PHILIP MORRIS
AUSTRALIA NEW ZEALAND PACIFIC ISLANDS

9 July 2020

The Secretary
Therapeutic Goods Administration
PO Box 100
Woden ACT 2606

By email: medicines.scheduling@health.gov.au

Dear Sir or Madam

Interim Decision referred to the Advisory Committee on Medicines and Chemicals Scheduling - Nicotine (Heated Tobacco Products)

The current Commonwealth Poisons Standard Schedule 7 lists nicotine as a poison but provides an exemption for nicotine in "tobacco prepared and packed for smoking" (cigarettes). On 31 October 2019, Philip Morris Limited ("PML") applied to the Scheduling Committee ("Committee") of the Therapeutic Goods Administration ("TGA") to amend Schedule 7 ("Application"), so that the exemption would also include nicotine in "tobacco prepared and packed for heating" ("Heated Tobacco Products" or "HTPs"). The amendment sought by PML would go no further than aligning the regulatory treatment of HTPs with that currently applied to cigarettes.

The Committee recommended that the treatment of nicotine in the current Schedule 7 remains appropriate and in the interim decision issued on 10 June 2020, the Delegate of the Secretary of the Department of Health ("Delegate") agreed with the recommendation. If the interim decision is confirmed, it will mean that, the only way that nicotine can be legally sold and purchased in Australia without a prescription is combustible tobacco products (apart from therapeutic treatments such as nicotine gum and patches), the most harmful way of consuming nicotine.

PML disagrees with the interim decision, including the Delegate's comments that *"using tobacco cigarettes as a relevant comparator is too narrow and does not fully reflect the matters I am required to take into account, under subsection 52E(1)…"* There are currently nearly 3 million Australians that smoke. Many of these smokers do not quit despite knowing it is the best choice they can make. Smoking rates in Australia have stagnated over recent years despite Australia having some of the world's toughest tobacco control measures.

Therefore, when considering the matters listed in subsection 52E(1) of the *Therapeutic Goods Act 1989* (Cth), it is imperative to consider the *relative* risks and benefits of exempting HTPs, namely, if these products were to be exempt, would they provide benefits (and/or create risk) *over and above* the existing status quo of continued smoking. Similarly, the purpose and extent of use as well as potential for abuse of the product

must be considered in light of evidence that shows that HTPs are used as an *alternative* to smoking by adult smokers, with very low rates of relapse by ex-smokers or initiation by unintended users, including youth.

The purpose, scientific assessment, and evidence in support of HTPs are founded in principles of harm reduction. Relevantly, the WHO Framework Convention on Tobacco Control defines "tobacco control" as "*a range of supply, demand and harm reduction strategies that aim to improve the health of a population by eliminating or reducing their consumption of tobacco products and exposure to tobacco smoke*." The WHO Study Group on Tobacco Product Regulation (TobReg) further concludes that "*the objective of reducing harm due to tobacco use is to decrease morbidity and mortality among persons who continue to use tobacco and nicotine and are unwilling or unable to quit, with due consideration of the effects at population level.*"

As a result of the Delegate having not used continued smoking as a relevant comparator, we believe that the scientific evidence on HTPs related to harm reduction was not adequately reflected on or considered in the interim decision.

We request that the Delegate reconsider the interim decision in light of the following points, including the evidence presented in Appendix 1.

1. The lack of consideration of the status quo of smoking and the potential of HTPs to reduce the smoking incidence as reported in other countries where HTPs are available

Australia has some of the world's toughest tobacco control measures. Despite these measures, the smoking rate has remained relatively flat since 2013-14 at just under 14%.[1] The decline in annual smoking rates is now lagging behind countries like the U.S., the U.K., Canada and New Zealand,[2] countries in which smoke-free products have been available for several years and are being adopted by adult smokers.

Smoking alternatives, such as HTPs and other alternative nicotine delivery systems ("ANDS") deliver nicotine while significantly reducing the exposure to harmful chemicals compared to smoking cigarettes. Many experts believe that making ANDS available can accelerate the decline in smoking rates by giving adult smokers who would otherwise continue smoking an opportunity to switch to a better alternative:

> *Alternative nicotine delivery systems are displacing large segments of the smoking market in various places, such as smokeless in Scandinavia, HnB in Japan, and vaping appears to be contributing to smoking cessation in the USA and the UK. These developments suggest that there are now sufficiently consumer-acceptable substitutes for smoking that the prohibition of high-toxin, addictive cigarettes is now feasible. […] The tobacco control movement needs to accept that viable substitutes for smoking are now available and work to develop the regulatory framework to speed the elimination of smoking.*[3]

[1] National Health Survey: First Results, 2017-18, Australian Bureau of Statistics, https://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/4364.0.55.001~2017-18~Main%20Features~Smoking~85

[2] Matt Young, Australia's shock smoking statistic, Daily Mercury (31 May 2018), https://www.dailymercury.com.au/news/smoking-decline-rates-in-australia-stall-as-expert/3429345/.

[3] Ron Borland, Strategies for eliminating smoked tobacco, 28 Tob Control. 251 (2019), https://tobaccocontrol.bmj.com/content/28/3/251.abstract; *See also* Mendelsohn C. et al., Could vaping help lower smoking rates in Australia?, 39 Alcohol Rev. 417, 415-418 (2020), https://onlinelibrary.wiley.com/doi/abs/10.1111/dar.13039 ("*Vaping appears to be lowering smoking rates in countries that allow its use. […] There is evidence that vaping has increased quit attempts and reduced national smoking rates in the UK and USA, where the decline in prevalence has accelerated. This contrasts with countries such as Australia with restrictive vaping policies where such declines in prevalence are not being observed");* Clive Bates, Nicotine without smoke: fighting the tobacco epidemic with harm reduction, 394 The Lancet 718-20 (Aug. 31, 2019)("*In Sweden, oral tobacco (snus) has impacted the smoked tobacco market such that, by 2017, daily smoking among adults had fallen to just about 5% compared with the European Union average of 24%."); See also* Song F. et al, Future smoking prevalence by socioeconomic status in England:

2. Cigarettes are the right comparator

As discussed above, given the proven harms from cigarette smoking, the lack of progress in reducing smoking rates, and the number of Australian smokers who will not quit,[4] continued smoking is the real-world status quo and therefore comparator against which to assess the potential benefits and risks of permitting the exemption for HTPs. Nearly three million Australians continue to smoke and there is no evidence, of which we are aware, that suggests this status quo will change significantly. It is therefore not appropriate when considering the matters listed in subsection 52E(1) to use a hypothetical comparator of an environment without cigarettes.

When conducting a scientific assessment of these products the Institute of Medicine states in their 2012 report on Scientific Standards for Studies on Modified Risk Tobacco Products (MRTPs) that the "*selection of an appropriate comparison product is essential for informed and accurate decision making"* and further on states that "*two reference products come to the forefront in terms of integration and synthesis of evidence: leading [cigarette] brands and smoking cessation products.*" Smoking Cessation is thereby considered the 'gold standard' and "*an aspirational goal for risk and exposure for MRTPs—in principle, the closer risks and exposures from the MRTP are to cessation products, the more confident a regulator can be in the chances for net public health benefit. Note that the use of this comparison product is not the same as studying whether the MRTP acts as an aid to smoking cessation. Rather, the goal is to compare how the risk or exposure reduction attained with use of the MRTP compares to smoking cessation of similar duration."*

The scientific evidence on HTPs available to date has clearly demonstrated that switching completely to HTPs significantly reduces the exposure to HPHCs compared to continued smoking approaching the levels observed upon smoking cessation, is significantly less toxic and leads to beneficial changes in clinical markers of disease. Therefore HTPs demonstrate a risk profile which is closer to that of cessation and significantly different to that of its primary comparator – conventional cigarettes.

In addition to considering benefits and risks by reference to a comparator of continued smoking, the Delegate should consider the evidence that shows that HTPs are used as an *alternative* to smoking by adult smokers. Data from countries where PMI's HTPs is available show that adult smokers are able to switch to these products and completely stop smoking cigarettes[5].

A study by researchers at the American Cancer Society showed that cigarettes sales in Japan decreased at an accelerated pace after the introduction of HTPs in the market. According to the study, cigarette sales had been declining by around 1.8% per year prior to the introduction of HTPs, but this accelerated to 9.5% per year following the introduction. The authors of the study concluded that HTPs "likely reduced cigarette sales in Japan".[6]

---

a computational modelling study, Tobacco Control (2020), https://tobaccocontrol.bmj.com/content/early/2020/05/23/tobaccocontrol-2019-055490 (the study provides evidence that smoking prevalence in England has been and is still expected to decline.)

[4] Australian Institute of Health and Welfare, Tobacco smoking, (accessed 26 June 2020), https://www.aihw.gov.au/getmedia/93461bbd-8d6b-4168-9b7b-e5bbd4f8b01f/infographic-ndshs-2016-tobacco-smoking.pdf.aspx

[5] https://philipmorrisinternational.gcs-web.com/static-files/5b3c93c8-f6c4-4acb-9d93-64d63168120d, Slide 21

[6] Stocklosa 2019 https://tobaccocontrol.bmj.com/content/29/4/381

Furthermore, the use among youth remains very low[7] and the use of HTPs by former smokers and initiation with HTPs by never smokers is very low (i.e., 1.0-2.1% for never and former smokers in Japan).[8]

A clear understanding that the comparator is a status quo in which many adult smokers will continue to smoke illuminates what is at stake here. For those people, the risks of continued smoking are consequential and well-established. At the same time, currently available evidence confirms HTPs are a better option than cigarettes, and we should not deprive Australian smokers while further long-term evidence is gathered on the scale of benefits. The scheduling of nicotine must be amended so that not only the most harmful nicotine-containing products, cigarettes, is available as a choice for current adult smokers who continue to smoke.

3. The lack of consideration of the real benefits of HTPs for adult smokers and the people around them

The interim decision states that, in assessing the literature, *"[the Delegate has] not identified compelling evidence to establish a public health benefit from greater access to nicotine in HTPs."* The interim decision does not identify what types of benefits were considered, or to which Australians those benefits would accrue. Moreover, it does not specify the evidentiary threshold that must be met to find a benefit from access to HTPs.

Data from the Australian Institute of Health and Welfare shows that one third of Australian smokers do not want to quit[9] even if it is indisputably the best choice they can make. According to the interim decision, these smokers would not benefit from access to HTPs. The Delegate does not however point to any mechanism that would cause HTPs to be as or more harmful than cigarettes.

Smoking-related harms are caused by repeated exposure to toxicants emitted by a burning cigarette. Smoking cessation, by eliminating exposure to combustion toxicants, is the best way to reduce the harm and risk of smoking-related disease. By the same reasoning, a substantial reduction in toxic exposures should lead to a reduction in adverse health effects. As the Institute of Medicine observed almost 20 years ago in its report, Clearing the Smoke: *"[t]here are sufficient data to suggest, that, for many diseases attributable to tobacco use, reducing risk of disease by reducing exposure to tobacco toxicants is biologically and clinically feasible."*[10]

On 7 July 2020, the U.S. FDA authorised the marketing of PMI's HTP as a modified risk tobacco product. In doing so, the agency concluded that the available scientific evidence demonstrates that PMI's HTP is appropriate for the promotion of public health and is expected to 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, and confirmed that:

- *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 significantly reduces your body's exposure to harmful or potentially harmful chemicals.*

[7] Kuwubara 2020 https://doi.org/10.1186/s12889-020-08916-x

[8] Osaki Y, et al. Field survey on drinking and smoking and the development of effective alcohol reduction intervention approaches for the prevention of lifestyle-related diseases, Annual Report of MHLW Research Committee, May 2018, available at https://mhlw-grants.niph.go.jp/niph/search/NIDD00.do?resrchNum=201709021A

[9] Australian Institute of Health and Welfare, Tobacco smoking, (accessed 26 June 2020), https://www.aihw.gov.au/getmedia/93461bbd-8d6b-4168-9b7b-e5bbd4f8b01f/infographic-ndshs-2016-tobacco-smoking.pdf.aspx

[10] Institute of Medicine. 2001. Clearing the Smoke: Assessing the Science Base for Tobacco Harm Reduction. Washington, DC: The National Academies Press. https://doi.org/10.17226/10029.

In particular, the agency determined:

> *[t]he company demonstrated that because the IQOS Tobacco Heating System heats tobacco and does not burn it, it significantly reduces the production of harmful and potentially harmful chemicals compared to cigarette smoke. Furthermore, studies showed switching completely from combusted cigarettes to the IQOS Tobacco Heating System significantly reduces the body's exposure to 15 specific harmful and potentially harmful chemicals. The toxicological assessment also found that, compared with cigarette smoke, IQOS aerosols contain considerably lower levels of potential carcinogens and toxic chemicals that can harm the respiratory or reproductive systems. Additionally, the FDA found that the applications supported the required consumer understanding findings.*[11]

The U.S. FDA's statement is in line with the evidence presented in the Application (further elaborated upon in Appendix 1) that demonstrates that, by removing combustion, the aerosol formed contains significantly fewer and lower levels of harmful chemicals compared to cigarette smoke and no new chemicals are formed that present a toxicological concern. Based on toxicological principles, including that of dose response, a substantial reduction in toxic exposures should lead to a reduction in adverse effects. While the science is still emerging on the magnitude of the benefits resulting from reduced exposure, for adult smokers who switch completely to HTPs, these benefits may be substantial — measured in years of increased life expectancy.[12] There is no credible scientific evidence that points to HTPs being equally or more hazardous than cigarettes. While these products are not risk free they represent a significantly better choice than continued smoking.

The interim decision appears to take an extreme position that is at odds with global public health experts and the principles of toxicology. The prospect of realising the benefit of reduced harm through reduced exposure to harmful and potentially harmful chemicals has long been recognised by experts, including those relied on by the WHO.[13] By referring to the lack of long-term data and raising the spectre of continuing intake of known and unknown toxic chemicals, the Delegate appears to conclude, without citing any corroborating evidence, that there is some biological mechanism for harm that could cause scientifically-substantiated

---

[11] https://www.fda.gov/news-events/press-announcements/fda-authorizes-marketing-iqos-tobacco-heating-system-reduced-exposure-information

[12] Slob W. et al., A method for comparing the impact of carcinogenicity of tobacco products: A case study on heated tobacco versus cigarettes, Risk Analysis (2020), https://onlinelibrary.wiley.com/doi/full/10.1111/risa.13482. *See also* Stephens et al. 2017, Comparing the cancer potencies of emissions from vapourised nicotine products including ecigarettes with those of tobacco smoke. Tobacco Control, 27. https://doi.org/10.1136/tobaccocontrol-2017-053808 and Mallock et al. 2019, Heated Tobacco Products: A Review of Current Knowledge and Initial Assessments. *Front. Public Health 7:287. doi: 10.3389/fpubh.2019.00287. See also* the U.S. FDA's findings on the MRTPA TPL at 11 that "*a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely in subsequent studies."*

[13] *See, e.g.,* WHO, Oslo Monograph: Advancing knowledge on regulating tobacco products (2000 ("*Governments are urged [to]: Evaluate and implement the most effective ways to achieve a unified regulatory framework for nicotine delivery products . . .Key terms of reference are to maintain a primary focus on harm reduction; develop better measurements of the constituents and impact of tobacco products with the aim of substantially reducing toxicity.")* https://www.who.int/tobacco/media/en/OsloMonograph.pdf*;* Scientific Advisory Committee on Tobacco Product Regulation (SACTob), Recommendation on smokeless tobacco products (2003) ("*Because nicotine appears to be responsible for a small proportion of tobacco-caused diseases relative to other tobacco constituents and emissions, there is considerable scope for developments that reduce the risks experienced by users of tobacco, but without undermining efforts to prevent initiation to tobacco use and promote cessation among established users."),* https://apps.who.int/iris/bitstream/handle/10665/42658/9241590556.pdf?sequence=1; WHO Study Group on Tobacco Product Regulation (TobReg), Report on the scientific basis of tobacco product regulation: fifth report of a WHO Study Group, WHO Technical Report Series 989 (2015) *(*Dr. Irina Stepanov states:*"A 'harm reduction' strategy to develop tobacco products that are less toxic and addictive could be an effective element of a comprehensive to reducing tobacco-related deaths and disease. . . As both addiction and the risks for many tobacco use-associated diseases are related to the level of exposure to tobacco constituents, reducing exposure should be an important component of tobacco control.")*

HTPs *not* to reduce risk for adult smokers. Such a conclusion is furthermore not supported by any scientific evidence to-date, including that submitted as part of the Application.

4. The unfounded characterisation of the toxicological results for the assessment of HTPs and failure to consider the totality of the evidence

The interim decision concludes that HTPs "*contain toxic compounds including carcinogens and that HTP aerosol can be cytotoxic and mutagenic and can potentially produce pathophysiological changes in human tissues comparable to those produced by cigarette smoke. HTPs are not risk-free*." We agree that HTPs are not risk-free. However, the Committee does not explain their scientific rationale to conclude that the levels of toxic compounds or their effects are comparable to those produced by cigarette smoke.

In announcing the pre-market authorisation of Philip Morris International Inc.'s ("PMI") tobacco heating system, the U.S. FDA stated that *"authorizing these products for the U.S. market is appropriate for the protection of the public health because, among several key considerations, the products produce fewer or lower levels of some toxins than combustible cigarettes."* The U.S. FDA concluded in their technical review of the PMTA application for PMI's HTP that while some constituents are increased compared to cigarette smoke, *"these chemicals are present in very low levels and potential effects are outweighed by the substantial decrease in the number and levels of HPHCs [harmful and potentially harmful constituents] found in combusted cigarettes."*[14] Furthermore, they stated, that "While it is possible that some harmful exposures could increase these exposures are unlikely to significantly impact the substantial reduction in exposure to HPHCs found when cigarettes smokers switch completely to IQOS[15]*.*

The interim decision states without further explanation that "*HTPs can expose users long term to a range of known and unknown toxicants.*" As outlined by Bentley et al (2020) for PMI's HTP, the aerosol is well characterised (>96% of the total aerosol mass; at ≥100 ng/stick), enabling informed regulatory decisions. The U.S. FDA also concluded that while some constituents are increased compared to cigarette smoke "*these chemicals are present in very low levels and potential effects are outweighed by the substantial decrease in the number and levels of HPHCs [harmful and potentially harmful constituents] found in combusted cigarettes*."[16] If the concern is about unknown toxicants in other HTPs, that concern can be addressed by measures well short of a ban, including by appropriate standards[17] and regulations.

[14] FDA News Release, FDA permits sale of IQOS Tobacco Heating System through premarket tobacco product application pathway, April 30, 2019, https://www.fda.gov/news-events/press-announcements/fda-permits-sale-iqos-tobacco-heating-system-through-premarket-tobacco-product-application-pathway; FDA IQOS PMTA Technical Project Lead Review (PMTA TPL), https://www.fda.gov/media/124247/download.

[15] FDA IQOS PMTA Technical Project Lead Review (PMTA TPL), https://www.fda.gov/media/124247/download; (Anal Bioanal Chem. 2020 Apr; "Comprehensive chemical characterization of the aerosol generated by a heated tobacco product by untargeted screening." 412(11):2675-2685. doi: 10.1007/s00216-020-02502-1.page 40

[16] FDA IQOS PMTA Technical Project Lead Review (PMTA TPL), https://www.fda.gov/media/124247/download; (Anal Bioanal Chem. 2020 Apr; "Comprehensive chemical characterization of the aerosol generated by a heated tobacco product by untargeted screening." 412(11):2675-2685. doi: 10.1007/s00216-020-02502-1.

[17] Russia, Ukraine, Kazakhstan, Kyrgyzstan, Egypt, Jordan, UAE are examples of countries that have issued standards for HTPs.

5. The apparent reliance on one scientific paper in support of the interim decision and the absence of any commentary on the totality of the scientific evidence

There is a growing list of publications on HTPs and the original Application cited over 100 publications available at that time. Therefore, it is not clear why the Delegate pointed to a single publication by a single tobacco control researcher, which does not contain any original data or research.[18]

The Delegate quotes the publication's finding that there is "no statistically detectable difference" between PMI's HTP and conventional cigarettes. However, the interim decision neither assesses the credibility of the single publication[19] nor explains how it outweighs other evidence, including findings of reduced toxic exposure by comparable regulators and third-parties.

6. Lack of consideration of the assessments of comparable regulators and independent researchers

The interim decision inaccurately characterises the U.S. FDA's review of one specific HTP, and omits important scientific and public health policy conclusions set out in the many third-party studies and assessments of comparable regulators submitted as part of the Application.

The Delegate states that *"HTPs are not Food and Drug Administration (FDA)-approved, which is a requirement for a tobacco product to be marketed with reduced exposure or risk claims."* This statement is misleading as the U.S. FDA does not approve tobacco or nicotine-containing products.[20]

The statement also does not fully reflect the marketing authorisation decisions the U.S. FDA is required to make. Under a Pre-Market Tobacco Product Application (PMTA), the U.S. FDA can authorise the sale of a new tobacco product if the agency determines that the product is "***appropriate for the protection of public health***."[21] In April 2019, after a rigorous scientific review and assessment of the risks and benefits to public health, the U.S. FDA authorised PMI's HTP for sale in the U.S., giving smokers in the U.S. access to the product. In contrast to the interim decision, when the U.S. FDA assessed the risks and benefits to the U.S. population as a whole, they recognised a clear benefit to adult smokers: *"potential to benefit certain individuals seeking to reduce their HPHC exposure."*[22]

---

[18] Stanton Glantz, PMI's own in vivo clinical data on biomarkers of potential harm in Americans show that *IQOS* is not detectably different from conventional cigarettes, *Tobacco Control* 2018;**27:**s9-s12, https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6202159/.

[19] A publication co-authored by Stanton Glantz, Electronic Cigarette Use and Myocardial Infarction Among Adults in the U.S. Population Assessment of Tobacco and Health, was retracted from publication in February 2020 by the editors of the Journal of the American Heart Association, over concerns that the study conclusion is unreliable. We submit that this retraction goes to the credibility of the Glantz publication on which the interim decision relied.

[20] *See, e.g.,* FDA Marketing Orders MR0000059-61, MR0000133, 7 July 2020 (MRTP Marketing Orders), https://www.fda.gov/media/139779/download ("*This order authorizing the marketing of these modified risk tobacco products does not mean FDA 'approved' the products . . ."*

[21] Prior to permitting the marketing of any new tobacco product, section 910 (c)(4) of the U.S. FD&C Act requires FDA to make a finding that the marketing of a new tobacco product is "appropriate for the protection of the public health". The statute provides that the basis for this finding shall be determined:

> with respect to the risks and benefits to the population as a whole, including users and nonusers of the tobacco product, and taking into account –
> (A) the increased or decreased likelihood that existing users of tobacco products will stop using such products; and
> (B) the increased or decreased likelihood that those who do not use tobacco products will start using such products.

[22] PMTA TPL at 64.

As set out in Section 3 above, since the interim decision was made, the U.S. FDA has authorised PMI's HTP to be marketed with reduced exposure information. [23] The authorisation should be carefully considered by the Committee and Delegate alongside the third-party studies and assessments of comparable regulators submitted as part of the Application and this response. The full Technical Project Lead assessment document can be accessed on the FDA site at https://www.fda.gov/media/139778/download.

Besides the U.S. FDA, several other regulators as well as independent researchers[24] have carefully assessed the evidence and concluded that the currently available evidence demonstrates switching to scientifically-substantiated HTPs reduces exposure to toxicants.

For example, the scientific evidence was reviewed by the Committee of Toxicology (COT) in the United Kingdom. The assessment concluded that, while HTPs are still harmful to health, "[t]*he exposure to compounds of concern in using heat-not-burn tobacco products is reduced compared to that from conventional cigarette smoke"* and thus "[t]*here would likely be a reduction in risk for conventional smokers deciding to use heat-not-burn tobacco products instead of smoking cigarettes."*[25]

Furthermore, researchers from the German Federal Institute of Risk Assessment conducted a review of the current literature on HTPs, concluding as follows:

> *The German Federal Institute for Risk Assessment confirmed in its previous study substantially reduced toxicant levels for selected HTPs and provided an initial assessment in 2017. The profound reduction (>99%) of key carcinogens according to Fowles and Dybing, such as benzene and 1,3 butadiene, as well as substantial overall reductions of toxicants is expected to affect health risks, if people abstain completely from other tobacco products. Nicotine levels are still in range of conventional cigarettes, limiting the risk to switch back to conventional tobacco smoking. […] In addition, there is a growing consensus that a complete switch to HTP can reduce exposure, as confirmed in recent investigations on biomarkers of exposure in smokers.*[26]

While the science is developing on the magnitude of the benefit,[27] third-party studies support the finding that, for adult smokers who switch completely to HTPs, the benefits may be substantial. The Netherlands Institute for Public Health and Environment (RIVM) calculated the change in cumulative exposure (CCE) of eight carcinogens in HTP emissions versus cigarette smoke reported in various peer-reviewed publications.

---

[23] FDA New Release, FDA authorizes marketing of IQOS Tobacco Heating System with 'reduced exposure' information, 7 July 2020, https://www.fda.gov/news-events/press-announcements/fda-authorizes-marketing-iqos-tobacco-heating-system-reduced-exposure-information; FDA IQOS MRTPA Technical Project Lead Review (MRTPA TPL), https://www.fda.gov/media/139778/download.

[24] Independent researchers from the University of Newcastle and James Cook University have also found that switching from CC to HTPs reduces exposure to toxicants. *See* Drovandi A. et al., Human biomarker exposure from cigarettes versus heat-not-burn devices: A systematic review and meta-analysis, Nicotine & Tobacco Research, Corrected Proof, (2019) https://academic.oup.com/ntr/advance-article-abstract/doi/10.1093/ntr/ntz200/5602686?redirectedFrom=fulltext ("*This review found that the potential for harm to humans is reduced when using HNB devices compared to conventional cigarettes, as indicated by significant reductions in BoE levels.")*]

[25] Committee on Toxicity, Statement on heat not burn tobacco products (2017), https://cot.food.gov.uk/committee/committee-on-toxicity/cotstatements/cotstatementsyrs/cot-statements-2017/statement-on-heat-not-burn-tobacco-products.

[26] Mallock N. et al., Heated tobacco products: A review of current knowledge and initial assessments, 7 Front. Public Health. 287 (2019), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6795920/.

[27] Mallock N. et al., Heated tobacco products: A review of current knowledge and initial assessments, 7 Front. Public Health. 287 (2019), https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6795920/ (*"Although a 99% reduction of some major carcinogens is expected to affect health risks, the magnitude or relevance of such putative reduction is not yet clear. A benefit is likely seen for especially the subset of long-term smokers that are unable to quit or to switch to another nicotine source with less HPHC exposure.")*

They conclude:

> *The CCE was estimated to be 10-to 25-fold lower when using HTPs instead of cigarettes. […] Overall, the conclusion seems to be warranted that consuming HTPs instead of cigarettes will be associated with a substantial increase in life expectancy, for the group of smokers who would die from cancer.*[28]

A study by Lachenmeier et al. concluded:

> *HNB tobacco reduced the risk of exposure to 9 out of the 20 most toxic compounds in tobacco beyond an MOE [margin of exposure] threshold of 10,000. While our results show that use of HNB products leads to a considerable risk reduction compared to conventional tobacco, the products cannot be considered completely "risk-free" due to risk of exposure to the remaining toxicants with MOE below the threshold.*[29]

If the interim decision is confirmed, Australia will diverge from other countries that have historically taken a similar approach to tobacco control, such as New Zealand and Canada. For example, in 2018, it was confirmed that HTPs may be legally imported, sold and distributed in New Zealand. The New Zealand Ministry of Health Regulatory Impact Statement[30] states that *"there is an opportunity, through better regulation (and public information), to support smokers to switch to significantly less harmful alternatives, substantially reducing the risks to their health and those around them."*

By contrast to the positions taken by comparable regulators around the world, the interim decision does not recognise any of the benefits that would flow to existing smokers if HTPs were made available to them.

7. The need to assess the risks of HTPs relative to the status quo (cigarette smoking)

After dismissing the possibility of any benefits for adult smokers switching to HTPs, the Committee identifies these risks:

- *Nicotine addiction either for new users of HTPs or new or continuing users of nicotine in tobacco prepared and packed for smoking.*
- *Re-normalising smoking especially among young people who would otherwise be at low risk of initiating nicotine addiction.*
- *Insufficient evidence regarding the nature of any risk of long-term use. HTPs contain harmful and potentially harmful constituents*
- *Risk of accidental exposure to children.*

---

[28] Slob W., et al. A method for comparing the impact on carcinogenicity of tobacco products: A case study on heated tobacco versus cigarettes, Risk Analysis (2020), https://onlinelibrary.wiley.com/doi/full/10.1111/risa.13482; *See also* Judith J. Prochaska and Neal L. Benowitz, Current advances in research in treatment and recovery: Nicotine addiction, Science Advances, 16 Oct. 2019, https://advances.sciencemag.org/content/advances/5/10/eaay9763.full.pdf (reviewing the evidence and concluding that *"[o]n the basis of current evidence, it is believed that e-cigarettes and heated tobacco will be very much less harmful than cigarette smoking, but how much less harmful is unknown."*)

[29] Lachenmeier D et al. (2018) Heat-not-burn tobacco products: The devil in disguise or a considerable risk reduction?, International Journal of Alcohol and Drug Research, 7(2), 8-11. https://ijadr.org/index.php/ijadr/article/view/250.

[30] New Zealand Ministry of Health Regulatory Impact Statement, (accessed 26 June 2020), https://www.health.govt.nz/system/files/documents/information-release/ris-support-smokers-to-switch-to-alternatives-jan-2019.pdf.

The Delegate adds: "*Nicotine presents a severe hazard from repeated use leading to potential addiction and a significant risk of producing irreversible toxicity, which may involve serious, acute or chronic health risks or death*."

As Professors Fairchild and Bayer have explained:

> *[R]egardless of how advocates position themselves on the question of cessation, the bar that must be met is not whether an alternative carries any risk, but whether there is enough evidence to suggest that the risks are less consequential than those of the behaviors in question. From this perspective, even uncertain evidence justifies action when the status quo—in the case of smoking, a projected one-billion deaths this century if left unchecked—is sufficiently threatening*.[31]

While the scientific evidence continues to develop, regulators must consider the evidence of the risks associated with *both* the existing product and the novel product designed as an alternative. "*Ultimately, the risk manager must decide whether to favor the mitigation of well-proven risks or of the more speculative risks*."[32] And while HTPs are not risk-free, the available evidence supports that the risks are significantly reduced than the well-proven risks of continued smoking.

The consequences for Australia of perpetuating the status quo by precluding HTPs are well-proven and substantial — many adults will continue to smoke and suffer the harms of smoking. By contrast, the risks identified by the Committee in relation to HTPs are, with the exception of that relating to nicotine addiction, more speculative. These risks are discussed in turn below.

Nicotine addiction: new users of HTPs and existing smokers

The risk of nicotine addiction is well proven, but insofar as existing smokers are concerned, the risk of addiction is no greater than that of combustible cigarettes. HTPs have been developed with the aim to reduce the harms caused by smoking by offering adult smokers an acceptable, cleaner form of nicotine delivery. By delivering similar levels of nicotine as combusted cigarettes - and having a comparable sensory and taste profile – HTPs are likely acceptable substitutes for current adult cigarette smokers. As U.S. FDA stated when authorising one such HTP: "*IQOS delivers nicotine in levels close to combustible cigarettes suggesting a likelihood that IQOS users may be able to completely transition away from combustible cigarettes and use IQOS exclusively*."[33] The U.S. FDA, moreover, goes deeper on the role of nicotine and explains on its website that:

> *Nicotine is what addicts and keeps people using tobacco products, but it is not what makes tobacco use so deadly. Tobacco and tobacco smoke contain thousands of chemicals. It is this*

[31] Fairchild, A. and Bayer, R., Smoke and fire over e-cigarettes, 347 Science 375 (2015), https://science.sciencemag.org/content/347/6220/375.

[32] John D. Graham and Jonathan Baert Wiener, Confronting Risk Tradeoffs, in *Risk vs. Risk: Tradeoffs in Protecting Health and the Environment* (Harvard University Press, 1995) at 31-32. To quote Professor Borland, *"[t]here is a risk that the strategy of downplaying relative risks may end resulting in the very thing it was designed to avoid: more smoking than there would otherwise be*."

