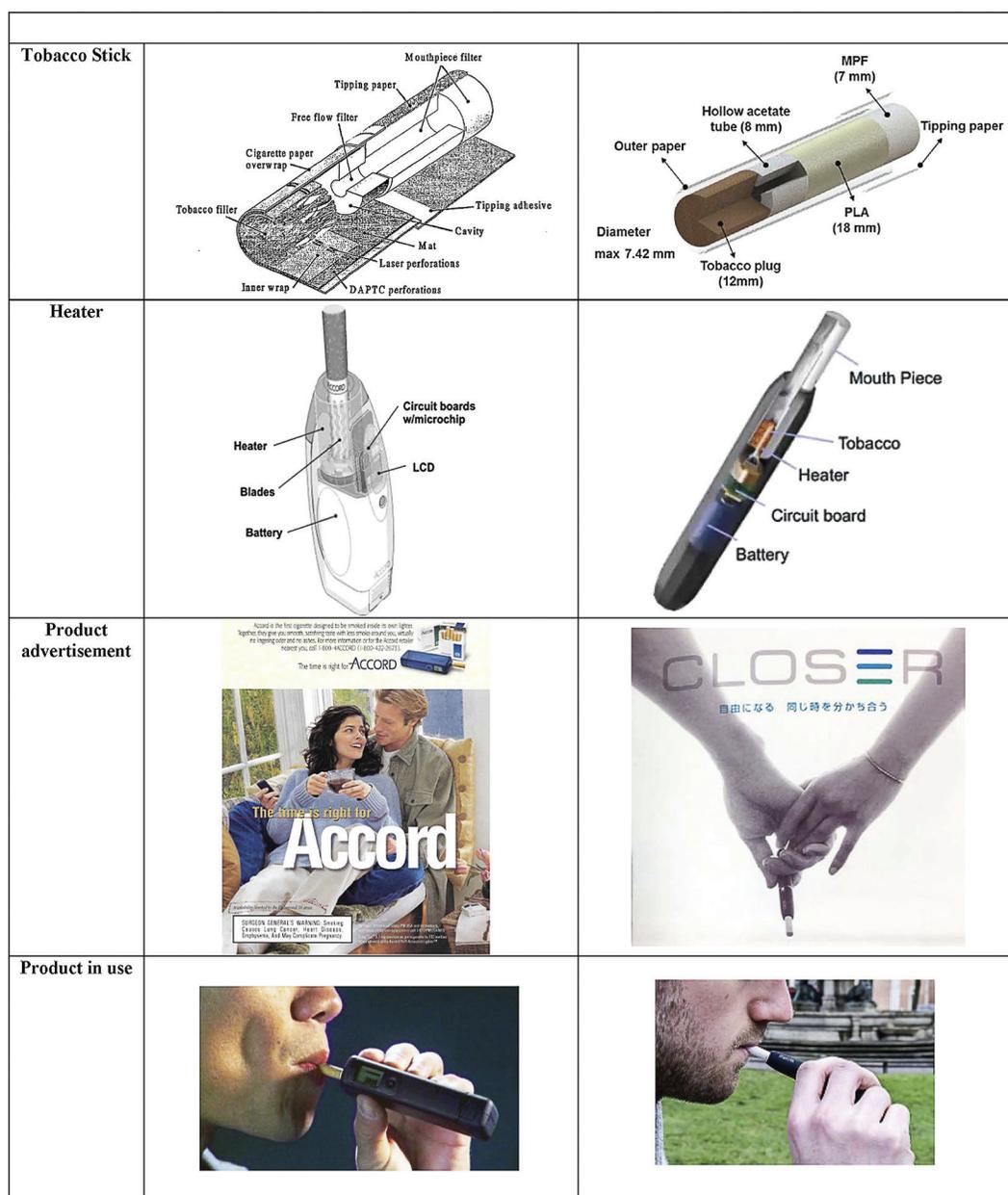


Figure 1 Visual comparison of Accord and IQOS tobacco stick, heating device structure, advertising and product demonstration. Photo credit for Product in Use images: www.vaping360.com and WGBH Educational Foundation.

the Accord Kit, PM stated that while 'Accord reduces certain harmful smoke compounds you inhale ... [(such) reductions ... have not been proven to lead to a reduction in smoking-related diseases'.²⁶ After asserting that Accord reduces carbon monoxide exposure by 98% compared with an ultra-light cigarette, PM asked rhetorically in the same brochure, 'Are we saying that Accord is a "safer" cigarette? No.'²⁶ The brochure also stated that 'public health authorities do not endorse either smoking fewer cigarettes or switching to lower-yield brands or a cigarette that heats rather than burns tobacco as a satisfactory way of reducing risk'.^{26 27} This is consistent with past and current research showing that the extent to which reduced exposure leads to reduced harm is unclear.^{28 29} Despite these clarifications, a 2003 PM presentation to the company's 'New Products Committee' reported that on average 11% of consumers exposed to Accord advertisements believed Accord to be less harmful than other cigarettes.³⁰

Outside of PM, research on Accord's safety was limited. Two independent studies compared Accord smokers' CO intake and heart rate to those of cigarette smokers, and found both levels to be lower in the Accord users.^{31 32} However, nicotine uptake for Accord smokers was slower than conventional cigarettes, leading smokers to 'compensate'; that is, inhale more deeply to extract more nicotine, thereby negating any health benefits of lower tar cigarettes.³¹

The significance of these findings, however, was undercut by the product's scant adoption. By 2003, PM had spent over \$400 million in operating expenses and almost \$70 million (inflation-adjusted to 2018) in capital expenses in developing subsequent versions³³ of Accord.³⁴ One PM study found that both Japanese and American consumers rejected Accord (although acceptance was higher in Japan) because of its taste ('hard to draw, perceived harshness, not enough taste, not enough puffs per cigarette') and inconvenience ('charging time, cigarettes per charge').³⁵ Accord also required smokers to adopt a new routine (eg, buying a new brand of cigarettes, recharging the battery pack), while the device itself required 'enhanced consumer support, product maintenance, spare parts, technology acceptance and product education', which most users found burdensome.²² PM discontinued Accord in 2006 after 8 years on the market.

PM's pursuit of normalisation

Accord was designed as a potentially reduced exposure product (PREP), with PM clarifying in external company communications that reduced exposure did not indicate reduced risk.³⁶ While PM contracted an advertising company to draft harm reduction advertisements for Accord in the USA, these advertisements were ultimately not used,¹² perhaps because tobacco companies were legally barred from making reduced risk or reduced exposure claims while Accord was available.³⁷ PM marketed the product instead as a low-smoke alternative,¹⁶ likely hoping to imply to consumers that Accord was safer than conventional cigarettes.

In 2000, as part of efforts to improve the company's beleaguered image, PM began lobbying for legislation that would grant the FDA authority over tobacco.³⁸ In 2001, 3 years after PM introduced Accord, the Institute of Medicine (IoM, now National Academies of Sciences, Engineering and Medicine) conditionally endorsed PREPs as potentially capable of reducing user risk.³⁹ Believing that reduced risk products could help 'normalise' the company,^{27 40} PM echoed IoM policy recommendations in arguing that potential legislation should create separate classifications for reduced exposure products and reduced

risk products. This distinction would enable PM to make reduced exposure claims for products like Accord, without having to wait for long-term evidence finding exposure reduction sufficient to indicate risk reduction.²⁷ The proposed legislation failed to pass Congress in 2004.

In 2007, a year after PM discontinued Accord, Kenneth Podraza, Vice President of Research and Development at PM USA, wrote to the Surgeon General in an effort to gain government endorsement of Accord. 'In the absence of FDA regulation', Podraza stated that PM 'now turn[ed] to you for guidance', asking that the Office of the Surgeon General determine if Accord is a PREP,⁴¹ likely in the hopes that the Surgeon General's designation of Accord as reduced exposure would generate increased consumer acceptance of either Accord (should it be reintroduced), or of future, similar products. The tobacco industry has long viewed third-party endorsements of industry products as crucial to those products' success.^{2 42} Podraza attributed Accord's commercial failure to both consumer rejection and the company's 'inability to communicate a potential reduced exposure message'.⁴¹

Reiterating PM's previous communications on Accord, Podraza clarified that while Accord may be a PREP it nonetheless 'has not been proven safer [as] substantial reductions in certain harmful compounds have not been proven to lead to a reduction in smoking-related diseases'.⁴¹ Podraza concluded his letter stating that PM would continue to develop future potentially reduced-risk products that smokers would hopefully accept.⁴¹ We found no evidence that the Surgeon General responded to Podraza. In 2008, PM briefly test-marketed a near-identical product, 'Heatbar' in Switzerland and Australia.^{16 43 44}

IQOS and Accord product design

In 2014, PMI introduced a new heated tobacco product, IQOS, in Italy and Japan. IQOS's moderate success in several markets as of 2018 is at least partly attributable to the current social and regulatory landscape. When Accord was available, public health authorities were unwilling to deem safe, new, unpopular products designated as 'cleaner' by the industry.² Since 2007, however, as the popularity of electronic cigarettes (e-cigarettes) increased,⁴⁵⁻⁴⁷ several prominent public health organisations⁴⁸⁻⁵¹ and health authorities^{52 53} have promoted e-cigarettes as safer alternatives to cigarettes. In the USA, the 2009 Family Smoking Prevention and Tobacco Control Act granted the FDA authority to regulate all tobacco products.⁵⁴ As part of this legislation, tobacco manufacturers could, for the first time, market preapproved products as 'modified risk tobacco products'.

In addition to its distinct context, IQOS has several notable design differences from Accord. IQOS cigarettes have more nicotine and more than six times as much tar per cigarette as Accord cigarettes. IQOS's HeatSticks are shorter than Accord's cigarettes (45 mm vs 62 mm), as is its tobacco plug (12 mm vs 32 mm). IQOS cigarettes also have less tobacco per cigarette than Accord (314 mg vs 407.6 mg), are burned at a lower temperature (~350°C vs 500°C) and the product kit is approximately US\$40 more expensive (inflation adjusted to 2018) than Accord's (table 1).

The products also share a number of similarities. Like Accord, IQOS maintains the core technology of heating rather than burning tobacco, which purportedly lowers users' exposure to harmful or potentially harmful constituents (HPHCs)—constituents linked to the most serious effects of tobacco use (eg, cancer, cardiovascular disease, respiratory effects, addiction). Both products work by activating a heating blade (eight iron-aluminide

alloy blades for Accord and one ceramic blade for IQOS), which then warm(s) the adjacent tobacco, and both products' electronic systems control the temperature of the blade and delimit the amount of puffs the user takes per cigarette (figure 1).

