



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

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May 2015

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CONFIDENTIALITY

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

APPLICANT'S DETAILS

- | | | |
|---|---|--|
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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.



Tammy Chan
Managing Director – 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) **in tobacco prepared and packed for heating.**

[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: C₁₀H₁₄N₂

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.

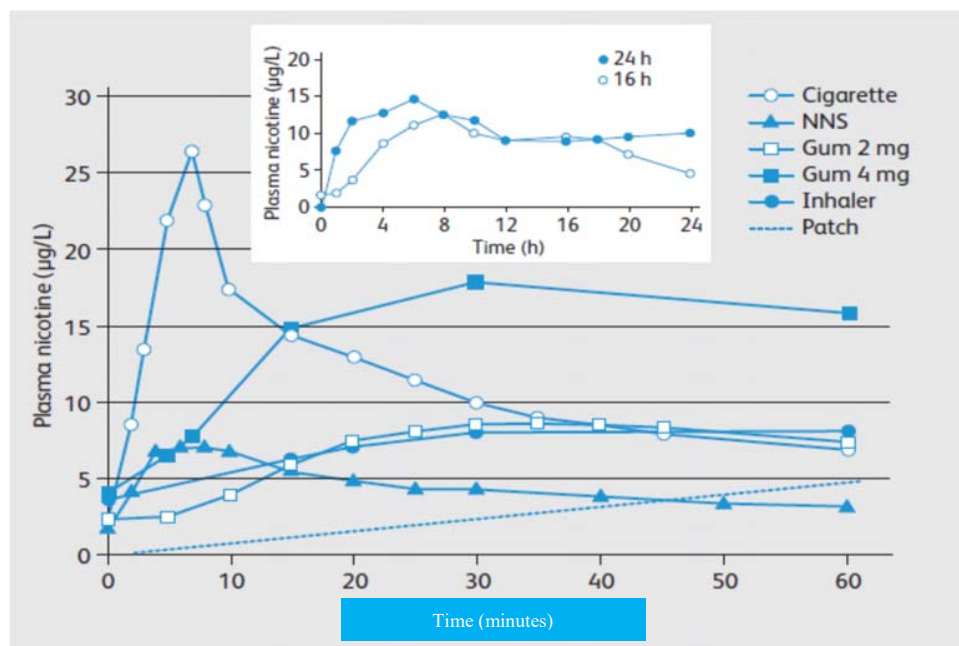


Figure 1: Venous plasma nicotine concentrations of nicotine and various NRTs

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 NRT³. 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.

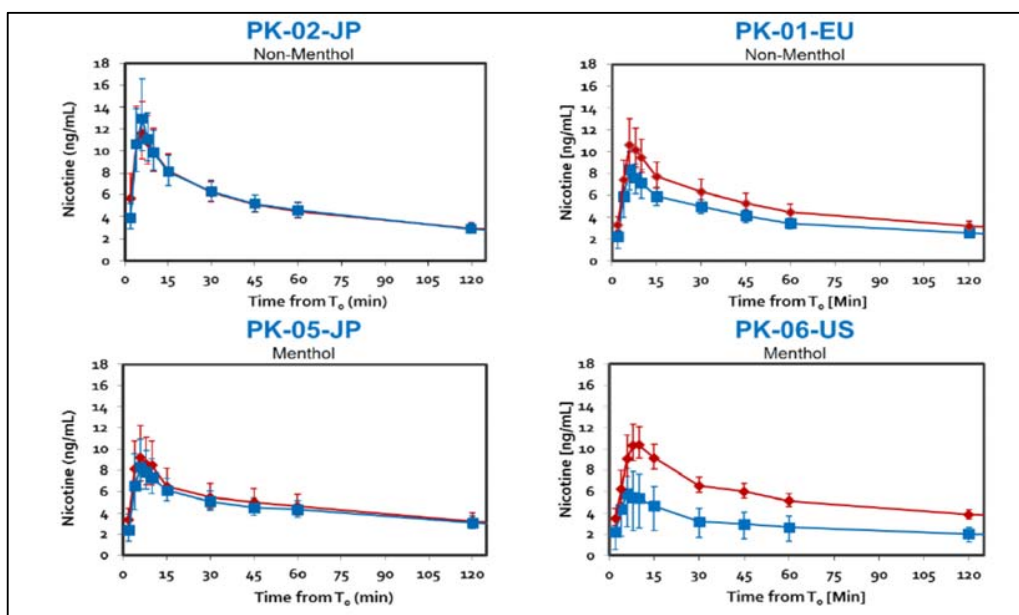


Figure 2: Geometric means and 95% confidence intervals of nicotine concentrations over 120 minutes with a single use of the THS or cigarette in Japan (JP), US, and Europe (EU) using EHTP Menthol or Regular. T_0 equals start of product use.

