From:	TGA Info
To:	Medicines Scheduling
Subject:	TRIM: [Email 1 of 7] Application to amend the Poisons Standard - Heated Tobacco Products [SEC=No Protective Marking] [SEC=UNCLASSIFIED] TGA:00751656
Date:	Monday, 4 November 2019 11:29:50 AM
Attachments:	Application to amend the Poisons Standard - Heated Tobacco Products.PDF Glossary.pdf Appendix 5 Examples of research conducted by independent researchers.pdf Appendix 4 Impact of HTP aerosol on the environment and on bystanders.pdf Appendix 2 Marketed HTP Devices and Consumables.pdf Appendix 6 Abuse Liability.pdf Appendix 1 Heated tobacco regulations.pdf Appendix 3 Independent scientific Publications.pdf image001.png

---

Good morning

Please ensure that any internal correspondence, including this forwarding email, is deleted prior to sending the response.

Please find attached an email from [redacted] - email: [redacted] - for your follow up and response. If your area is not the appropriate area to respond to this email please let us know.

If you are responding directly to an external enquiry, you are responsible for ensuring that the TGA customer service standards are met.

If your area does not have access to a generic email address, the RAS can send approved responses on your behalf from info@tga.gov.au, provided there is sufficient time for the service standards to be met.

If you have any questions about this email please contact Diana Belacic or Rachel Bernardi.

Kind regards

[redacted]

Regulatory Assistance Service

Regulatory Assistance and Information Services, Regulatory Engagement and Planning Branch

Phone: 1800 020 653 Fax: 02 6203 1605

Email: info@tga.gov.au

Therapeutic Goods Administration
Department of Health
PO Box 100
Woden ACT 2606 Australia

www.tga.gov.au

---------- Original Message ----------
From: [redacted]@pmi.com;
Received: 1/11/2019 10:29 AM
To: TGA Info (info@tga.gov.au);
Cc: [redacted]@pmi.com
Subject: [Email 1 of 7] Application to amend the Poisons Standard - Heated Tobacco Products [SEC=No Protective Marking]

From: [redacted]
Sent: Friday, 1 November 2019 9:49 AM
To: chemicals.scheduling@health.gov.au
Cc: [redacted]@pmi.com) ; [redacted]@pmi.com)
Subject: [Email 1 of 7] Application to amend the Poisons Standard - Heated Tobacco Products

The Secretary
Chemicals Scheduling Secretariat
By email: chemicals.scheduling@health.gov.au

Dear Sir or Madam

I **enclose** our application to amend the Poisons Standard along with the appendices. Literature references are attached in the following emails.

I would appreciate confirmation of receipt of the application and supporting documents by reply email.

Kind regards

[redacted] | **Philip Morris Limited**
[redacted]
L6, 30 Convention Centre Place, South Wharf, VIC, 3006

cid:image002.png@01D21EF1.2F6697D0

Application Documents Attached

1. Application to amend the Poisons Standard – Heated Tobacco Products
2. Glossary
3. Appendix 1 Heated tobacco regulations
4. Appendix 2 Marketed HTP Devices and Consumables
5. Appendix 3 Independent scientific Publications
6. Appendix 4 Impact of HTP aerosol on the environment and on bystanders
7. Appendix 5 Examples of research conducted by independent researchers
8. Appendix 6 Abuse Liability

Application to Amend the Poisons Standard

Australian Government

Department of Health

Request for Scheduling Exemption

31 October 2019

Philip Morris Limited. 30 Convention Centre Pl, South Wharf VIC 3006

Philip Morris Limited

For further guidance in using this form, refer to the *Scheduling Policy Framework for Medicines and Chemicals 1 February 2015* (SPF), in particular refer to Chapter 4: GUIDELINES FOR APPLICATIONS AND INFORMATION REQUIREMENTS, available at (https://www.tga.gov.au/publication/ahmac-scheduling-policy-framework-medicines-and-chemicals).

May 2015

CONTENTS

CONFIDENTIALITY

This application contains no material claimed to be commercial-in-confidence.

APPLICANT'S DETAILS

1	**Applicant's [Sponsor's] name**	Philip Morris Limited
2	**Applicant's [Sponsor's] Business Address**	30 Convention Centre Pl, South Wharf VIC 3006
3	**Business name (if applicable)**	Philip Morris Limited
4	**Date of submission**	31 October 2019
5	**Contact person**	[redacted]
6	**E-mail Address of contact person**	[redacted]@pmi.com [redacted]@pmi.com
7	**Postal address of contact person**	L6, 30 Convention Centre Pl, South Wharf VIC 3006
8	**Phone Number of contact person**	[redacted]
9	**Fax Number of contact person**	NA

DECLARATION

I, the undersigned, on behalf of Philip Morris Limited:

- declare that the information provided in this application is true and current;
- undertake not to publicly disclose the notices of interim decision or final decision in respect of this application, until (if relevant i.e. following referral to an expert advisory committee) these documents are published pursuant to subsections 42ZCZP and 42ZCZS of the Therapeutic Goods Regulations 1990, respectively.

[redacted] – Australia, New Zealand and Pacific Islands
Philip Morris Limited
31 October 2019

PART 1 – SUMMARY OF THE APPLICATION

PROPOSED SCHEDULING / RESCHEDULING OR OTHER CHANGE TO THE POISONS STANDARD

Schedule 7 - Amendment

In this application Philip Morris Limited requests that "tobacco prepared and packed for heating" is added as an additional exemption (d) to the current Nicotine entry in Schedule 7 of the Poisons Standard.

7 – Proposed Amendment

NICOTINE except:

(a) when included in Schedule 6;

(b) in preparations for human therapeutic use;

(c) in tobacco prepared and packed for smoking**; or**

(d) <u>in tobacco prepared and packed for heating.</u>

[Throughout this document we refer to products which are the subject of this amendment as Heated Tobacco Products (HTPs)]

In Australia, tobacco for smoking is the only tobacco allowed for sale. This is because "tobacco prepared and packed for smoking" is not scheduled as the result of an exemption from the nicotine entry in Schedule 7.

By a large measure, tobacco-related morbidity and mortality arise from one particular form of tobacco use – cigarettes. Decades of epidemiology demonstrate that the risks of serious disease, such as lung cancer, heart disease, and chronic obstructive pulmonary disease (COPD), are substantially higher among smokers than among non-smokers (Ramst and Wikmans, 2014). From the time this exemption in Schedule 7 was introduced, there has been considerable advancement in scientific understanding as a result of research and development, and new tobacco products that do not involve the combustion of tobacco have emerged globally. As a leading author in health policy has put it *"[a] diverse class of alternative nicotine delivery systems (ANDS) has recently been developed that do not combust tobacco and are substantially less harmful than cigarettes. ANDS have the potential to disrupt the 120-year dominance of the cigarette [and] ... may provide a means to compete with, and even replace, combusted cigarette use, saving more lives more rapidly than previously possible."*(Abrams et al., 2018).

HTPs are part of a new generation of non-combustible products that heat tobacco, in contrast to traditional combustible cigarettes (CCs) which burn tobacco. Throughout this document the term HTP(s) refers to a consumable product containing tobacco that is heated in a controlled manner to temperatures that do not result in combustion. The heating device may be an integral part of the consumable (e.g. a carbon heat source). More commonly, the tobacco is heated with the aid of a separate device into which the consumable tobacco product is inserted. In this latter case, the combination of consumable product and device may be referred to as a Tobacco Heating System (THS) or Electrically Heated Tobacco System (EHTS). The consumable tobacco product only

functions as intended when used in combination with the heating device. The context of the description should make it clear when either the consumable product per se is referred to, or when the combination as a system is referenced. Where there is ambiguity in the terminology, further clarification is provided in the text or in the Glossary.

Like "tobacco prepared and packed for smoking," HTPs contain nicotine that is naturally present in tobacco. While legally available and sold in more than 50 markets as of October 2019 (including the United States, New Zealand, Canada, the United Kingdom, South Africa and more than 20 EU countries), HTPs are not available in Australia because of the current provisions around nicotine in Schedule 7. The Institute for Global Tobacco Control tracks the regulatory landscape for HTPs for a selection of countries. As of November 2018, in the countries tracked, HTPs were legally available (either regulated or non-regulated) in 50 of those, and regulated in 35 (Appendix 1). However, at least one country – Norway – out of the few countries currently listed as having a ban is now working to reverse the ban.

Australia has advanced tobacco control and consumer protection measures, a comprehensive regulatory framework and structured tobacco cessation services and programmes. With this strong background, the country also has the ability to regulate HTPs, as do 35 other Organisation for Economic Co-operation and Development (OECD) countries. The major difference between Australia and the other OECD countries, is that Australia's ban on tobacco products other than for smoking, precludes the use of better tobacco products by smokers who do not quit. Turkey is the only other OECD country that has a similar practice.

This application provides information for the Committee's consideration on the toxicology, science and related developments with HTPs, supporting the conclusion that the scheduling of nicotine in Australia for non-therapeutic purposes, should be amended to exempt HTPs in the same way as "tobacco prepared and packed for smoking". This can be achieved by extending the exemption to "tobacco prepared and packed for heating."

HTPs are a better alternative for people who would otherwise continue to smoke. Smokers who switch to these products can significantly reduce their exposure to many of the toxic chemicals found in cigarette smoke. While not risk free, they are a better alternative to smoking. HTPs should be available to the close to three million Australians who are already smoking, the majority of whom would not otherwise quit as demonstrated by the plateaued reduction in smoking incidence over recent years. Updating Schedule 7 in this way would enable them to move away from cigarettes, the most harmful way to consume nicotine.

Products in this category are available in more than 50 markets. They have been recognised by various regulators, and governments are using a variety of approaches to market access. In April 2019, following a rigorous science-based review through the Premarket Tobacco Product Application (PMTA) pathway, the U.S. Food and Drug Administration (FDA) determined that authorising PMI's "Tobacco Heating System"[1]

[1] *IQOS* Tobacco Heating System (THS) consists of *IQOS* System Holder and Charger (*IQOS* device), Marlboro *HeatSticks*, Marlboro Smooth Menthol *HeatSticks* and Marlboro Fresh Menthol *HeatSticks*

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*" (FDA press release, 2019).

In Japan, HTPs have been available since November 2014 and are regulated under the Tobacco Business Act (The Japan Times, 2018). 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 (Regulatory impact statement, 2019) states "*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.*"

Norway is also considering a framework to enable smokers to have access to better products, while preventing the use of any tobacco or nicotine product by youth as reflected in the recently released new tobacco strategy for 2019-2021 by the Norwegian Ministry of Public Health: "*The Government's tobacco policy thus considers harm reduction for established smokers who are unable or unwilling to quit, and at the same time prevents the use of tobacco and nicotine dependence among children and youth. This is a balance which must be continuously assessed in light of the development in the market and new knowledge.*"[2]

With this application Philip Morris Limited is requesting that HTPs be added as an additional exemption to the current nicotine entry in Schedule 7 of the Poisons Standard. Our request is substantiated by the data referred in this application.

SUBSTANCE SUMMARY

Heated Tobacco Products

HTPs are part of a new generation of non-combustible tobacco products in which the tobacco is heated, in contrast to CCs in which the tobacco is burned. The fundamental principle of HTPs is to heat tobacco to temperatures below its ignition temperature (known to exceed 400 °C) (Nordlund et al., 2019) instead of burning it, to form a nicotine-containing aerosol that is not cigarette smoke. An internal or external heat source can be used to generate a nicotine containing aerosol from tobacco. The user draws on a mouthpiece at intervals to inhale volumes of the aerosol through the mouth. The number of draws is limited and the products are typically designed to mimic the average consumption time in a standard cigarette.

The aerosol generated by HTPs, and inhaled by the user, is fundamentally different from cigarette smoke. In the aerosol of HTPs, the levels of nicotine generated and inhaled are comparable to those found in cigarette smoke. When exhaled, HTP aerosol liquid droplets dissipate very rapidly in the environment compared to cigarette smoke.

Table 1 shows the differences between CCs and the new-generation non-combustible products for inhalation, such as HTPs and Electronic Nicotine Delivery Systems (ENDS).

[2] https://www regjeringen no/no/dokumenter/meld.-st.-19-20182019/id2639770/

Table 1: Comparison between traditional combustible cigarettes, HTPs and ENDS

	A. Tobacco prepared and packed for smoking	**B. Tobacco prepared and packed for heating / HTPs**	**C. Nicotine for vaping / ENDS**
Form of nicotine	Cured tobacco	Cured tobacco	Nicotine as a chemical substance
Category examples	Tobacco in cigarettes or cigars, roll your own	Tobacco in sticks, pods or capsules	e-cigarettes / nicotine salts / liquid for vaping
Scheduling status	Permitted for sale in Australia (not a scheduled poison and exempted from Schedule 7)	Not permitted for sale in Australia (scheduled poison. Not exempted from Schedule 7). **Exemption from Schedule 7 requested in this application**	Not permitted for sale in Australia (scheduled poison. Not exempted from Schedule 7). **Not included in the scope of this application**
Description of the category	Products made entirely or partly from leaf tobacco as the raw material, which are intended for smoking	Products made entirely or partly of leaf tobacco as raw material, which are heated without combustion to generate an inhalable aerosol	Products using a nicotine containing e-liquid are heated to generate an inhalable aerosol
Typical range of tobacco content	600-800 mg	260 - 320 mg (The composition of the tobacco in HTPs is different to that in cigarettes. They are specifically manufactured to deliver nicotine at a lower operating temperature)	None
Nicotine as an ingredient	No added nicotine. Nicotine content is from naturally occurring nicotine in tobacco	No added nicotine. Nicotine content is from naturally occurring nicotine in tobacco	Nicotine is added to the e-liquid. Content/ concentration of nicotine varies depending on product
Source of energy	Combustion of tobacco (e.g. initiated from matches, lighter) leading to various chemical reactions including formation of ash and smoke	The heating-system can be an internal or external heat source to aerosolise nicotine from tobacco. The user draws on the mouthpiece to inhale an aerosol through the mouth. No smoke or ash is formed	All e-cigarettes have three basic components: a battery powered heat source, an atomiser and a fluid (e-liquid). The e-liquid is heated by the battery powered heat source to produce an aerosol inhaled by the user. No smoke or ash is formed
Temperature range	Temperatures near the lit end of the cigarette (combustion zone) range from 800-900°C when a puff is taken	Temperature is controlled and ranges typically around or below 350°C (below the temperatures required for initiation of combustion)	Variable in terms of temperature
Output	Tobacco smoke is an aerosol consisting of gaseous, liquid, and solid materials. More than 6,000 constituents identified in cigarette smoke, of which about 100 are categorised as harmful or potentially harmful constituents (HPHCs)	The aerosol generated by HTPs consists of gaseous and liquid materials with no solid particles. Contains fewer HPHCs than cigarette smoke, and many of the HPHCs identified are present at lower levels (on average 90% lower) than in cigarette smoke [Refer to C]	Aerosol generated depends on consumable (e.g. e-liquid) and device (e.g. e-cigarette) design and performance. Content of aerosol generated is variable dependant on ingredients in the consumable
Examples	John Player Special and Horizon (Imperial Brands Plc); Winfield, Benson & Hedges (British American Tobacco Plc - BAT); Longbeach, Peter Jackson (Philip Morris International Inc). Approximately 60 brands and sub-brands available on the Australian market	HEETS with IQOS® (PMI); NeoStik with glo (BAT); Vapodes with Ploom® (Japan Tobacco International); Fiit with lil® (Korean Tobacco and Ginseng – KT&G). Approximately 12 brands available globally [Appendix 2]	MESH (PMI); Blu (Imperial); Vype (BAT); Multiple products available globally with significant variation in quality and content. Close to 8,000 e liquid flavours available globally

Toxicity of Heated Tobacco Products

As there is no combustion of the tobacco in HTPs, the number and levels of HPHCs in the aerosol from HTPs are significantly reduced compared with cigarette smoke. As a result, overall toxicity of HTPs is reduced in comparison to CCs. Therefore, users and bystanders are exposed to lower levels of Harmful and Potentially Harmful Constituents (HPHCs) in comparison to cigarette smoke, and to an aerosol that is significantly less toxic.

A thorough analysis of the aerosol generated by one of these products, PMI's HTP, was conducted by the manufacturer, together with a characterisation and quantification of the levels of 58 analytes and constituents, most of which are HPHCs. This analysis included all of the HPHCs prioritised by the U.S. FDA, Health Canada, the World Health Organization (WHO), and the International Agency for Research on Cancer (IARC). The assessment and data show that the PMI's HTP generates an aerosol with significantly lower levels of all classes of measured HPHCs compared to the smoke of the 3R4F reference cigarette on a per-unit (tobacco stick) and a per-unit-nicotine basis. On a per-unit basis, the levels of almost all constituents were reduced by at least 80%, and the majority by 90% to 99%. On both a per-stick and per-unit nicotine basis, the average reduction in the levels amongst all the HPHCs (excluding nicotine) is greater than 90%. Details of the specific HPHCs and the level of reductions are in [C].

Nicotine

Substance chemistry: Nicotine is a plant alkaloid naturally present in the tobacco plant, Nicotiana tabacum and related species (Solanaceae). Other plants in the Family Solanaceae such as red peppers, eggplant, tomatoes, and potatoes contain trace levels of nicotine.

Chemical name: (S)-3-(1-Methylpyrrolidin-2-yl) pyridine,
Molecular formula: $C_{10}H_{14}N_2$

When "tobacco prepared and packed for smoking" is smoked, nicotine is distilled from burning tobacco. On entering the body, it is metabolised and excreted with a plasma half-life of approximately one to two hours, although there is considerable variability from one individual to another. The metabolism reactions proceed utilising cytochrome CYP2A6, present in the liver. The rate of nicotine metabolism and excretion depends on a variety of factors such as gender, age, use of other medications, pregnancy and consumption of food (Streller and Roth, 2013), and is similar for both CCs and HTPs.

Toxicity of Nicotine

Nicotine is an addictive central nervous system (CNS) stimulant that causes either ganglionic stimulation in low doses or ganglionic blockage in high doses (PubChem). It exerts its pharmacological effects through binding to nicotinic acetylcholine receptors (nAChRs) which are expressed in cells throughout the body. While nicotine is the primary addictive component sustaining tobacco use, it has been recognised not to be the cause of the vast majority of harm associated with tobacco use. Products that deliver nicotine through processes other than combustion are expected to be associated with less toxicity. Authoritative reviews (Surgeon General, 2014; RCP, 2016; Niaura, 2016)

provide evidence of nicotine toxicity on various functions and these are summarised in **Table 2**.

Table 2: Nicotine toxicity

Nicotine toxicity	Toxicity
Addiction	Yes
Reproductive and developmental toxicity	Yes
Carcinogenic	No
Cardiovascular toxicity	No
Respiratory toxicity	No

Furthermore, based on safety information included in the Summary of Product Characteristics (SmPC) (MSD Manuals, 2018) or labels for currently marketed Nicotine Replacement Therapies (NRTs), nicotine class effect risks exist for any products containing nicotine, including NRTs. These nicotine class effect risks are similar for CCs and HTPs and include effects on the immune system, nervous system, cardiac and vascular system, respiratory and thoracic system among others.

Nicotine and Smoking-related Disease

Although addictive and not risk free, there is scientific consensus today that nicotine is not the primary cause of tobacco-related disease.

Referencing a Cochrane Database of Systematic Review (Stead et al., 2012), the Department of Health and The Royal Australian College of General Practitioners (RACGP) both state: "*Nicotine is the main substance in tobacco that causes addiction – it makes people dependent on cigarettes – but it is the other chemicals in combusted tobacco that cause cancer, accelerate heart disease and affect other areas of health*" (Department of Health in Australia; The Royal Australian College of General Practitioners).

The United States Surgeon General stated that "*Inhaling the complex chemical mixture of combustion compounds in tobacco smoke causes adverse health outcomes, particularly cancer and cardiovascular and pulmonary diseases through mechanisms that include DNA damage, inflammation, and oxidative stress*" (HHS, 2010).

The Royal College of Physicians (RCP) in its 2016 report on "Nicotine without smoke, Tobacco harm reduction" states (RCP, 2016): "*Nicotine is not, however, in itself, a highly hazardous drug. It increases heart rate and blood pressure, and has a range of local irritant effects, but is not a carcinogen* (IARC, 2015). *Of the three main causes of mortality from smoking, lung cancer arises primarily from direct exposure of the lungs to carcinogens in tobacco smoke, COPD from the irritant and pro-inflammatory effects of smoke, and cardiovascular disease from the effects of smoke on vascular coagulation and blood vessel walls. None is caused primarily by nicotine.*"

The U.S. FDA Center for Tobacco products stated that: "*The regulatory framework for reducing harm from tobacco must include nicotine - the chemical responsible for*

addiction to tobacco products - as a centerpiece. Nicotine, though not benign, is not directly responsible for the tobacco-caused cancer, lung disease, and heart disease that kill hundreds of thousands of Americans each year. The FDA's approach to reducing the devastating toll of tobacco use must be rooted in this foundational understanding: other chemical compounds in tobacco, and in the smoke created by combustion, are primarily to blame for such health harms." This also led to the FDA pursuing a regulatory framework for tobacco recognising "*that the core problem of nicotine lies not in the drug itself but in the risk associated with the delivery mechanism*" (Gottlieb and Zeller, 2017).

Products containing nicotine pose different levels of health risks to users with combustible products like CCs (currently exempted from Schedule 7), being the most harmful, NRTs being the least harmful, and the risk related to HTPs considered to be much closer to NRTs on the risk continuum than to cigarettes (FDA, 2019).

Range of uses of Nicotine

Products that contain nicotine are tobacco-containing products such as cigarettes, cigars, pipe tobacco, and chewing tobacco. Nicotine is also used in therapeutic smoking cessation products such as patches, gums, sprays and inhalers. Electronic cigarettes or "E-cigarettes" may contain 'purified nicotine and not tobacco' (American College of Medical Toxicology).

Smoking-cessation is undoubtedly the best way to reduce the risk of harm and disease caused by cigarette smoking. As the Institute of Medicine (IOM) of the National Academies has noted, smoking-cessation is the "gold standard" or highest potential for risk reduction. The closer the risks and exposures from alternative products to cigarettes are to cessation products, the more confident a regulator can be in the chances for net public health benefit, with the goal being to compare how the risk or exposure reduction attained compares to smoking cessation. The IOM states: "*On the opposite end of the spectrum of exposure and risk reduction is the 'gold standard' of smoking cessation (or tobacco cessation in the case of smokeless tobacco users). This provides an aspirational goal for risk and exposure for MRTPs (Modified Risk Tobacco Products) - 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.*" (IOM, 2012).

Even with NRTs and other interventions, there is evidence that the majority of smokers using smoking cessation medication do not complete the recommended course of treatment. Reasons for premature discontinuation of medication include relapse back to smoking, reported side effects and the perception that the medication has worked for the user and is no longer needed (Greenhalgh et al., 2018). As noted in the 2007 report by the Royal College of Physicians in the UK *"[s]ince nicotine is the primary addictive constituent of tobacco smoke, the harm reduction approach for those who cannot otherwise quit smoking tobacco or who want to reduce the impact their smoking has on themselves and others is to substitute cigarettes with less hazardous alternatives. Even though smoking-related harms may be merely reduced rather than removed by this approach, many lives could also be saved and much morbidity prevented.*"

(RCP, 2007). It is therefore imperative to also offer scientifically substantiated, less-harmful alternatives to Australians who are already – and will otherwise – keep smoking.

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. **Figure 1** showcases the plasma nicotine concentrations achieved by cigarettes and various NRTs.

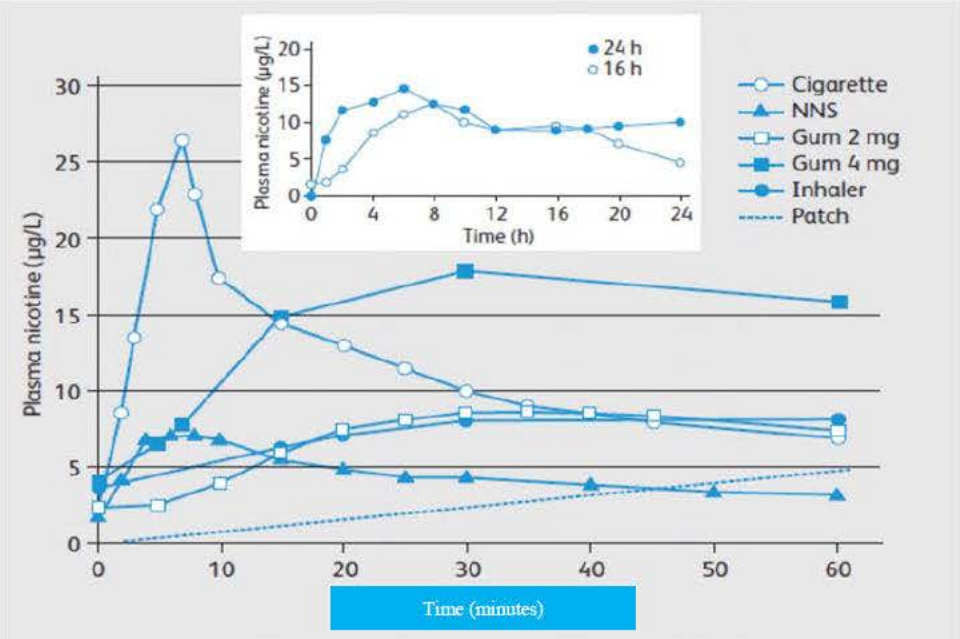


Figure 1: Venous plasma nicotine concentrations of nicotine and various NRTs

Venous plasma nicotine concentrations achieved over 1 h by a single cigarette and by single doses of various forms of nicotine replacement therapy (NRT – nicotine nasal spray (NNS), 2 and 4 mg gum, and nicotine patch). Inset: nicotine levels after a 16- and 24-h course of nicotine patch treatment over a 24-h period. (Reproduced from: Schneider et al., 2001)

In comparing nicotine concentrations of CCs with HTPs, four PK/PD studies were conducted in Japan, Europe and the U.S. with PMI's HTP using a randomised cross-over design to assess the rate and extent of nicotine uptake in subjects who use HTPs as compared to cigarettes and NRT[3]. The relationship between blood plasma nicotine (PK) concentration and suppressing the urge to smoke (PD) in adult smokers were also evaluated in these studies. This data is important to determine the extent to which adult smokers find a HTP acceptable as a cigarette substitute, although other factors such as taste and product design are also important in determining acceptance. The studies also

[3] 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

provide initial safety data (e.g. data on vital signs, clinical biochemistry, haematology, spirometry, electrocardiogram, adverse events). The results of these four PK/PD studies are shown in **Figure 2** where the red line shows the pharmacokinetic profile from volunteers using a single cigarette of their own brand and the blue line when they used a single HTP.

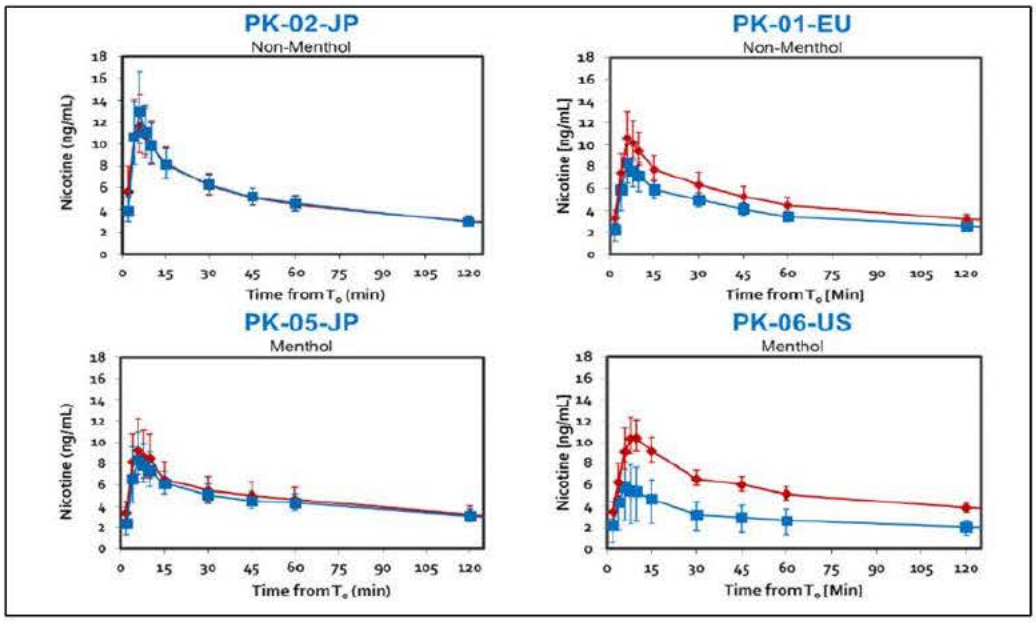


Figure 2: Geometric means and 95% confidence intervals of nicotine concentrations over 120 minutes with a single use of the THS or cigarette in Japan (JP), US, and Europe (EU) using EHTP Menthol or Regular. T_0 equals start of product use.

In assessing the public health impact of nicotine-containing products, it is important to consider the delivery systems and acceptability to the intended consumers to enable a transition from smoking CCs. The results of the PK/PD studies show that HTPs have a profile that is acceptable to smokers of CCs as a substitute.

In Summary

Currently, the use of nicotine in tobacco, other than in "tobacco prepared and packed for smoking", are included in Schedule 7 of the Poisons Standard as a result of the naturally occurring nicotine component of tobacco. This means that alternative nicotine delivery products, such as HTPs, cannot be sold in Australia and the only option for smokers who would otherwise continue to smoke are CCs - the most harmful way to use tobacco.

The current exemption "tobacco prepared and packed for smoking" permits the consumption of tobacco and nicotine in its more dangerous form (i.e. cigarette smoke). Adding to the exemption "tobacco prepared and packed for heating" would enable the availability of HTPs as a better alternative for current Australian smokers who do not quit. HTPs were developed based on the fundamental proposition that if combustion is eliminated, the level of harmful chemicals generated and inhaled is significantly reduced.

Delivery of nicotine in aerosol from a heated non-combusted tobacco product reduces the exposure to many of the chemicals found in cigarette smoke that are the main cause of tobacco smoking related disease. Specific HTPs, such as PMI's HTP, have been reviewed by several regulators globally and accepted as a better alternative than continued smoking for adult smokers who do not quit.

In addition to the U.S., PMI's HTP was authorised in countries such as Poland, Greece, Austria, and Portugal after thorough review of a scientific submission dossier. Furthermore, the scientific evidence was reviewed by the Committee of Toxicology (COT) in the UK both through a submission of the evidence and an oral presentation. The assessment concluded that, while still harmful to health, HTPs "*are likely to be less risky than smoking conventional cigarettes*" and also stated that: "*There would likely be a reduction in risk for conventional smokers deciding to use heat-not-burn tobacco products instead of smoking cigarettes.*" (COT, 2017)

OVERVIEW

Public Health Context of the Application

Smoking cessation is the best way for smokers to reduce the risk of developing smoking-related diseases. Cessation has been demonstrated by epidemiology to lead to reduced harm and risk of developing tobacco-related diseases.

In Australia, the government is actively focused on reducing the daily smoking rate, but most recently, smoking rates have only declined by 0.7 percentage points, from 14.5% to 13.8% between 2014-15[4] and 2017-18[5] respectively. In light of this apparent plateau, the Minister of Health decided, in August 2019, to extend the period in which to achieve a 10% daily smoking rate target from 2018 (as set in 2008 by the Council of Australian Government (COAG)) by a further seven years to 2025. To help achieve this, the Minister announced a $20 million National Anti-Tobacco Campaign over four years to

[4] Australian Bureau of Statistics, 2015, 4364.0.55.001 - National Health Survey: First Results 2014-15.

[5] Australian Bureau of Statistics, 2018, 4364.0.55.001 - National Health Survey: First Results 2017-18.

continue to reduce tobacco use.[6] Achieving the 10% target by 2025 will require incremental reductions in the daily smoking rate of over 0.5 percentage points year on year, which may be challenging given there has only been a 0.7% cumulative decrease over three years between the surveyed years 2014-15 to 2017-18. At this time, close to 3 million Australians still smoke. These smokers' best choice would be to quit, but, as the data above shows, the reality is that many will not. Indeed, Australian Institute of Health and Welfare (AIHW)[7] data shows that one third of smokers do not want to quit.

There is also a clear link between socio-economic disadvantage and smoking prevalence. The ABS National Health Survey (2017-18) found that while 21.7% of people in the first socio-economic quintile (the most disadvantaged) smoke, the smoking prevalence drops to 6.8% in the fifth quintile (the least disadvantaged), making it more important to support the less advantaged groups through a variety of interventions to reduce smoking.

Recognising the need for updates in strategic direction to reduce the harm from tobacco, a group of 26 leading tobacco control researchers, policy and communications experts participated in a process called the Strategic Dialogue on Tobacco Harm Reduction. Over two years (2007-2009), this group (which included some members of the WHO Study Group on Tobacco Product Regulation (TobReg)) collaborated to develop a strategic blueprint for research, policy and communications to reduce the harm from tobacco, and stated that *"[t]here is a very pronounced continuum of risk depending upon how toxicants and nicotine, the major addictive substance in tobacco, are delivered. Cigarette smoking is undoubtedly a more hazardous nicotine delivery system than various forms of non-combustible tobacco products for those who continue to use tobacco, which in turn are more hazardous than pharmaceutical nicotine products.*" (Zeller, 2009). Consequently, HTPs have a role to play in risk reduction by facilitating a move to a lower risk product for those smokers who do not quit.

Interest in reducing the harm associated with tobacco use continues to grow, and the WHO TobReg's most recent technical report included a section on HTPs, acknowledging "*marked increases in the number of scientific publications, data from national surveillance programmes/surveys and market developments with respect to ENDS and HTPs*" (WHO, 2019).

A report based on a general public survey of Australians found that "*38% of current smokers would prefer to switch to ENDS if the products were legally available. For non-smokers with smokers in the household, 53% would prefer the smoker to switch to ENDS*" (Frost & Sullivan, 2018).

In Australia, however, "tobacco prepared and packed for smoking" such as cigarettes are the only tobacco products permitted despite the uniform agreement among scientists and policy makers that CCs are the most harmful because they burn tobacco and generate smoke.

---

[6] https://www health.gov.au/ministers/the-hon-greg-hunt-mp/media/transcript-national-press-club-address

[7] https://www.aihw.gov.au/getmedia/15db8c15-7062-4cde-bfa4-3c2079f30af3/21028a.pdf

The reduction in risk afforded by HTPs means that the current scheduling keeps HTPs out of the market; and results in a greater level of continued harm from cigarette smoking than would otherwise be the case.

Not all tobacco products are the same

Smoking cessation is undoubtedly the best way for smokers to reduce the risk of developing smoking-related diseases. Though many smokers are interested in, and attempt to quit, the rates of long-term smoking cessation remain very low. According to the United States Surgeon General, (Surgeon General, 2010) although about 45% of smokers quit for a day, only approximately 5% achieve long-term abstinence for one year or more.

Additionally, some smokers try to reduce the number of cigarettes they smoke per day over their lifetime. A recent study (Inoue-Choi et al. 2018) demonstrated that death risk was lower among participants who decreased their daily consumption and observed similar patterns for smoking-related causes of death, with particularly strong associations for lung cancer and respiratory disease. Reductions in consumption meaningfully decreases death risk; however, the study concludes, cessation provided a larger benefit than even large declines in daily consumption. These results underline a fundamental principle of toxicology: the risk of occurrence of adverse health effects depends not only on the intrinsic toxicity of the substance but also on the conditions of exposure (e.g. route of ingestion, rate, amount, duration) to the chemical or chemical mixture under consideration.

Today, a range of scientifically studied HTPs has become available. They deliver nicotine, which is naturally present in tobacco, without burning the tobacco and many public health experts and governments agree that the use of these products presents less of a risk than use of CCs.

HTPs do not burn tobacco or produce smoke. Because of this, they emit significantly fewer HPHCs, and those present are found in significantly lower concentrations than in cigarette smoke. This has been confirmed by various public health authorities around the world. For example, in 2018, the Korea Ministry of Food and Drug Safety (MFDS) tested three HTPs7[8] by measuring nine HPHCs [9], as well as nicotine and "Tar". The MFDS confirmed that the average reduction in the levels of the nine HPHCs measured in the aerosol generated by these HTPs exceeded 90% compared with those found in the smoke generated by Korea's five most frequently sold cigarettes brands.

Because the formation and exposure to the known HPHCs present in cigarette smoke are substantially reduced in the aerosol generated by HTPs compared to cigarette

[8] https://www health.gov.au/ministers/the-hon-greg-hunt-mp/media/transcript-national-press-club-address

[9] https://ww2 frost.com/frost-perspectives/understanding-of-and-attitudes-towards-tobacco-harm-reduction-products/

smoke, and HTPs deliver nicotine in a way comparable to cigarettes, smokers can derive the amount of nicotine they are seeking while being exposed to significantly lower levels of harmful chemicals. This in turn has the potential to reduce the likelihood of smoking-related harm and disease. As stated in the U.S. FDA Advance Notice of Proposed Rulemaking (ANPRM)[10]:

"*For those smokers seeking to switch completely to a potentially less harmful nicotine delivery product (e.g., electronic nicotine delivery systems (ENDS)) to maintain their nicotine dose also would, to the extent that those products result in less harm, significantly reduce their risk of tobacco-related death and disease.*"

Additionally, a scenario in which HTPs aerosol would carry equal or greater disease risk than cigarette smoke would require "*implausible and unknown [disease] mechanisms.*"(Abrams et al., 2017)

More recently, in April 2019, the U.S. FDA Center of Tobacco Products (CTP) issued a marketing order for Philip Morris' Tobacco Heating System, to allow its introduction into the U.S. market (FDA press release, 2019). The decision of the U.S. FDA followed "*… a rigorous science-based review through the Premarket Tobacco Product Application (PMTA) pathway*" based on which "*... the agency determined that authorizing these products for the U.S. market is appropriate for the protection of the public health ....*" In its scientific review, the U.S. FDA, "*found that the aerosol produced by the product under consideration 'contains fewer toxic chemicals than cigarette smoke,' and many of the toxins identified are present at lower levels than in cigarette smoke. For example, the carbon monoxide exposure [resulting from this product] is comparable to environmental exposure, and levels of acrolein and formaldehyde are 89% to 95% and 66% to 91% lower than from combustible cigarettes, respectively.*" (FDA TPL Report, 2019, page 33)

These findings confirm PMI's scientific assessment results. Furthermore other HTP manufacturers and a growing list of independent laboratories, have performed similar measurements that further confirm these results, i.e., a substantial reduction in HPHC emissions.

This is precisely what HTPs are designed to do: reduce substantially the levels of HPHCs, the compounds identified throughout years of research on tobacco smoke as being the primary cause of smoking related diseases.

Key scientific findings in relation to PMI's Heated Tobacco Product

Scientific assessment of PMI's HTP[11] is comprised of 18 non-clinical and 10 clinical studies and incorporates elements of multiple scientific disciplines, including aerosol chemistry and physics; in vitro, in vivo and systems toxicology; clinical studies; as well

[10] Federal Register, Food and Drug Administration, Advance Notice of Proposed Rulemaking (ANPRM), Tobacco Product Standard for Nicotine Level of Combusted Cigarettes, published on March 16, 2018, available at: https://www federalregister.gov/documents/2018/03/16/2018-05345/tobacco-product-standard-for-nicotine-level-of-combusted-cigarettes

[11] Commercialized under the *IQOS* brand name in over 50 countries at the time of this submission.

as pre-and post-market assessments of consumer perception, behaviour, and actual use. These studies have been published in over 340 academic journals, papers and books.

Findings demonstrate that:

- The studied HTP generates no combustion and no smoke, but an aerosol with an average reduction in the levels of toxicants exceeding 90%, compared with cigarette smoke and no solid carbon-based nanoparticles.
- The aerosol contains nicotine at similar levels to cigarette smoke, which led the U.S. FDA to conclude that it suggests "*a likelihood that THS' [Tobacco Heating System] users may be able to completely transition away from combustible cigarettes and use it exclusively*".
- Laboratory studies confirm that these lower levels of toxicants result in the aerosol being significantly less toxic than cigarette smoke, and this was acknowledged in the WHO TobReg Technical Report "*PMI experiments showed that THS 2.2 aerosol did not contain solid carbon-derived particles, consistent with its claim of no combustion. In general, the levels of constituents were lower than in a comparison reference cigarette (1R6F, which has certified levels of many of the emissions of concern)*" (WHO, 2019). Since PMI used the 3R4F reference cigarette in scientific studies to assess its HTP, PMI compared the 3R4F with 1R6F reference cigarettes with its HTP under the ISO regimen and found the results in general comparable (Jaccard, 2019).
- Laboratory studies also confirm that the HTP studied has no negative impact on Indoor Air Quality.
- Clinical studies confirm the results of laboratory studies:
  - In two five-day and two three-month clinical studies (all conducted by reputable Clinical Research Organisations (CROs) in accordance with Good Clinical Practices (GCP), the data shows a significant reduction in the levels of exposure to 15 toxicants. Switching completely to the studied HTP achieved almost 95% of the overall reduction in exposure in comparison to smoking abstinence.
  - In one of PMI's most recent clinical studies, measuring the biological response of people who switch to the studied HTP for six months, compared with continued smoking, showed improvements in all eight measures of biological response studied, with statistical significance in five of the eight.
  - Pre-market randomised, controlled clinical studies with PMI's HTP have shown a certain level of dual use (usage of HTPs and CCs concurrently), especially in the beginning when adult smokers seek to make the transition and depending on the country of study conducted (5 clinical studies with more than 1,600 participants). However, post marketing data available on use behaviours show that the most prevalent form of using the studied HTP is to fully switch to the HTP rather than dual use with CCs.
  - The data available, also shows that the studied HTP is:
    - used by adult smokers who would otherwise continue to smoke;

- has generally low attractiveness to never smokers and former smokers;
- does not generally interfere with quitting intent; and
- has generally low attractiveness to youth.

The data also shows that scientifically substantiated HTPs have the potential to move adult smokers away from cigarettes. For example, as part of the PMTA for Philip Morris' HTP in the U.S., a pre-market Perception and Behavior Assessment study was conducted. Results from this study show that adult smokers with no intention to quit (N=381) reported substantial levels of positive 'Intention to Use' the product regularly, ranging between 16% and 32% across the different instances of PMI's HTP tested materials.

So far, over 73 independent studies and reviews of PMI's HTP (Appendix 3) validate different elements of the manufacturer's assessment approach or otherwise reach positive conclusions.

Other assessments of Heated Tobacco Products

Overseas regulators have considered HTPs and many of these agree that HTPs are a better choice than continuing to smoke cigarettes.

- Public Health England (PHE) compared heated tobacco products with cigarettes and stated:

  > "*Compared with cigarette smoke, heated tobacco products are likely to expose users and bystanders to lower levels of particulate matter and harmful and potentially harmful compounds (HPHC). The extent of the reduction varies between studies.*" (PHE, 2018)

- The U.K. Committee on Toxicity, an independent advisory committee to the U.K. Department of Health, conducted an independent assessment of two heated tobacco products and concluded:

  > "*…It is likely that there is a reduction in risk, though not to zero, to health for smokers who switch completely to heat-not-burn tobacco products.*" (COT, 2017)

- The German Federal Institute for Risk Assessment (BfR) conducted an independent assessment of PMI's HTP and found:

  > "*…levels of major carcinogens are markedly reduced in the emissions of the analysed [heat not burn] product in relation to the conventional tobacco cigarettes and that monitoring these emissions using standardized machine smoking procedures generates reliable and reproducible data which provide a useful basis to assess exposure and human health risks.*" (Mallock et al., 2018; Mallock et al., 2019)

The Scheduling decision

HTPs are not allowed in Australia because Schedule 7 of the Poison Standard allows nicotine exclusively for the treatment of animals (as permitted by Schedule 6), approved human therapeutic use or when in "tobacco prepared and packed for smoking." The purpose of this application is therefore to formally decouple tobacco use from smoking and allow its use when prepared and packed for heating.

In making a decision in relation to this application it is necessary to consider the risks and the benefits from the use of the substance—in this case "tobacco prepared and packed for heating". This is addressed in detail in section 2.1(A). The risk benefit analysis is positive in favour of the use of HTPs by current smokers who do not quit nicotine use altogether. On the basis of the evidence available, the risk benefit analysis considering the wider population is also positive.

Taking account of the scheduling factors and the cascading principles model used, Schedules 10 and 9 are not applicable. Neither Schedules 2, 3, 4 and 8, nor Schedules 5 and 6 are appropriate as "tobacco prepared and packed for heating" is neither a medicine nor a veterinary chemical. Given the risk benefit analysis against tobacco when "prepared and packed for smoking", it is appropriate that HTPs should also be exempted from the nicotine entry in Schedule 7.

The opportunity at hand

This application proposes that "tobacco prepared and packed for heating" be expressly exempted from Schedule 7 of the Poison Standard. The requested amendment proposes the application of the same unscheduled classification to HTPs as currently applies to CCs, loose tobacco for use in pipes and roll-your-own cigarettes. It should be noted that when "tobacco prepared and packed for smoking" was excluded from scheduling, HTPs did not exist (or were in early development stages). These products are now commercially available, scientifically substantiated and represent a far better choice than continued smoking. Accordingly, they can support policy to reduce cigarette smoking prevalence and provide an opportunity to improve public health by reducing, and eventually eliminating cigarette smoking.