IQOS and Accord advertising

IQOS's marketing has also resembled Accord's. A 2016 internal training for employees managing IQOS's social media presence revealed that, like Accord, IQOS is partially targeted at the hygiene-conscious, particularly 'those who want to reduce risks to their young families'.⁵⁵ PMI alerted employees that, as occurred with Accord, consumers may be turned off by the product's 'learning curve', different 'taste and satisfaction levels' and the required time commitment, estimated at 3 weeks, to become accustomed to the product experience.⁵⁵ Nonetheless, PMI stated in the same document that IQOS would 'change the way legal-age smokers smoke for the better'.⁵⁵

PMI also expects a number of indirect benefits to accrue to the company if consumers perceive IQOS to be safer than cigarettes. This is consistent with PM's hopes for earlier reduced risk products.^{27 40} A 2014 internal PMI document entitled '10 year Corporate Affairs Objectives and Strategies' frames IQOS as a key component in 'normalising' PMI's business more broadly, transforming the company into a 'trusted and indispensable partner ... bringing solutions to the table'.⁵⁶ In gaining the trust of the public and regulators, PMI hoped to both regain access to broader regulatory discussions from which it is currently excluded and reverse the trend of 'PMI/industry de-normalization ... [so as] to drive future growth'.⁵⁶

Such normalisation efforts will be most successful if smokers switch completely to IQOS. Nonetheless, research on corporate social responsibility programmes has shown that tobacco companies can use purported gestures of goodwill (such as developing 'safer' products) to increase access to policymakers and generate support for industry activity regardless of a given programme's effectiveness.^{38 57 58} In IQOS's case, the mere manufacture of a potentially safer product may be enough to earn PMI influence.^{59 60}

Comparing IQOS and Accord aerosol chemistry

In December 2016, PMI submitted a multi-million-page MRTP application to the FDA for the company to market IQOS in the USA with reduced-risk claims.⁸ While PM consistently clarified that reductions in exposure did not reduce user risk, PM's spin-off company, PMI, now claims that such reductions in exposure do indeed reduce user risk, asserting that 'switching completely [from cigarettes to IQOS] presents less risk of harm than continuing to smoke cigarettes'.⁶¹

Internal documents and statements by PMI scientists contradict these reduced risk claims about IQOS. In October 2015, an internal newsletter for Philip Morris Japan stated that while 'the "Tobacco Vapor" generated by the use of iQOS contains significantly lower levels of harmful or potentially harmful compounds', PMI has nonetheless 'not reached the point where we can say that it is "less harmful for adult smokers and those around them"⁶² (figure 2). In 2018, four former PMI scientists and researchers that worked on IQOS also claimed that the product's reduction of certain compounds does not necessarily render IQOS safer.⁶³

To assess one measure on which PMI bases IQOS's claims of reduced exposure and thus reduced risk, we compared aerosol chemistry data from PM's Scientific Data Summary (SDS) of Accord with information provided in PMI's MRTP application

for IQOS. PM assembled the SDS to detail Accord's product specifications and clinical and non-clinical research findings. An 'evolving document ... intended for scientific and regulatory discussions',³⁶ PM compiled the report from 2002 to 2006 to support reduced-risk claims for the Accord,⁶⁴ perhaps anticipating US governmental regulation of tobacco and the creation of a regulatory mechanism through which manufacturers could make reduced-exposure and/or reduced-risk claims for preapproved products.²⁷ Despite detailing reductions in HPHC exposure compared with reference cigarettes, PM stated in later versions of the SDS that the company made neither a reduced exposure claim for Accord,³⁶ nor a reduced risk claim, stating that 'reduc[ing] exposure to potentially harmful smoke constituents [did] not ... establis[h] whether the product decreases the hazard of smoking'.³⁶

In both PM's SDS for Accord and PMI's MRTP application for IQOS, industry scientists quantified levels of HPHCs in the products' mainstream aerosol. PMI frames IQOS as safer than conventional cigarettes partly because levels of 58 constituents (PMI-58) were lower in IQOS mainstream aerosol relative to 3R4F reference cigarette mainstream smoke. The MRTP application for IQOS does not report data on 18 compounds included in the SDS for Accord, many of which are nitrosamines and polycyclic aromatic hydrocarbons, all of which are known toxicants (table 2).

The MRTP application presents percent reduction of HPHC yields from IQOS compared with that of 3R4F reference cigarette on a per cigarette/stick basis as well as normalised by nicotine yields (per nicotine basis). The SDS for Accord provides only absolute HPHC yields. In addition, because Accord and IQOS were compared to different reference cigarettes (2R4F and 3R4F, respectively), which have different smoke constituent yields, the percent reductions of Accord and IQOS to their respective reference cigarettes are not comparable. Thus, we compared constituent yields from Accord and IQOS on a per stick basis, using values reported in the SDS for Accord and MRTP for IQOS (table 3). Based on levels of 25 constituents measured in both Accord and IQOS mainstream aerosol, 8 constituents appeared to be higher in Accord emissions while 17 appeared to be higher in IQOS emissions. When normalized by the weight of tobacco in the product, IQOS exposures were higher for 12 constituents and lower for 13 compared to Accord.

DISCUSSION

While Accord was a commercial failure, IQOS is situated in a distinct social and regulatory landscape, which may increase its chances of success. The decline of cigarette consumption in developed markets, the increased popularity of e-cigarettes, select public health endorsements of e-cigarettes and the creation of a legal mechanism in the USA through which manufacturers can now make reduced risk claims may all have increased both consumers' willingness to try new tobacco products, and PMI's willingness to designate new products as safer than conventional cigarettes. In 2017, PMI announced the establishment of a US\$1 billion foundation dedicated to partnering with public health and promoting PMI's portfolio of reduced harm products, chiefly IQOS.⁶⁵

Despite PMI's claims of IQOS's novelty,⁶⁶ the product appears to be a successor of Accord on the basis of product design, marketing and aerosol chemistry. Both products work by inserting a modified cigarette into a holder that heats, rather than burns tobacco. Both products' marketing implies reduced harm relative to cigarettes. While PMI claims that IQOS is

Tobacco Trivia Episode 3: What is "Tobacco Vapor"?

"Fountain-of-knowledge"
Taro-san

His assistant,
Hanako-san

We will provide you with useful information for your daily work in an easy-to-understand manner.

Summary

What is "Tobacco Vapor"?

- An aerosol which is generated when tobacco leaves are heated.
- The vapor mostly consists of water, glycerin and nicotine.
- Although we have not reached to the point where we can say that it is "less harmful", the "Tobacco Vapor" generated by the use of iQOS contains significantly lower levels of harmful or potentially harmful compounds compared to cigarette smoke.

Figure 2 Excerpt from an internal October 2015 Philip Morris Japan newsletter. To clarify employee understanding of IQOS, a mock employee asks: '... iQOS has a less harmful impact on health, right?' The company expert replies, 'No no no! While these [ambient air reductions] are important results, we have not reached the point where we can say that it is "less harmful" for both adult smokers and those around them.'⁷⁴

Table 2 Compounds listed in Philip Morris' Scientific Data Summary for Accord but not Philip Morris International's modified risk tobacco product application for IQOS

Polycyclic aromatic hydrocarbons	Benzo[b]fluoranthene, Benzo[k]fluoranthene, Benzo[j]fluoranthene, Ideno[1,2,3 cd]pyrene, Dibenz[a,h]pyrene, Dibenz[a,l]pyrene, Dibenz[a,e]pyrene, 5-methylchrysene
N-nitrosamines	N-Nitrosodimethylamine (NDMA), N-Nitrosoethylmethylamine (NEMA), N-Nitrosodiethylamine (NDEA), N-Nitrosodi-n-propylamine (NDPA), N-Nitrosodi-n-butylamine (NDBA), N-Nitrosopyrrolidine (NPYR), N-Nitrosopiperidine (NPIP)
Aliphatic nitrogen compounds	2-nitropropane
Aromatic amines	o-anisidine, 2-naphthylamine

reduced risk largely because it reduces users' exposure to harmful constituents, IQOS does not drastically improve users' exposure to toxic compounds than relative to Accord. PMI's claims for IQOS's comparative safety on the basis of reduced exposure are further undermined by internal documents from PMI's parent company: as late as 2007, PM executives and scientists claimed that reductions in exposure did not render Accord safer than conventional cigarettes.

One limitation of this study is that the Truth Tobacco Industry Documents Library is fragmented and incomplete, as it primarily comprises documents released through litigation. As a result, we may have missed documents relevant to our analysis, including information contained in the archive's many 'restricted' documents, which the industry protects under attorney/client privilege.⁶⁷ Given these limitations, there may be unreported differences in product design, marketing and aerosol chemistry between Accord and IQOS that could have informed our analysis.

Table 3 Comparison of Accord and IQOS constituent yields on a per cigarette basis based on data from Philip Morris' Scientific Data Summary and Philip Morris International's modified risk tobacco product application

Constituent	IQOS (abs. value)	Accord (abs. value)	3R4F (abs. value)	2R4F (abs. value)	IQOS (% of 3R4F)	Accord (% of 2R4F)	Ratio IQOS/Accord (abs. values)
1,3-Butadiene (µg)	0.207	2.2	89.2	36.7	0.23	5.99	0.09
4-Aminobiphenyl (ng)	7.8	0.113	3.21	1.24	243.0	9.1	69.0
Acetaldehyde (µg)	192	114	1602	670	12.0	17.0	1.68
Acetamide (µg)	2.96	0.592	13	4.72	22.8	12.5	5.00
Acrolein (µg)	8.32	16.2	158	61	5.3	26.6	0.51
Acrylonitrile (µg)	0.145	0.415	21.2	15.1	0.68	2.75	0.35
Benz[a]anthracene (ng)	2.65	<0.13	28.4	10.8	9.3	<1.20	>20.4
Benzene (µg)	0.452	0.413	77.3	53.7	0.58	0.77	1.09
Benzo[a]pyrene (ng)	0.736	<0.13	13.3	7.75	5.5	<1.68	>5.66
Carbon Monoxide (mg)	0.347	0.564	29.4	14.3	1.18	3.94	0.62
Catechol (µg)	14	4.53	84.1	45.9	16.6	9.87	3.09
Formaldehyde (µg)	14.1	7.41	79.4	18.6	17.8	39.8	1.90
Isoprene (µg)	6.55	35.4	891	386	0.74	9.17	0.19
Lead (ng)	2.23	<0.676	31.2	12	7.15	<5.63	>3.30
Nicotine (mg)	1.29	0.21	1.74	0.934	74.1	22.5	6.14
Nitrogen oxides (µg)	14.2	28.6	538	298	2.64	9.60	0.50
NNK (ng)	7.8	<12	244.7	150	3.19	<8.00	>0.65
NNN (ng)	10.1	15.2	271	166	3.73	9.16	0.66
o-Toluidine (ng)	1.1	0.773	96.2	56.6	1.14	1.37	1.42
Phenol (µg)	1.47	<0.01	15.6	8.27	9.42	<0.12	>147.0
Propionaldehyde (µg)	10.8	4.94	109	54.7	9.91	9.03	2.19
Styrene (µg)	0.577	0.176	13.9	5.85	4.15	3.01	3.28
Toluene (µg)	1.42	1.26	129	80.4	1.10	1.57	1.13
Tar (mg)	19.4	2.27	25	10.3	77.6	22	8.55
Total particulate matter (mg)	30.2	3.56	41.4	12.6	72.9	28.3	8.48

For all ratio values that are under one, IQOS has less of the given compound than Accord on a per stick basis. For all values that are over one, IQOS has more of the given compound than Accord on a per stick basis. IQOS reduces levels of 8 constituents compared with Accord, but raises them for 17 others. When normalized by the weight of tobacco in the product, IQOS exposures were higher for 12 constituents and lower for 13 compared to Accord.

