MRTPA

Section 2.7 Executive Summary

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Overview of Chapter 2.7

Chapter 2.7 presents a summary of this application as recommended in Section VIII (A)(2) of the FDA Draft Guidance for Modified Risk Tobacco Product Applications (MRTPA) (FDA 2012). Chapter 2.7 describes aspects of the application and summarizes the scientific findings with sufficient detail to enable a good general understanding of the data and information contained in the application. Chapter 2.7 is organized into seven sections:

2.7.1 Executive Summary of the Application

2.7.2 Proposed Modified Risk and Modified Exposure Claims

2.7.3 Modified Risk Tobacco Products and Harm Reduction

2.7.4 Product Description and Scientific Rationale

2.7.5 PMI Scientific Program for the Assessment of THS

2.7.6 The Scientific Basis for Modified Risk Tobacco Product Orders for THS

- Part A is the scientific framework and contains the results that demonstrate that the THS product will "significantly reduce harm and the risk of tobacco-related disease to individual tobacco users"
- Part B is a summary of the scientific work to demonstrate that the product will "benefit the health of the population as a whole, taking into account both the users of tobacco products and persons who do not currently use tobacco products"

2.7.7 Summary of Findings that Support a Modified Risk Tobacco Product Market Order

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2.7.1 EXECUTIVE SUMMARY

Philip Morris International (PMI[1]) is submitting this application under Section 911(g) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) requesting market orders under both §911(g)(1) (risk modification order) and §911(g)(2) (exposure modification order) for its novel Tobacco Heating System (THS), to be marketed as "*iQOS*[2]". PMI is submitting this application for THS as a Modified Risk Tobacco Product (MRTP) with three different variants, Marlboro *HeatSticks*, Marlboro Smooth Menthol *HeatSticks*, and Marlboro Fresh Menthol *HeatSticks*. This application provides the necessary information to support a marketing order for an MRTP with these claims (Section 2.7.2):

- Claim #1 under §911(g)(1): "Switching completely from cigarettes to the *iQOS* system can reduce the risks of tobacco-related diseases".
- Claim #2 under §911(g)(1): "Switching completely to *iQOS* presents less risk of harm than continuing to smoke cigarettes".
- Claim #3 under §911(g)(2): "Switching completely from cigarettes to the *iQOS* system significantly reduces your body's exposure to harmful and potentially harmful chemicals".

Background and Motivation

PMI recognizes that cigarettes are a dangerous product. Smokers are far more likely than nonsmokers to get heart disease, lung cancer, chronic obstructive pulmonary disease (COPD) and other diseases. It is well known that the best way to avoid the harms of smoking is never to start, and for smokers, the best way to reduce the harms of smoking and the risk of tobacco-related disease is to quit. For decades, the goal of reducing the harm caused by smoking has therefore relied on preventing smoking initiation and promoting smoking cessation.

However, smoking is addictive. While smoking cessation is one of the pillars of tobacco harm reduction, smoking cessation has proven difficult for many smokers. Although the smoking prevalence in the United States (US) has declined from 21% to 17% over the last decade, an estimated 40 million people currently smoke cigarettes in the US (CDC 2015). Cigarette smoking is the leading cause of preventable disease in the US,

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[1] We refer to Philip Morris International ("PMI") throughout this application. For clarity and ease of review, all of the following entities are included within the term "PMI": (1) Philip Morris International Inc., the general entity; (2) Philip Morris Products S.A., the MRTP applicant and the legal entity responsible for clinical trials and post marketing studies and surveillance, (3) Philip Morris International Management S.A., the legal entity responsible for market research and management services, (4) Philip Morris International Research Laboratories Pte. Ltd. responsible for pre-clinical *in vivo* studies, and (5) Philip Morris Manufacturing & Technology Bologna S.p.A. responsible for the manufacture of Tobacco Sticks. If you would like confirmation as to which entity is referenced, please let us know, and we will provide the information.

[2] THS will be commercialized under the "*iQOS*" and "IQOS" brand names, both of which are registered trademarks.

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accounting for more than 480,000 smoking-related deaths every year, and more than 16 million Americans live with a smoking-related disease. (HHS 2014). Consequently, there is an unmet need for alternative methods to reduce harm and smoking-related disease for over 40 million American smokers and one billion smokers worldwide who continue to smoke (IOM 2012).

In an effort to accelerate the decline in smoking prevalence and smoking-related population harm, Tobacco Harm Reduction is increasingly recognized as a valuable and promising approach. Tobacco Harm Reduction is based on switching smokers to markedly less harmful tobacco and nicotine products, or MRTPs.

PMI is convinced that this approach can contribute significantly to the improvement of public health, and has recently announced its goal to lead a full-scale effort to ensure that MRTPs ultimately replace cigarettes. Indeed, PMI envisions a smoke-free world where a broad range of MRTPs fully satisfies the continuing consumer demand for tobacco and nicotine products.

Towards this end, PMI has developed the THS system, to be marketed as "*iQOS*". The THS system consists of a device that heats, but does not burn, a proprietary Tobacco Stick ("*HeatSticks*"), creating an inhalable nicotine-containing aerosol that provides a range of consumer sensory attributes that appeal to adult smokers. The THS aerosol has significant reductions in, or absence of, toxicants when compared to cigarette smoke. For a smoker who switches to THS from cigarettes, this reduction in exposure to toxicants provides the foundation for the reduced harm rationale for this product as an MRTP. The product, if authorized by the Agency, will be marketed as a modified risk alternative to combusted/conventional cigarettes (CC).

Section 911(g)(1) of the FD&C Act states that the Food and Drug Administration (FDA) may issue a modified risk market order for a tobacco product if the sponsor satisfies a two-part "basis for approval". The applicant must demonstrate that the product "*as it is actually used by consumers, will (a) significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and (b) benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products*." (FDA 2012).

As the FDA has noted in its Draft Guidance, there is a substantial breadth of evidence necessary to support an order under Section 911(g). Accordingly, the Agency "*recommends that applicants provide information from a number of studies of different types in order to address the full range of areas of investigation set forth in section 911 of the FD&C Act*" (FDA 2012). For example, the Agency states that applications should include "*product analyses, nonclinical studies, studies in adult human subjects, and secondary data analyses and modeling*" (FDA 2012). PMI conducted extensive research in each of these areas and more. The totality of the scientific evidence generated for this application demonstrates that the THS product meets the two-part "basis for approval" under Section 911(g) of the FD&C Act and supports the issuance of a market order authorizing the marketing of THS as an MRTP.

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A. Reduction in Harm and the Risk of Tobacco-Related Disease to Individual Tobacco Users

PMI must demonstrate that THS, *"as it is actually used by consumers, will significantly reduce harm and the risk of tobacco-related disease to individual tobacco users"* (FDA 2012).

Smoking-related harm and disease are directly caused by the long-term exposure to the toxicants found in combusted tobacco smoke (HHS 2010). Consequently, smoking cessation is the most effective way to reduce the harm and risk of tobacco-related disease. This is because cessation eliminates the exposure to the Harmful and Potentially Harmful Constituents (HPHCs) contained in the smoke. Smoking cessation has therefore been referred to as the "gold standard" for the assessment of candidate MRTPs such as THS (IOM 2012).

Based on these principles, the assessment of THS needs to demonstrate that switching to THS leads to a reduction in exposure to HPHCs, which in turn leads to a significant reduction in harm. This reduction in harm is demonstrated when the biological effects of switching to THS approach those of smoking cessation.

With these principles in mind, we designed our multi-step THS assessment program.

The first step in the assessment program was the chemical characterization of the aerosol generated by THS, which confirmed that THS aerosol contains substantially reduced levels of HPHCs (~90% overall reduction) compared with CC smoke. Furthermore, we evaluated the effect of THS use on indoor air chemistry, to assess the potential exposure of nonusers of tobacco products to HPHCs. Indoor air chemistry studies were conducted to determine the concentrations of 18 different analytes under standardized indoor environmental conditions (residential, office, hospitality). Only nicotine and acetaldehyde were detected above baseline levels and their concentrations were well below threshold levels for chronic exposure under a variety of US and international exposure standards.

Second, three *in vitro* and two *in vivo* studies were conducted, using standard methods in toxicology, to compare the effects of THS aerosol with those of cigarette smoke. These studies showed a consistent and remarkable reduction in cytotoxicity, genotoxicity, respiratory organ toxicity and systemic toxicity of THS aerosol compared with cigarette smoke.

Third, advanced non-clinical systems toxicology enabled the detailed comparison of the effects of cigarette smoke and THS aerosol on biological mechanisms related to the causation of tobacco-related diseases. These studies employed computational methods to analyze a broad array of comprehensive molecular measurements (transcriptomics, proteomics, lipidomics), in addition to the standard measurements used in toxicity studies and the evaluation of disease endpoints in animal models of disease (emphysema, lung function and atherosclerotic plaque size).

Six systems toxicology studies are reported in this application. They cover a variety of human-derived *in vitro* model systems comparing the impact of THS aerosol with that of cigarette smoke on vascular inflammation, endothelial dysfunction and airway epithelium toxicity. These studies showed that THS aerosol exposure leads to significantly and

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consistently reduced perturbations of all biological mechanisms affected by cigarette smoke exposure. These mechanisms included oxidative stress, inflammation, DNA damage, xenobiotic metabolism and cell death.

One systems toxicology study was conducted *in vivo* using Apoe$^{-/-}$ mice, an animal model of disease that permits the concomitant assessment of atherosclerotic plaque growth, pulmonary function and emphysema. This 8-month study demonstrated that animals switched from cigarette smoke to THS aerosol exposure showed significant and consistent reductions of molecular changes, mechanistic perturbations and disease endpoints compared with the animals continuously exposed to cigarette smoke. The magnitude of the reductions observed in the animals switched from cigarette smoke to THS aerosol exposure was not different from that measured in animals in the smoking cessation group (animals switched to fresh air exposure).

Furthermore, lung inflammation, emphysema, and lung function measurements assessed in a chronic toxicity study in A/J mice showed significantly lower effects in THS aerosol exposed mice than in smoke exposed animals. The pulmonary outcomes in THS aerosol exposed mice were not different from those obtained in air exposed animals.

Fourth, clinical studies were conducted with adult smokers to evaluate the effects of switching from cigarette smoking to THS use. In these four studies conducted in the US, Europe and Japan, adult smokers were randomized to either continue smoking their usual cigarettes, completely switch to THS use, or smoking abstinence for a period ranging from five days (short-term studies in confinement) to three months (longer-term studies in ambulatory mode). Smokers who completely switched to THS showed a reduction in the 15 measured biomarkers of exposure (BoExp) to HPHCs and improvements in the six measured clinically relevant risk markers linked to mechanistic pathways involved in smoking-related diseases. For instance, the exposure reduction achieved by switching to THS preserved on average >90% of the exposure reduction observed in smokers who abstained from smoking for the duration of the studies. These results confirm that the reduced formation of HPHCs by THS leads to a reduced exposure in adult smokers, which in turn leads to an improvement of clinical risk markers.

Across all non-clinical studies, whether conducted *in vitro* or *in vivo,* the results were consistent and showed that THS aerosol exposure causes significantly less toxicity and overall adverse biological effects than exposure to cigarette smoke. These studies also confirm that THS aerosol does not introduce any new or increased risks compared with tobacco smoke. Furthermore, in all switching studies, whether conducted in animal models of disease or in clinical settings, the results consistently showed that the biological impact of switching to THS aerosol was directionally aligned with, and of similar magnitude, to smoking cessation.

The weight of evidence that THS *significantly reduces harm and the risk of tobacco-related disease to individual tobacco users* is compelling. The observed effects of switching from cigarettes to THS are globally consistent with the expectations set by the "gold standard" of smoking cessation, both in terms of magnitude and direction of the observed changes. All study results are consistent with findings from previously published clinical studies and plausible mechanisms of disease causation, including

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oxidative stress, inflammation, DNA damage, xenobiotic metabolism and cell death. Moreover, the accumulated evidence is coherent across human clinical studies, animal studies, human-derived *in vitro* models (cell cultures, organotypic tissue cultures) and *in vitro* toxicity tests.

B. Benefit the Health of the Population as a Whole

PMI must demonstrate that THS, "*as it is actually used by consumers, will benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products*."

In addition to significantly reducing the risk of tobacco-related diseases to smokers who switch to an MRTP, several important considerations will ensure that the product benefits the health of the population as a whole, including:

1. The relative and absolute health risks of using an MRTP must be accurately communicated to the public.
2. An MRTP should not increase initiation among non-users of tobacco products, and hence should not appeal to former users and never users.
3. An MRTP should not have a significant impact on the decision of a smoker who would otherwise quit smoking.
4. An MRTP should be sufficiently acceptable by and attractive to smokers to facilitate complete switching from cigarettes.
5. An MRTP must be easy to use and designed to prevent misuse.
6. The marketing of an MRTP should lead to a substantial and measurable reduction in the overall morbidity and mortality among individual tobacco users.

To address the first five objectives, PMI conducted nine Perception and Behavior Assessments (PBA) studies in the US.

First, to inform the public about the absolute (versus cessation) and relative (versus smoking) health risk of using THS, PMI developed and tested three scientifically accurate communications (proposed claims with associated warnings). Two communications were developed to convey that THS, while not risk free, is a lower risk alternative for smokers. The assessment of these two reduced risk communications demonstrated that two thirds of the consumers understood correctly that using THS is not risk free but presents less risk than cigarettes. A third communication (reduced exposure to HPHCs) was developed to convey that THS reduces exposure to HPHCs, but has not been demonstrated to reduce the risk of developing tobacco-related diseases compared with smoking cigarettes. The assessment of this communication showed that approximately two thirds of the consumers were able to comprehend that using THS would reduce their exposure to HPHCs. Consumers who were shown an explicit warning stating that the risk of tobacco-related disease had not been demonstrated were less likely to overestimate the potential of THS to reduce smoking-related disease. This highlights the importance of an explicit warning statement for the correct comprehension of the claim. Consistently, findings from the studies conducted on risk perception demonstrated

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that the perceived risk associated with THS is lower than cigarettes, which is the most hazardous tobacco product, and higher than Nicotine Replacement Therapies (NRTs) or Cessation.

Second, a series of PBA studies assessed the likelihood of initiation among non-users of tobacco products. Overall, these studies demonstrated that THS is not attractive to adult never smokers and it is minimally attractive to adult former smokers. Approximately 6% of adult former smokers and less than 1.2% never smokers expressed an intention to use THS.

Third, the same PBA studies also show that the THS communication did not have a significant effect on the intention of adult smokers with an intention to quit smoking. Additionally, they understood that THS is not a substitute for cessation.

Fourth, a combination of clinical and PBA studies showed that THS is an acceptable alternative to cigarettes for adult smokers. While PK/PD studies indicated that the nicotine delivery profile of THS is similar to that of cigarettes, the short-term (in confinement) and longer-term (in ambulatory mode) clinical studies showed that THS and cigarettes deliver nicotine at comparable levels and that THS effectively reduces the urge-to-smoke in a manner similar to cigarettes. These studies also indicated that THS had very similar scores for aversion, craving reduction, respiratory tract sensation, psychological reward and smoking satisfaction compared with cigarettes. Furthermore, an actual use study showed that after 6 weeks, approximately 15% of the study participants had switched from cigarettes to either exclusive or predominant use of THS. Finally, the availability of THS did not lead to an increase in their total tobacco product consumption.

Fifth, the actual use study also showed that there was a low level of misuse of THS, which, in combination with the results from a study assessing usability and comprehension of THS instruction for use, indicates that THS will be used as intended/designed.

Concerning the effect that marketing of THS may have on the health of the US population as a whole, the FDA has encouraged the inclusion of computational models to estimate the potential changes (positive or negative) in public health caused by the market introduction of an MRTP. PMI has developed and tested a Population Health Impact Model (PHIM) using well-established methods in mathematical modeling and simulation analysis. Using the likelihood of use based on hypothetical scenarios, combined with changes in relative disease risk predicted by the non-clinical and clinical data (i.e. reduction in probability of tobacco-related disease when switching from cigarette smoking to THS use), PMI conducted multiple simulations to evaluate the impact of introducing THS in the US market on smoking attributable deaths. The results of these simulations show that introduction of THS would result in a positive population health impact.

PMI has developed a Post-Market Assessment Program that will consist of post-market studies and data collected by passive surveillance. This program will enable the identification and collection of unanticipated and undesired events related to the use of THS after an MRTP market order is granted and the product is introduced into the US

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market. The program is also designed to capture and evaluate the impact of the product on consumer perception, behavior, and the health impact for individuals and the population as a whole. PMI will submit the findings from the Post-Market Assessment Program to FDA on an annual basis to ensure that the product continues to be of benefit to the overall health of the US population.

Conclusion

The totality-of-the-evidence generated across a broad array of scientific studies convincingly demonstrates that the THS product meets the criteria set out in Section 911(g) scientific basis for approval by (1) reducing harm and the risk of tobacco-related disease to individual tobacco users and (2) benefiting the health of the population as a whole. This robust pre-market assessment will be complemented by a post-market surveillance and study program.

2.7.2 PROPOSED MODIFIED RISK AND MODIFIED EXPOSURE CLAIMS

Philip Morris International (PMI) is submitting this application under Section 911(g) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) requesting market orders under both §911(g)(1) (risk modification order) and §911(g)(2) (exposure modification order) for its novel Tobacco Heating System (THS) to be marketed as "*iQOS*". PMI is submitting this application for THS as a Modified Risk Tobacco Product (MRTP) with three different variants, Marlboro *HeatSticks*, Marlboro Smooth Menthol *HeatSticks*, and Marlboro Fresh Menthol *HeatSticks*.

PMI is submitting this application for THS with three proposed claims.

The claims and associated warning statements developed and tested for a market order under or §911(g)(1) are:

Claim #1 (Section 2.7.6 Part B, Table 18):

- The *iQOS* system heats tobacco but does not burn it.
- This significantly reduces the production of harmful and potentially harmful chemicals.
- Scientific studies have shown that switching completely from cigarettes to the *iQOS* system can reduce the risks of tobacco-related diseases.