[33] FDA News Release, FDA permits sale of IQOS Tobacco Heating System through premarket tobacco product application pathway, April 30, 2019, https://www.fda.gov/news-events/press-announcements/fda-permits-sale-iqos-tobacco-heating-system-through-premarket-tobacco-product-application-pathway

mix of chemicals—not nicotine—that causes serious disease and death in tobacco users, including fatal lung diseases, like chronic obstructive pulmonary disease (COPD) and cancer. [34]

In relation to new users of HTPs, it is important to look at independent evidence, which shows that levels of uptake are low, as detailed below.

Risk of re-normalising smoking, especially among youth

The interim decision asserts that permitting sales of HTPs will introduce a risk of re-normalising smoking, particularly among youth. As stated before, evidence shows that HTPs are used as an *alternative* to smoking by adult smokers. The interim decision does not examine the available evidence on youth uptake. In fact, the evidence shows that youth uptake of HTPs is low. Following a comprehensive review of available evidence, the U.S. FDA stated that youth initiation with PMI's HTP is uncommon in places where the HTPs are marketed and concluded that:

Although the data for IQOS uptake by never smokers, former smokers, and youth is limited, there are some data from countries where IQOS is sold - Italy and Japan - which show low uptake by youth and current non-smokers. In these countries, the likelihood of uptake is slightly higher in former smokers, but still low. Appropriately, the population most likely to use IQOS are current CC [combustible cigarette] smokers.[35]

Several recent independent studies have been completed in various countries that investigated youth uptake of HTPs.

A recent independent study of over 60,000 middle and high school students commissioned by the Japanese Ministry of Health found that the use of HTPs was extremely low and much lower than smoking cigarettes. The proportion of students who had ever used HTPs was 1.1% for middle-school students (2.6% for cigarettes) and 2.2% for high-school students (5.1% for cigarettes). The percentage of daily users was 0.1% for both middle-school and high-school students (respectively 0.1% and 0.5% for cigarettes).[36]

The Federal Center for Health Education, an authority within the German Federal Ministry of Health, conducted a study among youth (ages 12-17) and young adults (ages 18-25) in 2018 that included questions on HTP consumption. The data showed that 0.3% of youth and 2.5% of young adults reported ever using HTPs, and 0.1% of youth and 0.5% of young adults reported using a HTP during the past 30 days. In contrast, 8.7% of youth and 32% of young adults reported being current smokers.[37] Furthermore, a 2018 study conducted in Switzerland by the independent foundation Addiction Suisse found that regular use of HTPs among 14 and 15-year-old boys and girls was below 2%.[38]

---

[34] [FDA cite] Royal College of Physicians (2016) Nicotine without smoke, Tobacco harm reduction, A report by the Tobacco Advisory Group of the Royal College of Physicians, April 2016, https://www.rcplondon.ac.uk/projects/outputs/nicotine-without-smoke-tobacco-harm-reduction-0

[35] FDA IQOS PMTA Technical Project Lead Review (TPL), available https://www.fda.gov/media/124247/download

[36] https://www.jstage.jst.go.jp/article/jea/advpub/0/advpub_JE20190199/_article
development of effective alcohol reduction intervention approaches for the prevention of lifestyle-related diseases, Annual Report of MHLW Research Committee, May 2018, available at
https://mhlwgrants.niph.go.jp/niph/search/NIDD00.do?resrchNum=201709021A.

[37] Federal Center for Health Education (BZgA), Smoking among teenagers and young adults in Germany: Findings from the Alcohol Survey 2018 and trends, Sept. 2018, https://www.bzga.de/fileadmin/user_upload/PDF/studien/Alkoholsurvey_2018_Bericht-Rauchen.pdf.

[38] Health Behaviour in School-aged Children (HSBC) : La consommation de substances psychoactives des 11 à 15 ans en Suisse – Situation en 2018 et évolutions depuis 1986.

Despite the above, there are measures that can be introduced to address any potential risk of youth uptake which are discussed below at section 8.

Risk of long-term use, lack of long term studies

Due to the complex nature and the time for smoking related diseases to develop, the available clinical evidence has to be considered in the context of the totality of available evidence on HTPs. In addition to the U.S. FDA's evaluation of data on PMI's HTP, there have been numerous independent studies, including government-sponsored analyses, which have evaluated HTPs. From January 2019 to February 2020 alone at least 90 peer-reviewed publications (Appendix 1, Attachment 1) and systematic reviews have been published on HTPs, in addition to studies on aerosol chemistry and toxicology.

While HTPs contain harmful and potentially harmful constituents, the interim decision does not acknowledge that scientifically substantiated HTPs can reduce exposure to tobacco toxicants compared to cigarettes. As the Institute of Medicine observed almost 20 years ago in its report Clearing the Smoke, "*there are sufficient data to suggest that, for many diseases attributable to tobacco use, reducing risk of disease by reducing exposure to tobacco toxicants is biologically and clinically feasible*."[39]

The interim decision does not suggest any mechanism by which reduced exposure to toxicants from switching from cigarettes to HTPs would lead to an increased risk of disease. The U.S. FDA stated in its July 2020 evaluation of PMI's HTP: "*[b]ased on this evidence, there is a substantial reduction in exposure to HPHCs when users switch completely from combusted cigarettes to IQOS."* Furthermore*: "With respect to the exposure modification order request the applicant has demonstrated . . . ,including that a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely in subsequent studies, and issuance of an order is expected to 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.."*[40]

Currently available evidence confirms that HTPs are a better option than cigarettes and we should not deprive Australian smokers while further long-term evidence is gathered on the scale of benefits.

Risk of accidental paediatric exposure

The interim decision asserts a risk of accidental paediatric exposure but fails to examine the evidence or compare the risk to cigarettes. The decision relies on the submission by NSW Poisons Information Centre ("PIC") in connection with the alleged risk of accidental exposure to children from heated tobacco sticks. But that submission did not point to any evidence of accidental paediatric exposure to heated tobacco sticks.

When using PMI's HTP as an example, accidental child exposure is not reported at higher rates compared to combustible tobacco products. Contrary to the statement by the NSW PIC that the levels of tobacco are the same in a HTP stick as compared to a cigarette stick, there is a lower amount of tobacco in PMI's HTP compared to cigarettes. Due to the lower amount of tobacco in PMI's HTP compared to cigarettes, the potential exposure to nicotine, for example in cases of accidental misuse following oral ingestion, is also much lower.[41] Given the data in PMI's submission demonstrating that accidental exposure by children was

[39] Institute of Medicine. 2001. Clearing the Smoke: Assessing the Science Base for Tobacco Harm Reduction. Washington, DC: The National Academies Press. https://doi.org/10.17226/10029

[40] MRTP TPL at 39-40

[41] (Ref.: PML Application - Section "Substance Summary" Table 1 showing differences between cigarettes and the new-generation non-combustible products for inhalation, such as HTPs and Electronic Nicotine Delivery Systems (ENDS) page 8; and Section (E) Potential for Misuse/Abuse of the Substance, page 56-66).

not higher than combustible tobacco products and were reported with less severe outcomes, this submission did not provide any basis for the Delegate's conclusion.

It is clear that many of the risks identified in the Interim Decision are speculative. The real question that must then be asked is whether it is *more beneficial* to mitigate the well-proven risks associated with continued smoking than to continue to deny adult smokers access to HTPs based on risks that are either no greater than those associated with continued smoking (i.e. nicotine addiction) or speculative and currently unsupported by available evidence.

8. Lack of consideration of whether the risks could be mitigated by measures short of a ban

The interim decision effectively denies adult smokers access to better alternatives to cigarettes, without examining if the identified risks could be mitigated in some way. We agree that preventing youth use of all tobacco and nicotine products is of critical importance in the context of harm reduction and that HTPs are for adults who would otherwise continue to smoke. But policies related to HTPs should strive for an equilibrium that is most likely to maximise population benefit while minimising the undesirable outcomes. According to Professor Levy and colleagues:

> *"Policies have the potential to mitigate harms of [ANDS] use (i.e. discouraging uptake by non-smokers) while maximizing potential benefits (i.e., promoting substitution by current cigarette smokers). We must adopt coherent policies that consider explicitly the benefits and risks of different classes of nicotine delivery products, rather than continuing the current ad hoc approach which fails to address adequately the product itself."*[42]

In authorising PMI's HTP, the U.S. FDA acknowledged that existing data from countries where the product is available showed low uptake by youth.[43] Nevertheless, the U.S. FDA determined that certain measures should be put in place to minimise youth use. Accordingly, the authorisation is accompanied by clear commercialisation guidelines pertaining to reporting, packaging, labelling, and advertising, with a particular focus on measures to avoid youth uptake.[44] Similarly, the Delegate should acknowledge in its assessment that many risks could be mitigated with targeted interventions to minimise youth use rather than depriving adult smokers by banning HTPs.

The right mix of policy measures can maximise the opportunities that innovation offers and many countries around the world have found ways to do this. On the other hand, bans on new products are too simplistic a formula and may lead to unintended outcomes. As fifty-three specialists in nicotine science and public health policy have written:

> *On a precautionary basis, regulators should avoid support for measures that could have the perverse effect of prolonging cigarette consumption. Policies that are excessively restrictive or burdensome on lower risk products can have the unintended consequence of protecting cigarettes from competition from less hazardous alternatives, and cause harm as a result.*

---

[42] Levy D. et al., The need for a comprehensive framework, 112(1) Addiction. 22-24, https://pubmed.ncbi.nlm.nih.gov/27936507/.
[43] FDA IQOS PMTA Technical Project Lead Review (PMTATPL), available https://www.fda.gov/media/124247/download *("[a]lthough the data for IQOS uptake by never smokers, former smokers, and youth is limited, there are some data from countries where IQOS is marketed – Italy and Japan – which show low uptake by youth and current nonsmokers. In these countries, the likelihood of uptake is slightly higher in former smokers, but still low. Appropriately, the population most likely to use IQOS are current [combustible cigarette] smokers."*)
[44] FDA, Premarket tobacco product marketing orders, https://www.fda.gov/tobacco-products/premarket-tobacco-product-applications/premarket-tobacco-product-marketing-orders.

> *Every policy related to low-risk, non-combustible nicotine products should be assessed for this risk.*[45]

The WHO Study Group on Tobacco Product Regulation (TobReg), considered the preeminent expert body concerning tobacco regulation at WHO, has emphasised that banning products is not the only option. In fact, TobReg has highlighted the importance of risk-related considerations when implementing an appropriate regulatory framework for tobacco and nicotine products: *"for the purposes of developing a regulatory approach for novel tobacco products, it may prove useful initially to distinguish new products according to their relative degree of difference from traditional combusted or non-combusted tobacco products."*[46] TobReg adds *that "appropriate regulatory strategies for novel, new or modified TRPs [tobacco or related products] will differ based on evaluation of their potential risks and benefits."*[47]

Australia's strong regulatory base in tobacco control, makes it well-placed to develop and implement a regulatory framework that permits the sale of HTPs, whilst simultaneously preventing initiation, encouraging cessation and protecting consumers.

9. Lack of consideration of the impact of denying adult smokers' access to HTPs

The interim decision does not consider the ethical implications of a decision to perpetuate a status quo in which the most harmful means to consume nicotine is available to all adults, but alternatives that can reduce exposure to toxic chemicals are not. As many adult smokers will not quit, denying these consumers access to better options curtails their choice as consumers. Under the status quo, cigarettes are much more easily accessible than better, smoke free alternatives and, hence, choice is limited to the most harmful option. As the scientific evidence accumulates, the status quo increasingly raises ethical questions for a democracy. Two public health experts from Australia have observed:

> *We think it is also unethical to deny smokers access to a product that may reduce their health risk while cigarettes are readily available and very few quit attempts succeed.*[48]

Others have addressed ethical considerations in the context of banning ANDS:

> *The key point is that the risk of ANDS use is very much lower than smoking – so what rationale could be used to restrict access to the much safer product while leaving the far more dangerous product widely available? There is no ethical, scientific or legal justification for denying smokers access to products that are a much safer way of using nicotine than smoking. The questions that policymakers should address is: how can a government justify depriving smokers access to these products while keeping the much more harmful cigarettes widely on the market?*[49]

---

[45] Letter from specialists in nicotine science and public health policy to Margaret Chan, former Director General, World Health Organization, (2014), https://nicotinepolicy.net/documents/letters/MargaretChan.pdf.
[46] WHO, Tobacco product regulation: basic handbook, August 2018, pages 55-56, https://apps.who.int/iris/bitstream/handle/10665/274262/9789241514484-eng.pdf?ua=1.
[47] *Id.* at 54.
[48] Coral E Gartner and Wayne D Hall, Should Australia lift its ban on low nitrosamine smokeless tobacco products, 188 (1) MJA 44, 45 (2008), https://www.mja.com.au/journal/2008/188/1/should-australia-lift-its-ban-low-nitrosamine-smokeless-tobacco-products#29.
[49] Clive Bates and David Sweanor, Rational tobacco and nicotine policy in Brazil: response to ANVISA, Public Consultation No. 314 (2017), https://www.clivebates.com/documents/BrazilResponseApril17.pdf.

10. Lack of clarity on how the Schedule 4 pathway could apply for HTPs and the implications thereof

The Delegate notes that: "*the current pathway to supply Schedule 4 nicotine products for smoking cessation is available for HTPs*" continuing that "*[a]n application for registration on the ARTG could be made, which would involve assessment of the safety, efficacy and quality by the TGA, consistent with the requirements for existing nicotine replacement products.*"

This statement fails to recognise that HTPs are designed as innovative consumer products that are better alternatives than cigarettes rather than to manage nicotine addiction as is the case with pharmaceutical products such as NRTs. They are for adult smokers who would otherwise continue to smoke and are not looking for a nicotine cessation aid.

Comparable regulators recognise that HTPs are not pharmaceutical products and are not regulated in that manner. Pharmaceutical products are held to different standards as they are designed to treat or cure medical problems. HTPs, on the other hand, offer a better substitution for smoking.

There is no evidence to suggest that HTPs are more hazardous than cigarettes — to the contrary. The interim decision would establish an unusual precedent of more highly regulating a less hazardous product than the incumbent product with proven harm – cigarettes.

Describing the Application as one for down-scheduling of nicotine in HTPs is inaccurate. That implies an intent to make the products more freely or widely available than is the existing situation for cigarettes. That is not the case. This Application seeks an exemption for HTPs to ensure consistency in the way tobacco products are treated by the Poisons Standard in Australia. Tobacco is already a highly regulated substance in Australia and HTPs would not be more widely available or less regulated than cigarettes.

Conclusion

Former U.S. Surgeon General C. Everett Koop has stated, "*We must not focus our efforts so narrowly on preventing tobacco use by youth that we send the message to smokers' that we have abandoned them—that their action is their own fault and we don't care about them.*"[50] Assessing 'the risks and benefits of the use of a substance' in products designed to displace cigarettes for adult smokers who would otherwise continue to smoke means, necessarily, keeping those adult smokers firmly in scope. Regulators in Australia must compare the risks associated with HTPs to the well-established hazards of continued use of cigarettes that are exempted from Schedule 7. Consideration for adult smokers also compels Australian regulators to thoroughly review the available research on HTPs and make an objective scientific assessment of how access to HTPs would affect adult smokers and public health.

PML will continue to urge for risk-proportionate regulation of smoke-free alternatives such as HTPs as it strongly believes Australian smokers who would otherwise continue to smoke deserve to have access to better alternatives are backed by evidence-based policy. Regulators in Australia are called to, and have the opportunity and the capacity to do a thorough review of the available research on HTPs and make an objective scientific assessment on how it would impact public health.

Confirming the interim decision and failing to amend Schedule 7 to exempt HTPs would be a missed opportunity for public health and, especially, for Australians who will otherwise continue to smoke. It will

[50] Koop, C.E., 03/08/1998. Don't Forget the Smokers. The Washington Post Available from: https://www.washingtonpost.com/archive/opinions/1998/03/08/dont-forget-the-smokers/3560fbed-880a-45ff-8669-110fd8b63509/

keep Australia out of step with the more than 50 countries of the world, including all of Australia's peers that enable their smokers to access better alternatives to combustible cigarettes. Furthermore, it will continue to deny Australian smokers — unlike smokers elsewhere — the choice to switch from cigarettes to a better alternative. Harm reduction is a component of tobacco control in many parts of the world. The Committee and Delegate's decision demonstrates that it is time for a broad-based policy discussion on harm reduction and how these less harmful ways of delivering nicotine can be made available to Australian smokers. We call for broader dialogue with the Committee and Delegate on harm reduction and the benefits such an approach can deliver for public health.

We thank you for your attention to this matter and would be available to present relevant data if required.

Yours sincerely

Tammy Chan
Managing Director
Philip Morris Limited

Mark Powell
Director, External Affairs
Philip Morris Limited

Appendices:

Appendix 1 – Detailed response and supplementary scientific clarifications

Appendix 1

Philip Morris Limited (PML) detailed response to the interim decision in relation to nicotine in Heated Tobacco Products

Summary of Joint ACCS-ACMS Advice/Recommendations to the Delegate

The Joint Meeting of the Advisory Committee on Chemicals Scheduling and the Advisory Committee on Medicines Scheduling recommended that the current scheduling of nicotine remains appropriate as there is insufficient evidence to support an exemption from Schedule 7 for nicotine in Heated Tobacco Products (HTPs).

Members noted that the relevant matters the Secretary is required to consider by subsection 52E(1) of the *Therapeutic Goods Act 1989* (Cth) (the Act) include (a) the risks and benefits of the use of a substance; (b) the purpose for which a substance is to be used and the extent of use of a substance; (c) the toxicity of a substance; (d) the dosage, formulation, labelling, packaging and presentation of a substance; (e) the potential for abuse of a substance; and (f) any other matters that the Secretary considers necessary to protect public health.

The Applicant's response to the matters considered by the Committee under subsection 52E(1) of the Act are provided in the following sections.

RISK AND BENEFIT OF THE USE OF A SUBSTANCE

The Committee did not identify any benefits of the use of nicotine when in tobacco when prepared and packed for heating, advising that the available evidence does not support that HTPs are a safer alternative to traditional tobacco products. The Committee identified the following risks:

- Nicotine addiction either for new users of HTPs or new or continuing users of nicotine in tobacco prepared and packed for smoking.
- Re-normalising smoking especially among young people who would otherwise be at low risk of initiating nicotine addiction.
- Insufficient evidence regarding the nature of any risk of long-term use, HTPs contain harmful and potentially harmful constituents.
- Risk of accidental exposure to children.

Applicant's Response

We do not agree that there are no benefits in use of nicotine when in tobacco prepared and packed for heating. There are significant benefits in using HTPs in place of cigarettes, with the latter being the most relevant comparator for the purposes of conducting a benefit/risk analysis. The Committee has only considered the benefits relative to not using tobacco products at all, rather than considered it for the population it is intended for (*i.e.*, as an alternative for people who already consume nicotine from cigarettes). As is the case for other products within the Poisons Standard, if a comparison was made on the use of the product in a population it is not intended for, the benefit/risk analysis would not be positive. In the benefit/risk analysis, trade-offs such as the following need to be considered:

- the continued use of cigarettes *vs* use of a cleaner form of nicotine delivery;
- the lack of long-term studies *vs* the existing scientific evidence on HTPs; and
- the possibility of initiation by non-smokers vs the benefits for existing smokers.

Benefits of HTPs when compared to cigarettes were highlighted in PML's Application (Application) dated 31 October 2019 and include:

Reduced numbers and levels of Harmful and Potentially Harmful Constituents (HPHCs) in the aerosol of HTPs

HTP manufacturers, independent researchers, and government-commissioned researchers have reported average reductions of HPHCs of around 90% - 95% in HTP aerosols compared with cigarette smoke (Schaller et al., 2016a; Schaller et al., 2016b; Li et al., 2018; Jaccard et al., 2017; Mallock et al., 2018; Forster et al., 2018, Bekki et al., 2017; Uchiyama et al., 2018; FDA 2019[51]).

The amount of HPHCs measured in the aerosol from specific HTPs are reduced by on average 90% in comparison to cigarette smoke (Forster et al., 2018; PMI 2018[52]). Furthermore, in contrast to cigarette smoke which contains high concentrations of both liquid and solid particles, the aerosol generated by the HTP studied by Pratte et al. (2017) contains only liquid droplets suspended in a gas phase.

Improved air quality

Public health authorities, including the World Health Organization (WHO), have concluded that Environmental Tobacco Smoke (ETS) (second-hand smoke) causes diseases, including lung cancer and heart disease, in non-smoking adults as well as conditions in children such as asthma, respiratory infections, cough, wheezing, otitis media (i.e., middle ear infection) and sudden infant death syndrome (WHO, 2000[53]). According to the WHO, "*Environmental tobacco smoke (ETS) is generated by the combustion of tobacco products. It is composed of sidestream smoke (SS), emitted from the smouldering tobacco between puffs, and exhaled mainstream smoke (MS) from the smoker*" (WHO, 2000[54]).

As there is no combustion of the tobacco in HTPs, the aerosol generated is not smoke. Therefore there is no ETS emitted during HTP use according to the WHO definition above. There is an environmental HTP aerosol that is predominantly emitted from exhalation of the HTP mainstream aerosol. When PMI's HTP was used indoors (in a controlled environment), out of 24 measured compounds, only nicotine, acetaldehyde and glycerine were measured at levels higher than background, although well below the exposure limits established in air quality guidelines (Mitova et al., 2016).

Enhanced Fire safety

In addition to the reduced impact on the air quality and on bystanders, HTPs also have a substantial advantage over combusted cigarettes in terms of their fire safety. According to a recent study (Coates, 2019), "*Numerous studies, both Australian and international, have found that smoking and smoking materials are amongst the most common sources of ignition*" in fire incidents. As HTPs do not combust tobacco, the temperature during use is low, and no net heat-generating processes occur in the tobacco, they are unlikely to initiate fires.

---

[51] U.S. Food and Drug Administration. 2019. Technical Project Lead for the PMTA submitted by Philip Morris Products S.A. on May 15, 2017; Available at: https://www.fda.gov/media/124247/download.

[52] Philip Morris Products S.A. Experimental Report for P1 Characterization. Version N°: 1.0. 2018; Available here: (April 26, 2018 Amendment: Submission of "P1 Characterization" Study (.zip – 25 MB) (added October 1, 2018)).

[53] World Health Organization Regional Office for Europe Copenhagen, Air Quality Guidelines for Europe. Second ed. 2000: WHO Regional Publications, European Series, No. 91.

[54] *Id.*

A fire safety expert and former head of the School of Civil Engineering at the University of Queensland reviewed the fire safety aspects of PMI's HTP, where he stated: "*the PMI-EHTS [PMI's HTP] does not represent a fire risk under any circumstance*"[55] as "*the maximum operation temperature reported does not exceed 320°C*" and "*Materials susceptible to fire initiation will represent significant heat sinks and their ignition temperatures are always higher than 320°C*".

In addition, the Japanese Fire and Disaster Management Agency (FDMA) committee reviewed the fire safety of HTPs, including PMI's HTP and concluded on 15 January 2019, that "*The three HTPs tested by the committee do not present the same level of fire risk as smoking as defined in fire regulations and fire prevention ordinances, and –The proliferation of HTPs is highly likely to contribute to a decrease in household fires*"[56].

The Applicant's response to the risks outlined by the Committee

Due to the complex nature and the time for smoking related diseases to develop, the available clinical evidence has to be considered in the context of the totality of available evidence on HTPs. In addition to the U.S. FDA's evaluation of data on PMI's HTP, there have been numerous independent studies, including government-sponsored analyses, which have evaluated HTPs. From January 2019 to February 2020 alone at least 90 peer-reviewed publications (Attachment 1) and systematic reviews have been published on HTPs, in addition to studies on aerosol chemistry and toxicology.

As already presented in our Request for Scheduling Exemption for HTPs, recent independent studies and studies conducted by the manufacturers available to date confirm that the **unintended use potential of HTPs is low**. While current adult smokers indicate a high intention to use HTPs, former smokers, youth and never smokers are either not or only minimally interested in HTPs (Ref.: PML Application - Section (E) Potential for Misuse/Abuse of the Substance, page 56-66).

Since the submission of the Application, **additional studies** published by independent researchers have reported data on actual use of HTPs and their effect, or lack of effect on unintended audiences such as former smokers, never smokers and youth. These studies support the conclusion that users of HTPs in the market are predominantly existing smokers. Of particular relevance are independent studies by Kotz et al., 2018; Brose et al., 2018; Kioi 2018; Tabuchi et al., 2018; Tabuchi et al., 2016; Miyazaki et al., 2018; Sutanto et al., 2019; Stoklosa et al., 2019; Kang et al., 2019; Lee et al., 2019; Kim et al., 2018; Wu et al., 2019; Nyman et al., 2018; Marynak et al., 2018 and Liu et al., 2019. Details of the referenced publications are provided in Attachment 2.

While some public health groups argue that the introduction of HTPs would slow down the decrease in smoking prevalence, there is growing evidence that introduction of HTPs has a considerable impact on consumption of cigarettes.

A recent study by Sutanto (Sutanto et al., 2020) indicated that most HTP users in Japan are also concurrently smoking cigarettes.[57] By contrast, in his assessment, Cummings (Cummings et al., 2020) concluded that the

[55] "*Scientific substantiation of the absence of combustion and no smoke formation in the Electrically Heated Tobacco Product (EHTP)*" available at: https://www.pmiscience.com/resources/docs/default-source/news-documents/scientific_substantiation_of_the_absence_of_combustion_and_no_smoke_formation_in_the_ehtp.pdf.

[56] Japanese Fire and Disaster Management Agency (FDMA) 2019. https://www.fdma.go.jp/en/post1.html. Available at: https://www.fdma.go.jp/singi_kento/kento/items/h300725_shiryo4-1.pdf

[57] The reported monthly HTP prevalence (2.7%) and exclusive HTP use (0.9%) are not derived from the study sample as claimed in the paper. The ITC wave 1 is not a representative sample of the general adult population but the baseline sample of a longitudinal

decline in cigarette sales in Japan has been accelerated by the introduction of HTPs. Since 2016, the introduction and growth in the sales of HTPs in Japan corresponds to the accelerated decline in cigarette-only sales.

Consistent with the experience in Japan, smoking rates in the U.K. also continue to decline. The decline in smoking prevalence is likely a consequence of multiple tobacco control measures, and availability of alternatives to cigarettes should be seen as one of them.

The recent study by Song (Song et al., 2020) projected future smoking prevalence in the U.K. and revealed what is needed to achieve the country's tobacco-free ambition by 2030. The author provides evidence that smoking prevalence in England has been declining, and is still expected to decline, although with substantial differences across socioeconomic groups. Importantly, the study results indicate that "[*a*]*bsolute inequalities in smoking are likely to decline and relative inequalities in smoking are likely to increase in future*." Inequalities in smoking are relevant to tobacco control policies. Further reduction in smoking prevalence will require the reduction of both absolute and relative inequalities in smoking by socioeconomic status. Nevertheless, the introduction of alternative products, such as HTPs and e-cigarettes, is expected to accelerate the decline in smoking prevalence.

Regarding accidental exposure to children, it needs to be re-emphasised that although cases of accidental exposure by children have been reported for some HTPs, the risks are similar to other tobacco products. When using PMI's HTP as an example, accidental child exposure is not reported at higher rates compared to combustible tobacco products. Contrary to the statement by the NSW PIC that the levels of tobacco are the same in a HTP stick as compared to a cigarette stick, there is a lower amount of tobacco in PMI's HTP compared to cigarettes. Due to the lower amount of tobacco in PMI's HTP compared to cigarettes, the potential exposure to nicotine, for example, in cases of accidental misuse following oral ingestion, is also much lower (Ref.: PML Application - Section "Substance Summary" Table 1 showing differences between cigarettes and the new-generation non-combustible products for inhalation, such as HTPs and Electronic Nicotine Delivery Systems (ENDS) page 8; and Section (E) Potential for Misuse/Abuse of the Substance, page 56-66).

Considering the above, we dispute the statement that there are no "[b]enefits of the use of nicotine when in tobacco when prepared and packed for heating". On the contrary, the available evidence, including data from independent research, indicate that HTPs constitute a better alternative to tobacco prepared and packed for smoking.

THE PURPOSE FOR WHICH A SUBSTANCE IS TO BE USED AND THE EXTENT OF USE

The Committee identified the purpose for which nicotine when in tobacco when prepared and packed for heating as a new nicotine-delivery device for the non-therapeutic use of tobacco.

study to described transitions between quota sampled groups of smokers, HTP users, HTP dual users, and non-users over time. Prevalence data was derived from the "Rakuten Insight panel", the source from which ITC Study in Japan sampled their pre-defined quotas of users. Although this information may not be evident from the publication it becomes understandable when studying the technical report of ITC Study in Japan. In summary, conclusions from this paper should be taken with caution because of the lack of clarity and the sampling method that applied quotas to recruit smokers, HTP users, etc. from the "Rakuten Insight panel".

Applicant's Response

The conclusion by the Committee that "[*t*]*he purpose for which nicotine when in tobacco when prepared and packed for heating is a new nicotine-delivery device for the non-therapeutic use of tobacco*" is factual and scientifically valid, as HTPs are not a therapeutic product intended as smoking cessation therapy but are a non-therapeutic, less hazardous alternative to cigarettes. However, it is unclear how the Committee's conclusion serves as an argument supporting the decision not to exempt nicotine in HTPs from Schedule 7 of the Poison Standard.

The fact that the product category is new cannot and should not *per se* constitute grounds for rejection. The decision needs to be based on the scientific assessment of the evidence presented in the Application. While the conclusion that nicotine, when in tobacco prepared and packed for heating, constitutes "*a new nicotine-delivery device for the non-therapeutic use of tobacco"* in fact explains the purpose of use, the extent of use has been discussed and explained in the Application. Scientifically, it is not appropriate to dismiss a product by simply associating its novelty with *a priori* assumed uncontrolled and unrestricted use.

Many experts and authorities agree that a risk continuum for tobacco and nicotine containing products exists, and that not all tobacco and nicotine-containing products are equally harmful. Such products range from exceptionally low-harm (e.g., Nicotine Replacement Therapy) to exceptionally high-harm (e.g., tobacco prepared and packed for smoking, *i.e.* cigarettes, cigars, hookah pipe), with HTPs being distinctly lower in their risk profile compared to cigarettes (Abrams et al., 2018). HTPs have been developed as alternatives to cigarettes and the intended purpose is to enable adult smokers who would otherwise continue to smoke to switch to HTPs and become abstinent from cigarettes. Switching completely to HTPs would significantly reduce smokers' exposure to HPHCs present in cigarette smoke, which are the main cause of smoking-related diseases.

In many developed countries, there are mechanisms in place for evidence-informed regulation of HTPs. In some countries, these products are officially recognised as Novel Tobacco Products or New Tobacco Products and smokers can access these as better alternatives to cigarettes.

The assessment standard needs to recognise that HTPs are alternatives to cigarettes for adult smokers who would otherwise continue to smoke, not therapeutic goods or cessation aids. HTPs should be scientifically assessed in a risk assessment/risk reduction context using a risk reduction assessment framework that takes into account the purpose of these products.

THE TOXICITY OF A SUBSTANCE

The Committee noted the following in relation to the toxicity of nicotine when in tobacco when prepared and packed for heating:

- *In vitro* data indicated that HTP aerosol can be cytotoxic and mutagenic, can product pathophysiological changes in human tissues.
- The response produced by HTP aerosol is similar to that produced by cigarette smoke with respect to the development of precancerous lesions such as hyperplasia and squamous metaplasia in the respiratory tract epithelium.
- On scientific and toxicological grounds nicotine when in tobacco when prepared and packed for heating meets Schedule 7 factors – that is it has a high to extremely high toxicity, presents a high

health hazard, requires special precautions for handling and has a high potential for causing harm at low exposure.

Applicant's Response

It is implausible that the substantially reduced exposure to HPHCs from HTP aerosols and the absence of new compounds of toxicological concern, taken together with the reduced toxicity of HTP aerosol, compared with cigarette smoke using *in vitro/in vivo* toxicology studies, will induce quantitative changes in human tissues that are comparable to those produced by cigarette smoke.