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 2014-15⁴ and 2017-18⁵ 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 HTPs⁷⁸ by measuring nine HPHCs⁹, 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 HTP¹¹ 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.pmscience.com/resources/docs/default-source/news-documents/pmi-tpsac_final-sponsor-presentation.pdf?sfvrsn=15dce06_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 2017¹⁴ 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)

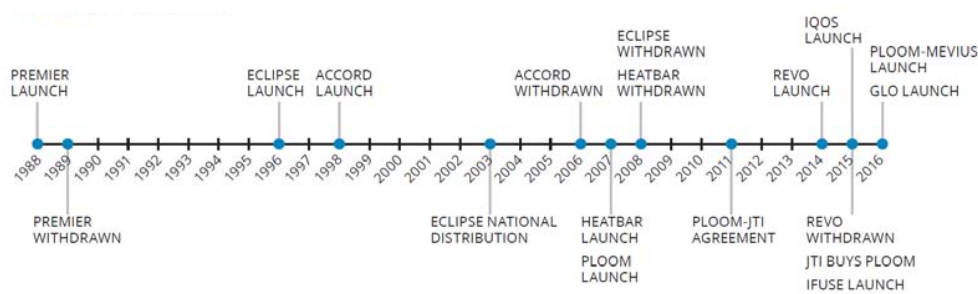


Figure 3: HTP Timeline

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 950°C. Immediately behind is the pyrolysis zone, where the temperatures are lower (200-600°C) 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
<p>The nicotine in HTPs present no additional risk over CCs.</p> <p>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.</p> <p>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.</p> <p>Nicotine content in HTPs is necessary for smokers to switch from cigarettes, if they do not quit nicotine entirely.</p> <p>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.</p>
Justification for the risk/benefit analysis
<ul style="list-style-type: none"> ○ 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: “<i>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</i>” (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

Risk Issue: HTP aerosol still contains HPHCs and other chemicals

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.

- 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.
- 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).
- **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 to quantify 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](#)).

- **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.
 - 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](#)).
 - 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 MRTTP 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
<p>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:</p> <ul style="list-style-type: none"> • 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. <p>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 :</p> <ul style="list-style-type: none"> • have generally low attractiveness to never smokers and former smokers; • do not generally interfere with quitting intent; and • have generally low attractiveness to youth. <p>In addition, HTPs would need to comply with a comprehensive framework of applicable Federal, State and Territory tobacco control laws.</p>
Justification for the risk/benefit analysis
<p>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.</p> <ul style="list-style-type: none"> ○ 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
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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).

- **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
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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
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- **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 daily¹⁹ 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).