To be associated with either of:

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SURGEON GENERAL'S WARNINGS:	PMI IMPORTANT WARNING:
• Smoking Causes Lung Cancer, Heart Disease, Emphysema, And May Complicate Pregnancy. • Quitting Smoking Now Greatly Reduces Serious Risks to Your Health. • Smoking By Pregnant Women May Result in Fetal Injury, Premature Birth, And Low Birth Weight. • Cigarette Smoke Contains Carbon Monoxide.	• Reduced risk does not mean no risk. The best way to reduce your risk of tobacco-related diseases is to completely quit tobacco use. • *HeatSticks* contain nicotine, which is addictive. • Using the *iQOS* system can harm your health.

Claim #2 (Section 2.7.6 Part B, Table 19):

- The *iQOS* system heats tobacco but does not burn it.
- This significantly reduces the production of harmful and potentially harmful chemicals.
- Switching completely to *iQOS* presents less risk of harm than continuing to smoke cigarettes.

To be associated with either of:

SURGEON GENERAL'S WARNINGS:	PMI IMPORTANT WARNING:
• Smoking Causes Lung Cancer, Heart Disease, Emphysema, And May Complicate Pregnancy. • Quitting Smoking Now Greatly Reduces Serious Risks to Your Health. • Smoking By Pregnant Women May Result in Fetal Injury, Premature Birth, And Low Birth Weight. • Cigarette Smoke Contains Carbon Monoxide.	• Less risk of harm does not mean no risk of harm. The best way to reduce your risk of tobacco-related diseases is to completely quit tobacco use. • *HeatSticks* contain nicotine, which is addictive.

The claim developed and tested for a market order under or §911(g)(2) is:

Claim #3 (Section 2.7.6 Part B, Table 20):

- The *iQOS* system heats tobacco but does not burn it.

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- This significantly reduces the production of harmful and potentially harmful chemicals.
- Scientific studies have shown that switching completely from cigarettes to the *iQOS* system significantly reduces your body's exposure to harmful or potentially harmful chemicals.

To be associated with either of:

SURGEON GENERAL'S WARNINGS:	**PMI IMPORTANT WARNING:**
• Smoking Causes Lung Cancer, Heart Disease, Emphysema, And May Complicate Pregnancy. • Quitting Smoking Now Greatly Reduces Serious Risks to Your Health. • Smoking By Pregnant Women May Result in Fetal Injury, Premature Birth, And Low Birth Weight. • Cigarette Smoke Contains Carbon Monoxide.	• It has not been demonstrated that switching to the *iQOS* system reduces the risk of developing tobacco-related diseases compared to smoking cigarettes. • *HeatSticks* contain nicotine, which is addictive. • Using the *iQOS* system can harm your health.

2.7.3 MODIFIED RISK TOBACCO PRODUCTS AND HARM REDUCTION

To provide the context for the scientific framework that is presented in this MRTP application, it is necessary to examine the underlying rationale for MRTPs and their role in reducing the harm and disease caused by cigarette smoking. Cigarette smoking is the leading causes of preventable disease in the United States and globally. 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). For many decades, the goal of reducing the harm caused by smoking has relied on two foundational principles, namely preventing smoking initiation and promoting smoking cessation. For smokers, smoking cessation is the best way to reduce the risk of harm and tobacco-related disease. Most smokers who quit the use of cigarettes benefit from a significant reduction in harm and risk of tobacco-related disease, with many smokers returning over time to near baseline levels of risk compared with the population of never smokers.

In recent years, a third opportunity to reduce the harm from tobacco products has emerged. This opportunity is based on switching consumers to less harmful tobacco and nicotine products that have significantly reduced levels of HPHCs, yet still deliver satisfying levels of nicotine. For instance, the '*FDA believes that the inhalation of nicotine (i.e. nicotine without the products of combustion) is of less risk to the user than*

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the inhalation of nicotine delivered by smoke from combusted tobacco products.' (FDA 2014). It is widely recognized that '*nicotine itself is not a highly hazardous drug*' (McNeil 2012) and that '*most of the harm caused by smoking arises not from nicotine but from other components of tobacco smoke*' (Royal College of Physicians 2016, Waldum 1996). This approach to tobacco harm reduction has not been without controversy, yet many authoritative public health agencies have recognized its potential, as evidenced by several reports by the UK Royal College of Physicians (Royal College of Physicians 2007) and the Tobacco Advisory Group of the UK Royal College of Physicians (Royal College of Physicians 2016). Both reports conclude that tobacco harm reduction, including the use of MRTPs, could offer a means to prevent millions of smoking-related deaths in the UK alone.

A similar case for less harmful tobacco products can be applied in the United States. Congress recognized the opportunity for modified risk products in 2009 when it passed the Family Smoking Prevention and Tobacco Control Act (FSPTCA), which established the authority of FDA over the regulation of tobacco products and established statutory requirements for MRTPs. The FSPTCA requires applicants to demonstrate that candidate products, as actually used, will (i) significantly reduce harm and the risk of tobacco-related disease to individual tobacco users, and (ii) benefit the health of the population as a whole, taking into account both the users of tobacco products and persons who do not currently use tobacco products. An important corollary of achieving population harm reduction with MRTPs is that consumers will actually use them, ideally replacing the use of more harmful products with products that significantly reduce the exposure to toxic compounds, thus reducing harm and the risk of tobacco-related disease. The following simple equation (Figure 1) illustrates the point that population harm reduction depends on both the availability of significantly lower risk products and a significant number of adult daily smokers willing to accept and switch to these products. Furthermore, as MRTPs are not risk free, these products should not attract persons who do not currently use tobacco products, i.e. never smokers or former smokers.



Figure 1: The Harm Reduction Equation

The magnitude of Population Harm Reduction depends on the magnitude of the Product Risk Reduction and the prevalence of use among adult smokers

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

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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) does not attract persons who do not currently use tobacco products (never smokers and former smokers) and (iii) does not negatively influence 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.

2.7.4 PRODUCT DESCRIPTION AND SCIENTIFIC RATIONALE

Development Rationale and Product Description for THS

PMI developed (see Section 3.2.1) the THS product to address both parameters of the *harm reduction equation* in order to maximize its potential to reduce population harm. Therefore, THS was developed to:

- minimize the individual consumer exposure to reduced levels of HPHCs that approach the full reduction achieved by smoking cessation, thereby reducing harm and the risk of tobacco-related disease and,
- be an alternative source of nicotine and an acceptable substitute for cigarettes in terms of taste and ritual for those adult smokers who do not have an intention to quit smoking.

THS was designed to generate an aerosol that has substantially fewer toxicants than conventional/combustible cigarette smoke. The key to reduced toxicity is the reduced formation of HPHCs, which are created primarily through combustion in cigarettes. Indeed, when tobacco in cigarettes is burned it generates smoke, which is a complex aerosol containing thousands of chemicals (Rodgman 2013). The FDA has listed 93 of those as HPHCs that are linked to the most serious health effects of tobacco use (FDA 2016a). No combustion takes place in THS (see below Section 2.7.5 A), which significantly reduces, or in many cases nearly eliminates, HPHCs typically associated with combustion. Furthermore, the absence of the high temperature combustion zone (i.e. the lit end of a cigarette) reduces the risk of accidental fires.

At the same time, THS is demonstrated to deliver tobacco taste, nicotine satisfaction and an acceptable ritual, which is important to providing an acceptable substitute for cigarettes to facilitate switching by current adult smokers.

Heating Instead of Burning Reduces Harmful Constituents

A cigarette burns at temperatures in excess of 600°C (Section 3.2.1). At such high temperatures, the tobacco burns to ash and generates smoke that contains more than 6,000 chemicals (Rodgman 2013). Public health authorities have classified some of those smoke constituents as likely causes of smoking-related diseases such as lung cancer, heart disease and emphysema. The United States Surgeon General (HHS 2010) concluded, "*Inhaling the complex chemical mixture of combustion compounds in tobacco smoke causes adverse health outcomes, particularly cancer and cardiovascular and*

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pulmonary diseases, through mechanisms that include Deoxyribonucleic Acid (DNA) damage, inflammation and oxidative stress."

Many of the HPHCs contained in smoke from burned tobacco are generated or released at temperatures in excess of 400ºC:

- Carbon monoxide (CO)
- Nitrogen oxide (NO)
- Hydrocarbons and aldehydes (such as formaldehyde and acrolein)
- Phenols
- Polycyclic aromatic hydrocarbons (PAH)
- 1,3-Butadiene, benzene, and styrene
- Tobacco-specific nitrosamines (TSNA)

THS generates a nicotine-containing aerosol by heating the tobacco in a manner that avoids combustion (Section 3.2.1), thus reducing the formation of many compounds identified as toxicants. The development of the heating system of THS has therefore been driven by two key objectives:

1. the optimization of the temperature to which the tobacco is heated to minimize the formation of a broad spectrum of HPHCs, while maintaining a satisfactory level of nicotine delivery and taste,
2. the implementation of robust temperature controls, which ensure a consistent reduction in HPHC formation across a broad range of usage conditions and consistent product performance.

During product development, PMI coupled technical development with consumer testing in adult smokers to minimize the formation of HPHCs while maximizing the acceptability of the product. THS has been shown to generate a consistent aerosol across a broad range of conditions of use, resulting in consistent product performance and a favorable smoker experience. Even under extreme puffing conditions designed to elicit unfavorable changes in aerosol chemistry, none of the studied puffing regimens significantly increased the level of nitrogen oxides in aerosol. This demonstrates the absence of combustion in THS even under extreme puffing conditions (Section 2.7.5).

Product Description

THS is a patented novel tobacco product, described in Section 3.1, with the commercial name of *iQOS*, consisting of three main components (Figure 2 A):

1. The Tobacco Stick, which is a novel, patent pending tobacco product containing uniquely processed tobacco made from tobacco powder. It is designed to function with the holder to produce an aerosol. In order to satisfy different consumer preferences, PMI is applying for THS as an MRTP with different variants: Marlboro *HeatSticks*, Marlboro Smooth Menthol *HeatSticks* (1.35 mg menthol in

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smoke per stick[2]), and Marlboro Fresh Menthol *HeatSticks* (2.3 mg menthol in smoke per stick[3]).

2. The Holder, into which the Tobacco Stick is inserted, heats the tobacco material by means of an electronically controlled heating blade (Figure 2 B).
3. The Charger used to recharge the holder after each use. The Charger stores sufficient energy for the use of approximately 20 *HeatSticks* and can be recharged from household power.

The Holder and the Charger, together with essential accessories (see Section 3.1), are collectively known as the Tobacco Heating Device (THD).

[3] Target levels in aerosol, using the Health Canada Intense smoking regime

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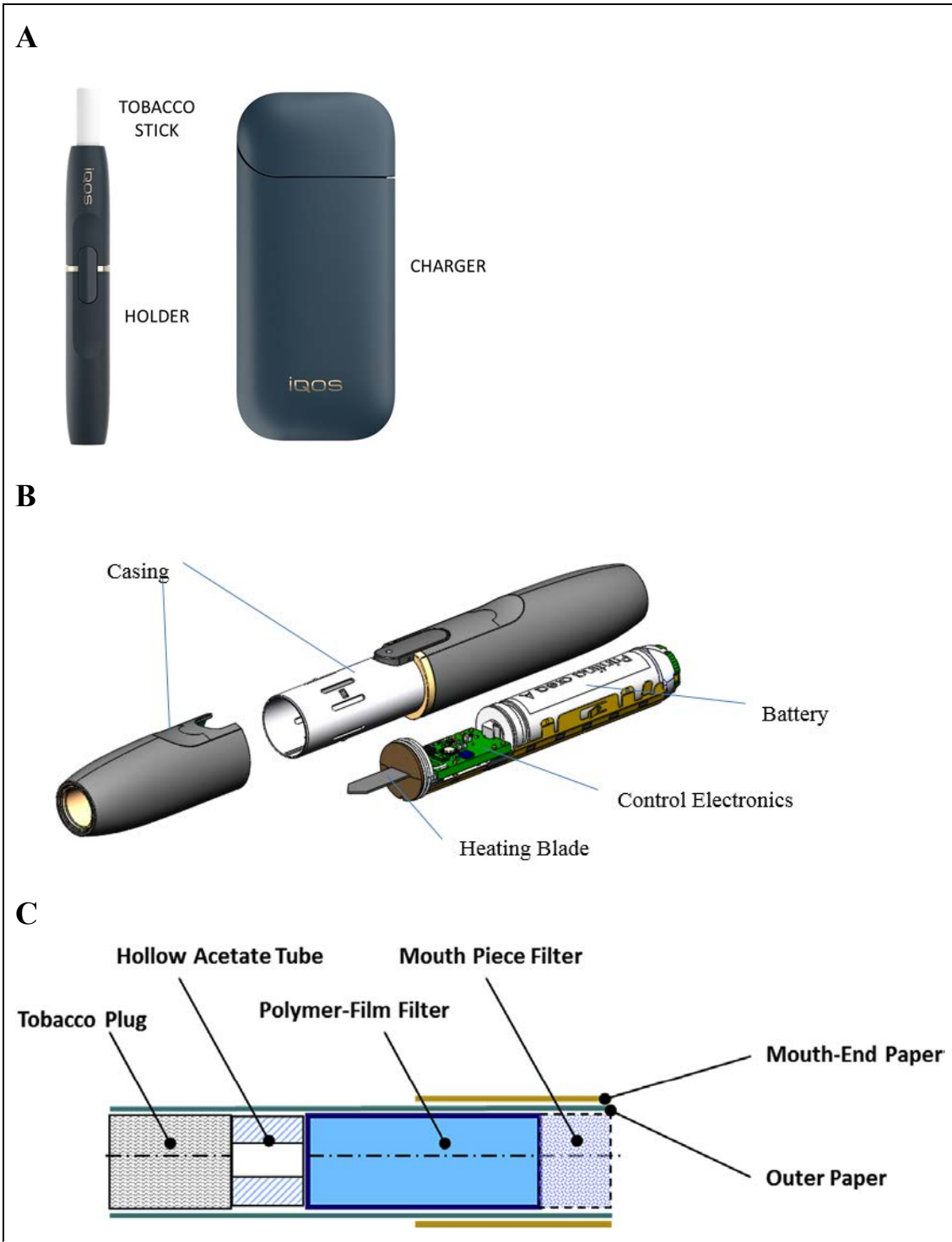


Figure 2: The THS components (A), a schematic exploded view drawing of the Holder (B) and a schematic cross-sectional view of the Tobacco Stick (C)

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The Tobacco Stick differs from a cigarette in significant ways. First, the Tobacco Stick does not contain tobacco cut-filler (tobacco leaf cut in small pieces found in cigarettes). Instead, the tobacco is ground and reconstituted into sheets (termed cast-leaf) following the addition of water, glycerin, guar gum and cellulose fibers. Second, the Tobacco Stick (Figure 2 C) contains much smaller amounts of tobacco compared with a cigarette. The weight of the tobacco plug in the Tobacco Stick is approximately 320 mg compared with the 550-700 mg cut-filler found in conventional cigarettes. The reconstituted tobacco cast-leaf is fashioned into a small plug through 'crimping' in a proprietary process. Third, unlike a cigarette, the Tobacco Stick contains two unique and independent filters: (i) a polymer-film filter to cool the aerosol and (ii) a low-density cellulose acetate mouthpiece filter to mimic the aspect of a cigarette. Furthermore, a hollow acetate tube separates the tobacco plug and the polymer-film filter.

To operate the THS product, the user inserts a Tobacco Stick into the holder and turns on the device by means of a switch. This initiates the heating of the tobacco via the heating blade inserted into the tobacco plug. The tobacco neither ignites nor burns. The electronically controlled heating, in combination with the uniquely processed tobacco, prevents combustion from occurring (Section 2.7.5). The holder supplies heat to the Tobacco Stick through the heating blade for a fixed period of approximately 6 min and allows up to 14 puffs to be taken during that time. The temperature of the heating blade is carefully controlled (Section 3.1) and the energy supply to the blade is cut if its operating temperature exceeds 350 °C. The temperature measured in the tobacco does not exceed 300 °C (Section 3.2.1).

In summary, THS is fundamentally different from a combustible cigarette and has been designed to heat tobacco with an electronically controlled heating blade that does not exceed the maximum operating temperature of 350 °C to prevent combustion. Furthermore, it has been designed to deliver a maximum of 14 puffs per Tobacco Stick within a maximum of 6 min. Unlike cigarettes, which burn tobacco and produce a complex mixture of HPHCs through combustion, THS heats tobacco to temperatures below the level of combustion, producing an aerosol with reduced amounts of HPHCs. This aerosol is composed mainly of water, glycerin and nicotine through evaporation/distillation processes. The tight temperature control of the heating blade, combined with the operation time and puff number limitations, ensure that THS generates a consistent aerosol across a broad range of conditions of use (including extreme ones), resulting in a consistent reduction in HPHC formation.

PMI applies rigorous processes and practices to ensure that THS is consistently produced and controlled according to the ISO 9000 quality management system (ISO 2016). The Quality Management System (QMS) covers all aspects of the production of THS, from materials, manufacturing facilities and equipment to the training of employees. An important part of the QMS is change control. PMI has implemented a robust change management process to ensure that, prior to implementation, any product variation is assessed with respect to product performance and regulatory impact. This process ensures product compliance with the declared standards, which are based on the evidence generated throughout the product assessment cycle.

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Scientific Rationale and Assessment Framework for THS

The scientific evidence to support a MRTP market order is challenging. First, the statute includes a public health standard that requires evidence of how the product will benefit both individual users of tobacco products and the population as a whole. Second, it is acknowledged that product-specific epidemiological evidence is not available and clinical trial data on disease outcome is limited due to the long latency of tobacco-related disease, which may take many years to manifest. Third, tobacco-related harm and disease is not defined by a single endpoint or even endpoints reflective of a single disease or biological mechanism. The etiology of tobacco-related disease is highly complex and multi-factorial. Therefore, the evaluation of relative risk compared to cigarette smoking must take into account the complex nature of the whole organism and the many biological mechanisms that are affected by smoking and that may lead to disease. The assessment of a candidate MRTP therefore needs to address this complexity by demonstrating through a broad array of indicators that – compared with smoking – the use of a candidate MRTP leads to a significant reduction in exposure to HPHCs, which in turn leads to a significantly reduced impact on mechanisms leading to tobacco-related diseases. PMI has addressed this complexity with the best available pre-market studies. Initiation of long-term epidemiological studies is only possible once the product is on the market.