The mutagenic and cytotoxic potencies of the mainstream aerosol fraction of PMI's HTP when evaluated by the Ames, mouse lymphoma and neutral red uptake assays were reduced by at least 85-95% compared with the mainstream smoke of 3R4F (Schaller et al., 2016).

It is unclear what data is being referred to when stating *HTPs can potentially produce pathophysiological changes in human tissues comparable to those of cigarette smoke*. We have previously cited studies that for example, demonstrate that in human organotypic epithelial tissue cultures (exposed to HTP aerosol at the air-liquid interface) displayed considerably lower perturbations of the DNA damage-response network than cultures exposed to cigarette smoke as demonstrated in oral, nasal and bronchial cultures (Iskandar 2017a; Iskandar 2017b; Zanetti 2016; Zanetti 2017).

The 90-day nose-only inhalation studies performed by PMI in rats exposed 6 hours/day to either fresh air (sham control) or 3 dose levels of either THS aerosol or reference cigarette smoke. The maximum exposure concentrations were selected to detect the maximum possible toxicities induced by PMI's HTP and reference cigarette items. Nasal lesions were observed predominantly in cigarette smoke-exposed rats included reserve cell hyperplasia of the respiratory epithelium, squamous epithelial metaplasia of the respiratory epithelium. Severity scores observed in HTP-exposed rats were significantly lower, with the exception at the uppermost level in the nose that did not differ between HTP aerosol and cigarette smoke. It is important to take into account that rats are obligate nose breathers, and that a greater drop in the histopathology scores was seen for PMI's HTP in the post-dose recovery phase of the study compared with cigarette smoke exposure (Wong et al., 2016). As toxicologists, Committee members will understand how such studies are designed to test for treatment effects at exposure levels above those that are achieved in terms of human exposure. The human relevance of the findings in rats should also be carefully considered. Therefore, to focus on a particular finding that is not relevant for the human situation without mention of the reduction in overall biological impact of the HTP under study compared with cigarette smoke is not scientifically valid.

As reported previously in our Application (PML Application - Page 50), the results from the 18-month chronic toxicity and carcinogenicity study in A/J mice, a larger number of mice (incidence) exposed to cigarette smoke had lung adenomas and carcinomas than mice exposed to air. In contrast, mice exposed to PMI's HTP aerosol did not show an increase in tumour incidence compared to those exposed to air. Furthermore, mice exposed to cigarette smoke had more lesions and tumours per mouse than those exposed to air (multiplicity). In contrast, mice exposed to HTP aerosol did not show an increase in tumour multiplicity compared to those exposed to air.

In conclusion, the histopathological results from the 90-day inhalation studies in rats showed some changes in the upper part of the respiratory tract from HTP exposure but in a sensitive mouse model for lung cancer, the incidence and multiplicity of tumours is much lower than for cigarette smoke, and is similar to air exposure.

With reference to meeting Schedule 7 factors, it is unclear how nicotine in tobacco prepared and packed for heating would have a different profile from nicotine in combustible cigarettes. The Committee stated that nicotine in HTPs "*has a high to extremely high toxicity, presents a high health hazard, requires special precautions for handling and has a high potential for causing harm at low exposure*." However, when tobacco packed and prepared for smoking is exempt, and nicotine content is no different in the case of tobacco prepared and packed for smoking than when tobacco is prepared and packed for heating, the Committee's statement about nicotine is difficult to understand. Nicotine is naturally present in tobacco and is neither available in a concentrated form to warrant special precautions for handling nor has a high potential for causing harm at low exposure when in the form of tobacco for heating.

We agree that Nicotine belongs in Schedule 7. However, HTP products contain tobacco which is exempted from Schedule 7. There is no evidence to suggest that HTPs are more hazardous than conventional cigarettes. Therefore, the Committee would be setting an unusual precedent in poisons scheduling if it were to make an equivalent (or less hazardous) product more highly regulated under the Poisons Standard. This approach would create a contradiction within Schedule 7.

THE DOSAGE, FORMULATION, LABELLING, PACKAGING AND PRESENTATION OF A SUBSTANCE

The Committee advised that:

- Nicotine when in tobacco when prepared and packed for heating functions by way of reconstituted tobacco leaf and excipients heated and consumed via inhalation.
- A HTP delivers comparable levels of nicotine as conventional combustible tobacco products.

Applicant's Response

We agree that HTPs are a tobacco product that generate a nicotine aerosol by heating. In assessing the public health impact of nicotine-containing products, it is important to consider the delivery system and acceptability to intended consumers to enable a transition away from smoking combustible cigarettes.

Besides taste, sensory experience and ritual, nicotine is an important part of acceptability of cigarette alternatives for smokers. For smokers to successfully transition to alternative nicotine products, the plasma concentration achieved by the alternative products need to mimic those delivered by cigarettes. The results of pharmacokinetic/pharmacodynamic (PK/PD)[58] studies show that HTPs have a PK profile that is acceptable to smokers of combustible cigarettes to act as a substitute.

HTPs are not risk-free and the best option is to quit using cigarettes and nicotine completely. However, for those smokers that continue to smoke, it is important to offer them a range of solutions beyond cigarettes that suit individual needs.

The amount of nicotine delivered from the tobacco in HTPs is physically, psychologically or socially not more harmful for current adult smokers who wish to switch to a better alternative product than the amount of nicotine delivered by tobacco prepared and packed for smoking.

[58] PMI's MRTP Applications, Section 6.2.1.2 PK/PD Overview of Studies, available at: https://www.fda.gov/tobacco-products/advertising-and-promotion/philip-morris-products-sa-modified-risk-tobacco-product-mrtp-applications#6

THE POTENTIAL FOR ABUSE OF A SUBSTANCE

The Committee advised that nicotine when in tobacco when prepared and packed for heating when used as intended carries a high risk of dependence.

Applicant's Response

Nicotine is a highly addictive substance. That is why many smokers do not give up smoking altogether, even with the use of smoking cessation products, and return to using cigarettes as their only legal means of obtaining nicotine. HTPs are intended for this group of people who are already addicted to nicotine and require an alternative method of self-administering the substance. As previously substantiated in our Request for Scheduling Exemption for HTPs, the potential for an HTP to cause dependence is comparable to cigarettes.

PMI's HTP dependence potential was assessed based on the review of available information from various sources, including product design and content, aerosol chemistry, human clinical and behavioural data. The nicotine exposure in humans under various use conditions, confirms the similarity of nicotine uptake for PMI's HTP vs. cigarettes. The other product features (design, handling and usage limitations, and delivery of toxicants with addiction potential other than nicotine) do not add an additional risk on the abuse liability (*Ref*.: Section (E) Potential for Misuse/Abuse of the Substance, page 56-66).

HTPs deliver generally comparable levels of nicotine to those delivered by cigarettes, and have a similar but not higher dependence potential as cigarettes.

OTHER MATTERS THAT THE SECRETARY CONSIDERS NECESSARY TO PROTECT THE PUBLIC HEALTH

The Committee advised that the current pathway for approval to supply products for smoking cessation is available for an HTP. An application for registration on the ARTG could be made, which would involve assessment of the safety, efficacy and quality by the TGA, consistent with the requirements for existing nicotine replacement products.

Applicant's Response

HTPs are designed as innovative consumer products that are better alternatives than cigarettes. They are for adult smokers who would otherwise continue to smoke and are not looking for a cessation aid. As an alternative to cigarettes they do help smokers stop smoking cigarettes, but they are not a cessation product.

HTPs should be scientifically assessed in a risk assessment/risk reduction context rather than in the context of efficacy, where benefits must outweigh risks. The risk reduction assessment framework applied to HTPs should take into account the purpose of these products. The assessment standard needs to recognise that HTPs are alternatives to cigarettes for adult smokers who would otherwise continue to smoke, not therapeutic goods or nicotine cessation aids. Therefore, it is appropriate to assess HTPs relative to the products which they are intended to replace, *i.e*., cigarettes (tobacco prepared and packed for smoking) for users who want to continue to use nicotine.

RESPONSE TO OTHER MATTERS PRESENTED BY THE SECRETARY IN THE INTERIM DECISION

Reference to Approval by the U.S. FDA

The conclusion that "*in the U.S. HTPs are not Food and Drug Administration (FDA)-approved, which is a requirement for a tobacco product to be marketed with reduced exposure or risk claims*" is misleading, especially for a person not familiar with the U.S. regulatory framework for tobacco products.

There is a prominent difference between approval and authorisation, and it needs to be considered in the right context. The U.S. FDA does not approve tobacco products but authorises their marketing. As already confirmed, on April 30, 2019, the U.S. FDA "*authorized the marketing of new tobacco products manufactured by Philip Morris Products S.A. for the IQOS "Tobacco Heating System" – an electronic device that heats tobacco-filled sticks wrapped in paper to generate a nicotine-containing aerosol."*[59] Since then the product has been commercialised and is available in the United States.

Regarding the Pre-Market Tobacco Product Application (PMTA), which is required to obtain authorisation to market a tobacco product, the statute[60] provides that the finding as to whether the marketing of a product for which a PMTA is submitted would be appropriate for the 'protection of the public health' shall be determined with respect to the risks and benefits to the population as a whole, including users and non-users of the tobacco product, and taking into account:

(a) the increased or decreased likelihood that existing users of tobacco products will stop using such products; and

(b) the increased or decreased likelihood that those who do not use tobacco products will start using such products.

When authorising the marketing of *IQOS* in the United States, the U.S. FDA determined that "*authorizing these products for the U.S. market is appropriate for the protection of the public health because, among several key considerations, the products produce fewer or lower levels of some toxins than combustible cigarettes*." and "[*w*]*hile the authorization of new tobacco products doesn't mean they are safe, the review process makes certain that the marketing of the products is appropriate for the protection of the public health, taking into account the risks and benefits to the population as a whole. This includes how the products may impact youth use of nicotine and tobacco, and the potential for the products to completely move adult smokers away from use of combustible cigarettes."*[61]

[59] Food and Drug Administration (FDA) press release (2019) FDA permits sale of *IQOS* Tobacco Heating System through premarket tobacco product application pathway, April 30, 2019, available at https://www.fda.gov/news-events/pressannouncements/fda-permits-sale-iqos-tobacco-heating-system-through-premarkettobacco-product-application-pathway

[60] In accordance with Section 910(c)(4) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), FDA may grant a Marketing Order authorizing marketing of a tobacco product when sufficient evidence shows that permitting a product to be marketed would be appropriate for the protection of the public health (APPH).

[61] FDA News Release, FDA permits sale of *IQOS* Tobacco Heating System through premarket tobacco product application pathway, April 30, 2019, available at https://www.fda.gov/news-events/press-announcements/fda-permits-sale-iqos-tobacco-heating-system-through-premarket-tobacco-product-application-pathway and FDA *IQOS* PMTA Technical Project Lead Review (TPL), available at https://www.fda.gov/media/124247/download))

Furthermore, on July 7, 2020, the U.S. FDA issued exposure modification orders for PMI's HTP (*IQOS* Tobacco Heating System),[62] concluding that "*The available scientific evidence demonstrates that the issuance of an exposure modification order for IQOS would be appropriate to promote the public health and is expected to 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.*"[63]

It is critical to emphasise that the U.S. FDA's conclusions are consistent with the scope of the Application in Australia to extend the Schedule 7 exemption to HTPs. The Schedule 7 exemption Application was made to allow the sale of HTPs in Australia in a similar manner to cigarettes, and not the sale of these products with reduced exposure or risk (or therapeutic) claims.

It is disappointing that it needs to be highlighted that while the U.S. FDA concluded that marketing of HTPs (IQOS) is appropriate for the protection of the public health an opposing decision has been made by the Secretary in Australia. Undoubtedly, Australia should set its own course. It is nevertheless striking that very different conclusions are being drawn based on the same scientific evidence and that in justifying the Australian decision, the position taken by the U.S. FDA has been misrepresented.

In light of the U.S. FDA's announcement and release of the Modified Risk Tobacco Product ("MRTP") authorisation for PMI's HTP, it is imperative that the scientific data driving that decision be considered by the Delegate in reaching a final decision.

The interim decision implies that the most dangerous form of nicotine-containing products (cigarettes) is a more appropriate consumer product than alternative tobacco products which "produce fewer or lower levels of some toxins than combustible cigarettes".

Consideration given to a biomarker study in making the decision

The Secretary stated that "*Independent researchers analysing data that Philip Morris provided to the U.S. FDA in support of marketing of their IQOS HTP product found no statistically detectable difference between IQOS and conventional cigarettes for 23 of the 24 non-cancer biomarkers of potential harm measured in Americans, and 10 of 13 measured in Japanese*."

The points raised in the referenced Glantz 2018 paper resulted from a review of clinical data on PMI's HTP submitted to the U.S. FDA in 2016 as part of its MRTP application. PMI conducted two 3-Month Reduced Exposure Studies in Japan and in the United States. These two studies were primarily designed to assess the extent of exposure reduction to HPHCs in smokers who switched to PMI's HTP in comparison with those who continued to smoke cigarettes. Furthermore, the studies compared the effects of switching to PMI's HTP with those of smoking abstinence. The studies allowed a comparison of the exposure reduction achievable when switching to the HTP with the maximum exposure reduction achieved by smoking cessation.

In these studies, PMI also monitored multiple biomarkers of potential harm (BOPH) to gain early indications as to whether the reduction in exposure leads to favourable changes in risk indicators. The BOPHs were selected based on the following criteria:

[62] Food and Drug Administration (FDA) press release (2020) regarding Philip Morris Products S.A. Modified Risk Tobacco Product (MRTP) Applications, July 7, 2020, available at https://www.fda.gov/tobacco-products/advertising-and-promotion/philip-morris-products-sa-modified-risk-tobacco-product-mrtp-applications

[63] Food and Drug Administration (FDA) *IQOS* MRTPA Technical Project Lead Review (TPL), page 13, available at https://www.fda.gov/media/139778/download

- They must be linked to smoking-related diseases (e.g., established through epidemiology);
- They must be responsive to smoking (smoking causes negative changes); and
- They must reverse upon smoking cessation (cessation causes positive changes).

The 24 BOPH included in the Reduced Exposure Studies were linked to smoking-related disease and responsive to smoking, following the selection criteria outlined above. However, there was less data reported in the literature for several of the BOPH included in these studies to confirm the response to smoking cessation. Therefore, several of the BOPHs included in the study were included to monitor their response to smoking cessation and were not necessarily expected to change over the duration of these studies.

This latter point was clearly outlined in the study protocols and seems to have been either not understood, overlooked or ignored by Glantz et al.

These studies were designed and powered to assess reduced exposure to HPHCs following switching to PMI's HTP and also compared to smoking abstinence, but were not designed or powered to assess the impact on BOPHs.

The BOPH changes observed following 3 months of HTP use were comparable to changes seen following cessation both in the direction and magnitude of the change. However, as presented in the PMI application, due to the limited sample size and duration of these studies, the results from the BOPH alone should not be considered to either prove or disprove a reduction in the risk of smoking-related diseases. When authorising the marketing of *IQOS* in the United States, the U.S. FDA determined that "[*t*]*he statistical reviewers evaluated the two 90-day studies and concluded that they were not designed to ascertain any effect associated with the "risk endpoints." The BOPH were secondary endpoints and were not the basis for sample size/power calculations; it is not clear from a statistical perspective whether the data generated from the studies are clinically meaningful*."[64]

Nevertheless, the U.S. FDA were able to confirm substantial reductions in exposure to the HPHCs exposure biomarkers measured in the studies, which approached the levels seen following smoking abstinence.

To complement the assessment of exposure reduction, PMI conducted a 6-month Exposure Response study with 984 adult American smokers which was designed and powered to assess the impact of switching to PMI's HTP on BOPH. The study was reported in our Application (Ref.: PML Application - Section (C) Toxicity and Safety of the Substance, page 53). Results at 6 months confirmed statistically significant improvements in 5 of the 8 BOPH and therefore clearly demonstrated significant favourable changes in BOPHs in smokers switching to PMI's HTP.

Australian researchers led by Drovandi et al. (2019) prepared a systematic review and meta-analysis on human Biomarker Exposure studies from cigarettes versus novel HTPs that concluded: "*Heat-not-burn devices such as 'IQOS' and 'glo' are marketed as 'reduced risk' tobacco products, and are claimed to reduce harm to smokers compared to conventional cigarettes. This review supports these claims, with all 12 BoEs that were analysed being significantly lower in the HNB participants compared to those using conventional cigarettes. These BoE reductions were greatest for several known carcinogens, including COHb, 2-AN, 4-ABP, and CEMA, indicating the potential for significantly reduced harm when using HNB devices in comparison to conventional cigarettes. In addition, levels of 8 of the 12 BoEs were statistically equivalent between the HNB*

[64] U.S. Food and Drug Administration. 2019. Technical Project Lead for the PMTA submitted by Philip Morris Products S.A. on May 15, 2017 (page 59); Available at: https://www.fda.gov/media/124247/download.

and abstinence participants, though the levels of some carcinogenic BoEs were significantly increased. HNB devices therefore may have a role in harm reduction though should not be considered as wholly safe."

It is critical for scientific studies to be considered for what they were designed for, correctly interpreted and translated for potential impact on individual and public health. Crucial to this use of scientific studies is an understanding of the experimental design. In the case of the Glantz et al paper, the conclusions were made based on results of a study that was not designed to demonstrate changes in BOPH and the results of a larger and longer study, actually demonstrating beneficial changes in BOPH were not reflected.

CONSIDERATION GIVEN TO THE WHO MARKETING MONITORING INFORMATION SHEET ON HEATED TOBACCO PRODUCTS

WHO statement

HTPs expose users to toxic emissions, some of which are specific to HTPs and which could also expose bystanders. The levels of some toxicants are higher and there are new substances absent in tobacco smoke which could potentially harm human health.

HTPs contain chemicals not found in cigarette smoke and may have associated health effects. Independent assessment of industry data shows that more than 20 harmful and potentially harmful chemicals are significantly higher than in reference cigarette smoke.

Applicant's Response

PMI conducted a full non-targeted differential screening on our HTP, which was submitted to the U.S. FDA on December 8, 2017, as part of the Premarket Tobacco Product Application (PMTA) for the marketing of the product in the USA. The results of the screening can be accessed on the U.S. FDA's website. The main conclusions of this assessment are:

- The non-targeted screening demonstrated that the aerosol in PMI's HTP is significantly less complex than cigarette smoke, with only 532 compounds present in the HTP aerosol (≥100ng/item) compared to 4800 in cigarette smoke (also ≥100ng/item) (Bentley et.al, 2020).
- Of a full toxicological evaluation of the compounds that were identified as being more abundant or unique in the HTP aerosol compared to 3R4F (reference cigarette) smoke, initially, only 3 compounds were found to be unique to the THS aerosol:
    1) cis-sesquisabinene hydrate, 61 ng/item;
    2) ethyl dodecanoate, 23 ng/item; and
    3) benzenemethanol, 4-hydroxy, 11 ng/item.

Further investigations show than benzenemethanol, 4-hydroxy, is described as present in cigarette smoke, Ethyl dodecanoate (ethyl laurate) is described as being used in tobacco ingredients but not present in tobacco smoke; and only Cis-sesquisabinene hydrate still not been identified in tobacco smoke or ingredients.[65]

- 4 additional compounds that were present in greater abundance in PMI's HTP compared to 3R4F cigarettes were found to be of potential toxicological concern:
    1) Glycidol (IARC 2A);

[65] "*The Chemical Components of Tobacco and Tobacco Smoke*" (p. 36) by A. Rodgman, TA. Perfetti, ISBN 9781466515482

2) 2-Furanemethanol (IARC 2B):
3) 3-Monochloro-1,2-propanediol (IARC 2B); and
4) Furfural (IARC 3).

- An evaluation of these compounds, based on the published inhalation toxicity literature, indicates that the levels of exposure to these compounds through the HTP aerosol are below the level of concern.
- This is further corroborated by the results of our extensive in vitro and *in vivo* toxicology testing which demonstrated that PMI's HTP showed significantly reduced overall toxicity (on average above 90%) compared to the 3R4F cigarette.
- In response to these findings the U.S. FDA summarised their review of these toxicological findings with the statement that "*Although some of the chemicals are genotoxic or cytotoxic, these chemicals are present in very low levels and potential effects are outweighed by the substantial decrease in the number and levels of HPHCs found in combusted cigarettes.*"[66]

A study by Kaunelienė et al. (Kaunelienė et al., 2018) aimed to analyse changes in indoor air quality following HTP use compared to changes after the use of conventional cigarettes, electronic cigarettes, waterpipe, incense, candle, and mosquito coils, and compared it to indoor air quality found in residential and public environments. The authors of the review research paper collected 37 scientific articles using the Web of Science search engine. Two types of indoor environments were considered: "controlled" (*i.e*. performed in environmentally controlled chambers) and "real-life" (i.e. residential, public or transport environments). Pollutants measured were aldehydes (formaldehyde and acetaldehyde), monoaromatic hydrocarbons (benzene and toluene), and particulate matter ($PM_{2.5}$). Overall, the usage of HTPs was related to significantly lower indoor air pollutant concentrations compared to researched pollution sources, although HTP use led to concentrations of indoor air pollutants comparable to e-cigarettes.

In a controlled environment, the use of HTPs resulted in the lowest concentrations of formaldehyde, benzene, toluene and $PM_{2.5}$ among most of researched pollution sources (conventional cigarettes, waterpipe, incense and mosquito coils). For instance, burning mosquito coils resulted in high concentration of $PM_{2.5}$ (4324 $\mu g/m^3$) while it remained below the limit of quantification (<14.7 $\mu g/m^3$) for HTP use. Similarly, exposure to significantly higher background levels of formaldehyde, benzene and toluene occurred in real-life public and transport environments compared to those levels observed with HTPs, measured in controlled study settings. For instance, the toluene concentration inside a car reached 1220 $\mu g/m^3$ whereas it remained below 1 $\mu g/m^3$ for PMIs HTP use.

This data is in accordance with PMI indoor air quality studies showing that the use of PMI's HTP results in levels of formaldehyde, benzene, toluene, and particulate matter ($PM_{2.5}$) not above the background level. Only nicotine, glycerin and acetaldehyde were measurable above background but significantly below levels outlined in air quality guidelines for indoor exposure (Mitova et al., 2016).

In summary, the data available for PMI's HTP shows that its use has no adverse effect on indoor air quality and bystanders' exposure considering threshold limits set by existing air quality guidelines and when used in a setting where regulatory norms of adequate ventilation are respected.

[66] U.S. Food and Drug Administration. Premarket Tobacco Product Marketing Order TPL (Technical Project Lead Review); Section 6 - Summary of Toxicological Findings: p42. https://www.fda.gov/media/124247/download. Accessed 10 Dec 2019.

The U.S. FDA concluded in their technical review of the PMTA for PMI's Heated Tobacco Product that while some constituents are increased compared to cigarette smoke, "*the exposure levels appear low and the available data does not preclude a conclusion the products are appropriate for protection of public health*" (p. 32).

WHO statement

The relationship between exposure and health effect is complex and reduced exposure to these harmful chemicals does not mean that they are harmless, nor does it translate to reduced risk in humans.

Applicant's Response

HTPs are products created to offer a better alternative to adult smokers who continue to smoke and are not risk-free. That is why these products are only intended for current adult smokers who would otherwise continue to smoke cigarettes, the most harmful way of consuming tobacco and nicotine.

Smoking-related harms are caused by repeated exposure to toxicants emitted by a burning cigarette. On the contrary, smoking cessation, by eliminating exposure to combustion toxicants, is the best way to reduce the harm and risk of smoking-related disease. Consequently, a substantial reduction in toxic exposures is expected to lead to a reduction in adverse health effects. As the Institute of Medicine observed almost 20 years ago in its report "Clearing the Smoke", "*there are sufficient data to suggest that, for many diseases attributable to tobacco use, reducing risk of disease by reducing exposure to tobacco toxicants is biologically and clinically feasible*."

In authorising the sale of PMI's HTP, and following a rigorous science-based review through the premarket tobacco product application (PMTA) pathway, the U.S. FDA "*determined that authorizing these products for the U.S. market is appropriate for the protection of the public health because, among several key considerations, the products produce fewer or lower levels of some toxins than combustible cigarettes.*"

Similarly, the U.S. FDA stated in its 2019 evaluation of PMI's HTP, "*although the studies conducted by the applicant do not demonstrate reduction in long-term disease risks, the currently available evidence indicates CC [combusted cigarette] smokers who switch completely to [PMI's HTP] will have reduced toxic exposures and this is likely to lead to less risk of tobacco-related diseases*."

Furthermore, several independent institutes and researchers have issued their assessments in this respect, such as German Federal Institute of Risk Assessment (BfR) (Mallock et al., 2019):

- "*Although a 99% reduction of some major carcinogens is expected to affect health risks, the magnitude or relevance of such putative reduction is not yet clear. A benefit is likely seen for especially the subset of long-term smokers that are unable to quit or to switch to another nicotine source with less HPHC exposure*.";

or Lachenmeier et al. (Lachenmeier et al., 2018):

- "*HNB tobacco reduced the risk of exposure to 9 out of the 20 most toxic compounds in tobacco beyond an MOE threshold of 10,000. While our results show that use of HNB products leads to a considerable risk reduction compared to conventional tobacco, the products cannot be considered completely "risk-free" due to risk of exposure to the remaining toxicants with MOE below the threshold*."

Additional supportive data is included in the recent publication of Slob at al. (Slob at al., 2020), in which the researchers developed a method for comparing the impact on carcinogenicity of tobacco products on behalf of the National Institute for Public Health and the Environment (RIVM, the Netherlands). As a case study, they compared the carcinogenicity of heated tobacco aerosol with cigarette smoke. The methodology applied focused on the change in cumulative exposure (CCE) to compare two tobacco/nicotine products instead of performing risk assessments of individual compounds to allow a better understanding as to whether and how the health impact may differ between the products.

To illustrate how the method works in a practical analysis, the method was applied to PMI's HTP using the data on 8 carcinogens that are common to both the HTP and cigarettes, and for which emission and cancer dose-response data were available for both. The change in CCE was estimated to be 10- to 25-fold lower for the HTP compared to cigarettes. The changes observed in the CCE indicate that the reduction in expected life span is substantially smaller for PMI's HTP users than smokers, based on available dose-response information. Using a recent study by Inoue-Choi et al. (Inoue-Choi et al., 2018) comparing the life expectancy of daily vs. non-daily smokers, where a 10 fold difference in exposure translated to 5 years longer expected life span, the authors state that it may be inferred that the health impact associated with a comparable CCE is substantial.

Even the lower bound of this uncertainty range would be associated with a substantial health impact in favour of the HTP. Assuming that the 8 carcinogens used in this analysis are a representative sample of all carcinogens in smoke, increasing the number of compounds in the analysis would make the CCE estimate more reliable but would most likely not dramatically change it.

Overall, consuming a HTP such as the one studied instead of cigarettes would be associated with a substantial increase in life expectancy compared to continued smoking for the subgroup of smokers who would die from cancer. Moreover, the authors also suggest, that the health impact would be greatest for habitual smokers who switch at a young age. It is also important to highlight that the authors make it clear that HTPs, are not risk-free and that there is still expected to be a negative health impact from consuming HTPs when compared to total abstinence from tobacco products.

ATTACHMENTS

Attachment 1	Overview of publications, including government-sponsored analyses, which have evaluated HTPs (reference period: January 2019 - February 2020)
Attachment 2	Independent studies assessing HTPs and/or *IQOS* use

REFERENCES

Abrams D. et al., Harm minimization and tobacco control: Reframing societal views of nicotine use to rapidly save lives, 39 Ann. Rev. Pub. Health. 193-213 (2018)

Bekki, K., et al., Comparison of Chemicals in Mainstream Smoke in Heat-not-burn Tobacco and Combustion Cigarettes. Journal of UOEH, 2017. 39(3): p. 201-207.

Bentley, M.C., Almstetter, M., Arndt, D., et al. (2020). Comprehensive chemical characterization of the aerosol generated by a heated tobacco product by untargeted screening. Anal Bioanal Chem.Brose, L. S., E. Simonavicius and H. Cheeseman (2018). Awareness and use of 'heat-not-burn' tobacco products in Great Britain. Tob Regul Sci 4(2): 44-50.

Coates, L., Kaandorp, G., Harris, J., van Leeuwen, J., Avci, A., Evans, J., George, S., Gissing, A., van den Honert, R. and Haynes, K., 2019, Preventable residential fire fatalities: July 2003 to June 2017, Bushfire and Natural Hazards CRC.

Cummings et al., 2020 Cummings K.M. et al., What is accounting for the rapid decline in cigarette sales in Japan?, 17 Int. J. Environ. Res. Public Health 2020, 3570 (2020)

Drovandi A. et al., Human biomarker exposure from cigarettes versus heat-not-burn devices: A systematic review and meta-analysis, Nicotine & Tobacco Research, Vol 22 (7), July 2020, Pages 1077–1085, https://doi.org/10.1093/ntr/ntz200

Forster, M., et al., Assessment of novel tobacco heating product THP1.0. Part 3: Comprehensive chemical characterisation of harmful and potentially harmful aerosol emissions. Regulatory Toxicology and Pharmacology, 2018. 93: p. 14-33.

Inoue-Choi et al. (2019) Non-Daily Cigarette Smokers: Mortality Risks in the U.S. Am J Prev Med 2019; 56(1):27−37. https://doi.org/10.1016/j.amepre.2018.06.025

Iskandar AR, Mathis C, Schlage WK, Frentzel S, Leroy P, Xiang Y, Sewer A, Majeed S, Ortega-Torres L, Johne S, Guedj E, Trivedi T, Kratzer G, Merg C, Elamin A, Martin F, Ivanov NV, Peitsch MC and Hoeng J (2017b) A systems toxicology approach for comparative assessment: Biological impact of an aerosol from a candidate modified-risk tobacco product and cigarette smoke on human organotypic bronchial epithelial cultures. Toxicology in vitro. 39:29-51.

Iskandar A, Martinez Y; Martin F, Schlage WK, Leroy P, Sewer A, Ortega-Torres L, Majeed S, Trivedi K, Guedj E, Frentzel S, Mathis C, Ivanov N, Peitsch MC, Hoeng J (2017c) Comparative Effects of a Candidate Modified-Risk Tobacco Product Aerosol and Cigarette Smoke on Human Organotypic Small Airway Cultures: A Systems Toxicology Approach. Toxicology Research (Cambridge), 6:930-946.

Iskandar AR, Titz B, Sewer A, Leroy P, Schneider T, Zanetti F, Mathis C, Elamin A, Frentzel S, Schlage W, Martin F, Peitsch MC, and Hoeng J (2017d) Systems Toxicology Meta-Analysis of In Vitro Assessment Studies: Biological Impact of a Modified-Risk Tobacco Product Aerosol Compared with Cigarette Smoke on Human Organotypic Cultures of the Respiratory Tract. Toxicology Research, 6:631-653.

Jaccard, G., et al., Comparative assessment of HPHC yields in the Tobacco Heating System THS2.2 and commercial cigarettes. Regulatory Toxicology and Pharmacology, 2017. 90: p. 1-8.

Kang, H., Cho, S.H. (2019). *Heated tobacco product use among Korean adolescents.* Tob Control. [Epub ahead of print]. doi: 10.1136/tobaccocontrol-2019-054949.

Kaunelienė V et al. (2018) A review of the impacts of tobacco heating system on indoor air quality versus conventional pollution sources; Chemosphere, Volume 206, September 2018, Pages 568-578

Kim, J., Yu, H., lee, S., Paek, Y.J. (2018) Awareness, experience and prevalence of heated tobacco product, IQOS, among young Korean adults. Tob control Aug 29.

Kioi, Y., Tabuchi, T. (2018) Electronic, heat-not-burn, and combustible cigarette use among chronic disease patients in Japan: A cross-sectional study. Tob. Induc. Dis. 2018; 16:41.

Kotz, D., Kastaun, S., (2018) E-Zigaretten und Tabakerhitzer: repräsentative Daten zu Konsumverhalten und assoziierten Faktoren in der deutschen Bevölkerung (die DEBRA-Studie). Bundesgesundheitsbl 2018: 61:1407–1414.