Similarly, we were only able to analyse one part of PMI's MRTP application. Nonetheless, the results of this analysis suggest that PMI's new claims of reduced health risk for IQOS are more likely the product of the current regulatory environment rather than a substantive improvement in the tobacco product's harm profile compared with its precursor, Accord. Scientific evidence supporting reduced harm claims based solely on reduced exposure remains in.^{28 29}

To prove that IQOS is safer than combustible cigarettes, PMI must show that IQOS 'significantly reduce[s] harm and the risk of tobacco-related disease to individual tobacco users and benefit[s] the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products'.⁶⁸ Studies related to health effects range from lab-based smoking machine studies to assess constituent concentrations in products and aerosols/smoke; in vitro and in vivo toxicology studies; clinical and human pharmacology studies to examine the subjective and health effects of product use in lab and ambulatory settings; and epidemiological studies to examine the longer-term effects of these products relative to smoking. Though PMI has conducted several of these studies with favourable results, studies must also address effects on youth uptake, and product appeal to former-smokers and never-smokers to determine population-level health effects. Given the lack of long-term data on the individual and population health effects of IQOS, we remain sceptical of PMI's claims of reduced risk through the use of predictive models.

Other independent research on IQOS has also contested IQOS's claims of comparative safety.⁶⁹⁻⁷² In analysing PMI's MRTP application, independent researchers have noted that PMI's conclusions of reduced population-level risk are based on data that factor in neither concerns of gateway effects for youth,⁷³ nor secondhand smoke and dual use.⁷⁴ Despite public communications about targeting solely adult smokers who would not otherwise quit,⁷⁵ PMI has so far marketed IQOS much like an upscale tech gadget,⁶ offered primarily in countries with declining smoking prevalence and rising cessation rates.⁷⁶

At the individual level, IQOS appears to cause damage to endothelial function, and the liver and the immune system at levels comparable to conventional cigarettes.^{77 78} In addition to showing toxicology yields from only a limited range of HPHC's present in IQOS's aerosol,⁷⁹ 22 of the constituents in the MRTP application had yields more than 200% higher than those present in conventional cigarettes, while another 7 had yields more than 1000% higher.⁷⁹ PMI's medical tests on human subjects also demonstrate 'no statistically detectable difference between IQOS and conventional cigarettes for 23 of the 24 biomarkers of potential harm'.⁸⁰ In January 2018, the FDA's Tobacco Products Scientific Advisory Committee concluded that PMI had not proven IQOS to be safer than conventional cigarettes.⁸¹

This paper joins these analyses in casting doubt on PMI's health claims for IQOS. Based on product specifications, marketing and aerosol chemistry, IQOS appears to represent less of a technical breakthrough than it does an attempt to capitalise

on a social and regulatory landscape more favourable than a similar precursor product's. When the regulatory environment prohibited reduced risk claims, PMI's parent company consistently stated that reduced exposure did not mean reduced risk. The FDA should take PM at its word.

What this paper adds

What is already known on this subject

- ▶ Philip Morris International (PMI) claims that IQOS reduces users' risk by reducing their exposure to harmful and potentially harmful constituents.
- ▶ From 1998 to 2006, PMI's parent company, Philip Morris (PM), marketed a strikingly similar heated tobacco product, Accord, with little commercial success.

What important gaps in knowledge exist on this topic

- ▶ Independent assessment of PMI's health claims for IQOS important, given the tobacco industry's long history of misrepresented and manipulated research.
- ▶ Analysis of internal communications surrounding Accord may help shed light onto PMI's understanding of IQOS.

What this paper adds

- ▶ PM scientists and executives consistently stated that Accord reduced users' exposure to harmful constituents but that these reductions did not render Accord safer than conventional cigarettes.
- ▶ IQOS's design and marketing are similar to Accord's.
- ▶ We found that when comparing the aerosol chemistry test results between Accord and IQOS there was not a consistent reduction in exposure to toxicants, calling into question PMI's current safety claims for IQOS, which are made on the basis of reduced exposure.

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Heated tobacco products: another tobacco industry global strategy to slow progress in tobacco control

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ABSTRACT

There has been a global decline in tobacco consumption that, if continued, will negatively impact the tobacco industry's profits. This decline led the industry to invent and market new products, including heated tobacco products (HTP). HTP are an extension of the industry's strategies to undermine government's tobacco regulatory efforts as they are being promoted as part of the solution for the tobacco epidemic. Under the moniker of 'harm reduction', the tobacco companies are attempting to rehabilitate their reputation so they can more effectively influence governments to roll back existing tobacco control policies or create exemptions for their HTP. Rolling back tobacco control policies will make it easier for the companies to renormalise tobacco use to increase social acceptability for all their products. When regulations are absent or when loopholes exist in classifying HTP as a tobacco product (thus subject to all tobacco control regulations), the industry's marketing of HTP is making these products more visible to the public and more accessible. Governments need to ensure that HTP are regulated as tobacco products or drugs and reject partnerships with the tobacco companies to promote 'harm reduction'. The tobacco companies remain the vector of the tobacco-caused epidemic and cannot be part of the global tobacco control solution.

INTRODUCTION

As of April 2018, Philip Morris International (PMI), British American Tobacco (BAT) and Japan Tobacco International (JTI) were aggressively promoting their 'heated tobacco products' (HTP, also called 'heat-not-burn' heated tobacco, smoke-free tobacco and other 'less risky' products around the world (table 1). Marketing for these products and media accounts of HTP launches in different countries explicitly state or imply that they are safer than cigarettes.¹⁻⁶ In a few instances, marketing materials claim that HTP are potentially helpful to smokers who want to quit.⁶

In the USA, claims of reduced risk (what US law calls a Modified Risk Tobacco Product or MRTP) must be approved by the Food and Drug Administration (FDA) before a tobacco company can market a product with reduced exposure or risk claims.⁷ In December 2016, PMI submitted a request to the FDA to market IQOS, one of its HTP as a MRTP, claiming that it is a reduced risk tobacco product. The application to sell in the USA without these claims falls under a different process.⁷ In particular, despite evidence to the contrary in their MRTP application,⁸⁻¹⁰ PMI claimed that smokers who switch completely to IQOS would experience a reduction in the health-related risks associated with

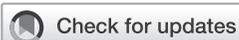
smoking.^{11 12} In January 2018, the FDA Tobacco Product Scientific Advisory Committee recommended against FDA approval of reduced risk claims for IQOS.¹³ This paper provides an overview of the global HTP market, the marketing claims that tobacco companies are making when promoting HTP, and the policy implications of HTP within the context of the tobacco industry's ongoing efforts to disrupt tobacco control progress. IQOS and the other HTP products represent a continuation of the tobacco industry's documented strategies to undermine effective tobacco control, including successful implementation of the WHO Framework Convention on Tobacco Control (FCTC).

Plans to rapidly introduce heated tobacco products

As of April 2018, the industry was rapidly introducing new HTP.^{14 15} In December 2014, PMI became the first company to make a large-scale launch of HTP, promoting IQOS. In Italy, rapid market penetration led to an increase in IQOS use, including intent to use IQOS among non-smokers and long-term former smokers who would otherwise remain tobacco-free.^{16 17} In the case of never smokers, HTP has the potential to cause harm, despite the tobacco companies' claim to the contrary.¹⁶ The finding that non-smokers and former smokers are using IQOS illustrates how the introduction of HTP can compound the harms caused by other tobacco products.

PMI built a US\$120 million production facility in Switzerland and announced, in June 2017 the building of a US\$320 million facility in Germany³ focused entirely on the development and production of HTP. PMI announced plans to double production capacity from 50 billion heatsticks (the disposable tobacco stick that fits in the IQOS device) in 2017 to 100 billion sticks in 2018.¹⁵ In Japan, IQOS quickly gained market share, reaching 10% of the tobacco market in less than 1 year. In 2017, JTI responded with the launch of Ploom TECH,¹ followed by BAT's glo.¹⁸

We do not know the exact number of countries where the tobacco industry is seeking approval to introduce HTPs in 2018, but a 115 page 2014 presentation by PMI Research and Development titled 'Reduced Risk Products Briefing'¹⁹ released by Reuters¹⁴ indicates that PMI aimed to reach 50 markets by the end of 2018. It appears that PMI selected the top 50 markets after considering volume of cigarettes sold, existing product regulation, the 'economical, political and legal environment' and likelihood of commercial success.¹⁹ BAT stated on its website in 2017 that it planned to have its 'potentially reduced risk products' in 40 markets



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Table 1 Availability of HTP by major cigarette company and country of availability (January 2018)

Company	Product	Year launched	Countries/Comments
British American Tobacco ⁹¹	iFuse* glo	2015 2016	Romania, Japan, Switzerland, Canada, South Korea, Russia
China National Tobacco Corporation / SMTA ⁹²	Not reported	Not launched	A few of the companies claim to have over 30 patents of HTP and continue to be engaged in research and development of these products. But none yet are in the market.
Imperial Brands ⁹³	Not reported	Not launched	Focusing on e-cigarettes at the moment, claims to have options to launch when it deems that time is right
Japan Tobacco International ⁹¹	Ploom TECH†	2016	Japan, Switzerland
KT&G Corp. ⁹⁴	lil	2017	South Korea
Philip Morris International‡ 6	IQOS TEEPS§	2014 Not yet launched	Canada, Guatemala, Colombia, Czech Republic, Denmark, France, Germany, Greece, Israel, Italy, Kazakhstan, Lithuania, Monaco, Netherlands, Poland, Portugal, Romania, Russia, Serbia, Slovak Republic, Slovenia, Spain, Switzerland, Ukraine, UK, South Africa, South Korea, Japan, New Zealand

*It is unclear that iFuse will remain in the market in Romania, where Glo was introduced in 2018.

†Ploom TECH is described as a hybrid between a HTP and a vaporiser. It is to be used with Mevius capsules. Mevius is one of JTI's best-selling cigarette brands. The capsules contain tobacco which are then heated by vapour.

‡PMI website states that it is developing a new heated nicotine delivery product that has no tobacco, STEEM, among other 'reduced risk' products.

§ We do not know what TEEPS stands for, it is not included in the product's description (<https://www.pmi.com/smoke-free-products/teeps-carbon-heated-tobacco-product>). HTP, heated tobacco product.

by the end of 2018.⁴ In April 2018, PMI shares dropped in value subsequent to its announcement of an earlier than expected plateauing of the Japanese IQOS market.²⁰

Regulatory considerations

A 2017 Reuters investigation found that before launching IQOS in a country, PMI engaged with high level government officials in attempts to convince regulators that IQOS had health benefits and therefore should not be subject to the same regulatory restrictions as cigarettes, including marketing, labelling and taxation.¹⁴ As Martin King, PMI's Asia President told *Asia Times* in a 2017 interview: 'Ensuring the right market infrastructure and regulatory frameworks are in place is essential to our overall launch schedule for Asia. Fundamentally, any potentially less-harmful alternative to cigarettes needs to be recognised by regulators and consumers as different from cigarettes—taxed differently, labelled differently, and with the freedom to communicate the product attributes openly; only then can smokers have the information they need to encourage them to switch to a smoke-free alternative'.² Similarly, in 2017 Ruth Dempsey, PMI's Director for Regulatory and Scientific Affairs, told the Costa Rican newspaper *Imprensa Libre* that existing regulations in some countries make it difficult for PMI to launch IQOS and suggested that countries needed to change their regulatory frameworks to allow PMI to communicate with consumers and explain the advantages of IQOS.³

In 2017 in Colombia, the Vice President of PMI affiliate Coltobaco, Humberto Mora, lamented that legislation they supposed to treat HTP differently than other tobacco products did not pass a Senate Committee. He stated that lacking specific regulation, the company's goal was to ensure that minors did not buy the product.²¹ Mora also claimed that HTP did not generate any toxic components associated with cardiovascular diseases and cancer.²²