It is clear from the growing body of scientific evidence available on HTPs, much of which is described in the body of this Application, that this request to amend Schedule 7 by including nicotine in "tobacco prepared and packed for heating" would result in a public health benefit. The nicotine risk profile is the same, whether in "tobacco prepared and packed for smoking" or in "tobacco prepared and packed for heating." For example, the data on PMI's HTP led the U.S. FDA to conclude that the aerosol of the product "*contains nicotine at similar levels as cigarette smoke*" which suggests "*a likelihood that users may be able to completely transition away from combustible cigarettes and use it exclusively.*" (FDA TPL Report, 2019)

HTPs generate significantly fewer and lower levels of HPHCs compared with CCs, and this has been consistently demonstrated over decades for various HTPs. Additionally, as stated by a number of experts during the review of one such HTP, a scenario in which the aerosol of the product at hand would carry equal or greater disease risk than cigarette smoke would require "*implausible and unknown [disease] mechanisms*." (Abrams et al., 2017)

The data show that scientifically substantiated HTPs have the potential to move smokers away from cigarettes. Across markets, between 70% and 80% of adult smokers who buy PMI's HTP use it predominantly or exclusively instead of smoking[12],[13] and the intention of non-smokers to use HTPs has been shown to be low. Improvements in air quality and reduction in fire danger are also positive aspects of HTPs.

This new product category presents an opportunity for Australia to improve public health by reducing smoking. Consequently, this application represents the opportunity to increase the probability that Australia will achieve its ambitious 2025 smoking rate target.

If the amendment requested is made, HTPs would need to comply with a comprehensive framework of applicable Federal, State and Territory tobacco control laws that already regulate:

- labelling, packaging and presentation of those products;
- the sale and purchase of those products (to adults above 18 years of age);
- the advertising and display of those products; and
- where those products may be consumed.

If not amended, the inclusion of nicotine in Schedule 7 will leave close to three million Australians who smoke with no other choice other than continuing to smoke or quit, but data shows that many won't choose the latter even if it is indisputably the best choice they have. The continued prevention of market access for HTPs will come at the cost of smokers continuing to smoke when they could be using a product that reduces their risk and the risks of the wider population associated with continued smoking.

Considering all content of this application and that (i) *"[s]cheduling is a regulatory intervention to reduce public health risk to an acceptable level"* (TGA, 2018) (ii) the particular scheduling under request requires both risk and benefit analysis from the use of the substance under consideration – nicotine – and that (iii) the most harmful way to consume nicotine enjoys an exemption from Schedule 7, **we request the Committee to accept the addition of nicotine in "tobacco prepared and packed for heating" as a standalone category exemption within Schedule 7 to the benefit of smokers and for the protection of public health.**

---

[12] The IQOS Heating System, Tobacco Products Scientific Advisory Committee, Jan. 24, 2018, at CC-87, available: https://www.pmiscience.com/resources/docs/default-source/news-documents/pmi-tpsac_final-sponsor-presentation.pdf?sfvrsn=15dcce06_2 (accessed Oct. 7, 2019).

[13] Data from Japan, where we launched IQOS in November 2014 and which is our most developed heated-tobacco market, are worth attention. Smoking prevalence between May 2014 and May 2018 fell from 19.7% to below 14.9%. The data on Japan report as of May of each year. During the same period, prevalence for tobacco use, including in heated tobacco, declined from 19.7% to 17.9%. This dramatic decline outpaces what we've seen occur in markets with even the most restrictive smoking control measures. By way of comparison, in Australia, where tobacco and nicotine alternatives to cigarettes are not available, smoking prevalence is roughly 14.2%, see Greenhalgh, EM, et. al., Chapter 1, *Prevalence of smoking—adults*. In Scollo, MM and Winstanley, MH [editors]. Tobacco in Australia: Facts and issues. Melbourne: Cancer Council Victoria (2019), available: http://www.tobaccoinaustralia.org.au/chapter-1-prevalence/1-3-prevalence-of-smoking-adults (accessed 10 Oct. 2019).

PART 2 – BODY OF THE APPLICATION

BACKGROUND

Tobacco naturally contains nicotine, which is currently included in Schedule 7 of the Poisons Standard. "Tobacco prepared and packed for smoking" is expressly exempted from Schedule 7. As a result of this exemption, "tobacco prepared and packed for smoking," such as CCs are not a scheduled poison.

When "tobacco prepared and packed for smoking" was originally exempted from scheduling, HTPs were in early stages of development. The technology behind HTPs has significantly evolved and these products are now available in more than 50 markets.

As far as the applicant is aware, this is the first time that HTPs have been considered for the purpose of scheduling in the Poisons Standard. As a result, HTPs would fall within the classification of nicotine in Schedule 7 of the Poisons Standard due to the nicotine naturally present in tobacco.

Therefore, this application is made to request exemption of "tobacco prepared and packed for heating" (HTPs) from Schedule 7 of the Poison Standard.

The most recent consideration of the scheduling of nicotine was based on an application of nicotine in liquid solutions intended for use in e-cigarettes. The final decision announced in March 2017[14] determined that the current scheduling of nicotine remained appropriate. The result of that consideration is that such liquids are included in Schedule 7 of the Poisons Standard. With this application, we present the scientific data for HTPs, which are a separate category [Table 1] of products to liquid nicotine for vaping.

Historical Context of Heated Tobacco Products

HTPs, also generally known as 'heat-not-burn' products, produce aerosols containing nicotine and other chemicals, which are inhaled by users. These tobacco products first appeared in the 1980s as shown in **Figure 3** below (WHO, 2018), though the first generation of commercial products were only officially launched in the late 1990s by RJ Reynolds (Eclipse) and PMI (Accord). Acceptance of these products was low due to sub-optimal taste and/or the bulky devices and, and they were subsequently withdrawn. In 2007, the second generation of electronic HTPs were launched.

[14] https://www.tga.gov.au/book-page/21-nicotine-0 (accessed on 12 September 2019)

Figure 3: HTP Timeline

Through continued Research and Development (R&D) into smoke free products, the current generation of HTPs were launched in 2014. Since PMI's HTP launched in Japan at the end of 2014, it has been introduced in more than 50 markets as of October 2019. Korean Tobacco and Ginseng (KT&G) also entered the HTP market with the launch of lil in the fourth quarter of 2017 in the Republic of Korea. KT&G is Korea's leading cigarette producer in a market that has witnessed the rapid conversion of cigarette users to HTPs, with lil intended to create a domestic presence. British American Tobacco (BAT) and Japan Tobacco (JTI) both launched HTPs in 2016 and have expanded their presence in various markets since.

In 2018, the global HTPs market was valued at USD 4.04 billion. Asia Pacific held the largest HTPs market share of about 73% in 2018 driven by the rise in consumption of these products in countries such as Japan and Korea (Market Research Report, 2019). Cigarette sales in Japan have declined significantly since the national introduction of HTPs. Prior to the introduction of HTPs the annual decline in cigarettes sales was about 2%-3.3% per year. In contrast, after the introduction of HTPs, cigarette sales declined by about 9.5% annually. This data was verified by an independent study (Stoklosa et al., 2019), investigating the effect of HTPs introduction on cigarette sales in Japan. The authors concluded that the introduction of HTPs in Japan was likely the main factor for the reduced cigarette sales.

In April 2019, the U.S. FDA determined that authorising the PMI's HTP 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 set specific requirements to ensure that only adult smokers use the product. These were (a) that existing restrictions on cigarette marketing apply (b) market requirements in the authorisation address initiation and cessation and (c) the authorisation considers increased/decreased likelihood of unintended scenarios and limiting those scenarios. The post-market requirements put in place by the U.S. FDA are aimed at monitoring market dynamics such as potential youth uptake.[15] The U.S. FDA authorisation is an example of a pragmatic – yet careful and strict – approach that enables innovation in the management of public health.

[15] https://www fda.gov/news-events/press-announcements/fda-permits-sale-iqos-tobacco-heating-system-through-premarket-tobacco-product-application-pathway

The absence of combustion in Heated Tobacco Products

Thermal processes that occur in cigarettes

When the tobacco in a cigarette is lit, it burns to form smoke, a complex mixture containing more than 6,000 compounds (Rodgman and Perfetti, 2013). Approximately 100 of these compounds are considered by health authorities to be toxicants. They are the result of the four main thermal decomposition processes that occur when a cigarette is lit – dehydration, volatile release, pyrolysis and combustion. The cigarette smoke formed, following tobacco combustion, is an aerosol containing liquid droplets and solid particles resulting from the combustion process.

Baker (Baker, 1987) measured the temperature changes during puffing of a cigarette using thermocouples and infrared probes inserted into the end of a burning cigarette with evolved gas concentrations measured using mass spectrometry. The burning zone of a cigarette is oxygen deficient and hydrogen rich comprising of two regions: an exothermic combustion zone, and an endothermic pyrolysis and distillation zone. As air is drawn into the cigarette during a puff, oxygen is consumed by the combustion of carbonised tobacco, forming the products carbon monoxide, carbon dioxide and water alongside the release of heat that sustains the whole burning process. The temperature in this combustion region reaches up to 950ºC. Immediately behind is the pyrolysis zone, where the temperatures are lower (200-600ºC) and the oxygen levels are low. Most of the smoke constituents are formed by endothermic processes in this region, and the concentrated aerosol is drawn down the cigarette rod to form mainstream smoke during a puff (Eaton, 2018). It is the self-sustaining exothermic combustion processes that provide the energy to break and remake chemical bonds of tobacco constituents that drives the formation of HPHCs.

Thermal processes that occur in HTPs

The fundamental principle of HTPs is to heat tobacco to temperatures below its ignition temperature (known to exceed 400 °C) (Nordlund et al., 2019) instead of burning it to form a nicotine-containing aerosol that is not cigarette smoke. When tobacco is heated to temperatures sufficient to vaporise volatile compounds including nicotine into an inhalable aerosol, but not high enough to burn the tobacco, the level of combustion-derived toxicants is substantially reduced in the generated aerosol.

Thermophysical modelling studies performed by Nordlund and Kuczaj (Nordlund and Kuczaj, 2016) have demonstrated that at the low temperatures of heating (<400 °C), as is the case in HTPs, the presence of a primer (an aerosol former), is required. HTPs use humectants such as glycerol as solvent carriers to produce aerosols that simulate combustible tobacco cigarette smoke. The aerosol formed is not smoke, as it is not a result of combustion and has a different composition to cigarette smoke, i.e., absence of solid particles and differences in the amounts of glycerol and water present in the HTPs aerosol in comparison to cigarette smoke.

Absence of combustion in HTPs can be evaluated in different ways: (i) by physical inspection of the tobacco after use to confirm no ash formation (ii) by using thermocouples to monitor the tobacco temperature at different positions relative to the heat source during product use - these measurements have demonstrated that temperatures in HTP are maintained below that necessary for ignition and combustion; and (iii) markers of combustion measured in the mainstream aerosol provide additional confirmation of the absence of combustion.

DETAILED CLAIMS AGAINST THE REQUIREMENTS OF THE SCHEDULING POLICY FRAMEWORK

PART 2.1 CRITERIA WHICH MUST BE ADDRESSED – PROPOSALS TO CHANGE PART 4 OF THE POISONS STANDARD – SCHEDULING OR RESCHEDULING OF SUBSTANCES

(A) RISKS AND BENEFITS ASSOCIATED WITH THE USE OF A SUBSTANCE

Today, many public health authorities agree that there is a broad continuum of risk among tobacco and nicotine containing products, with cigarettes at the highest end and nicotine replacement therapies at the lowest end of that spectrum. In line with the statements by the Royal College of Physicians, this continuum recognises that most of the harm caused by tobacco results from the burning of tobacco, as it is during the combustion process that most HPHCs found in cigarette smoke are formed. Public health authorities acknowledge that while nicotine is addictive and not risk free (and thus not appropriate for non-smokers, former smokers, youth or pregnant women), nicotine is not the primary cause of smoking-related diseases.

Recently, the U. S. FDA stated that "*The inhalation of nicotine (i.e., nicotine without the production of combustion) is of less risk to a user than the inhalation of nicotine delivered by smoke from combusted tobacco products*" (FDA, 2016) and that, while not risk free, "*nicotine has not been shown to cause the chronic disease associated with tobacco use.…*" (FDA, 2016).

Similarly, McNeil noted that "*Since nicotine itself is not a highly hazardous drug, encouraging smokers to obtain nicotine from sources that do not involve tobacco combustion is a potential means to reduce the morbidity and mortality they sustain, without the need to overcome their addiction to nicotine*" (RCP, 2012, p.31). Therefore, having access to products that deliver nicotine without the tobacco combustion, has the potential to reduce the risk of harm compared to continued smoking according to reputed health organisations including the U.S. FDA and the Royal College of Physicians. These products are intended for adult smokers who are not willing to quit tobacco or nicotine use.

For adult smokers to be willing to accept HTPs and switch away from combustible tobacco products to a less hazardous product, a key criterion is the acceptability of the sensorial experience HTPs can deliver. For this, the nicotine delivery profile and the resulting subjective effects of tobacco products are critical components of product satisfaction and its actual use by these adult smokers. The Royal College of Physicians states: "*The ideal harm-reduction device should therefore deliver nicotine in a manner as similar as possible to cigarettes, while at the same time maximising palatability and nicotine delivery to approximate the experience of cigarette smoking more closely*" (RCP, 2016, p.63).

HTPs were developed to provide the adult smoker with a sensory experience that mimics cigarette smoking as closely as possible while being as low as possible on the risk continuum, in comparison to cigarette smoking.

Because decisions on scheduling "*involve a risk-benefit consideration in the context of protecting public health*" (TGA, 2018), in order to inform the scheduling decision under request, we list below the risks and benefits associated with the use of the substance "nicotine" in HTPs.

Risk Issue: HTPs contain nicotine, which is addictive and carries certain health risks
Risk/benefit analysis
The nicotine in HTPs present no additional risk over CCs. **The nicotine contained in HTPs is delivered in an aerosol that comes from its natural presence in the tobacco component of the HTP. The nicotine contained in HTPs is addictive and carries certain health risks, particularly for children, pregnant women and adolescents.** The nicotine contained in HTPs and the method of delivery when used approximates as closely as possible the nicotine delivery profile of a cigarette, while replicating the ritual, taste and sensory experience of CCs and therefore facilitates the benefits associated with switching to a less harmful product by current adult smokers who would otherwise continue to smoke. Nicotine content in HTPs is necessary for smokers to switch from cigarettes, if they do not quit nicotine entirely. In addition, HTPs are only intended for adult smokers who would otherwise continue to smoke cigarettes, therefore reducing the risk of exposure for those most at risk.
Justification for the risk/benefit analysis
○ **HTPs contain tobacco and therefore also nicotine, similarly to cigarettes.** The nicotine content from HTPs is delivered in an aerosol that comes from its natural presence in tobacco. This is the same for the nicotine that is part of "tobacco prepared and packed for smoking." HTPs deliver nicotine in a manner as closely as possible to cigarettes. When used as intended, overdosing on nicotine is highly unlikely upon inhalation of HTP aerosols because the effects of inhaled nicotine occur rapidly (within seconds), limiting further intake. ○ **Importance of nicotine for HTP acceptance to smokers who would otherwise continue to smoke cigarettes.** HTPs were developed to provide the adult smoker with a sensory experience that mimics cigarette smoking as closely as possible while being as low as possible on the risk continuum, in comparison to cigarette smoking. By approximating as closely as possible the taste, satisfaction, nicotine profile, and ritual of smoking a cigarette, HTPs facilitate switching by current adult smokers who would otherwise continue to smoke. According to Royal College of Physicians, delivering nicotine in a manner as similar as possible to cigarettes is one of the key features of an ideal harm reduction device (RCP, 2016, p.63). U.S. FDA concluded in its press release related to the authorisation of the marketing of PMI's 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*" (FDA press release, 2019). ○ **HTPs are only intended for adult smokers that would otherwise continue to smoke cigarettes [E].** Other people should not use HTPs and refrain from tobacco or nicotine use all together, especially minors and pregnant or

Risk Issue: HTPs contain nicotine, which is addictive and carries certain health risks
breastfeeding women. Any nicotine-containing product, including HTPs, should not be used by, or sold to, minors. HTPs would need to comply with applicable Federal and State and Territory tobacco control laws [D].

Risk Issue: HTP aerosol still contains HPHCs and other chemicals
Risk/benefit analysis
HTPs still exposes users to HPHCs and may expose users to chemicals that are not present in the emissions from combusted cigarettes. These chemicals could carry some degree of toxicity, but the risk is low and outweighed by the reduction in exposure to HPHCs. HTPs expose users to: • A significantly less complex aerosol compared to cigarette smoke • Some HPHCs also found in cigarette smoke but at levels reduced by on average 90%-95% • Some chemicals that are not found in cigarette smoke • Liquid droplets but not carbon-based solid nanoparticles. A significant reduction in exposure to HPHCs leads to a reduction in adverse health effects according to the fundamental principles of toxicology. The significant reduction in exposure to the HPHCs, chemicals and solid particles associated with the consumption of cigarettes presents a significant opportunity to reduce the exposure of current smokers to HPHCs, which are the primary cause of the adverse health effects of smoking. These reductions are generally maintained even if HTP use would increase compared to previous combustible cigarette use.
Justification for the risk/benefit analysis
○ **HTPs still emit HPHCs, albeit at levels significantly lower than in cigarette smoke** [C]. HTP manufacturers, independent researchers, and governmental commissioned research have reported average reductions of HPHC levels 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 TPL Report, 2019). Public Health England (PHE) also found that "*heated tobacco products are likely to expose users and bystanders to lower levels of particulate matter and harmful and potentially harmful compounds (HPHC)*" (PHE, 2018) when comparing HTPs with cigarettes. ○ **HTP aerosols contain significantly fewer chemicals than cigarette smoke and are formed from liquid droplets:** The number of chemicals measured

in the aerosol from HTPs are significantly less than in cigarette smoke (Forster et al., 2018; PMI, 2018). For example, only 529 compounds were detected above 100 ng/stick in PMI's HTP, whereas over 4000 compounds were detected in the smoke from a reference cigarettes (PMI, 2018). Furthermore, in contrast to cigarette smoke which contains high concentrations of both liquid and solid particles, the aerosol generated by PMI's HTP (Pratte et al., 2017) contained no carbon-based solid nanoparticles but only liquid droplets.

- As a consequence, HTPs that significantly reduce the exposure to HPHCs compared to cigarette smoking are likely to achieve a significant reduction in adverse health effects. The U.K. Committee on Toxicity, an independent advisory committee to the U.K. Department of Health, independently assessed two HTPs and concluded that "*it is likely that there is a reduction in risk, though not to zero, to health for smokers who switch completely to heat-not-burn tobacco products*" (COT, 2017). The Science & Technology Committee of the U.K. House of Commons reached a similar conclusion, stating that HTPs "*contain tobacco which is heated rather than combusted, and [are] therefore likely to be less harmful compared to conventional cigarettes*" (UK House of Commons, 2018). All this, places them towards the lower risk end of the risk continuum and clearly differentiates them from the risk associated with combustible products, which are at the highest end of the continuum (FDA, 2016; RCP, 2016).

- **HTP aerosols may contain chemicals that are not present in the emissions from combusted cigarettes.** PMI performed an untargeted differential screening analysis (NTDA) of PMI's HTP aerosol, to identify potential new hazards contained in the aerosol compared to cigarette smoke beyond the known and listed HPHCs. The overall results confirm that heating rather than burning tobacco results in a significant reduction in the number of compounds (approximately 4300 peaks with a semi-quantified abundance ≥100 ng/stick for 3R4F vs. 750 for PMI's HTP). A follow up data evaluation identified a total of 529 chemical constituents. This number is smaller than the previous estimate of 750 because the full data analysis showed that many compounds were detected by more than one of the analytical methods applied, and accounting for these overlaps reduced the overall number of unique compounds vs. the numbers of identified chromatographic peaks.

- PMI identified 51 compounds that were present at higher levels and 3 compounds that were unique in the aerosol of PMI's HTP compared to the smoke of the reference cigarette, namely Cis-sesquisabinene hydrate, Ethyl dodecanoate and 4-Hydroxybenzyl alcohol.

- An evaluation for the likely origins of the constituents more abundant demonstrated that the majority are either: 1) flavors that are naturally found in cured tobacco or added to the tobacco, or 2) plant metabolites or 3)

Risk Issue: HTP aerosol still contains HPHCs and other chemicals
compounds that are the result of sugar (naturally present in tobacco) transformation upon heating. These results were expected based on blend differences between PMI's HTP and the reference cigarettes as well as the fact that PMI's HTP variants are flavored, unlike the reference cigarette used for testing. o PMI identified and reported four compounds of potential toxicological concern within this list of constituents, that were found either in the range of, or in higher quantities than, cigarette smoke, namely, Glycidol (IARC 2A), 2-Furanmethanol (IARC 2B), 3-Monochloro-1,2-propanediol (IARC 2B), Furfural (IARC 3). PMI's evaluation of these compounds, based upon published inhalation toxicology literature, indicates that the level of exposure to these compounds through the use of PMI's HTP are below the level of toxicological concern. o The U.S. FDA stated in their technical review of the PMTA application for PMI's HTP, that the "*aerosol contain some chemicals which are different from those found in combusted cigarettes*" (CC) (TPL Report, 2019).[6] "*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 CC*" (FDA, 2019). o **Reductions are generally maintained even if HTP use would increase compared to previous combustible cigarette use or by increasing product use intensity**. In a subsequent analysis of levels of HPHCs from PMI's clinical reduced exposure studies, we investigated the achieved exposure reduction when only the users of PMI's HTP with the highest daily product use (from the 75 percentile onwards) were analysed. The data showed, that the reduction of exposure achieved remains comparable to the average reduction in exposure of all users of PMI's HTP vs continued smoking and comparable to the average reduction in exposure achieved in the smoking abstinence groups. Furthermore, the operating temperature of PMI's HTP limits the effect of increasing product use intensity.

Risk Issue: HTPs have only been available for real-world evidence evaluation in market since 2014. Given the latency in the manifestation of smoking-related disease, there is a lack of long-term data <u>to quantify</u> the health effects related to HTP use.
Risk/benefit analysis
Tobacco-related morbidity and mortality arise in great part from one particular form of tobacco use – combustible tobacco, including tobacco prepared and packed for smoking. Decades of epidemiological data clearly demonstrate that the risks of

Risk Issue: HTPs have only been available for real-world evidence evaluation in market since 2014. Given the latency in the manifestation of smoking-related disease, there is a lack of long-term data to quantify the health effects related to HTP use.
serious disease, such as, lung cancer, heart disease, and COPD are substantially higher among smokers than non-smokers. The long-term health impact of HTP use and exposure to their emissions cannot be quantified at this time, due to the latency in the manifestation of smoking-related disease. Therefore, comparison of the disease risk from HTP aerosol exposure would require a comparable time frame. Important to note is that a quantification of disease risk reduction would need to be evaluated for each type of smoking related disease specifically. However, in the absence of long-term data relating to HTP use, the following must be taken into consideration: • the clear reduction in the exposure to the HPHCs, chemicals and solid particles when compared with smoking; • data from translational systems toxicology approaches and animal models of disease demonstrating reduction in perturbation of pathways leading to disease • data from randomised, controlled clinical studies demonstrating significant beneficial changes in clinical risk endpoints linked to smoking-related diseases • modelling approaches that predict the potential benefits HTPs can have on public health; • the support provided to these models by the real-world experience in markets where HTPs are already available. Delaying the availability of HTPs to Australian smokers who would otherwise not quit until after the data is gathered in other markets where HTPs are already available, puts at risk the significant opportunity to reduce smoking.
Justification for the risk/benefit analysis
○ **HTPs significantly reduce emissions and exposure to the HPHCs, chemicals and solid particles compared with smoking** (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 TPL Report, 2019, Luedicke et al., 2018, Haziza et al., 2019) . The harm and risk of smoking-related disease is mainly caused by exposure to HPHCs formed by tobacco prepared and packed for smoking. Epidemiological studies provide overwhelming evidence that the risk of smoking-related disease rises in a dose and time dependent manner with continued exposure to HPHCs. Epidemiological studies have also provided overwhelming evidence that harm and the risk of tobacco-related disease can be dramatically reduced by smoking cessation, i.e., by elimination of exposure to these toxicants. By eliminating the exposure to HPHCs, the chronic stimulus leading to disease development and progression is

Risk Issue: HTPs have only been available for real-world evidence evaluation in market since 2014. Given the latency in the manifestation of smoking-related disease, there is a lack of long-term data to quantify the health effects related to HTP use.
effectively removed, allowing for a normalization of cellular and tissue function over time. It follows from fundamental principles of toxicology, that a significant reduction in exposure to HPHCs toxicants should lead to a reduction in adverse health effects of smoking. In support of this biologically plausible argument, there are several peer-reviewed scientific studies concluding that significant reductions in smoking exposure leads to a reduced risk of smoking-related disease (Inoue-Choi et al, 2019, Benhamou et al. 1989, Godtfredsen et al. 2005, Hart et al. 2013, Lee 2013, Simmons et al. 2005, Song et al. 2008, Wald and Watt 1997). o **Data from translational systems toxicology approaches and animal models of disease show reduction in disease endpoints [C].** While long-term real-world evidence is not yet available animal models of disease can support the understanding of the reduction in adverse health effects. o PMI conducted a study in Apoe-/- mice to compare the impact of switching to the aerosol of PMI's HTP with continued exposure to cigarette smoke. This study was designed to allow for a simultaneous evaluation of disease endpoints for cardiovascular disease and respiratory disease. The study showed that while exposure to the smoke of a reference cigarette accelerated the growth of the atherosclerotic plaque in the aortic arch of continuously exposed animals, continuous exposure to PMI's HTP aerosols resulted in plaque areas that did not differ significantly from those seen in mice exposed only to air under the same experimental conditions. Switching to PMI's HTP after smoke exposure, halted the progression of atherosclerotic plaque growth. Similar results were observed for emphysematous changes which were evident after cigarette smoke exposure, whereas PMI's HTP aerosol exposed animals did not show any effect on lung function. Switching from smoke exposure to PMI's HTP aerosol or cessation resulted in stabilization of lung function, while continued 3R4F smoke exposure led to further impairment in lung function (Phillips et al. 2016, Lo Sasso et al. 2016, Titz et al. 2016). o An 18-month chronic inhalation carcinogenesis study was conducted in A/J mice to compare the effects of the PMI's HTP aerosol and cigarette smoke on lung tumor incidence and multiplicity. The study results of this study show that at the end of the life-long exposure period, a larger number (incidence) of A/J mice 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 tumor incidence compared to those exposed to air. Furthermore, mice exposed to cigarette smoke had more lesions and tumors per mouse than those exposed to air (multiplicity). In contrast, mice exposed to PMI's HTP aerosol did not show an increase in tumor

Risk Issue: HTPs have only been available for real-world evidence evaluation in market since 2014. Given the latency in the manifestation of smoking-related disease, there is a lack of long-term data to quantify the health effects related to HTP use.
multiplicity compared to those exposed to air (reference to U.S. FDA MRTP amendment for AJ study). ○ **Data from randomised, controlled clinical studies demonstrating significant beneficial changes in clinical risk endpoints linked to smoking-related diseases [C].** PMI conducted a 6-month exposure response study, which assesses the effect of switching from cigarette smoking to the use of PMI's HTP on clinical endpoints that are negatively affected by smoking, show positive changes upon cessation and are linked epidemiologically to smoking-related diseases. ○ The main outcome was a favorable change 6 months after baseline, with statistically significant improvements in 5 of 8 biomarkers of effect (HDL-C, WBC, FEV1%pred, COHb, Total NNAL) when smokers switched to PMI's HTP compared with those who continued to smoke cigarettes. All endpoints showed favorable changes in the same direction as with smoking cessation. Improvements in the biomarkers of effect are supportive of the research hypothesis, suggestive of disease risk reduction potential for smokers switching to PMI's HTP instead of continuing to smoke cigarettes (Luedicke et al., 2019). ○ **Prediction modelling of the potential effect HTPs can have on public health can help to supplement the lack of long-term data while the data is being generated**. Despite the lack of long-term studies on the impact of HTPs, outcomes of various modelling scenarios with the aim of predicting the potential effect of the introduction of HTPs into the market shows that many smoking-related deaths could be averted within the next decades (Djurdjevic et al., 2018). The introduction of HTPs would have to cause significant numbers of non-smokers to start using CCs and prevent large numbers of current smokers from quitting, in order to negate the potential positive effects. There is no indication of this happening in any country where HTPs are available. The U.S. FDA in their technical review of the PMTA application for PMI's HTP stated: "*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.*" (FDA press release, 2019).

Risk Issue: HTPs may be attractive to youth, never smokers, and former smokers or smokers with the intention to quit.

Risk/benefit analysis

The primary benefit of HTPs is that they provide a better choice for almost three million Australian smokers. There are concerns, however, that HTPs may:

- be attractive to persons who were not previously tobacco or nicotine users (including youth);
- attract former smokers to reinitiate tobacco use; or
- impact the intention of smokers to quit nicotine and tobacco use altogether.

The available studies of attractiveness, and the real-world evidence of use, do not support concerns that youth, never smokers, and former smokers will be attracted to HTPs. Instead, the available data indicates that HTPs :

- have generally low attractiveness to never smokers and former smokers;
- do not generally interfere with quitting intent; and
- have generally low attractiveness to youth.

In addition, HTPs would need to comply with a comprehensive framework of applicable Federal, State and Territory tobacco control laws.

Justification for the risk/benefit analysis

The available research [E] on HTPs demonstrates that it is used predominantly by adult smokers, while non-intended audiences show little intention to use them.

  - In an independent study conducted by Swiss researchers from Addiction Suisse (Delgrande et al., 2019), the authors found that regular use of HTPs among 14 and 15 year-old boys and girls is practically negligible and that that HTP use is essentially limited to cigarette smokers.
  - Another independent study conducted in Japan, the country with the highest use of HTPs among approximately 64,000 Japanese middle and high school students showed that only 0.1% of middle and high school students were daily users of HTPs (referred in the study as Heat-not-Burn tobacco products, or HnB) (Osaki, 2019).
  - A German Study on Tobacco Use (DEBRA) examining the prevalence of electronic cigarette and HTP use and associated socioeconomic factors and smoking behavior reported that ever use of HNB products in youth was low and only increased with increasing education and income (Kotz and Kastaun, 2018).

- **Post-market surveillance studies in Japan**, the country with the highest number of HTP users, show that only 2% of users of PMI's HTP were previously never tobacco/nicotine users (Afolalu et al., 2018).

Risk Issue: HTPs may be attractive to youth, never smokers, and former smokers or smokers with the intention to quit.
• **In considering the impact on current, former and never smokers**, the U.S. FDA found that authorising the marketing of PMI's HTP, would be "*appropriate for the protection of public health*" (FDA press release, 2019). In reaching this determination, the FDA considered the risks and benefits to the population as a whole, including users and non-users of tobacco products, and taking into account the increased or decreased likelihood that (a) existing users of tobacco products will stop using such products; and (b) those who do not use tobacco products will start using such products. The FDA concluded in its press release: "*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. Available data, while limited, also indicate that few non-tobacco users would be likely to choose to start using IQOS, including youth.*" (FDA press release, 2019) • **A regulatory framework can minimise and mitigate potential risks of unintended use of HTPs**, while encouraging adult smokers to quit smoking or switch to these less harmful alternatives, and help adult smokers move away from combusted cigarettes.

Risk Issue: HTP emissions may adversely affect the air quality and bystanders
Risk/benefit analysis
The public health benefits associated with switching to a lower risk product by current adult smokers who would otherwise continue to smoke will also apply to those who are exposed to HTP emissions instead of Environmental Tobacco Smoke (ETS). HTPs do emit some HPHCs, albeit at levels significantly lower than in cigarette smoke. Consequently, it should be expected that HTPs will pose a lower negative impact to bystanders when compared to CCs. These expectations have been confirmed in multiple studies which demonstrate that the use of the studied HTPs have no adverse effect on indoor air quality and bystanders' exposure. These studies were conducted to assess HTPs effect on air quality and to understand the risk for bystanders as part of studying the risk benefit assessment for HTPs (Appendix 4).
Justification of the risk/benefit analysis
○ **ETS (Environmental Tobacco smoke or secondhand smoke) is emitted from combusted cigarettes.** Public health authorities, including the World Health Organization (WHO), have concluded that ETS causes diseases, including lung cancer and heart disease, in non-smoking adults as well as adverse health-related conditions in children, such as asthma, respiratory infections, cough, wheezing, otitis media (middle ear infection), and sudden

Risk Issue: HTP emissions may adversely affect the air quality and bystanders
infant death syndrome (WHO, 2000). According to 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). o **There is no ETS emitted from HTPs.** Because there is no combustion of the tobacco in HTPs and the aerosol generated is not smoke, there is no ETS emitted during HTP use according to the definition of ETS by WHO (WHO, 2000). However, there is environmental HTP aerosol emitted during use, predominantly from exhalation of the HTP mainstream aerosol constituents. As the levels of HPHCs in the HTP mainstream aerosol are significantly reduced compared with mainstream cigarette smoke, the use of HTPs is by design, expected to have a substantially lower impact on the air quality and consequently on bystanders compared with cigarette smoking. The scientific evidence reported for PMI's HTP comprehensively demonstrates that its use has no adverse effect on 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 (Nordlund et al., 2019).

Risk Issue: HTPs may be a fire hazard
Risk/benefit analysis
HTPs generally contains electronics and rechargeable batteries that could become a fire hazard during use or charging. HTP consumables, are heated during use and do not combust, indicating a low risk of fire hazard but may pose some risk of initiating fires when discarded. Smoking was found to be the leading cause of preventable fire-related deaths in Australia. HTPs are unlikely to initiate fires, because they do not combust tobacco. Switching from smoking to using HTPs can be expected to provide fire reduction benefits by removing most common sources of ignition and reducing the risk presented by the leading cause of preventable fire-related deaths in Australia.
Justification for the risk/benefit analysis
o **Cigarette smoking related fire incidents:** 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. The study also concluded that smoking was found to be the leading cause of preventable fire-related deaths in Australia. Combusted tobacco products, such as cigarettes, present a significant fire risk when not being properly extinguished, when discarded intentionally in ash trays or garbage bins, or after inappropriate disposal in nature.

Risk Issue: HTPs may be a fire hazard
○ **HTPs are unlikely to initiate fires**, as HTPs do not combust tobacco, the temperature during use is low and no net heat generating processes occur in the tobacco. 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 [EHTP with THS] does not represent a fire risk under any circumstance*" (Torero, 2017) 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.*" Another internationally renowned combustion and fire safety expert in Japan, Professor Osamu Fujita, stated that "*For the three different compositions of municipal solid waste assessed; paper, textiles and polyurethane foam, the critical temperature for ignition is far above the tobacco temperature attained in the EHTP during EHTS [IQOS] operation*" (Fujita, 2016). Professor Osamu Fujita also stated after his review of the device safety of PMI's HTP that as long as the product "*is functioning as designed, the risk of the product acting as an ignition source is extremely low*" (Fujita, 2017). ○ **The Japanese National Fire Agency (JNFA)[16] exempted HTPs from the fire regulation** in Tokyo due to their low fire risk after a review by a JNFA committee of the fire safety of HTPs, including device safety and discarded consumables. The committee concluded 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. Following the review by the committee, Tokyo Fire Department announced in August 2019, that the three HTPs tested by the fire safety committee are not considered to be products for "smoking" under the fire regulations in Tokyo and are therefore exempt from the fire regulation in Tokyo due to their low fire risk. ○ **The devices used with HTPs are subject to independent control,** and it is important that the individual components of the heating system are subject to national and international safety standards and approvals. Using PMI's HTP as an example, international certifications are held for individual components (batteries, AC Adaptor, wiring etc.) prior to final system testing (IEC, EN,

[16] Japanese National Fire Agency, 2019. https://www fdma.go.jp/en/post1 html

Risk Issue: HTPs may be a fire hazard
CISPR, ICES, FFC, UL)[17]. Tobacco Stick Holders and Chargers are third-party tested and certified according to all applicable product safety regulations in each destination market (for example: CE, EAC, IC).

Overall Discussion on Risk/Benefit Ratio:

For any new product a risk- benefit analysis is a necessary and careful step that enables useful innovation to be introduced in a careful and informed way and helps to address concerns about potential risk or unintended use of a new product.

The task at hand is to find the sweet spot between maximising opportunity of the requested scheduling while minimising its unintended consequences. The key is to find the point that maximizes net benefits. In that regard, we should keep in mind the following statement by Professor Lorraine Daston: "*All-or-nothing outcomes — either everything under control or everything left to chance — are nonstarters. The debate must assay possibilities, probabilities, and desirabilities with a jeweller's balance*" (Daston, 2008).

The risk- benefit analysis for HTPs compared to continued cigarette smoking (allowed under the scheduling exemption "tobacco prepared and packed for smoking") – provided here shows that:

1. The nicotine in HTPs presents no additional risk over conventional cigarettes and facilitates the benefits associated with switching to a lower risk product by current adult smokers who would otherwise continue to smoke.
2. The significant reduction in exposure to HPHCs and solid particles associated with the consumption of cigarettes presents an important opportunity to reduce exposure to toxicants that are the primary cause of smoking related disease for current adult smokers who would otherwise continue to smoke.
3. The totality of evidence available on HTPs, including: the results from studies on HTP aerosol toxicity; data from translation systems toxicology approaches and animal models of disease; and data from randomised, controlled clinical studies; are consistent and coherent with the observed reduction in emissions and exposure to HPHCs. They also demonstrate that the fundamental principles of toxicology, i.e., a significant reduction in exposure to HPHCs leads to a reduction in adverse effects, holds true. This is in line with several peer-reviewed scientific studies which have concluded that significant reductions in tobacco smoking/exposure to tobacco smoke leads to a reduced risk of smoking-related disease.
4. Beyond the risk of an individual HTP user, modelling approaches that can help to predict the potential benefits HTPs can have on public health exist. Results

[17] IEC=International Electrotechnical Commission; EN= European Norm standards; CISPR = International Special Committee for Radio Protection; FFC = Federal Communications Commission; UL = Underwriters Laboratories standards; EAC= Eurasian Conformity standards; IC = Integrated Circuit

have been fairly consistent across models provided by industry and independent researchers.

5. Real-world experience from markets where HTPs are already available deliver product use trajectories as observed in real life. Such real-life observational studies of HTP use behaviors, indicate that
    - youth uptake of HTPs is limited; and
    - HTPs are mostly used by current adult cigarette smokers only with limited impact on never or former smokers and smokers who intent to quit

    An appropriate regulatory framework that minimises unintended use of HTPs (e.g., youth uptake), while encouraging adult smokers to quit smoking or switch to these less harmful alternatives, can further help Australia's adult smokers move away from combusted cigarettes.
6. HTPs present a negligible risk of fire and therefore will have significant benefits by reducing the risk of fire presented by cigarette smoking.

An important consideration in any risk-benefit analysis should be the consequences of not exempting HTPs from Schedule 7. Not exempting HTPs from Schedule 7 means preventing the introduction of products that can help to replace the most harmful form of nicotine use, i.e., "tobacco prepared and packed for smoking", and in consequence, results in the loss of a substantial opportunity to help further reduce the risk of adverse health effects of smoking by decreasing cigarette smoking prevalence. A further consideration would be the reframing of societal nicotine use through the lens of harm minimisation as an opportunity to enhance the impact of tobacco control efforts (Abrams et al., 2018), [F].

To conclude, the benefits of introducing the requested exemption in Schedule 7 are supported by the data above and throughout this application. Elevating risk aversion above risk minimisation, should be avoided as it comes with its own risks. An excessive focus on avoiding risks and uncertainties will mean that smokers who would otherwise continue smoking will be impacted: delay in accessing HTPs will be a lost opportunity. "*Good regulation is more than just minimizing risks; it is about maximizing gains in public health*." (Eichler et al, 2013).

(B) THE PURPOSES FOR WHICH A SUBSTANCE IS TO BE USED AND THE EXTENT OF USE OF THAT SUBSTANCE

HTPs are a class of non-combustible tobacco products for inhalation and a smoke-free source of nicotine which present a viable and acceptable alternative to cigarettes for current adult smokers who would otherwise continue to smoke.

The purpose of HTPs is to displace the use of "tobacco prepared and packed for smoking" which are already exempted from Schedule 7.

Historically, consumption of products subject to the existing exemption declined significantly in Australia, with current tobacco smoking prevalence falling from 29.5% in 1991 to 15.8% in 2013 (NDSHS, 2016). However, the Australian Institute of Health and Welfare found that "*The long-term decline in the daily smoking rate among people aged 14 or older slowed in 2016, only declining slightly from 12.8% in 2013 to 12.2% (this fall was not statistically significant).*" (NDSHS, 2016)

Similarly, the Australian Bureau of Statistics recently reported "*In 2017-18, just under one in seven (13.8%) or 2.6 million adults were daily smokers, while a further 1.4% of people also reported smoking, they did so on a less than daily basis. Since 1995, the proportion of adults who are daily smokers has decreased from 23.8% to 13.8% in 2017-18. Over recent years however, the daily smoking rate remained relatively similar (14.5% in 2014-15).*"[18]

This means that the Australian Government estimates that about 3 million Australians still smoke cigarettes which are subject to the existing schedule exemption, with 2.6 million Australians smoking daily[19] and smoking prevalence stagnating since 2013 with only not statistically significant declines achieved.

In line with the National Tobacco Strategy 2012-2018 and under the COAG National Healthcare Agreement by 2018 Australian governments have committed to:

- reducing the daily national smoking rate among Australian adults (aged 18 years or older) from 19.1% (age-standardised) in 2007-08 to 10%; and
- halving the daily national smoking rate among Aboriginal and Torres Strait Islander adults (aged 18 years or older) from 47.7%[20]

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

[19] Table 9: Smoking – Australia, 4364.0.55.001 - National Health Survey: First Results, 2017-18 , https://www.abs.gov.au/AUSSTATS/subscriber.nsf/log?openagent&4364055001do009_20172018.xls&4364.0.55.001&Data%20Cubes&F726C6735D369EBFCA2583610083D0A6&0&2017-18&12.12.2018&Latest

[20] https://meteor.aihw.gov.au/content/index.phtml/itemId/658540

On 14 August 2019, Health Minister, The Hon. Greg Hunt MP, announced as part of Long Term National Health Plan "*a new target of reducing smoking rates below 10 per cent by 2025.*"[21]

Displacement of combusted tobacco products by HTPs can help achieve the national target and is aligned to relevant COAG goals and objectives if HTPs actually represent an alternative that has a nicotine profile as well as ritual, taste and sensorial experience comparable to tobacco prepared for smoking and can therefore enable full switching and support cigarette smoking cessation. All this, while significantly reducing the exposure to HPHCs.

In April 2019, the U.S. FDA CTP issued a marketing order to allow the introduction of PMI's HTP into the U.S. market. The decision of the U.S. FDA followed *"....a rigorous science-based review through the premarket tobacco product application (PMTA) pathway" based on which, "...the agency determined that authorizing these products for the U.S. market is appropriate for the protection of the public health ....."* (FDA press release, 2019).

Part of this assessment was the review of available data on the intended actual use of the HTP considered, as described in this section, and the data available on unintended use as described in [E].

In their scientific review of PMI's HTP the U.S. FDA concluded that *"... 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.*"

The following part of this document illustrates examples of the data that were considered by the U.S. FDA for the above statement, as well as additional studies on other HTPs that are available for sale today in countries outside of the U.S.

Use as intended: Data on Product Use Behaviour

Data on product use behaviour in randomised, controlled clinical studies for a duration of up to six months are available with respect to HTPs. Overall these studies in current adult smokers, not willing to quit smoking and randomised to using a HTP, show that:

- Nicotine uptake and exposure varied between different HTPs but was overall comparable to cigarettes.
- Product consumption of HTPs was, on average, comparable to the use of cigarettes.
- The majority of the subjects in the HTP groups solely used HTPs.
- Product satisfaction was comparable between HTPs and cigarettes.

Nicotine exposure with the use of British American Tobacco's (BAT) HTP (glo) and PMI's HTP *IQOS* showed mostly comparable rates of uptake and exposure in

[21] National Press Club address — Long Term National Health Plan, https://www.health.gov.au/ministers/the-hon-greg-hunt-mp/media/national-press-club-address-long-term-national-health-plan

randomised controlled clinical studies in a confined and ambulatory setting compared to cigarettes (**Figure 4**) (Gale et al., 2019).

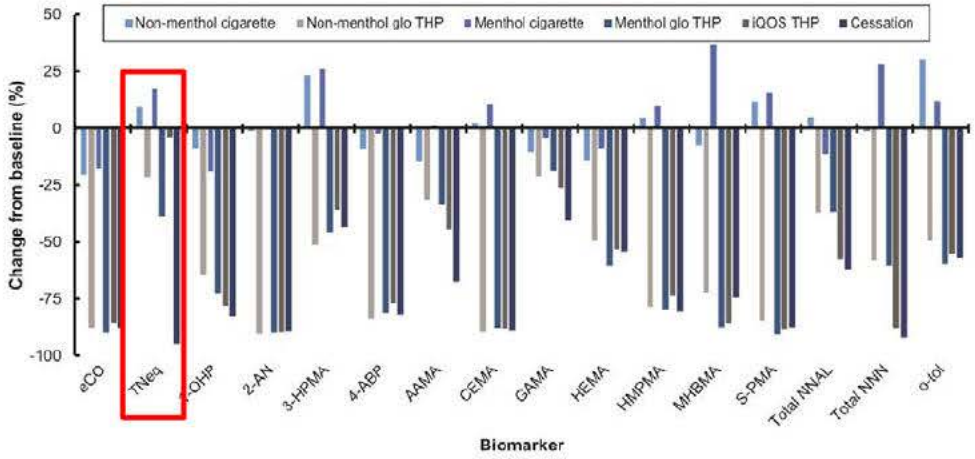


Figure 4 - Biomarker of exposure changes between baseline and days 6–7.