Causal Linkages between HPHC Exposure and Disease

The pathway from smoke/HPHC exposure to disease manifestation can be depicted as a chain of causally linked key (biological) events known as an Adverse Outcome Pathway (AOP) (Figure 3) (Ankley 2010, OECD 2013, Sturla 2014). This AOP begins with cigarette smoke/HPHC exposure that leads to molecular changes that cause the disruption of biological mechanisms, which in turn, cause cell/tissue changes. These changes then lead to physiological changes (e.g. organ/tissue damage), disease manifestations and population harm (e.g. mortality) (Smith 2016). The impact of cigarette smoke on this chain of causally linked events can be quantified using methods such as analytical chemistry, advanced –omics technologies (e.g. transcriptomics, proteomics, and metabolomics), cytology, histopathology, physiological measurement and eventually epidemiology. These data can be analyzed using statistical methods and advanced computational biology approaches.

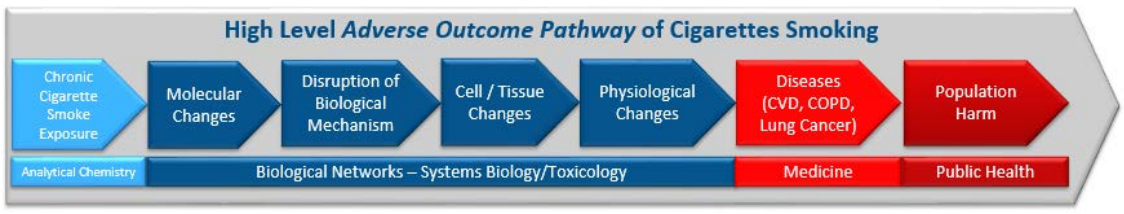


Figure 3: High Level Adverse Outcome Pathway (AOP) of Cigarette Smoking

Chronic exposure to cigarette smoke disrupts the biological homeostasis leading to adverse tissue changes and ultimately tobacco-related disease

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For most smokers, the effects of smoke exposure on adverse molecular, cellular, tissue and physiological responses are progressive with continued smoking and hence the risk of tobacco-related disease rises with time and dose of exposure.

Smoking Cessation – the Gold Standard for Assessing Risk Reduction

Smoking cessation has been demonstrated to lead to reduced harm and risk of tobacco-related diseases. For example, smoking cessation leads to decreased blood levels of hemostatic and inflammatory markers, important determinants in the subsequent development of cardiovascular disease or COPD (Wannamethee 2005). In the case of pulmonary function in smokers, cessation diminishes the decline of 1-sec forced expiratory volume (FEV1) levels of current smokers and improves pulmonary function by about five percent (HHS 1990). Similarly, smokers who quit show positive histologic changes in their lungs including the disappearance of cells with atypical nuclei which are replaced, over time, by cells with more normal appearance (HHS 1990). Most of the accrued risk of tobacco-related disease is therefore reversible over time for most smokers.

Figure 4 is a schematic that represents the level of disease risk that results from continued smoking and the changes in disease risk that occur with cessation. The risk of tobacco-related diseases increases with longer (and greater) exposure to cigarette smoke (red line). In contrast, smoking cessation results in a gradual reduction in risk of tobacco-related disease over time and, for many smokers, can fall to levels approaching that of a never smoker if given enough time. The predominant cause of this risk reduction is the elimination of exposure to the HPHCs contained in cigarette smoke, which correspond to eliminating the first causative event in the AOP depicted in Figure 3. Other factors, such as improvement in lifestyle (more physical exercise, improved diet), may accompany smoking cessation and further contribute to risk reduction. These factors, by themselves, do not significantly change the slope of accrued risk in smokers who do not quit. It is therefore critical to emphasize that:

1. it is the elimination of exposure to the HPHCs of cigarette smoke that leads to reduced harm and risk of tobacco-related disease,
2. a similar reduction in disease risk should be achieved by products that significantly reduce or eliminate exposure to HPHCs.

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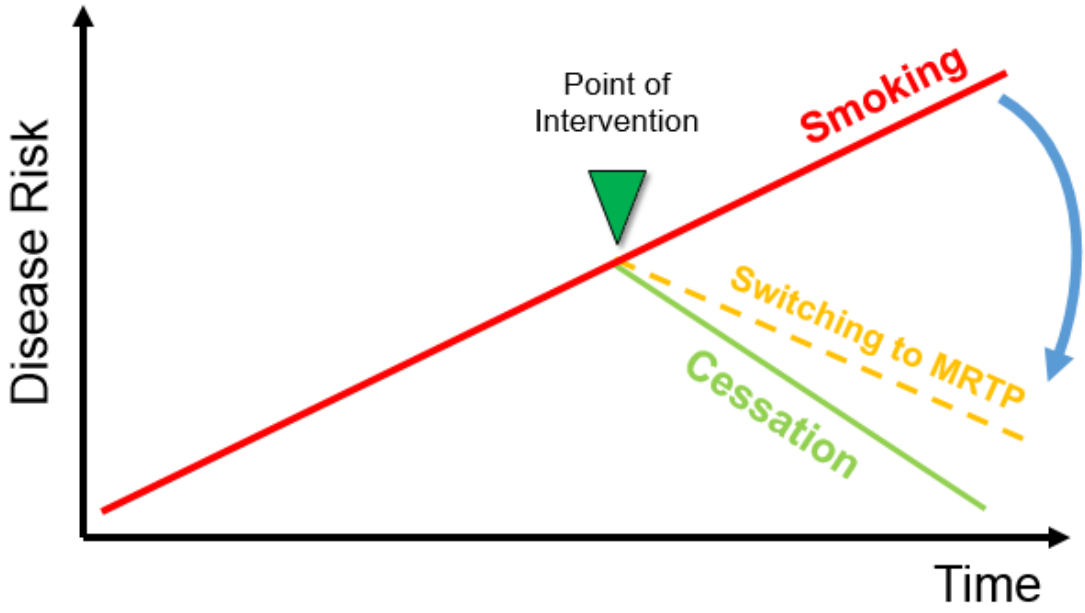


Figure 4: Risk framework for MRTP assessment

Conceptual depiction of the cumulated risk of smoking and the effect of cessation over time. These represent the two boundaries for the assessment of an MRTP: 1) comparing switching to an MRTP with continued smoking and 2) benchmarking switching against smoking cessation (gold standard). Note that the straight lines used in this figure are for illustration purposes only as the accumulation of disease risk and the reduction upon cessation and switching to an MRTP follow different trajectories for specific diseases.
Abbr.: MRTP = Modified Risk Tobacco Product

The risk reduction induced by smoking cessation is accompanied by predictable and measurable changes in each of the causally linked events depicted in Figure 3. First, smoking cessation effectively eliminates the first step in the causative chain, which is the exposure to HPHCs. It is then possible to observe and quantify substantial reductions in molecular changes, followed by significant reductions in biological network perturbations, cellular/tissue dysfunction, and eventually physiologic changes consistent with a reduced adverse impact (measurements of toxicity). By applying the same rigorous biological study framework to the assessment of an MRTP, it is possible to quantify the reductions in adverse impact induced by switching to an MRTP aerosol and compare these changes with those induced by cigarette smoke and to those caused by the "gold standard" of cessation.

An MRTP that causes a biological impact similar to cessation would meet the first basis for approval, namely to significantly reduce harm and the risk of tobacco-related disease for those consumers who would switch from cigarette smoking to MRTP use. As depicted in Figure 4 in the gold-shaded area, switching to tobacco products with dramatically reduced levels of (and exposure to) HPHCs would be expected to have a harm and risk reduction profile that could be very close to that seen with smoking

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cessation. In support of this biologically plausible argument, there are several peer-reviewed scientific studies that concluded that significant reductions in smoking/exposure leads to a reduced risk of tobacco-related disease (Benhamou 1989, Godtfredsen 2005, Hart 2013, Lee 2013, Simmons 2005, Song 2008, Wald 1997).

The scientific rationale for THS is supported by two lines of evidence:

1. The harm and risk of tobacco-related disease is caused by the exposure to HPHCs formed by combustible cigarettes. Epidemiological studies have provided overwhelming evidence that the risk of tobacco-related disease rises in a dose and time dependent manner with continued exposure to HPHCs. Exposure to tobacco smoke produces predictable and quantifiable biological changes across the AOP (Figure 3). These changes result in the chronic perturbation of biological networks, eventually overwhelming restorative/reparative mechanisms and thus leading to disease. The changes that occur across the AOP in response to tobacco smoke exposure can be estimated, providing the relative risk *comparator* for an MRTP (Figure 5). The FDA has previously commented on the plausibility that significant reductions in exposure to HPHCs can result in reductions in risk of harm and tobacco-related disease.[4]
2. Epidemiological studies have provided overwhelming evidence that harm and the risk of tobacco-related disease can be dramatically reduced by smoking cessation, which is the "gold standard" for assessing whether a product reduces the harm and risk of tobacco-related disease. By eliminating the first step in the AOP (exposure to HPHCs), the chronic stimulus leading to disease progression is effectively removed, allowing for a normalization of cellular and tissue function over time. The changes induced by eliminating exposure to HPHCs can be estimated, providing the absolute risk *benchmark* for an MRTP (Figure 5).

In summary, the benefit of an MRTP can be described as the relative (lower) risk compared with the cigarette comparator (Figure 5). The lower the relative risk of an MRTP in comparison with cigarettes is (i.e. the closer the outcome measures are to the cessation benchmark), the greater the harm and risk reduction potential of an MRTP. It is unlikely that any tobacco product will be free of risk. This remaining risk of an MRTP can be described as the absolute (greater) risk compared to the smoking cessation benchmark (Figure 5). In this application, we provide multiple demonstrations that the net biological effects of switching to THS aerosol, approach the net positive biological effects seen with smoking cessation.

[4] Premarket Tobacco Product Application (PMTA) Technical Project Lead (TPL) Review, FDA Center for Tobacco Products. PM000010-PM0000017, 2015

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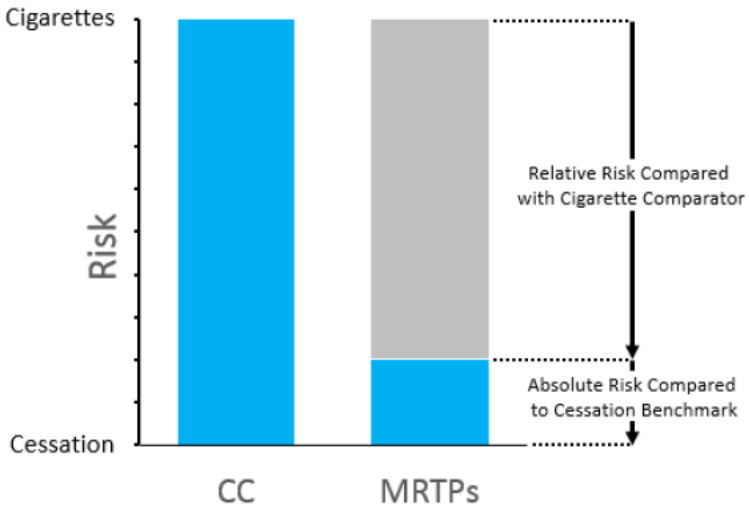


Figure 5: Comparative risk framework for MRTPs

Abbr.: CC = Conventional Cigarette, MRTPs = Modified Risk Tobacco Products

2.7.5 PMI SCIENTIFIC PROGRAM FOR THE ASSESSMENT OF THS

The PMI Scientific Program was developed to address the two-part "basis for approval" of Section 911(g) of the FD&C Act and thereby demonstrate that THS, as actually used by consumers, will:

A. Reduce harm and the risk of tobacco-related disease to individual tobacco users
B. Benefit the health of the population as a whole

Assessment Steps	Evidence Levels
7. Post-Market Studies and Surveillance	V. Reduced Population Harm
6. Consumer Perception and Behavior Assessment	
5. Clinical Studies	IV. Reduced Exposure and Risk
4. Systems Toxicology Assessments	III. Reduced Risk in Laboratory Models
3. Standard Toxicology Assessments	II. Reduced Toxicity in Laboratory Models
2. Aerosol Chemistry and Physics	I. Reduced Formation of HPHCs
1. Product Design and Control Principles	

Figure 6: The MRTP assessment program

Seven steps of assessment (1-7) lead to five levels of evidence (I-V)
Abbr.: HPHCs = Harmful and Potentially Harmful Constituents

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PMI used a sequential process (Smith 2016) consisting of the seven steps of assessment described in Table 1 and Figure 6. This process was designed to yield five levels of evidence (Figure 6). The totality of this evidence addresses the two-part "basis for approval" in the following manner:

A. To demonstrate that THS reduces harm and the risk of tobacco-related disease to individual tobacco users, PMI's goal was to demonstrate that THS achieved these four levels of evidence. They depend on the following key outcomes:
   I. Evidence Level I: THS aerosol must deliver significantly less HPHCs than cigarette smoke, and do this consistently along the product life cycle. (Data generated in assessment steps 1 and 2).
   II. Evidence Level II: THS aerosol must be significantly less toxic than cigarette smoke, and there should be no evidence that THS aerosol presents any new hazard compared with cigarette smoke. (Data generated in assessment step 3).
   III. Evidence Level III: THS aerosol must reduce the risk of harm and smoking-related diseases in laboratory models. (Data generated in assessment step 4).
   IV. Evidence Level IV: Switching from cigarette smoking to THS use must lead to significant reductions in exposure to HPHCs that approach the reductions caused by smoking abstinence, and, switching from cigarette smoking to THS use must result in changes in clinical risk markers that are aligned with those caused by smoking abstinence. These changes should be of a similar magnitude. (Data generated in assessment step 5).

B. To demonstrate that THS benefits the health of the population as a whole, PMI's goal was to demonstrate that THS achieves the fifth level of evidence, which depends on the following key outcomes:
   V. Evidence Level V: the THS product must be an acceptable alternative to cigarettes for adult smokers and be correctly used. The THS claims and risk must be correctly understood by smoker and nonsmokers. The likelihood that never smokers and former-smokers will initiate/re-initiate tobacco use with THS must be very low. Furthermore, THS must be shown to reduce risk of adverse health effects longer-term. While these long-term effect can only be assessed in post-market studies, PMI will assess the other outcomes prior to market introduction. (Data generated in assessment steps 5, 6 and 7).

In this application, PMI presents study results that address each of these five levels of evidence to justify a modified risk claim for THS.

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Table 1: PMI scientific program for the assessment of THS

Assessment Step	Description of the assessment step
A: Evidence on reduced harm and the risk of tobacco-related disease to individual tobacco users	
Step (1): Product Design and Control Principles	This step ensures that the product is manufactured to appropriate quality standards and is sufficiently characterized to meet product performance parameters. This includes the effective implementation of product design principles, manufacturing quality controls and the change management process.
Step (2): Aerosol Chemistry and Physics	This step focused on aerosol chemistry and physics analysis to demonstrate consistent and substantially reduced formation of HPHCs. Furthermore, the impact on indoor chemistry was analyzed.
Step (3): Standard Toxicology Assessment	This step consists of the standard toxicology assessment of THS aerosol in multiple *in vitro* and *in vivo* studies to demonstrate that THS aerosol is significantly less toxic than smoke from a reference-cigarette (3R4F).
Step (4): Systems Toxicology Assessment	This step consists of multiple *in vitro* and *in vivo* systems toxicology studies to demonstrate that THS aerosol reduces the risk of harm and disease in laboratory systems.
Step (5): Clinical Studies	PK/PD studies with adult smokers to assess how close the pharmacokinetic profile of nicotine delivered by THS is to that delivered by cigarettes, as this is an important factor to facilitate switching by adult smokers.
	Short- and longer-term clinical studies to demonstrate that exposure to HPHCs is reduced in adult smokers who use THS compared to cigarettes, and approaches the levels those who abstained during the study. Furthermore, the two longer-term studies also were designed to show that switching to THS leads to changes in clinical risk markers that are aligned with those seen in smoking cessation.
B. Evidence on benefit to the health of the population as a whole	
Step (6): Consumer Perception and Behavior Assessment (PBA)	This step consisted of qualitative and quantitative human studies to develop scientifically accurate product communications, evaluate the comprehension of these communications and measure Intention to Use as well as risk perception of THS among smokers and nonsmokers. Furthermore this step also studied the actual use of THS in a near to real-world setting.
Step (7): Post-Market Studies and Surveillance	This step includes a Population Health Impact Model designed to estimate the potential long-term public health impact of introducing an MRTP in the market. The model allows analyzing the impact of multiple scenarios on mortality.
	PMI has proposed a plan for post-market studies including safety surveillance, cross-sectional surveys to monitor prevalence and cohort studies to monitor the ongoing health effects of switching to THS. Evidence will be generated under a comprehensive program in real-world conditions following a market order and launch of the THS product.
Abbr.: 3R4F = Reference Cigarette, HPHC = Harmful and Potentially Harmful Constituents, MRTP = Modified Risk Tobacco Product, PBA = Perception and Behavior Assessment, PK/PD = Pharmacokinetics/Pharmacodynamics, PMI = Philip Morris International, THS = Tobacco Heating System	

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Appropriate comparison for substantiation of risk reduction

As stated in Section 2.7.3, the inclusion of the smoking cessation benchmark is critical in determining whether switching to THS aerosol will result in reduced harm and the risk of tobacco-related disease. Therefore, all studies conducted by PMI were designed as comparative studies, where either or both of the following references are used: (i) the smoke of the 3R4F reference cigarette or smoking cigarettes as the *comparator* and ii) fresh air or smoking cessation/abstinence as the *benchmark* or "gold standard". The focus of the studies was to determine two major outcomes.

1. First, how different are the biological effects caused by THS aerosol compared with those caused by smoking/cigarette smoke?
2. Second, how similar are the biological effects of switching to THS aerosol compared to those caused by smoking cessation/fresh air?

Within each step of the assessment, multiple studies were conducted. This approach generated a robust dataset to show consistent reduction in exposure, which leads to favorable changes in clinical risk markers as well as disease-related mechanisms.