In March 2017, the Ministry of Health of Israel allowed IQOS to enter the market without any restrictions that are applicable to cigarettes and exempted from the tax scheme for other tobacco products.²³ These decisions generated a strong protest from health advocacy groups who filed a court case to protest the Ministry's decision.²⁴ The announcement also ran counter previous statements by the Health Ministry's legal advisor. In January 2018, the Ministry reversed its position and convinced

the Minister of Finance to announce that HTPs would be taxed similarly to cigarettes.²⁵

As of April 2018, there were a range of regulatory approaches to HTP and most of the countries being targeted by the industry for launching HTP were facing the challenge of regulating HTP under existing tobacco control laws that may not explicitly include HTP, which may have made it easier for the companies to open up loopholes in existing laws to evade regulations that apply to all other tobacco products. At a minimum, all claims of harm reduction must be proven with robust, independent evidence,²⁶ and all regulatory measures of the FCTC should be applicable to the packaging, taxation, sales and marketing of HTP.⁷

Marketing heated tobacco products

Marketing of these products, and claims being made about them, need to be regulated.^{7 27} In 2016 in Japan, the appearance of IQOS in a popular television programme was followed by a rapid increase in IQOS use, highlighting the need to regulate HTP marketing and use.²⁸ The agency that represented the TV celebrities that included IQOS on their television show stated that 'they received absolutely no payment from Philip Morris or affiliated companies' to discuss IQOS on their show'.²⁹ In Canada, where marketing restrictions exist, PMI is using a series of direct to consumers marketing strategies, including events, and claims of a 'smoke-free future', highlighting the need for governments to develop regulatory framework around marketing claims.³⁰

The tobacco companies are using a series of claims in the marketing of HTP. Both in websites and statements to the media and investors, HTP are presented as less harmful but not risk-free. Some media accounts of product launches state that HTP reduce the levels of harmful tobacco components by 90%–95% compared with cigarettes, while others emphasise the lack of odour or visible emissions as part of marketing campaigns. It is important to note that as of April 2018, there is no evidence to confirm this claimed 90%–95% lower level of harm. Other marketing claims highlight that these products produce no smoke, that is, are smoke-free. Implied in these claims, in ads and stores globally, is that smokers should switch from cigarettes to these new, allegedly less harmful, products.

Reduced harm

In a July 2017 press release, JTI also claimed a 99% reduction on a list of tobacco product constituents that have been identified as harmful by WHO's Tobacco Product Regulation Expert Group.³¹ In a December 2017 press release, BAT made a similar claim for its HTP, glo, in Romania, where in addition to the 90%–95% reduction in harmful components, BAT claimed that the new product was aligned with WHO's recommendations for regulating tobacco products content.³² BAT qualified the 90%–95% claim with a footnote stating that this was based on an analysis of nine 'harmful components' in cigarettes that the WHO had identified as target for reduction. WHO responded with a statement in February 2018, stating that WHO was 'in no way endorsing BAT's product nor the company's claims concerning the product'.³³

Smoke-free

In 2017 in South Africa,^{34 35} PMI emphasised HTP as 'smoke-free' in its marketing. At the opening of an IQOS store in Cape Town PMI capitalising on the fact that South African law does not require 100% smoke-free public places (by allowing for designated smoking areas), Blaine Dodds, Head of Marketing for Reduced Risk Products at Philip Morris South Africa stated that the company was

extremely excited to partner with these malls which have agreed to allow the trial of this product indoors. The HeatSticks or heated tobacco units inserted in the IQOS device are not ignited, only heated and therefore do not generate smoke. The indoor air quality is not negatively impacted by the aerosol. This affords PMSA the opportunity to leverage the area of the store to demonstrate a smoke-free future to South Africans.³⁴

A footnote in the press release that quotes Dodds states that 'IQOS is not risk free. The best way to reduce tobacco related health risks is to quit tobacco use altogether'.³⁴

A June 2017 JTI press release emphasised the lack of odour from Ploom TECH in an effort to ensure that indoor use is not restricted.¹

In sum, by 2018, the tobacco companies were promoting HTP, globally as a reduced harm product and an option to address the tobacco epidemic. As in previous attempts of the tobacco industry to be a stakeholder in tobacco control,^{36–39} these marketing efforts were providing the tobacco companies with access to decision makers and opinion leaders, continuing the industry's efforts to influence the policy process to protect its profits.

Scientific and political engagement

The tobacco companies use HTP products as part of their broader political and public relations activities to position them as 'partners' to address the tobacco epidemic rather than as the vectors that are causing it. This is a similar strategy previously used by the tobacco industry to promote itself as a partner of public health in reducing the harms of tobacco, while obfuscating the scientific evidence pointing that harm reduction is achieved through tobacco control policies that decrease consumption.³⁹

PMI's 2014 internal '10 year Corporate Affairs Objectives and Strategies'⁴⁰ released as part of a series of investigations by Reuters outlines PMI's strategies to support its 'combustible and reduced risk (RPP) product businesses'. The strategy document provided a series of examples of activities to renormalise its business to regain access to the political and policy discussions related to tobacco control. One of the key objectives was to 'establish PMI as a trusted and indispensable partner, leading its

sector and bringing solutions to the table'. Another key objective was to 'define and pave the way for the right fiscal and regulatory frameworks to secure PMI's RPP portfolio as the pathway for future growth'.⁴⁰

According to this 'confidential internal use only' plan, PMI's 'external engagement' plans were:

1. Establish the concept of harm reduction as legitimate public policy in tobacco regulation.
2. Establish the legitimacy of tobacco companies to be a part of the regulatory debate on RPPs [reduced risk products] ('part of solution').
3. Leverage PMI's innovation and scientific research to establish credibility with stakeholders.
4. Identify and engage non-traditional third party stakeholders/allies (e-cigarette manufacturers and retailers, adult consumers of RPP products, tobacco harm reduction advocates, scientific community) globally and locally.
5. Develop compelling messages and materials to support our advocacy on RPP issues.
6. Amplify and leverage the debate on harm reduction around global events (eg, COP6).
7. Continue to engage with regulators globally.⁴⁰

As discussed below, these strategies echo the tobacco industry's decades-long efforts to undermine tobacco control and present itself as an 'indispensable' partner in all policy discussions.

The 2014 presentation by PMI titled 'Reduced Risk Products Briefing'¹⁹ released by Reuters¹⁴ (figure 1) described how PMI planned to invoke the tobacco industry's usual tools to influence the scientific and policy debate around tobacco control: funding of science, global media and public relations campaigns, use of consultants and support for individuals and groups that it perceives as adequate spokespeople for the company's message.^{41–46}

PMI released a full-page advertisement in newspapers on 2 January 2018 in the UK claiming that PMI was 'trying to give up cigarettes'.⁴⁷ In the ad, PMI explicitly expressed a desire to partner with local and national governmental authorities to support cessation services, including seeking 'governmental; approval to insert, directly into our cigarette packs, information on quitting and on switching'.⁴⁷ The advertisement did not mention HTP directly, but did pledge to 'expand the availability of new, alternative products in the UK'.⁴⁷ PMI also launched a website, nominally to communicate with smokers about quitting regular cigarettes called 'smoke-free future' (only available for consumers in the UK as of April 2018). PMI's communications surrounding HTP emphasised the company's nominal goal of a smoke free future, which is similar to the name of the Foundation for a Smoke-Free World PMI created and funded in 2017.

Foundation for a smoke-free world

As an apparent element of PMI's plan to expand the market for its HTP as well as rehabilitate the company's reputation, in 2017 PMI committed almost US\$1 billion (US\$80 million per year for 12 years⁴⁸) to create the Foundation for a Smoke-Free World.⁴⁹ The foundation website stated that its goal was to ultimately eliminate smoking worldwide and 'advancing the dialogue on smoking cessation and harm reduction'.⁴⁹ The foundation website also stated that it was in the process of developing a research agenda, after which it would release a call for research proposals. The new foundation has a strong goal of promoting HTP as a harm reduction alternative to smoking, in alignment with PMI's strategy to engage with the scientific community and 'amplify' the debate on harm reduction.^{36 37}

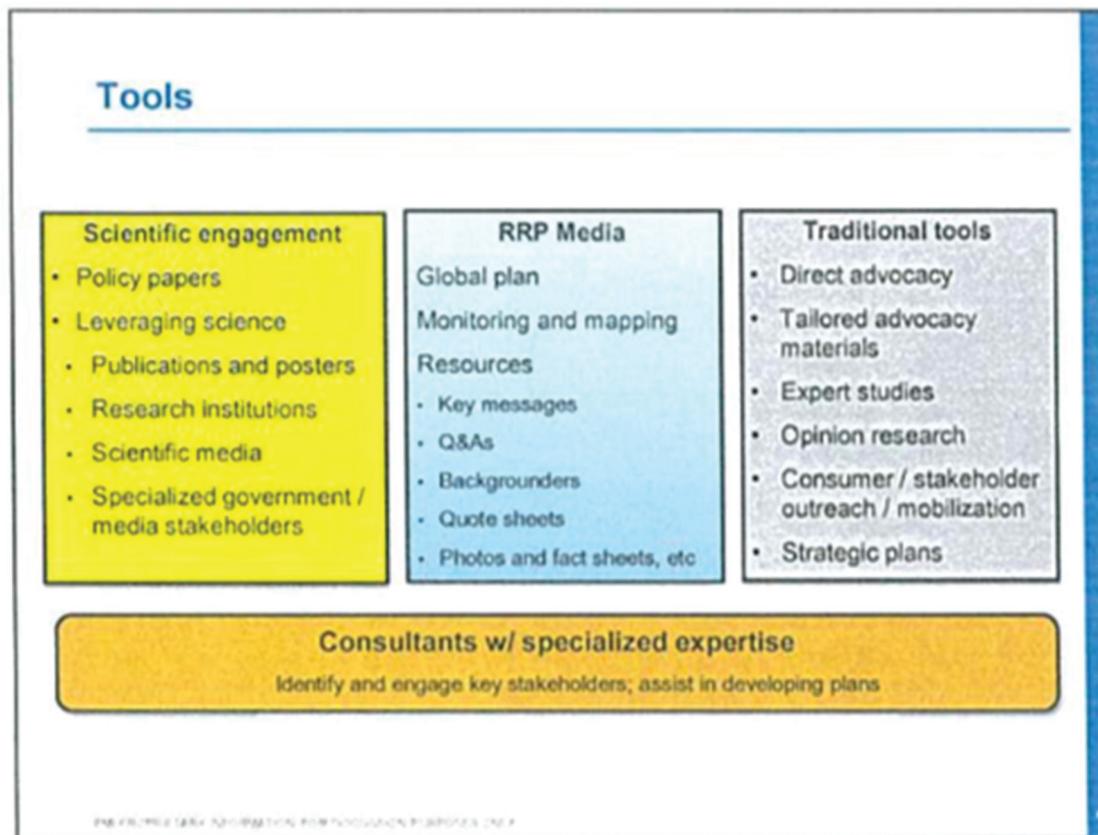


Figure 1 PMI's tools to expand access to markets for its alleged reduced risk products (Slide 22 of a 125 slide presentation titled 'Reduced Risk Products Briefing'¹⁸) released by Reuters¹⁴ as part of a series of reports on PMI activities. PMI, Philip Morris International.

PMI's motives for creating the foundation were questioned by every major health authority group in the world, including the WHO, Union for International Cancer Control and the Union.^{50–52} In January 2018, the deans of 17 schools of public health in the USA and Canada issued a statement declaring that their school would not collaborate with the foundation because they considered funding from the Foundation as being funding from the tobacco industry, which these schools have rejected. Several scholars^{37,53} identified the foundation as another tobacco industry public relations campaign, similar to previous foundations or research institutes the industry had created in the past to serve its political and public relations needs. The criticism also focused on the questionable independence of the foundation from PMI⁵⁴ and questioned the real intent behind the foundation's research agenda. Like its predecessor organisations, the foundation captured a few scientists and academics to promote an agenda that overlaps significantly with PMI's agenda, although research awards had not been announced as of April 2018.