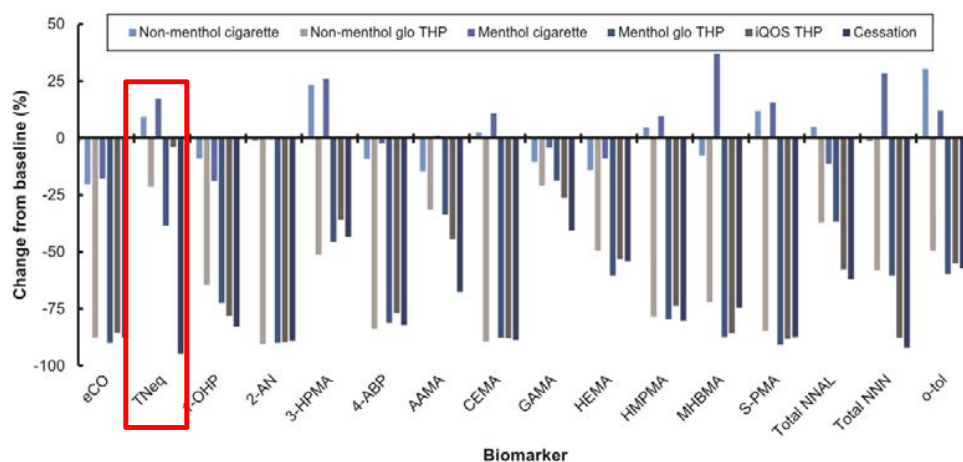


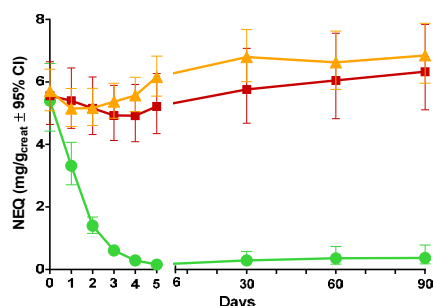
Figure 4 - Biomarker of exposure changes between baseline and days 6–7.

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.

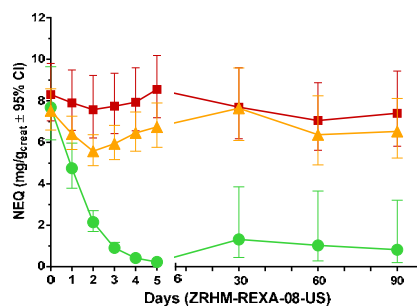
Abbreviations: eCO, exhaled carbon monoxide; TNeq, total nicotine equivalents (nicotine, cotinine, 3-hydroxycotinine and their glucuronide conjugates); 1-OHP, 1-hydroxypyrene; 2-AN, 2-aminonaphthalene; 3-HPMA, 3-hydroxypropylmercapturic acid; 4-ABP, 4-aminobiphenyl; AAMA, N-acetyl-S-(2-carbamoyl) cysteine; CEMA, 2-cyanoethylmercapturic acid; GAMA, N-acetyl-S-(2-hydroxy-2-carbamoyl) 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-nitrosornicotine; 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**).

Nicotine Uptake – 3 month Reduced Exposure Study in Japan



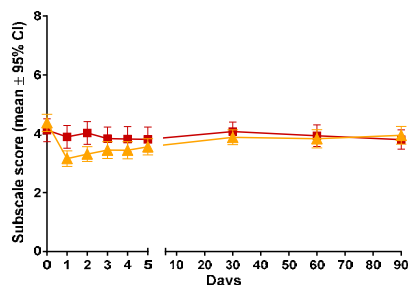
Nicotine Uptake – 3 month Reduced Exposure Study in the US



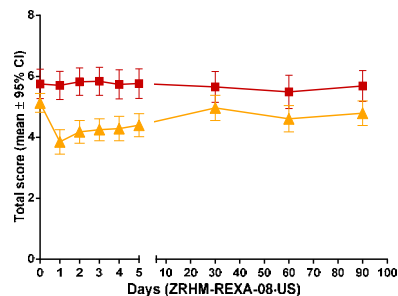
▲ HTP ■ Cigarettes ● SA

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

Product Satisfaction – 3 month Reduced Exposure Study in Japan



Product Satisfaction – 3 month Reduced Exposure Study in the U.S.



▲ HTP ■ Cigarettes

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).