2.7.6 THE SCIENTIFIC BASIS FOR APPROVAL

The following sections summarize the scientific findings that support each aspect of the *harm reduction equation* (Figure 1). The data are presented in the framework of the seven-step assessment outlined in Table 1. The findings and relevance of the scientific program are summarized in two parts:

A. Evidence on reduced harm and the risk of tobacco-related disease to individual tobacco users
B. Evidence on benefit to the health of the population as a whole

A Reduction in Harm and the Risk of Tobacco-Related Disease to Individual Tobacco Users

Part A of the scientific basis for approval will present the findings to demonstrate that switching from cigarette smoking to THS use *"will significantly reduce harm and the risk of tobacco-related disease to individual tobacco users."*

Product Design and Control Principles (Step 1)

As laid out in Table 1, this first step of the assessment ensures that THS is consistently manufactured to appropriate quality standards. The following section presents a brief description of the development environment, manufacturing quality control principles and the PMI Change Management Process (CMP). The details of product development, manufacturing and performance characterization are described in Section 3.

Development environment

THS was developed following a Quality System that is based on ISO 9000, which covers the general approach to design and development practices. This includes well-defined

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change control procedures including design change, assessment of the risk to product quality and performance, and full documentation of the product. Application of the ISO 9000-based Quality System ensures consistency for both the Tobacco Stick and the THD, including proper operational and temperature controls.

Manufacturing Quality

THS manufacturing quality control is based on a risk assessment, which defines the type and extent of control required at each point in the manufacturing process. The control strategy is defined as the combination of critical quality attributes for the materials, semi-finished products, and final product. Critical control and process parameters are those parameters, which may have an impact on a critical quality attribute of THS or importantly the THS aerosol. The quality of the final product is ensured by means of a Batch Release process, whereby a number of physical attributes of the THS (length, weight, diameter), as well as the yields of several constituents and analytes in the THS aerosol (nicotine, glycerin, triacetin, phenol, carbon monoxide, acrylamide), are assessed against predefined criteria. Batches that do not meet the predefined criteria are rejected.

Change Management and Comparability

The scientific studies to assess THS were conducted over a period of several years during which certain product changes were made to improve its performance and address issues related to commercial scale-up and production requirements. PMI had implemented a robust CMP to ensure that: (i) modifications to the THS did not affect the safety, quality, or performance of the product and (ii) the scientific assessment studies and data conducted with the earlier versions of THS were representative and equally applicable to the final (commercialized) products. PMI's CMP is informed by relevant recommendations from the FDA and the International Conference on Harmonization (ICH). The CMP entails identification, documentation, validation, verification, review, and approval of product changes before their implementation. It covers the full lifecycle of the product from design and development through manufacturing. The CMP is governed by the Change Management Board (CMB) – an internal panel of subject matter experts that includes product development, quality and regulatory specialists.

An important role of the CMB is to evaluate the potential impact of any change on the THS aerosol composition. This evaluation is based on measurements of the PMI list of analytes and constituents (see below and Table 2) and comparing these results with the product performance range (PPR). Following standard practice for comparative tobacco product assessments, the PPR is defined on a constituent-by-constituent basis, taking into account long-term analytical and agricultural variability (Belushkin 2015).

The comparison of every product change against a fixed PPR ensures that product performance does not evolve over time. This means that the number and level of HPHCs of a modified version of the THS are always within the PPR previously established for the Investigational THS used throughout pre-clinical, non-clinical and clinical investigations.

For example, prior to implementing any changes to the tobacco blend (which may arise due to agricultural variability or supply), the new blend is assessed by measuring the PMI

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list of analytes and constituents (see below and Table 2) in the aerosol from at least three manufacturing batches of Tobacco Stick containing the new blend. If the number and levels of the HPHCs fall within the limits of the PPR, the modified version of the Tobacco Stick is determined to be comparable to the Investigational Tobacco Stick. Should any differences be noted in the THS aerosol using a new blend, the potential biological impact of these differences is assessed through *in vitro* tests. The results of these studies are again compared with investigational product study results to ensure product comparability.

The PMI list of analytes and constituents does not cover the components of flavor systems. Therefore, the comparability of new flavor systems is directly determined through *in vitro* toxicity studies. The aerosol of any new flavor containing Tobacco Stick is tested in the Neutral Red Uptake cytotoxicity assay and, when applicable, (e.g. in case of changes in genotoxic substance levels in the product aerosol) in the Ames Bacterial Mutagenicity assay (*in vitro* mutagenicity). The results of these assessments are also compared with results generated with the Investigational Tobacco Stick to ensure product comparability.

In the event that the aerosol chemistry and/or the aforementioned *in vitro* tests cannot conclusively demonstrate the absence of impact of a change in aerosol composition and its biological activity, further studies such as *in vitro* studies with organotypic tissue cultures may be conducted. Product changes that clearly affect product performance, i.e. are not comparable, are rejected. A schematic overview of PMI's comparability assessment methodology is shown in Figure 7. The full scope of the QMS system is outlined in Section 3.

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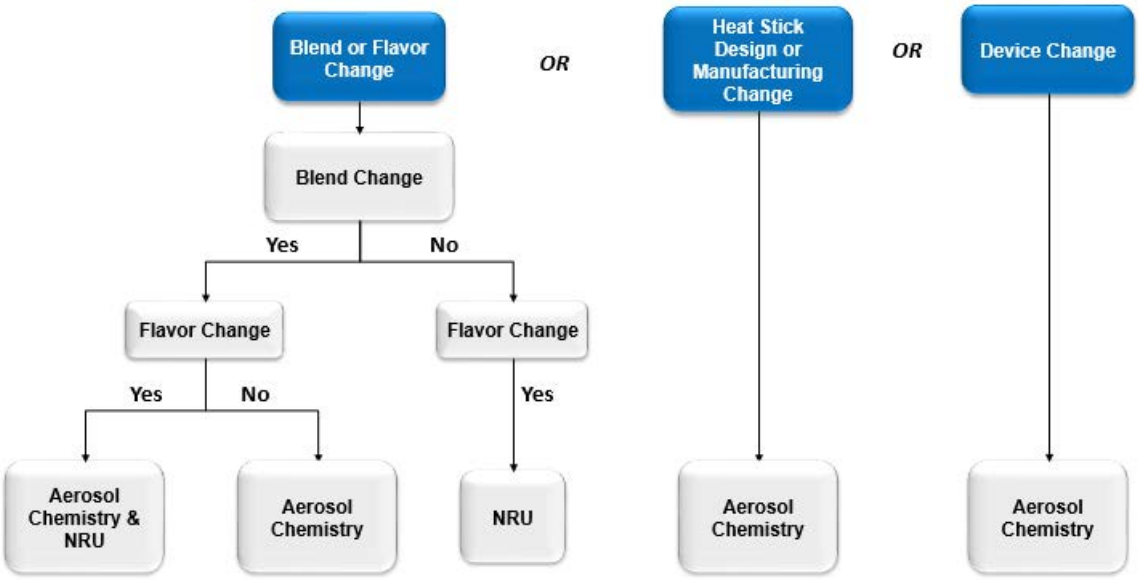


Figure 7: Comparability assessment decision tree for different types of possible product modifications

For flavor changes, only NRU is performed as aerosol chemistry is not designed to identify such changes.
Aerosol chemistry generally covering the PMI list of analytes and constituents
Abbr.: NRU – Neutral Red Uptake *in vitro* cytotoxicity test

Aerosol Chemistry and Physics (Step 2)

Step 2 of the assessment was designed to assess key properties of the aerosol generated by THS. The primary objective was to demonstrate that THS aerosol contains significantly reduced levels of HPHCs compared with cigarette smoke. The secondary objectives were:

- confirm the absence of combustion,
- assess the aerosol particle size to confirm that the aerosol is respirable, and
- assess the impact on indoor air quality.

This step mainly consisted of aerosol chemistry analysis across a comprehensive panel of HPHCs.

Assessment of aerosol composition

As previously mentioned, the development of a product that significantly reduces the formation of HPHCs compared with cigarettes is central to the PMI approach to harm reduction. THS aerosol was analyzed to identify and characterize its HPHC profile in comparison with cigarette smoke (Section 6.1.1) (Schaller 2016a). This comparison is informed based on a list of HPHCs that was published by the FDA in 2012 (FDA 2012). The FDA published a preliminary list of 93 HPHCs, which focuses on chemicals that are linked to the five most serious health effects of tobacco use (cancer, cardiovascular disease, respiratory effects, reproductive problems, and addiction). Of those 93 HPHCs, FDA identified a subset of 18 HPHCs that are representative of the chemical classes present on the full list and that manufacturers have to quantify and report to FDA

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(FDA 2012). PMI chose to include those 18 HPHCs in its testing protocols along with additional analytes (see Table 2) that fulfilled the following criteria:

1. Priority toxicants in tobacco smoke as listed by regulatory bodies
2. Smoke constituent with established biomarkers of exposure (smoke/aerosol constituents or metabolites) and are not already included in criterion 1
3. HPHCs which are predominantly formed below 400°C and are not already included in criterion 1
4. HPHCs which are predominantly formed above 400°C, and are not already included in criterion 1
5. Product-specific analytes (such as glycerol and menthol)
6. Availability of well-established testing and analytical methods

In total, PMI assessed 58 analytes, which are listed in Table 2.

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Table 2: PMI-58 list of analytes (excluding product-specific analytes)

Analyte/Constituent	Health risk	Analyte/Constituent	Health risk
Acetaldehyde**,#	CA, RT, AD	Hydroquinone	(CA?)
Acetamide	CA	Isoprene**	CA
Acetone	RT	Lead	CA, CT, RDT
Acrolein**,#	RT, CT	Mercury	CA, RDT
Acrylamide	CA	Methyl ethyl ketone	RT
Acrylonitrile**	CA, RT	4-(methyl-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK)**,#	CA*
3-aminobiphenyl	NA	Nickel	CA*, RT
4-aminobiphenyl**	CA*	Nicotine**	RDT, AD
1-aminonaphthalene**	CA	Nicotine Free Dry Particulate Matter (NFDPM)	
2-aminonaphthalene**	CA*	Nitric oxide (NO)	NA
Ammonia**	RT	Nitrobenzene	CA, RT, RDT
Arsenic	CA*, CT, RDT	Nitrogen oxides (NOx)	RT, CT, RDT
Benz(a)anthracene	CA, CT	N-nitrosoanabasine (NAB)	CA
Benzene**,#	CA*, CT, RDT	N-nitrosoanatabine (NAT)	NA
Benzo(a)pyrene**,#	CA*	N-nitrosonornicotine (NNN)**,#	CA*
1,3-butadiene**,#	CA*, RT, RDT	Phenol	RT, CT
Butyraldehyde	RT, CT	Propionaldehyde	RT, CT
Cadmium	CA*, RT, RDT	Propylene oxide	CA, RT
Carbon monoxide**,#	RDT	Pyrene	(CA?)
Catechol	CA	Pyridine	RT
Chromium	CA*, RT, RDT	Quinoline	CA
m-Cresol	CA, RT	Resorcinol	RT
o-Cresol	CA, RT	Selenium	RT
p-Cresol	CA, RT	Styrene	CA
Crotonaldehyde**	CA	Toluene**	RT, RDT
Dibenz(a,h)anthracene	CA	*o*-Toluidine	CA*
Ethylene oxide	CA*, RT, RDT	Total particulate matter (TPM)^	
Formaldehyde**,#	CA*, RT	Vinyl chloride	CA*
Hydrogen cyanide	RT, CT	Water^	

Abbr.: AD = Addictive, CA = Carcinogen, CT =Cardiovascular Toxicant, NA = Not Attributed, RDT = Reproductive or Developmental Toxicant, RT = Respiratory Toxicant, * denotes IARC group 1 carcinogens, ** denotes the 18 HPHCs mandated for reporting by FDA. # denotes the 9 HPHCs mandated for reporting by WHO.
^ TPM consists of the total mass of aerosol captured on a filter pad (known as Cambridge filter). NFDPM is equal to the TPM minus the quantity of water and nicotine. TPM and NFDPM may contain HPHCs, but are not standalone HPHCs. Water is not an HPHC.

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The 58 analytes listed in Table 2 include 54 HPHCs, water, nicotine, Total Particulate Matter (TPM) and Nicotine Free Dry Particulate Matter (NFDPM). The quantification of the 58 analytes listed in Table 2 was performed in compliance with published international standards and practices. The levels of HPHCs found in the THS (Regular) and THS Menthol (mTHS) aerosols were compared with the levels in the 3R4F reference cigarette smoke. All aerosols and smoke samples were generated according to international standards, using the Health Canada parameters (Health Canada 2012). The 3R4F reference cigarette is supplied to all tobacco manufacturers by the University of Kentucky, USA and has been a long-established standard for cigarette smoke chemistry.

First, PMI measured the nicotine content in 3R4F smoke and in both THS and mTHS aerosols. While the nicotine content of 3R4F smoke is on average 1.8mg/stick, the THS and mTHS aerosols contain respectively 1.3mg nicotine/stick and 1.2mg nicotine/stick.

Second, PMI measured the menthol levels in the aerosols from Marlboro Smooth Menthol *HeatSticks* and Marlboro Fresh Menthol *HeatSticks*. The averages from three batches are 1.2 mg/stick and 2.5 mg/stick respectively. The latter corresponds to the menthol in aerosol of the mTHS Tobacco Sticks used in the aerosol chemistry, non-clinical and clinical studies reported in this application.

Third, PMI compared the constituent yields of 3R4F with those of THS and mTHS to demonstrate that THS aerosols contain significantly reduced levels of HPHCs. On a per-stick basis, the majority of measured constituents was reduced by 90% to 99% (Figure 8). The average reduction over all HPHCs (excluding nicotine) was greater than 90%. On an equivalent nicotine basis, the average reduction over all HPHCs (excluding nicotine) was greater than 89%. Some HPHCs were below the limit of quantification or detection. The full results, including their relative weights, are presented in Section 6.1.1.

As shown in Table 2, each HPHC is associated with one or more health risks, the majority being known or probable human *carcinogens*. On a per-stick basis, these carcinogenic HPHCs were reduced on average by more than 90% in both THS and mTHS. Among them, TSNAs are of special interest as they are not generated by combustion but directly transferred from tobacco to smoke in CCs or to aerosol in THS. For instance, NNN and NNK are reduced by >95% in both THS and mTHS aerosols compared with 3R4F smoke. While their yields are influenced by parameters such as tobacco blend composition and manufacturing processes, their markedly reduced yields in THS aerosol are most likely due to a reduced level of evaporation in THS compared with 3R4F (Schaller 2016b). Indeed, a recent study (Forster 2015) showed that the percentage TSNAs released from the tobacco into the aerosol at temperatures between 100°C to 200°C was very low (<10%) compared to the amounts available in the tobacco rod.

The HPHCs classified as *cardiovascular* toxicants or *reproductive or developmental* toxicants (except nicotine) were reduced by more than 90% in both THS and mTHS. *Respiratory* toxicants were reduced by more than 87% in both THS and mTHS.

PMI has demonstrated that both THS and mTHS generate aerosols with significantly reduced levels of HPHCs (Schaller 2016a); the differences between the THS and mTHS aerosols are ≤ 6% on a per-stick basis. This was a significant first step towards

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demonstrating that switching from cigarettes to THS or mTHS reduces harm and the risk of smoking related diseases, particularly as many of these 58 analytes and constituents are linked to the most serious health effects of tobacco use.

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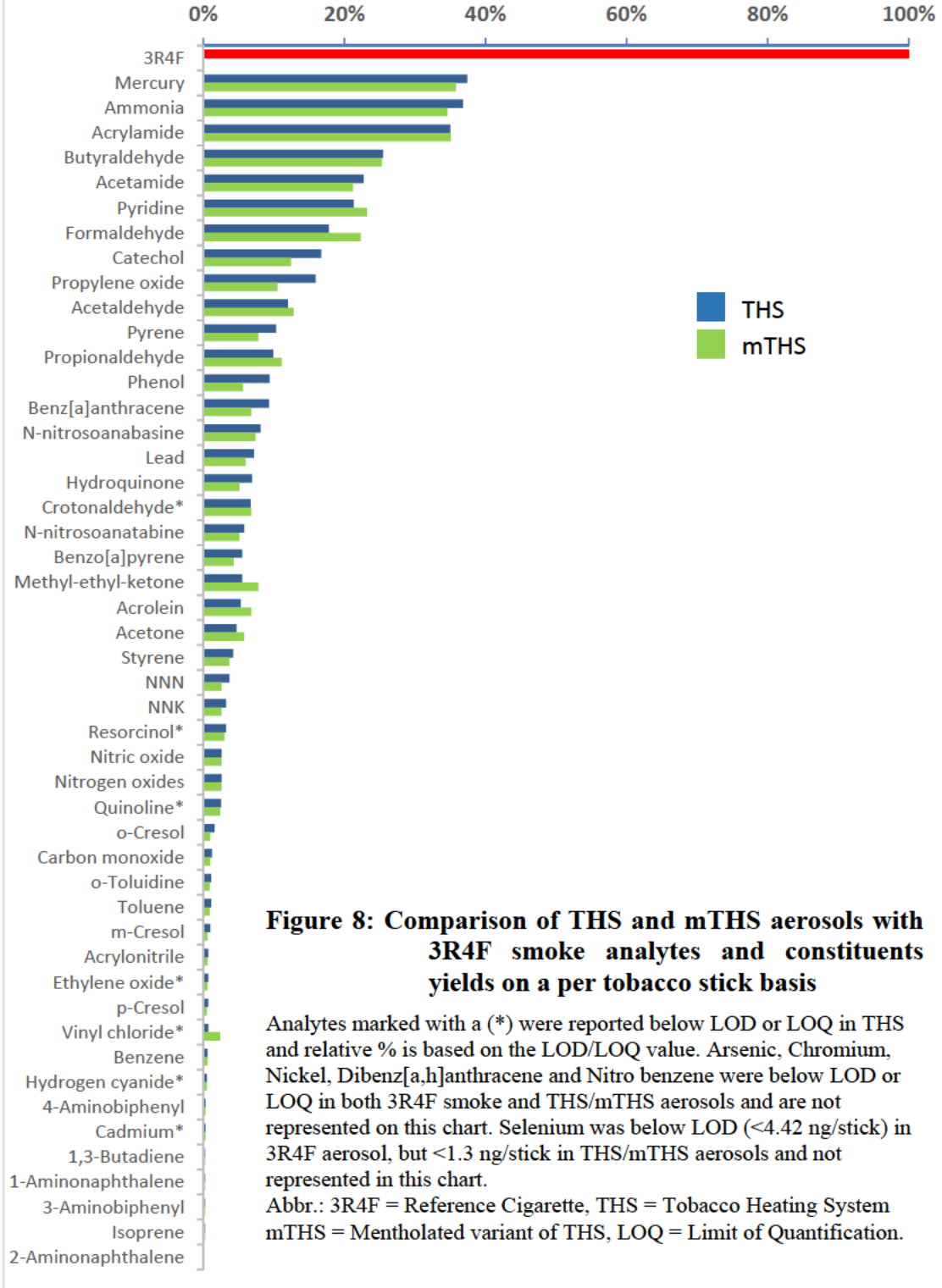


Figure 8: Comparison of THS and mTHS aerosols with 3R4F smoke analytes and constituents yields on a per tobacco stick basis

Analytes marked with a (*) were reported below LOD or LOQ in THS and relative % is based on the LOD/LOQ value. Arsenic, Chromium, Nickel, Dibenz[a,h]anthracene and Nitro benzene were below LOD or LOQ in both 3R4F smoke and THS/mTHS aerosols and are not represented on this chart. Selenium was below LOD (<4.42 ng/stick) in 3R4F aerosol, but <1.3 ng/stick in THS/mTHS aerosols and not represented in this chart.
Abbr.: 3R4F = Reference Cigarette, THS = Tobacco Heating System mTHS = Mentholated variant of THS, LOQ = Limit of Quantification.