DISCUSSION

The launching of the latest incarnation of HTPs is a reprise⁵⁵ of similar efforts in the past to use similar products to undermine tobacco control, particularly efforts that present the tobacco industry as a harm reduction partner.

As early as the 1960s, the tobacco companies developed alternative tobacco products with the goal of supplementing the cigarette market with products. A few of these products, such as RJ Reynolds (now Reynolds America, part of BAT) *Premier* and *Eclipse* and Philip Morris' *Accord* and *HeatBar*

were marketed but received poor ratings from customers, were commercial failures and were withdrawn.⁵⁵ It is possible the companies were not more aggressive in making 'reduced harm' claims on new products because of legal concerns: Claiming that the new products were safer would amount to an admission that cigarettes were dangerous, opening the door for litigation and political difficulties for the tobacco industry, including FDA regulation of new products and cigarettes in the USA.^{56–58} In addition, the FCTC did not ban cigarettes, one of the tobacco industry's fears. All these factors laid the foundation for the wave of HTP reduced risk claims in several countries that accompanied new HTP products starting around 2014. The introduction of these new products may also have been a response to the growing popularity of e-cigarettes beginning around 2007 after independent companies introduced them before the major multinational tobacco companies entered the e-cigarettes market.^{55, 57} Furthermore, the global decline of cigarette consumption and decrease in adult smoking prevalence (from 24% in 2007 to 21% in 2015), combined with the success of tobacco control, including implementation of the FCTC,^{59–62} may also have led the tobacco companies to consider alternative products to protect their profits and political interests. HTP serves both purposes by keeping consumers using the companies' tobacco products while providing the industry with an avenue to lobby for exemptions from FCTC and similar national regulations by claiming that HTP would be good for public health.⁵⁸ The PMI announcement in the UK⁴⁷ has been identified as integral to the overall tobacco industry strategy to present a changed image to the public while continuing to promote nicotine addiction.³⁶

In the 1990s, with growing pressure from litigation in the USA and increasing engagement of the WHO in supporting tobacco control globally, the tobacco industry worked to create divisions within tobacco control while seeking to reposition itself politically as part of the ‘solution’ to the problems created by tobacco use.⁴⁴ Philip Morris’ Project Sunrise, initiated in 1995, outlined a clear strategy to target certain individuals within the tobacco control community, question their credibility and integrity and work with them to promote alternative policy options that would be less harmful to the interests of the tobacco industry.³⁸ Project Sunrise implemented Philip Morris’ 10-year strategy to position itself as a ‘responsible’ company and a partner in tobacco control efforts, which would give heightened access to decision makers and the possibility to influence tobacco control regulations. Despite Philip Morris’ efforts, global tobacco control did advance, with the FCTC entering into force in 2005.⁴³

Since Project Sunrise, the tobacco industry has deployed a range of strategies to interfere with tobacco control, as described by the WHO.^{45 46} Among these strategies are efforts to create an image of ‘social responsibility’ and a commitment to work in partnership with governments to advance tobacco control, although neither of these initiatives have had any impact other than a public relations campaign for the tobacco industry.^{46 63–66} Another significant strategy the tobacco industry used in the early 2000s was to promote voluntary, self-regulation in an effort to prevent the FCTC from entering into force. This voluntary self-regulation focused on marketing and youth smoking prevention programmes (YSP). Both voluntary marketing regulation and industry-sponsored YSP have been demonstrated to be ineffective in addressing the tobacco epidemic.^{43 67–71}

An integral part of the tobacco industry’s efforts is to promote a variety of its products in ways that imply, overtly or not, that they pose less harm than conventional cigarettes. Such misleading discourse accompanied the launch of cigarette filters, machine-measured lower-tar cigarettes, non-cigarette tobacco products such as snus and other smokeless tobacco.^{39 72 73} All these efforts sought to avoid marketing restrictions and influence policy makers to support self-regulation instead of a mandatory and more restrictive regulatory framework.^{42 43 46} Scientific evidence, on the other hand, demonstrated that filters, decreasing the number of cigarettes smoked a day or switching to a different type of cigarette are not viable risk reduction options. Similarly, as of 2018, the tobacco industry was producing its own science, and planning to fund scientists, in an effort to create evidence to support its claims.

However, emerging science indicated that HTP are unlikely to be any ‘healthier’ than conventional cigarettes, including scientific data submitted by PMI as part of its MRTP application to the FDA.^{8 10 74–77} The industry’s claims are often speculative, emphasising the ‘potential’ for these new products to either reduce harm or reduce risk of tobacco use.^{78 79} Additionally, research has demonstrated that despite claims that there is not burning of tobacco, pyrolysis and charring occurs when using IQOS, releasing highly toxic formaldehyde cyanohydrin.⁸⁰ Others have shown that while there is a reduction in some toxic compounds, when comparing IQOS with regular cigarettes, these are not removed, and the clinical impact of exposure remains to be assessed.⁸¹ Nonetheless, the tobacco industry appears to be determined in using a ‘harm reduction’ frame in order to gain access to the policymaking table.

The tobacco industry’s use of the ‘harm reduction’ framework also serves to fracture the tobacco control movement, leaving it without a unified voice to communicate with the public, the media and with policy makers on the strategies

to advance tobacco control. The concept of harm reduction has traditionally been embraced in several public health fields such as clean needles for injectable drug use and has been explored by some tobacco control experts in the past,⁸² with enthusiasm for the possibility of harm reduction growing with the widespread availability of electronic cigarettes in certain markets.^{83–85} The tobacco industry frames harm reduction as a common ground with health advocates and a possible entry point to influence legislation and regulation of tobacco products.^{39 86 87}

As described by Peeters and Gilmore,³⁹ the 2001 Institute of Medicine report on the potential tobacco harm reduction (that was heavily influenced by industry interests⁸⁸) appears to have provided support for tobacco industry efforts to reframe harm reduction as a viable tobacco control policy option and, more importantly, to position itself as pivotal to achieving such harm reduction goals. Thus, in the past decade and a half, the tobacco industry became a vocal proponent of tobacco harm reduction and has invested millions of US dollars in research and development of new products, such as HTP, which the tobacco industry is now using to gain access to scientists, opinion leaders and decision makers as a ‘solution’ to address the tobacco epidemic. Elias and Ling⁸⁹ describe the role the tobacco industry played in funding the earliest efforts to promote ‘clean nicotine’ for harm reduction and conclude that the tobacco industry will continue to seek endorsement from health authorities to its proposition of HTP as a ‘harm reduction’ strategy.

If HTP manufacturers were seriously concerned about addressing the tobacco epidemic, they would immediately withdraw from dozens of court cases where they are challenging governments’ right to implement policies that protect the public’s health. Moreover, none of the tobacco companies that are promoting HTP have made any effort to actually reduce tobacco harm by curtailing marketing of tobacco products and has continued to vigorously oppose tobacco control measures and the implementation of the FCTC at national, regional and international levels.

FCTC Article 5.3

Governments that are a Party to the FCTC are urged to consider the regulatory options provided by the treaty when confronted with the tobacco industry’s pressure to enter new markets. There is nothing in the language of the treaty that precludes treating HTP as all other tobacco products (or a drug delivery system), including restriction of use in public places, applying labelling requirements, marketing restrictions and taxes.⁷ Additionally, Parties to the FCTC that choose to accept the tobacco industry as a stakeholder in addressing the tobacco epidemic are in breach of Article 5.3. Article 5.3 and its implementation guidelines⁹⁰ clearly state that there is an ‘irreconcilable conflict of interest’ between health policy and the tobacco industry. It further states that the tobacco industry is not, and could not, be a partner of governments in the implementation of tobacco control measures. Thus, governments must not engage, or participate, in tobacco industry-led ‘harm reduction’ efforts.

CONCLUSION

The introduction of the latest generation of HTP appears to be the latest chapter in the decades-old tobacco industry strategy of working to create partnerships with governments and health advocates, presenting these alleged ‘harm reduction’ products

as an option to address the tobacco epidemic. While health authorities should keep an open mind if independent compelling evidence that a true harm reducing tobacco product is developed and could support a harm reduction policy strategy, they should also keep in mind that the past has demonstrated that partnerships with industry benefit the corporate interests of the tobacco industry and harms countries' health and development. The evidence available to date does not convincingly demonstrate that the available HTPs will simply replace conventional cigarettes among current smokers without attracting youth or even that these products will substantially reduce health risks among users. Nevertheless, the tobacco industry has a well-developed media, public relations and scientific strategy to undermine tobacco control through HTP. It is reaching out to governments and scientists to co-opt them to promote HTP.¹⁴ LMICs, and scientists in these countries, are vulnerable to the appeal of industry funding and must be supported in resisting partnering with the industry and, for countries that are Parties to the FCTC, breaching its international commitments. It is unclear what impact, if any, multi-lateral trade agreements will have on the expansion of HTP markets or the regulation of these new products.

Despite the rapid introduction of HTPs, as of April 2018, the vast majority of countries did not yet have these products, which creates a window of opportunity to address the tobacco industry's latest 'harm reduction' offensive. But, time is of essence. The FCTC provides a legal framework that encourages countries to take a series of measures regarding novel tobacco products, from banning entry into market, to regulating advertisement, sales, packaging and use⁷ allowing Parties to address HTP before these products enter the market in an unregulated fashion.

What this paper adds

- ▶ After decades of increasing, global cigarette consumption is falling following implementation of the evidence-based policies in the WHO Framework Convention on Tobacco Control (FCTC).
- ▶ The tobacco companies are promoting heated tobacco products (HTP) as harm reduction as part of their effort to be 'part of the solution' to the tobacco epidemic.
- ▶ The tobacco companies are using strategies that they have used for decades to fracture tobacco control and promote tobacco 'harm reduction' in an attempt to renormalise tobacco use.
- ▶ Tobacco companies are introducing HTP in markets with little or no regulatory or marketing restraints despite the fact that reduced risks claims are unproven and likely false.
- ▶ All FCTC regulatory measures should apply to HTP.
- ▶ Governments in countries where HTP are not available should keep them out and if allowed in the market at all should be under the strict regulatory framework defined by the FCTC.

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Heated tobacco product regulation under US law and the FCTC

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ABSTRACT

Tobacco companies are marketing new 'heated tobacco products' (HTPs) composed of battery-powered holders, chargers and tobacco plugs or sticks. The non-tobacco HTP components have escaped effective regulation under many countries' tobacco control laws because they are packaged and sold separately from the tobacco-containing components. In the USA, HTPs cannot be marketed unless the Food and Drug Administration determines that allowing their sale would be 'appropriate for the protection of the public health'. Philip Morris International (PMI) is seeking permission to market its IQOS HTP in the USA with 'modified risk tobacco product' (MRTP) claims that it reduces exposure to harmful substances and is less harmful than other tobacco products. However, PMI has not submitted adequate scientific evidence required by US law to demonstrate that the product is significantly less harmful to users than other tobacco products, that its labelling would not mislead consumers, or that its marketing—with or without MRTP claims—would benefit the health of the population as a whole. Parties to the WHO Framework Convention on Tobacco Control (FCTC) must take measures to reduce tobacco use and nicotine addiction, and prevent false or misleading tobacco product labelling, advertising and promotions; the introduction of new HTPs must be assessed according to these goals. All components of HTPs should be regulated at least as stringently as existing tobacco products, including restrictions on labelling, advertising, promotion and sponsorship, sales to minors, price and taxation policies and smokefree measures. There is nothing in US law or the FCTC that prevents authorities from prohibiting HTPs.