Lachenmeier D. et al. (2019) Heat-Not-Burn Tobacco Products: The Devil in Disguise or a Considerable Risk Reduction?, IJADR, 2018, 7(2), 8 – 11, doi: 10.7895/ijadr.250

Lee, A., Lee, K.-S., Park, H. (2019). *Association of the Use of a Heated Tobacco Product with Perceived Stress, Physical Activity, and Internet Use in Korean Adolescents. National Survey.* Int. J. Environ. Res. Public Health. 16(6), 965. doi:10.3390/ijerph16060965

Li, X., et al., Chemical Analysis and Simulated Pyrolysis of Tobacco Heating System 2.2 Compared to Conventional Cigarettes. Nicotine & Tobacco Research, 2018: p. 1-8.

Liu X, Lugo A, Spizzichino L, et al. Heat-not-burn tobacco products: concerns from the Italian experience; Tob Control January 2019 Vol 28 No 1

Mallock, N., et al., Levels of selected analytes in the emissions of “heat not burn” tobacco products that are relevant to assess human health risks. Archives of Toxicology, 2018. 92(6): p. 2145-2149.

Mallock N. et al. (2019) Heated Tobacco Products: A Review of Current Knowledge and Initial Assessments. *Front. Public Health 7:287. doi: 10.3389/fpubh.2019.00287*

Marynak, K.L., Wang, T.W., King, B.A., Agaku, I.T., Reimels, E.A., Graffunder, C.M., (2018) Awareness and Ever Use of "Heat-Not-Burn" Tobacco Products Among U.S. Adults, 2017. Am JPrev Med 55(4):551-554.

Mitova et al (2016) Comparison of the impact of the Tobacco Heating System 2.2 and a cigarette on indoor air quality. Regulatory Toxicology and Pharmacology 80, 91-101

Miyazaki, Y., Tabuchi, T. (2018) Educational gradients in the use of electronic cigarettes and heat-not-burn tobacco products in Japan. PLoS One 13(1).

Nyman, A.L., Weaver, S.R., Popova, L., Pechacek, T.F., Huang, J., Ashley, D.L., Eriksen, M.P. (2018) Awareness and use of heated tobacco products among US adults, 2016-2017. Tob Control Aug 29.

Pratte, P., S. Cosandey, and C. Goujon Ginglinger, Investigation of solid particles in the mainstream aerosol of the Tobacco Heating System THS2.2 and mainstream smoke of a 3R4F reference cigarette. Human & Experimental Toxicology, 2017. 36(11): p. 1115-1120.

Schaller, J.-P., et al., Evaluation of the Tobacco Heating System 2.2. Part 2: Chemical composition, genotoxicity, cytotoxicity, and physical properties of the aerosol. Regulatory Toxicology and Pharmacology, 2016. 81 (Supplement 2): p. S27-S47.

Schaller, J.-P., et al., Evaluation of the Tobacco Heating System 2.2. Part 3: Influence of the tobacco blend on the formation of harmful and potentially harmful constituents of the Tobacco Heating System 2.2 aerosol. Regulatory Toxicology and Pharmacology, 2016. 81 (Supplement 2): p. S48-S58.

Slob W. et al. (2020) A method for comparing the impact of carcinogenicity of tobacco products: A case study on heated tobacco versus cigarettes, Risk Analysis, https://onlinelibrary.wiley.com/doi/full/10.1111/risa.13482

Song F, Elwell- Sutton T, Naughton F, et al. Tob Control Epub ahead of print: 23 May 2020. doi: 10.1136/ tobaccocontrol-2019-055490

Stoklosa M, Cahn Z, Liber A, et al. (2019) Effect of IQOS introduction on cigarette sales: evidence of decline and replacement, Tob Control 2019;0:1–7. doi:10.1136/tobaccocontrol-2019-054998

Sutanto, E.; Miller, C.; Smith, D.M.; O'Connor, R.J.; Quah, A.C.K.; Cummings, K.M.; Xu, S.; Fong, G.T.; Hyland, A.; Ouimet, J.; Yoshimi, I.; Mochizuki, Y.; Tabuchi, T.; Goniewicz, M.L. Prevalence, Use Behaviors, and Preferences among Users of Heated Tobacco Products: Findings from the 2018 ITC Japan Survey. *Int. J. Environ. Res. Public Health* **2019**, *16*, 4630.

Sutanto, E.; Miller, C.; Smith, D.M.; Borland, R.; Hyland, A.; Cummings, K.M.; Quah, A.C.; Xu, S.S.; Fong, G.T.; Ouimet, J.; et al. Concurrent Daily and Non-Daily Use of Heated Tobacco Products with Combustible Cigarettes: Findings from the 2018 ITC Japan Survey. *Int. J. Environ. Res. Public Health* **2020**, *17*, 2098.

Tabuchi, T., K. Kiyohara, T. Hoshino, K. Bekki, Y. Inaba and N. Kunugita (2016). Awareness and use of electronic cigarettes and heat-not-burn tobacco products in Japan. Addiction 111(4): 706-713.

Tabuchi, T., Shinozaki, T., Kunugita, N., Nakamura, M., Tsuji, I. (2018) Study Profile: The Japan "Society and New Tobacco" Internet Survey (JASTIS): A longitudinal internet cohort study of heat-not-burn tobacco products, electronic cigarettes and conventional tobacco products in Japan. Jepidemiol.

Uchiyama, S., et al., Simple Determination of Gaseous and Particulate Compounds Generated from Heated Tobacco Products. Chemical Research in Toxicology, 2018. 31(7): p. 585-593.

Wong E, Kogel U, Veljkovic E, Martin F, Xiang Y, Boue S, Vuillaume G, Leroy P, Guedj E, Rodrigo G, Hoeng J, Peitsch M, Vanscheeuwijck P, Evaluation of the Tobacco Heating System 2.2. Part 4: 90-day Rat Inhalation Study with Systems Toxicology Endpoints Demonstrates Reduced Exposure Effects Compared with Cigarettes Smoke; Regul. Toxicol. Pharmacol., 81 (S2) (2016), pp. S93-S122

World Health Organization Regional Office for Europe Copenhagen, Air Quality Guidelines for Europe. Second ed. 2000: WHO Regional Publications, European Series, No. 91.

Wu YS, Wang MP, Ho SY, Li HCW, Cheung YTD, Tabuchi T, et al. Heated tobacco products use in Chinese adults in Hong Kong: a population-based cross-sectional study. Tob Control. 2019. doi: 10.1136/tobaccocontrol-2018-054719. PubMed PMID: 31005892.

Zanetti et al (2016) Systems Toxicology Assessment of the Biological Impact of a Candidate Modified Risk Tobacco Product on Human Organotypic Oral Epithelial Cultures. Chem Res Toxicol 29: 1252−1269.

Zanetti et al (2017) Comparative systems toxicology analysis of cigarette smoke and aerosol from a candidate modified risk tobacco product in organotypic human gingival epithelial cultures: A 3-day repeated exposure study. Food Chem Toxicol. 101:15-35.

Attachment 1

Overview of publications, including government-sponsored analyses, which have evaluated HTPs
(reference period: January 2019 - February 2020)

LIST OF TABLES

Table 1: Scientific Publications performed or sponsored by PMI

Chemistry and Physics	
1.	**Bentley, M.C., Almstetter, M., Arndt, D., et al. (2020). Comprehensive chemical characterization of the aerosol generated by a heated tobacco product by untargeted screening. Anal Bioanal Chem.**
	A suite of untargeted methods has been applied for the characterization of aerosol from the Tobacco Heating System 2.2 (THS2.2), a heated tobacco product developed by Philip Morris Products S.A. and commercialized under the brand name *IQOS*®. A total of 529 chemical constituents, excluding water, glycerin, and nicotine, were present in the mainstream aerosol of THS2.2, generated by following the Health Canada intense smoking regimen, at concentrations ≥ 100 ng/item. The majority were present in the particulate phase (n = 402), representing more than 80% of the total mass determined by untargeted screening; a proportion were present in both particulate and gas-vapor phases (39 compounds). The identities for 80% of all chemical constituents (representing > 96% of the total determined mass) were confirmed by the use of authentic analytical reference materials. Despite the uncertainties that are recognized to be associated with aerosol-based untargeted approaches, the reported data remain indicative that the uncharacterized fraction of TPM generated by THS2.2 has been evaluated to the fullest practicable extent. To the best of our knowledge, this work represents the most comprehensive chemical characterization of a heated tobacco aerosol to date.
2.	**Cozzani, V., Barontini, F., McGrath, T. et al. (2020). An experimental investigation into the operation of an electrically heated tobacco system. Thermochim Acta. 684: 178475.**
	An experimental investigation of the thermal processes taking place in the tobacco substrate of a recently developed multicomponent electrically heated tobacco product (EHTP) that is part of an electrically heated tobacco system (EHTS – also referred to as the Tobacco Heating System 2.2) was carried out. Temperature profiles in the tobacco substrate of the EHTP were characterized using thermocouples positioned at different distances from the heater surface. The average maximum temperature of the tobacco measured 0.2 mm from the heater's surface was < 260 °C, well below the temperature required for the self-sustaining smoldering combustion of the tobacco substrate to occur. The chemical composition of the aerosol generated from the EHTP when the EHTS was operated under oxidative and non-oxidative atmospheres was investigated. The aerosol derived from the controlled heating of the tobacco substrate is comprised principally of water, nicotine and glycerol that are evaporated from the tobacco substrate. No significant change in aerosol composition and in the amounts of CO, NO and NOx were detected when comparing the aerosol formed under non-oxidative (where combustion processes cannot occur) and oxidative atmospheres.

3.	**Hofer, I., Gautier, L., Sauteur, E. et al. (2019). A Screening Method by Gas Chromatography-Mass Spectrometry for the Quantification of 24 Aerosol Constituents from Heat-Not-Burn Tobacco Products. Beitr. Tabakforsch Int. 28(7): 317-328**
	A screening method allowing the quantification of 24 aerosol constituents using gas chromatography-mass spectrometry has been developed to assess the aerosol chemistry of heat-not-burn tobacco products. The aim of this method was to quantify phenol, o-cresol, m-cresol, p-cresol, catechol, resorcinol, hydroquinone, 1,3-butadiene, isoprene, benzene, acrylonitrile, toluene, pyridine, styrene, 1,2-propylene glycol, menthol, 2-furanmethanol, acrylamide, naphthalene, nicotine, acetamide, quinoline, triacetin, and glycerine in the aerosol emitted by heated tobacco products. The aerosol was generated by an electrically heated tobacco system (PMI's Heated Tobacco System (THS 2.4)) with one single aerosol collection method, using the Health Canada smoking regimen and analyzed with two analytical methods. The method was validated according to the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use and the Association of Official Analytical Chemists guidelines. A regression model based on a linear relationship between concentration and response ratio with a 1/x weighting factor was selected for phenol, o-cresol, m-cresol, p-cresol, 1,3-butadiene, isoprene, benzene, acrylonitrile, toluene, pyridine, styrene, 2-furanmethanol, acrylamide, naphthalene and acetamide. A quadratic regression model with a 1/x weighting factor was chosen for catechol, resorcinol, hydroquinone, 1,2-propylene glycol, menthol, nicotine, quinoline, triacetin and glycerine. Coefficients of variation for repeatability were determined between 7.9% and 17.8% and for intermediate precision between 8.1% and 19.9%. The matrix effect of the heated tobacco aerosol extract was assessed by performing a recovery study, where the aerosol extracts were spiked at different concentrations for the compounds to be analyzed. In addition, the mainstream smoke from 3R4F reference cigarettes was analyzed, and results were compared with previously published studies. The method was successfully validated, providing data consistent with published data and it was shown to be selective, precise and accurate.
4.	**Jaccard, G., Djoko, D.T., Korneliou, A., et al. (2019). Mainstream smoke constituents and in vitro toxicity comparative analysis of 3R4F and 1R6F reference cigarettes. Toxicol Rep. 6: 222-231.**
	A new Kentucky reference cigarette, 1R6F, has been manufactured to replace the depleting 3R4F reference cigarette. The 3R4F Kentucky reference cigarettes have been widely used as monitor or comparator cigarettes for mainstream smoke analysis and in vitro and in vivo toxicological data of cigarettes and novel tobacco products. Both reference cigarettes were analyzed in the same laboratory during the same period of time with the goal of performing a comparison of 3R4F and 1R6F.

	On the basis of the results obtained from aerosol chemistry and in vitro assays, we consider that the 1R6F reference cigarette is a suitable replacement for the 3R4F reference cigarette as a comparator/monitor cigarette. Its specific use as a comparator for novel tobacco products was checked on the basis of a comparative test with the Tobacco Heating System 2.2 as an example.
5.	**Mitova, M.I., Bielik, N., Campelos, P.B. et al. (2019). Air quality assessment of the Tobacco Heating System 2.2 under simulated residential conditions. Air Qual Atmos Hlth. 12(7): 807-823.**
	Despite the growing popularity of new alternatives to traditional tobacco products, there is still limited evidence on their indoor effect in particular in residential spaces as specific environments where enforcement of air quality standards is difficult. Hence, the impact of the Tobacco Heating System 2.2 (THS, marketed as *IQOS*®) on indoor air quality was assessed under controlled experimental conditions using ventilation representative of residential buildings with natural ventilation. Smoking of cigarettes (*Marlboro Gold*®) at the same ventilation conditions and consumption rates was used as positive control. Before each THS 2.2 or Marlboro Gold® session, a background session with the same volunteers as for the product-use session was held. In the high-load simulated residential environment, out of the 24 measured airborne constituents, only the increase of the indoor concentrations of nicotine, acetaldehyde, and glycerin above the background was attributable to the use of THS 2.2. The quantified concentrations of these three airborne compounds were significantly below the harmful levels defined in the air quality guidelines. Smoking Marlboro Gold® resulted in much greater increases in the concentrations of all measured indoor air constituents, except for glycerin, and the indoor concentrations of several constituents exceeded the exposure levels set forth by cognizant authorities. Based on these data, it is reasonable to conclude that the use of THS 2.2 in environments where norms for indoor exposure in terms of adequate ventilation are respected does not adversely affect the overall indoor air quality.
Standard & SystemToxicology	
6.	**Boué, S., Schlage, W.K., Page, D. et al. (2019). Toxicological assessment of Tobacco Heating System 2.2: Findings from an independent peer review. Regul Toxicol Pharmacol. 104: 115-127.**
	Offering safer alternatives to cigarettes, such as e-cigarettes and heated tobacco products, to smokers who are not willing to quit could reduce the harm caused by smoking. Extensive and rigorous scientific studies are conducted to assess the relative risk of such potentially modified risk tobacco products compared with that of smoking cigarettes. In addition to the peer review of publications reporting individual studies, we sponsored a two-tier peer review organized by an independent third party who identified, recruited, and managed 7 panels of 5–12 experts whose identity remains unknown to us. The objective of this review was to obtain an independent perspective of the plausibility of the evidence generated by individual studies along with an assessment of the study methods used. The reviewers had access to all publications and raw data from preclinical and clinical studies via a web portal. The reviewers were asked questions regarding study design, methods,

	quality of data, and interpretation of results to judge the validity of the conclusions regarding the relative effects of the Tobacco Heating System 2.2 compared with cigarettes. Once their conclusions were submitted, the experts had the opportunity to participate in an anonymized online debate with their fellow panel members. The conclusions from this two-tiered peer review were: "*Overall, the results obtained in the peer review described here are supportive of the study designs, results, and interpretation of the studies assessing the potential MRTP THS 2.2*."
7.	**Boué, S., Goedertier, D., Hoeng, J. et al.. (2020). State-of-the-art methods and devices for the generation, exposure, and collection of aerosols from heat-not-burn tobacco products. Toxicol Res Appl. 4: 14611.**
	Tobacco harm reduction is increasingly recognized as a promising approach to accelerate the decline in smoking prevalence and smoking-related population harm. Potential modified risk tobacco products (MRTPs) must undergo a rigorous premarket toxicological risk assessment. The ability to reproducibly generate, collect, and use aerosols is critical for the characterization, and preclinical assessment of aerosol-based candidate MRTPs (cMRTPs), such as noncombusted cigarettes, also referred to as heated tobacco products, tobacco heating products, or heat-not-burn (HNB) tobacco products. HNB tobacco products generate a nicotine-containing aerosol by heating tobacco instead of burning it. The aerosols generated by HNB products are qualitatively and quantitatively highly different from cigarette smoke (CS). This presents technical and experimental challenges when comparing the toxicity of HNB aerosols with CS. The methods and experimental setups that have been developed for the study of CS cannot be directly transposed to the study of HNB aerosols. Significant research efforts are dedicated to the development, characterization, and validation of experimental setups and methods suitable for HNB aerosols. They are described in this review, with a particular focus on the Tobacco Heating System version 2.2. This is intended to support further studies, the objective evaluation and verification of existing evidence, and the development of scientifically substantiated HNB MRTPs.
8.	**Choukrallah, M.A., Sierro, N., Martin, F. et al. (2019). Tobacco Heating System 2.2 has a limited impact on DNA methylation of candidate enhancers in mouse lung compared with cigarette smoke. Food Chem Toxicol. 123:501-510.**
	Cigarette smoke exposure has been shown to correlate with changes in DNA methylation levels, however, the impact of cigarette smoke on DNA methylation at genome-wide scale is missing. Here, we used whole-genome bisulfite sequencing to assess the effects of cigarette smoke extract and aerosol from the Tobacco Heating System (THS) 2.2 on DNA methylation in lung and liver tissues from apolipoprotein E-deficient mice during an eight-month period of exposure. We found that in lung tissue, cigarette smoke mainly induced hypermethylation of candidate enhancers at late time points, while promoters were less affected. This effect was strongly reduced upon cessation or switching to THS 2.2. By contrast, chronic exposure to THS 2.2 had a limited effect on DNA methylation at both promoters and enhancers. We also identified members of the Ets and Fox families of transcription factors as potential players in the epigenetic response to cigarette smoke exposure in lung tissue. In contrast to the lung, DNA methylation in the liver was largely insensitive to all investigated exposures. In summary, our investigations indicate that cigarette smoke -related DNA methylation alterations are tissue-specific, occur mainly at enhancers and are strongly reduced upon smoking cessation or switching to THS2.2.

9.	**Hayes, A.W., Li, R., Hoeng, J. et al. (2019). New approaches to risk assessment of chemical mixtures. Toxicol Res Appl. 3: 1-10.**
	Assessing the risk of chemical mixtures is an intricate process that should integrate published laboratory data; comparisons with the composition, toxicity, and functionality of similar mixtures; complete analytical characterization of the mixture components; and in silico modeling. Various tiered assessment protocols have been proposed to address this need, and these protocols may be adapted on a case-by-case basis for both mixture-based and component-based evaluations. Emerging technologies have enabled rapid mixture testing in alternative animal models, such as human organotypic cultures and zebrafish. In addition, quantitative modeling that uses systems toxicology approaches can identify exposure-induced cellular and molecular alterations that would not be detected by standard toxicology assays. This review summarizes the approaches to risk assessment of complex chemical mixtures as presented at the Eighth International Congress of the Asian Society of Toxicology, June 2018.
10.	**Hoeng, J., Maeder, S, Vanscheeuwijck, P. et al. (2019). Assessing the lung cancer risk reduction potential of candidate modified risk tobacco products. Intern Emerg Med. 14(6): 821-834.**
	Smoking is the major cause of lung cancer. While the risk of lung cancer increases with the number of cigarettes smoked and the duration of smoking, it also decreases upon smoking cessation. The development of candidate modified risk tobacco products (cMRTP) is aimed at providing smokers who will not quit with alternatives to cigarettes that present less risk of harm and smoking-related disease. It is necessary to assess the risk reduction potential of cMRTPs, including their potential to reduce the risk of lung cancer. Assessing the lung cancer risk reduction potential of cMRTPs is hampered by (i) the absence of clinical risk markers that are predictive of future lung cancer development, (ii) the latency of lung cancer manifestation (decades of smoking), and (iii) the slow reduction in excess risk upon cessation and a fortiori upon switching to a cMRTP. It is, therefore, likely that only long-term epidemiology will provide definitive answers to this question and allow to first verify that a cMRTP reduces the risk of lung cancer and if it does, to quantify the reduction in excess lung cancer risk associated with a cMRTP. For this to be possible, the cMRTP would need to be available in the market and used exclusively by a large portion of current smokers. Here, we propose that a mechanism-based approach represents a solid alternative to show in a pre-market setting that switching to a cMRTP is likely to significantly reduce the risk of lung cancer. This approach is based on the causal chain of events that leads from smoking to disease and leverages both non-clinical and clinical studies as well as the principles of systems toxicology. We also discuss several important challenges inherent to the assessment of cMRTPs as well as key aspects regarding product use behavior.
11.	**Martin, F., Talikka, M., Ivanov, N. et al (2019). A Meta-Analysis of the Performance of a Blood-Based Exposure Response Gene Signature Across Clinical Studies on the Tobacco Heating System 2.2 (THS 2.2). Front Pharmacol. 10: 198.**

	As part of emerging tobacco harm reduction strategies, modified risk tobacco products (MRTP), alternatives to cigarettes that have the potential to reduce the individual risk and population harm compared with smoking cigarettes, are being developed to offer adult smokers who want to continue using tobacco and nicotine products. MRTPs are defined as any tobacco products that are distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products. One such candidate MRTP is the Tobacco Heating System (THS) 2.2, which does not burn tobacco but instead heats it, thus producing significantly reduced levels of harmful and potentially harmful constituents compared with cigarettes. The clinical assessment of candidate MRTPs requires the development of exposure-response markers to distinguish current smokers from either nonsmokers or former smokers with high specificity and sensitivity. Towards this end, a whole blood-derived gene signature was previously developed and reported. Four randomized, controlled, open-label, three-arm parallel group reduced exposure clinical studies have been conducted with subjects randomized to three arms: switching from cigarettes to THS 2.2, continuous use of cigarettes, or smoking abstinence. These clinical studies had an investigational period of five days in confinement, which was followed by an 85-day ambulatory period in two studies. Here we tested the previously developed blood-derived signature on the samples derived from those clinical studies. We showed that in all four studies, the signature scores were reduced consistently in subjects who either stopped smoking or switched to THS 2.2 compared with subjects who continued smoking cigarettes.
12.	**Phillips, B., Szostak, J., Titz, B. et al. (2019). A six-month systems toxicology inhalation/cessation study in ApoE$^{-/-}$ mice to investigate cardiovascular and respiratory exposure effects of modified risk tobacco products, CHTP 1.2 and THS 2.2, compared with conventional cigarettes. Food Chem Toxicol. 126: 113-141.**
	Smoking is one of the major modifiable risk factors in the development and progression of chronic obstructive pulmonary disease (COPD) and cardiovascular disease (CVD). Modified-risk tobacco products (MRTP) are being developed to provide substitute products for smokers who are unable or unwilling to quit, to lessen the smoking-related health risks. In this study, the ApoE$^{-/-}$ mouse model was used to investigate the impact of cigarette smoke (CS) from the reference cigarette 3R4F, or aerosol from two potential MRTPs based on the heat-not-burn principle, carbon-heated tobacco product 1.2 (CHTP 1.2) and tobacco heating system 2.2 (THS 2.2), on the cardiorespiratory system over a 6-month period. In addition, cessation or switching to CHTP 1.2 after 3 months of CS exposure was assessed. A systems toxicology approach combining physiology, histology and molecular measurements was used to evaluate the impact of MRTP aerosols in comparison to CS. CHTP 1.2 and THS 2.2 aerosols, compared with CS, demonstrated lower impact on the cardiorespiratory system, including low to absent lung inflammation and emphysematous changes, and reduced atherosclerotic plaque formation. Molecular analyses confirmed the lower engagement of pathological mechanisms by MRTP aerosols than CS. Both cessation and switching to CHTP 1.2 reduced the observed CS effects to almost sham exposure levels.

13.	**Poussin, C., Kramer, B., Lanz, H. et al. (2020). 3D human microvessel-on-a-chip model for studying monocyte-to-endothelium adhesion under flow - application in systems toxicology. ALTEX 37(1): 47-63.**
	Lifestyle and genetic factors can lead to the development of atherosclerosis and, ultimately, cardiovascular adverse events. Rodent models are commonly used to investigate mechanism(s) of atherogenesis. However, the 3Rs principles, aiming to limit animal testing, encourage the scientific community to develop new physiologically relevant in vitro alternatives. Leveraging the 96-chip OrganoPlate(R), a microfluidic platform, we have established a three-dimensional (3D) model of endothelial microvessels-on-a-chip under flow using primary human coronary arterial endothelial cells. As functional readout, we have set up an assay to measure the adhesion of monocytes to the lumen of perfused microvessels. For monitoring molecular changes in microvessels, we have established the staining and quantification of specific protein markers of inflammation and oxidative stress using high content imaging, as well as analyzed transcriptome changes using microarrays. To demonstrate its usefulness in systems toxicology, we leveraged our 3D vasculature-on-a-chip model to assess the impact of the Tobacco Heating System (THS) 2.2, a candidate modified risk tobacco product, and the 3R4F reference cigarette on the adhesion of monocytic cells to endothelial microvessels. Our results show that THS 2.2 aerosol-conditioned medium had a reduced effect on monocyte-endothelium adhesion compared with 3R4F smoke-conditioned medium. In conclusion, we have established a relevant 3D vasculature-on-a-chip model for investigating leukocyte-endothelial microvessel adhesion. A case study illustrates how the model can be used for product testing in the context of systems toxicology-based risk assessment. The current model and its potential further development options also open perspectives of applications in vascular disease research and drug discovery.
14.	**Szostak, J., Titz, B., Schlage, W. et al . (2020). Structural, functional, and molecular impact on the cardiovascular system in ApoE$^{-/-}$ mice exposed to aerosol from candidate modified risk tobacco products, Carbon Heated Tobacco Product 1.2 and Tobacco Heating System 2.2, compared with cigarette smoke. Chem-Biol Interact. 315: 108887.**
	Aim: To investigate the molecular, structural, and functional impact of aerosols from candidate modified risk tobacco products (cMRTP), the Carbon Heated Tobacco Product (CHTP) 1.2 and Tobacco Heating System (THS) 2.2, compared with that of mainstream cigarette smoke (CS) on the cardiovascular system of ApoE$^{-/-}$ mice. Methods: Female ApoE$^{-/-}$ mice were exposed to aerosols from THS 2.2 and CHTP 1.2 or to CS from the 3R4F reference cigarette for up to 6 months at matching nicotine concentrations. A Cessation and a Switching group (3 months exposure to 3R4F CS followed by filtered air or CHTP 1.2 for 3 months) were included. Cardiovascular effects were investigated by echocardiographic, histopathological, immunohistochemical, and transcriptomics analyses.

	Results: Continuous exposure to cMRTP aerosols did not affect atherosclerosis progression, heart function, left ventricular (LV) structure, or the cardiovascular transcriptome. Exposure to 3R4F CS triggered atherosclerosis progression, reduced systolic ejection fraction and fractional shortening, caused heart LV hypertrophy, and initiated significant dysregulation in the transcriptomes of the heart ventricle and thoracic aorta. Importantly, the structural, functional, and molecular changes caused by 3R4F CS were improved in the smoking cessation and switching groups. Conclusion: Exposure to cMRTP aerosols lacked most of the CS exposure-related functional, structural, and molecular effects. Smoking cessation or switching to CHTP 1.2 aerosol caused similar recovery from the 3R4F CS effects in the ApoE$^{-/-}$ model, with no further acceleration of plaque progression beyond the aging-related rate.
15.	**van der Toorn, M., Koshibu, K., Schlage, W.K. et al. (2019). Comparison of monoamine oxidase inhibition by cigarettes and modified risk tobacco products. Toxicol Rep. 6: 1206-1215.**
	The adverse effects of cigarette smoking are well documented, and the two main strategies for reducing smoking prevalence are prevention of smoking initiation and promotion of smoking cessation. More recently, a third and complementary strategy, tobacco harm reduction has emerged, aimed at reducing the burden of smoking-related diseases. This has been enabled by the development of novel products such as electronic cigarettes (e-cigarettes) and heated tobacco products, designed to deliver nicotine with significantly reduced levels of the toxicants that are emitted by cigarettes. Several potential modified risk tobacco products (pMRTP) have been reported to emit significantly less toxicants than cigarettes and significantly reduce toxicant exposure in smokers who switch completely to such products: These are two prerequisites for pMRTPs to reduce harm and the risk of smoking-related disease. However, concerns remain regarding the addictive nature of these products. Smoking addiction is a complex phenomenon involving multiple pharmacological and non-pharmacological factors. Although the main pharmacological substance associated with smoking addiction is nicotine, accumulating evidence suggests that nicotine mostly acts as a primary reinforcer and that other factors are involved in establishing smoking addiction. Inhibition of monoamine oxidases (MAO)—mammalian flavoenzymes with a central role in neurotransmitter metabolism—has also been suggested to be involved in this process. Therefore, we aimed to comparatively investigate the ability of several types of pMRTPs and cigarette smoke (3R4F) to inhibit MAO activity. The results showed that the heated tobacco product Tobacco Heating System (THS) 2.2 and the MESH 1.1 e-cigarette possessed no MAO inhibitory activity while 3R4F significantly inhibits the levels of MAO activity (3R4F MAO-A and B; > 2 µM nicotine). Snus products have similar inhibition profiles as 3R4F but for larger nicotine concentrations (snus MAO-A; ~68-fold, snus MAO-B; ~23-fold higher compared to 3R4F). These observations were confirmed by analytical datasets of potential MAO inhibitors emitted by these products. In conclusion, we have demonstrated that specific pMRTPs, namely THS 2.2 and MESH 1.1, have a significantly lower MAO-inhibitory activity than 3R4F. These findings provide a basis for further investigation of the role of MAO inhibitors in cigarette addiction as well as the implications of the findings for abuse liability of pMRTPs in comparison with cigarettes.

16.	**Zanetti, F., Zhao, X., Pan, J. et al. (2019). Effects of cigarette smoke and tobacco heating aerosol on color stability of dental enamel, dentin, and composite resin restorations. Quintessence Int. 50(2): 156-166.**
	Objectives: To test if cigarette smoke (CS) causes discoloration of enamel, dentin, and composite resin restorations and induces color mismatch between dental hard tissues and the restorations, and to compare the findings with the effects of aerosol generated by the tobacco heating system (THS) 2.2. Method and materials: Twenty-two human premolars were prepared with Class V cavities restored with Filtek Supreme Ultra (3M Espe) composite resin. Teeth were divided into two groups and exposed to either CS from 20 reference cigarettes (3R4F) or aerosol from 20 THS 2.2 tobacco heat sticks 4 days a week for 3 weeks. CIE L*a*b* color was assessed before and after exposure and brushing at 1, 2, and 3 weeks. Color match, marginal discoloration, marginal integrity, and surface texture of the Class V restoration were assessed according to a modified US Public Health Service (USPHS) criterion. Results: Marked discoloration of enamel and dentin was observed following 3 weeks of CS exposure ($\Delta E = 8.8 \pm 2.6$ and 21.3 ± 4.4, respectively), and color mismatch occurred between the composite resin restorations ($\Delta E = 25.6 \pm 3.8$) and dental hard tissues. Discoloration was minimal in the enamel, dentin, and composite resin restorations in the THS 2.2 group, and no color mismatch was observed after 3 weeks of THS 2.2 aerosol exposure. Conclusion: CS causes significant tooth discoloration and induces color mismatch between dental hard tissues and composite resin restorations. Reducing or eliminating the deposits derived from tobacco combustion could minimize the impact of tobacco products on tooth discoloration.
Clinical	
17.	**Haziza, C., de La Bourdonnaye, G., Donelli, A. et al. (2019). Reduction In Exposure To Selected Harmful And Potentially Harmful Constituents Approaching Those Observed Upon Smoking Abstinence In Smokers Switching To The Menthol Tobacco Heating System 2.2 For Three Months (Part 1). Nicotine Tob Res.**
	Introduction: The Tobacco Heating System (THS) is a “heat-not-burn” tobacco product designed to generate significantly lower levels of harmful and potentially harmful constituents (HPHC) and present lower risk of harm than cigarettes. This study assessed the exposure reduction to selected HPHC in smokers switching to menthol THS (mTHS) 2.2 compared with smokers continuing smoking menthol cigarettes (mCC) and smoking abstinence (SA) for five days in a confined setting, followed by an 86-day ambulatory period. Methods: One hundred sixty healthy adult U.S. smokers participated in this randomized, three-arm parallel group, controlled clinical study. Biomarkers of exposure to 16 HPHCs were measured in blood and 24-hour urine. Safety was monitored throughout the study. Information was also gathered on product evaluation, product use, subjective effects, and clinical risk markers (co-publication Part 2).