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Absence of combustion

A combustion process – burning and the formation of smoke with solid particles and high levels of HPHCs – is the defining characteristic of a cigarette. When a cigarette is lit, the combination of tobacco (fuel) and oxygen in the air generate a self-sustaining combustion process that consumes the tobacco. During the natural smoldering of a cigarette (between puffs), temperatures between 600°C and 800°C occur in the center of the burning cone (Baker 1975). During a puff, the temperature increases to more than 900°C at the periphery of the burning zone.

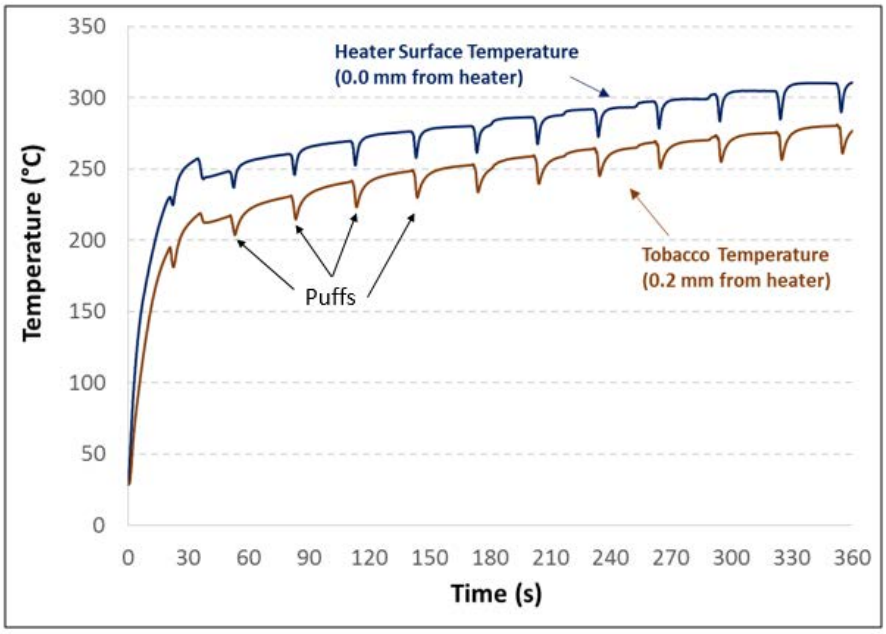


Figure 9: THS temperature profiles

Temperature profiles was measured at (i) the interface between the heating element and the tobacco substrate and (ii) in the tobacco plug (at 0.2 mm from the heating element) during product use. The reported temperatures are the average of five replicates

PMI has generated several lines of evidence demonstrating that there is no combustion in THS (Appendix A3.2.1-1):

1. The highest observed temperature of the tobacco in the Tobacco Stick is approximately 300°C (measured 0.2 mm from the heater blade) and cannot exceed 350°C (the programmed maximum temperature of the heater) (Figure 9). This is well below the temperature required for tobacco combustion (known to be in excess of 400°C); in fact, the temperature of most of the tobacco is significantly below 250°C (Section 3.2.1.1.2).
2. Contrary to the increase in temperature that occurs when a puff is taken with a lit-end cigarette, there is significant drop in the temperature of the tobacco in the

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Tobacco Stick when a puff is taken (Figure 9). More importantly, when the energy source is switched off, the temperature of the tobacco begins to decrease. Because combustion is a self-sustaining process, the decrease in temperature indicates an absence of combustion.

3. Since combustion does not occur, the structural integrity of the Tobacco Stick is retained after use. The tobacco is not consumed, as it is in a cigarette, and no ash is formed.
4. The aerosol generated by THS in an atmosphere of pure nitrogen (where combustion cannot occur) contained equivalent levels of HPHCs than the aerosol generated in air (21% oxygen). PMI tested THS in a chamber with air and in a chamber filled only with nitrogen, where one of the essential elements of combustion (oxygen) was absent. The aerosol was equivalent under both atmospheres supporting the view that combustion does not occur during THS use.
5. Combustion of tobacco in cigarettes generates solid ultra-fine particles with a median diameter below 100 nm (Pratte 2016), which have been shown to be cytotoxic (Fariss 2013). PMI analyzed both THS aerosol and cigarette smoke for the presence of solid particles by stripping them of their volatile constituents. This was achieved by passing the aerosol and smoke through a commercial Dekati thermo-denuder operating at 300°C. The analysis of the materials collected during this process by scanning electron microscopy revealed that the THS aerosol does not contain solid particles, and confirmed that cigarette smoke does (each 3R4F cigarette contains approx. 10^{12} ultra-fine particles) (Figure 10) (Pratte 2016).
6. Finally, as demonstrated above, the THS aerosol contains substantially lower levels of HPHCs compared to cigarette smoke. Importantly, nitrogen oxides (NO_x) and carbon monoxide (CO), two important combustion markers, were reduced by over 97%.

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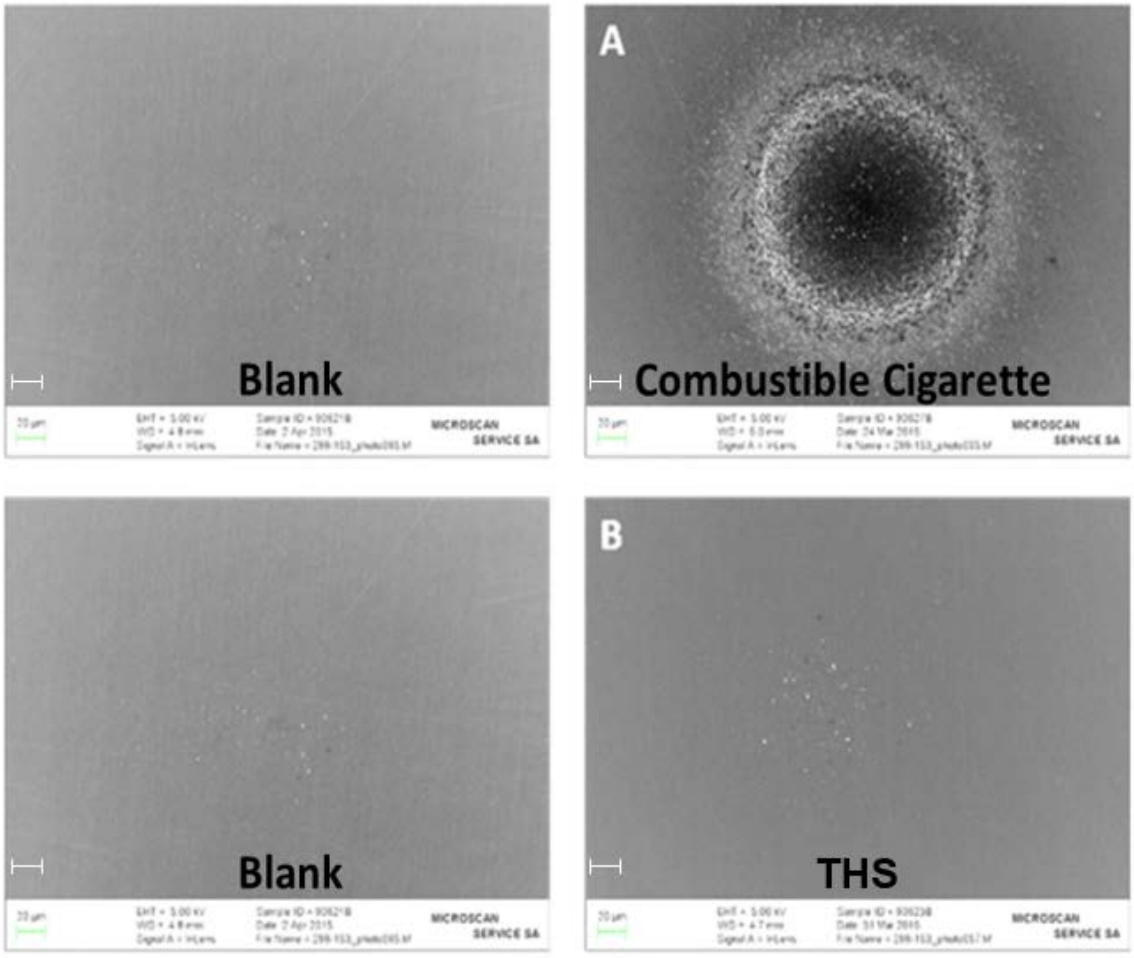


Figure 10: Comparison of scanning electron microscopy images determined for combustible cigarette smoke (3R4F reference cigarette) (A) and THS aerosol (B)

The scanning electron microscopy image of the respective blanks run prior to cigarette smoke and THS aerosol generation are shown on the left. The white scale bar (bottom left of each panel) corresponds to 20µm.

Abbr.: THS = Tobacco Heating System

In conclusion, there is convincing evidence that no combustion occurs in THS.

Assessment of aerosol particle size

The physical property of an aerosol is characterized by two main parameters. These are the Mass Median Aerodynamic Diameter (MMAD), and the Geometric Standard Deviation (GSD), which describes the distribution of the mass around the MMAD. Aerosol generated from heating tobacco is composed of liquid droplets, the size (and size distribution) of which determines whether they are respirable, as well as their behavior during inhalation. The aerosol droplets formed by cigarettes (MMAD = 0.8µm, GSD =

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1.3) are within the respirable range (i.e. below 4µm) and are known to grow in size when inhaled due to mechanisms such as hygroscopic growth and coagulation. However, the particles remain in the respirable range.

The droplet size distribution of the THS aerosol, produced using the Health Canada Intense regime, has been analyzed using the PIXE cascade impactor (the reference technique for inhaled pharmaceutical products). The droplet size distribution of THS aerosols (MMAD = 0.7µm, GSD = 1.5) falls within the respirable range (Section 6.1.1.3.3) and is not significantly different from that of cigarettes.

Assessment of Indoor Air Chemistry

The FDA Draft Guidance requires that MRTPs be assessed for their potential to expose non-users of tobacco products to HPHCs. Therefore, PMI conducted additional studies to assess the effects of THS use on indoor air chemistry quality (IAQ) in comparison to cigarette smoking (Section 5.1.2.2). Unlike the lit-end of a cigarette, which produces side stream smoke, THS emits minimal amounts of spontaneous aerosol. Therefore, THS has, by design, a substantially lower impact in IAQ than cigarettes.

The objective of the indoor air chemistry and quality studies was to assess the impact of THS compared with cigarette emissions. For that purpose, four environmental conditions were simulated according to EN 15251:2007: “Hospitality”, “Office”, and two “Residential” settings briefly described in the legend to Figure 11 (Goujon-Ginglinger 2015, Mitova 2016).

The impact of THS on IAQ was evaluated, using a panel of THS users, in an environmentally controlled room using ventilation conditions recommended for simulating “Office”, “Residential” and “Hospitality” environments. It was compared with that of smoking a lit-end cigarette (Marlboro Gold) (by a panel of smokers) under identical experimental conditions. The concentrations of eighteen indoor air constituents (respirable suspended particles (RSP) <2.5 µm in diameter), ultraviolet particulate matter (UVPM), fluorescent particulate matter (FPM), solanesol, 3-ethenylpyridine, nicotine, 1,3-butadiene, acrylonitrile, benzene, isoprene, toluene, acetaldehyde, acrolein, crotonaldehyde, formaldehyde, carbon monoxide, nitrogen oxide, and combined oxides of nitrogen) were measured. All testing methods were ISO 17025 accredited. The background concentrations of all constituents were determined when the panelists were present in the environmentally controlled room under equivalent conditions, but did not smoke or use THS. The experimental details are described in Mitova 2016.

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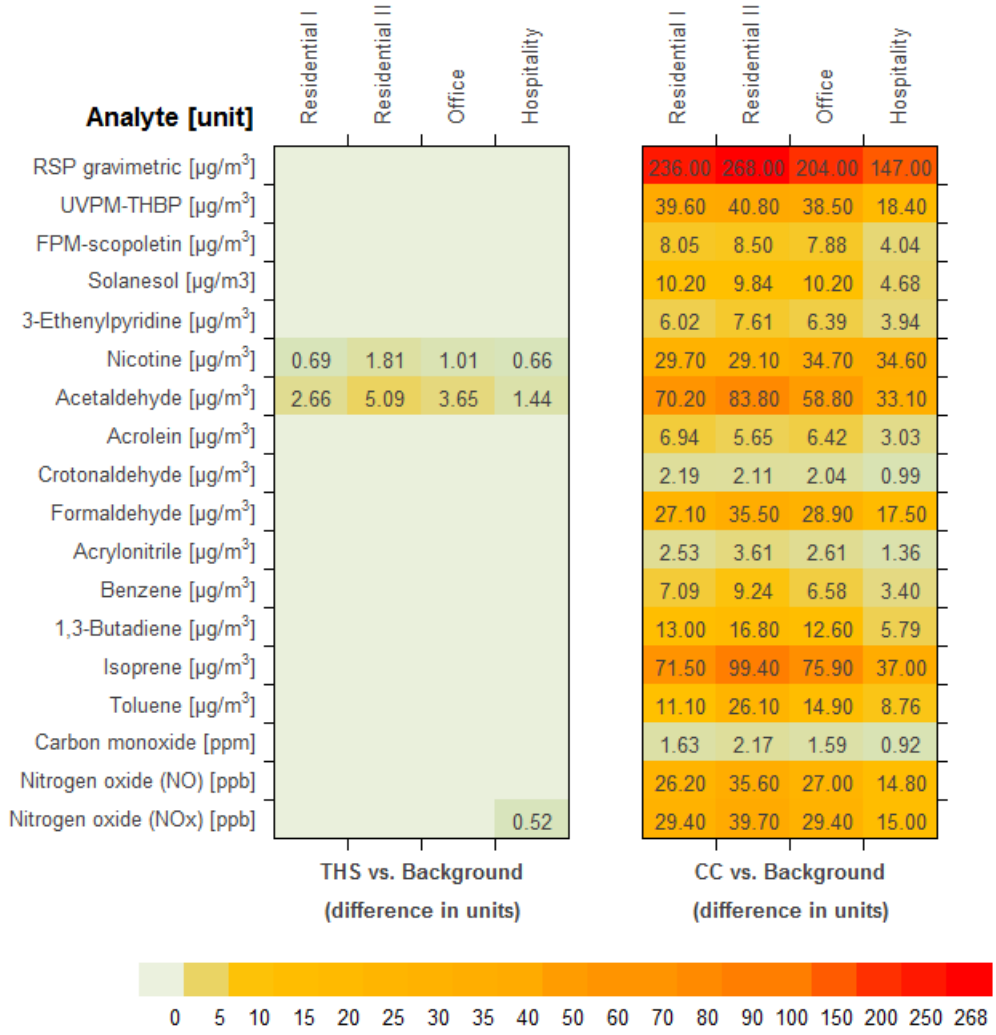


Figure 11: THS and cigarette indoor air chemistry assessment

Background levels are subtracted. Environmental conditions: "Hospitality": 7.68 air changes/h, 4 smokers consuming 2 items/h; "Office": 2.16 air changes/h, 2 smokers consuming 2 items/h; "Residential I": 1.68 air changes/h, 2 smokers consuming 1.5 items/h; "Residential II": 1.20 air changes/h, 2 smokers consuming 1.5 items/h.

Abbr. CC = Conventional Cigarette, FPM = Fluorescent Particulate Matter (FPM-scopoletin equivalent), RSP = Respirable Suspended Particles (RSP-gravimetric), THS = Tobacco Heating System, UVPM-THBP = Ultra-Violet Particulate Matter, VOCs = Volatile Organic Compounds. Items refers to *HeatSticks* and Marlboro Gold cigarettes.

The results of these measurements are summarized in Figure 11 (Goujon-Ginglinger 2015, Mitova 2016). When THS is used under any of the four simulated conditions, the concentrations of most studied analytes did not exceed their respective background concentrations. Only acetaldehyde and nicotine concentrations were increased above background concentrations under all simulated environmental conditions, but reaching a maximum of 5.09µg/m^3 and 1.81µg/m^3 respectively under "Residential II" conditions.

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This is most likely due to the aerosol exhaled by the panelists. In contrast, cigarette smoking resulted in far greater increases in acetaldehyde and nicotine concentrations reaching a maximum of 83.80µg/m^3 and 29.10µg/m^3 respectively under identical conditions. Furthermore, cigarette smoking results in a marked increase of all other measured indoor air constituents under all simulated environmental conditions.