'Heated tobacco products' (HTPs), also known as 'heat-not-burn' products,¹ use battery-powered systems to heat sticks of compressed tobacco, flavours and other chemicals to produce a nicotine aerosol to create a 'nicotine hit' that imitates cigarette smoking.² A commercial failure in previous decades,¹ major tobacco companies now promote HTPs in many countries as less harmful alternatives to conventional cigarettes, including Philip Morris International's (PMI) 'IQOS', Japan Tobacco International's 'Ploom TECH' and British American Tobacco's (BAT) 'glo'.³

The US Family Smoking Prevention and Tobacco Control Act⁴ (TCA) assigned the Food and Drug Administration (FDA) authority to regulate tobacco products, including modified (reduced) risk tobacco products (MRTP). The TCA requires premarket authorisation of all tobacco products (Section 910)⁴ and does not permit manufacturers to

market tobacco products with claims that they are 'modified risk tobacco products' (ie, the product is sold to reduce harm or the risk of tobacco-related disease, or to reduce consumers' exposure to harmful substances) without first demonstrating to FDA that these claims are supported by scientific evidence. (Section 911)⁴ FDA must refer all MRTP applications (MRTPA) to its Tobacco Products Scientific Advisory Committee (TPSAC) which must report its recommendations (which are advisory only) to FDA. (Section 911(f))⁴

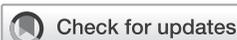
Outside the USA, the WHO Framework Convention on Tobacco Control⁵ (FCTC, the USA is not a party), and its implementing guidelines⁶ provide frameworks for parties to enact implementing national legislation, including prohibitions on misleading advertising (Article 11(1)(a))⁵ (Article 11 Guidelines for Implementation)⁶ and misleading packaging and labelling (Article 13(4)(a))⁵ (Article 13 Guidelines for Implementation)⁶ which serve similar purposes as MRTP review. Further, parties are 'encouraged to implement measures beyond those required' by the FCTC. (Article 2)⁵

When the TCA and FCTC were enacted, the tobacco companies were not marketing their current HTPs. This paper uses the specific case of IQOS to analyse how these regulatory frameworks do or should apply to HTPs and related reduced harm claims.

THE IQOS HTP IS AN INTEGRATED TOBACCO PRODUCT DESIGNED TO MAINTAIN NICOTINE ADDICTION

IQOS consists of three integrated components essential for its proper functioning: a holder (which heats the tobacco material via an electronically controlled heating blade), a charger (which recharges the holder after each use) and a tobacco stick ('HeatSticks' or 'HEETS') (figure 1). As PMI acknowledges, these three components collectively comprise IQOS⁷; the holder and charger have no independent function without the tobacco sticks, and the tobacco sticks cannot create a nicotine aerosol without the holder and charger. In its MRTP application, PMI describes the HeatStick as '*specifically designed to function with the holder to produce an aerosol [emphasis added]*'.⁸

PMI is taking advantage of this three-component design to package and sell the tobacco sticks separately from other IQOS components that do not contain tobacco, thereby evading existing tobacco control labelling, marketing and tax laws in some countries. For example, in Canada many chain convenience stores sell IQOS HEETS, but not the device itself, and store clerks inform customers to contact an IQOS representative to arrange for the



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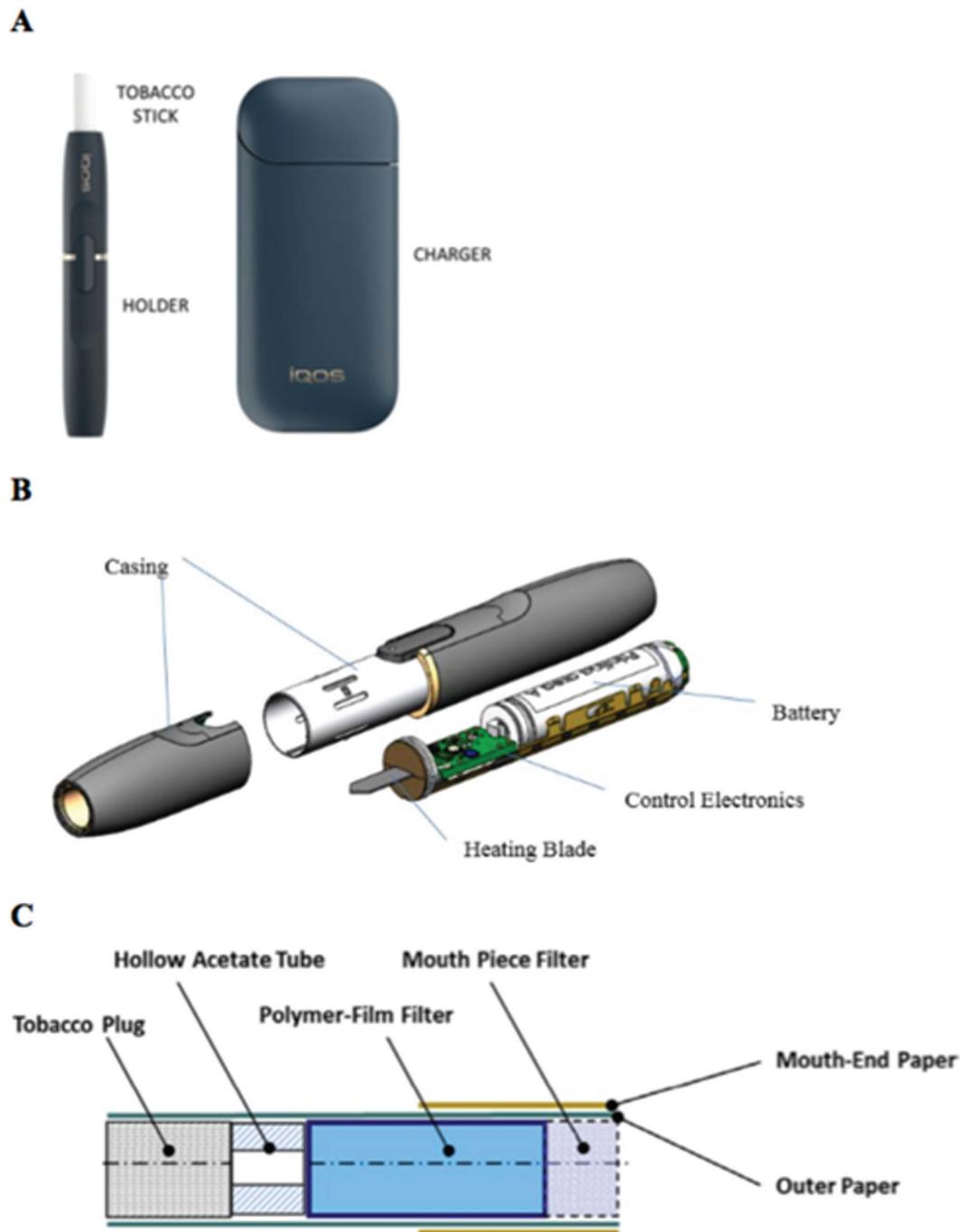


Figure 1 Schematic drawing of the IQOS showing its components (A), a schematic exploded view drawing of the holder (B), and a schematic cross-sectional view of the tobacco stick (C) (Executive Summary).⁷

device purchase.⁹ In Korea,¹⁰ PMI markets its IQOS holder, charger and related accessories in packages that do not contain the HEETS labelled only as 'IQOS' without any reference to tobacco or health warnings required on tobacco product packaging. PMI sells the HEETS in separate packages branded with Marlboro or other cigarette brands that include health warnings and comply with tobacco product packaging and labelling laws.

The product description of IQOS in PMI's MRTPA is heavily redacted,⁷ but states that the IQOS holder contains an electronic chip (firmware) used to 'control the temperature', 'detect puffs' and conduct other functions that control the user's nicotine intake. (Module 3.1, Product Description)⁷ PMI testified at the January 2018 TPSAC meeting that the

IQOS device is able to capture data such as the number of puffs taken, but said this information is used for diagnostic purposes if the device is returned.¹¹ Additionally, PMI testified to TPSAC that IQOS's Bluetooth functionality is used to deliver messages to consumers such as 'you haven't used your IQOS device today' and to remind them to reorder tobacco HeatSticks.¹¹ The fact that IQOS measures a user's puff-by-puff heating profile,^{11 12} integrates IQOS's Bluetooth capability with mobile phones and computers,¹³ and automatically reminds consumers to continuously use the device and to reorder tobacco sticks¹¹ suggests that it calibrates the delivery of nicotine to ensure not only 'satisfaction', but also the potential for PMI to customise the dose, speed of delivery

and continuous use of nicotine to maximise addictive potential for individual users.^{12 14 15}

REGULATION OF HTPS IN THE USA

How tobacco products are defined impacts how they are regulated.¹⁶ The TCA defines ‘tobacco products’ as ‘any product made or derived from tobacco that is intended for human consumption, *including any component, part, or accessory of a tobacco product...* [emphasis added]’. (Section 101(a))⁴ IQOS (including the HeatSticks, holder and charger) falls squarely under the FDA’s definition of ‘tobacco product’; PMI does not dispute that its IQOS product (including all three components) is a ‘tobacco product’ under US law⁷ and subject to most regulations that pertain to tobacco products (eg, premarket review (Section 910)⁴) and prohibition on distribution of free samples.¹⁷

The Deeming Rule, in which FDA took jurisdiction over tobacco products beyond cigarettes and smokeless tobacco, defines ‘component or part’ to include materials intended or expected to alter or affect the tobacco product’s performance, composition or characteristics¹⁸ and extends FDA’s regulatory authority to cover all tobacco products meeting the definition of ‘tobacco product’ including HTPs and their components and parts.¹⁹ Certain provisions of the Deeming Rule (eg, prohibition of sales to customers under age 18 and vending machine sales)²⁰ apply only to ‘covered tobacco products’ which ‘excludes any component or part that is not made or derived from tobacco’.^{18 20} The loophole FDA created in the Deeming Rule contradicts the clear definition of ‘tobacco product’ in the TCA⁴ which includes ‘any component, part, or accessory’. The loophole creates opportunities for companies to sell IQOS devices to youth in violation of the law’s intent.

Additionally, the Federal Cigarette Labeling and Advertising Act²¹ (FCLAA) defines ‘cigarettes’ as ‘any roll of tobacco wrapped in paper or in any substance not containing tobacco’ and the regulations implemented under the TCA incorporated this definition.¹⁸ Because the HeatSticks also meet the definition of ‘cigarettes’, additional restrictions that apply to cigarettes but not other tobacco products (eg, required cigarette warnings²² and prohibition of advertising on electronic communication media²³) should apply to the HeatSticks.