	Results: Nicotine uptake was comparable in both exposure groups (mTHS:mCC ratio of 96% on Day 90). On Day 5, biomarker of exposure levels to other HPHCs were reduced by 51% to 96% in the mTHS group compared with the mCC group, and these reductions were sustained for most biomarkers over the ambulatory period. After 90 days of use, the level of satisfaction with mTHS and suppression of urge to smoke were comparable to mCC. Conclusions: Switching from mCCs to mTHS significantly reduced the exposure to HPHCs to levels approaching those observed in subjects who abstained from smoking for the duration of the study.
18.	**Haziza, C., de La Bourdonnaye, G., Donelli, A. et al. (2019). Favorable Changes in Biomarkers of Potential Harm to Reduce the Adverse Health Effects of Smoking in Smokers Switching to the Menthol Tobacco Heating System 2.2 for Three Months (Part 2). Nicotine Tob Res.**
	Introduction: Tobacco Heating System (THS) 2.2, a candidate modified-risk tobacco product aims at offering an alternative to cigarettes for smokers while substantially reducing the exposure to harmful and potentially harmful constituents (HPHCs) found in cigarette smoke. Methods: One hundred and sixty healthy adult U.S. smokers participated in this randomized, three-arm parallel group, controlled clinical study. Subjects were randomized in a 2:1:1 ratio to menthol THS 2.2 (mTHS), menthol cigarette, or smoking abstinence (SA) for five days in confinement and 86 subsequent ambulatory days. Endpoints included biomarkers of exposure to HPHCs (reported in our co-publication, Part 1) and biomarkers of potential harm (BOPH). Results: Compliance (protocol and allocated product exposure) was 51% and 18% in the mTHS and SA arms, respectively, on Day 90. Nonetheless, favorable changes in BOPHs of lipid metabolism (total cholesterol and high- and low-density cholesterol), endothelial dysfunction (soluble intercellular adhesion molecule1), oxidative stress (8-epi-prostaglandin F2α), and cardiovascular risk factors (e.g., high-sensitivity C-reactive protein) were observed in the mTHS group. Favorable effects in other BOPHs, including ones related to platelet activation (11-dehydrothromboxane B2) and metabolic syndrome (glucose), were more pronounced in normal weight subjects. Conclusions: The results suggest that the reduced exposure demonstrated when switching to mTHS is associated with overall improvements in BOPHs, which are indicative of pathomechanistic pathways underlying the development of smoking-related diseases, with some stronger effects in normal weight subjects. Clinical trial registration: NCT01989156 (ClinicalTrials.gov). Implications: Switching to mTHS was associated with favorable changes for some BOPHs indicative of biological pathway alterations (e.g., oxidative stress and endothelial dysfunction). The results suggest that switching to mTHS has the potential to reduce the adverse health effects of smoking and ultimately the risk of smoking-related diseases.

19.	**Lüdicke, F., Ansari, S. M., Lama, N. et al. (2019). Effects of Switching to a Heat-Not-Burn Tobacco Product on Biologically-Relevant Biomarkers to assess a Candidate Modified Risk Tobacco Product: A Randomized Trial. Cancer Epidemiol Biomarkers Prev. 28(11): 1934-1943.**
	Background: Cigarette smoking increases the risk of chronic diseases; heating instead of burning tobacco can lower these risks. This study (with 984 adult American smokers) examined whether favorable changes occur in eight co-primary endpoints (HDL-C; WBC; FEV_1%pred; COHb; Total NNAL; sICAM-1; 11-DTX-B2; 8-epi-PGF2α) indicative of biological and functional effects when cigarette smokers switch to the heat-not-burn Tobacco Heating System 2.2 (THS). Additionally, these biomarkers of exposure (BoExp) were quantified: MHBMA; 3-HPMA; Total NNN; CEMA; 3-OH-B[a]P; HMPMA; Total 1-OHP; NEQ; CO exhaled. Methods: Participants were randomized to continued smoking of their preferred cigarette brand (n = 488) or to using THS (IQOS brand) (n = 496) for 6 months. THS has a maximum heating temperature of 350°C, delivering 1.21 mg nicotine/stick and 3.94 mg glycerin/stick under the Health Canada Intense smoking regimen. Results: The main outcome was a favorable change 6 months after baseline, with statistically significant improvements in 5 out of 8 biomarkers of effect (HDL-C; WBC; FEV1%pred; COHb; Total NNAL) when smokers switched to THS compared with those who continued to smoke cigarettes. Likewise, BoExp were markedly reduced. Conclusions: All endpoints showed favorable changes in the same direction as with smoking cessation and improved biological effects were observed in smokers who predominantly used THS compared with continued cigarette smoking, with similar nicotine levels in both groups. Improvements in 5 out of 8 biomarkers of effect is supportive of the research hypothesis, suggestive of disease risk reduction potential for smokers switching to THS instead of continuing to smoke cigarettes.
Behavioral	
20.	**Roulet, S., Chrea, C., Kanitscheider, C. et al. (2019). Potential predictors of adoption of the Tobacco Heating System by U.S. adult smokers: An actual use study [version 1; peer review: 1 approved, 2 approved with reservations]. F1000 Res. 8: 214.**
	Background: This was a pre-market actual use study with the Tobacco Heating System (THS), a candidate modified risk tobacco product, conducted with adult smokers in eight cities in the United States. The main goal of the study was to describe THS adoption in a real-world setting. The aim of this analysis was to identify potential predictors for adoption of THS using stepwise logistic regression method. Methods: This actual use study was an observational study assessing self-reported stick-by-stick consumption of the THS product compared with the use of commercial cigarettes over six weeks. The study aimed at replicating the usage of THS in real-world conditions with participants being able to consume cigarettes, THS, and any other nicotine-containing products (e.g., e-cigarettes, cigars, etc.) *ad libitum*.

	Results: 14.6% of participants adopted THS, which comprised 70% or more of their total tobacco consumption by the end of the observational period (in Week 6). The main predictors of adoption were the liking of the smell, taste, aftertaste, and ease of use of THS. The proportion of adoption was higher in participants aged 44 years and older and in Hispanic or Latino adult smokers. Additionally, adoption of THS was more likely in participants who had never attempted to quit smoking and in participants who smoked up to 10 cigarettes per day. Finally, the adoption of THS was higher in participants who consumed both regular and menthol THS compared with those who consumed only one THS variant. Conclusions: The main predictors of THS adoption were positive sensory assessment and the ease of use. Socio-demographic characteristics and smoking habits appeared much less important. Post-marketing studies will provide further insights on the impact of the THS at the individual and the overall population level.

Table 2: Scientific Publications sponsored by PMI or other Tobacco Product Manufacturers

Chemistry and Physics	
21.	**Kaunelienė, V., Meišutovič-Akhtarieva, M., Prasauskas, T. et al. (2019). Impact of Using a Tobacco Heating System (THS) on Indoor Air Quality in a Nightclub. Aerosol Air Qual Res. 19(9):1961-1968.**
	With the introduction of novel and potentially less polluting nicotine containing products to the market, the impacts of their usage to indoor air quality as opposed to conventional pollution sources must be reviewed and considered. This review study aimed to comparatively analyze changes in indoor air quality as the consequence of tobacco heating system (THS) generated pollution against general indoor air quality in various micro-environments, especially with combustion-based pollution sources present. Indoor concentrations of formaldehyde, acetaldehyde, benzene, toluene, nicotine and PM2.5 were reviewed and compared; concentrations of other harmful and potentially harmful substances (HPHCs) were discussed. Generally, the usage of THS has been associated with lower or comparable indoor air pollutant concentrations compared against other conventional indoor sources or environments, in most cases distinguishable above background, thus potentially being associated with health effects at prolonged exposures as any other artificial air pollution source. In the controlled environment the use of THS (as well as an electronic cigarette) resulted in the lowest concentrations of formaldehyde, benzene, toluene, PM2.5, among majority researched pollution sources (conventional cigarettes, waterpipe, incense, mosquito coils). The exposure to significantly higher pollution levels of benzene, toluene, and formaldehyde occurred in public environments, especially transport micro-environments. Such low levels of conventionally-assessed indoor pollutants resulting from the use of new nicotine containing products raise challenges for epidemiological studies of second-hand exposure to THS aerosol in real-life environments.
22.	**Koutela, N., Fernández, E., Saru, M.-L. et al. (2020). A comprehensive study on the leaching of metals from heated tobacco sticks and cigarettes in water and natural waters. Sci Total Environ. 714:136700.**
	The leaching behavior of Al, Cr, Ni, Cu, Zn, As, Se, Cd, Ba, Hg and Pb in water from two types of heat-not-burn tobacco sticks is presented here, and compared to that from conventional cigarettes. The total concentration of each metal in solid tobacco products was initially determined. Concentrations in used and unused tobacco sticks were similar and generally, lower than those in unused conventional cigarettes. Studies on the contribution of paper, filter and tobacco revealed that tobacco was the major source of metal contamination. Smoking conventional cigarettes reduced the total metal concentrations since a substantial amount of metals was retained in the ash; a post-consumption waste that is difficult to collect. Batch leaching tests were performed to determine dissolved concentrations as a function of time.

	With the exceptions of As and (in most cases) Hg that were not detected, metals were released at varying rates. At 24 h of soaking the percentage of metals leached ranged from 0.2 – 43%. The contribution of paper, filter and tobacco to the dissolved concentrations at 24 h of leaching was investigated and in almost all cases tobacco was the major source of metal contamination. The dissolved concentrations from ash were low as metals were strongly bound. Varying the pH, ionic strength and humic acids content at environmentally relevant values did not affect leaching of metals at 24 h of soaking. The use of river water, rain water and seawater as leachants was also not found to alter dissolved concentrations at 24 h compared to ultrapure water. The results presented here suggest that the consequences of improper disposal of tobacco products in the environment are two-sided and that next to the generation of plastic litter, discarded tobacco products can also act as point sources of metal contamination. Public education campaigns focusing on the environmental impact and best disposal practices are urgently needed.
23.	**Meišutovič-Akhtarieva, M., Prasauskas, T., Čiužas, D. et al. (2019). Impacts of exhaled aerosol from the usage of the tobacco heating system to indoor air quality: A chamber study. Chemosp. 223:474-482.**
	Aerosol particle, carbonyl, and nicotine concentrations were analysed as pollutants affecting indoor air quality during the usage of electrically-heated tobacco product - the Tobacco Heating System (THS). Quantitative experimental variables included THS use intensity as number of parallel users (1, 3, or 5), distance to the bystander (0.5, 1, or 2 m), as well as environmental conditions in a chamber: ventilation intensity as air changes per hour (0.2, 0.5, or 1 h−1), and relative humidity (RH, 30, 50 or 70%). The real-time particle number (PNC), CO and CO2 concentration, as well as off-line acetaldehyde, formaldehyde, nicotine, and 3-ethenylpyridine concentration was measured during and after the active usage. Use of THS resulted in a statistically significant increase of several analytes including nicotine, acetaldehyde, PM2.5, and PNC as compared to the background. The obtained levels were significantly lower (approximately 16, 8, 8 and 28 times for nicotine, acetaldehyde, PNC and PM2.5, respectively) compared to the levels resulting from conventional cigarette (CC) smoking under identical conditions. The maximum 30 min concentration of PNC (4.8 × 105 #/cm3), as well as maximum concentration of PNC (9.3 × 106 #/cm3) suggest that the intensive use of THS in a confined space with limited ventilation might cause substantially elevated aerosol concentrations, although these particles appeared as highly volatile ones and evaporated within seconds. Generally, the usage intensity (number of simultaneous users) prevailed as the most important factor positively affecting pollutant variations; another important factor was the distance to bystander.
24.	**Peñin-Ibañez, M. Martin, D., Gonzálvez, A.G. et al. (2019). A Comparative Study of Non-Volatile Compounds Present in 3R4F Cigarettes and iQOS Heatsticks Utilizing GC-MS. Am J Analyt Chem. 10:76-85.**
	It is now widely suggested that people who are dependent on nicotine should switch from ordinary tobacco smoking to alternative products, which at least reduce the overall harm from smoking. A number of alternatives are now popular, including electronic cigarettes and heatsticks.

	In this work comparative analysis of the smoke/aerosol emission from 3R4F standard cigarettes and iQOS heatsticks was undertaken. For this, gas chromatography-mass spectrometry (GC-MS) analysis was applied, to measure the non-volatile compounds of smoke/aerosol emission from individual samples, with the specific aim to determine their content of nicotine and selected other main components. All measurement data were collected under the Health Canada Intense (HCI) puffing regime. The most relevant findings of the present investigation can be summarized as follows. First, the number of measured aerosol components in the iQOS samples, with respect to those of 3R4F samples, was significantly lower (notably 37 versus 12 components). Second, the analysis of the iQOS and 3R4F GC-MS chromatographic fingerprints indicated a non-nicotine global component reduction (number and areas excluding nicotine) of larger than 80% for the iQOS samples in comparison to 3R4F samples. Third, the nicotine content of the iQOS aerosol was less than half that contained in the 3R4F smoke. The results from the present investigation indicate that—except for nicotine—smokers are exposed to a largely reduced number and amount of non-volatile, non-nicotine components in the iQOS heatstick aerosol, in comparison to those in the 3R4F cigarette smoke.
25.	**Shein, M., Jeschke, G. (2019). Comparison of Free Radical Levels in the Aerosol from Conventional Cigarettes, Electronic Cigarettes, and Heat-Not-Burn Tobacco Products. Chem Res Toxicol. 32(6):1289-1298.**
	Aerosols from electronic cigarettes and heat-not-burn tobacco products have been found to contain lower levels of almost all compounds from the list of Harmful and Potentially Harmful Constituents known to be present in tobacco products and tobacco smoke than smoke from conventional cigarettes. Free radicals, which also pose potential health risks, are not considered in this list, and their levels in the different product types have not yet been compared under standardized conditions. We compared the type and quantity of free radicals in mainstream aerosol of 3R4F research cigarettes, two types of electronic cigarettes, and a heat-not-burn tobacco product. Free radicals and NO in the gas phases were separately spin trapped and quantified by electron paramagnetic resonance (EPR) spectroscopy by using a smoking machine for aerosol generation and a flow-through cell to enhance reproducibility of the quantification. Particulate matter was separated by a Cambridge filter and extracted, and persistent radicals were quantified by EPR spectroscopy. Levels of organic radicals for electronic cigarettes and the heat-not-burn product, as measured with the PBN spin trap, did not exceed 1% of the level observed for conventional cigarettes and were close to the radical level observed in air blanks. The radicals found in the smoke of conventional cigarettes were oxygen centered, most probably alkoxy radicals, whereas a signal for carbon-centered radicals near the detection limit was observed in aerosol from the heat-not-burn product and electronic cigarettes. The NO level in aerosol produced by electronic cigarettes was below our detection limit, whereas for the heat-not-burn product, it reached about 7% of the level observed for whole smoke from 3R4F cigarettes. Persistent radicals in particulate matter could be quantified only for 3R4F cigarettes. Aerosols from vaping and heat-not-burn tobacco products have much lower free radical levels than cigarette smoke, however, the toxicological implications of this finding are as yet unknown.

Standard & System Toxicology	
26.	**Kirman, C.R., Simon, T.W., Hays, S.M. (2019). Science peer review for the 21st century: Assessing scientific consensus for decision-making while managing conflict of interests, reviewer and process bias. Regul Toxicol Pharmacol. 103:73-85.**
	Science peer review plays an important role in the advancement and acceptance of scientific information, particularly when used to support decision-making. A model for science peer review is proposed here using a large, multi-tiered case study to engage a broader segment of the scientific community to support decision making on science matters, and to incorporate many of the design advantages of the two common forms of peer review (journal peer review, science advisory panels). This peer review consisted of a two-tiered structure consisting of seven panels (five review panels in Tier 1, two review panels in Tier 2), which focused on safety data for a modified risk tobacco product (MRTP). Experts from all over the world were invited to apply to one or more positions on seven peer review panels. 66 peer reviewers were selected from available applicants using objective metrics of their expertise, and for some panels based upon a consideration of panel diversity with respect to demographic parameters (e.g., geographic region, sector of employment, years of experience). All peer reviewers participated anonymously in which a third-party auditor was used to provide independent verification of their expertise. Peer reviewers were provided electronic links to all review material which included access to publications, reports, omics data, and histopathology slides, with topic-specific panels focusing on topic-specific components of the review package. Peer reviews consisted either of single-round, or multi-round (e.g., modified Delphi) format. Peer reviewer responses to the charge questions were collected via an online survey system, and were assembled into a database. Responses in the database were subject to analyses to assess the degree of favorability (i.e., supportive of the review material), degree of consensus, reproducibility of replicate panels, hidden sources of bias, and outlier response patterns. Conclusions: By careful consideration of science peer review design elements we have shown that: 1) panel participation can be broadened to include scientists who would otherwise not participate; 2) panel diversity can be managed in an unbiased manner without adverse impacts to panel expertise; 3) results obtained from independent concurrent panels are shown to be reproducible; and 4) there are benefits of collecting input from expert panels via a structured format (i.e., survey) to support characterization of consensus, identification of hidden sources of bias, and identification of potential outlier
Clinical	
27.	**Gale, N., McEwan, M., Eldridge, A.C. et al. (2019). Changes in Biomarkers of Exposure on Switching From a Conventional Cigarette to Tobacco Heating Products: A Randomized, Controlled Study in Healthy Japanese Subjects. Nicotine Tob Res. 21(9):1220-1227.**
	Background: Smoking is a leading cause of numerous human disorders including pulmonary disease, cardiovascular disease, and cancer. Disease development is primarily caused by exposure to cigarette smoke constituents, many of which are known toxicants. Switching smokers

	to modified risk tobacco products (MRTPs) has been suggested as a potential means to reduce the risks of tobacco use, by reducing such exposure. Methods: This randomized, controlled study investigated whether biomarkers of toxicant exposure (BoE) were reduced when smokers switched from smoking combustible cigarettes to using a novel (*glo*™/THP1.0) or in-market comparator (*iQOS*/THS) tobacco heating product (THP). One hundred eighty Japanese smokers smoked combustible cigarettes during a 2-day baseline period, followed by randomization to either continue smoking cigarettes, switch to using mentholated or non-mentholated variants of *glo*™, switch to using a non-mentholated variant of *iQOS*, or quit nicotine and tobacco product use completely for 5 days. Baseline and post-randomization 24-h urine samples were collected for BoE analysis. Carbon monoxide was measured daily in exhaled breath (eCO). Results: On day 5 after switching, urinary BoE (excluding for nicotine) and eCO levels were significantly ($p < .05$) reduced by medians between 20.9% and 92.1% compared with baseline in all groups either using *glo*™ or *iQOS* or quitting tobacco use. Between-group comparisons revealed that the reductions in the glo™ groups were similar ($p > .05$) to quitting in many cases. Conclusions: *glo*™ or *iQOS* use for 5 days reduced exposure to smoke toxicants in a manner comparable to quitting tobacco use. THPs are reduced exposure tobacco products with the potential to be MRTPs. Implications: This clinical study demonstrates that when smokers switched from smoking combustible cigarettes to using tobacco heating products their exposure to smoke toxicants was significantly decreased. In many cases, this was to the same extent as that seen when they quit smoking completely. This may indicate that these products have the potential to be reduced exposure and/or reduced risk tobacco products when used by smokers whose cigarette consumption is displaced completely.
Behavioral	
28.	**Jones, J., Slayford, S., Gray, A. et al. (2020). A cross-category puffing topography, mouth level exposure and consumption study among Italian users of tobacco and nicotine products. Sci Rep. 10(1):12.**
	Actual use studies play a key part in evaluating the reduced risk potential of tobacco and nicotine products. This study was undertaken to determine the puffing topography, mouth level exposure (MLE) and average daily consumption (ADC) relating to two commercially available tobacco heating products (THPs) and a prototype electronic cigarette (or e-cigarette) among Italian non-mentholated 7 mg ISO tar cigarette smokers. The study was conducted in Milan, Italy, with three groups of approximately 50 participants. Groups 1 and 3 included adult smokers of 7 mg ISO tar tobacco cigarettes, and Group 2 consisted of both solus vapers and dual users of vapour and tobacco products. Amongst smokers, e-cigarette mean puff volumes (41.6 mL vs 41.3 mL) and mean puff durations (1.4 s vs 1.5 s) were similar to that of the cigarette, although the average usage session was significantly longer (1064.8 s vs 289.5 s) with a higher total number of puffs (58.6 vs 17.3), however this may be attributable to differences in product operation. There were no significant differences across puffing topography

	measurements observed between smokers (Group 1) and regular vapers/dual users (Group 2) when using the e-cigarette. As consistent with previous research, users took, on average, larger mean puff volumes when using a THP compared to the reference cigarette (C651), although puff numbers and puff durations remained similar. The average interval between puffs was considerably shorter for THP1.0(T) compared to THS2.4(T) (11.0 s vs 17.1 s). MLE to nicotine-free dry particulate matter and nicotine was significantly reduced for THP1.0(T) and THS2.4(T) compared to the tobacco cigarette (C651). MLE to nicotine was also significantly reduced for the e-cigarette (IS1.0(T)) compared to C651. The average daily consumption (ADC) of cigarettes by groups 1 and 3 were higher than the respective ADCs of both THP consumables. There were no significant differences in ADC when comparing the same product between different groups. Differences seen between sensory scores for each of the product categories may be attributed to fundamental differences in design and mode of operation resulting in very different characteristics of the aerosol generated.
Others	
29.	**Baidildinova, G.K., Mukhanova S.K., Sergaz, Sh. D. et al. (2019). Estimating a probability of reducing risks associated with smoking conventional cigarettes using the THS 2.2 (IQOS) technology. Meditsina (Almaty) = Medicine (Almaty). 2(200):42-50.**
	Objective: The aim of the current review was the collection and analysis of information about the tobacco heating system (THS) (commercialized as *IQOS*™) technology in comparison with conventional cigarettes (CC). Material and methods: The collection of data was performed with the help of PubMed database and other relevant sources including the website of official health regulating bodies (e.g., FDA, WHO, Publlic Health England) for articles published until 15 February 2018 that contained key phrases as "IQOS", "tobacco heating systems" ("THS"), "heat-not-burn", and other sources where the following characteristics of *IQOS* (THS 2.2) were described: chemical composition of the aerosol, studies conducted in vitro and in vivo, as well as clinical studies, and other relevant information such as potential THS aerosol carcinogenic properties, awareness, comments by critics, and others. Result and discussion: The results of the available information indicate that, THS aerosol is much less toxic comparing with CC smoke and can significantly reduce the harm and risk of development of tobacco-related diseases for smokers. However, it is advised to conduct the experiments with the expended list of Harmful and Potentially Harmful Consituents (HPHC) from FDA list. There is also a need in clinical research of a longer period with the racial diversity of subjects where the biomarkers corresponding to various tobacco disease condition could be studied. Conclusion: The use of THS technology could lead to significant reduction of risk harm. However, it still poses a risk and cannot be recognized as completely safe.

30.	**Marszałek, D., Niewada, M., Mela, A. et al. (2019). Comparison of tobacco heating products and conventional cigarette: a systematic review. J Health Policy Outcomes Res. 2.**
	Heat-not-burn products, which are supposed to reduce the harmful effects of exposure to cigarette smoke components (harm reduction approach), are under development. Comprehensive evaluation of the newest available on the market tobacco heating products (THPs) in comparison with conventional cigarettes (CC) within pre-clinical and clinical studies. A systematic review of the literature was performed in MEDLINE, EMBASE, The Cochrane Library, Center for Reviews and Dissemination databases. Primary clinical studies from the highest level of credibility (randomized controlled clinical trials), evaluating the use of THP compared to the use of a CC by smokers were searched. Additionally in order to study impact of passive smoking on health, pre-clinical studies and studies evaluating indoor air quality were included. In the review 9 randomized clinical trials, 37 pre-clinical studies and 6 studies evaluating the impact of heat-not-burn products on indoor air quality were included. Studies demonstrated that switching from CC to THP is associated with reduction of harmful and potentially harmful constituents' exposure and probable less harm in clinical risk markers in comparison with the continuation of smoking conventional cigarettes while maintaining comparable nicotine delivery. Results suggest no negative impact on indoor air quality when using THP in an indoor environment. THPs compared to CC smoking (within the analyzed risk factors) shows a tendency to limit negative health influence. The assessment of heat-not-burn product impact on the risk of smoking-related diseases requires further research and long-term observations.

Table 3: Independent Scientific Publications

Chemistry and Physics	
31.	**Cancelada, L., Sleiman, M., Tang, X. et al. (2019). Heated Tobacco Products: Volatile Emissions and Their Predicted Impact on Indoor Air Quality. Environ Sci Technol. 53(13):7866-7876.**
	This study characterized emissions from *IQOS*, a heated tobacco product promoted as a less harmful alternative to cigarettes. Consumable tobacco plugs were analyzed by headspace GC/MS to assess the influence of heating temperature on the emission profile. Yields of major chemical constituents increased from 4.1 mg per unit at 180 degrees C to 6.2 mg at 200 degrees C, and 10.5 mg at 220 degrees C. The Health Canada Intense smoking regime was used to operate *IQOS* in an environmental chamber, quantifying 33 volatile organic compounds in mainstream and sidestream emissions. Aldehydes, nitrogenated species, and aromatic species were found, along with other harmful and potentially harmful compounds. Compared with combustion cigarettes, IQOS yields were in most cases 1-2 orders of magnitude lower. However, yields were closer to, and sometimes higher than electronic cigarettes. Predicted users' daily average intake of benzene, formaldehyde, acetaldehyde and acrolein were 39 mug, 32 mug, 2.2 mg and 71 mug, respectively. Indoor air concentrations were estimated for commonly encountered scenarios, with acrolein levels of concern (over 0.35 mug m(-3)) derived from *IQOS* used in homes and public spaces. Heated tobacco products are a weaker indoor pollution source than conventional cigarettes, but their impacts are neither negligible nor yet fully understood.
32.	**Davis, B., Williams, M., Talbot, P. (2019). iQOS: evidence of pyrolysis and release of a toxicant from plastic. Tob Control. 28(1):34–41.**
	Objective: To evaluate performance of the I quit original smoking (*iQOS*) heat-not-burn system as a function of cleaning and puffing topography, investigate the validity of manufacturer's claims that this device does not burn tobacco and determine if the polymer-film filter is potentially harmful. Methods: *iQOS* performance was evaluated using five running conditions incorporating two different cleaning protocols. Heatsticks were visually and stereomicroscopically inspected preuse and postuse to determine the extent of tobacco plug charring (from pyrolysis) and polymer-film filter melting, and to elucidate the effects of cleaning on charring. Gas chromatography–mass spectrometry headspace analysis was conducted on unused polymer-film filters to determine if potentially toxic chemicals are emitted from the filter during heating. Results: For all testing protocols, pressure drop decreased as puff number increased. Changes in testing protocols did not affect aerosol density. Charring due to pyrolysis (a form of organic matter thermochemical decomposition) was observed in the tobacco plug after use. When the manufacturer's cleaning instructions were followed, both charring of the tobacco plug and melting of the polymer-film filter

	increased. Headspace analysis of the polymer-film filter revealed the release of formaldehyde cyanohydrin at 90°C, which is well below the maximum temperature reached during normal usage. Discussion: Device usage limitations may contribute to decreases in interpuff intervals, potentially increasing user's intake of nicotine and other harmful chemicals. This study found that the tobacco plug does char and that charring increases when the device is not cleaned between heatsticks. Release of formaldehyde cyanohydrin is a concern as it is highly toxic at very low concentrations.
33.	**Ishizaki, A., Kataoka, H. (2019). A sensitive method for the determination of tobacco-specific nitrosamines in mainstream and sidestream smokes of combustion cigarettes and heated tobacco products by online in-tube solid-phase microextraction coupled with liquid chromatography-tandem mass spectrometry. Analytica Chimica Acta. 1075:98-105.**
	A simple and sensitive method, using automated online in-tube solid-phase microextraction (SPME) coupled with liquid chromatography-tandem mass spectrometry (LC-MS/MS), was developed for the determination of four tobacco-specific nitrosamines (TSNAs) in mainstream and sidestream smoke of combustion cigarettes and heated tobacco products. These TSNAs were separated within 4 min on a Capcell Pak C18 MGⅢ column and detected in the positive ion mode by multiple reaction monitoring. The optimum in-tube SPME conditions were 30 draw/eject cycles of 40 µL of sample at a flow rate of 200 µL min−1 using a Supel-Q PLOT capillary column as an extraction device. The extracted TSNAs were easily desorbed from the column by passage of the mobile phase, with no carryover observed. This in-tube SPME LC–MS/MS method showed good linearity for four TSNAs in the 0.5–100 pg mL−1 ranges, with correlation coefficients above 0.9998 (n = 24), using stable isotope-labeled TSNAs as internal standards. The validation assays for limit of detection, limit of quantification, specificity, precision and accuracy of the analytes were consistent with the requirements recommended by the ICH guidelines. The validated method was utilized successfully to analyze four TSNAs in mainstream and sidestream smoke samples without any interference peaks. Overall recoveries of TSNAs spiked into smoke sample solutions were 97.3–104.6%. The developed method can automate the extraction, concentration and analysis of samples, and is sensitive and selective for TSNAs. This method was used to analyze TSNAs in mainstream and sidestream smoke samples of several commercially available combustion cigarettes and heated tobacco products. Results: The TSNA contents were significantly lower in the mainstream smoke of heated tobacco products than in the mainstream smoke of combustion cigarettes or else were not detectable. These differences may be due to the temperatures of combustion cigarettes (460 C) and heated tobacco products (250 - 260 C). These results suggest that combustion cigarettes are more harmful than heated tobacco products.

34.	**Jeong, W. T., Cho, H. K., Lee, H. R. et al. (2019). Comparison of the content of tobacco alkaloids and tobacco-specific nitrosamines in 'heat-not-burn' tobacco products before and after aerosol generation. Inhalation Inhal Toxicol. 30(13-14): 527-533.**
	Standardized methods for collecting smoke and for measuring smoke components in heat not burn tobacco product (HTP) are yet to be established, and there is a lack of consensus as to whether the content of HTP cigarettes can be assayed in the same manner as for conventional cigarettes. Since HTP cigarettes do not generate ash when smoked, we compared the levels of tobacco alkaloids (TAs) and tobacco-specific nitrosamines (TSNAs) of HTP cigarettes before and after aerosol generation. HTP cigarettes were smoked according to two international standardization methods. The TAs and TSNAs contents of the cigarettes were analyzed by UPLC-Q-TOF and UPLC-MSMS, respectively. Smoking was found to significantly decrease the content of nicotine, nornicotine, anatabine, and anabasine by 53 ~100% in all samples, and the maximum inhalable amounts of these entities were determined to be 4.24 µg /cig, 103.52 µg /cig, 258.72 µg/cig, and 33.03 µg /cig, respectively. By contrast, smoking significantly increased the content of NNK and NAB. We suggested that the reduced nicotine content minus the nicotine content remaining in the filter is an amount that could potentially be inhaled during smoking. The increase of NNK and NAB in HTP cigarette after aerosol generation is expected to be caused by the precursor, but more specific behavioral studies should be performed.
35.	**Li, X., Luo, Y., Jiang, X. et al. (2019). Chemical Analysis and Simulated Pyrolysis of Tobacco Heating System 2.2 Compared to Conventional Cigarettes. Nicotine Tob Res. 21(1):111-118.**
	Introduction: Tobacco Heating System 2.2 (THS 2.2, marketed as *iQOS*) is a heat-not-burn (HNB) tobacco product that has been successfully introduced to global markets. Despite its expanding market, few independent and systematic researches into THS 2.2 have been carried out to date. Methods: We tested a comprehensive list of total particulate matter (TPM), water, tar, nicotine, propylene glycol, glycerin, carbon monoxide, volatile organic compounds, aromatic amines, hydrogen cyanide, ammonia, N-nitrosamines, phenol, and polycyclic aromatic hydrocarbon under both ISO and HCI regimes. We also simulated pyrolysis of THS 2.2 heating sticks and made comparisons with conventional cigarette tobacco fillers using comprehensive gas chromatography-mass spectrometry (GC × GC-MS) to determine whether the specially designed ingredients help reduce harmful constituents. Results: Other than some carbonyls, ammonia, and N-nitrosoanabasine (NAB), the delivered releases from THS 2.2 were at least 80% lower than those from 3R4F. Tar and nicotine remained almost the same as 3R4F. Interestingly, the normalized yield of THS 2.2 to 3R4F under the HCI regime was lower than that under the ISO regime.