Data are median values expressed as a percentage of the baseline value. All data, except for eCO, were calculated using biomarker levels from 24-h urine collections at baseline and on days 6–7. eCO levels were calculated from data captured at a single timepoint at baseline and on day 7. n = 27–30 in each case.

Abbreviations: eCO, exhaled carbon monoxide; TNeq, total nicotine equivalents (nicotine, cotinine, 3-hydroxycotinine and their glucuronide conjugates); 1-OHP, 1-hydroxypyrene; 2-AN, 2-aminonaphthalene; 3-HPMA, 3-hydroxypropylmercapturic acid; 4-ABP, 4-aminobiphenyl; AAMA, N-acetyl-S-(2-carbamoylethyl) cysteine; CEMA, 2-cyanoethylmercapturic acid; GAMA, N-acetyl-S-(2-hydroxy-2-carbamoylethyl)cysteine; HEMA, 2-hydroxyethylmercapturic acid; HMPMA, 3-hydroxy-1-methylpropylmercapturic acid; MHBMA, monohydroxybutenyl-mercapturic acid; S-PMA, S-phenylmercapturic acid; NNAL, 4-(methylnitrosamino)1-(3-pyridyl)-1-butanol (NNAL); NNN, N-nitrosonornicotine; o-tol, o-toluidine.

Results from PMI's reduced exposure studies among smokers showed that nicotine uptake for HTPs and CCs are similar (**Figure 5**). The same studies showed, that product satisfaction ratings (which was assessed using the modified cigarette evaluation questionnaire, a validated and widely used assessment tool) for HTPs and CCs were mostly comparable at the end of the studies (**Figure 6**).

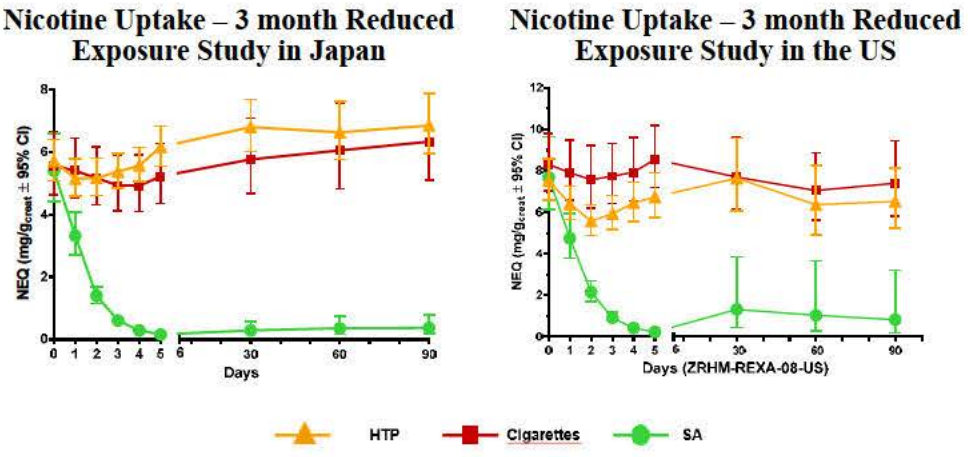


Figure 5 - Nicotine Uptake of PMI's HTP in 3 month Reduced Exposure studies in Japan and the U.S.

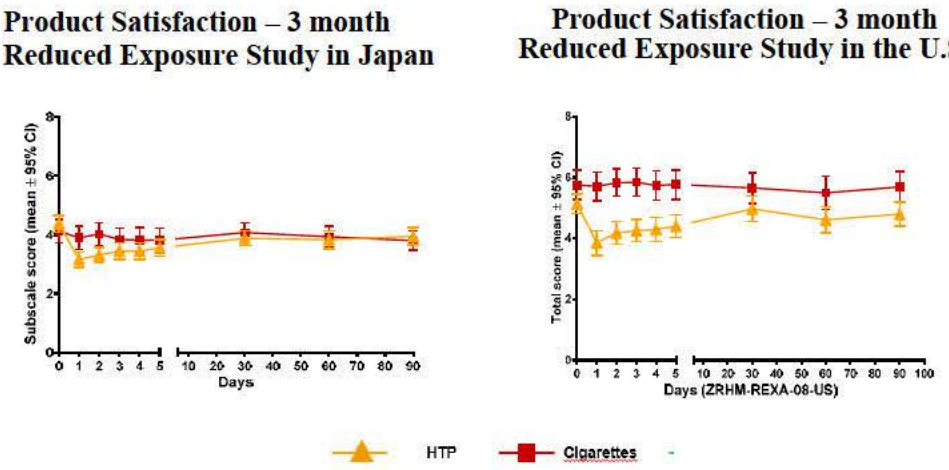


Figure 6 - Product Satisfaction of PMI's HTP in 3 month Reduced Exposure studies in Japan and the U.S.

Concerning product use, a randomised controlled study over seven days in confinement by BAT with their HTP showed that product use at baseline was comparable between study groups (15.2 to 17.4 cigarettes/day), and only a slight increase in product use count was observed for all study groups during the course in all study groups (**Figure 7**).

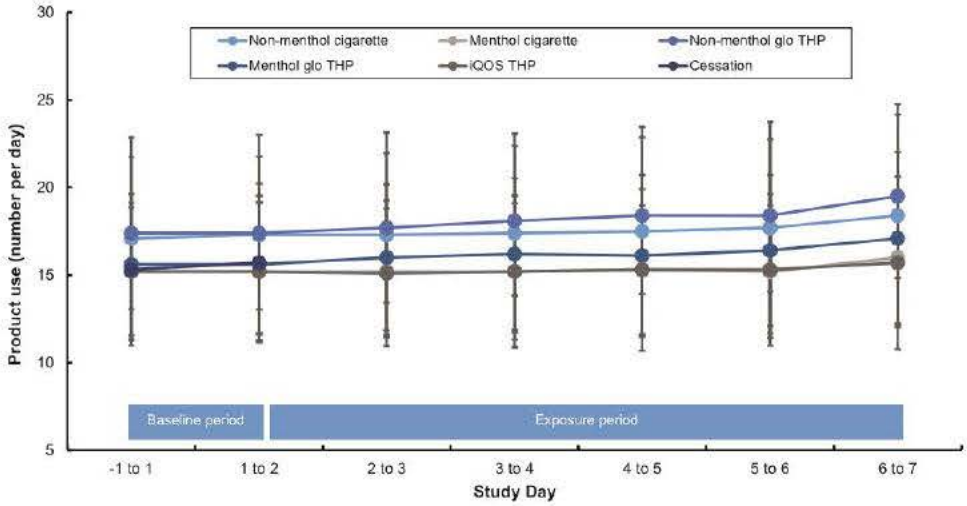


Figure 7 - Tobacco product consumption during the study. Data are mean (±SD) numbers of cigarettes smoked/tobacco heating product (THP) consumables used during each study day. N.B. the product use (numbers per day) were zero in the Cessation group during the confinement period.

In a 3-month reduced exposure study in Japan with PMI's HTP, mean daily product consumption on Day 90 was 12.7 HTPs/day (95% CI: 11.2, 14.3) for the HTP arm and 15.2 cigarettes/day for the cigarette arm (95% CI: 13.5, 16.8). The data for a U.S. sister study showed similar results (**Figure 8**).

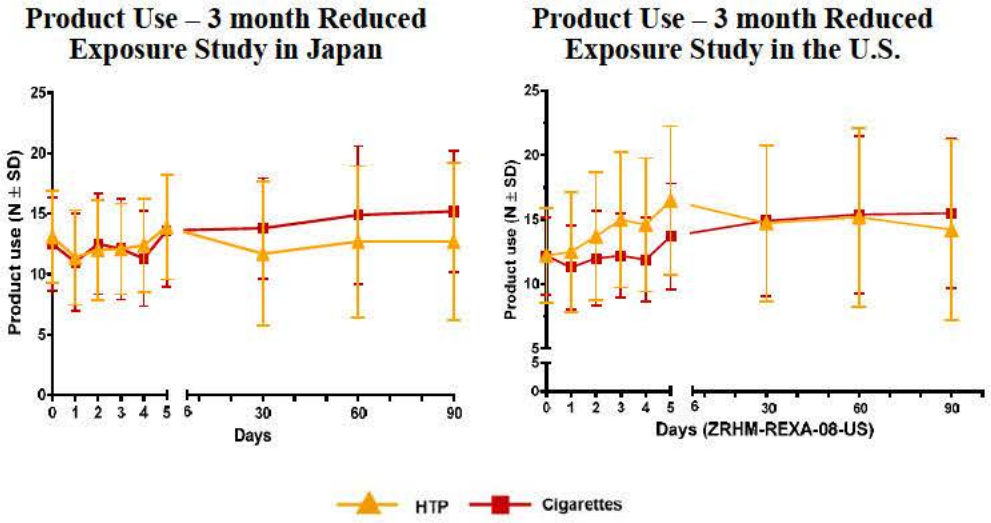


Figure 8 - Product Use of an HTP in 3 month Reduced Exposure studies in Japan and the U.S.

Furthermore, in the study in Japan subjects were highly compliant with their assigned product. Eighty-two percent of these subjects used the assigned HTP exclusively throughout the 85 days of the ambulatory period of the study (Luedicke et al., 2018).

The U.S. study was different in terms of product use compliance. During the 85-day ambulatory period, 42.5% of the subjects in the HTP group used the HTP 100% of the time and 58.8% of these subjects met the criteria for >95% of HTP use (Haziza et al., 2019).

Variations in product consumption, particularly during the first days of exposure to a new product with different characteristics compared with cigarettes, are expected and form part of the adaptation process to a new product such as HTP. These variations in product consumption observed soon after switching to the HTP disappeared over the course of the study.

Post market data: Post market data from a manufacturer-conducted cross-sectional survey in a representative sample of the general population and a sample of users of an HTP, as well as market research studies are available. For example, the first two waves of a cross-section survey conducted on PMI's HTP between December 2016 and July 2018 in Japan (n= ~2000 participants per wave in the HTP user sample) confirmed that around 70% of HTP users were using the HTP tested either exclusively or in combination with other smoke-free products, with the majority using the HTP exclusively (Langer et al., 2019).

In summary, the data available shows that:

1. HTPs deliver nicotine at similar, but not higher rates than cigarettes
2. Product use per day remains comparable to the use of cigarettes
3. HTPs can offer an acceptable and satisfying alternative for cigarette smokers who would otherwise continue to smoke.
4. The majority of study participants who used the tested HTP in clinical studies did switch to the product.

5. Post-market data on PMI's HTP shows that 70% of users of PMI's HTP were using the HTP either exclusively or in combination with other smoke-free products, with the majority used the HTP exclusively.

In short, HTPs represent a unique opportunity to curb cigarette smoking by current adult smokers in Australia who would otherwise continue to smoke cigarettes.

(C) TOXICITY AND SAFETY OF THE SUBSTANCE

As tobacco contains nicotine, Schedule 7 applies. The Scheduling Factors for Schedule 7 substances are addressed below and show that tobacco, when used as a heated substance (as in heated tobacco), is well below the toxicity and safety criteria for Schedule 7 and therefore, a specific exemption is appropriate.

Scheduling Factors S7

1. The substance has a high to extremely high toxicity

Acute oral LD50 (rat) is 50 mg/kg or less. Acute dermal LD50 is 200 mg/kg or less. Acute inhalation LC50 (rat) is 500 mg/m^3 (4 hours) or less. Dermal irritation is corrosive. Eye irritation is corrosive.

When non-animal test data are used, validated test results meeting the following GHS categories are taken to meet the factors for this schedule: Acute Toxicity Cat 1 or 2 (H300, H301, H310, H311); Corrosive Cat 1A. 1B, 1C (H314); Eye damage Cat 1-(H318).

The description of acute oral, dermal, inhalation toxicity of nicotine apply to exposure to the chemical, nicotine. This application deals with nicotine present in tobacco at levels naturally present in the tobacco plant. The levels of nicotine naturally present in tobacco is of the order of 0.3% to 0.5% of the tobacco plants dry weight (0.05% to 7% in tobacco leaf). HTPs contain up to 320 mg of tobacco and therefore exposure to nicotine through handling the consumable or inhaling the aerosol when the tobacco is heated is equivalent (or slightly less) compared to the exposure from tobacco prepared and packed for smoking. Similar considerations apply for skin and eye irritation for HTPs.

Therefore, as "tobacco prepared and packed for smoking" is exempt from Schedule 7, it is logical that "tobacco prepared and packed for heating", with equivalent (or slightly lower) exposure to nicotine, should also be exempt.

2. The substance has a high health hazard

The substance presents a severe hazard from repeated and unprotected use or a significant risk of producing irreversible toxicity, which may involve serious, acute or chronic health risks or even death if it is inhaled, taken internally or penetrates the skin.

HTPs generate an aerosol that contains nicotine for inhalation. The heating process is carefully controlled to ensure that combustion temperatures are not reached and consequently the aerosol produced is much simpler with reduced numbers and levels of HPHCs compared to cigarette smoke. **Figures 9** and **10** provide a graphical representation of the substantial reduction of HPHCs measured in two examples of HTPs when compared to cigarette smoke.

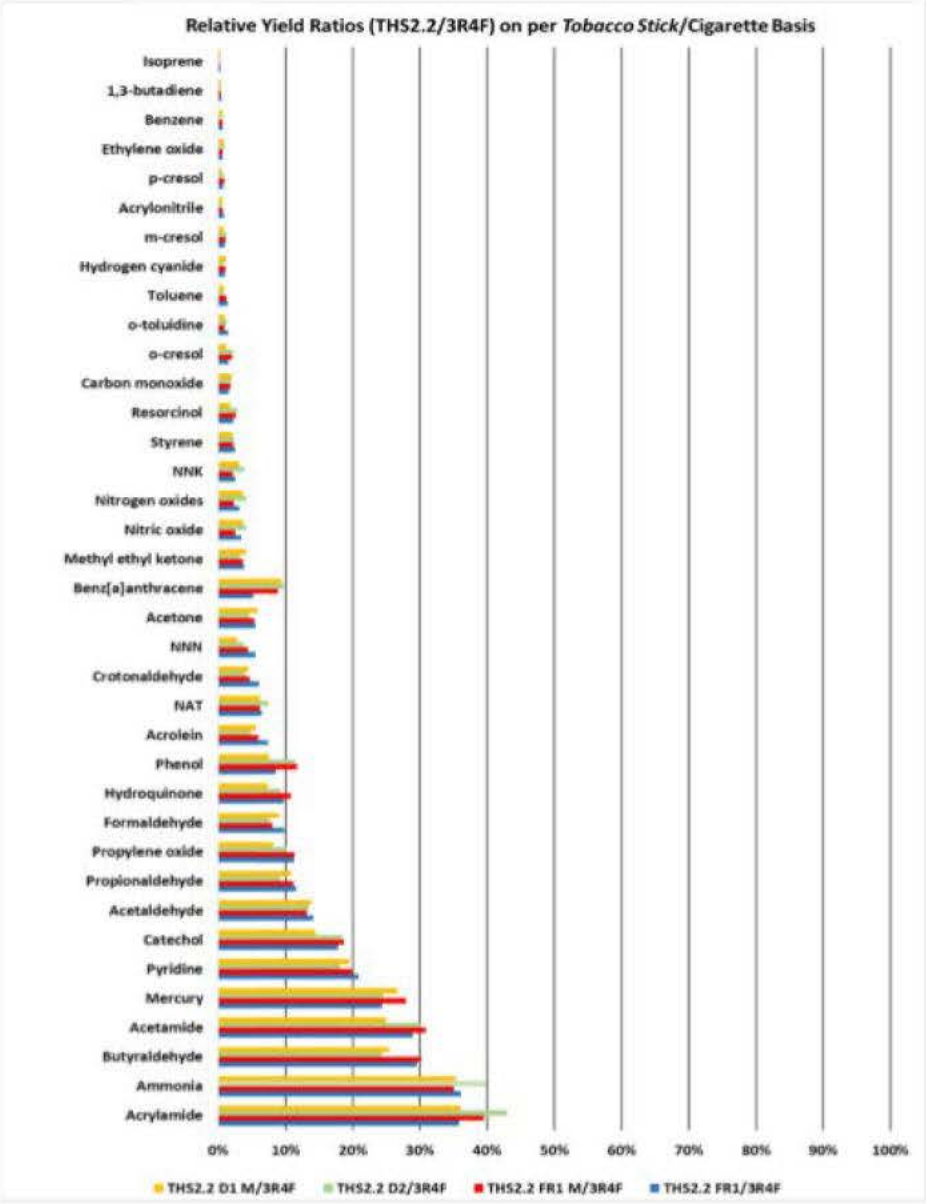


Figure 9. Mainstream aerosol levels (set at 100%) on a per-unit basis under the Health Canada Intense (HCI) puffing regime for HPHCs from PMI's HTP compared to the mainstream smoke HPHCs from the 3R4F reference cigarette.

When one value or more was below the LOQ, the results were not presented in the graphs (NAT: N-nitrosoanatabine, NNK: 4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone, NNN: N-nitrosonornicotine).

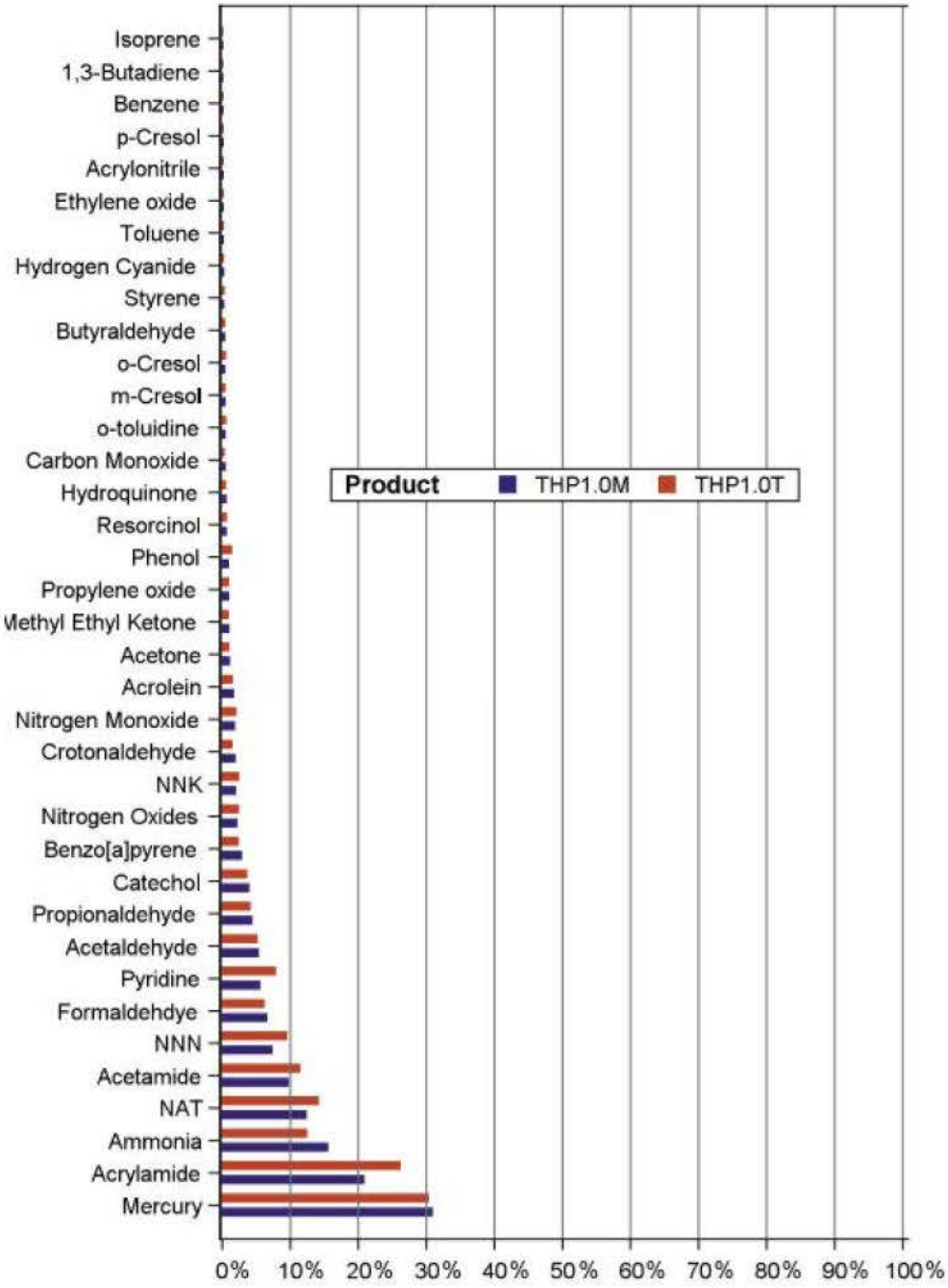


Figure 10. Relative abundances of mainstream HPHCs in THP1.0 (BAT) and 3R4F per consumable or cigarette generated using the HCI puffing regime.

(THP 1.0M = BAT Glo mentholated; THP 1.0T = BAT Glo regular) (Forster, M. et al, 2018)

The simpler chemistry (i.e. the number of compounds in HTP aerosols and the reduced amounts relative to cigarette smoke have been confirmed using sensitive analytical methods both targeted (analysing for known compounds using reference standard compounds to quantify their presence) and non-targeted methods (applying screening methods using gas and liquid chromatography coupled with

mass spectrometry) to semi-quantify the presence of other compounds present in the aerosol. This latter methodology allows for the detection and semi-quantification (and subsequent quantification of compounds of interest) to ensure that not only is the presence of known HPHCs reduced in the aerosol relative to cigarette smoke, but also that no new compounds of toxicological concern are being produced.

The published research for existing HTPs available in various markets, confirms the reduction in the amount and number of HPHCs but also confirms that there are detectable levels of certain HPHCs present in the aerosol. Therefore it is necessary to review the results of existing toxicology studies, to assess both the in vitro and in vivo toxicological impact, when compared to cigarette smoke. Results of studies published in peer-reviewed journals confirm that heating tobacco to below combustion temperatures results in a substantially reduced toxicological impact relative to cigarette smoke. This can be seen when assessing cytotoxicity, mutagenicity and genotoxicity in vitro (Schaller et al., 2016; Gonzalez Suarez et al., 2016; Jaunky et al., 2018; Thorne et al., 2018) as well as from in vivo inhalation toxicology studies results, where laboratory rodents have been exposed for periods between 90 days to 18 months and compared to animals exposed to cigarette smoke or fresh air (control) (Phillips et al., 2016; Wong et al., 2016; Oviedo et al., 2016).

For example, PMI conducted a study in Apoe-/- mice to compare the impact of switching to the aerosol of PMI's HTP with continued exposure to cigarette smoke and to smoking cessation. This study was designed to allow for a simultaneous evaluation of disease endpoints. An essential disease endpoint for cardiovascular disease is atherosclerotic plaque formation. While exposure to the smoke of a reference cigarette accelerated the growth of the atherosclerotic plaque in the aortic arch of continuously exposed animals, continuous exposure to PMI's HTP aerosol resulted in plaque areas that did not differ significantly from those seen in mice exposed only to air under the same experimental conditions. Cessation and switching from 3R4F smoke to PMI's HTP aerosol respectively both halted the atherosclerotic plaque growth that occurred in mice continuously exposed to 3R4F smoke. In the same study, lung function was also assessed. The results in animals exposed to cigarette smoke indicated emphysematous changes whereas PMI's HTP aerosol exposed animals did not show any effect on lung function, even compared with the sham mice at any of the time points of evaluation. Switching from smoke exposure to PMI's HTP aerosol or cessation resulted in stabilisation of the values, while continued 3R4F smoke exposure led to further impairment in lung function (Phillips et al. 2016, Lo Sasso et al. 2016, Titz et al. 2016).

In an 18-months inhalation study, A/J mice were exposed to mainstream aerosol from PMI's HTP at three test atmosphere concentrations of nicotine or to one concentration of smoke from 3R4F in whole body inhalation chambers according to the OECD Testing Guideline 453 (OECD, 2009). Exposures were carried out for 6 hours per day, 5 days per week. Female mice have been exposed to fresh air (Sham), to three concentrations of PMI's HTP aerosols and one of 3R4F smoke, and necropsies carried out after 1, 5, 10 and 18 months of inhalation exposure. Male mice were exposed to either fresh air or to the high test atmosphere concentration of PMI's HTP for 18 months. The study design is shown in **Figure 11**.

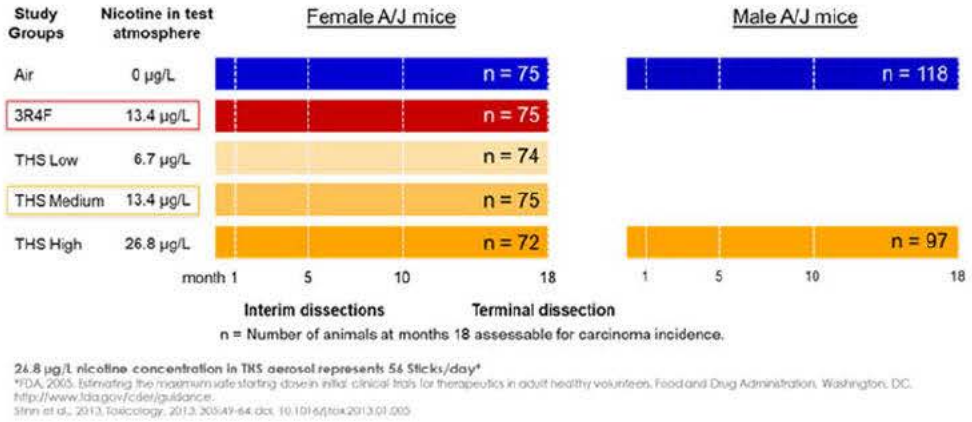
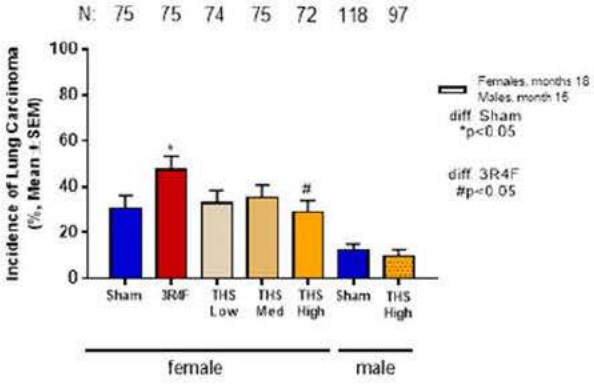


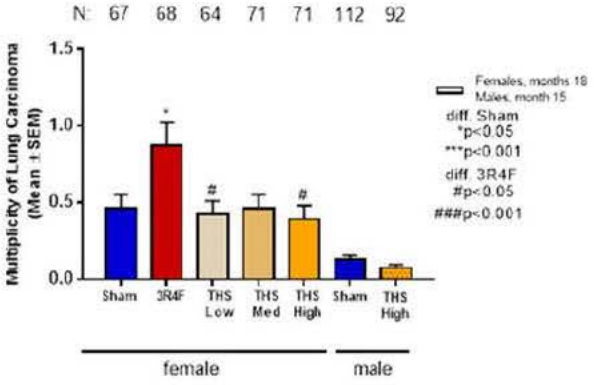
Figure 11: Study Design 18-month chronic toxicity and carcinogenicity study in A/J mice

The A/J mouse is highly susceptible to lung tumour formation and has been used widely in carcinogenicity testing. Exposure of the A/J mouse to carcinogens causes an increase in the numbers of animals that develop both adenomas and adenocarcinomas (incidence). In addition, a hallmark of carcinogen exposure in these mice is the occurrence of multiple lung tumours in any given animal (multiplicity). A/J mouse inhalation studies have been carried out with cigarette smoke and showed that exposure to cigarette smoke leads to lung tumours (Witschi, 2005; Stinn et al., 2013a; Stinn et al., 2013b).

The study results show that at the end of the life-long exposure period, a larger number (incidence) of A/J mice exposed to cigarette smoke had lung adenomas and carcinomas than mice exposed to air. In contrast, mice exposed to PMIs 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. The results are summarised in **Figures 12** & **13**.



Panel A



Panel B

Figure 12: Incidence (Panel A) and multiplicity (Panel B) of bronchoalveolar carcinoma.

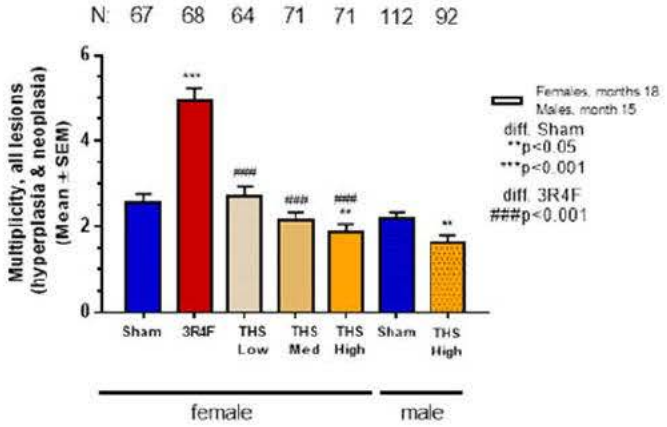


Figure 13: Multiplicity, all lesions: nodular hyperplasia, bronchoalveolar adenoma and carcinoma, terminal dissection.

In line with the evolving science of toxicology, mechanistic studies applying omics techniques have also been performed that further demonstrate the reduced biological impact on mechanisms known to lead to smoking related diseases, assessed *in vitro* (with human cells and organotypic cultures) and *in vivo* using laboratory rodents. (Poussin et al., 2016; Gonzalez Suarez et al., 2016; Iskandar et al., 2017a; Iskandar et al., 2017b; Phillips et al., 2016; Wong et al., 2016; Kogel et al., 2016; Toorn et al., 2018; Taylor et al., 2018).

In conclusion the results from the *in vitro* and *in vivo* studies confirm that tobacco for heating has a lower level of health hazard compared to tobacco prepared and packed for smoking.

3. The dangers of handling the poison are such that special precautions are required in its manufacture, handling or use.

The dangers associated with handling the substance are too hazardous for domestic use or use by untrained persons and warrant restrictions on its availability, possession or use.

Tobacco prepared and packed for smoking is widely available and whilst inhaling cigarette smoke is well known to be hazardous, this hazard is initiated when the cigarette is lit and the smoke inhaled. Handling unlit cigarettes does not require special precautions/restrictions other than keeping out of the reach of children. Precautions need to be taken once the cigarette is lit to avoid initiation of fires.

The situation is comparable for HTPs though in the absence of combustion, HTPs are unlikely to initiate fires [A].

4. The substance has a high potential for causing harm at low exposure

The substance should be available only to specialised or authorised users who have the skills necessary to handle the substance safely. Restrictions on their availability, possession, storage or use may apply.

"Tobacco prepared and packed for smoking" are limited for sale to adult smokers and are not otherwise limited to specialised or authorised users. The same considerations would also apply to HTPs.

Conditions for the use of HTPs require the same considerations because both CCs and HTPs contain tobacco. When compared to cigarette smoking the scientifically substantiated benefits of reduced exposure to HPHCs for both users and bystanders of HTPs are outlined below.

- Reduced Exposure studies, which assess whether adult smokers who switch completely to PMI's HTP reduce their exposure to HPHCs and how these reductions compare to adult smokers who continue to smoke and to adult smokers who quit smoking for the duration of the study:
    - In four reduced exposure studies (two 1-week in confinement and two 3-month ambulatory) participants showed rapid (within a couple of days of switching to PMI's HTP) and sustained reductions in biomarkers of HPHC exposure that approached the reductions in the group that stopped smoking (Haziza et al., 2016a; Haziza et al., 2016b; Luedicke et al., 2018; Haziza et al., 2019).

- A 6-month exposure response study, which assesses the effect of switching from cigarette smoking to the use of PMI's HTP on clinical endpoints known to be negatively affected by smoking, shows positive changes upon cessation as described in the literature and are linked epidemiologically to smoking-related diseases.
    - This study (with 984 adult American smokers) examined whether favourable changes occur in 8 co-primary endpoints (HDL-C, WBC, FEV1%pred, COHb, Total NNAL, sICAM-1, 11-DTX-B2, 8-epi-PGF2α) indicative of biological and functional effects when cigarette smokers switch to PMI's HTP. Additionally, biomarkers of exposure (BoExp) to HPHCs were quantified. The main outcome was a favourable change 6 months after baseline, with statistically significant improvements in 5 of 8 biomarkers of effect (HDL-C, WBC, FEV1%pred, COHb, Total NNAL) when smokers switched to PMI's HTP compared with those who continued to smoke cigarettes. Likewise, BoExp were markedly reduced. All endpoints showed favourable changes in the same direction as with smoking cessation and improved biological effects were observed in smokers who predominantly used PMI's HTP compared with continued cigarette smoking, with similar nicotine levels in both groups. Improvements in the biomarkers of effect are supportive of the research hypothesis, suggestive of disease risk reduction potential for smokers switching to PMI's HTP instead of continuing to smoke cigarettes (Luedicke et al., 2019).
    - Because PMI's HTP does not burn tobacco, the impact of use on indoor air quality is significantly lower than that of cigarette smoking (Mitova et al., 2016; Mitova et al., 2019).

Appendix 5 provides summaries of research conducted by independent researchers or regulatory authorities on the mainstream aerosol of HTPs and reference cigarette smoke.

Currently in Australia, "tobacco prepared and packed for smoking" is not a scheduled poison. However, tobacco products are subject to a comprehensive framework of applicable Federal, State and Territory tobacco control laws, as noted in Section (D) below. These regulations operate independently from the way in which "tobacco prepared and packed for smoking" is treated under the Poisons Standard. If the amendment requested is made, HTPs would also need to comply with those laws.

(D) DOSAGE, FORMULATION, LABELLING, PACKAGING AND PRESENTATION OF A SUBSTANCE

Exposure to nicotine from consuming HTPs is similar to that associated with the consumption of tobacco in cigarettes both in terms of the absolute dose, the bioavailability of that dose and the pharmacokinetic profile of the dose. Three independent and five manufacturer-funded studies have reported on nicotine levels in mainstream HTP aerosol (Simonavicius et al., 2018). One independent study used the International Organization for Standardization (ISO) machine smoking regimen and seven used the Health Canada Intense (HCI) regimen. Under the ISO regimen, the regular IQOS tobacco stick on average yielded 0.30 mg of nicotine, while under the HCI regimen nicotine levels in mainstream aerosol were 1.10–1.41 mg for *IQOS*, 0.46 mg for glo. The pharmacokinetic profile of nicotine from single use of an HTP has been reported by Brossard et al. (Brossard et al., 2017).

HTPs can be expected to be made available in a range of brands (Refer to Appendix 2). The exact form of each presentation made available commercially can be expected to vary depending on:

- the device with which it is to be used; and
- the regulatory requirements imposed on HTPs as a result of compliance with the comprehensive framework of Federal, State and Territory tobacco control laws.

In each case the product will contain tobacco prepared and packed in a way that facilitates its consumption in the device it is designed to be used with.

The likely presentations (**Figure 14**) include:

- tobacco packed in a shape which may resemble cigarettes (e.g."heatsticks", "Neo sticks"); and
- pods, capsules or plugs of tobacco that are inserted into the heating device. Such pods or plugs are likely to be contained in an outer wrapper of an appropriate material that contains the tobacco and facilitates the insertion of the pods or plugs into the device and their removal after use.

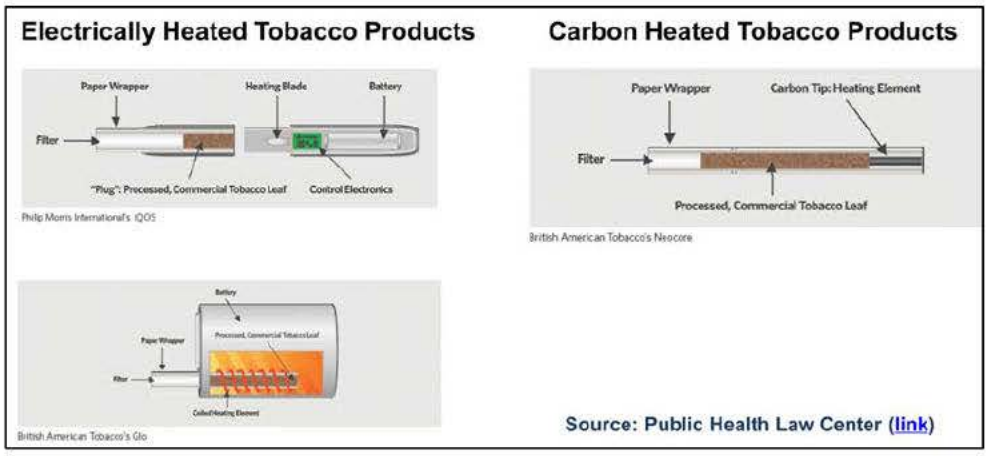


Figure 14: Types of HTPs

As is the case with “tobacco prepared and packed for smoking”, it can be anticipated that HTPs will be made available with different tobacco blends and amounts with resultant variations in relation to the nicotine content of the HTPs. These variations will be due to the composition of the tobacco, not additives.

Currently in Australia, “tobacco prepared and packed for smoking” is not a scheduled poison. However, tobacco products are subject to a comprehensive framework of applicable Federal, State and Territory tobacco control laws that regulate:

- how the products need to be packed and labelled, including what warnings need to be displayed on the packaging;
- who the products may be sold to (adults above 18 years of age);
- who may sell the products;
- the nature of advertising and point of sale display of products that is permissible; and
- where the products may be consumed.

These regulations operate independently from the way in which “tobacco prepared and packed for smoking” is treated under the Poisons Standard.

If the amendment requested is made, HTPs would also need to comply with those laws.

(E) POTENTIAL FOR MISUSE/ABUSE OF THE SUBSTANCE

Reports of Overdose:

When used as intended, the likelihood of nicotine overdose with HTPs is equivalent to cigarettes.

Signs and symptoms suggesting nicotine intoxication are due to the stimulation of the autonomic nervous system by nicotine and can occur if HTPs are used in excess, or ingested (e.g. accidentally by children). Toxic effects (such as nausea, dizziness and vomiting) of nicotine develop rapidly following acute overdose which lead to a reduction in HTP use if exposure is not accidental.

Taking PMIs HTP as an example, the risk of nicotine intoxication due to an excessive use of the HTP is not higher than with combustible cigarettes due to similar pharmacokinetic characteristics (Substance Summary).

Considering intentional or unintentional oral exposure to nicotine, more than 500 mg (6 to 7 mg/kg) of oral nicotine is an accurate estimate of the acute lethal oral dose in adults based on the data available in the literature today (Mayer, 2014). To put this in context, the nicotine content of PMI's HTP is, on average, 5 – 6 mg of nicotine/HTP. 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.

Unintentional ingestion of tobacco products is a major reason for infant and child toxic exposures all over the world (Vardavas et al., 2017; Kamboj et al., 2016; Bronstein et al., 2008). Studies have shown, that most of the exposure of children to nicotine is through ingestion (95.5%) or multiple routes including ingestion (2.8%), with only 1.7% through non-ingestion routes (Kamboj et al., 2016). Infants are susceptible to accidental tobacco ingestion because of a natural curiosity and a tendency for oral exploration (Goepferd, 1986; Johnson, 1997). Ingestion of as little as 1 mg of nicotine by a small child can produce symptoms such as nausea and vomiting (Goldfrank et al., 2006). Severe toxic effects of nicotine ingestion may include weakness, convulsions, unresponsiveness, and impaired respiration and ultimately may lead to respiratory arrest and death (Goldfrank et al., 2006).

Cases of accidental exposure by children have been reported for some HTPs and pose a similar risk as with any other tobacco product. However, using PMI's HTP as an example, accidental child exposure is not reported at higher rates compared to combustible tobacco products and with less severe outcomes.

Abuse:

The possibility of HTPs to cause dependence and the potential harm resulting from that dependence compared to other tobacco products constitutes the basis for the assessment of the abuse potential of HTPs. One approach to assess the abuse potential of HTPs is to follow the methodology as described by Carter in 2009 (Carter et al., 2009) (**Table 3**).

Table 3: Domains that can be used to assess abuse of HTPs Domains used for THS misuse/abuse assessment

Cluster	Domains / Components	Measurements
Product features	1. Product design	Product description and content (nicotine, menthol)
	2. Aerosol chemistry	Delivery of nicotine, acetaldehyde and ammonia
Likelihood of use	3. Pharmacokinetic effects	Nicotine pharmacokinetics (absorption rate and extent) Nicotine uptake
	4. Pharmacodynamic effects	Subjective effects
	5. Reinforcing effects	Product use behavior in various studies Perception (heath risks, addiction risk), comprehension Intention to use by various populations
Consequence of use	6. Impaired functioning	Cognitive assessment Psychomotor performance Withdrawal symptoms
	7. Physical dependence	Withdrawal symptoms
	8. Adverse events	Aversive adverse events Nervous system disorders

The likelihood that the self-administration of a product, such as HTPs, will result in persistent use or abuse is associated with its psychoactive or central nervous system effects, which can result in both positive and negative subjective effects, its reinforcing effects, and with tolerance, craving, and withdrawal that can result after repeated use of the product. A greater likelihood of dependence is associated with faster speed of nicotine delivery and its rewarding effects. Conversely, adverse effects from a product can also influence abuse, e.g., the occurrence of undesirable adverse health effects such as nausea can lower the likelihood of repeated self-administration.

The formulation and technical design of a product can also contribute to its misuse and/or abuse potential. For example, nicotine-containing products that are inhaled into the lungs are associated with faster rate of absorption (of nicotine) and tend to have greater abuse potential than products that are used orally or as a local application such as patches.

Other elements such as the addition of flavouring agents, the overall look and feel of the product or its possibly disruptive mode of use (vs. the usual way of smoking) may have a positive or negative impact on the overall product attractiveness and accordingly its potential for abuse.

HTPs and their potential for abuse using PMI's HTP as an example:

The potential for abuse with HTPs is illustrated in this section using PMI's HTP as an example and assessed using cigarettes ("tobacco prepared and packed for smoking" which is exempted from Schedule 7), as a comparator. Such comparison is appropriate as HTPs are intended to replace cigarettes in adult smokers who will otherwise continue smoking. The methodology from Carter (Carter et al., 2009) was applied.

PMI's HTPs abuse liability was assessed based on the review of available information from various sources, including product design and content, aerosol chemistry, human clinical and behavioral data. PMI's HTPs deliver generally comparable nicotine to that delivered by cigarettes. The nicotine exposure in humans under various use conditions, confirms the similarity of nicotine uptake PMI's HTPs 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 (**Table 4**).

Table 4 - Abuse Liability Assessment of HTPs Using the Example of PMI's HTPs (THS)

Domain	Measurements	Interpretation of Outcome
1. Product design	Nicotine content	THS = CC
	Menthol content	THS menthol = CC menthol
2. Aerosol Chemistry	Delivery of nicotine	THS = CC (3R4F)
	Delivery of acetaldehyde	THS < CC (3R4F)
	Delivery of ammonia	THS < CC (3R4F)
3. Pharmacokinetic effects	Nicotine pharmacokinetics single use	NRT < THS ≤ CC
	Nicotine pharmacokinetics repeated use	THS = CC
	Nicotine exposure at 3 months	THS = CC
4. Pharmacodynamic effects	Subjective effects early use	THS < CC THS regular < THS high menthol
	Subjective effects up to 3-month use	THS ≤ CC THS regular < THS high menthol
5. Reinforcing effects	Product use in clinical studies	THS ≤ CC
	Product use in near-to-real world	THS < CC
	Perception (health risk, addiction risk) and comprehension	THS = CC (smokers) THS ≥ CC (smokers with intention to quit) THS = CC (never- and former smokers
	Intention to use by never- and former smokers	THS = CC
6. Impaired functioning	Cognitive assessment	THS = CC
	Psychomotor performance	THS = CC
	Withdrawal symptoms	THS = CC
7. Physical dependence	Withdrawal symptoms short term	THS = CC
	Withdrawal symptoms up to 3 months	THS = CC
8. Adverse events	Aversive adverse events	THS = CC THS regular ≤ THS high menthol
	Nervous system disorders	THS = CC

The evidence indicates that cigarette smokers switching to PMI's HTPs keep their physical and/or psychological dependence to the tobacco product to a level not higher than the level associated with cigarette use. The tolerance to tobacco product use and/or the onset of withdrawal symptoms upon stopping the use of the tobacco product is maintained (not increased). Psychological dependence characterised by persistent

tobacco-seeking and tobacco-use behaviors, impairment in behavioral control, craving, and inability to abstain consistently is likely unchanged. Successful switching to PMI's HTPs requires several weeks of adaptation to transition due to the intended disruptive behavior and the necessary adaptation to product use.