Before being permitted to market a new tobacco product in the USA, manufacturers must first receive premarket authorisation from FDA through a premarket tobacco product application (PMTA), a ‘substantial equivalence’ (SE) order or an exemption from SE. (Section 910(a)(2))⁴ (The less rigorous SE pathway is not available to the current generation of HTPs because no HTPs with similar characteristics were marketed in the USA before 15 February 2007, (Section 910(a)(3))²⁴ and HTPs are not ‘minor modifications’ of any product that was marketed in the USA before 15 February 2007. (Section 905(j)(3))²⁴) A PMTA applicant has the burden of showing that the product ‘would be appropriate for the protection of the public health’, determined with respect to ‘the risks and benefits to the population as a whole, including users and nonusers’, taking into account the increased or decreased likelihood that existing users will stop using tobacco products, and non-users will start using them. (Section 910(c)(4))⁴ This stringent standard essentially requires the applicant to demonstrate that, on balance, ‘allowing the sale of the new product would likely reduce tobacco-related harms’.²⁵ Additionally, FDA is required to deny a PMTA for any product whose proposed labelling is ‘false or misleading in any particular’. (Section 910(c)(2)(C))⁴

Furthering its mission to protect the public health, the TCA aims to prevent the tobacco industry deception detailed in a US district court’s holding that tobacco companies deliberately deceive and mislead consumers about the harmfulness of their products with labelling and marketing^{26 27} and highlighted in the TCA’s ‘Findings’ section. (Section 2)⁴ In particular, the TCA gives FDA the authority to ‘ensure that there is effective oversight of the tobacco industry’s efforts to develop, introduce, and promote less harmful tobacco products’. (Section 3(4))⁴

The TCA defines an MRTP as ‘any tobacco product that is sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed products.’ (Section 911(b)(1))⁴ To secure an order permitting sales of tobacco products with modified-risk claims, a manufacturer must submit an application (MRTPA) to FDA demonstrating that the product, as actually used by consumers, will ‘significantly reduce harms and the risk of tobacco-related disease to individual tobacco users’ and ‘benefit the health of the population as a whole’, taking into account both users and non-users of tobacco products. (Section 911(g)(1))⁴ For products that cannot receive risk-modification orders, FDA may issue an exposure-modification order if the applicant has demonstrated that doing so ‘would be appropriate to promote the public health’ and the labelling and advertising is limited to representing that the product or its smoke is free of or contains a reduced level of a substance or presents a reduced exposure to a substance in tobacco smoke. (Section 911(g)(2)(A))⁴ Additionally, for an exposure-modification order, the applicant must demonstrate among other things that: (1) the product as actually used by consumers will not expose them to higher levels of other harmful substances compared with similar types of tobacco products currently on the market and its use would reduce overall morbidity and mortality among users; and (2) based on testing of actual consumer perception, the proposed labelling and marketing will not mislead consumers into believing that the product is less harmful or presents less risk of disease than other commercially marketed tobacco products. (Section 911(g)(2)(B))⁴ Furthermore, for both risk-modification and exposure-modification orders, FDA must ensure that ‘any advertising and labeling concerning modified risk products enable the public to comprehend the information concerning modified risk and to understand the relative significance of such information in the context of total health’ and tobacco-related harms. (Section 911(h)(1))⁴

The TCA authorises states to enact laws that are more stringent than TCA requirements, including measures ‘prohibiting the sale, distribution, possession, exposure to, access to, advertising and promotion of, or use of tobacco products by individuals of any age’. (Section 916)⁴

The PMI IQOS MRTP application

In December 2016, PMI submitted a multimillion-page MRTPA to FDA seeking permission to market IQOS in the USA with two modified-risk claims (‘switching completely from cigarettes to the IQOS system can reduce the risks of tobacco-related diseases’ and ‘switching completely to IQOS presents less risk of harm than continuing to smoke cigarettes’) and one modified-exposure claim (‘switching completely from cigarettes to the IQOS system significantly reduces your body’s exposure to harmful and potentially harmful chemicals’).⁷ In January 2018, PMI presented its IQOS MRTPA to TPSAC, and TPSAC found that PMI’s MRTPA failed to provide sufficient scientific evidence supporting its modified risk claims.^{11 13}

In March 2017, PMI submitted a PMTA²⁸ seeking authorisation to market IQOS in the USA which is required whether or not IQOS is marketed with MRTP claims. Accordingly, if FDA rejects PMI's application to market IQOS with MRTP claims, FDA could still grant PMI's application to market IQOS in the USA without any such claims.

PMI's harm-reduction claims are based on the principle that it is the inhalation of complex combustion compounds in tobacco smoke that causes adverse health outcomes, and since the IQOS device purportedly heats but does not burn the proprietary tobacco stick to create an inhalable nicotine-containing aerosol, it is less harmful than cigarette smoke.⁸ Contrary to these claims, harmful chemicals are created in the pyrolysis phase.²⁹

US law (Section 911(g)(1))⁴ places the burden on PMI to demonstrate that IQOS is appropriate for the protection of the public health before marketing it with MRTP claims and not on FDA or the public to demonstrate the product's harmfulness. However, a close reading of PMI's MRTPA reveals it did not meet this burden. PMI's own data fail to show consistently lower risks of harm in humans using IQOS compared with conventional cigarettes,^{30 31} that IQOS is associated with pulmonary and immunomodulatory harms not significantly different from conventional cigarettes,^{32 33} that IQOS use may be associated with hepatotoxicity and unexpected organ toxicity that has not been associated with conventional cigarettes^{34 35} and that IQOS use does not necessarily avoid the adverse cardiovascular effects of conventional cigarette smoking.^{36 37} In addition, data collected independently of PMI revealed IQOS does not consistently reduce exposure to harmful or potentially harmful chemicals.^{29 38–42} Moreover, Reuters published a report in December 2017 identifying irregularities in PMI's IQOS research.^{43 44} At its January 2018 meeting, TPSAC voted that PMI's MRTPA failed to provide scientific evidence supporting its modified risk claims.¹³

The evidence presented in PMI's MRTPA also failed to demonstrate a net public health benefit as required for both a PMTA order (Section 910(c)(4))⁴ and a MRTP order. (Section 911(g)(1))⁴ PMI did not demonstrate IQOS would benefit the health of the population as a whole, considering both users and non-users of tobacco products.^{45 46} Of particular concern, PMI failed to consider whether youth or adolescents or other non-users are likely to initiate tobacco use with IQOS,^{10 47 48} or whether users are likely to use IQOS concurrently with other tobacco products, rather than 'switch completely'.^{32 47 49} Based on the evidence presented in PMI's MRTPA, TPSAC found that there would be a low likelihood that US smokers would completely switch to IQOS use.¹³

The TCA also requires PMI's MRTPA to include scientific studies demonstrating that consumers will understand the proposed advertising and labelling and not be misled into believing the product is less harmful than it actually is. However, the evidence presented by PMI indicates that the IQOS labelling or advertising will not ensure accurate consumer perceptions of risk, smokers will not understand they would need to switch completely to IQOS to secure the purported benefits, and consumers will likely view the reduced-exposure claims as reduced-risk claims, rendering them inherently misleading.^{27 50 51} Independent research also demonstrates that adults and adolescents misinterpret reduced-exposure claims as communicating lower risk even when there is no explicit claim of lower risk.⁵² TPSAC also found that PMI failed to demonstrate that consumers would accurately understand the risks of IQOS as conveyed in PMI's proposed MRTP labelling and advertising.¹³

If PMI cannot revise its application to demonstrate that marketing IQOS would actually be 'appropriate for the protection of the public health' and its proposed labelling would not be misleading, FDA would be required by statute to deny PMI's applications, and PMI would not be permitted to market IQOS with or without any related modified-risk claims.

FDA's decisions regarding PMI's IQOS applications will influence how other governments regulate HTPs and related reduced-risk claims throughout the world. Indeed, PMI stated in its 2018 annual report, 'We remain focused on our aspiration to see IQOS launched in the United States' and 'Future FDA actions may influence the regulatory approach of other governments'.⁵³

REGULATION OF HTPS IN FCTC PARTY COUNTRIES

The objective of the FCTC is 'to protect present and future generations from the devastating health, social, environmental and economic consequences of tobacco consumption and exposure to tobacco smoke' and to reduce 'continually and substantially the prevalence of tobacco use'. (Article 3)⁵ The 181 parties to the FCTC commit to implementing legislative and other measures 'for preventing and reducing tobacco consumption, nicotine addiction and exposure to tobacco smoke', (Article 5)⁵ to inform every person of 'the health consequences, addictive nature and mortal threat posed by tobacco consumption', to prevent initiation and decreasing the consumption of tobacco products 'in any form', (Article 4)⁵ and to prevent and reduce 'nicotine addiction' in addition to tobacco consumption. (Article 5)⁵

The FCTC provides strong and broad support for parties to adopt measures protecting the public from the dangers of HTPs. Although the FCTC (negotiated between 1999 and 2003) does not specifically discuss HTPs, it was not intended to be limited to conventional cigarettes, smokeless tobacco and other tobacco products being marketed at the time. The objective of the FCTC is unequivocally to protect 'future generations' as well as present generations, (Article 3)⁵ and it anticipates the introduction of new products that would be introduced after treaty negotiations concluded in 2003. FCTC Article 2 encourages parties to implement measures that go beyond and are stricter than those required by the FCTC. (Article 2)⁵ Countries can choose various approaches to regulating HTPs consistent with FCTC's goals.

Regulating HTPs as tobacco products

FCTC Article 1 defines 'tobacco products' as 'products entirely or partly made of the leaf tobacco as raw material which are manufactured to be used for smoking, sucking, chewing or snuffing'. (Article 1)⁵ Unlike the definition under US law, the FCTC's definition of 'tobacco product' does not explicitly include 'any component, part, or accessory of a tobacco product'. However, because HTPs are integrated products that are partly made of tobacco and are used for smoking or sucking, some countries may interpret their laws to consider HTPs as tobacco products. Significantly, in its own documents and marketing claims, PMI refers to its 'IQOS system' as one integrated tobacco product. PMI states that IQOS's tobacco sticks are 'specifically designed to function with the holder', and refers to IQOS interchangeably as 'IQOS', 'the IQOS system, consisting of the tobacco sticks, holder, and charger' and as 'the Tobacco Heating System'.⁷ On its website, PMI markets the three main IQOS components as a singular tobacco product, the IQOS 'tobacco heating system'.⁵⁴

The fact that HTPs are considered 'tobacco products' under the FCTC is confirmed in several statements issued by the Convention Secretariat.⁵⁵ In 2016, the FCTC Conference of the Parties

(COP), the treaty's governing body, stated that 'All new and emerging tobacco products should be regulated under the WHO FCTC. This should include products such as vaporizers and any other novel devices which can be used for tobacco consumption and are not classified as electronic cigarettes.'⁵⁶ A 2017 WHO information sheet on HTPs stated, 'all forms of tobacco use are harmful, including HTPs', and recommended, 'HTPs should be subject to policy and regulatory measures applied to all other tobacco products, in line with the WHO FCTC.'⁵⁷

In September 2017, the FCTC Convention Secretariat addressed the introduction of new tobacco products such as HTPs and stated that parties are obligated under the FCTC to treat these and 'other novel tobacco or nicotine products' that may emerge in the same way other tobacco products are regulated.⁵⁵ Thus, parties should include HTPs in all restrictions currently applied to other tobacco products, including but not limited to regulation of the product's contents and disclosures, packaging and labelling requirements, comprehensive bans (or severe restrictions) on product advertising, promotion and sponsorship, protections from exposure to the product's smoke/aerosol, prohibitions on sales to minors, and price and tax measures.