	Conclusions: THS 2.2 delivered fewer harmful constituents than the conventional cigarette 3R4F. Simulated pyrolysis results showed that the lower temperature instead of specially designed ingredients contributed to the distinct shift. In particular, if smoking machines are involved to evaluate the HNB products, smoking regimes of heat-not-burn tobacco products should be carefully chosen. Implications: To our knowledge, few independent studies of HNB products have been published. In this paper, a comprehensive list of chemical releases was tested systematically and compared to those from 3R4F. Although THS 2.2 generates lower levels of harmful constituents, the nicotine and tar levels were almost identical to 3R4F.The results should be discussed carefully in the future when assessing the dual-use with other conventional cigarettes, nicotine dependence of HNB products, etc. This study also suggests that regulatory agencies should pay attention to the smoking regimes that are adopted to evaluate HNB tobacco products.
36.	**Loupa, G., Karali, D., Rapsomanikis, S. (2019). The trace of airborne particulate matter from smoking e-cigarette, tobacco heating system, conventional and hand-rolled cigarettes in a residential environment. Air Qual Atmos Health. 12: 1449-1457.**
	Indoor particle number concentrations and size distributions were monitored in a typical, residential living room, considering two independent variables: smoking activities (using e-cigarettes, tobacco heating systems (THS), conventional and hand-rolled cigarettes) and the operation of the air conditioning (AC) system. Each smoking device exhibited its own characteristic size distribution (its own "trace"), in the room atmosphere, which was also affected by the AC operation. All devices emitted ultrafine and fine particles especially in the range around 100 nm. The minimum average PM number or mass concentrations in any size were observed for the THS (either with the AC on or off). The PM1 number concentrations were maximum when conventional cigarettes were smoked, especially when the AC was off. In the case of the coarse particles, the PM(1–10) number concentrations were maximum when hand-rolled cigarettes were smoked (and AC was on). When the AC was off, the maximum PM(1–10) number concentration was recorded when the e-cigarette was used. The effect of the AC on particle number concentrations depended on their size and their origin. A factorial ANOVA corroborated that the two independent variables affected significantly (at $p < 0.05$) the airborne PM number concentrations. Specifically, low versus high air temperature, fan operation or not, affected differently particles in different size ranges and for different smoking activities.
37.	**Meehan-Atrash, J., Duell, A.K., McWhirter, K.J. et al. (2019). Free-Base Nicotine Is Nearly Absent in Aerosol from *IQOS* Heat-Not-Burn Devices, As Determined by 1H NMR Spectroscopy. Chem Res Toxicol. 32(6):974-976.**
	Heat-not-burn products, eg, I quit ordinary smoking (*IQOS*), are becoming popular alternative tobacco products. The nicotine aerosol protonation state has addiction implications due to differences in absorption kinetics and harshness. Nicotine free-base fraction (αfb) ranges from 0 to 1. Herein, we report αfb for *IQOS* aerosols by exchange-averaged ^{1}H NMR chemical shifts of the nicotine methyl protons in bulk aerosol and verified by headspace-solid phase microextraction-gas chromatography-mass spectrometry. The αfb ≈ 0 for products

	tested; likely a result of proton transfer from acetic acid and/or other additives in the largely aqueous aerosol. Others reported higher αfb for these products, however, their methods were subject to error due to solvent perturbation.
38.	**Salman, R., Talih, S., El-Hage, R., et al. (2019). Free-Base and Total Nicotine, Reactive Oxygen Species, and Carbonyl Emissions From IQOS, a Heated Tobacco Product. Nicotine Tob Res. 21(9): 1285-1288.**
	Introduction: *IQOS* is an emerging heated tobacco product marketed by Philip Morris International (PMI). Because the tobacco in *IQOS* is electrically heated and not combusted, PMI claims that it generates significantly lower toxicant levels than combustible cigarettes. To date, a few independent studies have addressed *IQOS* toxicant emissions, and none have reported reactive oxygen species (ROS), and the form of the nicotine emitted by the device. Methods: In this study, *IQOS* aerosol was generated using a custom-made puffing machine. Two puffing regimens were used: Health Canada Intense and ISO. ROS, carbonyl compounds (CCs), and total nicotine and its partitioning between free-base and protonated forms were quantified in the *IQOS* aerosol by fluorescence, high-performance liquid chromatography, and gas chromatography, respectively. The same toxicants were also quantified in combustible cigarette aerosols for comparison. In addition, propylene glycol and vegetable glycerin were also measured in the *IQOS* tobacco and aerosol. Results: *IQOS* and combustible cigarettes were found to emit similar quantities of total and free-base nicotine. *IQOS* total ROS (6.26 ± 2.72 nmol H_2O_2/session) and CC emissions (472 ± 19 µg/session) were significant, but 85% and 77% lower than levels emitted by combustible cigarettes. Conclusions: IQOS emits harmful constituents that are linked to cancer, pulmonary disease, and addiction in cigarette smokers. For a given nicotine intake, inhalation exposure to ROS and CCs from *IQOS* is likely to be significantly less than that for combustible cigarettes. Implications: *IQOS* is PMI's new heated tobacco product. PMI claims that because *IQOS* heats and does not burn tobacco it generates low toxicant yields. We found that one *IQOS* stick can emit similar free-base and total nicotine yields as a combustible cigarette. A pack-a-day equivalent user of *IQOS* may experience significant inhalation exposure of ROS and CCs compared to background air. However, substituting *IQOS* for combustible cigarettes will likely result in far lower ROS and carbonyl inhalation exposure for a given daily nicotine intake.
39.	**Schober, W., Fembacher, L., Frenzen, A. et al. (2019). Passive exposure to pollutants from conventional cigarettes and new electronic smoking devices (*IQOS*, e-cigarette) in passenger cars. Int J Hyg Environ Health. 222(3):486-493.**
	Smoking in car interiors is of particular concern because concentrations of potentially harmful substances can be expected to be high in such small spaces. To assess the potential exposure for occupants, especially children, we performed a comprehensive evaluation of the pollution in 7 passenger cars while tobacco cigarettes and new electronic smoking products (*IQOS*, e-cigarette) were being smoked. We collected data

	on the indoor climate and indoor air pollution with fine and ultrafine particles and volatile organic compounds while the cars were being driven. Smoking of an *IQOS* had almost no effect on the mean number concentration (NC) of fine particles (>300 nm) or on the PM2.5 concentration in the interior. In contrast, the NC of particles with a diameter of 25–300 nm markedly increased in all vehicles (1.6–12.3 × 104/cm^3). When an e-cigarette was vaped in the interior, 5 of the 7 tested cars showed a strong increase in the PM2.5 concentration to 75–490 µg/m^3. The highest PM2.5 levels (64-1988 µg/m^3) were measured while tobacco cigarettes were being smoked. With the e-cigarette, the concentration of propylene glycol increased in 5 car interiors to 50–762 µg/m^3, whereby the German indoor health precaution guide value for propylene glycol was exceeded in 3 vehicles and the health hazard guide value in one. In 4 vehicles, the nicotine concentration also increased to 4–10 µg/m^3 while the e-cigarette was being used. The nicotine concentrations associated with the *IQOS* and e-cigarette were comparable, whereas the highest nicotine levels (8–140 µg/m^3) were reached with tobacco cigarettes. Cigarette use also led to pollution of the room air with formaldehyde (18.5–56.5 µg/m^3), acetaldehyde (26.5–141.5 µg/m^3), and acetone (27.8–75.8 µg/m^3). Tobacco cigarettes, e-cigarettes, and the IQOS are all avoidable sources of indoor pollutants. To protect the health of other non-smoking passengers, especially that of sensitive individuals such as children and pregnant women, these products should not be used in cars.
Standard & System Toxicology	
40.	**Davis B., To V., Talbot P. (2019). Comparison of cytotoxicity of *IQOS* aerosols to smoke from marlboro Red and 3R4F reference cigarettes. Toxicol In Vitro. 61: 104652.**
	This study compared the cytotoxicity of *IQOS* aerosols to smoke from *Marlboro* Red (MR) and 3R4F reference cigarettes. Aerosol/smoke solutions were tested as the gas vapor phase (GVP), particulate phase (total particulate matter or TPM), or whole aerosol/smoke (WA), the latter being what smokers actually inhale. Cytotoxicities were evaluated using the LDH, MTT and neutral red uptake (NRU) assays in conjunction with eight different cell types, mainly from the respiratory system. Most test solutions did not compromise the plasma membranes of cells (LDH). However, mitochondrial activity (MTT) and dye uptake/lysosomal activity (NRU) were equally depressed by IOQS aerosols and cigarette smoke solutions at the high concentrations. Our NRU data with mouse 3T3 transformed fibroblasts were similar to those previously reported by the IQOS manufacturer and showed little cytotoxicity in the NRU assay. In both studies with 3T3 cells, the results were significantly different from 3RF4 cigarette smoke, suggesting reduced toxicity with *IQOS*.

	However, by expanding evaluations to a broader spectrum of cells that included respiratory system cells and by including higher concentrations of GVP, as well as WA, cytotoxicity equivalent to that of *Marlboro* Red and 3R4F cigarettes was frequently observed with *IQOS* aerosols in the MTT and NRU assays.
41.	**Sohal, S., Eapen, M., Naidu, V. et al. (2019). IQOS exposure impairs human airway cell homeostasis: direct comparison with traditional cigarette and e-cigarette. ERJ Open Res. 5(1): 00159-2018.**
	While cigarette smoking still remains one of the most pressing global health issues of our time, newer forms of smoking device have been introduced across the globe in the last decade. Electronic nicotine/non-nicotine delivery systems commonly known as electronic cigarettes (eCig) heat a solution (e-liquid) to create vapour; the latest addition to this list is the introduction of heat-not-burn (HNBs) tobacco products branded as IQOS. HNBs are hybrids between eCigs and traditional cigarettes i.e., they are equipped with a device that heats the product, without burning to generate aerosol and the product being heated is not a liquid but real tobacco. We used human bronchial epithelial cells (Beas-2B, ATCC CRL-9609) and primary human airway smooth muscle (ASM) cells (ATCC PCS-130-010). eCig vapour was generated using an eCig device (KangerTech 3rd Generation; KangerTech, Shenzhen, China) and e-liquid (Blu, Charlotte, NC, USA) (1.2% nicotine); *IQOS* aerosol was generated using HNB heat-sticks (Philip Morris, Tokyo, Japan) (1.4 mg nicotine); and cigarette-smoke-extract (CSE) was generated using *Marlboro* Red cigarettes (Philip Morris, Washington, DC, USA) (1.2 mg nicotine). eCig vapour/*IQOS* aerosol/cigarette smoke was "bubbled" through a T-75 flask containing 25-mL media at a constant rate with modification. This freshly generated (100%) eCig vapour, IQOS aerosol and CSE were diluted to the final working concentration and used immediately. Beas-2B or primary human ASM cells were treated with increasing concentrations of CSE, eCig vapour or IQOS aerosol for 72 h, and cell cytotoxicity (Thaizolyl blue tetrazolium bromide (MTT) and lactate dehydrogenase (LDH)), chemokine release (CXCL8), extracellular matrix (ECM) (collagen 1 and fibronectin) release and mitochondrial respiration (glycolysis and proton leak) were measured. GraphPad (La Jolla, CA, USA) was used for statistical analysis using one-way ANOVA followed by Bonferroni's multiple comparison test. Given our current findings and those of previous studies, in a manner very similar to cigarette smoke and eCigs, IQOS has the potential to increase oxidative stress and inflammation, infections, airway remodelling and initiate EMT-related changes in the airways of users of these devices. However, prospective clinical studies must be conducted to verify our in vitro, cell-based but highly important and novel findings on *IQOS*. Heat-not-burn (HNB) devices can alter vital physiological functions in the lung. HNB devices may not be a safer option than cigarette smoking or eCig vaping; this does not support the recommendation of their use over other nicotine delivery products.

42.	**Zagoriti, Z., El Mubarak, M.A., Farsalinos, K. et al. (2020). Effects of Exposure to Tobacco Cigarette, Electronic Cigarette and Heated Tobacco Product on Adipocyte Survival and Differentiation In Vitro. Toxics 8(1): 9.**
	Cigarette smoking (CS) causes significant morbidity worldwide, attributed to the numerous toxicants generated by tobacco combustion. Electronic cigarettes (ECIG) and heated tobacco products (HTP) are considered alternative smoking/vaping products that deliver nicotine through an inhaled aerosol and emit fewer harmful constituents than CS. However, their long-term impacts on human health are not well established. Nicotine exposure has been linked to lipolysis and body weight loss, while smoking has been associated with insulin resistance and hyperinsulinemia. Enhanced function of beige (thermogenic) adipocytes has been proposed as a means to reduce obesity and metabolic disorders. In this study, we compared the effect of extract-enriched media via exposure of culture medium to CS, HTP aerosol, and ECIG aerosol on the viability and the differentiation of 3T3-L1 pre-adipocytes to beige adipocytes. Only CS extract caused a decrease in cell viability in a dose- and time-dependent manner. Furthermore, relative lipid accumulation and expression levels of the adipocyte markers Pgc-1α, Ppar-γ and Resistin were significantly decreased in cells exposed to CS extract. Our results demonstrate that CS extract, in contrast to HTP and ECIG extracts, significantly impairs differentiation of pre-adipocytes to beige adipocytes and may therefore impact significantly adipose tissue metabolic function.
Clinical	
43.	**Beatrice, F., Massaro, G. (2019). Exhaled Carbon Monoxide Levels in Forty Resistant to Cessation Male Smokers after Six Months of Full Switch to Electronic Cigarettes (e-Cigs) or to A Tobacco Heating Systems (THS). Int J Environ Res Public Health. 16(20): 3916.**
	Cigarette smoke releases several toxic chemicals and carcinogens including carbon monoxide (CO). This study examined the levels of exhaled CO in smokers switching to electronic cigarettes (e-Cigs) or a tobacco heating system (THS) and their level of compliance six months after switching. On the basis of their own preferences, 40 male smokers unwilling or unable to stop smoking were switched to e-Cigs or THSs for six months (20 subjects in each group). Nicotine addiction and levels of carbon monoxide in the exhaled breath (eCO) were measured at baseline (the latter also at six months). The Shapiro Wilk test, graphical methods, Student T test or Mann–Whitney test were used to assess the normal distribution of variables and differences between the two groups after six months. The two groups showed no difference at baseline, but a significant higher addiction score in smokers choosing THS. E-Cig and THS showed significant reduced levels of eCO (both %COHb and COppm) after six months, which were within the range of non-smoker status. Reduced levels of %COHb did not significantly differ between the two groups, whilst the THS group had a significantly lower reduction in levels of COppm vs the e-Cig group ($p < 0.05$).

	Both e-Cigs and THSs are capable of significantly reducing eCO at least in the medium term, hence constituting a viable tobacco harm reduction approach in smokers who are unwilling or unable to stop smoking.
44.	**Biondi-Zoccai, G., Sciarretta, S., Bullen, C. et al. (2019). Acute Effects of Heat-Not-Burn, Electronic Vaping, and Traditional Tobacco Combustion Cigarettes: The Sapienza University of Rome-Vascular Assessment of Proatherosclerotic Effects of Smoking (SUR - VAPES) 2 Randomized Trial. J Am Heart Assoc. 8(6):e010455.**
	Background: Little clinical research on new-generation heat-not-burn cigarettes (HNBC) in comparison with electronic vaping cigarettes (EVC) and traditional tobacco combustion cigarettes (TC) has been reported. We aimed to appraise the acute effects of single use of HNBC , EVC, and TC in healthy smokers. Methods and Results: This was an independent, cross-over, randomized trial in 20 TC smokers, with allocation to different cycles of HNBC, EVC, and TC. All participants used all types of products, with an intercycle washout of 1 week. End points were oxidative stress, antioxidant reserve, platelet activation, flow-mediated dilation, blood pressure, and satisfaction scores. Single use of any product led to an adverse impact on oxidative stress, antioxidant reserve, platelet function, flow-mediated dilation, and blood pressure. HNBC had less impact than EVC and TC on soluble Nox2-derived peptide (respectively, P=0.004 and 0.001), 8-iso-prostaglandin F2α- III (P=0.004 and <0.001), and vitamin E (P=0.018 and 0.044). HNBC and EVC were equally less impactful than TCs on flow-mediated dilation (P=0.872 for HNBC versus EVC), H_2O_2 (P=0.522), H_2O_2 breakdown activity (P=0.091), soluble CD 40 ligand (P=0.849), and soluble P-selectin (P=0.821). The effect of HNBC and, to a lesser extent EVC , on blood pressure was less evident than that of TC, whereas HNBC appeared more satisfying than EVC (all P<0.05). Conclusions: Acute effects of HNBC , EVC, and TC are different on several oxidative stress, antioxidant reserve, platelet function, cardiovascular, and satisfaction dimensions, with TCs showing the most detrimental changes in clinically relevant features.
45.	**Frati, G., Carnevale, R., Nocella, C. et al. (2020). Profiling the Acute Effects of Modified Risk Products: Evidence from the SUR-VAPES (Sapienza University of Rome-Vascular Assessment of Proatherosclerotic Effects of Smoking) Cluster Study. Curr Atheroscler Rep. 22: 8.**
	Purpose of Review: Modified risk products (MRP) are promoted as a safer alternative to traditional combustion cigarettes (TCC) in chronic smokers. Evidence for their lower hazardous profile is building, despite several controversies. Yet, it is unclear whether individual responses to MRP differ among consumers. We hypothesized that different clusters of subjects exist in terms of acute effects of MRP. Recent Findings: Pooling data from a total of 60 individuals, cluster analysis identified at least three clusters (labelled 1 to 3) of subjects with different electronic vaping cigarettes (EVC) effects and at least two clusters (labelled 4 to 5) of subjects with different heat-not-burn cigarettes (HNBC) effects. Specifically, oxidative stress, platelet aggregation, and endothelial dysfunction after EVC were significantly different cluster-wise (all $p < 0.05$), and oxidative stress and platelet aggregation after HNBC were significantly different (all $p < 0.05$). In

	particular, subjects belonging to Cluster 1 appeared to have less detrimental responses to EVC usage than subjects in Cluster 2 and 3, as shown by non-significant changes in flow-mediated dilation (FMD) and less marked increase in Nox2-derived peptide (NOX). Conversely, those assigned to Cluster 3 had the worst reaction in terms of changes in FMD, NOX, and P-selectin. Furthermore, individuals belonging to Cluster 4 responded unfavorably to both HNBC and EVC, whereas those in Cluster 5 interestingly showed less adverse results after using HNBC than EVC. Results for main analyses were consistent employing different clusters, tests, and bootstrap. Summary: Individual responses to MRP differ and smokers aiming at using EVC or HNBC as a risk reduction strategy should consider trying different MRP aiming at finding the one which is less detrimental, with subjects resembling those in Cluster 1 preferably using EVC and those resembling Cluster 5 preferably using HNBC.
46.	**Maloney, S., Eversole, A., Crabtree, M. et al. (2020). Acute effects of JUUL and IQOS in cigarette smokers. Tob control. doi: 10.1136/tobaccocontrol-2019-055475.**
	Background: *JUUL* is an electronic cigarette that aerosolises a nicotine-containing liquid, while *IQOS* heats tobacco to produce an aerosol. Both are marketed to smokers, but their effects have seldom been examined in this population. Methods: Eighteen cigarette smokers (13 men) with no *JUUL* or *IQOS* experience completed a within-subject, laboratory study assessing nicotine delivery and subjective effects after controlled (10 puffs, ~30 s interpuff interval) and ad libitum (90 min) use of *JUUL*, *IQOS* or own-brand (OB) cigarettes. Results: *JUUL* increased mean plasma nicotine concentration significantly from 2.2 (SD=0.7) ng/mL to 9.8 (4.9) ng/mL after 10 puffs and to 11.5 (9.3) ng/mL after ad libitum use. *IQOS* increased mean plasma nicotine significantly from 2.1 (0.2) ng/mL to 12.7 (6.2) ng/mL after 10 puffs and to 11.3 (8.0) ng/mL after ad libitum use. OB increased mean plasma nicotine significantly from 2.1 (0.2) ng/mL to 20.4 (11.4) ng/mL after 10 puffs and to 21.0 (10.2) ng/mL after ad libitum use. Mean OB plasma nicotine concentration was significantly higher than *JUUL* and *IQOS*. OB increased expired carbon monoxide concentration, but *IQOS* and *JUUL* did not. 'Craving a cigarette/nicotine' and 'Urges to smoke' were reduced significantly for all products following the directed bout. Conclusions: Among smokers, *JUUL* and *IQOS* delivered less nicotine than cigarettes. Also, in this sample, *IQOS* and OB reduced abstinence symptoms more effectively than *JUUL*. Additional work with experienced *JUUL* and *IQOS* users is needed, as their nicotine delivery profiles and subjective experiences may differ.

Behavioral	
47.	**Czoli, C.D., White, C.M., Reid, J.L. et al. (2020). Awareness and interest in IQOS heated tobacco products among youth in Canada, England and the USA. Tob Control. 29(1): 89-95.**
	Introduction: Heated tobacco products (HTPs), such as *IQOS*, have been introduced in a growing number of international markets. However, little is known about perceptions of HTP products among youth. Methods: Data are from wave 1 of the International Tobacco Control Youth Tobacco and E-cigarette Survey (2017), a web-based cohort survey of people aged 16–19 years from Canada, England and the USA. Respondents (n=12 064) were shown an image of *IQOS* and asked about their awareness, interest in trying and susceptibility to trying the product. Youth awareness, interest in trying and susceptibility to trying *IQOS* were analysed using descriptive statistics, and logistic regression models were used to examine correlates of these outcomes. Results: Overall, 7.0% of youth reported awareness of *IQOS* (England=5.6%, Canada=6.4% and USA=9.1%) and 38.6% expressed interest in trying the product (England=41.8%, Canada=33.0% and USA=40.9%). Within each country, all key outcomes varied by smoking status: greater proportions of youth who were currently smoking or had a history of smoking reported being aware of, interested in trying and susceptible to trying *IQOS*. Interest and susceptibility to trying IQOS were associated with male sex, current tobacco use and current e-cigarette use. Across all countries, susceptibility to trying IQOS (25.1%) was higher than for tobacco cigarettes (19.3%), but lower than for e-cigarettes (29.1%). Conclusions: Awareness of HTPs, such as *IQOS*, is emerging among youth in Canada, England and the USA. Interest in trying these products is very high among smokers, but also present among non-smokers.
48.	**Dunbar, M.S., Seelam, R., Tucker, J.S. et al. (2020). Correlates of Awareness and Use of Heated Tobacco Products in a Sample of US Young Adults in 2018-2019. Nicotine Tob Res.**
	Introduction: Tobacco companies have devoted increased resources in recent years to developing and marketing heated tobacco products (HTPs) as alternatives to combustible products like cigarettes. However, little is known about correlates of awareness and use of these products in American young adults. Methods: Two thousand four hundred ninety-seven young adults (mean age = 21.6) completed survey items on HTP awareness and lifetime use in 2018-2019. Logistic regression models compared young adults who were (1) unaware of HTPs (reference group) with those who were, (2) aware of HTPs, and (3) had ever used HTPs on demographic, tobacco, and other substance use characteristics. Among current smokers, these groups were compared on cigarette use, dependence, and readiness to quit. Results: Approximately 12% of respondents (n = 293) were aware of HTPs, and 5% (n = 134) reported lifetime HTP use. Controlling for demographics, HTP awareness and use were both associated with greater use of all types of tobacco products, number of different tobacco

	products, and use of marijuana and other drugs. Among current smokers, HTP awareness and use correlated with heavier cigarette consumption, greater dependence, and past-month marijuana use, but not with recent quit attempts or thinking about quitting cigarettes. Conclusions: Awareness and use of HTPs among young adults were associated with greater use of tobacco products and other substances and, among current smokers, with greater cigarette dependence (but not cessation-related factors). As these products become increasingly available in the United States, additional surveillance and monitoring activities are needed to better understand use patterns, consequences, and reasons for using HTPs. Implications: Few studies have examined factors associated with awareness and use of heated tobacco products (HTPs) among US young adults. HTP awareness and lifetime use correlated with a range of factors, including male gender, white race/ethnicity, and tobacco and other substance use. Lifetime use of HTPs was low (5%); most lifetime HTP users reported history of other tobacco use, but a sizeable minority (14%) reported no other tobacco product use history. Among current cigarette smokers, cigarette dependence, poly-tobacco use, and marijuana use-but not cigarette cessation attempts or contemplation-were associated with greater likelihood of awareness and use of HTPs.
49.	**Fung, M.D.T., Diemert, L.M., Zhang, B. et al. (2020). Awareness and Perceived Risk of Heated Tobacco Products. Tob Regul Sci. 6(1): 15-19.**
	Objectives: Heated tobacco products (such as *IQOS*) and e-cigarettes have been introduced and advertised in a variety of ways despite inconclusive evidence regarding their safety and benefit for smoking cessation. In this study, we examine the awareness, use, and perceived risk of these products among recent smokers. Methods: In 2017, we conducted an online survey of 727 current and recent smokers in Ontario. We asked participants about their awareness, use, and perceived risk of heated tobacco products and e-cigarettes. Results: Among respondents, 10% were aware of heated tobacco products, and 3% had ever used them. Compared to non-ecigarette users, e-cigarette users were more likely to agree with statements that heated tobacco is less harmful than regular cigarettes, e-cigarette use is less harmful than regular cigarettes, and both products can help smokers stop smoking regular cigarettes. Conclusions: Respondents who used e-cigarettes were more likely to have positive perceptions about heated tobacco and may be more susceptible to the marketing of these products. It is important to monitor the use of multiple nicotine products to inform policies and programming for these products.

50.	**La Torre, G., Dorelli, B., Ricciardi, M. (2019). Smoking E-Cigarette and Heat-not-Burn products: validation of the SECRHET questionnaire. Clin Ter. 170(4):e247-e251.**
	Background: The nicotine market has rapidly evolved with the emergence of newer forms of smoking device that have been expanded worldwide, such as electronic cigarettes (eCig) which heat a solution (e-liquid) to create vapour and heat-not-burn (HNB) tobacco products, which heats tobacco at a temperature below the point of combustion. Their use is increasing at an alarming rate; it is believed it will surpass the use of traditional cigarettes in next 5 years, mostly among never-smokers and young people. Objective: There are not many studies investigating knowledge and behaviour about heat tobacco products (HTP) among teenagers, so the aim of this study is to validate the SECRHET questionnaire (Smoking E-CigaRette and HEat-noT-burn products) on knowledge and behaviour on cigarette and HTP among youth.Methods: The study was conducted in February and March 2019 inside Sapienza University of Rome and high school Giulio Cesare of Rome. A self-administered anonymous questionnaire was performed to investigate smoking habits and measures knowledge about HTP among Italian teenagers. Outcomes: A sample of 60 students took part in the validation of the questionnaire. The overall Cronbach's alpha was 0,635, corresponding to a sufficient reliability. Conclusion: There is little or no data on consumption or perceptions of HTP products among youth and evidence suggests the usefulness of a standardized and validated questionnaire available to monitoring of awareness, interest in trying and prevalence of use of these novel products among young people.
51.	**Lee, J.G.L., Blanchflower, T.M., O'Brien, K.F. et al. (2019). Evolving IQOS packaging designs change perceptions of product appeal, uniqueness, quality and safety: a randomised experiment, 2018, USA. Tob Control. 28:e52-e55.**
	Background: Globally, the tobacco industry is promoting heated tobacco products. These products may represent a strategy to promote dual use of tobacco products. One product, *IQOS* from Philip Morris International, is being proposed in the USA for marketing as a less harmful product. The visual design of tobacco products can influence consumers by implying product characteristics. Thus, we sought to test the impact of *IQOS* packaging designs on cognitive, affective and behavioural intention responses. Methods: From existing *IQOS* packages used globally, we developed three *IQOS* packages that decreasingly linked the product to the Marlboro brand. In September to October 2018, we assigned participants randomly to one package in an online experiment. All participants (n=954) were US adults reporting current smoking and no colour blindness. The experiment used quota sampling to ensure diversity by gender, sexual orientation, race, ethnicity and education. Measures were informed by the Context of Consumption Framework. To assess differences in ratings, we conducted non-parametric Kruskal–Wallis tests with post hoc comparisons using Dunn's test. Results: We found significant differences in cognitive indicators including appeal (H=6.87, p=0.03), uniqueness (H=15.68, p<0.01), brand equity–quality (H=122.35, p<0.01) and perceived safety compared with other tobacco products (H=14.27, p<0.01). Participants rated

	packages similarly on affective and behavioural intention measures. All were rated low for talking to others about the product and high for interest in trying with a coupon. Conclusion: Linking or separating *IQOS* products with a well-established cigarette brand changes how adult smokers respond to the product. Regulators should consider the visual design of packaging.
52.	**McKelvey, K., Baiocchi, M., Halpern-Felsher, B. (2020). PMI's heated tobacco products marketing claims of reduced risk and reduced exposure may entice youth to try and continue using these products. Tob control. doi: 10.1136/tobaccocontrol-2019-055318.**
	Importance: Philip Morris International (PMI) is seeking Food and Drug Administration's (FDA) authorisation to market IQOS as a modified risk tobacco product and to make marketing claims of reduced risk and reduced exposure. Such claims may be misunderstood by youth, thereby increasing their risk for tobacco initiation.Objective: To assess youth (mean age 19.3, SD=1.7) understanding and perceptions of PMI's proposed consumer marketing claims of reduced risk and reduced exposure, we embedded a randomised controlled experiment into a survey of 450 California youth (April to August 2018). Participants were randomised to see 'reduced exposure', 'reduced risk' or neither claim. Perceptions of *IQOS*-related health risks and general harm and understanding of the term 'switching completely' as used in PMI's proposed claims were compared. Results: Mean expectancies to experience specific health risks did not differ by claim exposure. The reduced exposure group's perceptions of general harm did not differ from those of controls nor from the reduced risk group. The reduced risk group had the largest proportion who perceived *IQOS* as moderately/less harmful (n=78, 52%); controls the largest proportion perceiving *IQOS* as quite/extremely harmful (n=91, 63%). While 71% of the sample understood the term 'switch completely' correctly as used in the reduced risk (n=194, 71%) and reduced exposure (n=206, 72%) claims, more than 1 in 4 did not. Conclusions: FDA and other regulators must use caution when considering allowing claims of reduced risk or reduced exposure to appear on retail tobacco packaging. Youth misunderstand such claims, and misperceptions of harm are known to lead to tobacco-use initiation.
53.	**Tompkins, C.N.E., Burnley, A., McNeill, A. et al. (2020). Factors that influence smokers' and ex-smokers' use of IQOS: a qualitative study of *IQOS* users and ex-users in the UK. Tob Control. doi: 10.1136/tobaccocontrol-2019-055306.**
	Background: One of the most widely available heated tobacco products is *IQOS* by Philip Morris International. However, there is a lack of independent research exploring *IQOS* initiation and subsequent use among smokers and ex-smokers. Aims: To (1) explore the reasons why smokers and ex-smokers use and continue/discontinue *IQOS* and (2) consider implications for future research and policy. Participants: Adult (18+) current (n=22) and ex-users (n=8) of IQOS who either currently smoked or quit smoking in the last 2 years.