Therefore, based on the totality of available evidence for PMI's HTPs related to the abuse liability domains assessed considering the likelihood of use and consequence of use, PMI's HTPs shares a similar but not higher abuse liability than cigarettes (**Table 4**). The full abuse liability assessment which PMI provided to the U.S. FDA as part of its MRTP for "THS" can be accessed on the FDA website[22] (Appendix 6).

Based on publicly available evidence on the domains described in **Table 3**, it can be concluded that it is more likely than not that other HTPs available on the market keep their physical and/or psychological dependence to the tobacco product to a level not higher than the level associated with cigarette use. Based on available aerosol chemistry data and considerations from the literature, the addiction potential of HTPs in general resides primarily with nicotine delivery (concentration in HTP aerosol and nicotine uptake during product use) which is within the range of nicotine delivered by cigarettes. Concerning the speed of nicotine uptake, HTPs do not show differences in nicotine pharmacokinetic profile when compared to the consumption of CCs.

Furthermore, the tolerance to tobacco product use and/or the onset of withdrawal symptoms upon stopping the use of the tobacco product is comparable to CCs. Data available on psychological dependence characterised by persistent tobacco-seeking and tobacco-use behaviours, impairment in behavioural control, craving, and inability to abstain consistently) indicates that these remain likely unchanged. These results therefore suggest an abuse liability potential of HTPs similar to CCs (Berthet et al., 2018).

Misuse:

Possibility to light up and smoke the HTPs: The technical design of various HTPs (e.g. HEETS for IQOS or NeoSticks for glo) involves additional features, e.g. an aluminium co-laminated paper, which is added to avoid misuse and prevent ignition of a tobacco stick with a lighter, like a traditional combustible cigarette (Mayer, 2014; Christensen, 2013; Schipper et al., 2014).

Possibility to use HTPs with counterfeit products: The possibility exists that HTPs can be used in combination with counterfeit products (i.e., the original HTP device with a counterfeit stick). This risk can be mitigated by clear and open communication that the benefits of switching to an HTP can only be achieved when used as intended and as described by the manufacturer. PML is working closely with the Australian government to eradicate illicit and counterfeit trade in CCs and loose leaf tobacco. These efforts would extend to counterfeit HTPs.

[22] Abuse Liability Assessment provided by PMI to the U.S. FDA as part of PMI's modified risk tobacco product application for THS, available at: https://www.fda.gov/tobacco-products/advertising-and-promotion/philip-morris-products-sa-modified-risk-tobacco-product-mrtp-applications#6

Unintended Use:

Use by youth, never smokers and former smokers: Knowledge about who uses HTPs together with how and why such products are used constitutes important aspects that need to be considered in the assessment of misuse and/or abuse potential of HTPs. Other elements such as the addition of flavouring agents, the overall design, look and feel of the product or its possibly disruptive mode of use (vs. the usual way of smoking) may have a positive or negative impact on the overall product attractiveness and accordingly its potential for abuse.

Data about the initiation by persons who were not previously tobacco or nicotine users (including youth), former smokers reinitiating tobacco use, and impact on the intention of smokers to quit nicotine and tobacco use altogether need to be considered in the assessment of the unintended use potential of HTPs. In general, 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, particularly adult smokers with no intention to quit smoking, non-smokers, former smokers, youth and never smokers are either not or only minimally interested in HTPs.

Results from two independent studies giving insight into the use patterns and unintended use potential of different tobacco products are summarised in **Table 5** below, including the use of HTPs by youth.

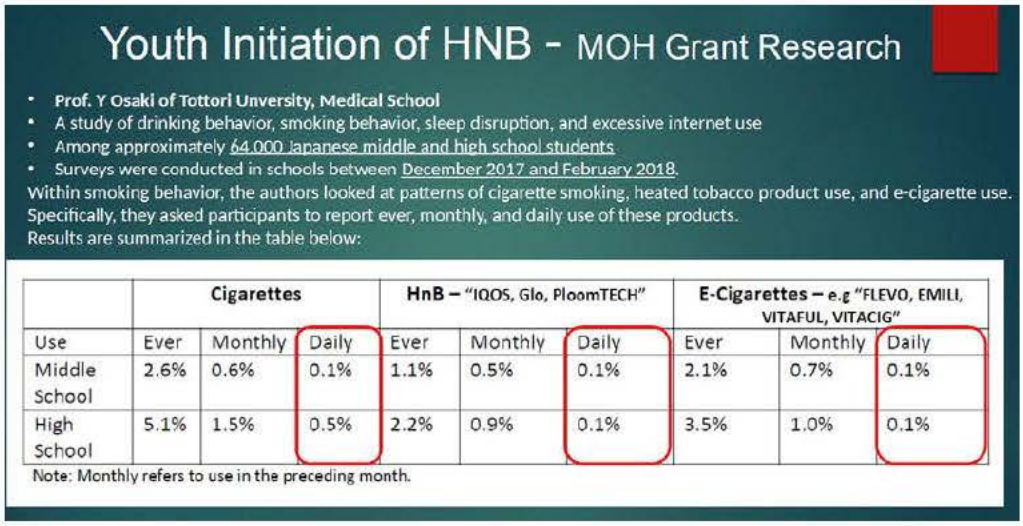
Table 5 - Overview of recent independent studies giving insight into the use patterns and misuse/abuse potential of different tobacco products

Study	Country	Design/Methodology	Outcome
An online survey of users of tobacco vaporizers, reasons and modes of utilisation, perceived advantages and perceived risks. Study by Queloz and Etter (Queloz and Etter, 2019)	Responses received from: Switzerland (83%), France (11%), Greece (1%), Italy (1%), Russia (1%), Norway (1%), Canada (1%).	An online questionnaire collected from October 2016 to January 2018 in self-selected visitors aged >18 to an anti-addiction website operated in Switzerland. Survey sample: 170 valid responses, out of whom 104 were users of tobacco vaporizers. For homogeneity, only 102 users of the Brand 1 tobacco vaporizer were included in analysis, as there were only two users of other vaporizers. Note: it is clear from the study that the product identified as "Brand 1" is PMI's IQOS.	• About half of the study population were current cigarette smokers (57%), the rest were former cigarette smokers, • The median age was 41, and the median duration of utilisation of the tobacco vaporizer 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). The authors concluded the following “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."
Health Behaviour in School-aged Children (HBSC) study (Delgrande et al., 2019)	Switzerland	A paper-pencil self-administered standardized question survey with two versions of the survey: - a short survey intended for those aged 11-13, and - a long survey intended for students from 14-15. The questionnaires were sent to the class teachers in early 2018 and the teachers had about 3 months to distribute them for completion in the classroom during school time. Participation in the survey was voluntary and anonymous. The dataset for 2018 includes data from 11,121 pupils aged 11 to 15 years. The aim of the study was to observe the health behaviours of 11-to-15-year-old adolescents and to document the evolution of these over time.	• In 2018, the proportion of pupils reporting having smoked cigarettes at least once in their life increased considerably with age: 5.7% of 11 year-old boys and about 2% of 11 year-old girls have smoked cigarettes and this proportion increased to 35.4% (boys) and 29.8% (girls) respectively, among 15 year-olds, • Among 15 year-olds, 9.7% of boys and 7.7% of girls smoked cigarettes at least once per week; respectively 5.6% of boys and 3.5% of girls of this age smoked on a daily basis, • About half of the 15 year-old daily smokers smoked up to 5 cigarettes per day and one third smoked 6-10 cigarettes per day. Hence, about one out of six of the 15 year-old daily smokers smoked more than 10 cigarettes a day, • Only few pupils had ever used heated tobacco products: less than 2% of boys and of girls aged 15", • More pupils have tried e-cigarettes than cigarettes, • The most reported reason for e-cigarette use was curiosity and desire to try something new.

Further information about the unintended use of HTPs among youth can be derived from the study conducted by Prof Osaki of Tottori University, Medical School (Osaki, 2019). This independent study was conducted in Japan, the country with the highest use of HTPs (in total three HTPs are on the market in Japan). The study investigated drinking behaviour, smoking behaviour, sleep disruption, and excessive internet use among approximately 64,000 Japanese middle and high school students. The surveys were conducted in schools between December 2017 and February 2018.

Within smoking behaviour, the authors looked at patterns of cigarette smoking, HTP use, and e-cigarette use. Specifically, they asked participants to report ever, monthly, and daily use of these products. The study results showed that only very few middle and high school students (0.1%) were daily users of HTPs (referred in the study as Heat-not-Burn tobacco products, or HnB) (Osaki, 2019).



Youth Initiation of HNB - MOH Grant Research

- **Prof. Y Osaki of Tottori University, Medical School**
- A study of drinking behavior, smoking behavior, sleep disruption, and excessive internet use
- Among approximately 64,000 Japanese middle and high school students
- Surveys were conducted in schools between December 2017 and February 2018.

Within smoking behavior, the authors looked at patterns of cigarette smoking, heated tobacco product use, and e-cigarette use. Specifically, they asked participants to report ever, monthly, and daily use of these products.
Results are summarized in the table below:

	Cigarettes			HnB – "IQOS, Glo, PloomTECH"			E-Cigarettes – e.g "FLEVO, EMILI, VITAFUL, VITACIG"		
Use	Ever	Monthly	Daily	Ever	Monthly	Daily	Ever	Monthly	Daily
Middle School	2.6%	0.6%	0.1%	1.1%	0.5%	0.1%	2.1%	0.7%	0.1%
High School	5.1%	1.5%	0.5%	2.2%	0.9%	0.1%	3.5%	1.0%	0.1%

Note: Monthly refers to use in the preceding month.

Other independent researchers have reported different results on awareness, intention to try and susceptibility to try HTPs. For example a study by Czoli et al. (Czoli et al., 2019) used data 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 to describe the interest in using IQOS in these three countries. 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%). By smoking status, current smokers were the most interested group in trying IQOS (England = 91.4%, Canada = 92.1% and USA = 96.3%). Although continued research on monitoring awareness and interest in trying HTPs are very important it will be even more important to monitor and understand actual use of HTPs amongst all segments of the population, including non-smokers and youth in order to understand how intention to try and awareness translate into real product use. The study by Czoli was completed in countries where availability of HTPs is still limited (Canada and UK) or HTPs were not yet sold at the time of the study (USA). In contrast, the three studies from Japan and Switzerland listed above provide real market data of product use where several HTPs are available in the

market since 2016. Because HTPs would need to comply with a comprehensive framework of applicable Federal, State and Territory tobacco control laws, it is expected that this risk is further mitigated.

Another study by Liu et al. reported on the use of PMI's HTP in Italy using a nation-wide face-to-face survey in those aged 15 years or older. They found that 1.4% of participants had ever used PMI's HTP. Overall, 1.0% of never, 0.8% of former and 3.1% of current smokers have tried PMI's HTP according to the authors. The authors then extrapolated the results of the study to the Italian population ≥ 15 years. In order to minimize potential biases and misinterpretations it would have been more appropriate to express the results as a percentage of the total sample size and indicate the level of precision by including confidence intervals for the various point estimates (Liu et al., 2018; Liu et al. 2019).

Additionally, in order to interpret the results of this study, it is important to consider that there is a clear difference between "trial" and "established use" (IARC). In other words, it is not adequate to translate the levels of trial detected in a sample into future levels of established use in the general population (Liu et al., 2018; Liu et al. 2019).

As an example, data from the 2010 Global Youth Tobacco Survey Italian data showed that 60.3% (CI 52.7–67.3) of participants of 15 years replied yes to the question "Have you ever tried or experimented with cigarette smoking, even one or two puffs?". However, only 12.7% (CI 9.1–17.5) of the study participants reported smoking cigarettes daily (Charrier, et al, 2014).

In addition, the results provided by Liu et. al. show that the percentage of current smokers that have tried PMI's HTP (3.1%) is three times higher than that of ex-smokers (0.8%) and never smokers (1.0%). Similarly, the percentage of current smokers with intention to try PMI's HTP (5.0%) is ten times higher than that of ex-smokers (0.5%) and around three times higher than that of never smokers (1.7%) Overall, the authors' findings suggest that PMI's HTP is, in fact, more appealing to current smokers than to ex- and never smokers. (Liu et al., 2018; Liu et al. 2019).

This data is in line with results from PMI pre-market studies in the U.S. and post-market data in Japan.

Pre-market studies on PMI's HTP conducted by PMI showed low "Intent to Use"[23] among Adult Former Smokers (between 1.0% and 6.4% of study subjects, depending on the product message tested) and Adult Never Smokers (between 0% and 2.1% of study subjects, depending on the product message tested). The results for young Adult Never Smokers are consistent with those observed in Adult Never Smokers (between 0% and 1.1% of study subjects, depending on the product message tested. This data was confirmed in post-market surveillance studies in Japan (conducted by PMI), the country with the highest number of HTPs users. The data from these studies shows that only 2% of users of PMI's HTP were previously never tobacco/nicotine users (Afolalu et al., 2018).

[23] Positive *Intention to Use* referred in the study to the proportion of subjects whose response to the single item assessing intention to use the EHTP was either *Very Likely* or *Definitely*.

In summary, data from industry and independent researchers generally shows that HTPs:

i. Are mainly used by adult smokers who would otherwise continue to smoke;
ii. have generally low attractiveness to never smokers and former smokers;
iii. do not generally interfere with quitting intent; and
iv. have generally low attractiveness to youth.

Recently the U.S. FDA CTP issued a market order letter for PMI's HTP to allow the introduction of this tobacco product into the U.S. market. In their scientific review the U.S. FDA found that "Available data, while limited, also indicate that few non-tobacco users would be likely to choose to start using IQOS, including youth" (FDA press release, 2019).

Currently in Australia, "tobacco prepared and packed for smoking" is not a scheduled poison. However, tobacco products are subject to a comprehensive framework of applicable Federal, State and Territory tobacco control laws.

Potential for conversion into Schedule 8 or Prohibited Substance: Conversion into Schedule 8 or Prohibited Substances is not required based on the available scientific evidence. The amount of nicotine that is present in HTPs, and subsequently transferred to the aerosol, pose similar risk in comparison to tobacco prepared and packed for smoking, which are exempt from Schedule 7.

For example, according to the EU CLP classification, toxicity of nicotine in concentration below 2.5% has not been classified whereas nicotine concentrations above 2.5% up to 16.6% have been classified as toxic if swallowed (Bibra, 2014). It needs to be emphasised that nicotine concentrations in HTPs as well as in HTP aerosols are substantially lower than the toxicologically unclassified concentration of < 2.5%.

(F) ANY OTHER MATTER THAT MAY BE RELEVANT TO THE SCHEDULING OF A SUBSTANCE

The Concept of Population Harm Reduction and Tobacco Harm Reduction (THR)

The following, simple equation illustrates that population harm reduction depends on both the availability of significantly less harmful products and a significant number of adult daily smokers willing to accept and switch to these products.

The Harm Reduction Equation

Figure 15 - The Harm Reduction Equation (Figure adapted from Clive Bates presentation to E-Cigarette Summit (19 Nov 2013))

The harm reduction equation is written as a "multiplication function" to illustrate that the achieved population harm reduction is a function of how much risk can be reduced by a product "multiplied" by its acceptance and usage among smokers.

This means that a significant contribution to population harm reduction would be achieved by a product with very low risk (compared with cigarettes) that (i) is widely accepted by smokers, (ii) has low attraction to persons who do not currently use tobacco products (never smokers and former smokers) and (iii) has limited effect on smokers who intend to quit. Conversely, low product acceptance would offset even the strongest reduced risk product profile, negating any significant population benefit.

Similarly, a product with a marginal risk reduction profile, but with wide consumer acceptance, would also not result in significant population benefit.

It is important to note, whether harm reduction is achieved or not will always have to be measured based on the "population net benefit" achieved. This means, that between the extreme scenarios described above, any variation in between can achieve a population net benefit and therefore demonstrate successful harm reduction. This goes hand in hand with the important note that products intended to reduce the harms of smoking are not risk free, and that harm minimisation but not harmlessness is the objective of any harm reduction approach.

Abrams et al. (Abrams et al., 2018) explored the benefits and harms to public health of alternatives to tobacco smoking, highlighting products and their risks along the harm minimisation continuum (**Figure 16**).

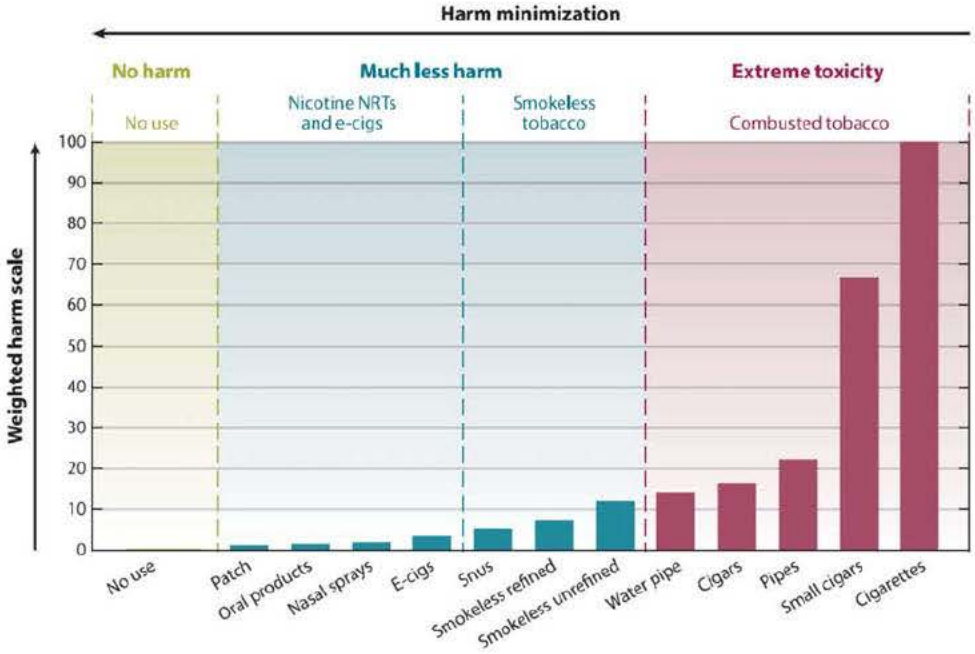


Figure 16: Products along the harm minimisation continuum. Depicts four panels representing classes of products: "Products containing tobacco are depicted as "combusted" or "smoked" (panel 1, right) and "non-combusted" or "smokeless" (panel 2, right middle). Smokeless products are far less harmful than smoked tobacco, but there is variation in the smokeless tobacco category; low nitrosamine Swedish-type snus is lower in relative harm than unrefined tobacco. Heat-not-burn tobacco products (e.g., heat sticks) would also fall into this panel. Panel 3 (left middle) depicts the class of nicotine delivery products without any tobacco (e-cigs/e-vapor products and NRTs). Panel 4 (left) depicts no use and thus no exposure." (**Abrams et al., 2018**)

The authors state that the harm minimisation continuum suggests that all nicotine-containing products are not equally harmful and, instead, range from exceptionally low harm (e.g., NRT) to exceptionally high harm (e.g., combusted tobacco such as cigarettes, cigars, hookah pipe).

The authors concluded that a reframing of societal nicotine use through the lens of harm minimisation is an opportunity to enhance the impact of tobacco control efforts. "*If we lose this opportunity, we will have blown the single biggest public-health opportunity ever to get rid of cigarettes and replace them with a much safer form of nicotine for everybody.*" David S. Abrams, Professor, New York University College of Global Public Health[24].

Adoption of THR by public health groups and regulators

Many public health experts advocate that governments adopt the policy of THR to complement the other major strategies for reducing smoking-related harm (i.e., prevention and cessation). "Tobacco harm reduction focuses on encouraging the use of

[24] https://www.theatlantic.com/ideas/archive/2019/10/danger-vaping-bans/600451/

less dangerous forms of tobacco/nicotine by those who prefer not to abstain from all tobacco/nicotine products." (Kiviniemi and Kozlowski, 2015).

The U.K. Royal College of Physicians (RCP) stated in 2007 (RCP, 2007) and reiterated in 2016 (RCP, 2016) that "*as most of the harm caused by smoking arises not from nicotine but from other components of tobacco smoke, the health and life expectancy of today's smokers could be radically improved by encouraging as many as possible to switch to a smoke-free source of nicotine.*" Indeed, the RCP stated "*Harm reduction, as a complement to conventional tobacco control policies, could … offer a means to prevent millions of deaths among tobacco smokers in the UK alone.*"

Furthermore, many public health authorities agree that there is a broad continuum of risk among tobacco and nicotine containing products, with cigarettes at the highest end and nicotine replacement therapies at the lowest end of that spectrum. This continuum recognizes that most of the harm caused by tobacco results from the burning of tobacco. Non-combustible tobacco and nicotine containing products are therefore differentiated from the risk associated with combustible tobacco products and placed close to the lower end of risk on this risk continuum (FDA, 2016; RCP, 2016).

In the most recent development in the regulation of reduced risk products, the U.S. FDA announced on 22 October 2019 that, for the first time, it has authorised the marketing of products through the modified risk tobacco product (MRTP) pathway. Authorisations were provided for eight Swedish Match USA, Inc. snus smokeless tobacco products after reviewing scientific evidence submitted by the company that supports this claim[25]. These products had previously been authorised for U.S. sale without modified risk claims by the FDA in 2015 in response to filings of premarket tobacco applications (PMTAs). The recent authorisation allows the manufacturer to market these products with the claim "*Using General Snus instead of cigarettes puts you at a lower risk of mouth cancer, heart disease, lung cancer, stroke, emphysema, and chronic bronchitis.*"

In an effort to help prevent youth access and exposure, the agency has also placed stringent advertising, promotion and packaging restrictions on the products. The modified risk orders are product-specific and limited to five years. There are various other products, including HTPs, being evaluated and reviewed by the FDA through the MRTP pathway, and it is expected that more such products would be assessed through this pathway in the coming months and years in line with the shift towards less harmful products.

Independent Australian reviews supporting the role of HTPs in public health

Researchers from Australian universities have conducted independent studies and reviews on tobacco alternatives and concluded that these products are important considerations for public health. Modelling conducted by researchers from the University of Otago, Griffith University, the University of Queensland and The University of Melbourne suggested that a fairly permissive regulatory environment around vaporised nicotine products achieves net health gain and cost savings, albeit

[25] https://www fda.gov/tobacco-products/advertising-and-promotion/swedish-match-usa-inc-mrtp-applications

with wide uncertainty (Petrović-van der Deen et al., 2019). The results suggest that "*optimal strategies will also be influenced by targeted smoking cessation advice, regulations around chemical constituents of these products, and marketing and age limits to prevent youth uptake of vaping.*" Following on from the study, Professor Tony Blakely (The University of Melbourne) and Associate Professor Coral Gartner (University of Queensland) stated that: "*Australia should now commence a process of developing a regulatory framework that balances the risks and benefits offered by these products, as is happening in Canada and New Zealand.*"[26]

A recent meta-analysis conducted by Australian researchers assessed the literature for randomised controlled trials comparing levels of biomarkers of exposure (BoE) between CCs and heat-not-burn tobacco devices. The analysis reviewed ten non-blinded, randomised controlled trials conducted between 1st January 2010 and 13th August 2019, involving a total of 1,766 participants and found that all 12 BoEs assessed were significantly lower for users of HTPs in comparison to users of CCs. Additionally, eight of the twelve BoEs assessed were found to be statistically equivalent to smoking abstinence. The authors further concluded: "*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*" (Drovandi et al., 2019).

[26] https://pursuit.unimelb.edu.au/articles/access-to-e-cigarettes-will-improve-australia-s-health

PART 2.2 CRITERIA WHICH MUST BE ADDRESSED – PROPOSALS TO CHANGE PARTS 1-3 OR PART 5 OF THE POISONS STANDARD

Other chemicals are first assessed using the factors for Schedules 10 and 9. However the highly restricted criteria for Schedule 9, relating to the propensity for dependence and abuse, means that very few substances are likely to be considered for, or included in, this schedule. If the factors for Schedules 10 or 9 are not applicable, the substance is assessed against the Schedule 7 factors.

Using the cascading principle and scheduling factors, HTPs have been assessed as follows by the applicant:

Schedule 10 -Does Not Apply

1) The substance poses such a high public health risk, including potential risk, that its sale, supply and/or use require very strict control, with access generally being prohibited. The potential health risk does not include potential for abuse, diversion into illicit products or other factors which would warrant inclusion in Schedule 9.

Combustible tobacco products are widely available for sale in Australia and are subject to other controls, outside of the scope of the Poisons Standard.

2) The substance has a public health risk that substantially outweighs the benefit to the extent that no other Schedule would provide appropriate public access to any proposed or known products. The serious public health risk may be restricted to particular uses.

Tobacco prepared and packed for smoking is already excluded from scheduling as a poison in the Poisons Standard (as a result of the exemption from Nicotine as included in Schedule 7). HTP (which is also a tobacco product), for all the reasons discussed in the application, should also be excluded from scheduling by the addition of a further exemption from the Nicotine entry in Schedule 7.

Schedule 9 – Does Not Apply

1. The substance is included in either Schedule IV to the United Nations Single Convention on Narcotic Drugs, 1961 or in Schedule I to the United Nations Convention on Psychotropic Substances 1971.

Tobacco including HTPs, is not included in these International Conventions.

2. The substance has no currently established therapeutic value and is likely to present a high risk of dependency, abuse, misuse or illicit use.

The substance is not a therapeutic product. The risk of dependency is no greater than that presented by tobacco prepared and packed for smoking (which is already excluded from scheduling as a poison in the Poisons Standard as a result of the exemption from Nicotine as included in Schedule 7).

A high level of control is required through prohibition of manufacture, possession, sale or use to prevent abuse, misuse or diversion into illicit activities.

Tobacco including HTPs, is subject to separate controls outside of the scope of the Poisons Standard.

The benefits of use are substantially outweighed by the risks, and dangers are such as to warrant limiting use to strictly controlled medical and scientific research.

Information has been presented to show that HTPs are less toxic than combustible tobacco prepared and packed for smoking. Tobacco (in loose form or in cigarettes) is a legal product in Australia and is subject to separate controls outside of the scope of the Poisons Standard.

Schedule 7 – Applies

Tobacco, due to the naturally occurring nicotine content in tobacco, is currently included in Schedule 7 of the Poisons Standard unless exempted. As a result of an exemption from the nicotine entry in Schedule 7, tobacco prepared and packed for smoking is not a scheduled poison.

As per Section C, HTPs have been shown to be less toxic than combustible cigarettes and therefore should also be excluded from scheduling by the addition of a further exemption from the Nicotine entry in Schedule 7.

CONCLUSION

In Australia, Schedule 7 of the Poison Standard currently provides that nicotine is a dangerous poison unless in "tobacco prepared and packed for smoking".

The requested amendment proposes the same unscheduled classification for HTPs as currently applies to tobacco-based cigarettes, loose tobacco for use in pipes and roll-your-own cigarettes by adding "tobacco prepared and packed for heating**"** as an express exemption from Schedule 7 of the Poison Standard.

When Australia exempted "tobacco prepared and packed for smoking" from scheduling, non-combustible alternatives to cigarettes did not exist. This is no longer the case. Alternatives such as HTPs do exist, are available in more than 50 markets and represent a far better choice than continued smoking.

While HTPs have been commercialised relatively recently, they have been studied for decades. Over the past five years, as the current generation of HTPs have become widely available, many have been studied and some have undergone comprehensive scientific assessment. It is clear from this growing body of scientific evidence, including those conducted by independent organisations and health authorities, that this request to amend Schedule 7 by including nicotine in "tobacco prepared and packed for heating" would result in a public health benefit. Underlying this is the premise that burning tobacco, which doesn't occur in HTPs (but is currently permitted by Schedule 7) is responsible for the formation and emission of the vast majority of toxicants contained in cigarette smoke, and considered to be the primary cause of smoking-related diseases.

As Prof. Abrams challenges: *"[C]ould ANDS[27] be leveraged to effectively compete with cigarettes, eventually making smoking obsolete sooner than would otherwise be possible? Can many types of ANDS, when decoupled from deadly toxins in combusted tobacco smoke, be accepted by the public and by its health, regulatory, and advocacy bodies as an extraordinary opportunity to save lives rather than as a threat to the success of past tobacco control efforts? These questions are contentious, and their answers are complicated. Addressing opportunities for ANDS requires re-examination of the role that nicotine plays in sustaining smoking and the role that nicotine can play in reducing smoking when delivered in a safer, yet appealing manner*."

This application represents the opportunity for a scientific-based reframing of nicotine's role. As a first step, "tobacco prepared and packed for heating" must be exempted from Schedule 7. Without this step, no other can be made to realise the public health opportunity these products bring compared to the already allowed "tobacco prepared and packed for smoking."

[27] Alternative Nicotine Delivery Systems (ANDS) defined as noncombusted refined nicotine (e.g., e-cigarettes, heat-not-burn and other emerging products, as well as smokeless and NRT), See Abrams, D. et al., *Harm Minimization and Tobacco Control: Reframing Societal Views of Nicotine Use to Rapidly Save Lives*, 39 ANNU. REV. PUBLIC HEALTH, 193 (2018), available at https://www.annualreviews.org/doi/pdf/10.1146/annurev-publhealth-040617-013849.

HTPs generate significantly fewer and lower levels of harmful chemicals compared with cigarettes, and this has been consistently demonstrated for various HTPs. A scenario in which the aerosol of the product at hand would carry equal or greater disease risk than cigarette smoke would require "*implausible and unknown [disease] mechanisms.*" (Abrams et al., 2017)

The data show that scientifically substantiated HTPs have the potential to move smokers away from cigarettes. For example, between 70% and 80% of adult smokers who buy PMI's HTP use it predominantly or exclusively instead of smoking.

Concerns over unintended consequences are legitimate and should be taken very seriously. However, the data currently available (collected both pre-market and post-market by manufacturers and independent researchers) does indicate that HTPs have limited attractiveness to never smokers or former smokers. In general, HTPs do not discourage smokers who intend to quit, to stop using tobacco or nicotine. HTPs have generally a low appeal to youth, and data shows youth uptake of HTPs is limited.

If not amended, the inclusion of nicotine in Schedule 7 will leave close to three million Australians who smoke with no other choice other than continuing to smoke or quit. Data shows that many won't choose the latter even if it is indisputably the best choice they have. HTPs represent an opportunity to curb cigarette smoking by offering these smokers, an alternative that has a comparable nicotine profile as well as ritual, taste and sensorial experience to "tobacco prepared and packed for smoking" while significantly reducing the exposure to harmful chemicals. A failure to amend presents a significant risk of a missed opportunity (a Type II error) for adult smokers who would otherwise switch completely to HTPs resulting in an increase to their total cigarette pack-years. This potential missed opportunity is a key part of the challenge expressed by Prof Abrams "*...if smokers could be shifted from smoking to consuming clean nicotine (i.e., without smoke), many lives would be saved. The safest course is to stop smoking or, better, never to start. But a harm minimization approach recognizes that demanding absolute perfection is often counterproductive and that, when a harmful behavior cannot be eliminated, it is necessary to reduce its adverse health consequences.*" (Abrams 2018)

In making scheduling decisions, it is appropriate to recall that: (i) "[*s*]*cheduling is a regulatory intervention to reduce public health risk to an acceptable level*" (TGA, 2018); (ii) the particular scheduling request requires both risk and benefit analysis from the use of the substance under consideration; and (iii) the most harmful way to consume nicotine *already* enjoys an exemption from Schedule 7.

Considering all available evidence on HTPs, it is no longer justifiable to only allow the use of nicotine in "tobacco prepared and packed for smoking", its most harmful form. It is time to broaden the scope of the exemption by adding nicotine in "tobacco prepared and packed for heating" to the list of exemptions. To quote the former U.S. FDA Commisioner, Dr. Scott Gottlieb, "*It's incumbent upon us as regulators to explore both the potential public health benefits and the risks of this new technology with an open mind.*" (Gottlieb, S. 2017).

In light of the above, we respectfully request the Committee to accept the addition of *nicotine in "tobacco prepared and packed for heating"* as a standalone category exemption within Schedule 7.

PART 3 – SUPPORTING DATA

SUPPORTING DATA SUMMARY

This application refers to tobacco rather than nicotine as a pure chemical substance, and the requested change to Schedule 7 is a class exemption for tobacco prepared and packed for heating rather than a specific product.

That being the case, much of the information contained in this application is focused on comparing HTP products which conventional cigarettes.

Supporting data is by way of reference to published papers, regulatory decisions and policy statements, as noted in the bibliography. This includes peer reviewed journal papers relating to studies performed by the tobacco industry and other researchers.

The supporting data and references fall into four general categories

1) Published statistics and peer reviewed papers of independent research on the effects (including use, misuse and abuse) of nicotine and tobacco, in various forms.
2) Information on studies performed by industry such as Philip Morris International and British American Tobacco on HTP vs conventional cigarettes.
3) Regulatory opinions and decisions from comparable overseas regulators including, but not limited to, the U.S. FDA, New Zealand Ministry of Health, UK Committees on Toxicology, Carcinogenicity and Mutagenicity of Chemicals in Food, Consumer Products and the Environment, WHO and the Japanese National Fire Agency.
4) Policy statements and opinion pieces from other government agencies, UK Royal College of Physicians, Royal Australian College of General Practitioners and other peak bodies and stakeholders.

In particular, in the Risks and Benefits Section A, there is compelling evidence provided by independent researchers and the tobacco industry in relation to the reduced level of HPHCs in HTPs, relative to conventional cigarettes and, how this may affect overall health outcomes and indoor air quality. These are illustrated in the following publications: (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 TPL Report, 2019, PMI 2018, Pratte et al 2017, FDA 2019, FDA 2016, Royal College of Physicians 2016, WHO 2009, WHO 2000, Nordlund et al 2019). There is also supporting details on the impact of HTP aerosol on the environment and bystanders (Appendix 4).

Additional information on some current brands of HTPs, relevant to Section D of the application, is located in Appendix 2. PMI's HTP is one of the most studied HTPs and Appendix 3 lists publications and reviews for the product.

The risks of abuse and misuse (including attractiveness to youth, never-smokers or former smokers) are summarised in Section A and thoroughly discussed in Section E. THS abuse liability was assessed based on the review of available information from various sources, including product design and content, aerosol chemistry, human clinical and behavioural data and an example comparison is provided between IQOS and conventional cigarettes using the methodology of Carter 2009.

Section C provides evidence on reduced toxicity of HTPs in comparison to CCs, as well as additional details on independent assessments by comparable regulators and agencies (Appendix 5).

An overview of recent independent studies giving insight into the use patterns and misuse/abuse potential of different tobacco products has been provided with reference to Queloz and Etter, 2019, Delgrande et al., 2019 and Osaki, 2019.

Section E also includes reference to Appendix 6 which provides the full abuse liability assessment provided by PMI to the U.S. FDA as part of PMI's Modified Risk Tobacco Product application for THS.

Section F discusses the concept of tobacco harm reduction as well as the approach taken by comparable regulators.

Studies by PMI that are included in this application are peer reviewed publications or information in the public domain such as FDA submission dockets. Study reports are available for all studies relating to PMI's HTP and can be supplied if required.

All references used within the body of the document are hyperlinked to the Bibliography for ease of readability.

SUPPORTING DATA DETAILS

Additional data to substantiate indicated data points in the submission has been included as addenda in the following appendices:

Appendix 1: Countries that Regulate Heated Tobacco Products
Appendix 2: Marketed HTP Devices and Consumable
Appendix 3: List of independent studies and reviews of PMI's HTP
Appendix 4: Impact of HTP aerosol on the environment and on bystanders
Appendix 5: Examples of research conducted by independent researchers or regulatory authorities on the mainstream aerosol of the HTPs and reference cigarette smoke
Appendix 6: Abuse Liability

A Glossary of terms and abbreviations is also provided for ease of reference.

Data, including independent studies that have been conducted by medical institutions, have been provided by way of reference to peer reviewed journals and published papers, regulatory decisions and policy statements.

COPIES OF PAPERS REFERENCED

Copies of papers referenced are included as separate attachments and have been uploaded with the application.

All work referenced, copied and submitted for the purposes of this application, and used by the Commonwealth, can be taken to be authorised by the Commonwealth under section 183 of the Copyright Act 1968 (Cth).

PART 4 – BIBLIOGRAPHY

Abrams DB., Glasser AM., Pearson JL., Villanti AC., Collins LK., Niaura RS., 2018, Harm Minimization and Tobacco Control: Reframing Societal Views of Nicotine Use to Rapidly Save Lives, 39 Ann. Rev. Pub. Health 193

Abrams et al. (2017) Submission to Tobacco Products Scientific Advisory Committee on Modified Risk Tobacco Product Applications for IQOS System (Dec. 14, 2017), available at https://www.fda.gov/media/110535/download

Afolalu EF, Langer P, Prieto L, Skiada D, Dobrynina M, Sponsiello-Wang Z, Weitkunat R, Lüdicke F (2018) Patterns of Use Behaviors in a Sample of Japanese "Heat-Not-Burn" Tobacco Product (IQOS), presented at CORESTA 2018, available at: https://www.pmiscience.com/library/publication/patterns-of-use-behaviors-in-a-sample-of-japanese

American College of Medical Toxicology, Nicotine, available at: https://www.acmt.net/_Library/Public_Affairs/ACMT_FAQ_Nicotine_.pdf

Australian Bureau of Statistics, 2015, 4364.0.55.001 - National Health Survey: First Results 2014-15.

Australian Bureau of Statistics, 2018, 4364.0.55.001 - National Health Survey: First Results 2017-18.

Baker, R.R., 1987 A review of pyrolysis studies to unravel reaction steps in burning tobacco. J. Anal. Appl. Pyrolysis 11, 555-573.

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.

Benhamou E, Benhamou S, Auquier A, Flamant R. Changes in patterns of cigarette smoking and lung cancer risk: results of a case-control study. British Journal of Cancer. 1989; 60(4):601-4.

Berthet A. Jacot Sadowski I., Zurcher K., Guenin V., Gendre A., Auer R., Vernez D., Cornuz J.; "Heated" tobacco products: what you need to know; Rev Med Suisse 2018; 14:1935-41

Bibra Toxicology advice and consulting. EU Classification of nicotine mixtures under CLP Regulation 1272/2008. 2014. Available at https://echa.europa.eu/documents/10162/76d24a79-e356-483e-9bae-16c241002684

Bronstein, A.C. et al. 2008 Annual Report of the American Association of Poison Control Centers' National Poison Data System (NPDS): 25th Annual Report. Clin Toxicol (Phila) 46, 927-1057 (2008)

Brossard, P. et al., 2017 Nicotine pharmacokinetic profiles of the Tobacco Heating System 2.2, cigarettes and nicotine gum in Japanese smokers. Regul Tox and Pharm. 89, 193-199.

Carter LP, Stitzer ML, Henningfield JE, O'Connor RJ, Cummings KM, Hatsukami DK.; Abuse Liability Assessment of Tobacco Products Including Potential Reduced

Exposure Products (PREPs); Cancer Epidemiology, Biomarkers & Prevention; 2009 Dec;18(12):3241-62. doi: 10.1158/1055-9965.EPI-09-0948

Charrier, Lorena, Berchialla, Paola, Galeone, Daniela, Spizzichino, Lorenzo, Borraccino, Alberto, Lemma, Patrizia, Dalmasso, Paola, and Cavallo, Franco, Smoking Habits among Italian Adolescents: What Has Changed in the Last Decade?, Hindawi Publishing Corporation, BioMed Research International, Volume 2014, Article ID 287139, 8 pages http://dx.doi.org/10.1155/2014/287139

Christensen L. Three cases of attempted suicide by ingestion of nicotine liquid used in e-cigarettes. Clinical Toxicology. 2013;51:290

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

Committees on Toxicity, Carcinogenicity and Mutagenicity of Chemicals in Food, Consumer Products and the Environment, Statement on the toxicological evaluation of novel heat-not-burn tobacco products (Dec. 2017), available at https://cot.food.gov.uk/cotstatements/cotstatementsyrs/cot-statements-2017/statement-on-heat-not-burn-tobacco-products.

Czoli CD, White CM, Reid JL, RJ OC, Hammond D. Awareness and interest in IQOS heated tobacco products among youth in Canada, England and the USA. Tob Control. 2019:0:1-7. doi: 10.1136/tobaccocontrol-2018-054654. PubMed PMID: 30696783.

Daston, Life, Chance & Life Chances, 137 DAEDALUS 5 (2008), Volume 137, Issue 1, Winter 2008 p.5-14

Delgrande Jordan, M., Schneider, E., Eichenberger, Y, & Kretschmann, A. (2019). La consommation de substances psychoactives des 11 à 15 ans en Suisse – Situation en 2018 et évolutions depuis 1986 - Résultats de l'étude, Health Behaviour in School-aged Children (HBSC) (rapport de recherche No 100). Lausanne: Addiction Suisse. https://www.hbsc.ch/pdf/hbsc_bibliographie_342.pdf.

Department of Health in Australia, Nicotine Replacement Therapy, available at: https://www.health.gov.au/internet/main/publishing.nsf/Content/tobacco-nicotine-replacement (Accessed on 1 August 2019)

Djurdjevic S, Lee PN, Weitkunat R, Sponsiello-Wang Z, Lüdicke F, Baker G, 2018. Modeling the Population Health Impact of Introducing a Modified Risk Tobacco Product into the U.S. Market. Healthcare 2018, 6(2), 47; https://doi.org/10.3390/healthcare6020047

Drovandi A, Salem S, Barker D, Booth D, Kairuz T, Human Biomarker Exposure from Cigarettes versus Novel Heat-Not-Burn Devices: A Systematic Review and Meta-Analysis, Nicotine & Tobacco Research, ntz200, https://doi.org/10.1093/ntr/ntz200

Eaton, D., et al., 2018 Assessment of tobacco heating product THS1.0. Part 2: Product design, operation and thermophysical characterization. Regul. Tox and Pharm 93, 4-13.

Eichler et al, The Risks of Risk Aversion in Drug Regulation, NATURE REVIEWS, DRUG DISCOVERY, VOLUME 12, DECEMBER 2013

Food and Drug Administration (FDA) (2016), Deeming Tobacco Products To Be Subject to the Federal Food, Drug, and Cosmetic Act, as Amended by the Family Smoking Prevention and Tobacco Control Act; Restrictions on the Sale and Distribution of Tobacco Products and Required Warning Statements for Tobacco Products. 21 CFR Parts 1100, 1140, and 1143. Available from: https://www.federalregister.gov/articles/2016/05/10/2016-10685/deeming-tobacco-products-to-be-subject-to-the-federal-food-drug-and-cosmetic-act-as-amended-by-the

Food and Drug Administration (FDA) (2019), Nicotine: The Addictive Chemical in Tobacco Products, available at: https://www.fda.gov/tobacco-products/products-guidance-regulations/nicotine-addictive-chemical-tobacco-products (Accessed on 6 September 2019)

Food and Drug Administration (FDA) (2019), Technical Project Lead Report for the IQOS PMTA submitted by Philip Morris Products S.A. on May 15, 2017 available at: https://www.fda.gov/tobacco-products/premarket-tobacco-product-applications/premarket-tobacco-product-marketing-orders

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/press-announcements/fda-permits-sale-iqos-tobacco-heating-system-through-premarket-tobacco-product-application-pathway.

Forster M., McAughey J., Prasad K., (2018) Assessment of tobacco heating product THP1.0. Part 4: Characterisation of indoor air quality and odour. Regul Toxicol Pharmacol 2018;**93**:34–51. doi:10.1016/j.yrtph.2017.09.017

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.

Frost and Sullivan, Understanding of and Attitudes Towards Tobacco Harm Reduction Products, Insights from the Australian Public and Healthcare Professionals, December 2018

Fujita, O. (2017) Report Review of IQOS Tobacco Heating Device Model:2.4 Device Safety Report.

Fujita, O. and Y. Hui, Final Report for Collaborative Research between HU-PMI. Will a used and discarded Electrically Heated Tobacco Product cause fire in a trash box, forest and grass-land? Technical expert report dated July 22, 2016.

Gale N, McEwan M, Eldridge AC, Fearon IM, Sherwood N, Bowen E, McDermott S, Holmes E, Hedge A, Hossack S, Wakenshaw L, Glew J, Camacho OM, Errington G, McAughey J, Murphy J, Liu C, Proctor CJ, Changes in Biomarkers of Exposure on Switching From a Conventional Cigarette to Tobacco Heating Products: A Randomized, Controlled Study in Healthy Japanese Subjects, Nicotine & Tobacco Research, Volume 21, Issue 9, September 2019, Pages 1220–1227, https://doi.org/10.1093/ntr/nty104

Godtfredsen NS, Prescott E, Osler M. Effect of smoking reduction on lung cancer risk. JAMA 2005; 294(12):1505-10.

Goepferd, S.J. Smokeless tobacco: a potential hazard to infants and children. J Am Dent Assoc 113, 49-50 (1986).