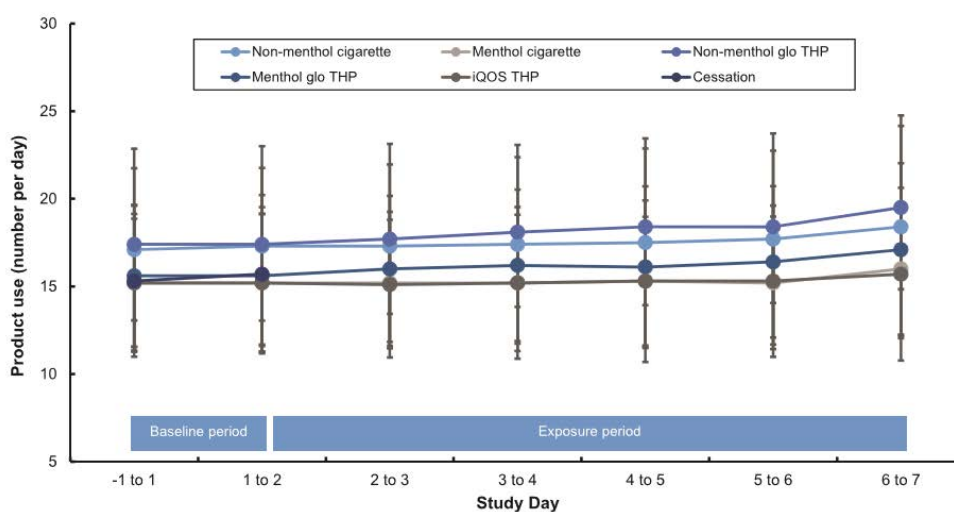


Figure 7 - Tobacco product consumption during the study. Data are mean (±SD) numbers of cigarettes smoked/tobacco heating product (THP) consumables used during each study day. N.B. the product use (numbers per day) were zero in the Cessation group during the confinement period.

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).

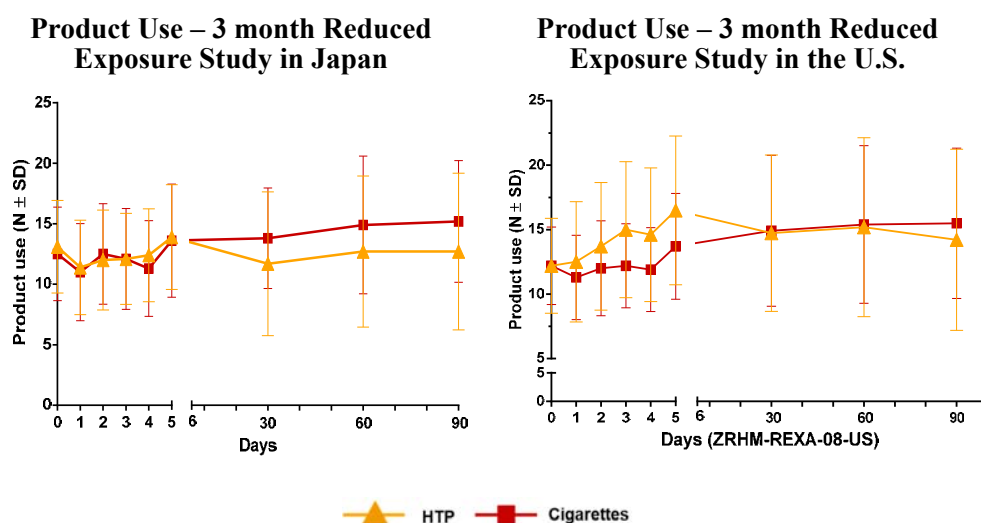


Figure 8 - Product Use of an HTP in 3 month Reduced Exposure studies in Japan and the U.S.

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/m³ (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.