	Methods: Qualitative interview study in London, UK. Results: Six main factors influenced initiation and use of *IQOS*: (1) Health—wanting to reduce/quit smoking and perceptions of reduced harm (while understanding *IQOS* was not risk-free). Branded packaging, absence of pictorial warnings and physical health improvements conveyed reduced harm. (2) Financial—including high start-up costs, but cheaper ongoing costs than smoking. (3) Physical—mixed views on enjoyment and satisfaction. Sensory experiences influenced use including discreetness, cleanliness, reduced smell and tactile similarities relative to combustible cigarettes. (4) Practical—issues of accessibility, shortcomings with maintenance/operation limited ongoing use, whereas use in smoke-free places increased use. (5) Psychological—similarities in rituals and routines, although new practices developed to charge and clean; some liked trailblazing new technology. (6) Social—improved social interactions from using IQOS instead of smoking, but with more limited shared social experiences for some. Conclusion: For some, *IQOS* facilitated smoking substitution. Factors such as packaging, labelling, risk communication, price and smoke-free policies appear to influence initiation and use.
54.	**Wu, Y.S., Wang, M.P., Ho, S.Y. et al. (2019). Heated tobacco products use in Chinese adults in Hong Kong: a population-based cross-sectional study. Tob Control. doi: 10.1136/tobaccocontrol-2018-054719.**
	Introduction: We investigated heated tobacco products (HTPs) use and associated factors in Chinese adults in Hong Kong where HTPs are not formally marketed yet, and cigarette smoking prevalence was the lowest in the developed world. Methods: A population-based landline telephone survey in 2017 interviewed 5131 (45.2% male; 26.7% aged ≥60) adults to collect information on awareness, intention to use, ever use of HTPs, cigarette smoking status and sociodemographic characteristics. Descriptive statistics were weighted by the age, sex and smoking status of the Hong Kong adult population. Sociodemographics were mutually adjusted in logistic regression to yield adjusted ORs (AORs) for awareness of HTPs, controlling for smoking status. Results: Overall, 11.3% (95% CI 10.0% to 12.7%) were aware of HTPs and 1.0 % (0.8%–1.2%) had ever used it. Awareness was associated with aged 40–49 years (AOR 1.37, 95% CI 1.01 to 1.87) or 30–39 years (2.03, 1.41–2.91) (vs ≥60 years), born in Hong Kong (1.37, 1.11–1.68) and higher monthly household income (p for trend 0.001). Ever HTP users had higher educational attainment and monthly household income, and more were aged 30–39 and economically active (all p<0.003). In never HTP users, intention to use HTPs (7.3%, 4.9%–10.8%) were more prevalent in respondents with similar characteristics (all p<0.008). More current (vs never) smokers were aware of HTPs, intent to use HTPs and had ever used HTPs (all p<0.001). Conclusion: Higher socioeconomic status was associated with HTP use and intention to use. Public health education on HTPs is needed especially for this high-risk group.

Post-Marketing	
55.	**Aokage, T., Tsukahara, K., Fukuda, Y., Tokioka, F., Taniguchi, A., Naito, H., Nakao, A. (2019) Heat-not-burn cigarettes induce fulminant acute eosinophilic pneumonia requiring extracorporeal membrane oxygenation. Respir Med Case Rep. 26: 87-90.**
	Background: Although the cause of acute eosinophilic pneumonia (AEP) has not yet been fully clarified, cigarette smoking is reported to be a risk factor for developing AEP. The heat-not-burn cigarette (HNBC) was developed to reduce the adverse effects of smoke on the user's surroundings. However, the health risks associated with HNBCs have not yet been clarified. We report a successfully treated case of fatal AEP presumably induced by HNBC use. Presentation of case: A 16-year-old man commenced HNBC smoking two weeks before admission and subsequently suffered from shortness of breath that gradually worsened. The patient was transferred to emergency department and immediately intubated because of respiratory failure. Computed tomography showed mosaic ground-glass shadows on the distal side of both lungs with a PaO2/FIO2 ratio of 76. The patient required veno-venous extracorporeal membrane oxygenation (ECMO) for severe respiratory failure. He was diagnosed with AEP by clinical course and detection of eosinophils in sputum; thus, methylprednisolone was administrated. The patient was weaned off ECMO four days after initiation and extubated the sam day after. He fully recovered without sequelae.Conclusion: As far as we know, our patient is the first case of AEP induced by HNBC use successfully treated with ECMO. Emergency physicians must be aware that HNBCs can induce fatal AEP.
56.	**Bar-Zeev, Y., Levine, H., Rubinstein, G. et al. (2019). IQOS point-of-sale marketing strategies in Israel: a pilot study. Isr J Health Policy Res. 14;8(1):11.**
	Background: Philip Morris International's *IQOS* ("I Quit Ordinary Smoking") device has increasingly penetrated the global tobacco market. In Israel, among the first countries with *IQOS* in its market, the *IQOS* device is sold in specialty stores and online; the heat sticks – *HEETS* – are sold at traditional retailers. Advertising restrictions in many contexts including Israel have shifted industry marketing efforts to point-of-sale (POS). Given the nuances of *IQOS* and *HEETS* product distribution and the importance of POS marketing, we conducted a pilot study of IQOS POS marketing strategies. Methods: Data collectors assessed product offerings, pricing, promotional strategies, and placement in a sample of 15 *IQOS* retailers (10 convenience stores, 3 grocery stores, 2 tobacco shops) in three Israeli cities (Beer-Sheva, Haifa, Jerusalem). Results: All retailers sold cigarettes; many carried other forms of tobacco (e.g., cigar products). Average price for a *HEETS* package was 30.2 Shekels (SD = 2.7); average price for the least expensive cigarette pack was 27.4 (SD = 1.5). *HEETS* were on average 9.5% more expensive than cigarettes. Posted ads were uncommon; rather, product displays were prominent. *HEETS* packages were often placed in a separate

	display box, at higher and more noticeable positions, and closer to consumers. Additionally, 11 retailers placed cigarettes and 10 placed *HEETS* near youth-oriented merchandise; 9 retailers placed cigarettes and *HEETS*, respectively, within 1 m of the floor. Conclusions: This study represents an initial step in assessing *IQOS* POS practices – critical in advancing the ability to facilitate related research and regulation of emerging tobacco products in Israel and more broadly.
57.	**Chung-Hall, J., Fong, G.T., Meng, G. et al. (2020). Effectiveness of Text-Only Cigarette Health Warnings in Japan: Findings from the 2018 International Tobacco Control (ITC) Japan Survey. Int J Environ Res Public Health, 17(3): 952.**
	Health warnings are an effective strategy for communicating the health harms of smoking, encouraging quitting, and preventing smoking initiation. This study examines the effectiveness of existing text-only health warnings, identifies key predictors of warning effectiveness, and assesses support for pictorial warnings in Japan. Data are from the 2018 International Tobacco Control (ITC) Japan Survey, a cohort survey of adult cigarette smokers (n = 3306), dual users of cigarettes and heated tobacco products (n = 555), and non-cigarette smokers (n = 823). Weighted multivariable logistic regression models were used to assess predictors of warning effectiveness and support for pictorial warnings. Overall, 15.6% of respondents noticed warnings, and 7.9% read or looked closely at warnings. Overall, 10.3% of smokers and dual users said the warnings stopped them from having a cigarette, and 7.2% avoided warnings. Overall, 27.5% of respondents said the warnings made them think about health risks of smoking, but only 2.7% of smokers and dual users said the warnings made them more likely to quit. Overall, 57.6% of respondents supported pictorial warnings. The weak effectiveness of Japan's text-only warnings is consistent with that in other countries with similar warnings. There is majority support for pictorial warnings in Japan, although the level of support is lower than in other countries.
58.	**Chung, S.J., Kim, B.-K., Oh, J.H., et al. (2020). Novel tobacco products including electronic cigarette and heated tobacco products increase risk of allergic rhinitis and asthma in adolescents: Analysis of Korean youth survey. Allergy. doi:10.1111/all.14212.**
	Background: The effect of novel tobacco products, such as electronic cigarettes (EC) and heated tobacco products (HTP), on allergic rhinitis (AR) and asthma is not well known. Objective: To evaluate the health effect of novel tobacco products on asthma and AR. Methods: This study was conducted using large survey data on Korean middle and high school students. The relationship between current asthma/AR and novel tobacco products user status was evaluated. In order to compare the combined effects of conventional cigarette (CC), EC, and HTP use on current allergic diseases, the participants were classified into 18 groups based on CC (current, former, and never), EC (current, former, and never), and HTP (ever and never) status.

	Results: A total of 60,040 participants representing 2,850,118 Korean adolescents were analyzed. Of all participants, 6.7%, 2.7%, and 2.9% were current CC, current EC, and ever HTP users, respectively. Current CC and ever HTP use was significantly associated with current asthma and AR in adjusted models. Current EC showed association with current AR but the association with asthma disappeared in the adjusted model. Among 18 groups, the groups including current CC use showed higher risk of current AR and asthma than never HTP-never EC-never CC group. The odds ratio of current asthma especially increased more in those who used EC and/or HTP with CC concurrently than those in the never HTP-never EC-current CC user group.Conclusion: Using EC and/or HTP in adolescents might enhance the adverse effect of CC on AR and asthma.
59.	**Churchill, V., Weaver, S.R., Spears, C.A. et al. (2020). IQOS debut in the USA: Philip Morris International's heated tobacco device introduced in Atlanta, Georgia. Tob Control. doi: 10.1136/tobaccocontrol-2019-055488 .**
	Following the Food and Drug Administration's (FDA) April 2019 authorisation on their premarket tobacco product application, Philip Morris (PM) has officially launched its heated tobacco product, *IQOS*, in the USA in October 2019 in Atlanta, Georgia. *IQOS* consists of a charger and a holder, into which tobacco sticks, called '*HeatSticks*' in the USA, are inserted. The blade in the holder heats tobacco in a *HeatStick*, producing an aerosol. Prior to the US launch, *IQOS* was available in 43 countries. PM has also submitted to the FDA a modified risk tobacco product application for *IQOS* (decision pending). Research has shown that cigarette marketing techniques, such as heavy price promotions and using attractive models in advertisements, increase the risk of smoking initiation, especially among adolescents and young adults. *IQOS* has used both techniques in the short time since their launch in the USA. Continued close monitoring of *IQOS* marketing is needed to understand the implications of *IQOS*'s marketing strategies on tobacco use going forward.
60.	**Hejlová, D., Schneiderová, S., Klabíková Rábová, T. et al. (2019). Analysis of Presumed IQOS Influencer Marketing on Instagram in the Czech Republic in 2018–2019. Adiktologie. 19(1): 7-15.**
	Background: Heated tobacco products (HTP) are novel electronic devices that produce an aerosol by heating modified tobacco. In July 2017, Philip Morris launched a heated tobacco product, *IQOS*, on the Czech market. The release of IQOS was promoted by a massive marketing campaign using various marketing channels.Aim: This paper presents an analysis of the influencers' posts promoting a heated tobacco product (HTP), *IQOS*, produced by Philip Morris, in the Czech Republic. Methods: Critical discourse analysis (CDA) was used to uncover the hidden power relationships in both textual and visual representations of *IQOS* in Instagram posts. We analysed the posts of 22 Czech influencers identified with the hashtags #IQOSambassador, #IQOSambasabor, #IQOSlounge, #IQOSveVarech, and #mujIQOS, together with associated pictures and videos on Instagram. Results: The hashtag #iqosambassador was used internationally in 940 posts (as of May 16, 2019). Our findings show subtle forms of persuasion that associate the *IQOS* product with an aspirational, exclusive lifestyle, healthy living, and a relaxed atmosphere within a

	community of friends. Preliminary results also show that influencers promoted IQOS to any and all Instagram users (including children and non-smokers). Covert advertising was indicated indirectly by the use of hashtags (#notriskfree, #onlyforadults, and #iqosambassador), which might be evidence that the influencers were paid indirectly by a digital marketing or PR agency. Conclusions: Czech celebrities and influencers have been actively presenting *IQOS* in their posts and videos since 2018 on Instagram. They present *IQOS* as a gateway to an aspirational, healthy, attractive and celebrity lifestyle. The preliminary results are being published as a part of a larger interdisciplinary research project by Charles University, Prague.
61.	**Hwang, J.H., Ryu, D.H., Park, S.-W. (2019). Heated tobacco products: cigarette complements, not substitutes. Drug Alcohol Depend. doi: 10.1016/j.drugalcdep.2019.107576.**
	Background: In Korea, the sale of the first heated tobacco product (HTP), *IQOS*®, commenced in June 2017. This study evaluates the rates of HTP use and examines HTP users' smoking patterns of various tobacco products. Methods: The study analyzed the 2018 Korea Community Health Survey data of a Korean provincial division, which includes 11 cities and 14 counties. Of 21,100 participants, the proportion of current HTP users was calculated and their smoking patterns, in regard to cigarette use, were examined. A multinomial logistic regression model was used to evaluate the related factors of HTP use. Results: The proportion of current HTP users (HTP use within the past 30 days) was 2.13% of the study population. Of these current HTP users, 96.25% were dual users of cigarettes. The adjusted odds ratio (AOR) for current HTP use increased proportionately with frequency and amount of cigarette consumption with statistical significance. The AOR values showed a quadratic curve, descending after the peak value for moderate daily smokers (10–19 cigarettes/day) (Ptrend<0.001, Pquadratic<0.001). Current cigarette smokers who also used HTPs were not associated with an intention to quit cigarette smoking within a month. Conclusions: Given the smoking pattern of HTP users in terms of mutual use with cigarettes, HTPs might not be an alternative to cigarettes as tobacco companies claim.
62.	**Jun, J. 2020. Social Response to the FDA Authorization of Heated Tobacco Products (HTPs). Tob Reg Sci. 6(1): 20-29.**
	Objectives: The US Food and Drug Administration (FDA) approved sales of heated tobacco products (HTPs) on April 30, 2019. In this paper, I provide a preliminary analysis of social media conversations regarding HTPs and the FDA authorization in the first 60 days. Methods: I examined 574 tweets regarding HTPs to assess tweet characteristics and semantic networks of HTPs.Results: Tweets were more likely to be neutral or anti-HTPs than pro-HTPs regardless of the author type (except for tobacco industry) or genre of the post. There was a small gap (6.4%) between the proportion of pro-HTPs and anti-HTPs among personal tweets. The proportion of pro-HTPs was larger in tweets posted by men (vs women and no sex specified) and from rural areas (vs urban). Nearly one-third of the sample mentioned cigarettes or e-cigarettes, even though the size of posts making claims on inferiority/superiority of HTPs was small.

	Conclusions: Social media conversations on risks of HTPs as well as surveillance on young consumer target marketing is occurring, and it will be important to assess the impact of tobacco companies' launch of HTP sales in the US to assess public perceptions on HTPs. Continuing surveillance of HTP marketing and risk perceptions will inform tobacco regulations.
63.	**Kang, H., Cho, S.H. (2019). Heated tobacco product use among Korean adolescents. Tob Control. doi: 10.1136/tobaccocontrol-2019-054949.**
	Background: Heated tobacco products (HTPs) may compromise decades-long efforts to marginalise the tobacco industry. Their appeal to adolescents imposes a risk of a new tobacco epidemic. Empirical evidence on the behavioural patterns of HTP use among adolescents is required. We investigated the prevalence of HTP use and the association between use of HTPs and e-cigarettes and attempts to quit smoking cigarettes. Methods: Nationally representative cross-sectional survey data of South Korean adolescents aged 12–18 years (mean age: 15 years) were used. The survey was conducted 1 year after the introduction of HTPs in Korea. A total of 59 532 adolescents were identified. Descriptive statistics and multiple logistic regression results are presented. Results: In all, 2.8% of South Korean adolescents were ever HTP users. Among these, 75.5% were current cigarette users, 45.6% were current e-cigarette users and 40.3% were concurrent users of cigarettes and e-cigarettes. Unlike ever use of e-cigarettes, which was associated with a higher likelihood of cigarette quit attempts (adjusted OR (aOR)=1.35, 95% CI: 1.16 to 1.58), no difference in cigarette quit attempts was found for ever use of HTPs (aOR=1.07, 95% CI: 0.91 to 1.26). Conclusion: Considering the recent introduction of HTPs to the Korean market and less than 1% prevalence of e-cigarette when first introduced, the prevalence of ever HTP use among Korean adolescents is an important concern. The results showing high polytobacco use and the lack of an association between HTP use and cigarette quit attempts call for a ban on HTP advertisements with modified harm claims.
64.	**Kang, S.Y., Lee, S., Cho, H.-J. (2020). Prevalence and predictors of heated tobacco product use and its relationship with attempts to quit cigarette smoking among Korean adolescents. Tob Control. doi: 10.1136/tobaccocontrol-2019-055114.**
	Introduction: Heated tobacco products (HTPs) have been available in the Korean market since June 2017. In this study, we examined the prevalence and predictors of HTP use among Korean adolescents and the association between HTP and electronic cigarette (EC) use and attempts to quit conventional cigarette (CC) smoking. Methods: We analysed the data of a representative sample (n=60 040) of 13–18-year-old middle-school and high-school students in Korea who had participated in the 14th Korea Youth Risk Behavior Web-based Survey in 2018.

	Results: The prevalence of ever HTP use among Korean adolescents was 2.9% (men: 4.4%, women: 1.2%), a year after the introduction of HTPs in the Korean market. Furthermore, 81.3% of the 1568 ever HTP users were triple users of HTPs, ECs and CCs. Multivariate analysis revealed that ever HTP use was greater among men, higher-grade students, current CC and/or EC users and risky alcohol drinkers. Among current CC smokers, ever users of ECs (28%–30%) and ever HTP users and current EC users (48%) were more likely to have attempted to quit CC smoking than those who had never used HTPs and ECs. However, there were fewer HTP and/or EC ever users among ever CC smokers who successfully quit smoking. Conclusions: Many adolescents, especially CC and EC users, had already used HTPs shortly after the introduction of HTPs in Korea. The use of newer types of tobacco products is associated with lower odds of abstinence from CCs; therefore, it is important to protect adolescents from them.
65.	**Kinjo, A., Kuwabara, Y., Fujii, M. et al. (2019). Heated tobacco product smokers in Japan identified by a population-based survey. J Epidemiol. doi: 10.2188/jea.JE20190199.**
	Background: In this study, we aim to estimate the prevalence of heated tobacco product (HTP) smokers three years after the launch of HTPs in Japan. Methods: Our study, performed in February 2018 in Japan, had a cross-sectional population-based design. A total of 4,628 adult participants (2,121 men and 2,507 women) were randomly sampled from all regions of Japan. The response rate was 57.9%. Interviews were conducted by trained investigators who visited participants' homes. A survey on current (past 30 days) and lifetime tobacco use (including e-cigarettes and HTPs), as well as numerous sociodemographic factors, was conducted.Results: The age-adjusted rates (95% confidence interval) and estimated number of lifetime-HTP smokers were 14.1% (12.5-15.6%; 7.11 million men) and 3.7% (2.9-4.4%; 1.99 million women). The age-adjusted rates (95% confidence interval) for current HTP smokers were 8.3% (7.1-9.6%; 4.21 million men) and 1.9% (1.3-2.4%; 1.02 million women). Multiple variables were found to be associated with a higher prevalence of current HTP use, including being male, aged 20–39 years old, a current Internet user, a risky drinker, or a heavy episodic drinker. HTP use was also higher among men with 10 years or more of education, women with 15 years or less of education, and men with middle- or high-level household incomes. Conclusion: We concluded that HTP use has increased substantially in Japan. However, regulations for HTPs are weaker than those for combustible cigarettes in Japan. Thus, HTPs should be subjected to the same regulations as combustible tobacco products.
66.	**Kreitzberg, D. S., Murthy, D., Loukas, A. et al. (2019). Heat not burn tobacco promotion on Instagram. Addict Behav. 91:112-118.**
	Conclusion: HNB are the newest class of tobacco product that may be appealing to the core demographics of Instagram users - young, interested in style/fashion, and active consumers. Our study demonstrated, HNB promotion on Instagram is overwhelmingly online retailer and HNB user generated buoyed by fan communities and IQOS employees. The prevalence of online retailers, indexing HNB under style/fashion categories, and use of health, flavor, and cessation terms are important to consider when these products enter the U.S.

	market as underaged youth may have access to HNB products and exposure to biased messaging through Instagram. Moreover, exposure to tobacco content on Instagram may normalize tobacco products and increase the social acceptability of tobacco use. If not an outright ban, Instagram could limit exposure to tobacco content among users ages 13 to 18. Findings from this study should inform health promoters andsurveillance among regulators to prevent circumvention of tobacco control regulations as has been found with other tobacco products.
67.	**Lee, A., Lee, S.Y. & Lee, K. (2019). The Use of Heated Tobacco Products is Associated with Asthma, Allergic Rhinitis, and Atopic Dermatitis in Korean Adolescents. Sci Rep 9, 17699**
	The increasing use of new and emerging tobacco products has raised public health concern worldwide. This study aimed to assess the association between tobacco product use and the risk of allergic diseases. We used cross-sectional data of 58,336 students aged 12–18 years from the 2018 Korea Youth Risk Behavior Survey. This study considered three tobacco products, namely cigarettes, electronic cigarettes (e-cigarettes), and heated tobacco products. Descriptive analyses, as well as simple and multinomial logistic regression analyses with a complex sampling design, were performed. Multiple tobacco use had an association with the risk of each allergic disease. Use of each tobacco product was significantly associated with an increased risk of multi-morbidity of asthma, allergic rhinitis, and atopic dermatitis. Furthermore, lifetime use of each tobacco product was associated with the prevalence of atopic dermatitis. This highlights the importance of paying close attention to smoking by adolescents and its association with allergy epidemics. Future research should consider intensity of smoking and/or severity of allergic symptoms.
68.	**Lee, A., Lee, K.-S., Park, H. (2019). Association of the Use of a Heated Tobacco Product with Perceived Stress, Physical Activity, and Internet Use in Korean Adolescents. National Survey. Int. J. Environ. Res. Public Health. 16(6), 965.**
	The awareness and use of the recently introduced heated product in the global tobacco market is rapidly increasing. Few studies have investigated the association of this product's use with health-related factors. To examine the association of the heated tobacco product (HTP)'s use with perceived stress, physical activity, and internet use, we analyzed data from the Korea Youth Risk Behavior Survey using multinomial logistic regression models. The participants included 60,040 students from middle school and high school. There were significant associations between high perceived stress and cigarette use only, dual use of cigarette and e-cigarette, triple use of cigarette, e-cigarette, and HTP; a negative association between HTP's use and perceived stress; positive association between physical activity and tobacco use; and not using the internet significantly increased the odds of use of all types of tobacco products. A smoking

	prevention program, tailored to meet the needs of different types of tobacco product users, is recommended. A program aimed at not only increasing awareness of perceived risk but also decreasing perceived benefits of risky behaviors, should also be considered. Further research using a longitudinal design to test the causal relationship of tobacco product use with perceived stress, physical activity, and internet use is warranted.
69.	**Liber, A.C. (2019). Heated tobacco products and combusted cigarettes: comparing global prices and taxes. Tob Control. 28(6): 689-691.**
	Background: Heated tobacco products (HTPs) have received excise tax rates that are lower than combusted cigarettes in most of the countries in which the products are sold as tobacco companies claimed their purported reduced risk products deserved such light touch treatment. This study sought to determine if HTPs are cheaper to use than combusted cigarettes when the cost of purchasing an expensive heating device upfront was considered. Methods and data: Product price data for tobacco heating devices, as well as cobranded heated tobacco and combusted cigarettes for 2014-2017 for 34 countries was obtained from Euromonitor International. Results: Only in 17 of 46 country-year cases with adequate data were HTPs less expensive to use than combusted cigarettes over a year. Discussion:The tax advantages being given to HTPs may instead of providing a price signal to a consumer looking to switch, be providing a profit signal to tobacco companies to switch over to selling more HTPs and fewer combusted cigarettes. The implications of these dynamics for public health are unclear.
70.	**Liu, X.; Lugo, A.; Spizzichino, L. et al. (2019). Heat-not-burn tobacco products: concerns from the Italian experience. Tob Control. 28(1):113-114.**
	Introduction: Heat-not-burn (HNB) tobacco products are disposable tobacco sticks heated, rather than combusted, by an electronic device to generate an aerosol containing nicotine. *IQOS* is the brand name of such a product by Philip Morris International, launched in 2014 in Italy as a pilot country for the European market. *IQOS* is now in commerce in 30 countries, including 19 European ones, and applications have been submitted to market it as a modified risk tobacco product in the USA. Most safety data on this new tobacco product come from research conducted by the tobacco industry. The few independent toxicological studies confirm that HNBs release harmful and potentially harmful substances, although at reduced levels as compared with conventional cigarettes. To our knowledge, the only available studies on the use of HNBs are two repeated online surveys on Japanese adult population, showing a prevalence of *IQOS* users of 0.3% in 2015, 0.9% in 2016 and 3.6% in 2017. We investigated HNB awareness and use in Italy, where *IQOS* is the only available HNB. Methods: In 2017, we conducted a face-to-face survey of 3086 subjects selected through multistage sampling to be representative of the general Italian population aged ≥15 years (52.4 million inhabitants). Besides information on general sociodemographics, smoking and e-cigarette use, participants were asked about their awareness and use of *IQOS*.

	Results: One in five (19.5%) respondents were aware of *IQOS*, 1.4% have tried it and 2.3% intended to try it. Overall, 1.0% of never smokers, 0.8% of ex-smokers and 3.1% of current cigarette smokers have tried *IQOS*. Correspondingly, 1.2% of never e-cigarette users, 2.9% of ex-e-cigarette users and 7.7% of current e-cigarette users have tried *IQOS*. Discussion: Almost 3 years after having been launched, use of *IQOS* is still limited in the Italian population. However, our data indicate that 739 000 Italians have already tried *IQOS*, including 329 000 never smokers.
71.	**Mathers, A., Schwartz, R., O'Connor, S. et al. (2019). Marketing *IQOS* in a dark market. Tob Control. 28(2): 237-238.**
	Introduction: Phillip Morris International (PMI) is pushing hard to promote *IQOS* heat-not-burn cigarettes in Ontario, Canada. Canada regulates *IQOS* as a tobacco product so that the robust tobacco marketing ban creates challenges to its promotion. Methods: We collected data on *IQOS* promotion in 49 retail outlets, and through interviews with clerks and observations outside an *IQOS* store. Results: The dominant marketing channel is the visible availability of *IQOS* in a large number of tobacco retail outlets—1029 across Ontario. Several stores display the price of 'heated tobacco' on one of three price signs which are permitted despite Ontario's total display ban. *IQOS* boutique stores are the locus of aggressive promotion including exchanging a pack of cigarettes or lighter for an *IQOS* device, launch parties, 'meet and greet' lunches and after-hour events. Outside the store, promotion includes a prominent *IQOS* sign, a sandwich board sign reading 'Building a Smoke-Free Future' and sales representatives regularly smoking *IQOS*. Membership services: Upon acquiring an *IQOS* device one can register to access the *IQOS* website store5 and receive customer support services, a map of retail locations and a product catalogue. Members receive regular email invitations to complete surveys with opportunities to win prizes. Conclusions: These promotion activities have undoubtedly made substantial numbers of Ontarians aware of *IQOS*. Yet, the government has not provided guidance as to absolute and relative potential harms. Our observations of tactics to promote a new tobacco product in a dark market may inform government regulatory policy and non-governmental organisation efforts wherever heat-not-burn products are introduced.
72.	**Obertova, N., Navratil, T., Zak, I. et al. (2020). Acute exposures to e-cigarettes and heat-not-burn products reported to the Czech Toxicological Information Centre over a 7-year period (2012-2018). Basic Clin Pharmacol Toxicol. doi: 10.1111/bcpt.13393.**
	E-cigarettes and heat-not-burn cigarettes (HNBC) present new health risks due to their rising popularity, high content of nicotine and serious adverse effects.

	The objective of the study was to analyse the cases of acute exposure to e-cigarettes, e-liquids and HNBC products containing nicotine that led to toxicological consultations at our poisons control centre during a 7-year period (2012-2018) and identify the categories of special concern that require further investigation and intervention. The demographic, toxicological and clinical data were analysed by descriptive statistics. Poisoning severity score (PSS) was estimated. From 119,229 consultations, 148 cases concerned acute exposure to e-cigarettes. Children and adolescents were exposed in 91 (61%) cases, including exposure of neonates and infants in 54 (36%) cases. The main route of exposure was ingestion in 129 (87%), inhalation in nine (6%), ocular in six (4%) and intravenous administration in three (2%) cases. The source of exposure was the cartridge with e-liquid (107; 72%), refillable tank in 29 (20%) and HNBC refill in nine (6%) cases. The reason for exposure was accidental in 110 (74%), incorrect application of the device in 10 (7%), abuse in six (4%), suicide attempt in six (4%) and other/unknown in 16 (11%) cases. The dose estimation was severe/lethal in 6 (4%), toxic in 53 (36%), low-to-moderate in 35 (24%) and unknown in 54 (36%) cases. Vomiting was observed in 38 (26%) patients; 72% of patients were hospitalised. In symptomatic cases, 41 patient had PSS 1, 12 patients had PSS 2 and one patient had PSS 3. Activated charcoal was applied in 57 (39%) patients, and symptomatic treatment was recommended in 75 (51%) patients. Cases of unintentional exposure of children demonstrate the need for preventive risk reduction measures.
73.	**Pinkas, J., Kaleta, D., Zgliczyński, W.S. et al. (2019). The Prevalence of Tobacco and E-Cigarette Use in Poland: A 2019 Nationwide Cross-Sectional Survey. Int J Environ Res Public Health. 16(23): 4820.**
	Monitoring of tobacco use is one of the key tobacco control activities. This study aimed to assess the current prevalence and patterns of tobacco and e-cigarette in Poland as well as to investigate socioeconomic factors associated with cigarette smoking and e-cigarette use. This cross-sectional study was carried out in 2019, on a representative nationwide sample of 1011 individuals aged 15+ in Poland. Daily tobacco smoking was declared by 21.0% of participants; 1.3% of participants were occasional tobacco smokers, and 10.7% were former tobacco smokers. Heated tobacco was used by 0.4% of participants. Ever e-cigarette use was declared by 4.0% of participants and 1.4% were current e-cigarette users. A higher proportion of daily smokers was observed among men than women (24.4% *vs*. 18.0%; $p < 0.0001$). The age group 30 to 49 years, of a lower educational level and living in a medium-sized city (between 20,000 and 500,000 residents), was significantly associated with current daily smoking. This is the most up-to-date study on the prevalence of smoking in Poland. Further tobacco control activities are needed to reduce tobacco use in Poland
74.	**Queloz, S., Etter, J.F. (2019). An online survey of users of tobacco vaporizers, reasons and modes of utilization, perceived advantages and perceived risks. BMC Public Health. 19(1): 642.**
	Background: Tobacco vaporizers heat tobacco without burning it, to produce an inhalable aerosol. Various models have recently appeared on the market, mostly manufactured by the tobacco industry, but few of the studies published on tobacco vaporizers are independent from the manufacturers.