Goldfrank LR, N.L., Howland & MA, L.N., Flumenbaum NE, Hoffman RS,. Goldfrank's Toxicologic Emergencies. 8th ed. New York, NY: McGraw-Hill; 1221–1230 (2006)

Gonzalez Suarez I, Martin F, Marescotti D, Guedj E, Acali S, Johne S, Dulize R, Baumer K, Peric D, Goedertier D, Frentzel S, Ivanov N, Mathis C, Hoeng J and Peitsch MC (2016) In vitro Systems Toxicology assessment of a candidate Modified Risk Tobacco Product shows reduced toxicity compared to a conventional cigarette. **Chemical Research in Toxicology**, 29:3-18. (PMID: 26651182)

Gottlieb S, Zeller M, (2017) Nicotine-Focused Framework for Public Health, N Engl J Med 2017; 377:1111-1114 DOI: 10.1056/NEJMp1707409

Greenhalgh EM, Stillman S, & Ford C, 7.16 Pharmacotherapies, In Scollo, MM and Winstanley, MH [editors], Tobacco in Australia: Facts and issues. Melbourne: Cancer Council Victoria; 2018, available from: http://www.tobaccoinaustralia.org.au/chapter-7-cessation/7-16-pharmacotherapy

Greenhalgh, EM Stillman S, & Ford C, Chapter 1, Prevalence of smoking—adults. In Scollo, MM and Winstanley, MH [editors]. Tobacco in Australia: Facts and issues. Melbourne: Cancer Council Victoria (2019), available from: http://www.tobaccoinaustralia.org.au/chapter-1-prevalence/1-3-prevalence-of-smoking-adults (accessed 10 Oct. 2019).

Hart C, Gruer L, Bauld L. Does smoking reduction in midlife reduce mortality risk? Results of 2 long-term prospective cohort studies of men and women in Scotland. Am J Epidemiol. 2013; 178(5):770-9.

Haziza C, de La Bourdonnaye G, Donelli A, Poux V, Skiada D, Weitkunt R, Baker G, Picavet P, Lüdicke F (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. doi: 10.1093/ntr/ntz013.

Haziza C, de La Bourdonnaye G, Merlet S, Benzimra M, Ancerewicz J, Donelli A, Baker G, Picavet P and Luedicke F. (2016a) Assessment of the reduction in levels of exposure to harmful and potentially harmful constituents in Japanese subjects using a novel tobacco heating system compared with conventional cigarettes and smoking abstinence: a randomized controlled study in confinement. **Regulatory Toxicology and Pharmacology**, 81:489-499. (PMID: 27693654).

Haziza C, De La Bourdonnaye G, Skiada D, Ancerewicz J, Baker G, Picavet P and Luedicke F (2016b) Evaluation of the Tobacco Heating System 2.2. Part 8: 5-day randomized reduced exposure clinical trial in Poland. **Regulatory Toxicology and Pharmacology**, 81 Suppl 2:S139-S150. (PMID: 27816672).

IARC Handbook of Cancer Prevention Volume 12, Methods for Evaluating Tobacco Control Policies, Chapter 3.1, 2008 .

Inoue-Choi M, Hartge P, Park Y, Abnet CC, Freedman ND. Association Between Reductions of Number of Cigarettes Smoked per Day and Mortality Among Older Adults in the United States. Am J Epidemiol. 2019; 188(2):363-371.

Inoue-Choi M, McNeel TS, Hartge P, Caporaso NE, Graubard BI, Freedman ND (2018) Non-Daily Cigarette Smokers: Mortality Risks in the U.S., Am J Prev Med. 2019 Jan;56(1):27-37. doi: 10.1016/j.amepre.2018.06.025

Institute of Medicine, Scientific Standards for Studies on Modified Risk Tobacco Products (2012), available at: https://www.nap.edu/catalog/13294/scientific-standards-for-studies-on-modified-risk-tobacco-products

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 (2017) 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 Aerodigestive Tract. **Toxicology Research (Cambridge)**, 6:631-653. (PMID: 30090531).

Iskandar, A. et al., 2017b Comparative effects of a candidate modified-risk tobacco product Aerosol and cigarette smoke on human organotypic small airway cultures: a systems toxicology approach. Toxicol. Res**.**, 2017, **6**, 930-946

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.

Jaccard, Guy, Tafin Djoko, Donatien, Korneliou, Alexandra, Stabbert, Regina, Belushkin, Maxim, Esposito, Marco (2019) Mainstream smoke constituents and in vitro toxicity comparative analysis of 3R4F and 1R6F reference cigarettes. Toxicology ReportsVolume 6, Pages 222-231

Jaunky, T. et al., 2018 Assessment of tobacco heating product THP1.0. Part 5: In vitro dosimetric and cytotoxic assessment. Reg. Tox. Pharm., 93,52-61.

Johnson, C.P. & Blasco, P.A. Infant growth and development. Pediatr Rev 18, 224-42 (1997).

Kamboj, A., Spiller, H.A., Casavant, M.J., Chounthirath, T. & Smith, G.A. Pediatric Exposure to ECigarettes, Nicotine, and Tobacco Products in the United States. Pediatrics 137(2016).

Kiviniemi M.T., Kozlowski L.T (2015) Deficiencies in public understanding about tobacco harm reduction: results from a United States national survey. Harm Reduction Journal 2015, 512:21 (July 2015).

Kogel, U., Titz, B., Schlage, W. K., Nury, C., Martin, F., Oviedo, A., Lebrun, S., Elamin, A., Guedj, E., Trivedi, K., Ivanov, N. V., Vanscheeuwijck P, Peitsch, MC and Hoeng J (2016) Evaluation of the Tobacco Heating System 2.2. Part 7: Systems toxicological assessment of a mentholated version revealed reduced cellular and molecular exposure effects compared with cigarette smoke. **Regulatory Toxicology and Pharmacology**, 81 Suppl 2:S123-S138. (PMID: 27818347).

Kotz, D. & Kastaun, S. Bundesgesundheitsbl (2018) 61: 1407. https://doi.org/10.1007/s00103-018-2827-7

Langer P, Prieto L, Rousseau C, Formey A, Skiada D, Afolalu E, Sponsiello Z, Fischer K, Baker G, Weitkunat R, Tobacco product use after the launch of a heat-not-burn alternative in Japan: results of two cross-sectional surveys, presented at GFN Europe, Warsaw 13 –16 June 2019, available at: https://www.pmiscience.com/library/publication/tobacco-product-use-after-the-launch-of-a-heat-not-burn-alternative-in-japan-results-of-two-cross-sectional-surveys

Lee PN. The effect of reducing the number of cigarettes smoked on risk of lung cancer, COPD, cardiovascular disease and FEV1 – A review. Regul Toxicol Pharmacol. 2013; (67):372-81.

Li 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

Liu X, Lugo A, Spizzichino L, Tabuchi T, Pacifici R, Gallus S, (2018). Heat-not-burn tobacco products: Concerns from the Italian experience. Tobacco Control. 28. tobaccocontrol-2017. 10.1136/tobaccocontrol-2017-054054.

Lo Sasso, G., B. Titz, C. Nury, S. Boué, B. Phillips, V. Belcastro, T. Schneider, S. Dijon, K. Baumer, D. Peric, R. Dulize, A. Elamin, E. Guedj, A. Buettner, P. Leroy, S. Kleinhans, G. Vuillaume, E. Veljkovic, N. V. Ivanov, F. Martin, P. Vanscheeuwijck, M. C. Peitsch and J. Hoeng (2016a). Effects of cigarette smoke, cessation and switching to a candidate modified risk tobacco product on the liver in Apoe$^{-/-}$ mice – a systems toxicology analysis. Inhal Toxicol 28(5): 226-240. (PMID: 27027324)

Luedicke F, Ansari SM, Lama N, Blanc N, Bosilkovska M, Donelli A, Picavet P, Baker G, Haziza C, Peitsch M, Weitkunat R (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 Epidemiology, biomarkers and prevention**, e-pub ahead of print. (PMID: 31270101).

Luedicke FP, Picavet P; Baker, G.; Haziza, C.; Poux, V.; Lama, N.; Weitkunat, R. (2018) Effects of Switching to the Tobacco Heating System 2.2 Menthol, Smoking Abstinence, or Continued Cigarette Smoking on Biomarkers of Exposure: A Randomized, Controlled, Open-Label, Multicenter Study in Sequential Confinement and Ambulatory Settings (Part 1). Nicotine & Tobacco Research.;20(2):161-172. doi: 10.1093/ntr/ntw287. PubMed PMID: 28177489

Mallock et al., 2019 Heated Tobacco Products: A Review of Current Knowledge and Initial Assessments. Frontiers in Public Health. 7:287. doi: 10.3389/fpubh.2019.00287

Mallock 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

Market Research Report. Heated Tobacco Products Market Size, Share & Trends Analysis Report By Product (Stick, Leaf), By Distribution Channel (Online, Offline), By Region, And Segment Forecasts, 2019 – 2025, Grand View Research, 2019,

available at: https://www.grandviewresearch.com/industry-analysis/heated-tobacco-products-htps-market

Mayer B., How much nicotine kills a human? Tracing back the generally accepted lethal dose to dubious self-experiments in the nineteenth century. Arch Toxicol. 2014;88(1):5-7. doi: 10.1007/s00204-013-1127-0. PubMed PMID: 24091634; PubMed Central PMCID: PMCPMC3880486.

Mitova MI, Bielik N, Campelos PB, Cluse C, Goujon-Ginglinger C, Jaquier A, Gomez Lueso M, Maeder S, Pitton C, Poget L, Polier-Calame J, Rotach M, Rouget EGR, Schaller M, Tharin M and Zaugg V (2019) Air quality assessment of the Tobacco Heating System 2.2 under simulated residential conditions. **Air Quality, Atmosphere & Health,** 12:807-823.

Mitova MI, Campelos PB, Goujon-Ginglinger CG, Maeder S, Mottier N, Rouget EG, Tharin M and Tricker AR (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. (PMID: 27311683).

MSD Manuals, Kenilworth, NJ, USA: Merck Sharp & Dohme Corp.; 2018 [cited 2018], available from: https://www.msdmanuals.com/professional .

National Drug Strategy Household Survey (NDSHS) 2016—key findings, available at: https://www.aihw.gov.au/reports/illicit-use-of-drugs/ndshs-2016-key-findings/contents/tobacco-smoking

Niaura R, Re-thinking nicotine and its effects, Dec. 02, 2016, available at: https://www.truthinitiative.org/sites/default/files/media/files/2019/08/ReThinking-Nicotine_0.pdf

Nordlund, M., et al., (2019) Scientific substantiation of the absence of combustion and no smoke formation in the Electrically Heated Tobacco Product (EHTP), version 1.0. Scientific substantiation report dated January 21, 2019, Philip Morris Products S.A. https://www.pmiscience.com/library/publication/scientific-substantiation-of-the-absence-of-combustion-and-no-smoke-formation-in-the-electrically-heated-tobacco-product-ehtp

Nordlund, M., Kuczaj, A.K. 2016. Modeling aerosol formation in an electrically heated tobacco product. Int. J. Chem. Mol. Nucl. Mater. Metal. Eng. 10, 334-346

Osaki Y., Chief investigator, Professor, Division of Environmental and Preventive Medicine, Faculty of Medicine, Tottori University. http://researchers.adm.tottori-u.ac.jp/html/100000120_en.html

Oviedo A, Lebrun S, Kogel U, Ho J, Tan WT, Titz B, Leroy P, Vuillaume G, Bera M, Martin FT, Rodrigo G, Esposito M, Dempsey R, Ivanov NV, Hoeng J Peitsch MC and Vanscheeuwijck P (2016) Evaluation of the Tobacco Heating System 2.2. Part 6: 90-day OECD 413 rat inhalation study with systems toxicology endpoints demonstrates reduced exposure effects of a mentholated version compared with cigarette smoke. **Regulatory Toxicology and Pharmacology**, 81 Suppl 2:S93-S122. (PMID: 27818348)

Petrović-van der Deen FS, Wilson N, Crothers A, Cleghorn CL, Gartner C, Blakely T, Potential Country-level Health and Cost Impacts of Legalizing Domestic Sale of

Vaporized Nicotine Products, Epidemiology: May 2019, Vol 30, Issue 3, p 396-404, doi: 10.1097/EDE.0000000000000975

Philip Morris Products S.A., Experimental Report for P1 Characterization. Version N°: 1.0. 2018; Available from: https://www.fda.gov/tobacco-products/advertising-and-promotion/philip-morris-products-sa-modified-risk-tobacco-product-mrtp-applications September 21, 2018 Amendment: Submission of an Amended Study Report as part of "P1 Characterization" and an Updated Clinical Study (.zip – 376 MB) **(**added November 29, 2018**)** (April 26, 2018 Amendment: Submission of "P1 Characterization" Study (.zip – 25 MB) (added October 1, 2018)).

Phillips, B., E. Veljkovic, S. Boue, W. K. Schlage, G. Vuillaume, F. Martin, B. Titz, P. Leroy, A. Buettner, A. Elamin, A. Oviedo, M. Cabanski, E. Guedj, T. Schneider, M. Talikka, N. V. Ivanov, P. Vanscheeuwijck, M. C. Peitsch and J. Hoeng (2016). An 8-month systems toxicology inhalation/cessation study in Apoe-/- mice to investigate cardiovascular and respiratory exposure effects of a candidate modified risk tobacco product, THS 2.2, compared with combustible cigarettes. Toxicol Sci 149(2): 411-432. (https://www.pmiscience.com/library/8-month-systems-toxicology-inhalationcessation-study-apoe-mice-investigate-cardiovascular) (PMID: 26609137)

Poussin C, Laurent A, Peitsch MC, Hoeng J and De Leon H (2016) Systems toxicology-based assessment of the candidate modified-risk tobacco product THS2.2 for the adhesion of monocytic cells to human coronary arterial endothelial cells. **Toxicology**, 339:73-86. (PMID: 26655683)

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.

PubChem, Nicotine, Compound Summary, available at: https://pubchem.ncbi.nlm.nih.gov/compound/Nicotine (Accessed on 6 September 2019)

Public Health England, Evidence review of e-cigarettes and heated tobacco products 2018 (Feb. 2018), available at https://www.gov.uk/government/publications/e-cigarettes-and-heated-tobacco-products-evidence-review

Queloz, S. and 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 19:642 https://doi.org/10.1186/s12889-019-6957-0

Ramst, L. & Wikmans, T., Mortality Attributable to Tobacco Among Men in Sweden and Other European Countries: An Analysis of Data in a WHO Report, Tobacco Induced Diseases, 12:14 (2014)

Regulatory impact statement, Supporting smokers to switch to significantly less harmful alternatives, Ministry of Health, New Zealand, January 7, 2019, available at: https://www.health.govt.nz/about-ministry/legislation-and-regulation/regulatory-impact-statements/supporting-smokers-switch-significantly-less-harmful-alternatives

Rodgman, A., Perfetti, T.A. 2013. The chemical component of tobacco and tobacco smoke. Second edition CRC Press, Boca Raton, USA.

Royal Australian College of General Practitioners, Supporting smoking cessation, available at: https://www.racgp.org.au/clinical-resources/clinical-guidelines/key-racgp-guidelines/view-all-racgp-guidelines/supporting-smoking-cessation/pharmacotherapy/nicotine-replacement-therapy (Accessed on 1 August 2019)

Royal College of Physicians (2007) Harm reduction in nicotine addiction: helping people who can't quit. Available from: http://shop.rcplondon.ac.uk/products/harm-reduction-in-nicotine-addiction-helping-people-who-cant-quit?variant=6509405637

Royal College of Physicians (2012) Fifty Years since Smoking and Health: Progress, lessons and priorities for a smoke-free UK. UK Centre for Tobacco Control Studies. Available from: https://www.rcplondon.ac.uk/projects/outputs/fifty-years-smoking-and-health

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, available at: https://www.rcplondon.ac.uk/news/next-steps-long-journey-tobacco-harm-reduction

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.

Schipper EM, de Graaff LC, Koch BC et al. A new challenge: suicide attempt using nicotine fillings for electronic cigarettes. Br J Clin Pharmacol. 2014;78(6):1469

Schneider NG, Olmstead RE, Franzon MA, Lunell E, The nicotine inhaler: clinical pharmacokinetics and comparison with other nicotine treatments. Clinical Pharmacokinetics 2001;40:661–84.8

Simmons MS, Connett JE, Nides MA, Lindgren PG, Kleerup EC, Murray RP, Bjornson WM, Tashkin DP. Smoking reduction and the rate of decline in FEV(1): results from the Lung Health Study. Eur Respir J. 2005; 25(6):1011-7

Simonavicius E., McNeill A., Shahab L., Brose; Heat-not-burn tobacco products: a systematic literature review; Tob Control 2018;0:1–13. doi:10.1136/tobaccocontrol-2018-054419

Song YM, Cho HJ. Risk of stroke and myocardial infarction after reduction or cessation of cigarette smoking: a cohort study in Korean men. Stroke. 2008; 39(9):2432-8. Epub 2008 Jul 10.

Stead LF, Perera R, Bullen C, Mant D, Hartmann-Boyce J, Cahill K, Lancaster T, Nicotine replacement therapy for smoking cessation, Cochrane Database of Systematic

Reviews 2012, Issue 11. Art. No.: CD000146. DOI: 10.1002/14651858.CD000146.pub4 available at: https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD000146.pub4/full

Stinn, W., Berges, A., Meurrens, K., Buettner, A., Gebel, S., Lichtner, R.B., Janssens, K., Veljkovic, E., Xiang, Y., Roemer, E., and Haussmann, H.J. (2013a). Towards the validation of a lung tumorigenesis model with mainstream cigarette smoke inhalation using the A/J mouse. Toxicology 305, 49-64.

Stinn, W., Buettner, A., Weiler, H., Friedrichs, B., Luetjen, S., van Overveld, F., Meurrens, K., Janssens, K., Gebel, S., Stabbert, R., Haussmann HJ (2013b). Lung inflammatory effects, tumorigenesis, and emphysema development in a long-term inhalation study with cigarette mainstream smoke in mice. Toxicol Sci 131, 596-611.

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

Streller K, Roth S, Starker Tobak - Unsere Lust und Last mit der Zigarette, Chem. Unserer Zeit **2013**, 47, 248–268. DOI: 10.1002/ciuz.201300636, available at: https://www.chemistryviews.org/details/ezine/7164151/The_Chemistry_of_Tobacco__Part_4.html

Surgeon General's Report (2014): The Health Consequences of Smoking—50 Years of Progress, available at: https://www.cdc.gov/tobacco/data_statistics/sgr/50th-anniversary/index.htm

Taylor, M. et al., 2018 Assessment of novel tobacco heating product THP1.0. Part 6: A comparative in vitro study using contemporary screening approaches. Reg. Tox. Pharm., 93, 62-70.

The Japan Times, June 30, 2018. No authors listed. Japan to restrict heated tobacco use but give up on indoor smoking ban ahead of 2020 Tokyo Olympics, available from: https://www.japantimes.co.jp/news/2018/01/30/national/science-health/japan-restrict-heated-tobacco-use-give-indoor-smoking-ban-ahead-2020-tokyo-olympics/#.WnE2WrllKUm

Therapeutic Goods Administration (TGA), Scheduling Handbook – Guidance for amending the Poisons Standard (version 1.0, January 2018), TGA, available at: https://www.tga.gov.au/book-page/version-history

Thorne, D. et al., 2018 Assessment of novel tobacco heating product THP1.0. Part 7: Comparative in vitro toxicological evaluation. Reg. Tox. Pharm., 93, 71-83.

Titz, B., S. Boue, B. Phillips, M. Talikka, T. Vihervaara, T. Schneider, C. Nury, A. Elamin, E. Guedj, M. J. Peck, W. K. Schlage, M. Cabanski, P. Leroy, G. Vuillaume, F. Martin, N. V. Ivanov, E. Veljkovic, K. Ekroos, R. Laaksonen, P. Vanscheeuwijck, M. C. Peitsch and J. Hoeng (2016). Effects of cigarette smoke, cessation and switching to two heat-not-burn tobacco products on lung lipid metabolism in C57BL/6 and Apoe-/- mice - an integrative systems toxicology analysis. Toxicol Sci 149(2): 441-457. (https://www.pmiscience.com/library/effects-cigarette-smoke-cessation-and-switching-two-heat-not-burn-tobacco-products-lung) (PMID: 26582801).

Toorn, M. et al., 2018 The biological effects of long-term exposure of human bronchial epithelial cells to total particulate matter from a candidate modified-risk tobacco product. Toxicology In Vitro 50, 95-108

Torero, J.L., Review of "The Electrically Heated Tobacco System and the Electrically Heated Tobacco Product", Technical expert report dated October 27, 2017.

U.S. Department of Health and Human Services (HHS). Surgeon General's Report: How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease, Executive Summary [Internet]. 2010 [updated 2010; cited 2016 Jun 23]. Available from: http://whyquit.com/CDC/SGR_2010_How_Tobacco_Smoke_Causes_Disease.pdf

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

UK House of Commons, Science and Technology Committee, E-Cigarettes, 7th Report of Session 2017-2019 (Aug. 17, 2018), available at: https://publications.parliament.uk/pa/cm201719/cmselect/cmsctech/505/505.pdf.

Vardavas, C.I. et al. Characteristics and outcomes of e-cigarette exposure incidents reported to 10 European Poison Centers: a retrospective data analysis. Tob Induc Dis 15, 36 (2017).

Wald NJ, Watt HC. Prospective study of effect of switching from cigarettes to pipes or cigars on mortality from three smoking related diseases. BMJ. 1997; 314(7098):1860-3.

WHO Report on the Global Tobacco Epidemic, 2009, Implementing smoke-free environments, ISBN: 978 92 4 156391 8

WHO Study Group on Tobacco Product Regulation. Report on the scientific basis of tobacco product regulation: seventh report of a WHO study group, 24 October 2019, https://www.who.int/publications-detail/who-study-group-on-tobacco-product-regulation-report-on-the-scientific-basis-of-tobacco-product-regulation-seventh-report-of-a-who-study-group

Witschi, H., A/J mouse as a model for lung tumorigenesis caused by tobacco smoke: strengths and weaknesses. Exp Lung Res, 2005. 31(1): p. 3-18.

Wong ET, Kogel U, Veljkovic E, Martin F, Xiang Y, Boue S, Vuillaume G, Leroy P, Guedj E, Rodrigo G, Ivanov NV, Hoeng J, Peitsch MC, Vanscheeuwijck P. (2016)

Evaluation of the Tobacco Heating System 2.2. Part 4: 90-day OECD 413 rat inhalation study with systems toxicology endpoints demonstrates reduced exposure effects compared with cigarette smoke. Regul Toxicol Pharmacol. 81 Suppl 2: S59-S81

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

World Health Organization (WHO), Heated Tobacco Products (HTPs), Market Monitoring Information Sheet, July 2018, WHO/NMH/PND/18.7, available at:

https://apps.who.int/iris/bitstream/handle/10665/273459/WHO-NMH-PND-18.7-eng.pdf?ua=1

Zeller M, The Strategic Dialogue on Tobacco Harm Reduction: A Vision and Blueprint for Action in the U.S., Tobacco Control, 18(4): 324–332, (Aug. 2009), doi: 10.1136/tc.2008.027318.

APPENDIX 1: HEATED TOBACCO REGULATIONS

Countries that Regulate Heated Tobacco Products **November, 2018**

The following summary is based on feedback from Ministry of Health and tobacco control policy experts in jurisdictions where we are tracking country-level e-cigarette policies. Information is current as of November 19, 2018 and is subject to change.

Policy summary by country

Argentina

Heated tobacco products are not regulated.

Azerbaijan

Heated tobacco products are not regulated.

Bahrain

Heated tobacco products are not regulated.

Belgium

Regulation of heated tobacco products is unknown or unclear.

Brunei Darussalam

Heated tobacco products are regulated as tobacco products, under Section 3 of the Tobacco Order which regulates any tobacco products that are intended, labeled or described as suitable for inhaling, chewing or any oral use other than smoking.

Cyprus

The EU Tobacco Products Directive (specifically Article 19 on novel tobacco products), as transposed by the Health Protection (Tobacco Control) Law of 2017, is applied to heated tobacco products. There are provisions on reporting/notification and health warning labeling.

Denmark

Although it should be covered under the EU Tobacco Product Directive, regulation of heated tobacco products is unclear.

Ecuador

Heated tobacco products are regulated the same as e-cigarettes and other tobacco products in accordance with Article. 1 of the Tobacco Control (LORCT) Regulations.

England

The EU Tobacco Products Directive (specifically Article 19 on novel tobacco products), is applied to heated tobacco products. There are provisions on reporting/notification and health warning labeling. Heated tobacco products are notified to Public Health England (PHE) as the competent authority for tobacco products. So far, only two products (iQOS and IFuse) have been properly notified.

Fiji

Heated tobacco products are regulated in the same way that e-cigarettes are. See link for summary on Fiji's e-cigarette regulation.

Finland

Heated tobacco products are not regulated.

France

The EU Tobacco Products Directive (specifically Article 19 on novel tobacco products), is applied to heated tobacco products. There are provisions on reporting/notification and health warning labeling.

In addition, France taxes heated tobacco products under the classification "Autres tabacs à fumer" ("other smoking tobacco products").

Georgia

Use of heated tobacco products in public places and transportation is prohibited as is advertising and promotion of these products in accordance with the Law of Georgia on Tobacco Control.

Germany

Regulation of heated tobacco products is unclear. However, heated tobacco products are taxed like pipes.

Iceland

Heated tobacco products are not regulated.

Indonesia

Regulation of heated tobacco products is unclear.

Iran

Importation, production and sale of heated tobacco products is banned.

Ireland

Heated tobacco products must comply with existing tobacco control legislation.

Israel

Heated tobacco products are regulated as tobacco products. The Finance Committee voted to enact and implement a new tax order for heated tobacco products, thereby taxing heated tobacco sticks (HEETS) the same as cigarettes.

Italy

Heated tobacco products may be regulated by Law 188/2014 as smokeless tobacco products "tabacchi da inalazione senza combustion" ("tobacco product for inhalation without combustion"). Further, the EU Tobacco Products Directive (specifically Article 19 on novel tobacco products), as transposed by Italian law n.6/2016, may be applied to heated tobacco products. There are provisions on reporting/notification and health warning labeling depending on how they are classified (i.e. as novel tobacco products or smokeless tobacco).

Jamaica

Heated tobacco products are regulated as tobacco products in accordance with the Public Health (Tobacco Control) (Amendment) regulations 2014.

Japan

Heated tobacco products are regulated by the Health Promotion Act, as amended. Because smoking is defined to include smoke/vapor from burned or heated tobacco, heated tobacco products should be included in the smoking ban that the amendments stipulate. Smoking is completely banned in Type A facilities: schools, hospitals, children's facilities, government facilities, passenger cars and planes. However, in practice, use of heated tobacco products is allowed in Type B facilities (i.e. other public places including restaurants and passenger ships and trains). Heated tobacco products are currently taxed as pipe tobacco under the Tobacco Tax Act and sale to minors is restricted in accordance with Article 5 on the Act on Prohibition of Smoking by Minors. Further, heated tobacco products are regulated by the Tobacco Business Act.

Lao

Heated tobacco products are not regulated.

Luxembourg

The EU Tobacco Products Directive (specifically Article 19 on novel tobacco products), is applied to heated tobacco products. There are provisions on reporting/notification and health warning labeling.

Malaysia

Heated tobacco products are regulated under the Control of Tobacco Product Regulation (Amendment) 2015, where smoking is defined as inhaling and expelling the smoke or vapor of any tobacco product and includes the holding of or control over any ignited, heated or vaporized tobacco product.

Maldives

Heated tobacco products are regulated as tobacco products (which is defined as any product that contains tobacco or its extracts in any form) in accordance with the Tobacco Control Act (Law 15/2010). The Tobacco Control Act requires tobacco products not previously sold in the Maldives or introduced to the Maldivian market to obtain approval from the Ministry of Health.

Sale to minors under 18 years is prohibited as is sale via vending machines, post, internet or automated service where age cannot be verified prior to purchase.

The law currently requires all tobacco products imported, manufactured or sold to carry text warnings covering a minimum of 30% of the surface area of the front and back of the pack/package. The five approved messages should be rotated periodically (rotational frequency not specified). Health warnings are also required to be placed at venues selling tobacco products as well as in designated smoking areas in eateries.

All forms of advertising, promotion and sponsorship are prohibited.

Use of heated tobacco products is prohibited where smoking is banned.

In accordance with Act No. 31/79 (Export Import Act of Maldives), 200% of the cost, insurance and freight (CIF) value of tobacco products (other than cigarettes) and articles used in the consumption of tobacco products, are levied at the time of importation; further, a 6% goods and services tax (GST) is levied at the time of sale. However, gadgets used in the consumption of heated tobacco products are taxed as electronic devices rather than as articles used for consumption of tobacco products.

Malta

Because heated tobacco products are being classified by manufacturers as smokeless tobacco products, they are subject to Legal Notice 67 which bans the import, manufacture, sale, etc. of any smokeless tobacco product.

Mexico

Heated tobacco products are not regulated.

Moldova

Heated tobacco products are regulated as novel tobacco products and are regulated by the Law on Tobacco Products. Heated tobacco products are exempted from the tobacco legal provisions on presentation and promotion.

Nepal

Heated tobacco products are regulated as tobacco products and their use is defined as "consumption of a tobacco product" by Tobacco Product (Control and Regulation) Act, 2010.

The law prohibits advertising, promotion and sponsorship. Use in public places is prohibited. The law requires warning messages depicting harmful effects of tobacco products to be placed on the packaging.

Netherlands

The EU Tobacco Products Directive (specifically Article 19 on novel tobacco products), is applied to heated tobacco products. There are provisions on reporting/notification and health warning labeling.

New Zealand

A 2018 New Zealand District Court decision (*Philip Morris v Ministry of Health*) permits the sale of heated tobacco products under the 1990 Smoke-free Environments Act. In accordance with the law, heated tobacco products should not be sold or advertised to minors (under 18 years). In a statement, the New Zealand Ministry of Health plans to develop a risk-proportionate regulatory framework for products covered by the 1990 Smoke-free Environments Act, including heated tobacco products.

Norway

Heated tobacco products are banned in Norway under Regulations no. 1044 of 13 October 1989 Concerning the Prohibition against New tobacco and Nicotine Products.

Pakistan

Regulation of heated tobacco products is unclear.

Palau

Regulation of heated tobacco products is unclear.

Panama

Resolution no. 0953 of May 15, 2018 prohibits the sale of heated tobacco products, including of component parts intrinsic to heated tobacco products. It also prohibits use in places where smoking is prohibited.

Paraguay

Regulation of heated tobacco products is unclear.

Philippines

Heated tobacco products are not regulated.

Poland

Tax of 1141.29 Polish Zloty per kilogram and 31.41% of the weighted average retail selling price of smoking tobacco is applied to heated tobacco products.

Portugal

The EU Tobacco Products Directive (specifically Article 19 on novel tobacco products), as transposed by Law No. 37/2007 is applied to heated tobacco products. There are provisions on reporting/notification and health warning labeling. Heated tobacco is subject to the tobacco excise tax. The tax rate applied is the same rate as for combustible tobacco (which includes fine-cut tobacco for rolling cigarettes and other smoking tobacco products). There is a 15% ad valorem tax and 0.080 euros/gram tax.

Romania

The EU Tobacco Products Directive (specifically Article 19 on novel tobacco products), as transposed by Law 201/2016 is applied to heated tobacco products. There are provisions on reporting/notification and health warning labeling. The Fiscal Code regulates them under "non-harmonized excise" products. All the other regulations do not define/include them in any way. The tax structure is included in the applicable Fiscal Code, Title VIII, non-harmonized excise taxes.

Scotland

The EU Tobacco Products Directive (specifically Article 19 on novel tobacco products), is applied to heated tobacco products. There are provisions on reporting/notification and health warning labeling. Their composition must be notified to reference labs for approval and the products must comply with the Directive to be marketed. In UK and Scottish law these products cannot be advertised or promoted and cannot be displayed for sale – similar to cigarettes.

Senegal

Heated tobacco products are regulated as tobacco derivatives in accordance with Law No. 2014-14 (Concerning the Manufacture, Packaging, Labeling, Sale and Use of Tobacco).

Seychelles

Heated tobacco products are regulated as tobacco products in accordance with the Tobacco Control Act 2009.

Slovenia

Heated tobacco products are regulated by the Law on Restriction on the Use of Tobacco or Tobacco-related Products Act (OUTP) as tobacco-related products.

South Africa

Heated tobacco products are considered and regulated as tobacco products in accordance with the Tobacco products Control Act 83 of 1993 (as amended).

Spain

Heated tobacco products are regulated as novel tobacco products in accordance with Royal Decree 579/2017, of June 9, 2017. Therefore, Law 28/2005 (Sanitary Measures Against Smoking, and Regulating the Sale, Supply, Consumption and Advertising of Tobacco Products) which restricts the sale, advertising, promotion and sponsorship, and use in public places, also applies to heated tobacco products.

See Public Health Commission publication.

Sweden

The EU Tobacco Products Directive (specifically Article 19 on novel tobacco products), as transposed by The Tobacco Act—Law (1993:581) on tobacco (12 f §) is applied to heated tobacco products. There are provisions on reporting/notification and health warning labeling. The Public Health Agency of Sweden has regulatory authority over these products; however, this authority has not been exerted.

Switzerland

Heated tobacco products are considered tobacco products, i.e. they can be marketed like other tobacco products, without being subject to a preliminary approval; however, the warnings and taxation do not correspond to those of cigarettes.

Tajikistan

Heated tobacco products are regulated as tobacco products in accordance with the Law on Limiting the Use of Tobacco Products which extends the definition of tobacco products to include electronic products that deliver nicotine.

Thailand

Heated tobacco products are classified as e-cigarettes according to the definition of e-cigarette under the Consumer Board Announcement and MOC Announcement. As such, their sale and importation are banned under existing regulations. See e-cigarette policy summary for Thailand.

Timor-Leste

Heated tobacco products are regulated by Decree-Law N. º 14 /2016 of June 8 on the Tobacco Control Regime, which places restriction on use in public places, as well as prohibits their sale and marketing.

Turkey

Heated tobacco products are tobacco products by definition and thus regulated under the tobacco control law (Law on Prevention and Control of Hazards of Tobacco Products).

Turkmenistan

Heated tobacco products are prohibited.

Wales

The EU Tobacco Products Directive (specifically Article 19 on novel tobacco products), is applied to heated tobacco products. There are provisions on reporting/notification and health warning labeling. Heated tobacco products are taxed at the same rate as hand rolled tobacco, which is currently at £234.79 per kilogram. A Value Added Tax of 20% of the retail price is also applied.

APPENDIX 2: MARKETED HTP DEVICES AND CONSUMABLES

Appendix 2: Marketed HTP Devices and Consumables

Company	Product	Brand	Markets available
BAT	Consumable	Dunhill (for glo)	Bulgaria
BAT	Consumable	Kent (for glo)	Romania, Japan, Russia, Azerbaijan, Ukraine
BAT	Consumable	Kool (for glo)	Japan
BAT	Consumable	Neo (for glo)	Switzerland, Japan, Croatia, South Korea, Malaysia, Ukraine, Greece, Czech Republic, Kazakhstan, Poland, Serbia, Italy
BAT	Device	Glo Express	Italy, Romania
BAT	Device	Glo nano	Romania, Italy
BAT	Device	Glo series 1	Malaysia. Switzerland, Serbia
BAT	Device	Glo series 2	Poland, Romania, Malaysia, Japan, Croatia, Ukraine, Greece, Kazakhstan, Russia, Bulgaria, South Korea, Czech Republic, Azerbaijan
BAT	Device	Glo series 2 mini	Japan, Croatia, South Korea, Ukraine, Greece, Kazakhstan, Russia, Bulgaria,
CNTC	Consumable	COO (for MOK)	South Korea, Maldives
CNTC	Consumable	Kuanzhai (for KungFu)	South Korea
CNTC	Consumable	MC (for MC)	South Korea
CNTC	Device	MOK	South Korea, Maldives
CNTC	Device	MOK mini	South Korea, Maldives
CNTC	Device	KungFu	South Korea
CNTC	Device	MC 2.0 (Mate)	South Korea
Imperial	Consumable	iD (for Pulze)	Japan
Imperial	Device	Pulze	Japan
JTI	Consumable	Mevius (for Ploom S)	Japan
JTI	Device	Ploom S	Japan
KT&G	Consumable	Fiit (for lil)	South Korea
KT&G	Device	lil mini	South Korea

KT&G	Device	lil Plus	South Korea
PMI	Consumable	HEETS	Japan, Korea, Malaysia, New Zealand, Albania, Armenia, Belarus, Bosnia & Herz., Israel, Kazakhstan, Moldova, Russia, Serbia, Ukraine, Andorra, Azores, Bulgaria, Canary Islands, Corsica, Croatia, Cyprus, Czech Republic, Denmark, France, Germany, Greece, Hungary, Italy, Latvia, Lithuania, Madeira, Netherlands, Poland, Portugal, Romania, Slovak Republic, Slovenia, Spain Mainland, Sweden, Switzerland, United Kingdom,, Canada, Caribbean Other, Colombia, Dominican Republic, Guatemala, PMIDF (PMI Duty Free), Palestine Auth. Area, Reunion, South Africa, Turkish Cyprus, UAE
PMI	Consumable	Marlboro	Japan
PMI	Device	iQOS	As per HEETS consumables

Note: As at September 2019

APPENDIX 3 – INDEPENDENT PUBLICATIONS

2019

1. Andrikopoulos, G.I., Zagoriti, Z., Topouzis, S. et al. (2019). Oxidative stress induced by electronic nicotine delivery systems (ENDS): Focus on respiratory system. Curr Opin Toxicol. 13:81-89.
2. Barben, J., Künzli, N. (2019). [Smoking prevention: new trends and challenges]. Swiss Medical Forum 19(3334): 531-536.
3. Barben, J., Schuurmans, M.M., Zürcher, A., et al. (2019). [Reduced-Risk, ineffective strategy against tobacco]. Bulletin des médecins suisses, 100(3132):1041-1044. [Article in French].
4. 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. 8(1):11.
5. 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).
6. 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.
7. 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.
8. Clapp, P. W., Jadelis, C. T., Wu, J. et al. (2019). Characterization of the physical and thermal properties of new and emerging tobacco product (NETP) emissions. J. Aerosol. Med. Pulm. Drug. Deliv. 32(3):A31.
9. 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.
10. Crooks, I. (2019). In vitro mutagenicity of gas-vapour phase extracts from flavoured and unflavoured heated tobacco products. Toxicology Rep. doi: 10.1016/j.toxrep.2019.10.007.
11. 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. doi: 10.1016/j.tiv.2019.104652.
12. 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.
13. Eke, B.C., Başaran, R., Güven, N.M. (2019). An overview of iQOS® as a new heat-not-burn tobacco product and its potential effects on human health and environment. Turk J Pharm Sci. 16(3):371-374.
14. Farsalinos, K., Diamantopoulou. E., Panagiotopoulou, E. et al. (2019). Patterns of use, past smoking status, and biochemically verified current smoking status of heated tobacco product (IQOS) shops customers: preliminary results. Chest. 155(6):A387.
15. Formoso, G., Celani, M.G., Minozzi, S. et al. (2019). Heated tobacco and politics in Italy. BMJ. 365:l4189.
16. Freeman, B., Hefler, M., Hunt, D. (2019). Philip Morris International's use of Facebook to undermine Australian tobacco control laws.Public Health Res Pract. 29(3):e2931924.
17. Gong, S., Liu, W., Huang, P. et al. (2019). Puff-by-puff release of main aerosol components from two commercial heat-not-burn tobacco products.Tobacco Science and Technology. 52(2):62-71.
18. Górski, P. (2019). E-cigarettes or heat-not-burn tobacco products - advantages or disadvantages for the lungs of smokers. Adv Respir Med. 87(2):123-134.

19. Gravely, S., Driezen, P., Ouimet, J. et al. (2019). Prevalence of awareness, ever-use and current use of nicotine vaping products (NVPs) among adult current smokers and ex-smokers in 14 countries with differing regulations on sales and marketing of NVPs: cross-sectional findings from the ITC Project. Addiction. 114(6):1060-1073.
20. Gupta, R., Gupta, S., Sharma, S. et al. (2019). Risk of Coronary Heart Disease Among Smokeless Tobacco Users: Results of Systematic Review and Meta-Analysis of Global Data. Nicotine Tob Res. 21(1):25-31.
21. Hitosugi, M., Tojo, M., Shiomi, N., et al. (2019). Criminal mercury vapor poisoning using heated tobacco product. Int J Legal Med. 133(2):479-481.
22. Hwang, J.H., Ryu, D.H., Park, S.-W. (2019). Heated tobacco products: cigarette complements, not substitutes. Drug Alcohol Depend. 204:107576.
23. Ibañez, M.P., 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.
24. 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.
25. 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.
26. Jabba, S.V., Jordt, S.E. (2019). Risk Analysis for the Carcinogen Pulegone in Mint- and Menthol-Flavored e-Cigarettes and Smokeless Tobacco Products. JAMA Intern Med. doi: 10.1001/jamainternmed.2019.3649.
27. Jackson, S.E., Shahab, L., Kock, L. et al. (2019). Expenditure on smoking and alternative nicotine delivery products: a population survey in England. Addiction. 114(11):2026-2036.
28. 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.
29. 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.
30. 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. 11:1-7.
31. Kang, H., Cho, S.H. (2019). Heated tobacco product use among Korean adolescents. Tob Control. doi: 10.1136/tobaccocontrol-2019-054949.
32. Kastaun, S., Kotz, D. (2019). [Should advertising for electronic cigarettes and heated tobacco products be banned in Germany? Results of a representative survey (DEBRA study)]. Bundesgesundheitsbl. doi: 10.1007/s00103-019-03017-6.
33. 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.
34. Kistler, C.E., Ranney, L.M., Sutfin, E.L. et al. (2019). Product attributes important to US adult consumers' use of electronic nicotine delivery systems: a discrete choice experiment. BMJ Open. 9(8):e027247.
35. Kopa, P.N., Pawliczak, R. (2019). 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. doi: 10.1080/15376516.2019.1669245.
36. 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.

37. Lauterstein, D., Savidge, M., Chen, Y. et al. (2019). Nonanimal toxicology testing approaches for traditional and deemed tobacco products in a complex regulatory environment: Limitations, possibilities, and future directions. Toxicol In Vitro. doi: 10.1016/j.tiv.2019.104684.
38. 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.
39. 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. doi: 10.1136/tobaccocontrol-2018-054910.
40. 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.
41. 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.
42. Malela, S., Scott, A., Thickett, D. (2019). Effects of IQOS on macrophage viability and function. ERJ Open Research 5(suppl 2):PP130.
43. Mallock, N., Hutzler, C., Henkler-Stephani, F. et al. (2019). Heated Tobacco Products: A review of current knowledge and initial assessments. Front Public Health. 7:287.
44. Marsden, D.G., Loukas, A., Chen, B. et al. (2019). Associations between frequency of cigarette and alternative tobacco product use and depressive symptoms: A longitudinal study of young adults. Addict Behav. 99:106078.
45. McAlinden, K.D., Sohal, S.S, Sharma, P. (2019). There can be smoke without fire: warranted caution in promoting electronic cigarettes and heat not burn devices as a safer alternative to cigarette smoking. ERJ Open Res. 5: 00114-2019.
46. 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.
47. 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.
48. Mendes. A. (2019). Smoking cessation in 2019. Br J Community Nurs. 24(3), pp. 144–145.
49. Mohanty, D.; Lippmann, S. (2019). We must counsel against heat-not-burn cigarettes. J Fam Pract. 68(1):E2-E3.
50. 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.
51. Newland, N., Lowe, F.J., Camacho, O.M. et al. (2019). Evaluating the effects of switching from cigarette smoking to using a heated tobacco product on health effect indicators in healthy subjects: study protocol for a randomized controlled trial. Intern Emerg Med. 14(6):885-898.
52. Nistorescu, N., Pop Ananda, D., Croitoru Mircea, D. (2019). Difficulties in measuring the amount of cyanide by various method and their application in the toxicological risk assessment of classic cigarettes versus IQOS system. Acta Medica Marisiensis. 65(S1):58.
53. Ozga-Hess, J.E., Felicione, N.J., Ferguson, S.G. et al. (2019). Piloting a clinical laboratory method to evaluate the influence of potential modified risk tobacco products on smokers' quit-related motivation, choice, and behavior. Addict Behav. 99:106105.
54. Pisinger, C., Mackay, J. (2019). New Tobacco Products Do Not Protect Public Health. Ann Am Thorac Soc. doi: 10.1513/AnnalsATS.201905-411PS.