The maximum acetaldehyde concentration during use of THS under "Residential II" conditions was well below the minimal risk level for chronic exposure (140 µg/m^3) of the California Office of Environmental Health Hazard Assessment (OEHHA 2008) and the proposed exposure limit of 200 µg/m^3 in the European Union (Kotzias 2005). Similarly, the maximum nicotine concentration during use of THS under "Residential II" conditions was well below the indicative occupational exposure limit of 500 µg/m^3 in the European Union (EU and Council 2006) and the permissible exposure limit of 500 µg/m^3 defined by the U.S. Occupational Safety and Health Administration (Occupational Safety and Health Administration 1978).

Summary of aerosol chemistry assessment (Step 2)

In summary, the chemical analysis of the THS and mTHS aerosols (Step 2) have demonstrated that they contain similarly reduced levels of HPHCs compared with 3R4F cigarette smoke, and that THS use does not negatively impact air quality. Furthermore, the studies show that THS does not cause the combustion of the Tobacco Stick and that the THS aerosol is within the respirable range. Therefore, PMI met its objectives for Evidence Level I.

Standard Toxicology Assessment (Step 3)

Steps 1 and 2 of the assessment program showed that heating tobacco, instead of burning, leads to the reduced formation of HPHCs by THS compared with cigarettes. The objective of Step 3 of the assessment is to evaluate whether the reduction in HPHC levels delivered by the THS aerosol results in a concomitant reduction in toxicity. Reduced toxicity is a prerequisite for reduced risk of harm and smoking-related disease. Studies designed to evaluate the absolute and relative toxicity of the THS aerosol are critical to substantiate the reduced-risk profile of THS. The studies consisted of standard toxicology assessments across multiple *in vitro* and *in vivo* test systems. The assessment included a range of well-established and internationally recognized toxicological assays. All studies were performed according to the Organisation for Economic Co-operation and Development (OECD) Good Laboratory Practice (GLP) guidelines (OECD 1998).

In vitro assessment of cytotoxicity and genotoxicity

PMI performed three *in vitro* assays to assess the cytotoxicity and the genotoxicity of THS and mTHS aerosol fractions (Section 6.1.2.2). These assays were the Neutral Red Uptake (NRU) cytotoxicity assay (Section 6.1.2.2.1), the Ames bacterial mutagenicity assay (Section 6.1.2.2.2) and the Mouse Lymphoma Mammalian Mutagenicity Assay (MLA) (Section 6.1.2.2.3). The studies are designed to compare the effects of the total particulate matter (TPM) and gas vapor phase (GVP) of the THS and mTHS aerosols with those of the corresponding fractions of 3R4F reference cigarette smoke (Table 3). The findings of all three studies were consistent with reduced toxicity of THS aerosol.

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The NRU assay results showed that on a per mg nicotine basis, the *in vitro* cytotoxicity of the THS and mTHS aerosol fractions was reduced by approximately 90% for both TPM and GVP compared with the 3R4F reference item.

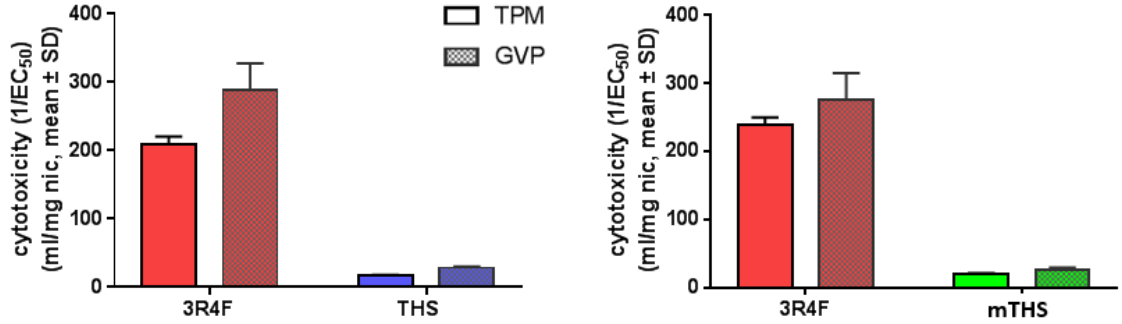
The results from the Ames assay of bacterial mutagenicity showed that TPM of THS and mTHS aerosols had no mutagenic activity in the different strains tested (even at 10-fold higher levels of exposure compared with 3R4F) whereas reproducible mutagenic responses were observed for the TPM from 3R4F. Similarly, the results from the MLA showed that in any of the testing conditions, THS and mTHS aerosol TPM and GVP were at least eight-fold less mutagenic than 3R4F (mutagenic responses with lowest observable genotoxicity effect levels (LOGEL)).

The combined results of cytotoxicity and genotoxicity testing has demonstrated that THS and mTHS are significantly less cytotoxic and genotoxic than the smoke from cigarettes (Schaller 2016a).

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Table 3: *In vitro* assessment of THS aerosol

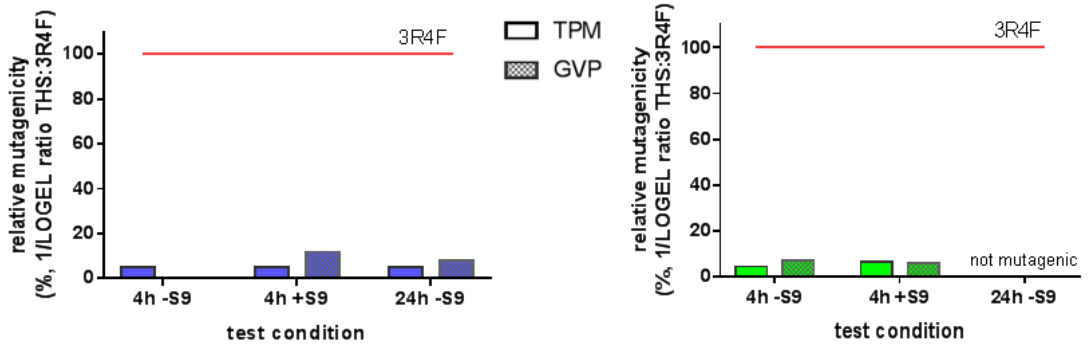
A. Cytotoxicity assessment	
Assay	**Neutral Red Uptake (NRU) assay**
Description	• Cell survival/viability assay based on the ability of viable cells to incorporate and bind NR. • Cytotoxicity is expressed as a concentration dependent reduction of the uptake of NR after chemical exposure, thus providing a sensitive, integrated signal of both cell integrity and growth inhibition
Results	• TPM and GVP of THS aerosol (regular and menthol) were tested in comparison to the corresponding fractions of 3R4F reference cigarette smoke. • Concentration of TPM and GVP that have reduced the number of viable cells by 50% (EC_{50}) were determined for THS aerosol and 3R4F smoke. • THS: On a per mg nicotine basis, the *in vitro* cytotoxicity of the aerosol fractions was reduced by 91.7% for TPM and 90.2% for GVP compared with 3R4F. • mTHS: On a per mg nicotine basis, the *in vitro* cytotoxicity of the aerosol fractions was reduced by 91.8% for TPM and 90.6% for GVP compared with 3R4F.
	
Cytotoxicity of 3R4F, THS and mTHS on nicotine basis.	
B. Genotoxicity assessment	
Assay	**Ames bacterial mutagenicity assay (Ames assay)**
Description	• Sensitive bacterial cell reverse mutation assay testing the ability of a chemical substance or mixture to induce mutations in DNA. • In the absence of an external histidine source, bacterial cells cannot grow to form colonies. • Colony growth is resumed if a reversion of the mutation occurs, allowing the intrinsic production of histidine. • Spontaneous reversions occur with each of the strains. • TPM is tested in the absence and the presence of metabolic activation (S9-fraction) in five *Salmonella typhimurium* strains: TA98, TA100, TA102, TA1535, and TA1537. • Mutagenic compounds cause an increase in the number of revertant colonies relative to the background level.

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Results	• Ames assay was performed with TPM from 3R4F smoke and THS aerosol • All bacterial strains used showed the expected response with a control substance. • TPM from THS and mTHS aerosols did not show mutagenic activity, over the dose range tested (up to 10mg/plate), in the different strains tested, while reproducible mutagenic responses were observed for the TPM from 3R4F smoke in strains TA98, TA100 and TA1537 in the presence of S9.
Assay	**Mouse Lymphoma Assay (MLA)**
Description	• Mammalian cell mutation assay used to test the ability of a chemical substance or mixture to induce mutations in DNA. • Cytotoxicity is determined by measuring the relative cloning efficiency (survival) or relative total growth of the cultures after the treatment period. • Mutagenicity is determined in 2 independent tests using different testing conditions, i.e. upon incubating cells for 4h or 24h with aerosol fractions. The 4h treatment is done in absence or presence of metabolic activation with S9.
Results	• Mouse lymphoma cells were exposed to TPM and GVP from either THS aerosol or 3R4F smoke and sub-cultured to determine cytotoxicity and allow phenotypic expressions of induced mutations prior to mutant selection. • The 24h testing conditions did not show reproducible mutagenic responses for any of the aerosol fractions across the studies. • THS: In the 4h testing conditions, TPM of the aerosol was at least 14-fold less mutagenic than 3R4F on a nicotine basis; GVP of the aerosol was at least 8-fold less mutagenic than 3R4F on an item basis (mutagenic responses with LOGEL). • mTHS: In the 4h testing conditions, TPM of the aerosol was at least 9-fold less mutagenic than 3R4F on a nicotine basis; GVP of the aerosol was at least 14-fold less mutagenic than 3R4F on an item basis (mutagenic responses with LOGEL).



Percentage of relative mutagenicity reduction in THS (left panel) and mTHS (right panel, on a per item basis, calculated from LOGELs.

When repeat tests yielded different LOGEL ratios, the lowest value (most mutagenic) is shown.

Abbr.: 3R4F = reference cigarette, DNA = Deoxyribonucleic Acid, EC_{50} = concentration of exposure that reduces the number of viable cells by 50%, GVP = Gas Vapor Phase, LOGEL = Lowest Observational Genotoxic Effect Levels, mTHS = Tobacco Heating System menthol variant, NR = Neutral Red, NRU = Neural Red Uptake, THS = Tobacco Heating System, TPM = Total Particulate Matter

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In vivo toxicology assessment

90-day sub-chronic inhalation study in rats

In addition to the *in vitro* toxicological assessment, PMI conducted two independent 90-day inhalation studies according to the OECD Testing Guideline 413 (Section 6.1.2.3.1). The first study was conducted with THS (Figure 7) (Wong 2016) and the second with a mentholated variant (mTHS) (Oviedo 2016). The objective of these studies was to compare the systemic toxicity and respiratory tract effects of the THS aerosols and cigarette smoke in Sprague-Dawley rats. In both studies, animals were nose-only exposed (6 hours/day, 5 days/week, 13 weeks) to three target concentrations of THS aerosol, and to one or more concentrations of 3R4F smoke. As 3R4F smoke is very different from THS aerosol, the concentrations of the exposure atmospheres were calibrated based on nicotine concentrations (e.g. for 3R4F 23 µg nicotine/L corresponds to 300 g/L of TPM). The concentrations of THS and mTHS aerosols were set at 15, 23 and 50 µg nicotine/L in both studies. For cigarette smoke, the concentrations were set at 8, 15 and 23 µg nicotine/L in the THS study or at 23 µg nicotine/L in the mTHS study. The mTHS study included animals exposed to mentholated reference cigarettes (MRC) with aerosol menthol concentrations matching those in mTHS. The highest aerosol concentration used in both THS and mTHS studies was twice that of the highest cigarette smoke concentration, which corresponds to the maximum tolerable carbon monoxide concentration under the exposure conditions of the studies. A control arm (sham) with animals exposed to fresh conditioned air under the same experimental conditions was included in both studies.

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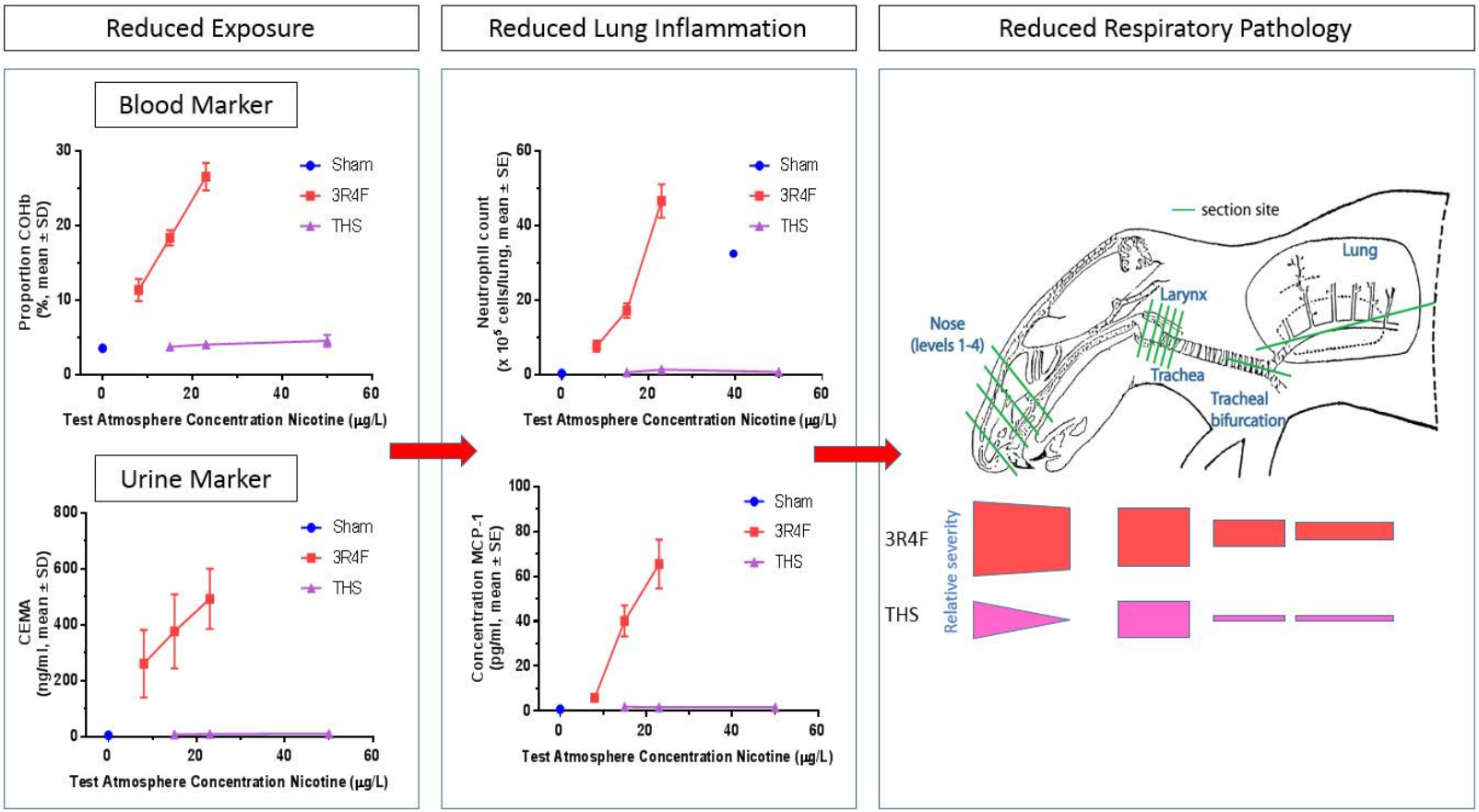


Figure 12: Summary of the 90-day inhalation study results

This *in vivo* study was conducted to compare the toxicity of THS with that of 3R4F. The reduced exposure to HPHCs leads to reduced lung inflammation, which in turn leads to reduced respiratory pathology findings.

Abbr. 3R4F = Reference Cigarette 3R4F, THSR = Tobacco Heating System Regular (without menthol), COHb = Carboxyhemoglobin, CEMA = 2-cyanoethylmercaturic acid, MCP-1 = monocyte chemoattractant protein 1.

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To confirm the appropriate exposure of the animals, cigarette smoke and aerosol exposures were monitored by on-line carbon monoxide measurements and daily determinations of both nicotine and TPM concentrations in the breathing zone of the exposure chambers. Using blood and urine samples, the uptake of the aerosol was monitored through quantification of BoExp to key HPHCs as well as the main nicotine metabolites. PMI observed that the lower irritancy of the THS aerosol (compared with 3R4F smoke) resulted in a slightly higher THS aerosol uptake compared with 3R4F smoke (Table 4A). Nevertheless, animals exposed to THS aerosols were exposed to markedly lower levels of HPHCs, even at a nicotine dose twice as high as the highest 3R4F smoke exposure (Section 6.1.3.2.4).

An overview of key endpoints is shown in Table 4. The data obtained across all endpoints (e.g. in-life observations, clinical pathology, histopathology, and lung inflammation) demonstrate that THS aerosol is significantly less toxic than 3R4F smoke. THS aerosol exposure, compared with the effects of sham exposure, reveals slight systemic toxicity of THS. These changes have also been observed in animals exposed to aerosolized nicotine (Phillips 2015a). Similar results have been obtained when exposing rats to mTHS aerosol, showing a lower toxicity than both 3R4F and mentholated reference cigarette smoke.

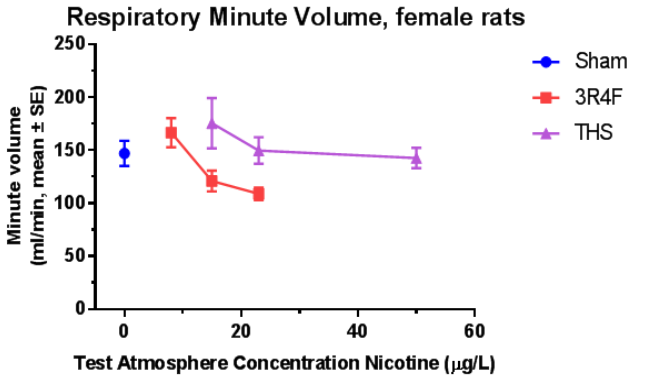
Taken together, these studies demonstrate that the reduced exposure to HPHCs achieved with both THS and mTHS aerosols leads to a significantly reduced toxicity profile of THS/mTHS aerosol compared with cigarette smoke. Furthermore, the effects induced by THS aerosol exposure were not different from those induced by mTHS aerosol exposure.