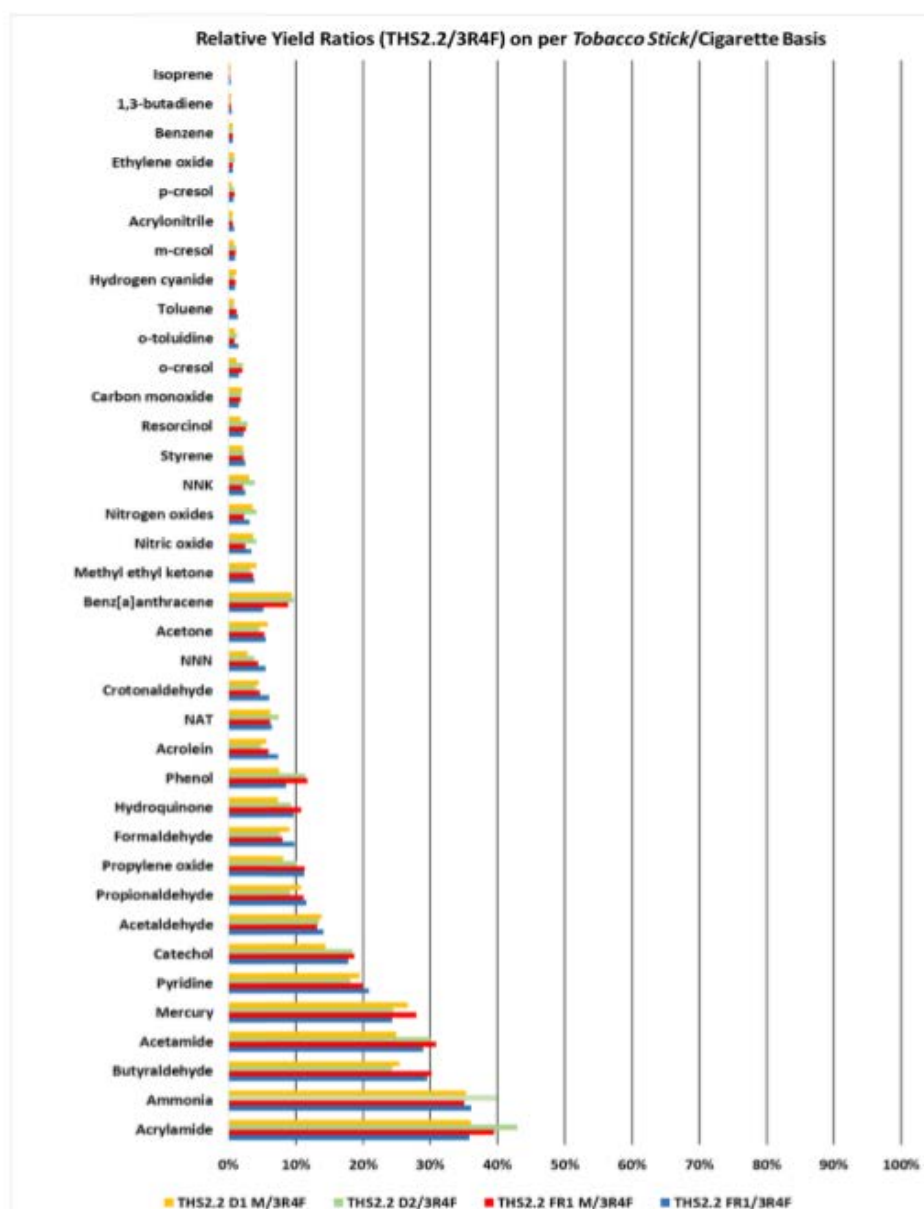


Figure 9. Mainstream aerosol levels (set at 100%) on a per-unit basis under the Health Canada Intense (HCI) puffing regime for HPHCs from PMI's HTP compared to the mainstream smoke HPHCs from the 3R4F reference cigarette.

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-nitrososornicotine).