55. Polosa, R., Farsalinos, K. ,Prisco, D. (2019). Health impact of electronic cigarettes and heated tobacco systems. Intern Emerg Med. 14(6):817-820.
56. Polosa, R., Urso, S., Farsalinos, K. E. (2019). Response to "New tobacco products, a threat for tobacco control and public health of Mexico". Salud Publica Mex. 61(4):552-553.
57. Poynton, S., Sutton, J., Goodall, S. et al. (2019). A novel hybrid tobacco product that delivers a tobacco flavour note with vapour aerosol (Part 1): Product operation and preliminary aerosol chemistry assessment. Food Chem Toxicol. 106(Pt A):522-532.
58. Prochaska, J.J, Henriksen, L. (2019). PMI reduced-risk claims and upselling of IQOS via Reviti life insurance. Tob Control. doi: 10.1136/tobaccocontrol-2019-055145.
59. 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.
60. Quinto, C. B. (2019).[Promoter of health]. Bulletin des médecins suisses, 100(34):1099-1099.
61. Ravara S. (2019). The ERS position paper on heated tobacco products. Tob Prev Cessation. 5(Supplement):A29. doi:10.18332/tpc/105322. doi: 10.18332/tpc/105322.
62. Reynales-Shigematsu L.M., Roa-Rodríguez, R., Barrington-Trimis, J.L., et al. (2019). [Current and emerging issues in tobacco prevention and control]. Salud Publica Mex. 61:436-447.
63. Savareear, B., Escobar-Arnanz, J., Brokl, M. et al. (2019). Non-targeted analysis of the particulate phase of heated tobacco product aerosol and cigarette mainstream tobacco smoke by thermal desorption comprehensive two-dimensional gas chromatography with dual flame ionisation and mass spectrometric detection. J Chromatogr A. 1603:327-337.
64. 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.
65. 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.
66. 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. doi: 10.1016/j.arbres.2019.
67. Sohal; S.; Eapen, M.; Naidu, V.; (2019). IQOS exposure impairs human airway cell homeostasis: direct comparison with traditional cigarette and e-cigarette. ERJ Open Res. 11;5(1). pii: 00159-2018.
68. St Helen, G., Benowitz, N.L., Ko, J. (2019). Differences in exposure to toxic and/or carcinogenic volatile organic compounds between Black and White cigarette smokers. J Expo Sci Environ Epidemiol. doi: 10.1038/s41370-019-0159-9.
69. Stone, E., Marshall, H. (2019). Tobacco and electronic nicotine delivery systems regulation. Transl Lung Cancer Res. 8(Suppl 1):S67-S76.
70. Strong, D.R., Messer, K., White, M. et al. (2019). Youth perception of harm and addictiveness of tobacco products: Findings from the Population Assessment of Tobacco and Health Study (Wave 1). Addict Behav. 92:128-135.
71. Thorne, D., Leverette, R., Breheny, D. et al. (2019). Genotoxicity evaluation of tobacco and nicotine delivery products: Part Two. In vitro micronucleus assay. Food Chem Toxicol. 132:110546.
72. 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.

2018

73. Adriaens, K., Van Gucht, D., Baeyens, F. (2018). IQOS™ vs. e-Cigarette vs. Tobacco Cigarette: A Direct Comparison of Short-Term Effects after Overnight-Abstinence. Int J Environ Res Public Health. 15:2902.
74. Berthet, A., Jacot Sadowski, J., Zurcher, K. et al. (2018). Heated tobacco products: what do you need to know? Rev Med Suisse, 14(625):1935-1941.
75. Bialous, S.A., Glantz S.A. (2018). Heated tobacco products: another tobacco industry global strategy to slow progress in tobacco control. Tob Control. 27(Suppl 1):s111-s117.
76. Brose, L.S., Simonavicius E., Cheeseman, H. (2018). Awareness and use of 'heat-not-burn' tobacco products in Great Britain. Tob Regul Sci. 4(2):44-50.
77. Caponnetto, P., Maglia, M., Prosperini, G., et al. (2018) Carbon monoxide levels after inhalation from new generation heated tobacco products. Respir Res. 19(1):164.
78. Cho, Y.J., Trasher, J.F. (2018). Flavour capsule heat-sticks for heated tobacco products. Tob Control. doi:10.1136/tobaccocontrol-2018-054472 .
79. Chun, L., Moazed, F., Matthay, M., et al. (2018). Possible hepatotoxicity of IQOS. Tob Control. 27:s39–s40.
80. Crooks, I., Neilson, L., Scott, K., et al. (2018). Evaluation of flavourings potentially used in a heated tobacco product: Chemical analysis, in vitro mutagenicity, genotoxicity, cytotoxicity and in vitro tumour promoting activity. Food and Chemical Toxicol. 118: 940-952.
81. Czoli, C.D., White, C.M., Reid, J.L., et al. (2018). Awareness and interest in IQOS heated tobacco products among youth in Canada, England and the USA. Tob Control. doi: 10.1136/tobaccocontrol-2018-054654.
82. Dautzenberg, B., Dautzenberg, M.D. (2018). Le tabac chauffé : revue systématique de la littérature. Rev Mal Respir. 36(1):82-103.
83. Davis, B., Williams, M., Talbot, P. (2018). iQOS: evidence of pyrolysis and release of a toxicant from plastic. Tob Control. 28:34-41.
84. Eaton, D., Jakaj, B., Forster, M. et al. (2018). Assessment of tobacco heating product THP1.0. Part 2: Product design, operation and thermophysical characterisation. Regul Toxicol Pharmacol. 93:4-13.
85. Elias, J., Dutra, L.M., St Helen, G., et al. (2018). Revolution or redux? Assessing IQOS through a precursor product. Tob Control. 27:s102–s110.
86. Elias, J., Ling, P.M. (2018). Invisible smoke: third-party endorsement and the resurrection of heat-not-burn tobacco products. Tob Control. 27:s96–s101.
87. El-Toukhy, S., Baig, S.A., Jeong, M., et al. (2018). Impact of modified risk tobacco product claims on beliefs of US adults and adolescents. Tob Control. 27:s62–s69.
88. Farsalinos, K.E., Yannovits, N., Sarri, T et al. (2018). Carbonyl emissions from a novel heated tobacco product (IQOS): comparison with an e-cigarette and a tobacco cigarette. Addiction. 113(11):2099-2106.
89. Farsalinos, K.E., Yannovits, N., Sarri, T. et al. (2018). Nicotine delivery to the aerosol of a heat-not-burn tobacco product: comparison with a tobacco cigarette and e-cigarettes. Nicotine Tob Res. 20(8):1004-1009.
90. Forster, M., McAughey, J., Prasad, K. et al. (2018). Assessment of tobacco heating product THP1.0. Part 4: Characterisation of indoor air quality and odour. Regul Toxicol Pharmacol. 93:34-51.
91. Foster, M., Fiebelkorn, S., Yurteri, C. et al. (2018). Assessment of novel tobacco heating product THP1.0. Part 3: Comprehensive chemical characterisation of harmful and potentially harmful aerosol emissions. Regul Toxicol Pharm. 93:14-33.

92. Gale, N., McEwan, M., Eldridge, A.C. et al. (2018). 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.
93. Gasparyan, H., Mariner, D., Wright, C. et al. (2018). Accurate measurement of main aerosol constituents from heated tobacco products (HTPs): Implications for a fundamentally different aerosol. Regul toxicol Pharmacol. 99:131-141.
94. Gee, J., Prasad, K., Slayford, S. et al. (2018). Assessment of tobacco heating product THP1.0. Part 8: Study to determine puffing topography, mouth level exposure and consumption among Japanese users. Regul Toxicol Pharmacol. 93:84-91.
95. Glantz, S.A. (2018). Heated tobacco products: the example of IQOS. Tob Control. 27(Suppl 1):s1-s6.
96. Glantz, S.A. (2018). PMI's own in vivo clinical data on biomarkers of potential harm in Americans show that IQOS is not detectably different from conventional cigarettes. Tob Control. 27:s9–s12.
97. Hair, E.C., Bennett, M., Sheen, E. et al. (2018). Examining perceptions about IQOS heated tobacco product: consumer studies in Japan and Switzerland. Tob Control. 27(Suppl 1):s70-s73.
98. Haswell, L.E., Corke, S., Verrastro, I., et al. (2018). In vitro RNA-seq-based toxicogenomics assessment shows reduced biological effect of tobacco heating products when compared to cigarette smoke. Sci Rep. 8:1145.
99. Humbel, F., Sattler, A., Schuurmans, M.M. (2018). Erhitzter Tabak und «Heat not Burn»-Tabakprodukte. Praxis. 107:315-322.
100. Jenssen, B.P., Walley, S.C., McGrath-Morrow S.A. (2018). Heat-not-burn tobacco products: tobacco industry claims no substitute for science. Pediatrics. 141(1):e20172383.
101. Kauneliene, V., Meisutovic-Akhtarieva, M., Martuzevicius, D. (2018) A Review of the Impacts of Tobacco Heating System on Indoor Air Quality versus Conventional Pollution Sources. Chemosphere. 206:568-578.
102. Kaur, G., Muthumalage, T., Rahman, I. (2018). Mechanisms of toxicity and biomarkers of flavoring and flavor enhancing chemicals in emerging tobacco and non-tobacco products. Toxicol Lett. 288:143-155.
103. Kawamura, K., Yamada, K., Morioka, I. (2018). Health Effects Accompanying the Transition from Cigarettes to Heat-not-burn Tobacco: Nicotine Dependence, Nicotine Withdrawal Symptoms, and Changes in Smoking Behaviors. Nihon Eiseigaku Zasshi. 73(3): 379-387.
104. Kim, J., Yu, H., Lee, S. et al. (2018). Awareness, experience and prevalence of heated tobacco product, IQOS, among young Korean adults. Tob Control. 27(Suppl 1):s74-s77.
105. 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. 16:41.
106. Kotz, D., Kastaun, S. (2018) E-Zigaretten und Tabakerhitzer: repräsentative Daten zu Konsumverhalten und assoziierten Faktoren in der deutschen Bevölkerung (die DEBRA-Studie). Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 61(11): 1407-1414.
107. Kreitzberg, D.S., Murthy, D., Loukas, A., et al. (2018). Heat not burn tobacco promotion on Instagram. Addict Behav. 91:112-118.
108. Lachenmeier, D.W., Anderson, P., Rehm, J. (2018). Heat-Not-Burn Tobacco Products: The Devil in Disguise or a Considerable Risk Reduction?. The International Journal of Alcohol and Drug Research, 7(2):8-11.
109. Leigh, N.J., Palumbo, M.N., Marino, A.M. et al. (2018). Tobacco-specific nitrosamines (TSNA) in heated tobacco product IQOS. Tob Control. 27(Suppl 1):s37-s38.
110. Leigh, N.J., Tran, P.L., O'Connor, R.J. et al. (2018). Cytotoxic effects of heated tobacco products (HTP) on human bronchial epithelial cells. Tob Control. 27(Suppl 1):s26-s29.

111. Lempert L.K., Glantz, S.A. (2018). Heated tobacco product regulation under US law and the FCTC. Tob Control. 27(Suppl 1):s118-s125.
112. Liber, A.C. (2018). Heated tobacco products and combusted cigarettes: comparing global prices and taxes. Tob Control. doi: 10.1136/tobaccocontrol-2018-054602.
113. Lindblom, E.N. (2018). Should FDA Try to Move Smokers to E-Cigarettes and Other Less-Harmful Tobacco Products and, If So, How. Food Drug Law J. 73(2):276-318.
114. Liu, X., Lugo, A., Spizzichino, L. et al. (2018) Heat-Not-Burn Tobacco Products Are Getting Hot in Italy. J Epidemiol 28(5):274-275.
115. Mallock, N., Böss, L., Burk, R. et al. (2018). Levels of selected analytes in the emissions of "heat not burn" tobacco products that are relevant to assess human health risks. Arch Toxicol. 92:2145-2149.
116. Mathers, A., Schwartz, R., O'Connor, S. et al. (2018). Marketing IQOS in a dark market. Tob Control. 28(2):237-238.
117. Max, W.B., Sung, H., Lightwood, J., et al. (2018). Modelling the impact of a new tobacco product: review of Philip Morris International's Population Health Impact Model as applied to the IQOS heated tobacco product. Tob Control. 27:s82–s86.
118. McKelvey, K., Popova, L., Kim, M. et al. (2018). IQOS labelling will mislead consumers. Tob Control. 27(Suppl 1):s48-s54.
119. Miyashita, L., Grigg, J. (2018). Effect of the iQOS electronic cigarette device on susceptibility *to S. pneumoniae* infection. J Allergy Clin Immunol, 141(2):AB28.
120. 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):e0191008.
121. Moazed, F., Chun, L., Matthay, M.A. et al. (2018). Assessment of industry data on pulmonary and immunosuppressive effects of IQOS. Tob Control. 27:s20–s25.
122. Munakata, S., Ishimori, K., Kitamura, N. et al. (2018). Oxidative stress responses in human bronchial epithelial cells exposed to cigarette smoke and vapor from tobacco- and nicotine-containing products. Regul Toxicol Pharmacol. 99:122-128.
123. Murphy, J., Liu, C., McAdam, K. et al. (2018). Assessment of tobacco heating product THP1.0. Part 9: The placement of a range of next-generation products on an emissions continuum relative to cigarettes via pre-clinical assessment studies. Regul Toxicol Pharm. 93:92-104.
124. Nabavizadeh, P., Liu, J., Havel, C.M. et al. (2018). Vascular endothelial function is impaired by aerosol from a single IQOS HeatStick to the same extent as by cigarette smoke. Tob Control. 27(Suppl 1):s13-s19.
125. Pacitto, A., Stabile, L., Scungio, M. et al. (2018). Characterization of airborne particles emitted by an electrically heated tobacco smoking system. Environ Pollut. 240:248-254.
126. Pemberton, M,N. (2018). Oral cancer and tobacco: developments in harm reduction. Br Dent J. 225: 822–826.
127. Pieper, E., Mallock, N., Henkler-Stephani, F. et al. (2018). "Heat not burn" tobacco devices as new tobacco industry products: health risks". Bundesgesundheitsblatt Gesundheitsforschung Gesundheitsschutz. 61(11):1422-1428.
128. Popova, L., Lempert, L.K., Glantz, S.A. (2018). Light and mild redux: heated tobacco products' reduced exposure claims are likely to be misunderstood as reduced risk claims. Tob Control. 27(Suppl 1):s87-s95.
129. Rosen, L.J., Kislev, S. (2018). IQOS campaign in Israel. Tob Control. 27:s78–s81.

130. Rychert, M. (2018). New Zealand court dismisses ministry of health case against 'heat-not-burn' tobacco products, highlighting the need to future-proof tobacco control laws. Addiction. 113(10):1953-1954.
131. Salman, R., Talih, S., El-Hage, R., et al. (2018). Free-Base and Total Nicotine, Reactive Oxygen Species, and Carbonyl Emissions From IQOS, a Heated Tobacco Product. Nicotine Tob Res. 21(9):1285-1288.
132. Sharman, A., Zhussupov, B., Sharman, D., et al. (2018). Lung Function in Users of a Smoke-Free Electronic Device With HeatSticks (iQOS) Versus Smokers of Conventional Cigarettes: Protocol for a Longitudinal Cohort Observational Study. JMIR Res Protoc. 7(11):e10006.
133. Si, X., Tang, J., Zhu, R. et al. (2018). Aerosol particle size distribution from an electrical heat-not-burn product under ISO and HCI smoking regimes. Tobacco Science and Technology, 51(8):47-52.
134. Simonavicius, E., McNeill, A., Shanab, L. et al. (2018). Heat-not-burn tobacco products: a systematic literature review. Tob Control. 240:248-254.
135. Smitha, T.T., Hatsukamib, D., Benowitzc, N.L., et al. (2018). Whether to push or pull? Nicotine reduction and non-combusted alternatives - Two strategies for reducing smoking and improving public health. Prev. Med. 117:8-14.
136. St. Helen, G., Jacob III, P., Nardone, N., et al. (2018). IQOS: examination of Philip Morris International's claim of reduced exposure. Tob Control. 27:s30–s36.
137. Staal, Y.C., van de Nobelen, S., Havermans, A. et al. (2018). New Tobacco and Tobacco-Related Products: Early Detection of Product Development, Marketing Strategies, and Consumer Interest. JMIR Public Health Surveill. 4(2):e55.
138. Stepanov, I., Woodward, A. (2018). Heated tobacco products: things we do and do not know. Tob Control. 27:s7–s8.
139. Stephens, W.E. (2018). Comparing the cancer potencies of emissions from vapourised nicotine products including e-cigarettes with those of tobacco smoke. Tob Control. 27:10-17.
140. Tabuchi, T., Gallus, S., Shinozaki, T. et al. (2018). Heat-not-burn tobacco product use in Japan: its prevalence, predictors and perceived symptoms from exposure to secondhand heat-not-burn tobacco aerosol. Tob Control. 27:e25-e33.
141. Tabuchi, T., Shinozaki, T., Kunugita, N. et al. (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. J Epidemiol. doi: 10.2188/jea.JE20180116.
142. Takahashi, Y., Kanemaru, Y., Fukushima, T. et al. (2018). Chemical analysis and in vitro toxicological evaluation of aerosol from a novel tobacco vapor product: A comparison with cigarette smoke. Regul Toxicol Pharmacol. 92:94-103.
143. Thorne, D., Breheny, D., Proctor, C. et al. (2018). Assessment of novel tobacco heating product THP1.0. Part 7: Comparative in vitro toxicological evaluation. Regul Toxicol Pharm. 93:71-83.
144. Uchiyama, S., Noguchi, M., Tagaki, N. et al. (2018). Simple Determination of Gaseous and Particulate Compounds Generated from Heated Tobacco Products. Chem Res Toxicol. 31(7):585-593.
145. Yoshida, J. (2018). Abstract. The Rise of Heat-Not Burn Tobacco in Japan: A "Hot" Issue for Tobacco Control. J Thorathic Oncol. 13(10):S271.
146. Yuki, D., Takeshige, Y., Nakaya, K., et al. (2018). Assessment of the exposure to harmful and potentially harmful constituents in healthy Japanese smokers using a novel tobacco vapor product compared with conventional cigarettes and smoking abstinence. Regul Toxicol Pharmacol. 96:127-134.

2017

147. Auer, R., Concha-Lozano, N., Jacot-Sadowski, I. et al. (2017). Heat-not-burn tobacco cigarettes: smoke by any other name. JAMA Intern Med. 177(7):1050-1052.
148. Auer, R., Cornuz, J., Berthet, A. (2017). Perplexing conclusions concerning heat-not-burn tobacco cigarettes—reply. JAMA Intern Med. 177(11):1699-1700.
149. Bekki, K., Inaba, Y., Uchiyama, S. et al. (2017). Comparison of chemicals in mainstream smoke in heat-not-burn tobacco and combustion cigarettes. J UOEH 39(3):201-207.
150. Breheny, D., Adamson, J., Azzopardi, D. et al. (2017). A novel hybrid tobacco product that delivers a tobacco flavour note with vapour aerosol (Part 2): *In vitro* biological assessment and comparison with different tobacco-heating products. Food Chem Toxicol. 106(Pt A):533-546.
151. Caputi, T.L. (2017). Heat-not-burn tobacco products are about to reach their boiling point. Tob Control. 26:609-610.
152. Caputi, T.L., Leas, E., Dredze, M. et al. (2017). They're heating up: Internet search query trends reveal significant public interest in heat-not-burn tobacco products. PLoS One. 12(10):e0185735.
153. Caruso, M., Polosa, R. (2017). Perplexing conclusions concerning heat-not-burn tobacco cigarettes. JAMA Intern Med. 177(11):1699.
154. Chen, C. (2017). Change and challenge: outlook for development of new tobacco products. Acta Tabacaria Sinica. 23(3):14-18.
155. Gale, N., McEwan, M., Eldridge, A.C. et al. (2017). A randomised, controlled, two-centre open-label study in healthy Japanese subjects to evaluate the effect on biomarkers of exposure of switching from a conventional cigarette to a tobacco heating product. BMC Public Health. 17(1):673.
156. Ichitsubo, H., Kotaki, M. (2017). Indoor air quality (IAQ) evaluation of a Novel Tobacco Vapor (NTV) product. Regul Toxicol Pharmacol. 92:278-294.
157. Jaunky, T., Adamson, J., Santopietro, S. et al. (2017). Assessment of tobacco heating product THP1.0. Part 5: In vitro dosimetric and cytotoxic assessment. Regul Toxicol Pharm. 93:52-61.
158. Kim, M. (2017). Philip Morris International introduces new heat-not-burn product, IQOS, in South Korea. Tob Control. 27:e76-e78.
159. Kvasha, Y.A. (2017). Evaluation of electronic nicotine delivery system (ENDS) effects on cardiovascular disease risk, based on endothelium function as factor of its determination. Health of Ukraine Medical Newspaper.
160. Marynak, K.L., Wang, T.W., King, B.A. et al. (2018). Awareness and Ever Use of "Heat-Not-Burn" Tobacco Products Among U.S. Adults, 2017. Am J Prev Med. 55(4):551-554.
161. Nau, J.Y. (2017). Que penser du tabac chauffe «a moindre nocivite»? Rev Med Suisse. 13:972-973.
162. Protano, C., Manigrasso, M., Avino, P. et al. (2017). Second-hand smoke generated by combustion and electronic smoking devices used in real scenarios: Ultrafine particle pollution and age-related dose assessment. Environ Int. 107:190-195.
163. Ruprecht, A., Sioutas, C., De Marco, C. et al. (2017). Comparative assessment of the side-stream aerosols emitted from heat-not-burn tobacco devices, e-cigarettes and traditional cigarettes. Eur Respir. J. 50:OA1977.
164. Ruprecht, A.A., De Marco, C., Saffari, A. et al. (2017). Environmental pollution and emission factors of electronic cigarettes, heat-not-burn tobacco products and conventional cigarettes. Aerosol Sci Technol. 51(6):674-684
165. Rychert, M. (2017). New Zealand's legal action against IQOS postponed, consultation with big tobacco follows. New Zealand Med. J. 130(1465):109-111.

166. Savareear, B., Lizak, R., Brokl, M., et al. (2017). Headspace solid-phase microextraction coupled to comprehensive two-dimensional gas chromatography–time-of-flight mass spectrometry for the analysis of aerosol from tobacco heating product. J Chromatogr A. 1520:135-142.
167. Taylor, M., Thorne, D., Carr, T. et al. (2017). Assessment of novel tobacco heating product THP1.0. Part 6: A comparative in vitro study using contemporary screening approaches. Regul Toxicol Pharm. 93:62-70.
168. Veronese, C., Ruprecht, A.A., de Marco, C. et al. (2017). Fumo di sigaretta, vapore di e-cig e "fumo freddo": un confronto tra le emissioni di sostanze nocive (Cigarette smoke, e-cig vapor and "heat-not-burn": a comparison between the emissions of toxic compound). Tabaccologia. 1:17-23.

2016

169. Kamada, T., Yamashita, Y., Tomioka, H. (2016). Acute eosinophilic pneumonia following heat-not-burn cigarette smoking. Respirol Case Rep. 4(6).
170. Nyman, A.L., Weaver, S.R., Popova, L. et al. (2018). Awareness and use of heated tobacco products among US adults, 2016-2017. Tob Control. 27(Suppl 1):s55-s61.
171. Protano, C., Manigrasso, M., Avino, P. et al. (2016). Second-hand smoke exposure generated by new electronic devices (IQOS® and e-cigs) and traditional cigarettes: submicron particle behaviour in human respiratory system. Ann Ig 28(2):109-112.
172. Tabuchi, T., Kiyohara, K., Hoshino, T. et al. (2016). Awareness and use of electronic cigarettes and heat-not-burn tobacco products in Japan. Addiction. 111(4):706-713.

2015

173. Miura, N., Yuki, D., Minami, N. et al. (2015). A study to investigate changes in the levels of biomarkers of exposure to selected cigarette smoke constituents in Japanese adult male smokers who switched to a non-combustion inhaler type of tobacco product. Regul Toxicol Pharmacol. 71(3):498-506.
174. O'Connell, G., Wilkinson, P., Burseg, K.M.M. et al. (2015). Heated tobacco products create side-stream emissions: implications for regulation. J Environ Anal Chem. 2(5):163.

2014

175. Sakaguchi, C., Kakehi, A., Minami, N. et al. (2014). Exposure evaluation of adult male Japanese smokers switched to a heated cigarette in a controlled clinical setting. Regul Toxicol Pharmacol. 69(3):338-47.

APPENDIX 4 – IMPACT OF HTP AEROSOL ON THE ENVIRONMENT AND ON BYSTANDERS

Indoor air quality refers to the air quality within buildings, especially as it relates to the health and comfort of building occupants. In an effort to better understand the impact of the HTP aerosol on bystanders, PMI conducted several studies to assess the effects of the HTP on indoor air quality (IAQ) when used indoors. The purpose of these studies was not to establish evidence in support of overcoming existing smoking bans, but to fully characterise the impact of HTP use on the environment and on bystanders.

Unlike the lit-end of a cigarette which produces side stream smoke, a significant source of environmental tobacco smoke (ETS), also called second-hand smoke, the THS does not produce side stream smoke.

As a consequence, the emissions released, and the main impact on IAQ, when the HTP is used results from the exhalation of the aerosol by the user. The studies were conducted under well-controlled and representative conditions, based on accepted building standards, and were benchmarked against national and international standards for exposure to environmental pollutants. The indoor air chemistry was measured with study volunteers present in the room but not using the product (i.e. to obtain the background value) and again when the volunteers were using HTPs, and the values obtained were compared.

Of the 23 indoor air constituents measured, the concentrations of 20 constituents did not exceed the background level. The three compounds that were above the background levels in the air, and could be attributed to HTP use, were nicotine, glycerol, and acetaldehyde. However, glycerol is not an air pollutant and the concentrations of nicotine and acetaldehyde were much lower than the levels measured after cigarette smoking and far below the limits established by existing air quality guidelines. To better understand the impact of day-to-day activities on air quality, and to prepare the assessment of the impact of HTP use in real-life settings, PMI conducted studies on the impact of activities of daily living, such as using cosmetics, preparing food on a table-top appliance, or simply the prolonged presence of people, on air quality in an indoor environment. The results of these studies showed that day-to-day activities led to significant emissions of volatile organic compounds, which would need to be considered when assessing the impact of HTP use on bystanders in real-life settings.

PMI also conducted scientific studies in real-life settings, such as coffee rooms, in *IQOS* stores, and in a restaurant where HTP use was allowed.

In a study conducted in Japan, in a restaurant where HTP use was allowed but cigarette smoking was not, PMI sought to better understand both the emissions of the HTP in a real-life setting. More importantly, it was to assess the impact on urinary biomarkers of the employees working in the restaurant as well as the customers. To our knowledge, this is the first such study of this kind for novel products. The results indicated that:

- The use of HTP did not generate ETS and did not negatively affect air quality as measured by nicotine, tobacco-specific nitrosamines (TSNA), respirable suspended particles and the carbonyls acrolein, crotonaldehyde, acetaldehyde, and formaldehyde in air in a real-life setting. It was performed considering existing air quality guidelines and

where regulatory norms for occupational exposure in terms of adequate ventilation were respected.

- Non-smokers did not have an increase in exposure to nicotine and TSNAs due to passive exposure to the environmental HTP aerosol. This was tested by assessing their urinary biomarkers of exposure.
- Non-smokers were not exposed to higher levels of acrolein, crotonaldehyde, ethylene oxide, and benzene in a real-life setting due to passive exposure to the environmental HTP aerosol by means of assessing their urinary biomarkers of exposure.

These studies confirmed that the HTP does not produce ETS and does not negatively affect 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

https://www.ncbi.nlm.nih.gov/pubmed/27311683

APPENDIX 5 – Examples of research conducted by independent researchers or regulatory authorities on the mainstream aerosol of the HTPs and reference cigarette smoke.

1. Japan: National Institute of Public Health (Bekki et al., 2017)
The Department of Environmental Health, National Institute of Public Health in Japan, one of the WHO Tobacco Laboratory Network (TobLabNet) laboratories analyzed nicotine, tar, carbon monoxide (CO) and tobacco-specific nitrosamines (TSNAs) in the mainstream aerosol and tobacco fillers of IQOS regular and IQOS menthol, and compared their concentrations with those from reference cigarettes (3R4F and 1R5F) using WHO TobLabNet methods.
The authors conclude "*In this study we could provide important information* ***showing that the concentration levels of hazardous compounds in the mainstream smoke of IQOS are much lower than those in conventional combustion cigarettes****." Although it is low concentration, toxic compounds are definitely included in the mainstream smoke of IQOS.*

2. UK: Independent Scientific Advisory Committees on Toxicity (COT), Carcinogenicity (COC) and Mutagenicity (COM)
The UK Committee on Toxicity (COT), with support from the Committee on Carcinogenicity (COC) and Committee on Mutagenicity (COM) assessed the toxicological risks from novel heat-not-burn tobacco products and compared these risks to those from conventional cigarettes. The Committee has reviewed evidence on two heated tobacco products, *IQOS* (PMI) and *iFUSE* (BAT). The Committees stated *"For both products, there were some HPHCs where the reduction was approximately 50%, but the reduction in a number of other HPHCs was greater than 90%, with many of the compounds being below the limits of detection or quantification for the assays used"* and *"Overall, the Committees conclude that while there is a likely reduction in risk for smokers switching to heat-not-burn tobacco products, there will be a residual risk and it would be more beneficial for smokers to quit smoking entirely."* Statement on the toxicological evaluation of novel heat-not-burn tobacco products published on the 12th of December 2017 by the UK Committee on Toxicity (COT):
https://cot.food.gov.uk/sites/default/files/heat_not_burn_tobacco_statement.pdf

3. The China National Tobacco Quality Supervision and Test Centre ("CNTQSTC"), a member of the WHO Tobacco Laboratory Network (TobLabNet), published on the 8th of January 2018 an independent study in Nicotine & Tobacco Research comparing the HPHCs present in IQOS aerosol and 3R4F reference cigarette smoke (Li et al, 2018)
This peer reviewed publication by Li et al (2018) "Chemical Analysis and Simulated Pyrolysis of Tobacco Heating System 2.2 Compared to Conventional Cigarettes" includes % reduction results of carbon monoxide and 25 Harmful and Potentially Harmful Constituents (HPHCs) in *IQOS* aerosol versus 3R4F reference cigarette smoke using the ISO and Health Canada intense testing regime. The authors stated "*The majority of mainstream constituents of THS 2.2 were reduced compared to 3R4F [reference cigarette]*." Specifically, they found that compared to the 3R4F reference cigarette, *IQOS* produced "*more than 90% [lower levels of] HPHCs, except for carbonyls, ammonia, and NAB, which were about 50–80% lower*." The authors cautioned *"that reduction of harmful constituent emissions cannot be interpreted as equivalent to a proportionate harm/risk reduction for smokers."*

4. Laboratory studies performed by The German Federal Institute for Risk Assessment (BfR)

On 5 May 2018, the German Federal Institute of Risk Assessment (BfR) published the results of their independent assessment of *IQOS*. The study, published in *Archives of Toxicology*, analysed the *IQOS* aerosol using the Health Canada Intense Smoking Regimen. In its report, BfR concludes:

Our study confirms that levels of major carcinogens are markedly reduced in the emissions of the analysed HNB product in relation to the conventional tobacco cigarettes and that monitoring these emissions using standardized machine smoking procedures generates reliable and reproducible data which provide a useful basis to assess exposure and human health risks. Importantly, our data confirms absolute values for selected toxicants in the emissions of the analysed HNB that are in agreement with data published by the manufacturer (Schaller et al. 2016). The herein confirmed reductions of relevant toxicants by about 80% - 99% are substantial, leading to the relevant question of putatively reduced health risks.

Link to the report: https://link.springer.com/epdf/10.1007/s00204-018-2215-y?author_access_token=m2gTAwzR8lN1XHHPyz2Egve4RwlQNchNByi7wbcMAY7B4pkXqsqfUkMAy

5. Independent Testing by FDA

In order to verify chemical and physical data submitted to the U.S. FDA as part of PMI's Modified Risk Tobacco Product Applications (MRTPAs) for IQOS, the U.S. FDA commissioned independent testing at the FDA's Southeast Tobacco Laboratory (STL) in October 2017. The constituents tested were selected based on the characteristics of the EHTP. STL reported the value for NFDPM as "tar". There were some differences between the applicant's analytical and aerosol generation methods and those used by STL. Preliminary assessment of the data indicated that the levels of acrolein, formaldehyde and benzo[a]pyrene measured by STL were higher than the values reported by the applicant; however, these three HPHCs were still significantly lower than the levels in the mainstream smoke of the reference cigarette 3R4F. Greater than 90% reduction was observed for acrolein and benzo[a]pyrene, and greater than 80% reduction was observed for formaldehyde in the aerosol compared to 3R4F. The levels of NFDPM (quoted by STL as tar) and nicotine determined by STL were similar to the levels reported by the applicant. Finally, the levels of ammonia, NNN, and NNK in the EHTP measured by STL were similar to the levels reported by the applicant.

Link to the FDA Briefing Document published on the 22nd of January 2018:
https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/UCM593109.pdf

APPENDIX 6 – ABUSE LIABILITY

TABLE OF CONTENTS

Table of Tables

Table of Figures

Appendix

6.2.3. Abuse Liability Summary

6.2.3.1. Background

In the draft guideline issued by Food and Drug Administration (FDA) in 1990, the term ‘‘abuse liability’’ refers to the likelihood that a drug with psychoactive or central nervous system effects will sustain patterns of non-medical self-administration that result in disruptive or undesirable consequences. In other words abuse liability is conceptualized through variations in either the likelihood/severity of self-administration or the likelihood/severity of undesirable consequences (FDA 1990). A more recent FDA draft guideline (USDHHS 2010) has restricted the definition of dependence potential (used interchangeably with abuse liability) and refers to a drug that is used in nonmedical situations, repeatedly or even sporadically, for the positive psychoactive effects it produces.

The Modified Risk Tobacco Product (MRTP) Application Draft Guidance for Industry defines abuse liability as the likelihood that individuals will develop physical and/or psychological dependence on the tobacco product (USDHHS 2012). Thus, the FDA Center for Tobacco Products’ (CTP) use of the term abuse liability is similar to assessing nicotine dependence using DSM-IV/DSM-V diagnostic (medical) criteria and defines it as dependence liability: nicotine use is characterized, both, as for a substance use disorder (dependence/abuse), and for a substance-induced disorder (withdrawal symptoms).

The public health perspective encompasses dependence potential assessment to address the pharmacologically determined risk of abuse and the risk of harm resulting from abuse (see Figure 1).

Figure 1. Abuse Liability – Public Health Insight

There is a continuum of reinforcement value (reinforcement is generally defined as the capacity of an agent to sustain self-administration), and in theory, a desirable MRTP should be more reinforcing than nicotine replacement therapy (NRT) products (IOM 2012). It should be sufficiently reinforcing so as to attract smokers away from conventional cigarettes but not enough to encourage the widespread dependent use of the product by individuals who were previously nonusers, or who would have quit smoking (IOM 2012).

It was part of PMI program to evaluate perceived risk perception, acceptance of the Tobacco Heating System (THS), and assess subjective effects already in pre-market and

at the time of the MRTP application. Consumer behavior and use pattern will continue to be monitored post market (See Module 8). The evaluation of dependence potential alone is insufficient to assess the product impact on the individual health or the population as a whole. Assessment of abuse liability of THS should also consider the risks and/or harm resulting from dependence, and be comparative, e.g., to other tobacco/nicotine products.

PMI therefore considers a balanced view of abuse liability assessment (ALA) taking into account the potential of the product to cause dependence and the potential harm resulting from that dependence compared to other tobacco products. This is achieved for THS by evaluating various ALA domains (components) covering the majority of facets (as described in Carter 2009) involved in abuse liability (see Table 1). The likelihood that the self-administration of a product (or a drug) will result in persistent use or abuse is associated with its psychoactive or central nervous system effects, which can result in both positive and negative subjective effects, its reinforcing effects, and with tolerance, craving, and withdrawal that can result after repeated use of the product.

A greater likelihood of dependence is associated with faster speed of nicotine delivery and its rewarding effects. Conversely, adverse effects from a product can also influence abuse, e.g., the occurrence of undesirable adverse health effects such as nausea can lower the likelihood of repeated self-administration. The formulation and technical design of a product can also contribute to its abuse liability. For example, nicotine-containing products that are inhaled into the lungs are associated with faster rate of absorption (of nicotine) and tend to have greater abuse liability than products that are used orally.

Other elements such as the addition of flavorant agents, the overall look and feel of the product or its possibly disruptive mode of use (vs. the usual way of smoking) may have a positive or negative impact on the overall product attractiveness and accordingly its potential for abuse

Table 1. ALA Domains Used for THS Abuse Liability Assessment

Cluster	Domains / Components	Measurements
Product features	1. Product design	Product description and content (nicotine, menthol)
	2. Aerosol chemistry	Delivery of nicotine, acetaldehyde and ammonia
Likelihood of use	3. Pharmacokinetic effects	Nicotine pharmacokinetics (absorption rate and extent) Nicotine uptake
	4. Pharmacodynamic effects	Subjective effects
	5. Reinforcing effects	Product use behavior in various studies Perception (heath risks, addiction risk), comprehension Intention to use by various populations
Consequence of use	6. Impaired functioning	Cognitive assessment Psychomotor performance Withdrawal symptoms
	7. Physical dependence	Withdrawal symptoms
	8. Adverse events	Aversive adverse events Nervous system disorders

Derived from Carter 2009

Several studies conducted by PMI on THS contribute to the assessment of THS abuse liability. These studies are listed in Table 2 together with relevant endpoints. None of these studies were specifically designed to test addiction potential, but they collectively cover the majority of ALA components.

Table 2. THS Studies Relevant for ALA

Study Types	Studies	Endpoints
Product analysis and nonclinical studies	Product characterization / chemistry • THS Regular • THS Menthol 1 (low menthol) • THS Menthol 2 (high menthol)	Nicotine yields Acetaldehyde yields Ammonia yields
	in vitro and i*n vivo* studies	None relevant for ALA

(table continues)

Study Types	Studies	Endpoints
Randomized Clinical studies	Single use pharmacology studies with THS Regular • ZRHR-PK-01-EU • ZRHR-PK-02-JP Single use pharmacology studies with THS Menthol (high menthol) • ZRHM-PK-05-JP • ZRHM-PK-06-US	Nicotine pharmacokinetics (PK) (rate and extent of absorption) after 1-day nicotine washout Subjective effects Solicited adverse events
	5-day reduced exposure studies with THS Regular • ZRHR-REXC-03-EU • ZRHR-REXC-04-JP	Nicotine pharmacokinetics (repeated use) Nicotine uptake Subjective effects Product use in confinement Human puffing topography Withdrawal symptoms Solicited adverse events
	3-month reduced exposure studies with THS Menthol (high menthol) • ZRHM-REXA-07-JP • ZRHM-REXA-08-US	Nicotine uptake Subjective effects Product use in confinement and ambulatory Human puffing topography Withdrawal symptoms Solicited adverse events
Perception and behavior assessment studies and market research tests	Label, labeling and marketing material assessment studies • THS-PBA-05-RRC-US • THS-PBA-05-RRC2-US • THS-PBA-05-REC-US	Intent to use Comprehension Risks (health risks, addiction risk) perception
	Usability and Comprehension study • THS-PBA-06-US	Ability to understand and correctly comply with the instruction of use
	6-week actual use study with THS Regular and THS Menthol 1 • THS-PBA-07-US	Tobacco products use (THS, CC, others)
	4-week whole offer tests (WOT) with various THS variants • Analysis of WOT data	Product use from 5 market research studies outside the US
Surveillance	Passive safety surveillance	Unsolicited adverse events

While most of the endpoints relevant for ALA were measured in adult smokers at different time points depending on the duration of product use, some, such as intent to use or risk perception, were also measured in non-smokers (including young adults) without being using THS during the study (see Table 3).

Table 3. ALA Endpoints and THS Use Duration in Humans

ALA Domain	Endpoints	No use	Single use	5 days	4 weeks	6 weeks	3 months	Post-market
Study type (number of studies)	*PK/PD (n=4)*		X					
	REXC (n=2)			X				
	REXA (n=2)			X			X	
	PBA05 (n=3)	X						
	PBA07 (n=1)					X		
	WOT (n=5)				X			
	Surveillance							X
Pharmaco-kinetics	Nicotine PK		X	X				
	Cotinine			X			X	
	NEQ			X			X	
Pharmaco-dynamics	QSU-brief		X	X			X	
	MCEQ		X	X			X	
	FTND						X	
Reinforcing effects	Product use		X	X	X	X	X	
	Intent to use	X				X		
	Risk perception	X				X		
	Comprehension	X						
Impaired functioning	MNWS			X			X	
	Solicited AEs		X	X			X	
	Unsolicited AEs				X	X		X
Physical dependence	MNWS			X	X		X	
	FTND						X	
Adverse events	Aversive AEs		X	X	X	X	X	X
	Nervous system		X	X	X	X	X	X

Abbreviations. AEs: adverse events; FTND: Fagerström test for nicotine dependence; MCEQ: modified cigarette evaluation questionnaire; MNWS: Minnesota nicotine withdrawal symptoms; NEQ: nicotine equivalents; QSU: Questionnaire on smoke urges
Type of studies. PBA: perception and behavior assessment; PK/PD: pharmacokinetics /pharmacodynamics (pharmacology) clinical study; REXA: reduced exposure ambulatory; REXC: reduced exposure in confinement; WOT: whole offer test.

Close to 13'000 individuals participated in eight clinical studies, five whole offer test (WOT) market research studies and five perception and behavior assessment (PBA) studies, contributing to the ALA of THS. The smoking status of these study populations is shown in Table 4. The general characteristics of study population were as follows:

- Clinical studies: adult daily smokers in good health conditions with no intention to quit smoking within the next three months
- Label, labeling and marketing material assessment studies: adult smokers with no intention to quit smoking; adult smokers with intention to quit smoking, adult former smokers (having quit smoking more than 30 days ago) and adult never-smokers (had smoked fewer than 100 CC in their life), including young adult never-smokers age between legal age and 25 years of age
- Other studies: adult daily smokers.

Table 4. Study Populations and Smoking Status at Enrolment

	Smokers with No Intention to Quit (a)	Smokers with Intention to Quit	Former Smokers	Never Smokers	Never Smokers LA - 25	Total
Clinical studies						939
• ZRHR-PK-01-EU	62					
• ZRHR-PK-02-JP	65					
• ZRHM-PK-05-JP	73					
• ZRHM-PK-06-US	64					
• ZRHR-REXC-03-EU	169					
• ZRHR-REXC-04-JP	166					
• ZRHM-REXA-07-JP	175					
• ZRHM-REXA-08-US	165					
Label, labeling & marketing material assessment studies						
• THS-PBA-05-RRC-US	472	472	471	477	478 (b)	2255
• THS-PBA-05-RRC2-US	471	475	469	468	471 (b)	2247
• THS-PBA-05-REC-US	479	479	480	480	480 (b)	2272
Usability & comprehension study						
• THS-PBA-06-US	258					258
Observational studies						
• THS-PBA-07-US (FAS)	1106					1106
• Whole offer tests						3922
○ Japan	868					
○ Italy	800					
○ Germany	605					
○ Switzerland	581					
○ South Korea	1068					
Grand Total	**7647**	**1426**	**1420**	**1425**	**1429**	**12'999**

FAS: full analysis set population: LA-25: age between adult legal age and 25 years
(a) ncludes also adult daily smokers with intention to quit not specified
(b) subset of never smokers LA-25 are also in the never-smokers group
[Source: Respective study reports, Module 7, Section 7.3.1, Section 7.3.2 and Section 7.3.3]

Across clinical studies, smokers of menthol CC were not evidently more dependent to nicotine (based on FTND scores at baseline) than smokers of non-menthol CC at baseline. Proportions of heavy smokers (reporting smoking more than 19 CC per day) were ranging from 36 to 48% and from 32 to 50% in menthol CC smokers and in non-menthol CC smokers, respectively. Proportions of smokers with severe nicotine dependence (FTND score between 7 and 10, as defined in study protocols) were ranging from 8 to 34% (highest proportion in US study ZRHM-REXA-08-US) and from 11 to 27% (highest proportion in Polish study ZRHR-REXC-03-EU) in menthol CC smokers and in non-menthol CC smokers, respectively.

African Americans represented a significant proportion of subjects/participants enrolled in the studies conducted in the US, ranging from approximately 13% to 55% across studies and study arms (27.5% in the actual use study THS-PBA-07-US).

6.2.3.2. ALA Domain 1 - Product Design

The product design of THS is described in detail in Module 3, Section 3.1. In summary, THS is a system composed by three main components (see Figure 2):

- A Tobacco Stick, which is designed to function with the Holder.
- A Holder, which is a slim electrical heating unit that heats the tobacco stick in a controlled manner and stores enough energy for a single experience. The power supply for the Holder is the Charger.
- A Charger, which holds enough energy for approximately 20 experiences and can be recharged from household power. The Charger stores the Holder when not in use, and provides a safe, secure environment for the cleaning process of the heater blade. These two units, together with essential accessories, are collectively known as the Tobacco Heating Device (THD).

Figure 2. Picture of Tobacco Heating System

The Holder and the Tobacco Stick deliver puffs over a period of about 6 minutes or 14 puffs (whichever comes first), with the LED indicating the end of the inhalation experience. Once this cycle is complete, the Holder must be recharged before a new Tobacco Stick can be used.

There are three tobacco stick variants expected to be inu·oduced in the US market, THS Regular and THS Menthol with two menthol levels (Menthol 1 and Menthol 2, also refened as low menthol and high menthol, respectively – see Module 3). Dming the comse of the assessment of THS in humans, several variants (tobacco blends / flavor systems) were used (see additional details in Module 6, Section 6.1.5, Appendix 1).

The THS product design has an advanced technology and sophisticated look, which may be atu·active for some consumers while it could be seen as cumbersome and/or dismptive for others. Due to its technology, THS requires more handling than a u·aditional cigarette, such as charging the holder after the use of each tobacco stick, charging time for the holder (approximately six minutes , and holder cleaning. Other potential dism tive limitations include b) .ll)

[redacted], and the absence of buming (the length of the tobacco stick remains unchanged after use and there is no production of ash, i.e. no flicking ritual). Similarly, due to the absence of bruning of the tobacco stick, the lack of combustion byproducts with "flavoring"/ organoleptic characteristics may be seen as atuactive for some consumers and bystanders (e.g., less smell) and less satisfying for others. Product satisfaction (see Section 6.2.3.5) and actual product use (see Section 6.2.3.6) are proxy measures on product acceptance influenced by product design featmes.