	The goals of this study were to explore who uses tobacco vaporizers, how these products are used, reasons for utilization, perceived advantages and risks. Methods: Online questionnaire collected from October 2016 to January 2018 in self-selected visitors aged > 18 to an anti-addiction website. Results: We obtained 170 valid responses, of whom 104 were using tobacco vaporizers. For homogeneity, we included only the 102 users of the Brand 1 tobacco vaporizer in our analysis, as there were only two users of other vaporizers. Among these 102 vaporizer users, about half were current cigarette smokers (57%), the rest were former cigarette smokers. The median age was 41, and the median duration of utilization was 9 months. Most (88%) used the vaporizer daily, 8% were occasional users and 4% were past users. Among current smokers, 80% were currently trying to reduce their cigarette consumption and 29% were trying to quit. The vaporizer was used mainly to replace cigarettes (94%), because it was perceived to be less toxic than cigarettes (89%), to help stop smoking or to avoid starting smoking again (72%), or to reduce cigarette consumption (71%). Current smokers who were daily or occasional vaporizer users reported smoking a median of 8.0 cigarettes per day, compared with 20.0 per day before they started to use the vaporizer ($p < 0001$, Wilcoxon signed-rank test). Conclusions: In this online sample of early adopters, Brand 1 was by far the most frequently used tobacco vaporizer. It was used by current or former smokers only, mainly to replace cigarettes, and satisfaction ratings were good. Users considered the tobacco vaporizer to be less toxic than cigarette smoke and perceived it to be helpful for reducing or stopping smoking.
75.	**Stoklosa, M., Cahn, Z., Liber, A. et al. (2019). Effect of IQOS introduction on cigarette sales: evidence of decline and replacement. Tob Control. doi: 10.1136/tobaccocontrol-2019-054998.**
	Background: Philip Morris International, one of the largest transnational cigarette manufacturers, has heavily invested in its new heated tobacco product, *IQOS*, marketing it aggressively as a less harmful alternative to cigarette smoking. The company's assertions that the product replaces cigarettes in a market have never been independently tested. The objective of this study is to determine whether introduction of *IQOS* affected cigarette sales in a large economy. Data and Methods: Using 2014 to 2018 monthly retailer panel data from Japan, we analyse whether different dates of *IQOS* introduction across Japan's regions are reflected in the patterns of cigarette sales in those regions. A series of placebo models are estimated to test if events other than *IQOS* introduction could have better explained the observed trends in cigarette sales. Results : Cigarette sales begin to substantially decline at the time of the introduction of *IQOS* in each of 11 Japanese regions (Chow tests p<0.001). *IQOS* introduction, which varied across regions, better predicted the timing of cigarette sales decline than any one time applied to all regions simultaneously (a national-level exogenous shock) and than nearly all possible rearrangements of the true *IQOS* introduction months among the regions (exact permutation test's p value from 0.02 to 0.13, depending on the study approach).

	Conclusions: The introduction of *IQOS* likely reduced cigarette sales in Japan. The net population health impact, however, cannot be assessed without resolving several key uncertainties related to the direct harms of *IQOS* and the precise patterns of both smoking and *IQOS* use.
76.	**Sutanto, E., Miller, C., Smith, D.M. et al. (2019). Prevalence, Use Behaviors, and Preferences among Users of Heated Tobacco Products: Findings from the 2018 ITC Japan Survey. Int J Environ Res Public Health. 16(23): E4630.**
	Heated tobacco products (HTPs), such as *IQOS*, *glo*, and *Ploom* TECH, with a variety of flavored tobacco-containing inserts, have reportedly achieved a significant market share in Japan. We analyzed data from Wave 1 of the ITC Japan Survey, a nationally representative web survey conducted in February to March 2018 among 4684 adult participants to estimate the prevalence of HTP use, describe characteristics of HTP users, and explore user preferences for HTP device and flavor. The overall prevalence of monthly HTP use was 2.7% (1.7% daily use). Virtually all HTP users were current cigarette smokers (67.8%) or former smokers (25.0%); only 1.0% of HTP users were never smokers. Among HTP users, *IQOS* was the most frequently reported brand used (64.5%), and menthol was the most common flavor reported (41.5%). IQOS was used more by younger respondents and those who reported daily use, while *Ploom* TECH was more popular among older respondents and non-daily HTP users. This is one of the first non-industry funded studies to explore the use of HTPs in Japan.
77.	**Tabuchi, T., Shinozaki, T., Kunugita, N. et al. (2019). Study Profile: The Japan "Society and New Tobacco" Internet Survey (JASTIS): A longitudinal internet cohort study of heat-not-burn tobacco products, electronic cigarettes and conventional tobacco products in Japan. J Epidemiol. 29(11): 444-450.**
	Background: Japan became the first country where heat-not-burn tobacco products were sold. Therefore, there was no information for actual status on the actual use status or the harms of heat-not-burn tobacco products. The objectives of the study profile are to generate data that can be freely available to external researchers, and to create collaborative research projects in the future. Methods: The Japan "Society and New Tobacco" Internet Survey (JASTIS) is a longitudinal internet cohort study which investigates perception, attitude, and use of heat-not-burn tobacco, electronic cigarettes (e-cigarettes), and conventional tobacco products in Japan. The survey also includes demographic, health-related, and socioeconomic factors. Participants were randomly selected and invited from internet panelists. The baseline survey was closed when the target number of respondents who had answered the questionnaire was met. Results: The study includes three cohorts (1-3) from the 2015 baseline survey and a cohort (4) from the 2017 baseline survey: cohorts 1 and 4 were recruited based on sex and age: men and women aged 15-69 years (n = 8,240 for cohort 1 and n = 5,897 for cohort 4); cohorts 2 and 3 were created using status-based recruiting: e-cigarette and/or heat-not-burn tobacco ever users (n = 2,188; cohort 2) and

	combustible cigarette smokers without e-cigarette/heat-not-burn tobacco experience (n = 724; cohort 3). The completion rates were 8.5% to 9.9%. All subjects were followed and assessed annually. Response rates for the follow-up survey were 65.5% in 2016, 55.3% in 2017, and 50.9% in 2018. Because Internet-based responders are not a representative sample of the general population of Japan, we conducted adjustment to account for "being an internet survey respondent" and reported tobacco product use in Japan. A recent JASTIS study reported that prevalence of IQOS current-use among Japanese adults had rapidly increased from 0.3% in 2015 to 3.6% in 2017. Conclusion: The JASTIS study provides the first estimates for heat-not-burn tobacco use in the world and e-cigarette use in Japan.
Others	
78.	**Baran, W., Madej-Knysak, D., Sobczak, A. et al. (2020). The influence of waste from electronic cigarettes, conventional cigarettes and heat-not-burn tobacco products on microorganisms. J Hazard Mater. doi: 10.1016/j.jhazmat.2019.121591.**
	Tobacco smoking, especially conventional cigarettes, is widespread throughout the world. Simultaneously, there is a growing interest in new alternative products that allow delivering nicotine to the users' organisms, including electronic cigarettes and heat-not-burn tobacco products. However, there are few scientific reports regarding the effect of waste generated from the above-mentioned products on microorganisms. The aim of the manuscript was to investigate the influence of substances leached from conventional cigarette butts, butts from heat-not-burn tobacco products, cartridges and e-liquids for electronic cigarettes on microorganisms. The commercial multispecies MARA (microbial assay for risk assessment) test and non-selected microorganisms from the Brynica River (Poland), as well as an effluent from the wastewater treatment plant (Sosnowiec-Zagórze, Poland), were used in the ecotoxicity assessment of the investigated waste. The results of the experiments revealed that the waste from electronic cigarettes, i.e. cartridges and e-liquids, does not pose a considerable threat to the microbiocenosis. On the other hand, a particularly strong ecotoxic effect on the investigated microorganisms has been reported for leachate from smoked cigarette butts and butts from heat-not-burn tobacco products. Their high ecotoxicity combined with a high supply is worrying and it can require interventions to protect the aquatic environment. The retention of the waste can have an adverse effect on microorganisms in reservoirs surface waters or a sludge activity in wastewater treatment plants.
79.	**Drovandi, A., Salem, S., Barker, D. et al. (2019). Human Biomarker Exposure from Cigarettes versus Novel Heat-Not-Burn Devices: A Systematic Review and Meta-Analysis. Nicotine Tob Res. doi: 10.1093/ntr/ntz200.**
	Introduction: Novel tobacco products require independent research to assess their safety. This study assessed the current literature for trials comparing levels of biomarkers of exposure (BoE) between conventional cigarettes and heat-not-burn (HNB) devices.

	Methods: Ten databases were searched using terms including: 'heat not burn', 'iqos', 'teeps', 'mrtp', 'tobacco heating', and 'glo', between 1st January 2010 and 13th August 2019. Randomised controlled trials assessing comparative BoE levels in humans using either conventional cigarettes or novel HNB devices were eligible. BoE were tabulated, and differences between the intervention and control groups analysed and combined using a random effects meta-analysis.Ten non-blinded, randomised controlled trials were eligible, involving a total of 1,766 participants. Studies regularly reported on 12 BoE (including nicotine). HNB devices assessed included the 'IQOS' and 'glo' devices, and 'precursor' (being developed) HNB devices. In comparison to conventional cigarettes, all 12 BoEs assessed were significantly lower for participants assigned to a HNB device. In comparison to smoking abstinence, HNB devices were statistically equivalent for eight BoEs and significantly elevated for four BoEs. Conclusions: This review found that the potential for harm to humans is reduced when using HNB devices compared to conventional cigarettes, as indicated by significant reductions in BoE levels. Whilst these results support tobacco manufacturer claims of improved safety, the small number of studies included, limited range of BoE assessed, and involvement of the tobacco industry necessitate further independent research to confirm the HNB devices as being a safer alternative to conventional cigarettes.Implications: This study supports claims made by tobacco manufacturers on the improved safety of heat-not-burn tobacco devices in comparison to conventional cigarettes. These novel devices lead to reduced exposure to key biomarkers, which are linked to the health consequences attributed to tobacco use. This has strong implications for international public health as well as further research and policy development relating to the safety aspects and legalities of novel tobacco products.
80.	**Jankowski, M., Brożek, G.M., Lawson, J. et al. (2019). New ideas, old problems? Heated tobacco products – a systematic review. Int J Occup Med Environ Health. 32(5):595-634.**
	Heated tobacco products (HTPs) are a form of nicotine delivery intended to provide an alternative to traditional cigarettes. The aim of this systematic review was to present the current state of knowledge on HTPs with an emphasis on the potential impact of HTP use on human health. During the preparation of this systematic review, the literature on HTPs available within Medline/PubMed, EMBASE, CINAHL, ScienceDirect, and Google Scholar was retrieved and examined. In the final review, 97 research papers were included. The authors specifically assessed the construction and operation of HTPs, as well as the chemical composition of HTP tobacco sticks and the generated aerosol, based on evidence from experimental animal and cellular studies, and human-based studies. HTPs were found to generate lower concentrations of chemical compounds compared to traditional cigarettes, except for water, propylene glycol, glycerol, and acetol. The nicotine levels delivered to the aerosol by HTPs were 70–80% as those of conventional combustion. The results of in vitro and in vivo assessments of HTP aerosols revealed reduced toxicity, but these were mainly based on studies sponsored by the tobacco industry. Independent human-based studies indicated that there was a potentially harmful impact of the active and passive HTP smoking on human health. Currently, a large body of knowledge on HTP exposures and health effects is provided by the tobacco industry (52% of identified studies).

	Based on the available evidence, HTPs produce lower levels of toxic chemicals, compared to conventional cigarettes, but they are still not risk-free.
81.	**Kopa, P. N., Pawliczak, R. (2019). Health consequences of smoking – focusing on alternative smoking methods. Alergol Pol Pol J Allergol. 6(3): 100-109.**
	When e-cigarettes and, later on, heat-not-burn products were introduced to the market, it was hypothesized that they could have some positive effect on smoking cessation and reduction of smokers' exposure to dangerous substances. Despite some of their benefits, toxicological studies show the presence of some hazardous substances in their vapors, which may affect smokers' health in a similar way as tobacco cigarette compounds. There is a small amount of research studying the effects of these alternative cigarettes on health consequences in humans. In addition, the great majority of them compare only health effects of switching to e-cigarettes or heat-not-burn (HnB) products, without specifying their impact on non-smokers. Long-term exposure effects of e-cigarettes and heat-not-burn cigarettes and their effect on maternal health or fetus development are still unknown.
82.	**Kopa, P.N., Pawliczak, R. (2020). IQOS - a heat-not-burn (HnB) tobacco product - chemical composition and possible impact on oxidative stress and inflammatory response. A Systematic Review. Toxicol Mech Methods. 30(2): 81-87.**
	Objectives: This work attempts to summarize current knowledge about *IQOS*, the heat-not-burn tobacco products, their chemical composition and possible impact on oxidative stress and inflammatory response. Materials and Methods: The literature search was performed between January and April 2019 by a combination of terms: 'IQOS smoking', 'IQOS cigarette', 'I quit original smoking cigarette', 'heat-not-burn products', 'HnB tobacco products'. Results: The aim of IQOS system is to minimalize the exposure of its smokers to dangerous substances present in cigarette smoke and to lower the probability of development of tobacco-related diseases. As current studies suggest, this new heat-not-burn tobacco product emits significantly lower concentrations of tar, carbonyls, VOCs, CO, free radicals or nitrosamines when compared to conventional cigarette, and thus it may reduce health risk for smokers. However, it does not eliminate this risk of development of tobacco-related diseases. Discussion: For conventional tobacco smokers the *IQOS* products may be an alternative option, which helps to reduce exposure to hazardous and potentially hazardous constituents. However, for never-smokers using the *IQOS* cigarettes may develop addiction or increase exposition to some substances, which may increase probability of tobacco-related diseases. Moreover, emission of unexpected substances depends on device cleaning strategy and puff regiments. Conclusions: There is only limited data about *IQOS* effect on smokers' health. Future investigation, especially comparison with healthy never-smokers or study of chronic exposure to *IQOS*, is needed.

83.	**Mallock, N., Pieper, E., Hutzler, C. et al. (2019). Heated Tobacco Products: A review of current knowledge and initial assessments. Front Public Health. 7:287.**
	The health risks of tobacco smoking have been documented in numerous studies and smoking rates have declined in developed countries over the last 50 years. Today, we know that cigarette smoking is the major cause of preventable deaths due to tobacco smoke induced diseases. As a consequence of an increased awareness of smoking-related health risks, heated tobacco products (HTPs) are marketed as reduced toxicant alternatives to conventional tobacco products. Manufacturers claim that levels of toxicants and hazardous compounds are significantly reduced, implying that inhalation of the modified aerosol is less harmful compared to conventional cigarettes. In this manuscript, previous assessments of HTPs are briefly summarized, including a short discussion on challenges with the adaption of standard analytical methods used for tobacco smoke. The reliability of analytical data is important for risk assessment approaches that are based on reduced toxicant exposure. In order to assess a putative reduction of health risks, an integrated study design is required that should include clinical studies and epidemiology data. One manufacturer applied for a classification as a Modified Risk Tobacco Product (MRTP) in the United States, based on extensive toxicological studies that have also been published. However, data are not yet sufficient for a reliable assessment or recognition of putatively reduced health risks. Challenges regarding a classification in Europe are also discussed briefly in this review.
84.	**Ratajczak, A., Jankowski, P., Strus, P. et al. (2020). Heat Not Burn Tobacco Product—A New Global Trend: Impact of Heat-Not-Burn Tobacco Products on Public Health, a Systematic Review. Int J Environ Res Public Health. 17(2): 409.**
	Introduction: The use of heat-not-burn tobacco products (HnB) is being adopted increasingly as an alternative to smoking combusted products, primarily cigarettes. Substantial controversy has accompanied their marketing and use in the public health context. In this study, we aimed to consider the probable impacts of HnB tobacco products use on public health. Methods: In May 2019, we conducted a systematic review of 15 studies concerning awareness and use of IQOS (abbrv. I Quit Ordinary Smoking) selected from three databases: Cochrane, PubMed, and Embase regarding public health. Results: All key outcomes varied by smoking status: more young adults who were currently smoking reported being aware of, interested in trying, and prone to trying heat-not-burn tobacco products. Interest in trying HnB products was also present among non-smokers, which raises concerns regarding new smokers. Interestingly, susceptibility to trying IQOS (25.1%) was higher than for traditional cigarettes (19.3%), but lower than for e-cigarettes (29.1%). Conclusions: Present studies suggest that HnB tobacco products have the potential to be a reduced risk product for public health compared to conventional cigarettes, considering indirectly the potential effects on the chronic diseases which are traditionally linked to traditional cigarette use as well as second hand exposure, but further studies are needed to determine whether this potential is likely to be realized.

	The process of HnB tobacco products becoming increasingly popular is of a global scale. Only small differences between countries on different continents regarding popularity and use of HnB tobacco products have been reported.
85.	**Signes-Costa, J., de Granda-Orive, J,I, Ramos Pinedo, Á. et al. (2019). Official Statement of the Spanish Society of Pulmonology and Thoracic Surgery (SEPAR) on Electronic Cigarettes and IQOS®. Arch Bronconeumol. 55(11): 581-586.**
	The use of novel tobacco products, particularly the electronic cigarette (EC) and partial tobacco combustion devices (HnB systems: Heat not Burn), has increased exponentially, particularly among adolescents and young people. The health authorities and scientific societies have shown concern about issues surrounding safety and effectiveness (as a method of smoking cessation). A study of the available scientific evidence has concluded that the safety of the vapor or fumes inhaled by the users of these devices cannot be guaranteed. Contradictory results from various clinical trials and meta-analyses also mean that these devices cannot be recommended for their effectiveness in cessation, especially when safe and effective treatments are available to help quit smoking (varenicline, nicotine replacement therapy, and bupropion, combined with psychological counseling). Conclusions: Our analysis, conducted using the available evidence, prompts the SEPAR to conclude with a few warnings about ECs and HnB devices, in particular *IQOS®*, the only system available in Spain.The growth experienced by ECs, in particular the so-called pods, has alarmed the health authorities, since teenage users of *Juul®* (atype of pod that contains high amounts of nicotine) have levels ofurinary cotinine that are almost double those found in smokers ofCCs. This confirms initial fears that these devices are becoming a gateway to nicotine addiction. Even though tobacco companies insist that their devices replace CCs, the reality is that smokers become dual users. Studies carried out in ECs and *IQOS®* confirm that the emission of toxic substances is quite probably lower than with CCs; however, it is clear that safety in the short, medium and long term is not guaranteed. Moreover, there is a demonstrated risk to people, especially children, who passively inhale the fumes and vapors of these devices. It should be noted that toxicity should not be compared between CCs and these devices, but between the use of these devices and abstinence from any type of tobacco use. It is not natural to smoke.With regard to effectiveness in smoking cessation, we currently we do not have sufficient scientific evidence (randomized, double-blind, placebo-controlled clinical trials with no methodologicaldeficiencies and more rigorous observational studies) to conclude that ECs help to reduce the consumption of cigarettes and quit smoking. This, coupled with the safety problems associated their use, means that these devices cannot yet be recommended as atreatment for smoking cessation, especially when we currently have sufficient scientific evidence that demonstrates that the only safe and effective treatment for help quitting smoking is the use of drugs (varenicline, NRT, and bupropion) in combination with psychological counselling.
86.	**Simonavicius, E., McNeill, A., Shahab, L. et al. (2019). Heat-not-burn tobacco products: a systematic literature review. Tob Control. 28(5): 582-594.**
	Objective: To review peer-reviewed evidence on heat-not-burn tobacco products (HnB), their secondhand emissions and use by humans; to identify differences between independent and industry-funded studies.

	Data sources Medline, Embase, PsycINFO, ProQuest, Scopus and Web of Science databases were searched up to 6 November 2017 for studies on HnB published after December 2009; reference lists were screened and other researchers contacted, yielding 637 records. Study selection: Thirty-one publications on HnB secondhand emissions (n=16) or use by humans (n=15) were selected by two reviewers with excellent agreement (k=0.75). Data extraction: Data on authors' affiliations, HnB products, secondhand emissions and human exposure were extracted by one reviewer. Two reviewers assessed the quality of experimental HnB studies using the Effective Public Health Practice Project tool. Data synthesis: Twenty out of 31 studies were affiliated with tobacco industry. Studies on secondhand emissions varied by methodology, products and comparators. Compared with cigarettes, HnB delivered up to 83% of nicotine and reduced levels of harmful and potentially harmful toxicants by at least 62% and particulate matter by at least 75%. Experimental HnB use studies were limited to one product, reductions of human exposure to toxicants varied between 42% and 96%. HnB use suppressed urges to smoke, but participants rated HnB less satisfying than cigarettes. While limited by methodological heterogeneity, findings were largely similar for independent and industry-funded studies. Conclusions: Studies on HnB secondhand emissions and human use were heterogeneous and largely affiliated with the manufacturers. HnB exposed users and bystanders to toxicants, although at substantially lower levels than cigarettes.
87.	**Conklin, D.J., Schick, S., Blaha, M.J. et al. (2019). Cardiovascular injury induced by tobacco products: assessment of risk factors and biomarkers of harm. A Tobacco Centers of Regulatory Science compilation. Am J Physiol Heart Circ Physiol. 316(4): H801-H827.**
	Although substantial evidence shows that smoking is positively and robustly associated with cardiovascular disease (CVD), the CVD risk associated with the use of new and emerging tobacco products, such as electronic cigarettes, hookah, and heat-not-burn products, remains unclear. This uncertainty stems from lack of knowledge on how the use of these products affects cardiovascular health. Cardiovascular injury associated with the use of new tobacco products could be evaluated by measuring changes in biomarkers of cardiovascular harm that are sensitive to the use of combustible cigarettes. Such cardiovascular injury could be indexed at several levels. Preclinical changes contributing to the pathogenesis of disease could be monitored by measuring changes in systemic inflammation and oxidative stress, organ-specific dysfunctions could be gauged by measuring endothelial function (flow-mediated dilation), platelet aggregation, and arterial stiffness, and organ-specific injury could be evaluated by measuring endothelial microparticles and platelet-leukocyte aggregates. Classical risk factors, such as blood pressure, circulating lipoproteins, and insulin resistance, provide robust estimates of risk, and subclinical disease progression could be followed by measuring coronary artery Ca^{2+} and carotid intima-media thickness. Given that several of these biomarkers are well-established predictors of major cardiovascular events, the association of these biomarkers with the use of new and emerging tobacco products could be indicative of both individual and population-level CVD risk associated with the use of these products. Differential effects of tobacco products (conventional vs. new and emerging products) on different indexes of cardiovascular injury could also provide insights into mechanisms by which they induce cardiovascular harm.

88.	**Jacob, M. (2019). Looking Back and Ahead: The Food and Drug Administration's Regulation of the Tobacco Industry and Next-Generation Products. Adv Dent Res. 30(1):22-25.**
	Regulatory policy toward tobacco significantly affects oral health because tobacco use is a driver of diseases that manifest themselves in or near the oral cavity. Tobacco use in the United States has been associated with millions of cases of periodontal disease. Researchers have identified the role of combusted and noncombusted tobacco products in promoting cancers of the head and neck, leading to disease and premature death. Tobacco companies have moved increasingly toward so-called next-generation products (NGPs)-products that may emit fewer toxins than combustible forms of tobacco. Although NGPs may negatively affect the lungs and other bodily systems, they shift the injection site of nicotine from the lungs to the oral cavity and oral tissues. Because the long-term effects of NGPs are unknown, this tobacco marketing development has profound implications for oral disease. The US Food and Drug Administration exercises regulatory authority over tobacco products. The tobacco industry has avoided meaningful regulation of its products, especially smokeless forms. By publishing new research, oral health scientists can meaningfully shape the climate in which the administration's policy making occurs.
89.	**Ito, S., Taylor, M., Mori, S., et al. (2019). An inter-laboratory in vitro assessment of cigarettes and next generation nicotine delivery products. Toxicol Lett. 315:14-22.**
	In vitro testing can facilitate the rapid assessment of next generation nicotine delivery products (NGPs) with comparisons to combustible tobacco products. In vitro assays for cytotoxicity and oxidative stress were employed at BAT (UK) and JT (Japan) to test total particulate matter (TPM) of a scientific reference cigarette and aerosol collected mass (ACM) of a commercially available E-cigarette and two tobacco heating products (THP). 3R4F TPMs were generated using the Health Canada intense (HCI) regimen, a modified regime (mHCI) for the THP ACMs and the CORESTA recommended method no. 81 for the E-cigarette ACM. Human lung cells were exposed to the test product TPM/ACMs at concentrations between 0-200 µg/ml followed by the employment of commercially available assays for endpoint analysis that included reactive oxygen species (ROS) generation, the glutathione ratio (GSH:GSSG), activation of the antioxidant response elements (ARE) and cellular viability. TPM/ACM nicotine concentrations were quantified using a UPLC-PDA technique. At both laboratories the 3R4F TPM induced significant and dose-dependent responses in all in vitro assays, whereas no significant responses could be measured for the NGP ACMs. In conclusion, both laboratories obtained comparable results across all endpoints therefore demonstrating the utility of the in vitro techniques combined with standardised test products to support the assessment of NGPs.
90.	**Muhammad-Kah, R.S., Pithawalla, Y.B., Boone, E.L. et al. (2019). A Computational Model for Assessing the Population Health Impact of Introducing a Modified Risk Claim on an Existing Smokeless Tobacco Product. Int J Environ Res Public Health. 16(7): E1264.**
	Computational models are valuable tools for predicting the population effects prior to Food and Drug Administration (FDA) authorization of a modified risk claim on a tobacco product. We have developed and validated a population model using best modeling practices. Our model consists of a Markov compartmental model based on cohorts starting at a defined age and followed up to a specific age accounting

	for 29 tobacco-use states based on a cohort members transition pathway. The Markov model is coupled with statistical mortality models and excess relative risk ratio estimates to determine survival probabilities from use of smokeless tobacco. Our model estimates the difference in premature deaths prevented by comparing Base Case ("world-as-is") and Modified Case (the most likely outcome given that a modified risk claim is authorized) scenarios. Nationally representative transition probabilities were used for the Base Case. Probabilities of key transitions for the Modified Case were estimated based on a behavioral intentions study in users and nonusers. Our model predicts an estimated 93,000 premature deaths would be avoided over a 60-year period upon authorization of a modified risk claim. Our sensitivity analyses using various reasonable ranges of input parameters do not indicate any scenario under which the net benefit could be offset entirely.

Attachment 2

Details of independent studies assessing HTPs and/or IQOS use

Reference	Country	Study Design	Participants	Outcome measures	Summary of findings
Brose et al., 2018	UK	Cross sectional	A sample of 12,696 people completed the survey and responses were weighted to be representative of the population.	Heated tobacco product awareness, trial and current use	Among all participants, 9.3% (95% CI: 8.8-9.8) reported awareness; this included 0.9% (95% CI: 0.8–1.1) who had tried or used the products in the past and 0.8% currently using (95% CI: 0.7–1.0). Use of HnB tobacco products differed ($p \leq .001$) with age, sex, socioeconomic status, smoking, and e-cigarette use; however, the only association with at least a small effect was e-cigarette users reporting higher prevalence than non-users [$\chi2(9) = 674.1$, $p < .001$; $V = 0.133$].
Kang et al., 2019	Korea	Cross sectional	59,532 adolescents aged 12-18 years	HTP ever use and quit attempts	In all, 2.8% of South Korean adolescents were ever HTP users. Among these, 75.5% were current cigarette users, 45.6% were current e-cigarette users and 40.3% were concurrent users of cigarettes and e-cigarettes. Unlike ever use of e-cigarettes, which was associated with a higher likelihood of cigarette quit attempts (adjusted OR (aOR) = 1.35, 95% CI: 1.16 to 1.58), no difference in cigarette quit attempts was found for ever use of HTPs (aOR = 1.07, 95% CI: 0.91 to 1.26).
Kim et al., 2018	Korean	Cross sectional	228 adults aged 19-24 years	Ever and current use of *IQOS* specifically	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 used 10–20 *HEETS* sticks a

Reference	Country	Study Design	Participants	Outcome measures	Summary of findings
					day. The current *IQOS* users decided to use *IQOS* because they believed it was less harmful. 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).
Kioi et al., 2018	Japan	Cross sectional	4432 subjects aged 40-69 years who were either healthy or suffered from hypertension, diabetes, cerebrovascular disease, COPD, asthma, atopic dermatitis, cancer, or mental disorders.	Ever and current use of HTP	Percentage of heated tobacco product current or ever use was low (<0.1%) among both men and women.
Kotz & Kastaum 2018	Germany	Cross sectional	18,415 subjects aged 14 years and older	Ever and current use of HTP and risk perception	Among current smokers and recent ex-smokers (<12 months smoke-free), 0.3% (95% CI = 0.09–0.64%) currently used HTPs, and 6.0% (95% CI = 5.0–7.2%) had ever used them. Consumption of HTPs increased with increasing education and income. The majority perceived HTPs as somewhat (41.0%, n = 25) or much (14.8%, n = 9) less harmful, and 37.7% (n = 23) as equally harmful compared with tobacco cigarettes.
Lee et al., 2019	Korea	Cross sectional	60,040 students from middle school	HTP ever use	The prevalence of heated tobacco ever use was 0.1% in the total population, the prevalence of dual use of cigarettes and heated tobacco was

Reference	Country	Study Design	Participants	Outcome measures	Summary of findings
					0.3%, the prevalence of e-cigarette and heated tobacco ever use was 0.2% and the prevalence of all three product ever use combined was 2.3%.
Liu et al., 2019	Italy	Cross sectional	3086 subjects aged 15 years or above	Awareness, intention to use and current use of *IQOS* specifically	One in five (19.5%) respondents were aware of *IQOS*, 1.4% have tried it and 2.3% intended to try it. Overall, 1.0% of never smokers, 0.8% of ex-smokers and 3.1% of current cigarette smokers have tried *IQOS*. Correspondingly, 1.2% of never e-cigarette users, 2.9% of ex-e-cigarette users and 7.7% of current e-cigarette users have tried *IQOS*.
Marynak et al., 2018	US	Cross sectional	4107 adults aged ≥18 years.	Awareness and ever use of HTP	A total of 5.2% of U.S. adults were aware of HTPs, including 9.9% of current cigarette smokers. Overall, 0.7% of U.S. adults, including 2.7% of current smokers, reported ever use of HTPs. Odds of ever use were higher among current smokers (AOR = 6.18) than never smokers, and higher among adults aged <30 years (AOR = 3.35) than those aged ≥30 years.
Miyazaki et al., 2018	Japan	Cross sectional	7338 respondents aged 18±69 years in 2015 (3632 men and 3706women).	Ever and current use of HTP	Use of HTPs was 1.8% in current smokers, 1.0% in former smokers and 0.1% in never smokers.
Nyman et al., 2018	US	Cross sectional	Data from the 2016 and 2017 Tobacco Products and Risk Perceptions Surveys of national probability samples of US adults,	Ever and current use of HTP	2.2% of adults had ever used HTPs and 1.1% were current users of heated tobacco products.

Reference	Country	Study Design	Participants	Outcome measures	Summary of findings
			conducted online during September–October 2016 (n = 6014) and August–September 2017 (n = 5992)		
Stoklosa et al., 2019	Japan	Cross sectional	2014 to 2018 monthly retailer panel data	Impact of different dates of *IQOS* introduction across Japan's regions on the patterns of cigarette sales	The introduction of *IQOS* likely reduced cigarette sales in Japan. Cigarette sales begin to substantially decline at the time of the introduction of *IQOS* in each of 11 Japanese regions (Chow tests $p < 0.001$). *IQOS* introduction, which varied across regions, better predicted the timing of cigarette sales decline than any one time applied to all regions simultaneously (a national-level exogenous shock) and then nearly all possible rearrangements of the true *IQOS* introduction months among the regions (exact permutation test's p value from 0.02 to 0.13, depending on the study approach).
Sutanto et al., 2019	Japan	Cross sectional	Wave 1 of the International Tobacco Control Japan Survey (February–March 2018), tobacco product users and non-users, aged 20 years and older (n = 4684); the main analytic sample was	Prevalence of HTP use within indoor public spaces among tobacco users compared to combustible cigarettes	HTP use is less common than CC use within indoor public spaces. Overall, 15.6% of current tobacco users in Japan declared that they used HTPs within indoor public spaces. Any HTP use within indoor public spaces was significantly lower than any CC use (80.1% vs. 96.7%). Dual HTP + CC users reported using CCs more frequently than using HTPs within indoor public spaces (97.7% vs. 76.0%).

Reference	Country	Study Design	Participants	Outcome measures	Summary of findings
			current tobacco users (n = 4069)		
Tabuchi et al., 2018	Japan	Cohort	8240 individuals (15–69 years old in 2015) followed up to 2017	Ever and current use of *IQOS* and other HTP	Prevalence of *IQOS* users increased from 0.3% in January–February 2015 to 0.6% in January–February 2016 and up to 3.6% in January–February 2017, while estimated rates of use of other HnB tobacco products remained low in 2017.
Wu et al., 2019	Hong Kong	Cross sectional	5131 (45.2% male; 26.7% aged ≥60) adults	Intention to use and ever use of HTP	1.7% of males had ever used HTP and 11.1% had intention to use them (in never users of heated tobacco products), while 0.4% of females had ever used them and 2.9% intended to use them. By smoking status, 8.9% of current smokers were ever users and 28.8% intended to use them in the future, 0.6% of former smokers were ever users and 3.5% intended to use them in the future while 0.05% of never smokers were ever users and 2.7% intended to use them in the future.