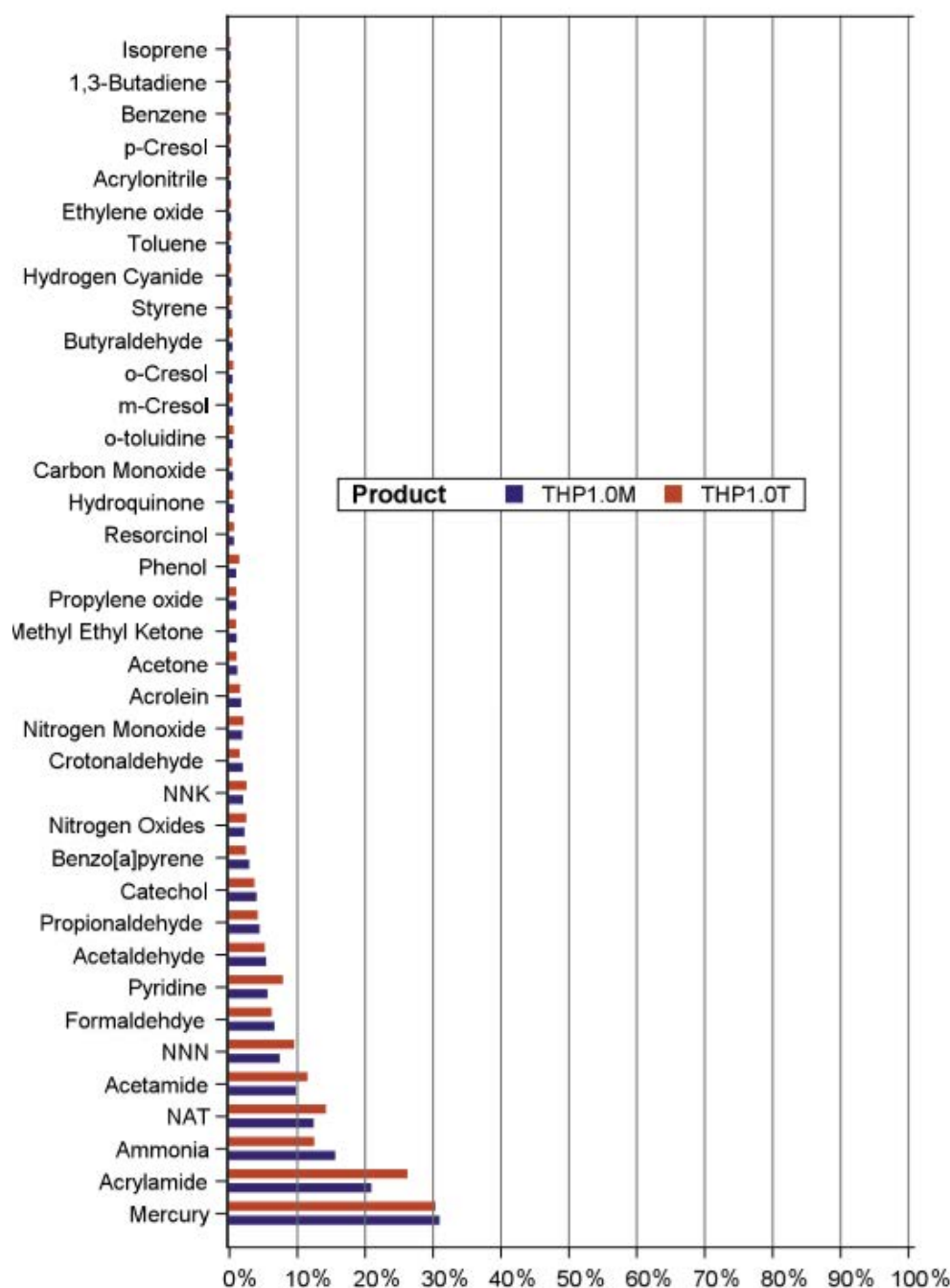


Figure 10. Relative abundances of mainstream HPHCs in THP1.0 (BAT) and 3R4F per consumable or cigarette generated using the HCI puffing regime.

(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](#).

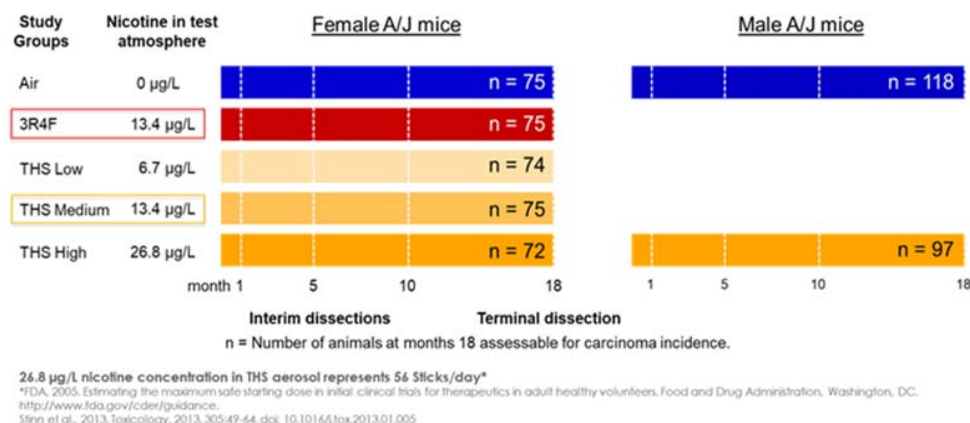
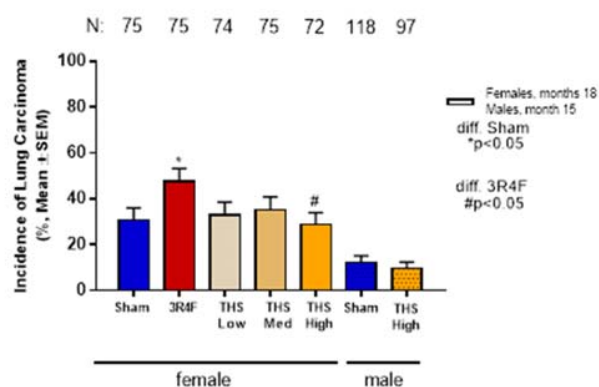


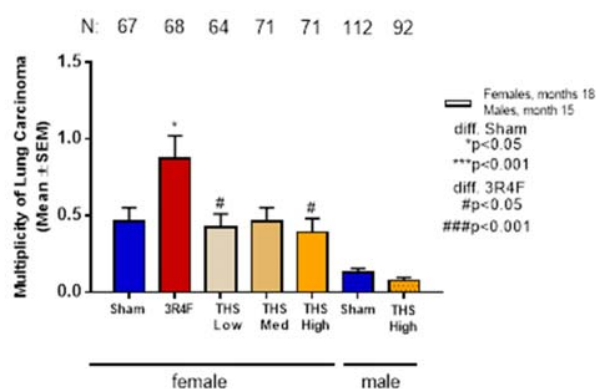
Figure 11: Study Design 18-month chronic toxicity and carcinogenicity study in A/J mice

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.