6.2.3.2.1. Nicotine in Tobacco Stick

The relative content nicotine in the tobacco filler (see Table 5) for both THS Regular and THS Menthol tobacco sticks (armmd 18mg/g tobacco, 1.8%) is toward the lower range of nicotine content in CC marketed in the US (1.84% – 2.41%) (Bodnar 2012) and approximately 20% below the 2.25% level found in the reference cigarette 3R4F (Eldridge 2015). Due to the two to three-fold lower weight of the THS tobacco plug (vs. CC), the average nominal nicotine content is substantially lower (around 4.4 to 4.8mg/stick) than in a CC. However, it is more relevant to discuss abuse liability based on nicotine deliveries, i.e., nicotine yields in aerosol from THS tobacco stick (see Section 6.2.3.3.1).

Table 5. Nicotine Content in THS Tobacco Filler (3 Batches)

	THS Regulat·vatiant	THS Menthol! (low menthol)	THS Menthol 2 (high menthol)
Nicotine per gram tobacco (l!g/g, average per batch)	17809 – 17827 – 17942	18246 - 18564 – 18791	17591 – 17759 – 18000

[Source: Module 3, Section 3.3)

6.2.3.2.2. Menthol in Tobacco Stick

The menthol yields in the two THS Menthol tobacco stick variants expressed as menthol in aerosol (MIA) are 0.7mg ISO (1.5mg Health Canada Intense regime) per unit for Menthol 1 (low menthol) and 1.2mg ISO (2.26mg Health Canada Intense) for Menthol 2 (high menthol) (see Module 3, Section 3.1, Tobacco Stick Ingredients, for menthol quantity in tobacco). Another high menthol variant (MIA 1.2mg ISO) was assessed in some clinical studies (see Table 2). The menthol level in both menthol variants (Menthol 1 and Menthol 2) are within the range of menthol cigarettes currently marketed in the US. In a report prepared by Altria Client Services (ALCS) for the Tobacco Products Scientific Advisory Committee (TPSAC) meeting held in 2011 on mentholated cigarettes (ALCS 2010), levels of menthol in whole cigarette (tobacco filler and filter) and menthol in smoke were measured in 64 US cigarettes (period 2008 – 2009), representing 80% of US market share of menthol CC segment. The levels of menthol in smoke ranged from 0.35 to 1.29mg/cig (approximately 80% within the range 0.47 to 0.82mg/cig) and levels in whole cigarette from 2.6 to 9.8mg/cig. A recent work published by the FDA CTP (Ai 2015) found the menthol levels in whole cigarettes (from 22 most popular US CC) ranging from 2.9 to 19.6mg/cig. Excluding the three products exceeding 10mg/cig, the menthol levels were ranging from 2.9 to 7.2mg/cig, confirming results from ALCS study.

The FDA's opinion (USDHHS 2013) based on the thorough review of available scientific information relevant to the impact of menthol tobacco products on public health, is summarized as follows: "*While there is little evidence to suggest that menthol cigarettes are more or less toxic or contribute to more disease risk to the user than nonmenthol cigarettes, adequate data suggest that menthol use is likely associated with increased smoking initiation by youth and young adults. Furthermore, the data indicates that menthol in cigarettes is likely associated with greater addiction. Menthol smokers show greater signs of nicotine dependence and are less likely to successfully quit smoking. These findings, combined with the evidence indicating that menthol's cooling and anesthetic properties can reduce the harshness of cigarette smoke and the evidence indicating that menthol cigarettes are marketed as a smoother alternative to non-menthol cigarettes, make it likely that menthol cigarettes pose a public health risk above that seen with non-menthol cigarettes*.".

PMI conducted recently a literature review on menthol in cigarettes (See draft manuscript in Appendix A.6.2.3.1). The conclusion of PMI's review provides an additional insight which differs from FDA's opinion. The goal was to determine if menthol and non-menthol cigarette smokers differ with respect to time to first cigarette (TTFC) and successful smoking cessation via a meta-analysis of published results. For 13 independent estimates, menthol smokers displayed a small but statistically significant shorter TTFC<5 min (random-effects odds ratio (OR) = 1.12; 95% confidence interval (CI), 1.04-1.21), while 17 independent estimates provided a non-significant difference for TTFC<30 min (random-effects OR = 1.06; 95% CI, 0.96-1.16). For cessation studies, meta-analysis of 30 published estimates indicated a decreased likelihood for menthol cigarette smokers to quit (random-effects OR = 0.87; 95%CI, 0.80-0.96). There was no difference between cessation rates for Caucasian menthol and non-menthol cigarette smokers, but the results support that African American menthol cigarette smokers find it

more difficult to quit. Adjustment of cessation for socioeconomic status eliminated any statistically significant advantage for smoking cessation in non-menthol smokers. In conclusion, these results suggest that the observed differences in cessation rates between menthol and non-menthol cigarette smokers can consistently be explained by differences in socioeconomic status and that menthol cigarettes do not differ from their non-mentholated counterpart for cigarette addiction.

6.2.3.3. ALA Domain 2 - Addictive HPHCs in THS Aerosol

The FDA (USDHHS 2012a) has issued the full list of harmful and potentially harmful constituents (HPHC), including four HPHCs classified as addictive (nicotine, nornicotine, anabasine and acetaldehyde). In the FDA draft guideline on abbreviated list of HPHCs (USDHHS 2012b), the list of addictive HPHCs is restricted to nicotine and acetaldehyde.

The THS aerosol chemistry methodology and results for THS variants are summarized in Module 6, Section 6.1.1. Aerosol chemistry data were generated under Health Canada Intense smoke regime laboratory conditions as these conditions are more representative of the human smoking topography patterns). HPHC yields from THS aerosol were compared to the Kentucky reference cigarette 3R4F.

The HPHC yields with addiction potential (USDHHS 2012b), i.e., nicotine and acetaldehyde, are presented in Table 6. Two additional compounds, menthol and ammonia, not listed as HPHCs with addictive potential, are also considered here. Menthol, as an ingredient in the mentholated Tobacco Stick variants and ammonia yields in THS aerosol are reviewed as these two constituents are subject to many discussions on their potential direct or indirect role on addiction as mentioned in recent reports issued by the FDA (USDHHS 2013), by the Surgeon General (USDHHS 2014) and by the European Commission (SCENIHR 2016). Menthol is discussed above in Section 6.2.3.2.2.

Table 6. Comparative Aerosol Chemistry THS (Nicotine, Acetaldehyde and Ammonia) vs. 3R4F

Aerosol Constituents (Health Canada Intense Regime)	THS Regular	THS Menthol 1 (low menthol)	THS Menthol 2 (high menthol)
Nicotine (mg/stick) – mean (SD)	1.29 (0.047)	1.19 (0.05)	1.17 (0.03)
Acetaldehyde			
• Nominal yield (µg per stick) – mean (SD)	192 (11.6)	206 (6)	192 (9)
• Relative yield per mg nicotine vs. 3R4F	16.2%	19.9%	19.1%
Ammonia			
• Nominal yield (µg per stick) – mean (SD)	12.2 (0.973)	11.1 (1.1)	10.7 (0.943)
• Relative yield per mg nicotine vs. 3R4F	49.8%	53.6%	66.0%

SD: standard deviation
[Source: Module 6, Section 6.1.1]

6.2.3.3.1. Nicotine in THS Aerosol

The average nicotine delivery in aerosol from the three THS variants, Regular, Menthol 1 and Menthol 2, under Health Canada intense regime are 1.29mg/stick, 1.19mg/stick, and 1.17mg/stick respectively (see Table 6). This is within the lower-end range (1.32 to 4.92mg nicotine per cigarette) from a representative sample of cigarettes sold on the US market in 2009 (Bodnar 2012). Nicotine yields from THS are approx. 25%, 35% and 40% lower vs. the Kentucky reference cigarette 3R4F for THS Regular THS Menthol 1 and THS Menthol 2, respectively as well below (approx. 36%, 41% and 42%, respectively) the 2mg median nicotine yields from 31 US CC brands as detailed in Module 6, Section 6.1.1.

6.2.3.3.2. Minor Tobacco Alkaloids and Acetaldehyde in THS Aerosol

There are no available data for THS on minor tobacco alkaloids (i.e., nornicotine and anabasine). Information from published literature is provided. Nicotine represents usually more than 95% of all alkaloids found in tobacco (Lisko 2013). Other minor tobacco alkaloids (including nornicotine and anabasine) have been measured in 50 popular US cigarettes and their yields in tobacco were found to be at one order of magnitude lower that nicotine and at similar levels to those measured in the Kentucky reference cigarette 3R4F (Lisko 2013).

As compared to 3R4F on a per mg nicotine basis, the amount of acetaldehyde delivered in the THS aerosol under Health Canada intense regime is approx. 84%, 80% and 88% lower for the THS Regular, THS Menthol 1 and THS Menthol 2 variant, respectively (see Table 6). It is unclear what this reduction means in term of THS abuse liability in humans as the currently knowledge is limited to *in vivo* experimental data suggesting a potential role of acetaldehyde in ethanol addiction (Hoffman 2013).

In a recent review published by the FDA CTP, the authors concluded that further research is needed to determine the abuse potential of non-nicotine tobacco smoke constituents (Hoffman 2013).

6.2.3.3.3. Ammonia in THS Aerosol

Ammonia yields in aerosol from THS variants (11.1, 12.2 and 10.7µg/stick, Health Canada intense regime and approximately half of the yield measured in 3R4F, see Table 6) can be qualified as low when compared to published literature (see McKinney 2011), where the ammonia yield is 10.1 µg/cigarette (Federal Trade Commission regime) for the low level ammonia cigarette. The average ammonia yields in THS aerosol is also 69.3% lower than the median yields from 31 US CC brands, as detailed in Module 6, Section 6.1.1.

Unprotonated nicotine ("freebase") and its role to reinforce nicotine delivery through presence of ammonia in tobacco has been raised as possible concern but could not be substantiated. Comparing arterial blood nicotine pharmacokinetics of high diammonium phosphate and low diammonium phosphate containing cigarettes, no differences were detected between CC with high or low ammonia yields (McKinney 2011).

More recently, the European Commission's opinion on additives in tobacco products, despite some studies indicating that ammonium compounds increases the pH of the smoke which would consequently increase the amount of unprotonated/free nicotine, is that it cannot be concluded that it may result in faster and increased absorption of nicotine (SCENIHR 2016).

Based on the above considerations, it is reasonable to conclude that the ammonia yields in THS aerosol would not affect the nicotine pharmacokinetics and therefore do not raise an abuse liability concern for THS.

6.2.3.3.4. Conclusion on Aerosol Chemistry

Based on available aerosol chemistry data and considerations from the literature, the abuse liability resides primarily with nicotine delivery (yield in aerosol) which is within the range (toward the lower range) of nicotine delivered by CC, supporting a similar abuse liability THS vs. CC.

6.2.3.4. ALA Domain 3 - Nicotine Exposure in Humans

For a long time, health scientists viewed smoking as primarily psychological and social, rather than under a pharmacological or biological point of view. The 1988 report of the Surgeon General, reviewing new available scientific evidence on smoking and addiction, concluded that: "Cigarettes and other forms of tobacco are addicting" and "Nicotine is the drug in tobacco that causes addiction" (USDHHS 2014, p30). Addiction to nicotine arises from a combination of genetic, environmental and pharmacological factors, but the characteristics of the nicotine delivery system are also crucially important (RCP 2007). This section will not discuss the mechanisms involved in nicotine addiction but will focus on specific nicotine pharmacokinetic characteristics known to be influential in nicotine addiction, such as the rate and extent of nicotine absorption, nicotine exposure and how these characteristics from THS compare with those from CC.

Four clinical studies have been conducted with THS Regular and four with THS (high) Menthol (see Table 2 and Table 7). The yield of menthol in aerosol from THS Menthol was 1.20mg/stick ISO for these four studies. The THS use instructions were described in the study protocols and summarized in Table 7. Apart from the ambulatory period of the two 3-month studies, during which the use of tobacco and nicotine products was self-reported in a diary, the product use was controlled and closely monitored by study staff. Smokers of nonmenthol CC were enrolled in clinical studies with the THS Regular variant, while smokers of menthol CC were enrolled in the THS Menthol variant studies.

Nicotine exposure was measured in all 8 clinical studies as follows:

- Nicotine pharmacokinetics after single use of THS and CC, and after THS and NRT product use in the four crossover studies
- Nicotine and cotinine pharmacokinetics after five days of repeated use of THS and CC *(ad libitum* exclusive use within a large but fixed use time window), and
- Nicotine exposure over 3 months of actual use of THS and CC, based on plasma cotinine and urinary excretion of nicotine and its five major metabolites, referred as nicotine equivalents (NEQ) (*ad libitum* actual use).

Table 7. Product Use Instruction in Clinical Studies

Study Code	Country	Study Design	Exposure Duration	THS Use Instructions
THS Regular				
ZRHR-PK-01-EU	Poland	Cross-over	1-stick use	Puffing as desired
ZRHR-PK-02-JP	Japan	Cross-over	1-stick use	Puffing as desired
ZRHR-REXC-03-EU	Poland	3-arm parallel	5 days	*Ad libitum* exclusive use
ZRHR-REXC-04-JP	Japan	3-arm parallel	5 days	*Ad libitum* exclusive use
THS Menthol				
ZRHM-PK-05-JP	Japan	Cross-over	1-stick use	Puffing as desired
ZRHM-PK-06-US	USA	Cross-over	1-stick use	Puffing as desired
ZRHM-REXA-07-JP	Japan	3-arm parallel	3 months	*Ad libitum* exclusive 5 days in clinic and then 85 days ambulatory
ZRHM-REXA-08-US	USA	3-arm parallel	3 months	*Ad libitum* exclusive 5 days in clinic and then 85 days ambulatory

[Source: clinical study reports in Module 7.3.1]

6.2.3.4.1. Nicotine Pharmacokinetics after Single Use

The four single use clinical pharmacology studies were conducted in confinement settings, following the same crossover design. After at least 24 hours of smoking abstinence/nicotine washout, and following the single use of THS (puffing and inhaling as desired by subjects) and comparators (CC or NRT), serial blood samples were collected during 24 hours for the determination of nicotine plasma concentrations. Standard non-compartmental pharmacokinetics (PK) parameters were derived to compare the rate and extent of nicotine absorption in THS vs. CC and THS vs. NRT products (nicotine 2mg gum in Japan, and nicotine nasal spray in US and Europe). The maximum concentration (C_{max}) of nicotine in plasma and the time to C_{max} (t_{max}) were the two PK parameters used as a proxy for the rate (speed) of nicotine absorption while the area under the curve (plasma concentration vs. time) until last quantifiable nicotine plasma concentration ($AUC_{(0\text{-last})}$) represents the amount of nicotine absorbed in the body. Geometric least square means of ratio THS/CC and THS/NRT were carried out to compare C_{max} and AUC results. The full description and detailed results are provided in Module 6, Section 6.2.1.

Across the four single use clinical pharmacology studies, the time course of nicotine plasma concentrations after THS use was broadly similar to the time course after CC use, with a rapid peak within approximately six minutes (see Figure 3 and Figure 4). Of particular interest in the Japanese studies (ZRHR-PK-02-JP with THS Regular, and ZRHM-PK-05-JP with THS Menthol), mean ratios and median t_{max} were similar,

suggesting that menthol does not have a deleterious impact on nicotine exposure after single use.

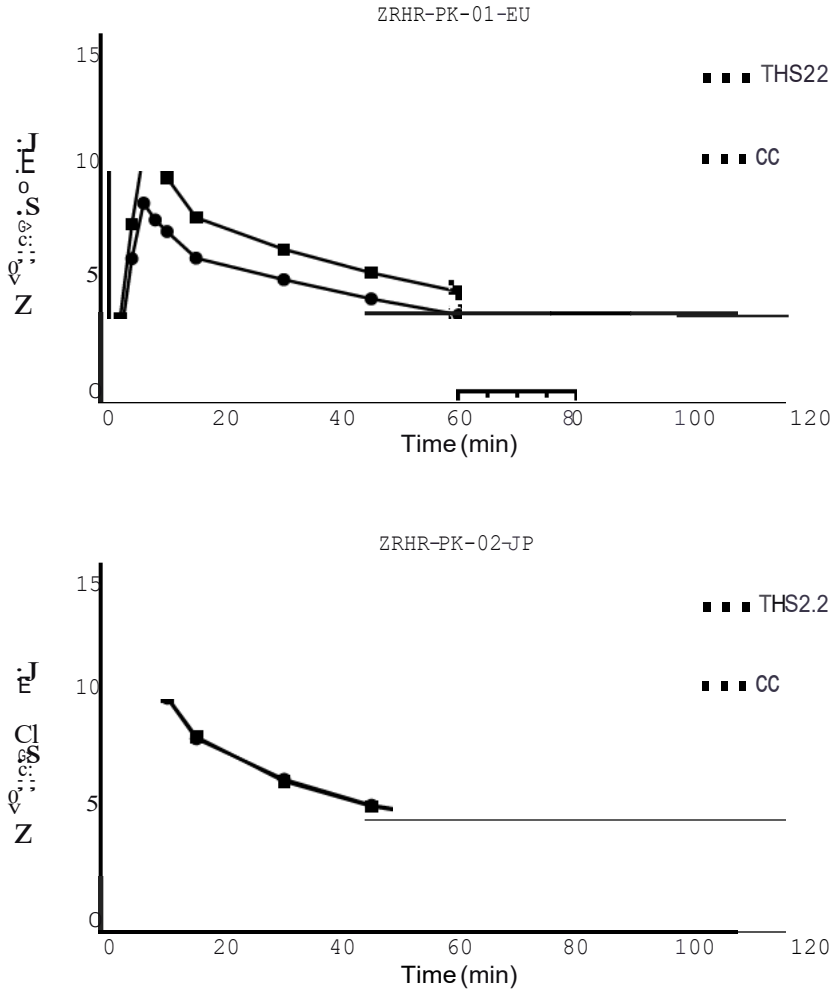


Figure 3. Plasma Nicotine after Single Use of THS Regular and CC

[Sotu·ce: Appendix 15, Figtu·e 15.1.2.1.1 ZRHR-PK-01-EU ; Appendix 15, FigtU·e 15.1.2.1.1 ZRHR-PK-02-JP]

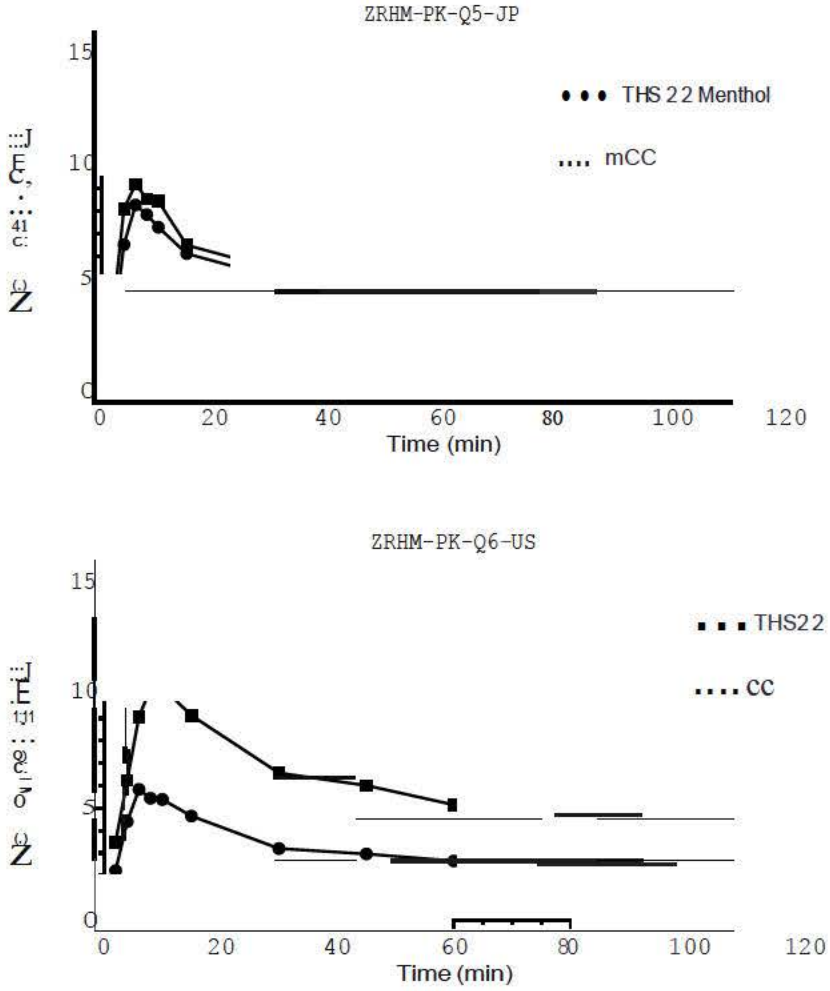


Figure 4_ Plasma Nicotine after Single Use of THS Menthol and CC

[Sotu·ce: Appendix 15,Figtu·e 15.1.2.1.1 ZRHM-PK-05-JP; Appendix 15,Figure 15.1.2.1.1 ZRHM-PK-06-US]
mCC: menthol conventional cigarette

The rate and amount of nicotine abs0 lption after single use of THS was higher than after NRT, with time to peak shorter than after NRT gum (see Figure 6) and with time to peak similar to nicotine nasal spray (see Figure 5).

Figure 5. Plasma Nicotine after Single Use ofTHS and Nicotine Nasal Spray

[Sotu-ce: Appendix 15,Figtu·e 15.1.2.1.2. ZRHR-PK-01-EU ; Appendix 15, Figlll'e 15.1.2.1.2 ZRHM-PK-06-US]
NNS : nicotine nasal spray

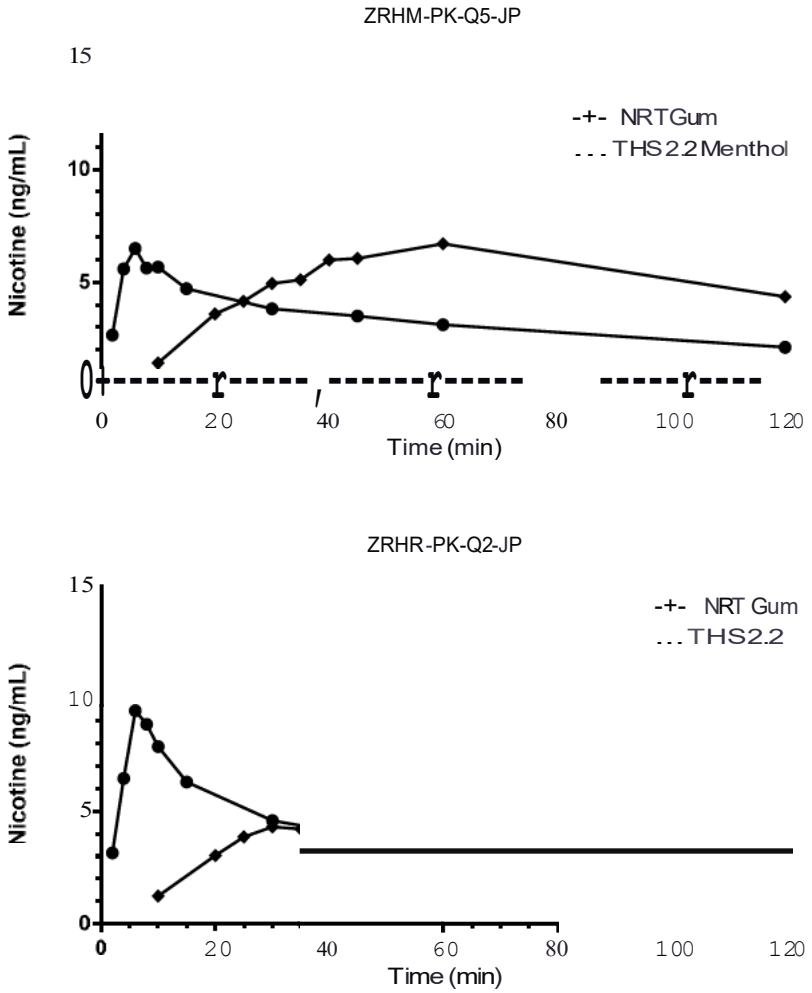


Figure 6_ Plasma Nicotine after Single Use of THS and Nicotine 2mg Gum

[Som·ce: Appendix 15, Figtu·e 15.1.2.1.2 ZRHR-PK-02-JP; Appendix 15, Figtu·e 15.1.2.1.2 ZRHM-PK-05-JP]

These study results suggest that the THS Regular and THS Menthol abuse liability, with respect to nicotine phannacokinetics after single use in non-experienced users, is higher than for NRT products and is not higher than for CC.

6.2.3.4.2. Nicotine Pharmacokinetics after Repeated Use

The two 5-day reduced exposure clinical studies were conducted in confinement settings, following the same three-arm parallel (THS, CC, and smoking abstinence (SA)) design. Study details and results are described in Module 6, Section 6.2.2. THS and CC use was closely monitored by study staff to ensure exclusive use of allocated product. Nicotine and cotinine plasma concentrations were measured twice a day (morning and evening) from baseline to Day 5 and once in the morning on Day 6 in all three study arms. In addition, serial blood samples were collected during the last day of repeated product use for the determination of nicotine and cotinine plasma concentrations. Standard non-compartmental pharmacokinetics parameters were derived for comparison of the rate (observed peak plasma concentration C_{peak}) and extent of nicotine absorption (weighted average plasma concentration C_{avg}) in THS vs. CC. The extent of nicotine exposure (nicotine uptake) was also evaluated daily by measuring the urinary excretion of nicotine and five major nicotine metabolites (namely cotinine, *trans*-3'-hydroxycotinine and their respective glucuronides) referred to as nicotine equivalents (NEQ) in all three arms. NEQ represents approximately 85 to 90% of the systemic nicotine dose/nicotine uptake (Benowitz 1999).

The results of systemic nicotine uptake, plasma cotinine and nicotine repeated dose PK after THS use were broadly similar to the results after smoking CC, but they were fairly heterogenic across the four studies and inconsistent with product use, suggesting that the adaptation to product is not yet achieved after five days of THS use. These results support the trend toward similar abuse liability (in its pharmacokinetics component) THS vs. CC observed after THS single use.

6.2.3.4.3. Three-month Nicotine Exposure and Nicotine Metabolism

Following a first week in confinement (see above Section 6.2.3.4.2), the two 3-month reduced exposure clinical studies were conducted during three months (85 days) in ambulatory settings. The studies had the same 3-arm parallel (THS, CC, and SA) design. As mentioned in Table 7, subjects allocated to THS were instructed to use THS exclusively, but the concomitant use of other tobacco products was not exclusionary. Cotinine plasma concentrations and urinary NEQ measurements were repeated at Day 30, Day 60, and Day 90. CYP2A6 activity (molar ratio of plasma *trans*-3'-hydroxycotinine and cotinine) was used to explore potential changes in nicotine metabolism upon switching to THS. Study details and results are described in more derails in Module 6, Section 6.2.2.

Urinary excretion of NEQ is a valuable parameter, directly reflecting the average nicotine exposure of the last 3 to 4 days, accounting for all the self-titration methods adopted by THS users to obtain the satisfying nicotine levels. The elimination half-life of nicotine in urine is 11 hours (Benowitz 1999), which represents a more stable nicotine exposure biomonitoring measurement compared to plasma nicotine.

As the terminal half-life of cotinine in plasma is much longer (16 hours) than for plasma nicotine (2 hours) (Benowitz 1999) concentrations of cotinine in plasma are also used as a proxy for nicotine exposure. Plasma cotinine is therefore used as an indirect

measurement for the nicotine exposure covering nicotine/tobacco use for the last 3 – 4 days.

fu both Japanese and US studies, per-protocol populations, the time courses of urinary NEQ (geometric mean) were broadly similar in THS (subjects characterized as predominantly THS users) vs. CC smokers (see Figure 7 and Figure 8). Similar outcomes were observed for plasma cotinine. Results from the full analysis set (i.e. including subjects using THS in combination with other tobacco products to various degrees, i.e. dual use) remain similar. For example, in ZRHM-REXA-08-US, the full analysis set population, the mean ratio THS/CC plasma cotinine and ratio THS/CC NEQ were 107.24% (vs. 104.30% in the per-protocol population) and 99.69% (vs. 96.30% in the per-protocol population), respectively, indicating that combined use of THS with other nicotine/tobacco products did not lead, on average, to nicotine overexposure.

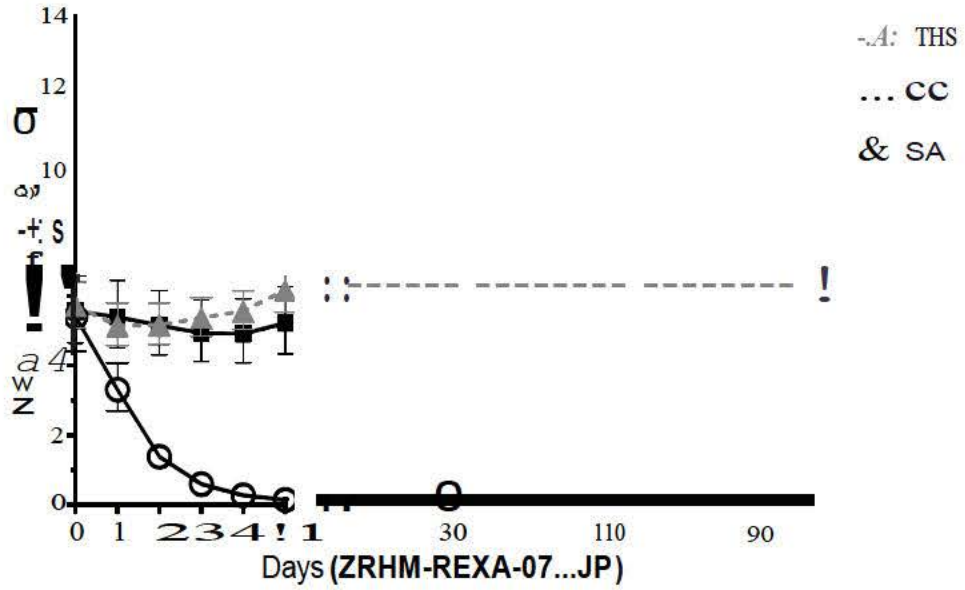


Figure 7. Nicotine (NEQ) in Urine during Study ZRHM-REXA-07-JP

NEQ is expressed in mg excreted in mine per g of creatinine
Abbreviations: creatinine (creat), Tobacco Heating System (THS), Conventional Cigarette (CC), Smoking Abstinence (SA), confidence intervals (CI).
[Source: Clinical Study Rep01t ZRHM-REXA-07-JP: section 11.2.4.1, Appendix 15, Table 152.4.18.1 and Table 15.2.4.18 2, Table90 and 91 and Appendix 15, Table 152.4.44]

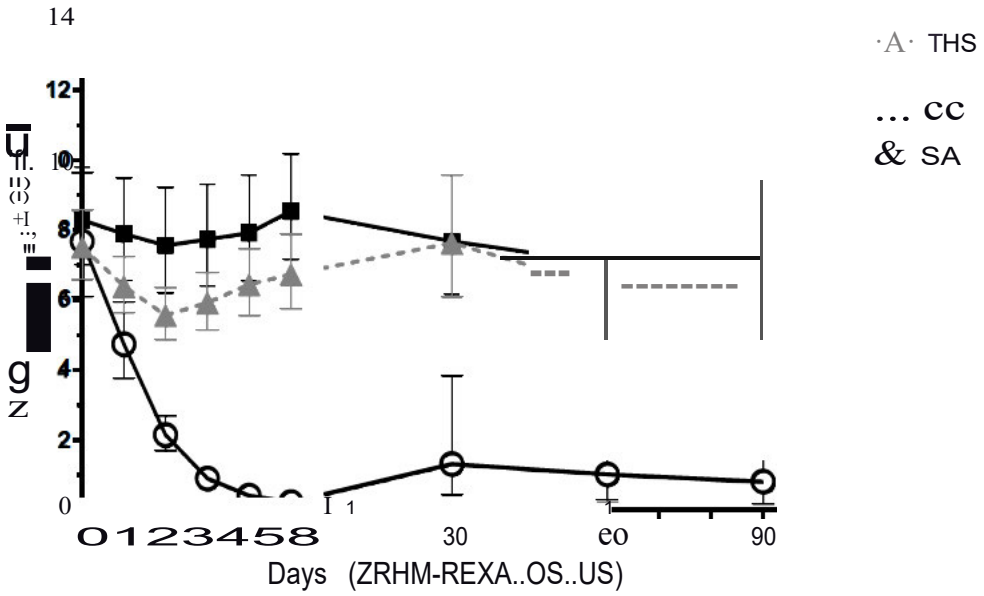


Figure 8. Nicotine (NEQ) in Urine during Study ZRHM-REXA-08-US

NEQ is expressed in mg excreted in w-ine per g of creatinine
Abbreviations: creatinine (creat), Tobacco Heating System (THS), Conventional Cigarette (CC), Smoking Abstinence (SA), confidence intervals (CI).
[Source: Clinical Study Rep01t ZRHM-REXA-08-US: section 112.4.1, Table 98 and 99 and Appendix 15, Table 152.4.18.1 and Table 152.4.18.2]

CYP2A6 enzymatic activity (driving the metabolism of nicotine into cotinine) – also called CYP2A6 phenotype - can be used as an indirect measure of nicotine metabolism. The baseline levels of CYP2A6 activity were markedly different between studies, with levels ranging from 26.05% to 44.31% across all aims and studies. Across studies, the profiles of CYP2A6 activity over time were comparable in the THS aims to those observed in the CC anns. By contrast, CYP2A6 activities of subjects abstinent from smoking increased during the confmement periods of all studies, but then decreased during the ambulat01y periods of the 3-month studies, remaining higher than in THS users and CC smokers. These results (data not shown, see detailed results in Module 6, Section 6.2.2) suggest that the nicotine metabolism remains unchanged upon switching from CC to THS, and therefore would not explain changes in cotinine levels, if any, after switching from CC to THS.

The nicotine exposure measured by plasma cotinine and by NEQ is an outcome of nicotine yield in the aerosol, the intrinsic nicotine phannacokinetic prope1ties followed by product use adaptation and nicotine self-titration. Product use adaptation is discussed in Section 62.3.6.1. The results suggest that 1) exposure to nicotine upon THS use (including dual use) tend to be siinilai· with nicotine exposure with CC, and 2) self-titration / product use adaptation requires one month or more to reach a level close to CC. The data do not suggest that switching paitially or completely to THS Menthol increases the exposure to nicotine. It can be reasonably assumed, extrapolating the 5-d.ay

data, that the nicotine exposure with THS Regular would not behave differently upon actual use.

The results suggest that after three months of product use, the THS abuse liability, with respect to nicotine exposure upon three months of THS use, is at par with CC.

6.2.3.4.4. Conclusion on Nicotine Pharmacokinetics and Exposure

The speed (rate) and amount of nicotine absorption, the levels of exposure to nicotine, measured by systemic nicotine levels (nicotine in plasma, cotinine in plasma, nicotine and metabolites excreted in urine), the absence of apparent changes in nicotine metabolism (based on CYP2A6 activity) upon various conditions and duration of use in the context of randomized clinical studies, do not indicate a higher risk of abuse liability with THS both variants, for smokers switching to THS, when compared to CC. The THS abuse liability is higher than for NRT products. With respect to nicotine pharmacokinetics, the abuse liability of THS could be considered as follows: NRT < THS ≤ CC.

6.2.3.5. ALA Domain 4 - Pharmacodynamic Effects

Several questionnaires were administered in the eight clinical studies, measuring subjective effects when smokers switch to THS, thus, contributing to gauge the pharmacodynamics effects of the product. These questionnaires assess various dimensions of abuse liability such as craving (urges to smoke), the impact of the product on smoking satisfaction, enjoyment of respiratory tract sensation, psychological reward, aversion, craving reduction and nicotine dependence. Evaluation of subjective withdrawal symptoms is discussed in Section 6.2.3.8. Description of these study endpoints and related results are provided in more details in Module 6, Section 6.2.1 (single use pharmacological clinical studies) and in Module 6, Section 6.2.2 (reduced exposure clinical studies).

6.2.3.5.1. Urges-to-Smoke

In the four single use pharmacological clinical studies, craving (urges-to-smoke) and craving relief was assessed by the serial self-administration of the brief questionnaire for smoking urges (QSU-brief) prior to product use and during 12 hours post product use. QSU-brief was also administered daily during the confinement period of the four reduced exposure clinical studies and at each of the visits during the ambulatory period of the two 3-month studies. QSU-brief is the most widely used smoking craving questionnaire (Carter 2009).

Across all eight clinical studies, THS consistently provided a similar relief to smoking urges (cigarette craving) for THS and for CC users when assessed with the QSU-brief, based on the evaluation of the 95% confidence interval of mean differences THS-CC for the three QSU-brief score (total score, subscale score 1 - positive experience and subscale score 2 - alleviation of negative experience). This was observed in serial measurements after single use, in daily measurements in 5-day studies and at monthly visits in the per-protocol subjects from the 3-month studies.

6.2.3.5.2. Product Evaluation - Satisfaction

THS and CC were evaluated in terms of smoking satisfaction, enjoyment of respiratory tract sensation, psychological reward, aversion and craving reduction, using the modified cigarette evaluation questionnaire (MCEQ). MCEQ is widely used for assessing reinforcing and aversive effects of smoking. The MCEQ was self-administered once in the morning of THS use and of CC use, daily in confinement settings and monthly in ambulatory settings.

The results of MCEQ were interpreted based on the review of 95% confidence interval of THS-CC differences for the five subscales across the eight clinical studies (See Table 8). Apart from ZRHM-REXA-07-JP, in which all subscales were rated as not different, in all other studies, there were one or several subscales rated as lower, meaning that THS provided less satisfaction to users than CC. The aversion subscale was generally rated as not different with one exception: THS was more aversive than CC in ZRHR-REXC-03-EU study, mimicking the high difference in adverse events incidence rates between the two 5-day studies, see Module 6, Section 6.1.5. In the repeated use studies for both menthol and regular THS variants, the general observed trend was toward an even less satisfying experience during the first one or two days of use (data not shown here; details available in respective clinical study reports).

Table 8. Overview of Differences THS – CC for MCEQ Subscales

Study	Smoking Satisfaction	Enjoyment Respiratory Tract Sensations	Psychological Reward	Aversion	Craving Reduction
ZRHR-PK-01-EU	Lower	Lower	Not different	Not different	Lower
ZRHR-PK-02-JP	Lower	Lower	Lower	Not different	Not different
ZRHM-PK-05-JP	Lower	Lower	Not different	Not different	Not different
ZRHM-PK-06-US	Lower	Lower	Lower	Not different	Lower
ZRHR-REXC-03-EU					
• Day 5	Lower	Lower	Lower	Higher	Lower
ZRHR-REXC-04-JP					
• Day 5	Lower	Not different	Lower	Not different	Not different
ZRHM-REXA-07-JP					
• Day 5	Not different	Not different	Not different	Not different	Not different
• Day 90	Not different	Not different	Not different	Not different	Not different
ZRHM-REXA-08-US					
• Day 5	Lower	Not different	Not different	Not different	Lower
• Day 90	Not different	Not different	Not different	Not different	Not different

Not different when 0 is included in 95% confidence interval THS-CC
Lower when entire 95% confidence interval < 0
Higher when entire 95% confidence interval > 0;
[Source: Clinical study reports ZRHR-PK-01-EU, Table 15.2.4.15, ZRHR-PK-02-JP Table 15.2.4.15; ZRHM-PK05-JP Table 15.2.4.15; ZRHM-PK-06-US Table 15.2.4.15, ZRHR-REXC-03-EU Table 15.2.4.48; ZRHR-REXC-04-JP Table 15.2.4.48; ZRHM-REXA-07-JP Table 15.2.4.38.1; and ZRHM-REXA-08-US Table 15.2.4.55.1]

Five-day study results suggest that the THS Menthol variant seems to play a role by providing a better satisfaction than with the THS non-menthol variant, for some (but not

all) of the components (e.g., enjoyment of the respiratory tract sensations, psychological reward, aversion) with variations across studies. Potential impact of menthol (in contrast to the non-menthol, "Regular" THS variant) on satisfaction may be linked to menthol pharmacological properties (cooling and anesthetic properties, nicotine harshness reduction and smoother alternative for smokers).

6.2.3.5.3. Nicotine Dependence

The Fagerström test for nicotine dependence (FTND) is the most widely used questionnaire to characterize the "severity" of the dependence to nicotine in smokers (e.g. as part of therapeutic strategies). For exploratory purposes, the FTND questionnaire was completed by subjects at baseline and at day 90 in the two 3-month studies. At baseline, Japanese subjects were scored as less dependent to nicotine than American subjects (See Table 9); as mentioned above in Section 6.2.3.1, 34.4% of subjects enrolled in the US study ZRHM-REXA-08-US were rated as having severe nicotine dependence (FTND score between 7 and 10 as defined in respective study protocols) at baseline as compared to the 14.0% in the Japanese study ZRHM-REXA-07-JP. The validity of the FTND is questionable when used to assess heated tobacco product as it was only validated for CC (Fagerström 2012). In our two studies, it is unclear if subjects answered the questionnaire considering the behavior with THS, with CC or both. An overview of FTND scores at baseline and at Day 90 is shown in Table 9. While results suggest a decrease in nicotine dependence upon smoking cessation (in subjects reported as successfully abstinent), a differential evolution was not observed in subjects allocated in THS or in CC arms.

Table 9. Nicotine Dependence in 3-month Studies

FTND Score	Baseline Median (min-max)	Day 90 Median (min-max)	Comment
ZRHM-REXA-07-JP			
• THS arm	4 (1-8)	4 (0-9)	Unchanged in THS and CC arms
• CC arm	4 (1-8)	4 (0-7)	
• SA arm	5 (0-9)	3 (0-8)	2-point decrease in SA arm
ZRHM-REXA-08-US			
• THS arm	6 (1-10)	5 (1-9)	1-point decrease in THS and CC arms
• CC arm	6 (1-9)	5 (2-9)	
• SA arm	6 (2-8)	1.5 (0-3)	Unreliable results for SA arm as only 9 subjects were abstinent and only 4 completed day 90 questionnaire

[Source: clinical study report ZHRM-REXA-07-JP Table 15.2.4.34.1; and ZRHM-REXA-08-US Table 15.2.4.51.1]

6.2.3.5.4. Conclusion on Pharmacodynamics Effects

Pharmacodynamics effects upon switching to THS do not fully correlate to nicotine exposure, especially in the short-term. This was outlined in study ZRHR-REXC-03-EU,

where no differences in THS vs. CC were observed for QSU-brief, in contrast to a lower craving reduction from MCEQ with THS vs. CC (less effective than CC), while average nicotine systemic exposure was 12% higher vs. CC. Despite its central role in tobacco use, nicotine is increasingly recognized as a secondary rather than a primary (or at least not the unique) reinforcer, as other pharmacological (including flavorant agents) and non-pharmacological factors may play a role in product use satisfaction and sustained self-administration (Fagerström 2012).

In the short-term (the first days of use), the general observed trend was toward a less rewarding/satisfying product, which may be explained by 1) the time needed to adapt and self-titrate the nicotine systemic exposure, and 2) the disruptive behavior due to the product design and differences in the organoleptic components of the THS aerosol. The results suggest that the menthol variant may provide an extra-benefit in term of reward and enjoyment but does not cover the craving relief as good as with CC.

In a longer term (after one month of use of THS Menthol), there are no longer differences in pharmacodynamic effects in THS vs. CC, with the exception of craving reduction which was not as good as with CC in the US study; as noted, subjects enrolled in the US study had, on average, a nicotine dependence level higher than subjects from the Japanese study and nicotine yields in US CC are on average higher than Japanese CC.

With respect to pharmacodynamics effects, the abuse liability of THS could be considered as follows: THS (THS Regular < THS high menthol) < CC during the first days of use and then THS (THS Regular < THS high menthol) ≤ CC.

6.2.3.6. ALA Domain 5 - Reinforcing Effects

Complementary to positive and negative reinforcing effects associated with pharmacological effects, reinforcing effects are also viewed from a product use behavior lens, i.e. how the product is perceived by smokers, and nonsmokers (never-smokers and former smokers), what is their intention to try and use THS vs. other tobacco products and actually how smokers use the product both in controlled settings and in near-to-real world situations.

6.2.3.6.1. Product Use Behavior in Clinical Studies

The design of the clinical studies, in terms of instructions to product use, should be considered as supportive to understand product self-administration, as puffing was allowed as desired in single stick use studies (no imposed regime, the only limitation being the limitations set in the product design with pre-determined cap in number of puffs and use duration – see Section 6.2.3.2) and product use was *ad libitum* in repeated use studies, with concomitant or intermittent use of other tobacco products (dual use) being possible but not encouraged (see Section 6.2.3.4.3) in ambulatory period of the 3-month reduced exposure studies.

Puffing behavior (from human puffing topography) results from the clinical studies (see detailed results and interpretation in Module 6, Section 6.2.2) have shown that

smokers switching from CC to THS have adapted their puffing methods at both puff and product use experience level.