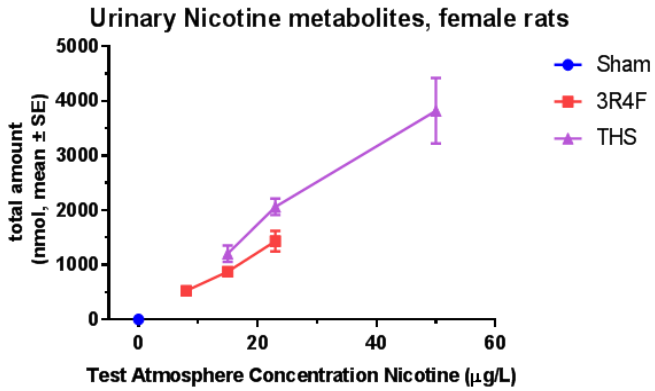
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Table 4: Sub-chronic 90-day inhalation studies - selected endpoints and results. Full results available in Section 6.1.2.3.1.

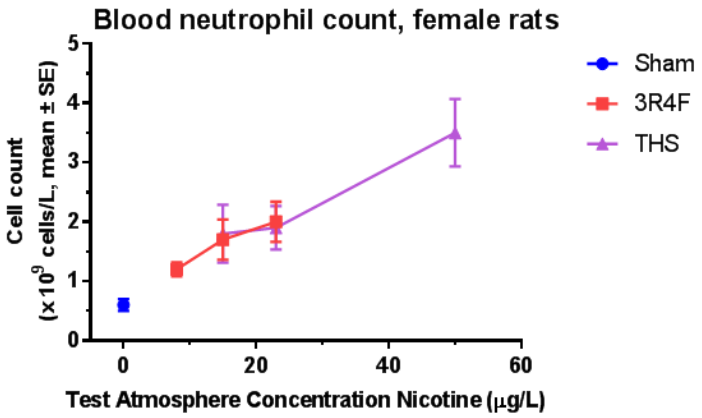
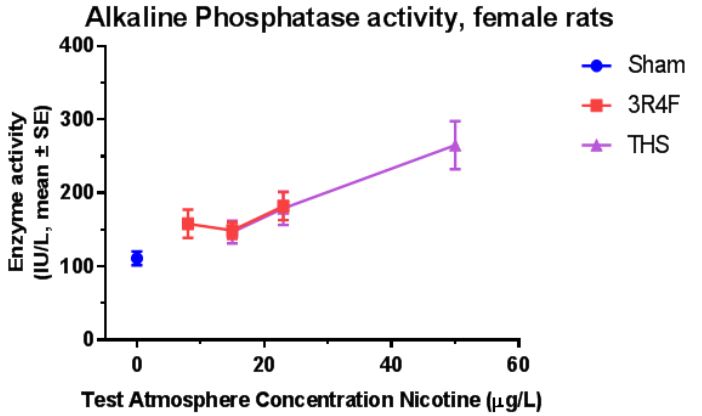
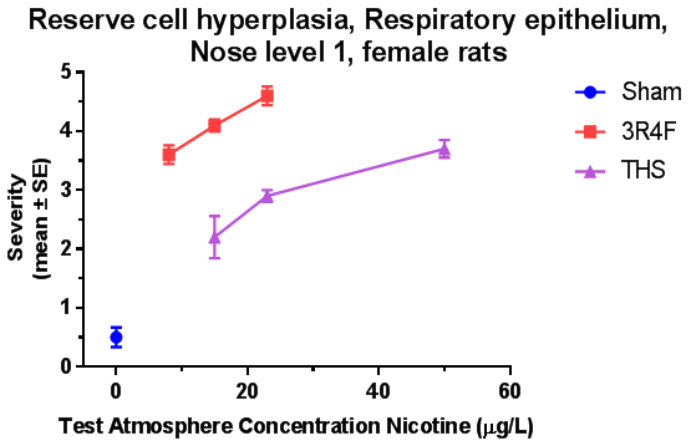
A: 90-day inhalation study conducted with THS	
Endpoint	**Outcome**
Body weight development	Lower weight gain in male 3R4F-exposed group compared to THS and sham group.
In-life health status and mortality	No remarkable exposure-related in-life observations in all groups with the exception of a few incidences of mild to moderate tremor occurring in rats exposed to the aerosols with high nicotine concentration. No test-substance-related mortality was observed.
Respiratory Physiology and aerosol uptake	Higher respiratory minute volume in THS aerosol exposed rats compared with 3R4F. The lower irritancy of the THS aerosol results in a higher aerosol uptake compared with 3R4F.





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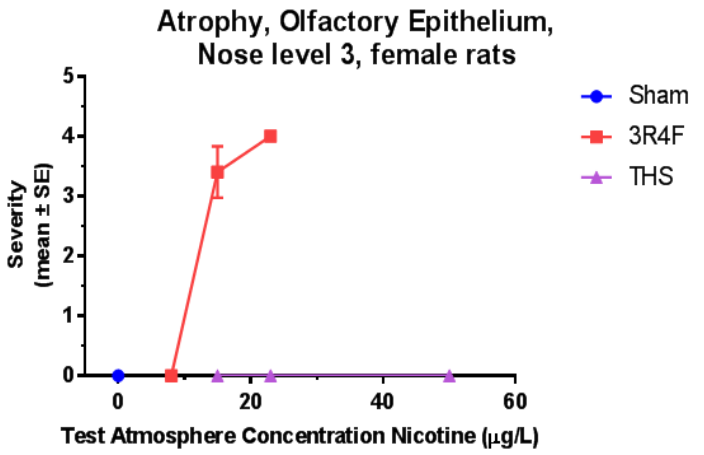
Clinical pathology parameters	Nicotine concentration-dependent changes in THS aerosol and 3R4F smoke exposed rats compared to sham exposure included higher blood neutrophil count, higher liver enzyme activities and lower glucose and cholesterol concentrations. This was paralleled by higher liver, adrenal gland and lower thymus weights. Higher lung, larynx, and trachea weights upon THS aerosol exposure, but less pronounced than in 3R4F smoke-exposed rats.	 
Histopathology of the respiratory tract	Changes observed in the respiratory tract of THS aerosol exposed rats were of lower severity than those in 3R4F smoke-exposed rats. In the nasal cavity THS aerosol caused changes (minimal to moderate severity) only in the epithelia at nose level 1 and 2 (hyperplasia and squamous metaplasia of the respiratory epithelium), not at nose level 3 and 4.	

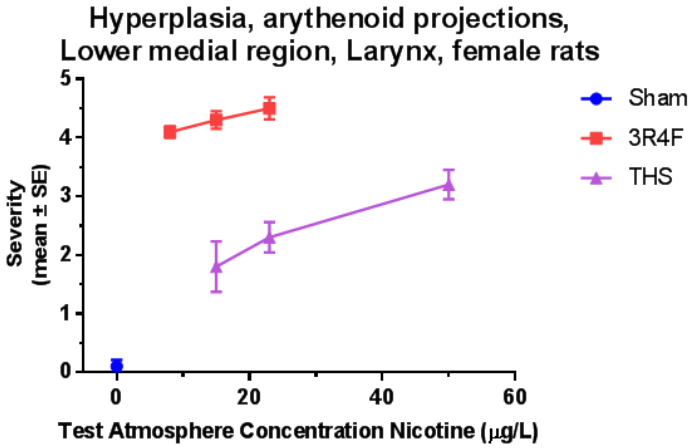
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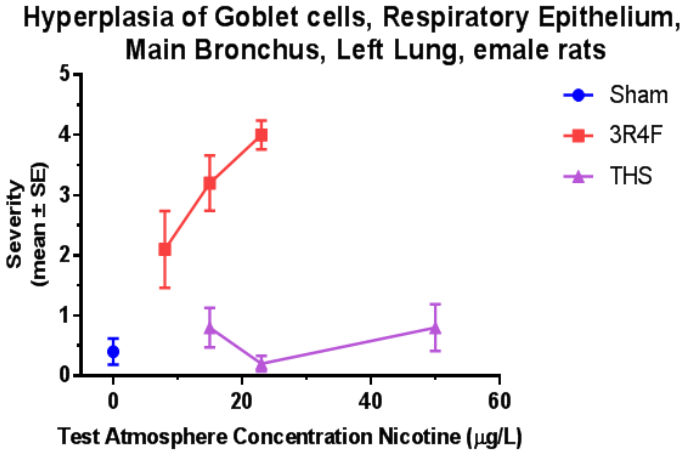
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In the larynx, THS aerosol exposed rats showed minimal to moderate hyperplastic epithelial changes with significantly less severity than 3R4F exposed rats.





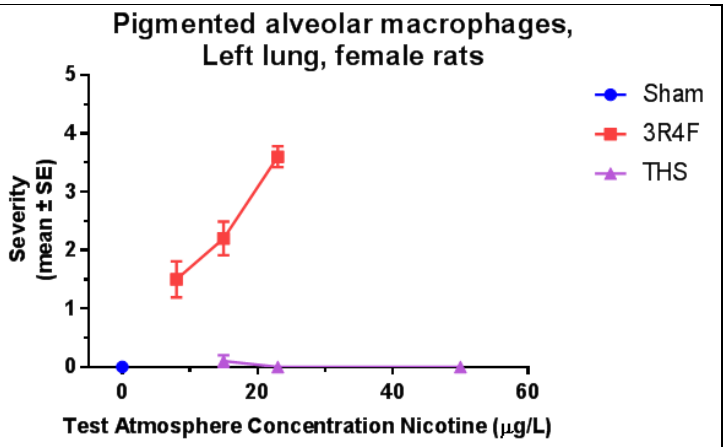
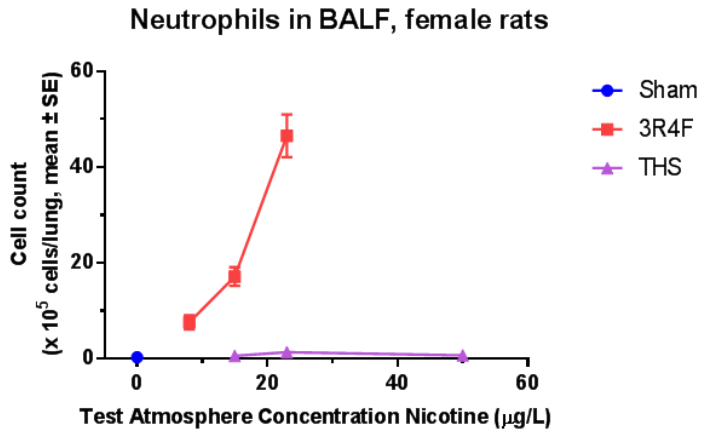
In the trachea and main bronchus, THS aerosol exposure caused minimal changes; there were no pigmented alveolar macrophages in the lung.



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Lung inflammation	No significant changes in immune cell counts in bronchoalveolar lavage fluid in THS aerosol exposed rats. Cytokines concentrations in bronchoalveolar lavage fluid were much lower in THS and sham as compared with smoke exposed rats.	
B: 90-day inhalation study conducted with mTHS		
Body weight development	Lower weight gain in male 3R4F and MRC-exposed groups compared with THS and sham groups	
In-life health status and mortality	No remarkable exposure-related in-life observations in all groups with the exception of a few incidences of mild to moderate tremor occurring in rats exposed to the aerosols with high nicotine concentration. No test-substance-related mortality.	
Clinical pathology parameters	Nicotine concentration-dependent changes in mTHS aerosol, 3R4F, and MRC smoke exposed groups compared to sham included higher blood neutrophil count, lower lymphocyte count, higher liver enzyme activities and lower glucose and cholesterol concentrations. This was paralleled with higher liver, adrenal gland and lower thymus weights. Higher lung, larynx, and trachea weights upon mTHS aerosol exposure, but less pronounced than in 3R4F and MRC smoke-exposed rats.	
Histopathology of the respiratory	Changes observed in the respiratory tract of mTHS aerosol exposed rats were of lower severity than those in 3R4F and MRC smoke-exposed rats.	

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tract	In the nasal cavity mTHS aerosol caused changes (minimal to moderate severity) only in the epithelia at nose level 1 (hyperplasia and squamous metaplasia of the respiratory epithelium); minimal or no changes at nose level 2 and no changes at nose level 3 and 4. In the larynx, mTHS aerosol exposed rats showed minimal to mild hyperplastic epithelial changes and squamous metaplasia to a significantly less severity than 3R4F and MRC exposed rats. In the trachea and main bronchus, no relevant mTHS aerosol exposure effects were noted; there were no pigmented alveolar macrophages in the left lung; no difference from sham.
Lung inflammation	No significant changes in immune cell counts present in bronchoalveolar lavage in mTHS aerosol exposed rats Cytokines in bronchoalveolar lavage fluid were much lower in mTHS and sham as compared with smoke exposed rats
Abbr. 3R4F = Reference Cigarette 3R4F, MRC = mentholated reference cigarettes, mTHS = Tobacco Heating System menthol variant, THSR = Tobacco Heating System Regular (without menthol).	

A/J mouse inhalation study

To assess the combined chronic toxicity and carcinogenicity upon exposure of mice to THS aerosol, compared with 3R4F smoke, a lifetime study was conducted with A/J mice (Section 6.1.2.3.2). This mouse strain has been shown to be susceptible to develop pulmonary emphysema and an increase in lung tumors upon exposure to cigarette smoke. In an 18-month A/J inhalation study, mice were exposed to fresh air (sham), 3R4F smoke corresponding with a test atmosphere concentration of 13.4µg/L nicotine, or THS aerosol equivalent to nicotine concentrations of 6.7 (Low), 13.4 (Medium) or 26.8µg/L (High). Mice were exposed for 6 hours per day, 5 days per week, for up to 18 months following OECD Test Guideline 453 (OECD 1998).

While the analysis of the 18 months dissection time point is ongoing, key data from the interim dissections at months 1, 5 and 10 are part of this application. These include the histopathological evaluation of respiratory tract organs, lung function and markers of pulmonary inflammation (the latter two were only collected at months 1 and 5). The final study report will be submitted to FDA upon its completion.

BALF analysis

Analysis of BALF confirmed lung inflammation in 3R4F smoke exposed A/J mice, with higher total free lung cell counts at months 1 and 5 relative to sham animals. In contrast, neither total free lung cells nor differential cell counts were different between sham and the THS aerosol exposed animals. In addition, of 54 soluble mediators analyzed in BALF, 39 analytes including inflammatory, chemotactic, and growth factors were increased in samples of 3R4F smoke exposed compared with sham exposed animals at month 1. Similarly, 38 of 53 analytes were increased in BALF samples of 3R4F smoke exposed animals compared with sham exposed animals at month 5. In contrast, only one analyte (myoglobin) showed a concentration-dependent increase in the BALF of THS aerosol exposed A/J mice at month 5.

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Histopathology analysis

The nasal respiratory and olfactory epithelia displayed moderate to marked reserve cell and goblet cell hyperplasia as well as squamous metaplasia following exposure to 3R4F smoke. In contrast, THS aerosol exposure induced only minimal to mild hyperplasia in the nose. Similarly, reserve cell hyperplasia and squamous metaplasia in the larynx were prominent histopathological findings in 3R4F smoke exposed animals, which occurred less frequently and extensively in those exposed to THS aerosol, irrespective of exposure concentration. In contrast to 3R4F smoke-exposed mice, no epithelial cornification was developed in the THS aerosol-exposed animals. In addition, typical cigarette smoke exposure related epithelial changes, including epithelial hyperplasia and squamous metaplasia, were found at the carina of bifurcation at months 5 and 10, while tracheas from A/J mice exposed to THS aerosol did not exhibit any remarkable exposure-related effects.

The lungs of 3R4F smoke exposed animals exhibited inflammatory cell infiltrates from month 1 onward, and these were absent in the animals from the THS and sham study groups. Histopathological evaluation confirmed the presence of mild to moderate emphysematous lesions in mice exposed to 3R4F smoke for 5 and 10 months. In contrast, lungs of THS aerosol exposed mice showed no signs of the alveolar destruction typical of emphysema.

Lung function

The impact of cigarette smoke on lung function over time was measured through quantitative pressure, flow, and volume relationships in the respiratory tract – (PV loops). In the A/J mouse study, lung function was assessed at months 1 and 5. Cigarette smoke exposed animals showed an upward/leftward shift in PV loops from the sham curve, indicative of emphysematous changes (Figure 13). THS aerosol exposed animals did not show any effect on lung function (PV loop) compared with the sham mice at both time points of evaluation and irrespective of the exposure dose. In addition, neither the increased compliance, nor the reduced elastance and resistance observed in 3R4F smoke exposed mice was observed in the THS aerosol exposed animals. These results are in good agreement with PMI's previous findings in Apoe$^{-/-}$ mice (Phillips 2016) and C57BL/6 mice (Phillips 2015b).

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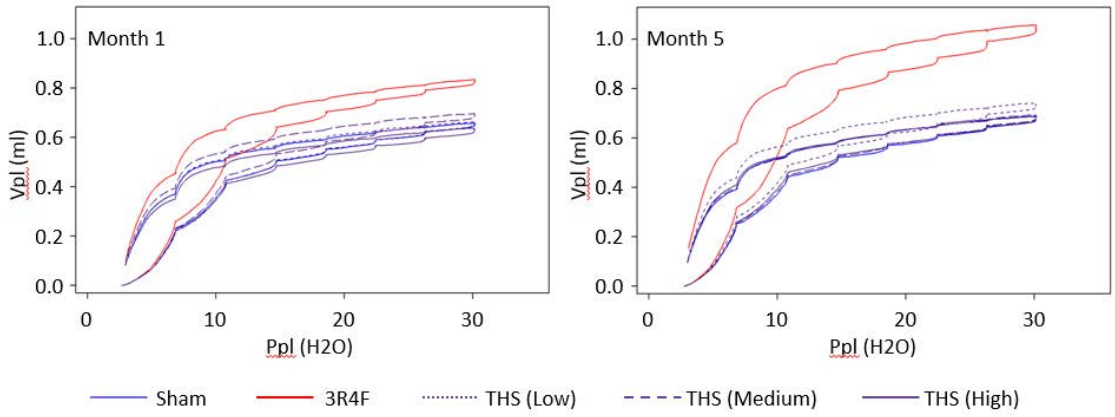


Figure 13: Lung function measurements in the A/J mouse inhalation study at months 1 and 5 – PV loops

Abbr. 3R4F = Reference Cigarette 3R4F, THS = Tobacco Heating System

The combined results of both 90-day inhalation studies have demonstrated that the THS and mTHS aerosols are significantly less toxic than cigarette smoke across a wide range of toxicological endpoints *in vivo*. Moreover, the results of the A/J mouse inhalation study have shown no lung function impairment in the THS exposed animals, which confirms the overall reduced respiratory tract toxicity of the THS aerosol.