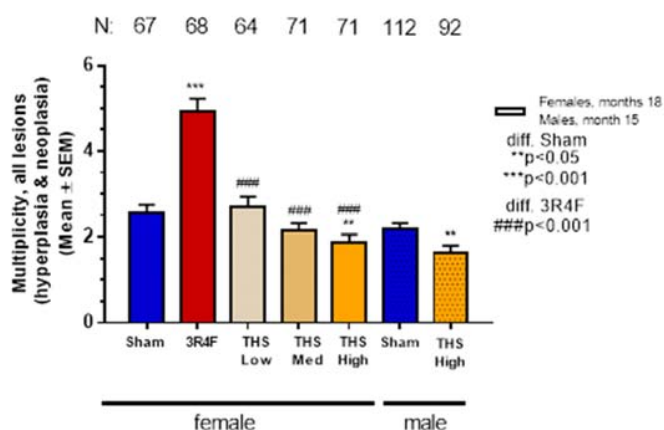


Figure 13: Multiplicity, all lesions: nodular hyperplasia, bronchoalveolar adenoma and carcinoma, terminal dissection.

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:
 - o 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.
 - o 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-PGF2 α) 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](#)).
 - o 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.

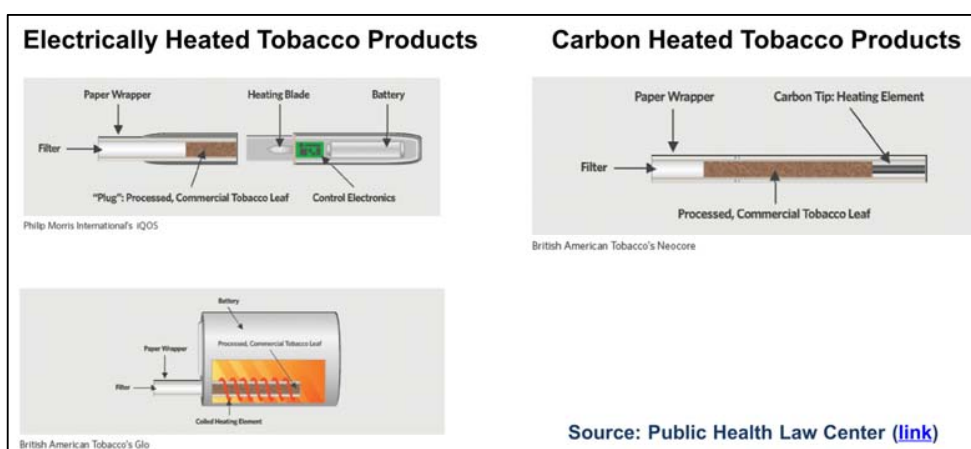


Figure 14: Types of HTPs

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 PMI's 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 (health 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
5. Reinforcing effects		THS regular < THS high menthol
	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)
6. Impaired functioning	Intention to use by never- and former smokers	THS = CC
	Cognitive assessment	THS = CC
	Psychomotor performance	THS = CC
7. Physical dependence	Withdrawal symptoms	THS = CC
	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 website²² (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
<p>An online survey of users of tobacco vaporizers, reasons and modes of utilisation, perceived advantages and perceived risks.</p> <p>Study by Queloz and Etter (Queloz and Etter, 2019)</p>	<p>Responses received from:</p> <p>Switzerland (83%), France (11%), Greece (1%), Italy (1%), Russia (1%), Norway (1%), Canada (1%).</p>	<p>An online questionnaire collected from October 2016 to January 2018 in self-selected visitors aged >18 to an anti-addiction website operated in Switzerland.</p> <p>Survey sample: 170 valid responses, out of whom 104 were users of tobacco vaporizers.</p> <p>For homogeneity, only 102 users of the Brand 1 tobacco vaporizer were included in analysis, as there were only two users of other vaporizers.</p> <p>Note: it is clear from the study that the product identified as "Brand 1" is PMI's IQOS.</p>	<ul style="list-style-type: none"> • 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). <p>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</p>