Variations in product use (see study details and results in Module 6, section 6.2.2), in pruticula.r during the first days of exposure to a new product with different characteristics compru·ed to subjects own brand(s) of CC rue expected and prut of the adaptation process to a new product such as THS. These variations in product use observed eruly after switching to THS disappeared to the most extent when followed up for a period of more than 30 days to levels comparable of what was obse lved at baseline and to the levels of use rep01ted for CC at the end of the ambulat01y period. The time course of product use in the US study ZRMH-REXA-08-US is presented as an exrunple in Figure 9. Pattems of product use were different between the study population in Japan and in the U.S., with for Japan, higher rates of adherence to use the allocated product and almost no dual-use with CC or other nicotine-containing products (at 3 months, 84.6% of exclusive THS users among subjects randomized to THS) compru·ed to the study in the U.S. (55.0% exclusive THS users at 3 months).

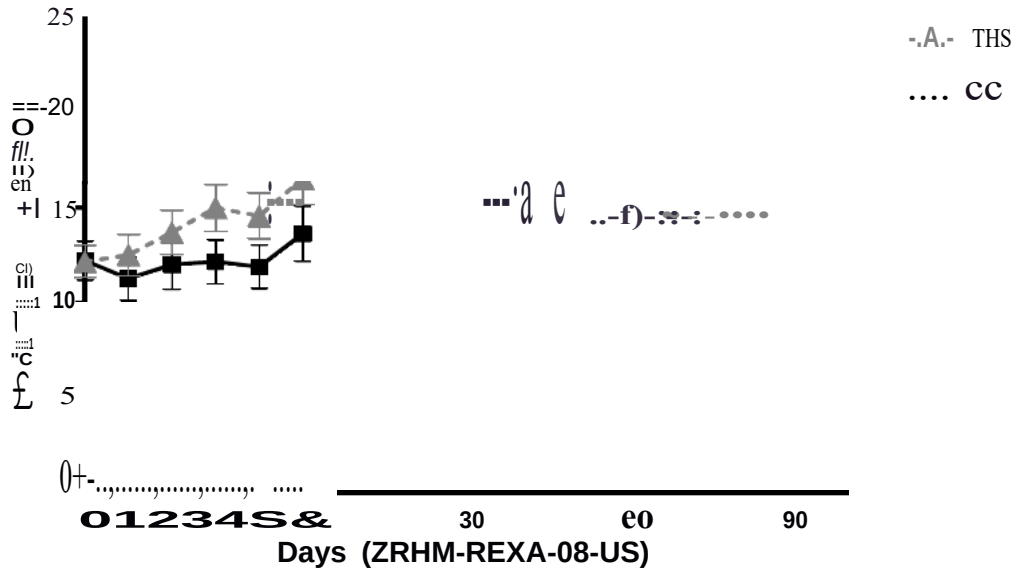


Figure 9. Product use - ZRHM-REXA-08-US **Full** Analysis Set

Overall, when taken together with nicotine exposure results (see Section 6.2.3.4), the transient variations in THS use and the subsequent puffing behavior adaptations show that subjects switching to THS (fully or pa1tially) self-titrate their nicotine intake, i.e. seeking nicotine levels similru·they rue used to with CC. Thus, the product use behaviors obse1ved in clinical settings do not raise an abuse liability concem higher than for CC.

6.2.3.6.2. Product Use in Near-to-Real-World Conditions

Two type of obse1vational (non-inte1ventional) studies evaluated how smokers actually use THS over a period of four weeks (five WOT market research studies conducted

outside the US) and over a period of six weeks (THS-PBA-07-US conducted in the US) (see Table 2 and Table 4).

MarketResearchStudiesinEuropeandAsia

The five WOT market research studies (Europe and Asia) were conducted in adult smokers from two or more large cities and representative of the local market adult smokers population based on quotas (see countries in Table 2). The studies started with a first phase assessing the responses to THS (regular and/or menthol variants) based on one THS Tobacco Stick trial and to hypothetical marketing material, followed by a second phase (only smokers having indicated a non-negative purchase interest, with a score of at least 3 on the 5-point intention to purchase scale [1 = definitely not, 5 = definitely]), assessing the THS actual use (start of use, switch to THS, combined use of CC and THS, switch back to CC) characterizing the overall consumption of tobacco products. Details on study design and results are presented in Module 6, Section 6.2.2. These WOT studies provide an initial insight on product use.

Across the five studies, it is noteworthy there was approx. 11% to 28% attrition between phase 1 and phase 2, suggesting that THS has a limited appeal to a portion of adult smokers after the first exposure to it.

Across the five studies, approx. 36% to 76% started to use THS (use of ≥100 THS tobacco sticks) within the 4 weeks of observation (highest proportions in Asian populations) with peak at week 2 and week 3, suggesting that smokers need a rather limited time to adopt the THS product. Across studies, 10% to 37% of adult smokers switched to THS (>70% of tobacco products use is THS use). Most of the THS switchers switched during the first week (approx. 18% to 47% among starters) and very few (<4%) switched back to CC during the last week of study. These results suggest that the adoption of THS is either rapid or non-existent. Consistent across the 5 WOT studies, and even with a behavior of combined use of THS and CC reported in approx. 40% to 60% of participants, the overall tobacco products use (THS + CC) remained stable during the 4 weeks of observation, suggesting that THS is not promoting increase of tobacco product use.

ActualUseStudyintheUS

The six-week actual use study, THS-PBA-07-US, used the same principles as for the WOT. The THS-PBA-07-US study was conducted in 8 limited geographic areas of the US. Special attention was given to the sampling of participants aiming at approximating the adult smoker distribution contained in the Centers for Disease Control and Prevention report (CDC 2012) in terms of sex (male/female), age (young adults from legal age (LA) to 25yr, adults 25-44yr and adults 45+yr), race (minorities (including African Americans) and Whites) and income (below 45'000 USD / ≥ 45'000 USD). Similar to the WOT studies, only adult daily smokers who expressed a positive intention to use (score of at least 4 on the 6-point intention to use scale [1 = definitely not, 6 = definitely]) THS after being exposed to the THS marketing material were eligible to participate in the observational study period. THS Regular and THS Menthol were available to study participants for free. Stick-by-stick consumption of CC and THS was recorded by study participants in an electronic diary. Study participants were interviewed at baseline and at

the end of the study via a computer-assisted web interview (CAWI). Interim computer-assisted telephone interviews (CATI) were executed twice. Study details and results are available in Module 6, Section 6.2.2, and in study report THS-PBA-07-US, in Module 7.3.2.

From an abuse liability point of view, the actual use study THS-PBA-07-US could be used as a proxy for the evaluation of choice procedures (participants were given the possibility to choose to use the THS variant(s) they wish to use) and the evaluation of self-administration (participants were fully free to use the THS as much as they wanted), with the caveat of getting the product for free over 6 weeks and of having a cap for tobacco sticks supply to individuals based on their self-reported daily CC use (using an inflation factor of 3). The full analysis set population (N=1106) is considered relevant to evaluate product use for the ALA.

During the analysis of safety data from THS-PBA-07-US (safety population with the 1158 participants who used at least one THS tobacco stick, see Module 7.3.1, THS-PBA-07-US safety summary report), 44.2%, 38.1% and 17.7% of participants used THS Menthol only, THS Regular only, both variants, respectively. The majority of participants who used THS Menthol only were White (54.3%) followed by African Americans (41.6%). Majority (66.5%) of African Americans have used THS Menthol only, approx. twofold higher proportion than for White (35.0%).

Three main product usage categories were defined: THS sticks use (THS use represents ≥70% of THS + CC use), combined use (THS use between 30% and 70% of THS + CC use) and CC use (THS use ≤30% of THS + CC use). The average daily use of CC and THS (units per day) as reported in electronic diary is shown in Table 10. The overall number of tobacco products consumed on average per day (CC + THS) remain stable in the three main product usage categories, suggesting that THS is not an incentive to increase tobacco use all together, concurring with findings from WOT studies.

Table 10. THS and CC Use per Day in THS-PBA-07-US (FAS Population)

Mean (SD)	FAS overall (n=1106)	THS use at Week 6 (n=141)	Combined use at Week 6 (n=217)	CC use at Week 6 (n=607)
During baseline period				
• Number of CC	10.2 (7.22)	9.0 (5.89)	9.3 (6.34)	10.9 (7.69)
During observational period				
• Number of THS sticks and CC	9.3 (6.56)	8.1 (5.37)	8.9 (6.21)	9.9 (6.75)
• Number of CC	6.3 (5.78)	1.4 (1.57)	4.8 (3.72)	8.3 (6.32)
• Number of THS sticks	3.0 (3.57)	6.7 (4.82)	4.1 (3.06)	1.7 (1.99)

FAS: full analysis set
[Source: Study report THS-PBA-07-US, Table 18, Table 15.2.3.11, Table 15.2.4.1, Table 15.2.4.2, and Table 15.2.4.3]

Trajectories of use patterns are presented in details in Module 6, Section 6.2.2. More than 33% of the FAS population started to use THS (≥100 THS tobacco sticks over the 6 weeks) with the two most frequent trajectories being THS use as of first week (14.4%) and combined use along the 6 weeks (10.7%) among starters. Approximately 15% of the FAS population adopted THS (i.e. THS use category). The use of THS in combination with CC (i.e. combined use) was reported by 22.4% of the FAS population at Week 6. The proportion of exclusive THS use was stable, between 7% and 8% of the FAS population, on a weekly basis. The proportion of participants who switched back to CC (CC use category) after having switched (THS use category) during the 6 weeks observational period was 15.5%. At the end of the study, the majority of participants (FAS population) would probably (21.3%) or definitely (39.5%) not buy the product, while approx. half of the adopters (THS use category at Week 6) would probably (31.2%) or definitely (15.9%) buy it (5-point rating scale ranging from "1=definitely would buy it" to "5=definitely would not buy it"). This intention to buy should be put in perspective to sensorial findings, as the median score for taste, smell and aftertaste was 3.0 (min-max 1-7 Likert scales ranging from a 1 - don't like at all - to 7 – like it very much – scale). About half of the FAS population did not like the taste (53.5%), the smell (53.7%) and aftertaste (58.2%).

The results of this study are consistent with results from WOT studies conducted abroad. Results suggest that, for adult smokers, THS is not as appealing as CC (i.e. lower abuse potential), as only a portion of smokers offered to use THS transitioned to THS use, without promoting an increase in tobacco product use all together.

6.2.3.6.3. Intent to Use and Risk Perceptions by Adult Smokers

Three label, labeling and marketing material assessment studies (THS-PBA-05-RRC-US, THS-PBA-05-RRC2-US and THS-PBA-05-REC-US, see Table 4) sharing the same study design, but testing different marketing material, were conducted in the US. Study participants were only exposed to one instance of label, labeling and marketing material and there was no THS use. The measurements included intent to use (intention to try at least once, intention to use regularly), change in the intention to quit smoking and all tobacco products (in smokers with the intention to quit), comprehension of messages (label, labeling and marketing material) and risk (Perceived Health Risks, Perceived Addiction Risk and perceived Harm to Others) perception for THS and for the comparators (CC, e-cigarettes, NRT products, and smoking cessation). Data was acquired by using a Computer-Assisted Self Interviewing methodology. The study population included adult smokers with no intention to quit CC (have smoked at least 100 CC and no intention to quit within the next 6 months), adult smokers with intention to quit CC (have smoked at least 100 CC and intention to quit within the next 6 months), adult former smokers (had smoked more than 100 CC in their life and quit smoking CC more than 30 days ago) and adult never smokers (had smoked less than 100 CC in their life and never been a daily smoker). A fifth group was composed of adult never smokers between legal smoking age and 25 years of age (LA-25 adult never smokers), in order to oversample young adults who never smoked. These five groups were randomly allocated to five arms (i.e., THS Brochure with Surgeon General's warnings, THS brochure with PMI Important Warning, THS Tobacco Sticks Pack with Surgeon General's warnings, THS Tobacco Sticks Pack with PMI Warning and THS Direct Mail with PMI Warning). Study details and results are described in Module 6, Section 6.2.2 (product use) and in Module 6, Section 6.4.1 (consumer understanding and perception).

The PMI Important Warnings tested in the three PBA-05 studies are presented in Table 11.

Table 11. Reduced Risk and Reduced Exposure Claims Assessment

Study	Assessed PMI Important Warnings
THS-PBA-05-RRC-US	Reduced risk claim 1 – PMI Important Warning with 3 statements: • "Reduced risk does not mean no risk. The best way to reduce your risk of tobacco-related diseases is to completely quit tobacco use." • "HeatSticks™ contain nicotine which is addictive." • "Using the iQOS system can harm your health."
THS-PBA-05-RRC2-US	Reduced risk claim 2 – PMI Important Warning with 2 statements • "Less risk of harm does not mean no risk of harm. The best way to reduce your risk of tobacco-related diseases is to completely quit tobacco use." • "HeatSticks™ contain nicotine which is addictive."
THS-PBA-05-REC-US	Reduced exposure claim – PMI Important Warning with 3 statements • "It has not been demonstrated that switching to the iQOS system reduces the risk of developing tobacco-related diseases compared to smoking conventional cigarettes." • "HeatSticks™ contain nicotine, which is addictive." • "Using the iQOS system can harm your health."

The Surgeon General's warnings (currently mandated for CC) tested in the three PBA-05 studies are as follows:

- "Smoking causes lung cancer, heart disease, emphysema, and may complicate pregnancy."
- "Quitting smoking now greatly reduces serious risks to your health.";
- "Smoking by pregnant women may result in fetal injury, premature birth, and low birth weight.";
- "Cigarette smoke contains carbon monoxide."

The effect of the label, labeling and marketing material in current smokers is presented below. The effects in former smokers and in never smokers is presented in the next section (see Section 6.2.3.6.5).

Overall, THS-PBA-05-RRC-US, THS-PBA-05-RRC2-US, THS-PBA-05-REC-US studies showed consistent results among adult smokers with or without intention to quit smoking over the three THS claims proposed (see Table 11), the different materials tested, and between the PMI and Surgeon General's warnings.

The proportion of participants who expressed the intention to try THS (ranging from 30.2% to 51.6%) was generally 10% higher than the intention to use in both smokers with or without intention to quit smoking.

Substantial levels of intention to use THS were reported within the intended segment of the population i.e. adult smokers with no intention to quit CC: positive intention to use

THS[1] was between 28.4% and 38.9%, between 20.2% and 37.9%, and between 20.8% and 36.8% across all arms, in THS-PBA-05-RRC-US, THS-PBA-05-RRC2-US, THS-PBA-05-REC study, respectively.

Similar substantial levels of intention to use THS were observed within adult smokers with the intention to quit CC (positive Intention to Use THS was between 21.3% and 35.1% across all arms, across the 3 studies). At the same time, the levels of change in intention to quit smoking CC in smokers with change in intention to quit were between 4.3% and 11.6%, between 1.1% and 11.8% and between 4.2% and 9.4% across all arms, in THS-PBA-05-RRC-US, THS-PBA-05-RRC2-US, THS-PBA-05-REC, respectively. Some of these smokers viewed THS as a mean to help them on their path to stop smoking but understood it is not a substitute to cessation.

Across the 3 PBA-05 assessment studies, PMI Important Warning and Surgeon General's warnings were associated with similar comprehension levels (proportion of correct answers ranging from 46.8% to 78.4% for global comprehension) across the different materials tested (i.e., THS Brochure, Tobacco Sticks Pack, and THS Direct Mail). At the same time, for the 2 studies that tested communication with reduced risk claims (THS-PBA-05-RRC-US and THS-PBA-05-RRC2-US), higher levels of correct comprehension of disease risk were found for the THS Brochure when associated with the PMI Important Warning, than when associated with Surgeon General's warnings. This was found despite of the fact that the information on disease risk for THS was contained within the main body of the THS Brochure, which was identical between Arm 1 and Arm 2, and not referred to in either type of warning. Likewise, in the study testing THS communications with a reduced exposure claim (THS-PBA-05-REC-US), disease risk information was consistently better comprehended when presented in materials with PMI Important Warning compared to materials with Surgeon General's warnings. An explanation could be that the combination of the claim with the PMI Important Warning reflects a coherent set of product-specific information concerning reduced risk.

A marginal proportion of subjects (<6% across all arms in THS-PBA-05-RRC-US study, <4% in THS-PBA-05-RRC2-US study and <4% in THS-PBA-05-REC-US study) indicated that THS is risk-free.

Consistent across studies, study arms and study population groups (smokers with or without intention to quit), the perceived health risk and the perceived addiction risk for THS was below that of CC, higher than NRT products and/or cessation, and similar to e-cigarettes. The perceived addiction risk is discussed in more details in Section 6.2.3.6.6.

Overall, the exposure to the proposed THS communications does not suggested a greater risk of abuse, based on intent to use (intention to try at least once, intention to use regularly), comprehension of messages (label, labeling and marketing material) and risk (Perceived Health Risks, and Perceived Harm to Others) and perception for THS and for

[1] Positive *Intention to Use* THS (operationalized as the sum of % "*Very Likely"* and % "*Definitely"* responses for the first item of *Intention to Use*), by study arm and smoking status group.

the comparators (CC, e-cigarettes, NRT products, and smoking cessation). Two aspects may need to be explored postmarket on their potential effect on product use behavior as i) a small proportion (usually less than one out of ten) adult smokers with intention to quit smoking and all tobacco products had expressed to change their intention to quit (at least transiently) after being exposed to THS communication material, and ii) as the THS addiction risk (Perceived Addiction Risk) is perceived as lower than for CC (even with the Surgeon's General mandated warnings).

6.2.3.6.4. Comprehension of THS Instructions to Use by Adult Smokers

THS-PBA-06-US was a single-arm usability and comprehension_study conducted in four US cities to evaluate whether adult daily smokers can and are likely to comply with any instruction of product use and to verify consumer understanding about key communication messages of the product instruction for use. The study was conducted via one-to-one interviews in 258 adult smokers. Special attention was given in regards to sampling with quotas of at least 30% of males, 30% of females, 30% aged 18-40yr, 30% aged 40yr+ and 30% of high school education or less. Study details are presented in Module 6, Section 6.2.2.

The majority of use tasks (charging the holder, how to consume the stick, end of stick use, how to remove a stuck stick from the holder) were executed correctly by more than two-third of the participants. A few tasks (how to insert the stick into the holder, how to remove the stick with the pull-pull technique, how to heat clean the holder, how to use cleaning tool) were less well executed. Key messages such as not using the device with a CC or not to smoke the THS tobacco stick as a CC were well comprehended by 85% and 95% of users, respectively. The second message should be put in perspective with misuse observations from study THS-PBA-07-US where 4.8% of participants reported to have smoked at least once the THS tobacco stick as a CC, by lighting it. About half of these (23 of 47, 48.9%) reported one occasion of misuse, 14 participants (29.8%) reported 2 to 4 occasions, 7 participants (14.9%) reported 5 to 9 occasions and 3 participants (6.4%) reported 10 times or more occasions of misuse. This misuse was more likely due to negligence (the habit of smoking) rather than toward any intentional way to use THS Tobacco Stick like a CC.

The level of comprehension of THS instructions to use and the anecdotal misuse cases at hand do not pose an abuse liability concern.

6.2.3.6.5. Intent to Use by Former Smokers and Never Smokers

Overall, THS-PBA-05-RRC-US, THS-PBA-05-RRC2-US, THS-PBA-05-REC-US studies (see additional information in above Section 6.2.3.6.4, in full details in Module 6, Section 6.3.1) showed consistent results on intent to use among non-users of CC over the three claims proposed, the different materials tested, and between the PMI and Surgeon General's warnings. There was only a small intention to try/use THS among all three examined non-smoker groups. Intent to use THS was slightly higher for adult former smokers (in the range of 1 to 10%), while adult never smokers had no more than 2.1 % of positive intention to try/use across the different materials throughout all three studies. Similarly, positive responses throughout all tested materials were no more than 3.0% of positive intention to try/use for LA-25 adult never smokers.

Consistent across studies and study arms, the perceived health risk for THS by former smokers was below that of CC, higher than NRT products and/or cessation, and similar to e-cigarettes. The perceived addiction risk is discussed in Section 6.2.3.6.6.

Importantly for public health protection, the results provide evidence that the low levels of intention to try or use in adult non-smokers were in the same range than for CC and e-cigarettes. We conclude that the existent low levels of Intent to Use THS among non-smokers exposed to THS communication materials were not specific to THS, but rather represent either a general interest in tobacco or nicotine-containing products and/or unsystematic variance within the data. The results for young adult never smokers (LA-25 adult never smokers) are consistent with those observed in adult never smokers. Thus our current results provide no evidence that exposure to THS communication generated intent to initiate tobacco with THS among young adult never smokers. THS is neither targeted towards, nor attractive to young non-smokers and is likely to have a non-differentiated effect compared to other commercialized tobacco products already on the market when it comes to initiation of tobacco use among young adults.

From an abuse liability point of view, the study results suggest that the proposed communication on reduced risk claim or on reduced exposure claim would not encourage adult former smokers and adult never smokers to initiate tobacco use. Similarly, the PBA-05 studies results also indicated that very few (almost no) adult never smoker young adults (LA-25 - best approximation of the larger group of legal age and below) were interested in using THS after viewing THS communication materials.

6.2.3.6.6. Perceived Addiction Risk

Consistent across THS-PBA-05-RRC-US, THS-PBA-05-RRC2-US and THS-PBA-05-REC-US, and across study arms and study population groups within these three studies, the level of perceived addiction risk for THS was below that of CC, higher than NRT products and/or cessation, and similar to e-cigarettes, regardless of the type of claim or marketing material. Details are presented in Module 6, Section 6.4.1. The perceived addition risk for THS by young adult never smokers (legal age to 25 years old) remains at a similar level than with adult never-smokers, rating THS less addictive than CC and at par with e-cigarettes.

Study findings are in line with two recently published scientific articles (surveys conducted in the US) on e-cigarettes where e-cigarette users perceive e-cigarettes as less addictive than conventional cigarettes (Berg 2015, Harrell 2015), concurring with Fagerström's commentary (Fagerström 2012). Fagestrom commented that, besides the central role of nicotine, other pharmacological and non-pharmacological determinants in CC may play a role in the development of tobacco abuse.

6.2.3.6.7. Conclusions on Reinforcing effects

From a product use behavior lens from various situations and populations, it appears that the abuse liability of THS is not worse than CC in smokers with no intention to quit. A small proportion (less than 10%) of smokers having the intention to quit smoking may delay their quit attempt and may perceive THS as an alternative to CC. The proportion of never-smokers who intent to try or use THS was not exceeding 3%. The risk of addiction

with THS was perceived as lower than for CC, higher than for NRT products and similar to e-cigarette.

6.2.3.7. ALA Domain 6 - Impaired Functioning

Psychomotor performance and cognitive evaluation are proposed by some experts for the assessment of impaired functioning (Carter 2009). These endpoints were not measured in our assessment program Despite some controversies on the solely role of nicotine on addiction (see Section 6.2.3.5.4), it is assumed that, based on the accepted concept of associating most of tobacco addiction to pharmacokinetic and pharmacodynamic properties of nicotine, psychomotor and cognitive functioning would remain unchanged (or marginally affected) as no or limited differences were observed between THS and CC, with respect to nicotine pharmacokinetic (see Section 6.2.3.4.4) and product pharmacodynamic (see Section 6.2.3.5.4) properties.

No notable differences were observed for nicotine withdrawal symptoms in THS vs. CC (see more details in Section 6.2.3.8.)

There were no signals from adverse events associated with or related to THS suggesting impaired functioning different from CC (More details in Section 6.2.3.9.2).

In terms of impaired functioning and based on limited data at hand, it is assumed that THS abuse liability is not different from CC.

6.2.3.8. ALA Domain 7 - Physical Dependence

The FTND questionnaire is discussed in Section 6.2.3.5.3 as it accounts also for psychosocial determinants of tobacco dependence.

The Minnesota nicotine withdrawal scale (MNWS) questionnaire is considered for the assessment of physical dependence and was administered in the four reduced exposure clinical studies. MNWS Score 1 is based on nine validated questions and Score 2 on six additional questions thought to be associated with nicotine withdrawal. The 24-hour recall questionnaire was completed by the subjects. MNWS was administered daily in the 5-day clinical studies with MNWS total score, score 1 and score 2. MNWS score 1 only was used in the 3-month clinical studies, daily during the confinement period and then at each monthly visit. More details can be found in Module 6, Section 6.2.2.

Consistently across the 4 studies, the MNWS scores increased sharply upon smoking cessation, with a peak after 1 to 2 days of smoking abstinence, and usually returning to baseline values with 1 week (1 month in ZRHM-REXA-04-JP).

In the 5-day studies (THS Regular vs. CC, exclusive use), the daily time course of MNWS scores was similar for THS and CC arms. There were no statistically significant differences between the two arms, based on the analysis of 95% confidence intervals.

In the 3-month studies (THS Menthol vs. menthol CC), the time course of MNWS scores was similar for THS and CC arms, in the per-protocol population (i.e., predominantly THS users in the THS arm). There were no statistically significant differences between the two arms, based on the analysis of 95% confidence intervals.

In conclusion, there were no notable differences in MNWS scores between subjects who switched to THS use (both menthol and regular variants) and subjects who continued to smoke CC, i.e., no changes in physical dependence were observed, thus suggesting an abuse liability for THS similar to CC with respect to physical dependence.

6.2.3.9. ALA Domain 8 - Adverse Events

Adverse events (AEs) were monitored during the course of all clinical studies. Apart from cough assessment, there were no specific AEs of special interest to be reported and monitored. Adverse events spontaneously reported by respondents in market research tests with THS use, by study participants enrolled in the THS-PBA-07-US study and by THS consumers in postmarket settings were collected and assessed. AEs and other safety evaluations are described in details in Module 6, Section 6.1.5.

Reported adverse events are considered from two point of views. On one hand, there are aversive adverse events which may refrain smokers to switch to THS, or non-smokers to initiate use, such as events which may be seen as cumbersome or annoying (e.g., nausea, vomiting, dizziness, coughing, and throat irritation). However, such events are also likely to occur when never-smokers initiate CC smoking. When initiating smoking, tolerance to aversive adverse events develops and/or certain events become part of the smokers "normal life" (see as an example cough as described in Module 6, section 6.1.5). On the other hand, there are events, mainly belonging to the central nervous system or to the psychiatric system, which are signals for substance abuse or which are seen as desirable by some smokers (e.g., looking for a "high" or for improved cognitive / psychomotor performance). Similarly, there is a tenuous threshold between pleasure and pain, the enjoyable respiratory tract sensations vs. throat irritation being a typical example.

6.2.3.9.1. Aversive Adverse Events

Nausea and dizziness are two symptoms which are articulated in the MCEQ questionnaire (See Section 6.2.3.5.2). The aversion MCEQ subscale for THS was reported in clinical studies as not different to CC, except in study ZRHR-REXC-03-EU (higher), which may put in perspective with higher (+12%) nicotine exposure. Such correspondence between aversion and nicotine exposure was not observed at five days with THS Menthol flavor, suggesting some interactions with menthol and its pharmacological properties (see FDA's opinion, in Section 6.2.3.2.2).

Nausea, vomiting and dizziness were reported in some of the clinical studies (often as related to THS use) for both THS regular and menthol variants, with within-study incidence rates from 1.3% to 11.3%. Surprisingly, in study ZRHR-REXC-03-EU reporting a higher score in aversion subscale in THS vs. CC, dizziness was not reported as an AE, and nausea/vomiting was only reported in the smoking abstinence arm.

Nausea and dizziness were among the most often reported AEs in passive surveillance (in WOT studies, except the WOT study conducted in Japan where safety data were not collected, and in THS-PBA-07-US, see details in Section 6.1.5.7). Nausea represents 10.1% and 5.8% of all AEs spontaneously reported by THS Regular users and THS Menthol users, respectively, while dizziness was 2.6% and 4.7% of all reported AEs, respectively. No definite conclusion could be made on the potential role of the menthol

flavor on reducing the incidence of aversive adverse events as, for the AE showing the greatest apparent difference, i.e. nausea, the proportional reporting rate THS Regular / THS Menthol is 1.8 when using premarket safety surveillance data and 2.8 when using safety data limited to THS-PBA-07-US, i.e., below the threshold of 3 to 5, from spontaneously reported AEs, usually accepted for the determination of a safety signal associated with a product (Evans 2001).

Other AEs and health complaints, such as cough, throat irritation and dry throat may also be part of aversive adverse events, which may overall contribute to the lower satisfaction observed during the initial use of THS, as reported in clinical studies. They could also have played a negative role on the THS use rate in THS-PBA-07-US.

6.2.3.9.2. Nervous System Disorders and Psychiatric Disorders

Very few AEs suggesting reinforcing substance abuse were reported in clinical studies, with two cases of dysphoria in ZRHR-PK-02-JP, one case of abnormal dreams during the first week of use in study ZRHM-REXA-07-JP. Psychiatric disorders and nervous system disorders usually associated with tobacco withdrawal were more likely reported upon smoking abstinence (as no pharmacotherapy options were proposed in the studies). From passive surveillance, no psychiatric disorders AEs were reported and all reported nervous system disorders AEs should be considered as aversive AEs. More details are available in Module 6, Section 6.1.5, Human Safety Summary).

Nicotine/tobacco withdrawal symptoms are described in more details in Section 6.2.3.8.

The analysis and interpretation of adverse events does not suggest differences in abuse liability THS vs. CC.

6.2.3.10. Overview on Abuse Liability Assessment

THS abuse liability was assessed in contrast to conventional cigarettes, based on the review of available information from various sources, including product design and content, chemistry, human clinical and behavioral data. THS tobacco sticks contain nicotine, a (highly) addictive substance with nicotine delivery broadly similar to CC. The nicotine exposure in humans under various use conditions, confirms the similarity of nicotine uptake THS vs. CC, indicating a similar abuse liability for THS vs. CC. The other product features (design, handling and usage limitations, and delivery of toxicants with addiction potential other than nicotine) do not seem to add an additional risk on the abuse liability on top of the nicotine (see Table 12). The consequences of THS use, in term of components associated with abuse, are not worse than with CC.

Table 12. Abuse Liability Domains Overview

Domain	Measurements	Interpretation of ALA Outcome
1. Product design	Nicotine content	THS = CC
	Menthol content	THS Menthol = CC menthol
2. Aerosol chemistry	Delivery of nicotine	THS = CC (3R4F)
	Delivery of acetaldehyde	THS < CC (3R4F)
	Delivery of ammonia	THS < CC (3R4F)
3. Pharmacokinetic effects	Nicotine pharmacokinetics single use	NRT < THS ≤ CC
	Nicotine pharmacokinetics repeated use	THS = CC
	Nicotine exposure at 3 months	THS = CC
4. Pharmacodynamic effects	Subjective effects early use	THS < CC THS regular < THS high menthol
	Subjective effects up to 3-month use	THS ≤ CC THS regular < THS high menthol
5. Reinforcing effects	Product use in clinical studies	THS ≤ CC
	Product use in near-to-real world	THS < CC
	Perception (health risks, addiction risk) and comprehension	THS = CC (smokers) THS ≥ CC (smokers with intention to quit) THS = CC (never- and former smokers)
	Intention to use by never and former smokers	THS = CC
6. Impaired functioning	Cognitive assessment	THS = CC
	Psychomotor performance	THS = CC
	Withdrawal symptoms	THS = CC
7. Physical dependence	Withdrawal symptoms short term	THS = CC
	Withdrawal symptoms up to 3 months	THS = CC
8. Adverse events	Aversive adverse events	THS = CC THS regular ≤ THS high menthol
	Nervous system disorders	THS = CC

The collected evidence indicates that CC smokers switching to THS keep their physical and/or psychological dependence to the tobacco product to a level not higher to the level associated with CC use. The tolerance to tobacco product use and/or the onset of withdrawal symptoms upon stopping the use of the tobacco product is maintained (not increased). Psychological dependence characterized by persistent tobacco-seeking and tobacco-use behaviors, impairment in behavioral control, craving, and inability to abstain

consistently) is likely unchanged. On the other side, switching to THS requires several weeks of efforts due to the intended disruptive behavior and the necessary adaptation to the product use.

The available information suggests that THS meets the IOM recommendation (see Section 6.2.3.1), for a desirable MRTP that should be more reinforcing than nicotine replacement therapies. It should be sufficiently reinforcing so as to attract smokers away from conventional cigarettes but not enough to encourage the widespread dependent use of the product by individuals who were previously nonusers, or who have quit smoking. There are two points which may require verification in the postmarket setting, as 1) smokers willing to quit smoking may want to switch to THS (at least transiently), and 2) the addiction risk is perceived as lower than CC by smokers, former smokers and never-smokers, currently not supported by the pharmacological (mainly related to nicotine) evidence collected so far.

6.2.3.11. Abuse Liability Conclusion

Based on the totality of available evidence covering abuse liability domains from THS product features, likelihood of use and consequence of use, THS shares a similar abuse liability than conventional cigarettes, and there is no significant evidence of THS attractiveness to nonusers of tobacco. The actual usage patterns and use/smoking trajectories in smokers, never-smokers, former smokers and smokers with intention to quit remain to be verified in postmarketing conditions. The abuse potential of THS should be balanced against the observed trends in biological and functional health improvements (see Section 6.1.6) as well as against the subsequent projected harm reduction to the population (see Section 6.5.6).

6.2.3.12. List of References

1. Ai 2015

   Ai J. Menthol Content in US Marketed Cigarettes; Nicotine & Tobacco Research; 2015.

2. ALCS 2010

   Altria. Background Information to the Tobacco Products Scientific Advisory Committee, Menthol Discussion; Altria; 2010. Available at http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/UCM218779.pdf. Accessed 30-May-2016.

3. Benowitz 1999

   Benowitz NL. Nicotine Chemistry, Metabolism, Kinetics and Biomarkers; Handbook of Experimental Pharmacology; 1999.

4. Berg 2015

   Berg CJ. Perceived Harm, Addictiveness, and Social Acceptability of Tobacco Products and Marijuana Among Young Adults: Marijuana, Hookah, and Electronic Cigarettes Win; Substance Use & Misuse; 2015.

5. Bodnar 2012

   Bodnar JA. Mainstream smoke chemistry analysis of samples from the 2009 US cigarette market; Regulatory Toxicology and Pharmacology; 2012.

6. Carter 2009

   Carter LP. Abuse Liability Assessment of Tobacco Products Including Potential Reduced Exposure Products (PREPs); Cancer Epidemiology, Biomarkers & Prevention; 2009.

7. CDC 2012

   Centre for Disease Control and Prevention. Preventing tobacco use among youth and young adults: a report from the Surgeon General. Rockville: US Department of Health and Human Services 2012

8. Eldridge 2015

   Eldridge A. Variation in tobacco and mainstream smoke toxicant yields from selected commercial cigarette products; Regulatory Toxicology and Pharmacology; 2015.

9. Evans 2001

Evans SJ. Use of proportional reporting ratios (PRRs) for signal generation from spontaneous adverse drug reaction reports; Pharmacoepidemiology and Drug Safety; 2001.

10. Fagerström 2012

Fagerström K. Determinants of Tobacco Use and Renaming the FTND to the Fagerström Test for Cigarette Dependence; Nicotine & Tobacco Research; 2012.

11. FDA 1990

Subcommittee on Guidelines for Abuse Liability Assessment, Drug Abuse Advisory Committee, Food and Drug Administration, U.S. Public Health Service. Draft Guidelines for Abuse Liability Assessment; Food & Drug Administration; 1990. Available at http://legacy.library.ucsf.edu/tid/qji52e00/pdf

12. Harrell 2015

Harrell PT. Expectancies for Cigarettes, E-Cigarettes, and Nicotine Replacement Therapies Among E-Cigarette Users (aka Vapers); Nicotine & Tobacco Research; 2015.

13. Hoffman 2013

Hoffman AC. Abuse Potential of Non-Nicotine Tobacco Smoke Components: Acetaldehyde, Nornicotine, Cotinine, and Anabasine; Nicotine & Tobacco Research; 2013.

14. IOM 2012

Committee on Scientific Standards for Studies on Modified Risk Tobacco Products; Institute of Medicine. Scientific Standards for Studies on Modified Risk Tobacco Products; Institute of Medicine; 2012. Available at http://www.nap.edu/catalog.php?record_id=13294

15. Lisko 2013

Lisko JG. Application of GC-MS/MS for the Analysis of Tobacco Alkaloids in Cigarette Filler and Various Tobacco Species; Analytical Chemistry; 2013.

16. McKinney 2011

McKinney DL. Evaluation of the Effect of Ammonia on Nicotine Pharmacokinetics Using Rapid Arterial Sampling; Nicotine & Tobacco Research; 2011.

17. RCP 2007

Tobacco Advisory Group of the Royal College of Physicians. Harm reduction in nicotine addiction, Helping people who can't quit; Royal College of Physicians; 2007.

18. SCENIHR 2016

Scientific Committee on Emerging and Newly Identified Health Risks. Final Opinion on Additives used in tobacco products (Opinion 1) Tobacco Additives I; European Commission; 2016. Available at http://ec.europa.eu/health/scientific_committees/policy/index_en.htm

19. USDHHS 2010

Department Of Health And Human Services (USDHHS) Food and Drug Administration. Guidance for Industry Assessment of Abuse Potential of Drugs; USDHHS; 2010. Available at http://www.fda.gov/cder/guidance/index.htm

20. USDHHS 2012

Department Of Health And Human Services (USDHHS) Food and Drug Administration. Modified Risk Tobacco Product Applications DRAFT GUIDANCE. USDHHS; 2012. Available at http://www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM297751.pdf

21. USDHHS 2012a

U.S. Department Of Health And Human Services (USDHHS) Food and Drug Administration. Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke; Established List [Federal Register notice]. USDHHS; 2012. Available at http://www.fda.gov/ AdvisoryCommittees/CommitteesMeetingMaterials/ TobaccoProductsScientificAdvisoryCommittee/ default.htm

22. USDHHS 2012b

U.S. Department Of Health And Human Services (USDHHS) Food and Drug Administration. Reporting Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke Under Section 904(a)(3) of the Federal Food, Drug, and Cosmetic Act, DRAFT GUIDANCE; USDHHS; 2012. Available at http://www.fda.gov/tobaccoguidance

23. USDHHS 2013

U.S. Department Of Health And Human Services (USDHHS) Food and Drug Administration. Preliminary scientific evaluation of the possible public health effects of menthol versus nonmenthol cigarettes [report]. Food and Drug Administration; 2013. Available at http://www.fda.gov/downloads/UCM361598.pdf

24. USDHHS 2014

U.S. Department Of Health And Human Services (USDHHS). The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General, 2014. Atlanta: Centers for Disease Control and Prevention (US); National Center for Chronic Disease Prevention and Health Promotion (US); Office on Smoking and Health (US); 2014. Available at http://www.surgeongeneral.gov/library/reports/50-years-of-progress/index.html

Glossary

Abbreviation	Definition
3R4F	Reference cigarette produced by the University of Kentucky
ABS	Australian Bureau of Statistics
ANDS	Alternative Nicotine Delivery Systems
ANPRM	Advance Notice of Proposed Rulemaking, FDA (U.S.)
AUC	Area under the concentration-time curve
$AUC_{(0\text{-}24\ h)}$	Area under the concentration-time curve from 0 to 24 hours
$AUC_{(0\text{-}last)}$	Area under plasma concentration-time curve from start of product use to time of last quantifiable concentration
$AUC_{(0\text{-}t')}$	Partial AUC, where t' is the subject-specific time of maximum nicotine concentration
BAT	British American Tobacco
BfR	German Federal Institute for Risk Assessment
BoExp/ BoE	Biomarker(s) of exposure. A chemical, its metabolite, or the product of an interaction between a chemical and some target molecule or cell that is measured in the human body (e.g. cotinine in blood or urine for second-hand tobacco smoke, benzene metabolites in urine for traffic-related pollution)
CC	Conventional cigarette, Combustible cigarette
CI	Confidence interval
CISPR	International Special Committee for Radio Protection
CLP	Classification, Labelling and Packaging (E.U.)
C_m	Maximum nicotine concentration
C_{max}	Maximum plasma concentration
C_{min}	Minimum plasma drug concentration
CNS	Central Nervous System
COAG	Council of Australian Government
COHb	Carboxyhemoglobin
COPD	Chronic obstructive pulmonary disease
COT	Committee of Toxicology (U.K.)
CROs	Contract Research Organisation
CTP	Center of Tobacco Products, FDA (U.S.)
CVD	Cardiovascular disease
DoH or DOH	Commonwealth Department of Health

EAC	Eurasian Conformity standards
EHTP	Electrically Heated Tobacco Product. Typically consists of a consumable product (such as tobacco sticks or *HeatSticks*) that contains tobacco which is electrically heated
EHTS	Electrically Heated Tobacco Systems
EN	European Norm standards
ENDS	Electronic Nicotine Delivery Systems
ETS	Environmental tobacco smoke. Also known as secondhand smoke, it is a complex mixture of chemicals generated during the burning and smoking of tobacco products to which a person is unintentionally exposed, most commonly in the home, formerly in public places. It comes from both the smoke from the tip of the cigarette and the smoke that the smoker is exhaling
FCTC	Framework Convention of Tobacco Control (W.H.O.)
FDA	Food and Drug Administration (U.S.)
FDA-18	Abbreviated FDA list of 18 HPHCs in smoke/aerosol
FDA-18 + 6	Abbreviated FDA list of 18 HPHCs in smoke/aerosol + 6 tobacco constituents
FDA-93	Established FDA list of 93 HPHCs in tobacco products and tobacco smoke
FEV_1	Forced expiry volume in 1 second
FFC	Federal Communications Commission (U.S.)
HC	Health Canada (including Health Canada list of 44 constituents in the mainstream smoke of tobacco products)
HCI	Health Canada Intense (puffing regime). First described by Health Canada, when taking one puff of 55 ml volume and 2 s duration every 30 s with 100 % of the ventilation zone on the cigarette filter blocked
HD	Heart Disease
HDL-C	High Density lipoprotein-C
HeatSticks	Specially designed heated tobacco consumables that contain tobacco and is intended for exclusive use with the *IQOS* holder
HNB or HnB	Heat-not-burn. Refers to tobacco that is heated instead of lit or burnt. Also referred to as a Heated Tobacco Product (HTP)
HPHCs	Harmful and potentially harmful constituent(s). Chemical compounds in tobacco products or tobacco smoke that cause or could cause harm to smokers or nonsmokers
HTP	Heated Tobacco Product. The consumable product (such as tobacco sticks or *HeatSticks*) that contains tobacco for heating
IAQ	Indoor air quality
IARC	International Agency for Research on Cancer
IC	Integrated Circuit

IEC	International Electrotechnical Commission
IOM	Institute of Medicine
iQOS and *IQOS*	Commercial names (both registered trademarks) of PMI's Tobacco Heating Device
ISO	International Organization for Standardization
JNFA	Japanese National Fire Authority
JTI	Japan Tobacco International
KT&G	Korean Tobacco & Ginseng
LOQ	Limit of Quantitation/ Quantification
MFDS	Ministry of Food and Drug Safety (Korea)
MLA	Mouse Lymphoma Assay
MRTP	Modified risk tobacco product
MRTPA	Modified risk tobacco product application
NFDPM	Nicotine-Free Dry Particulate Matter
NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
NNS	Nicotine Nasal Spray
NTDA	Non Targeted Differential Analysis
NRT	Nicotine replacement therapy
OECD	Organization for Economic Co-operation and Development
PHE	Public Health England
PK	Pharmacokinetics
PK/PD	The relationship between blood plasma nicotine (PK) concentration and suppressing the urge to smoke (PD) in adult smokers
PM USA	Philip Morris U.S.A.
PMI	Philip Morris International, which is comprised of the following entities: (1) Philip Morris International Inc., (2) Philip Morris Products S.A., (3) Philip Morris International Management S.A., (4) Philip Morris International Research Laboratories Pte. Ltd., and (5) Philip Morris Manufacturing & Technology Bologna S.p.A
PMI-58	List of constituents and analytes defined by PMI that are quantified in the THS aerosol
PML	Philip Morris Limited, the Australian Philip Morris International subsidiary
PMTA	Premarket tobacco product application
R&D	Research and Development
RCP	Royal College of Physicians (U.K.)
REX	Reduced exposure studies
REXA	Reduced exposure studies in ambulatory settings

REXC	Reduced exposure studies in confinement settings
RACGP	Royal Australian College of General Practitioners
RRP	Reduced risk product(s)
SA	Smoking Abstinence
SmPC	Summary of Product Characteristics
To	Time point of first product use during study day
"Tar"	Nicotine-Free Dry Particulate Matter (NFDPM)
THD	Tobacco Heating Device (Holder and Charger)
THS	Tobacco Heating System (Tobacco Heating Device + HTP/Tobacco Sticks). Combination of consumable product (HTP) plus heating device. Also referred to as an EHTS (Electrically Heated Tobacco System) if the heat source is electronic.
Tobacco Sticks	Tobacco containing sticks (resembling cigarettes) manufactured to be used as part of the THS. May also be sometimes referred to as Heat Sticks.
T_{max}	Time to the maximum concentration
TPM	Total particulate matter
TSNA	Tobacco-specific N-nitrosamines
Type II Error	A Type I error is the rejection of a true null hypothesis, whereas Type II error describes the error that occurs when one fails to reject a null hypothesis *that is actually false.* In other words, it produces a false positive. The error rejects the alternative hypothesis, even though it does not occur due to chance.
UL	Underwriters Laboratories standards
US SURG	United States Surgeon General
WBC	White blood cell (count)
WHO	World Health Organization