In March 2017, Israel became the first country to regulate IQOS as a tobacco product and apply all tobacco product restrictions to IQOS,⁵⁸ and in March 2018 Israel's Finance Committee approved applying Israel's cigarette tax to IQOS.⁵⁹

Prohibiting HTPs

The simplest and most effective way to deal with HTPs under the FCTC would be to prohibit the introduction of HTPs which is supported by the FCTC's goals, including protecting future generations from the devastating health consequences of tobacco consumption, (Article 3)⁵ preventing the initiation of tobacco products 'in any form' (Article 4)⁵ and preventing and reducing 'nicotine addiction'. (Article 5)⁵ Historical arguments against banning cigarettes (eg, that it would lead addicted smokers to seek nicotine elsewhere and create a black market)⁶⁰ do not apply to a ban on products like HTPs that have yet to be introduced or are as yet a minor segment of the nicotine market.

By introducing IQOS or other HTPs, tobacco companies are likely to increase tobacco consumption, increase nicotine addiction, increase initiation among youth and non-smokers,^{61 62} undermine efforts to denormalise and significantly reduce tobacco use,⁶³ and create a new market of tobacco products that once established will be difficult to control. PMI has introduced IQOS in some markets where it is treated differently from cigarettes under existing regulatory frameworks, allowing it to advertise IQOS and engage in intensive one-to-one marketing to switch current smokers to IQOS which would not be permitted under those countries' FCTC-aligned tobacco control legislation.^{9 60} The fact that IQOS could be programmed to maximise addictive potential (discussed above) is of particular concern.

Recent experience with e-cigarettes suggests that introducing new, highly addictive tobacco products where cigarettes are available may increase initiation and encourage dual use, especially among youth, and sustain nicotine addiction in violation of the FCTC's principles.⁶⁴⁻⁶⁶

Some FCTC parties have already effectively banned HTPs. For example, in 2015 Singapore banned emerging tobacco products including e-cigarettes and devices that are smoked or mimic smoking.⁶⁷ In Australia, nicotine is a scheduled poison, so products containing nicotine for human consumption are

prohibited unless for 'human therapeutic use' (cigarettes are grandfathered).⁶⁸

Definitions in national implementing legislation

The statutory systems of each of the 181 parties to FCTC differ, and the legal mechanisms for drafting, amending or interpreting laws will be specific to each country. Because many parties enacted national legislation to implement the FCTC before the current generation of HTPs were being marketed, some countries' laws use definitions of 'tobacco products' that are ambiguous with regard to HTPs. Removing any ambiguity or potential for misunderstanding will make it more difficult for tobacco companies to claim there are loopholes that exempt HTPs or any HTP components from tobacco control laws.

As discussed above, tobacco companies are seeking to take advantage of this ambiguity by disassembling their integrated tobacco products and selling the components that do not contain tobacco in separate packages and even separate stores to evade labelling and advertising laws. Parties to the FCTC should ensure that all of the tobacco control measures contained in the FCTC apply to all components of the HTP system, whether sold as a single system or as separate components.

Analogous to the situation where IQOS holders and chargers are sold separately from IQOS tobacco sticks, hookah waterpipes are often sold separately from hookah tobacco. Responding to the potential problems this poses in regulating warning labels, in November 2016 COP issued a decision stressing the need for all parties to fully implement all FCTC articles in all aspects of waterpipe use.⁶⁹ We found one country, Turkey, whose labelling laws explicitly require health warnings to be placed on hookah bottles and waterpipe tobacco packages.⁷⁰

Countries should interpret their definitions to include HTPs (and other new tobacco products), and, if necessary to avoid ambiguity, amend their definitions, for example, 'tobacco products' means products entirely or partly made of tobacco which are manufactured to be used for inhaling, smoking, sucking, chewing, snuffing or by any other means (see, eg, definitions of 'tobacco products' found in Thailand, the Philippines, Cambodia, Oman and Uganda).⁷¹ Alternatively, countries could add language to clarify that their existing definitions of tobacco products include components like the US definition, and ensuring that all regulations that apply to tobacco products also apply to their components. COP should issue an opinion recommending that parties subject HTPs to all FCTC regulatory measures applied to tobacco products and prohibit tobacco industry attempts to evade these measures.

Countries could also clarify and broaden the definition of 'smoking' in their laws. The FCTC Article 8 Guidelines recommended defining 'smoking' as 'being in possession or control of a lit tobacco product regardless of whether the smoke is being actively inhaled or exhaled'. (Article 8)⁶ Countries that adopted this language should change the definition so that it would clearly include HTPs. This could be accomplished by explicitly adding HTPs to the definition of smoking. COP should issue a decision recommending all parties to ensure their definition of 'smoking' includes HTPs and other new tobacco products that may emerge.

Packaging, advertising and marketing

FCTC Article 11 requires parties to adopt measures that prohibit packaging and labelling that promotes a tobacco product 'by any means that are false, misleading, deceptive or likely to create an erroneous impression about its characteristics, health effects,

hazards or emissions', including any figurative or other sign 'that directly or indirectly creates the false impression that a particular tobacco product is less harmful than other tobacco products'.⁷² FCTC defines 'tobacco advertising and promotion' to mean 'any form of commercial communication, recommendation or action with the aim, effect or likely effect of promoting a tobacco product or tobacco use either directly or indirectly'. (Article 1(c))⁵ FCTC's Article 13 advertising, promotion and sponsorship provisions (Article 13(2))⁵ urge parties to adopt comprehensive bans of all tobacco product advertising, promotion and sponsorship to reduce consumption of tobacco products. The Article 13 Guidelines for Implementation (Article 13)⁶ underscore that such a 'comprehensive ban' applies to *all* kinds of tobacco promotion without exception, including *indirect* advertising, acts that are likely to have a promotional effect and commercial communications. For example, in addition to traditional media and internet advertisements, Article 13 'advertising, promotion and sponsorship' restrictions include display of tobacco products at points of sale, packaging and product features (including colours, logos, pictures and materials), brand stretching and corporate social responsibility campaigns. (Article 13)⁶

The Article 13 Guidelines are particularly relevant to current IQOS promotions, including its 'smoke-free future' campaign⁷³ and its product features and marketing that appeal to youth and adolescents, including using packaging that uses colours, logos and materials that mimic iPhones, and selling IQOS in stores that imitate Apple computer stores.^{9 10 61 62} It is important to recognise that any advertising or promotion of IQOS, including in particular promotions of the holder alone or any other IQOS component that has been separated for marketing purposes from the essential tobacco sticks, is promoting tobacco within the meaning of the FCTC because it is not only *likely* to promote a tobacco product or use, but its *specific aim* is to promote use of the IQOS tobacco sticks (HeatSticks or HEETS). Neither the IQOS holder nor the IQOS tobacco sticks have any utility other than when used together. Following this reasoning, in April 2018, Lithuania's tobacco regulator fined a PMI subsidiary for advertising the IQOS device, determining the device is subject to the same advertising restrictions as other tobacco products⁷⁴ based on its view that 'this device can only be used to smoke tobacco products'.⁷⁵

As of May 2018, PMI was promoting IQOS as a less harmful alternative to cigarettes.^{3 9 50 60 76} Because these claims have not been substantiated with scientific evidence, they violate FCTC's Article 11 and Article 13 prohibitions. PMI's 'smoke-free future' campaign⁷³ appears designed to renormalise tobacco use, rather than to treat tobacco dependence or promote the end of tobacco.⁶³ In February 2018, WHO issued a statement condemning BAT's promotional statements for its glo HTP implying that WHO endorsed glo as a less harmful alternative to conventional cigarettes and said, 'There is no evidence to demonstrate that HTPs are less harmful than conventional tobacco products'.⁷⁷

In countries that cannot enact comprehensive bans, Article 13(4) states that at a minimum, parties shall prohibit 'all forms of tobacco advertising, promotion and sponsorship that promote a tobacco product by any means that are false, misleading or deceptive or likely to create an erroneous impression about its characteristics, health effects, hazards, or emissions'. (Article 13(4))⁵ Under this provision, countries should prohibit PMI from all forms of advertising or promoting IQOS. In the absence of such a prohibition, at a minimum, countries should not permit PMI to market IQOS with unsubstantiated explicit or implicit claims that it is safer than conventional cigarettes, including through

using deceptive packaging or colours to alter consumers' perceptions of the product's harmfulness.⁷⁸⁻⁸³

Since scientific evidence does not support PMI's reduced risk claims about IQOS, they are false, misleading and/or deceptive and likely to create misperception about IQOS's health impacts, just as 'light' and 'mild' claims were found to mislead consumers.^{26 27} Therefore, they are prohibited under Articles 11 and 13.

CONCLUSION

Tobacco manufacturers are using unsubstantiated claims of reduced health risks associated with their new HTPs and aggressive marketing campaigns that are especially effective among youth and adolescents to introduce and market their latest versions of supposedly 'safer cigarettes'. The companies have not provided evidence to demonstrate that these new products are actually less harmful, and there is evidence that the companies' marketing claims mislead consumers. Companies have tried to evade existing laws intended to regulate tobacco products, including HTPs, by breaking apart the products and selling the components separately.

Because the tobacco sticks can only be used when attached to the HTP heating devices, sales prohibitions, youth access and advertising and labelling laws (including FCLAA restrictions that apply to cigarettes in the USA) should apply to the complete HTP system, including all components. Loopholes in laws and regulations (including the FDA's Deeming Rule) that would allow HTPs to evade tobacco control restrictions if the holder is sold separately from the tobacco stick should be eliminated. PMI's aggressive marketing techniques for IQOS using targeted

What this paper adds

- ▶ Many tobacco companies are developing heated tobacco products (HTPs) that are being marketed with unsubstantiated claims of reduced harm compared with conventional cigarettes.
- ▶ Companies have sold the non-tobacco components of HTPs separately from the tobacco-containing components to exploit ambiguity in governments' 'tobacco product' definitions to evade tobacco control laws and public health restrictions.
- ▶ Philip Morris International has not submitted the adequate scientific evidence required by US law demonstrating that marketing IQOS in the USA would be 'appropriate for the protection of the public health', or demonstrating that IQOS is significantly less harmful to users than other tobacco products, that its labelling would not mislead consumers or that its marketing—with or without modified risk claims—would benefit the health of the population as a whole.
- ▶ The WHO Framework Convention on Tobacco Control (FCTC) provides a strong framework for parties outside the USA to enact and enforce laws to effectively regulate HTPs; parties should revise their laws to remove ambiguity and ensure that HTPs are covered by national laws.
- ▶ The USA and parties to the FCTC should ensure that all components of HTPs are regulated at least as stringently as tobacco products and are subject to all tobacco control laws that apply to other tobacco products, including restrictions on misleading labelling, advertising, promotion and sponsorship, sales to minors, price and taxation policies, and smokefree measures.

customer interventions and sophisticated technologies to capture data, monitor use and convert customers should concern privacy and public health advocates. Policy-makers in places that do not prohibit the sale of HTPs should amend or enact comprehensive tobacco control laws that ensure HTPs are captured for the purposes of all tobacco product restrictions under the TCA and FTC measures, including smokefree laws, advertising, promotion and sponsorship, packaging and labelling, taxation, and content regulation as appropriate. Under no circumstances should HTPs be treated less strictly than combustible tobacco products.

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Patient consent Not required.

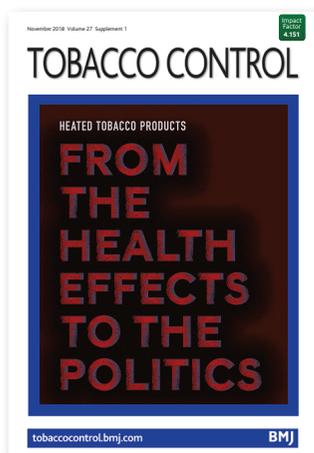
Provenance and peer review Not commissioned; externally peer reviewed.

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