			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	<p>A paper-pencil self-administered standardized question survey with two versions of the survey:</p> <ul style="list-style-type: none"> - a short survey intended for those aged 11-13, and - a long survey intended for students from 14-15. <p>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.</p> <p>The dataset for 2018 includes data from 11,121 pupils aged 11 to 15 years.</p> <p>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.</p>	<ul style="list-style-type: none"> • 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 nationwide 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.

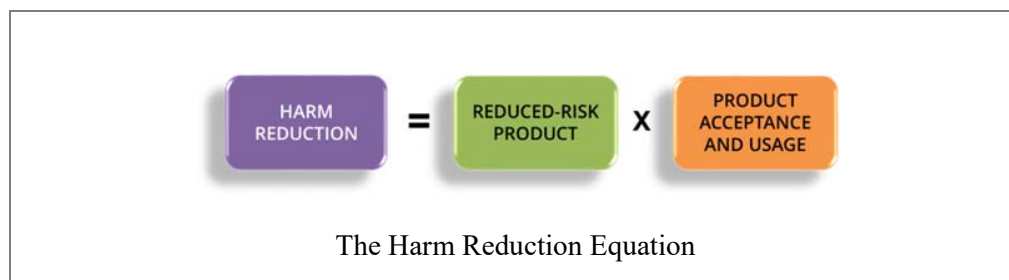


Figure 15 - The Harm Reduction Equation (Figure adapted from Clive Bates presentation to E-Cigarette Summit (19 Nov 2013))

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](#)).

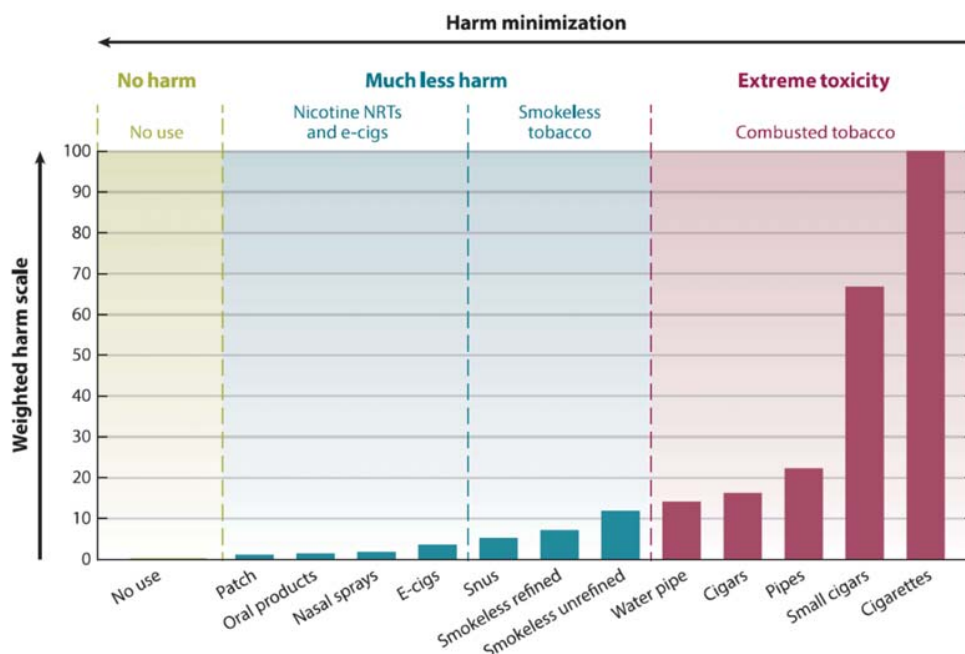


Figure 16: Products along the harm minimisation continuum. Depicts four panels representing classes of products: “Products containing tobacco are depicted as “combusted” or “smoked” (panel 1, right) and “non-combusted” or “smokeless” (panel 2, right middle). Smokeless products are far less harmful than 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 Health²⁴.

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 claim²⁵. 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 ANDS²⁷ 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 Commissioner, 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.