Summary of standard toxicology assessment (Step 3)

In summary, PMI has conducted multiple *in vitro* and *in vivo* standard toxicology studies using a range of biological test systems and numerous endpoints. Taken together, the results of Step 3 of the assessment have demonstrated that both THS and mTHS aerosols are substantially (and similarly) less toxic than cigarette smoke. PMI has thus demonstrated that reduced exposure to HPHCs leads to reduced toxicity and has met the objectives for Evidence Level II (Reduced Toxicity in Laboratory Models).

Systems Toxicology Assessment (Step 4)

The first two steps of the assessment program showed that heating tobacco, instead of burning, leads to the reduced formation of HPHCs by THS compared with cigarettes. This reduction in HPHC formation leads to a concomitant reduction in toxicity as demonstrated in Step 3. The primary objective of Step 4 of the assessment was to evaluate whether these reductions led to reduced risk of disease in laboratory models. The secondary objective was to evaluate whether switching from smoke to THS aerosol exposure led to changes that approach those of cessation in laboratory models. Towards this end, PMI conducted systems toxicology studies across several *in vitro* systems and an animal model of disease. The *in vitro* studies provided comparative data about the effects of THS aerosol and cigarette smoke on disease-associated biological mechanisms. The *in vivo* study enabled a comparative evaluation of the effects of THS aerosol,

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cigarette smoke, switching and cessation across the High Level Adverse Outcome Pathway (AOP) of cigarette smoking depicted in Figure 3.

Systems Toxicology is the integration of classical toxicology with quantitative analysis of large sets of molecular and functional measures of changes occurring across multiple levels of biological organization (Sturla 2014). Systems toxicology further informs on the observations/findings of traditional toxicological approaches by examining the changes in molecular pathways underlying adverse outcomes and disease causation (Sturla 2014). This new approach to toxicology has been enabled by modern –omics technologies (e.g. genomics, metabolomics, proteomics, transcriptomics) combined with sophisticated computational biology methods.

Systems toxicology allows for the identification of biological networks and molecular pathways that are affected by exposure to active substances. This provides a more comprehensive understanding of the exposure-induced molecular, cellular and tissue-level events and their causal relationships with adverse outcomes. This knowledge can then be applied to a detailed, mechanism-by-mechanism, assessment of product risk. This approach is useful when comparing the biological effects of MRTPs with those of cigarettes since it can detect whether reductions in exposure translate into reduced perturbations of critical biological processes including Inflammation, Cell Stress, Cell Proliferation, Tissue Repair and Angiogenesis, and Cell Fate (Boue 2015). Many of these biological processes have been causally linked to tobacco-related diseases such as cardiovascular, pulmonary and lung cancer. Sophisticated computational biology approaches allow a quantification of the perturbation of each biological network (Network Pertubation Amplitudes) (Martin 2012, Martin 2014) and their aggregation into an overall relative biological impact factor (RBIF) (Thomson 2013). These approaches demonstrate how biological network perturbations are related to disease causation. A substantial reduction in perturbation of all relevant networks provides a solid mechanistic foundation for stating that an MRTP is associated with lower risks of tobacco-related diseases.

PMI has applied this approach (Figure 14) (Hoeng 2012, Hoeng 2014, Sturla 2014) across a variety of *in vivo* and *in vitro* systems to compare the impact of THS aerosol with that of cigarette smoke exposure. The results of several studies have been published in the peer-reviewed literature and are summarized in the following sections.

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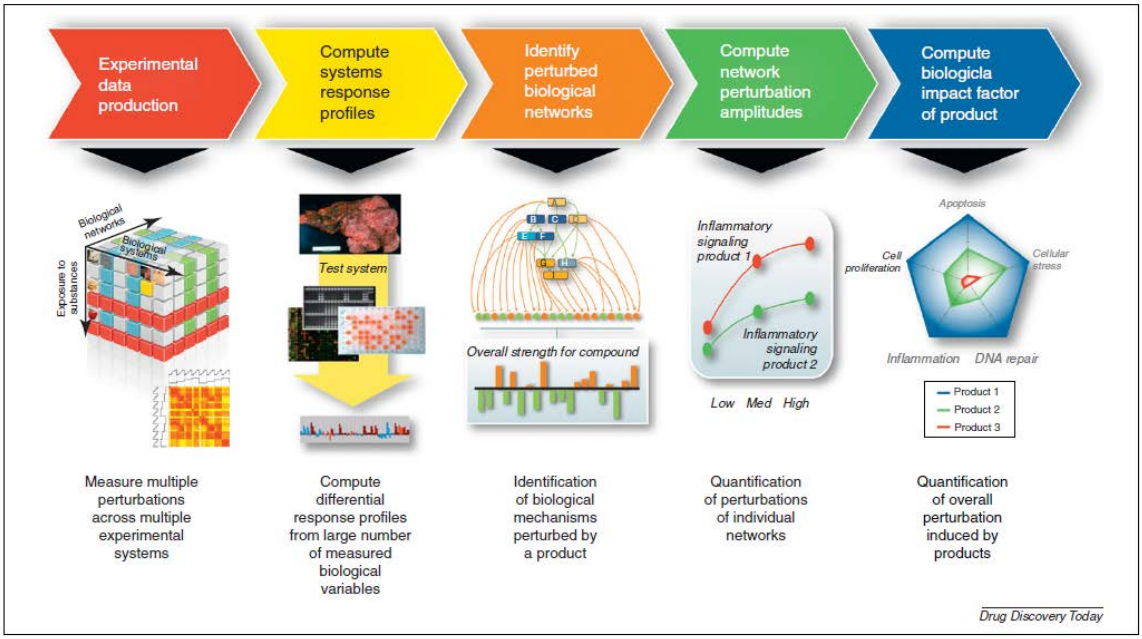


Figure 14: PMI Systems Toxicology Approach

Source: Hoeng 2012

In vitro systems toxicology assessment

Respiratory model systems in vitro

PMI studied the impact of direct exposure to whole 3R4F smoke and THS aerosol of human organotypic tissue cultures of oral, nasal, and bronchial epithelia grown at the air-liquid interface.

In the first study (Zanetti 2016), human organotypic oral (buccal) epithelium tissue cultures were exposed to multiple concentrations of either 3R4F smoke or THS aerosol and were observed for up to 72 h post-exposure. The systems toxicology approach included cellular assays (e.g. cytotoxicity, cytochrome P450 activity), measurement of secreted pro-inflammatory markers, histological analysis, and comprehensive investigations of the buccal epithelium transcriptome (mRNA and miRNA) utilizing computational network models (Boué, 2015). As expected, cigarette smoke exposure led to concentration-dependent adaptive and pro-inflammatory responses, while THS aerosol exposure led to minimal tissue responses and minimal disruption of biological networks associated with inflammation (Section 6.1.4.4.1.1.3).

A similar comparative exposure study (Iskandar 2016) was performed in human organotypic nasal epithelium cultures, which measured changes in cytotoxicity, cytochrome P450 activity, pro-inflammatory markers, tissue morphology and cilia beating frequency. The study was complemented by a computational network biology analysis of global mRNA and miRNA changes. Cultures exposed to THS aerosol displayed significantly lower toxic responses than those exposed to 3R4F smoke. The

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cilia beating frequency remained unaffected by THS aerosol exposure at all doses and time points, while 3R4F smoke exposure led to a rapid decline in cilia beating frequency. This functional endpoint was further corroborated by the finding that FoxJ1, the transcription factor that regulates the cilia-related genes, was strongly affected by 3R4F smoke exposure but not by THS aerosol exposure. The levels of five secreted inflammatory mediators were significantly lower in THS exposed cultures than 3R4F smoke exposed cultures at equivalent nicotine concentrations. In addition, network-based gene expression analysis revealed that all biological network perturbations induced by exposure to 3R4F smoke were significantly attenuated in THS aerosol exposed cultures. Overall, THS aerosol was shown to have a significantly reduced overall biological impact on nasal cultures than 3R4F smoke at equivalent nicotine concentrations (Section 6.1.4.4.1.1.4).

Similarly, the biological impact of cigarette smoke and THS aerosol exposure was studied using human organotypic bronchial epithelium cultures. Cultures exposed to 3R4F smoke exhibited concentration-dependent toxicity and biological network perturbations (Inflammation, Cell Stress, Cell Proliferation, and Cell Fate). In contrast, cultures exposed to THS aerosol showed significantly lower biological network perturbations and toxicity at equivalent, nicotine-based, concentrations of 3R4F smoke. For example, the highest 3R4F smoke exposure concentration (0.25mg nicotine/L) elicited approximately 40% cytotoxicity at 48 and 72 hours post exposure, whereas THS aerosol exposure, at a similar nicotine concentration, showed no cytotoxicity (Section 6.1.4.4.1.1.5).

Moreover, comparative exposure studies between 3R4F smoke and THS aerosol were conducted in conventional monolayer cultures of primary normal human bronchial epithelial cells utilizing real-time cellular analysis and high-content screening in combination with microarray-based transcriptomics (Gonzalez-Suarez 2016). Cigarette smoke exposure caused concentration-dependent responses for all toxicity parameters with at least one of the three smoke concentrations, and caused significant network perturbations in multiple biological networks, particularly in those related to Cell Stress. At comparable concentrations, the fractions of THS aerosol had no toxic effects and an overall lower biological impact. Overall, the data indicate that THS aerosol is markedly less toxic than 3R4F smoke (Section 6.1.4.4.1.1.2).

Cardiovascular model systems in vitro

Several *in vitro* mechanistic assays were performed to compare the impact of THS aerosol with that of 3R4F smoke on biological mechanisms related to the initial steps leading to atherosclerosis (Section 6.1.4.4.1.1.1). These studies were conducted using primary human coronary arterial endothelial cells (HCAEC) and two monocytic cell lines, THP-1 and Mono Mac 6 (MM6). These cells have been shown to be affected by cigarette smoke, which causes impairment of their normal function (Poussin 2015, van der Toorn 2015).

The first study evaluated the adhesion of monocytes to endothelial cells in response to THS aerosol or 3R4F smoke. In this assay (Poussin 2016), HCAECs were treated for 4 h

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with conditioned media from human monocytic Mono Mac 6 cells that had been incubated with:

1. low and high concentrations of aqueous extracts of either THS aerosol or 3R4F smoke for 2 h (indirect treatment).
2. unconditioned media (direct treatment).
3. fresh aqueous extracts of THS aerosol and 3R4F smoke extracts (fresh direct treatment).

The cigarette smoke extract promoted the adhesion of monocytes to HCAECs via distinct direct and indirect concentration-dependent mechanisms. Ten- and 20-fold higher concentrations of THS aerosol extract were necessary to elicit effects (adhesion and molecular changes) similar to those measured with 3R4F smoke extract in both fresh direct and indirect treatments, respectively.

The second assay measured monocyte (THP-1 cells) chemotaxis and their trans-endothelial migration in response to treatment with aqueous THS aerosol and cigarette smoke extracts using flow cytometry and ELISA assays. Both 3R4F smoke and THS aerosol induced concentration-dependent decreases in the integrity of the HCAEC monolayer. However, the changes induced by THS aerosol were more than one order of magnitude lower than those induced by 3R4F smoke. In addition, 3R4F significantly inhibited the efflux of monocytic cells across the HCAEC monolayer, whereas the inhibitory effect of THS aerosol extracts on monocyte efflux was approximately 18 times lower (van der Toorn 2015). Overall, these results support findings from other *in vitro* and *in vivo* studies that THS aerosol could pose much less risk of cardiovascular disease compared with tobacco smoke.

In vivo systems toxicology assessment

PMI conducted two *in vivo* studies, which combined a standard toxicology study design with high-throughput analyses such as transcriptomics, proteomics, and lipidomics as previously described (Kogel 2014). These studies were designed to allow for a simultaneous evaluation of both classical toxicology endpoints and the perturbations of disease-related biological processes using a systems toxicology approach (Kogel 2014). Performing both classical toxicity endpoint evaluations and systems toxicology analysis within the same study allowed PMI to draw direct correlations between toxicity endpoints and the molecular mechanisms derived from the results of high-throughput analyses such as transcriptomics, proteomics and lipidomics (Kogel, 2014, Phillips 2015b).

These two 90-day rat inhalation studies were conducted according to the OECD Test Guideline 413. One study was conducted on rats exposed to 3R4F smoke or THS aerosol (Wong 2016); the other study used a mentholated THS (mTHS) product and a mentholated cigarette comparator (MRC) (Oviedo 2016). As described above for both studies, the effects on the classical inhalation toxicology endpoints were considerably less pronounced in THS aerosol exposed rats compared with cigarette smoke exposed rats.

The systems toxicology analysis demonstrated the THS (Wong 2016) and mTHS aerosols (Kogel 2016) caused significantly reduced perturbations of all biological networks affected by 3R4F and MRC smoke (Section 6.1.4.4.1.2.1). For instance, the relative

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biological impact factors (RBIF) of THS aerosol exposure in the lung were reduced by 94% and 96% in male and female rats, respectively, compared with 3R4F smoke exposure at the higher comparable concentration (Section 6.1.4.4.1.2.1.1). Similar results were obtained for mTHS compared with cigarette smoke (Section 6.1.4.4.1.2.1.2).

Apoe-/- Switching Study

To mimic the framework for MRTP assessment depicted in Figure 4, PMI conducted a switching study in Apoe$^{-/-}$ mice to compare the impact of switching to THS aerosol with continued exposure to cigarette smoke and to smoking cessation. This study was designed to allow for a simultaneous evaluation of disease endpoints, classical toxicology endpoints and the perturbations of disease-related biological processes using a systems toxicology approach. The comparative assessment included the quantification of BoExp, molecular, cellular, histopathological and physiological changes that underlie the development and progression of COPD and CVD along the AOP depicted in Figure 3 (Phillips 2016, Lo Sasso 2016b, Titz 2016) (Section 6.1.4.4.1.2.2).

The Apoe$^{-/-}$ mouse is a well-understood model of both cardiovascular disease and pulmonary disease and has been used in discovery research of new therapeutic agents to treat human disease (Lo Sasso 2016a). Experimental evidence demonstrates that cigarette smoke exposure accelerates atherosclerosis in Apoe$^{-/-}$ mice. Apoe$^{-/-}$ mice, exposed to cigarette smoke for three months, then switched to air for another three months (mimicking smoking cessation), showed an aortic plaque area that was smaller than mice continuously exposed to cigarette smoke for six months. The cessation animals also showed a favorable change in their plaque and plasma lipid profiles as well as a 50% reduction in aortic arch cholesterol. These findings indicate that this mouse model is capable of recapitulating at least some of the cardiovascular benefits of smoking cessation seen in humans (Lietz 2013). Cigarette smoke induces a pulmonary inflammatory response in the Apoe$^{-/-}$ mouse, characterized by influx of leukocytes into the lungs and elevated levels of pro-inflammatory mediators and proteolytic enzymes in the bronchoalveolar lavage fluid (BALF) (Boué 2013). This inflammatory response eventually results in alveolar destruction similar to that of emphysema, suggesting that the Apoe$^{-/-}$ mouse is a useful model for cigarette smoke-induced COPD. For these reasons, PMI used Apoe$^{-/-}$ mice to compared the effects of THS aerosol with those of cigarette smoke on both atherosclerotic plaque and emphysema progression (Lo Sasso 2016a).

In this switching study, Apoe$^{-/-}$ mice were exposed to either smoke from the 3R4F reference cigarette, the aerosol from THS or filtered fresh air (Phillips 2016). After two months of exposure to 3R4F smoke, designated animals were switched to THS aerosol exposure (switching group) or to filtered fresh air (cessation group) for up to six months. At designated time points progression of CVD and COPD indicators were assessed: hematology, clinical chemistry, pulmonary inflammation, lung histopathology and morphometry, pulmonary function, atherosclerotic plaque formation in the aortic arch as well as a broad panel of molecular changes (transcriptomics, proteomics and lipidomics) in various tissues.

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Exposure to HPHCs

The exposure to selected HPHCs (4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone (NNK), acrolein, benzene, and acrylonitrile) was assessed by quantifying their respective BoExp in urine (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), 3-hydroxypropyl mercapturic acid (HPMA), S-phenyl-mercapturic acid (S-PMA), and 2-cyanoethylmercaturic acid (CEMA)). These BoExp are commonly used as clinical biomarkers of cigarette smoke exposure. 3R4F smoke and THS aerosol exposed animals showed an equivalent level of nicotine exposure (Phillips 2016), which was in line with the nicotine concentration in the test atmosphere (29.9mg/m^3).

Cigarette smoke exposure increased all BoExp levels relative to sham across all study time points. As expected, the levels of BoExp in THS aerosol exposed mice showed no significant difference compared with sham-exposed animals (Figure 15).

Furthermore, cigarette smoke exposure resulted in elevated 8-hydroxy-2'-deoxyguanosine (8-OHdG) levels, compared with sham animals, although this increase was not statistically significant. There were no changes in urinary 8-OHdG levels following continuous THS exposure, switching or cessation. Both malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), markers of lipid peroxidation, were detected at significantly higher levels in mice exposed to 3R4F smoke than in sham exposed animals at months 6 and 8 ($p<0.05$) (Figure 16). No differences were noted in THS aerosol exposed mice or mice subjected to either cessation or switching.

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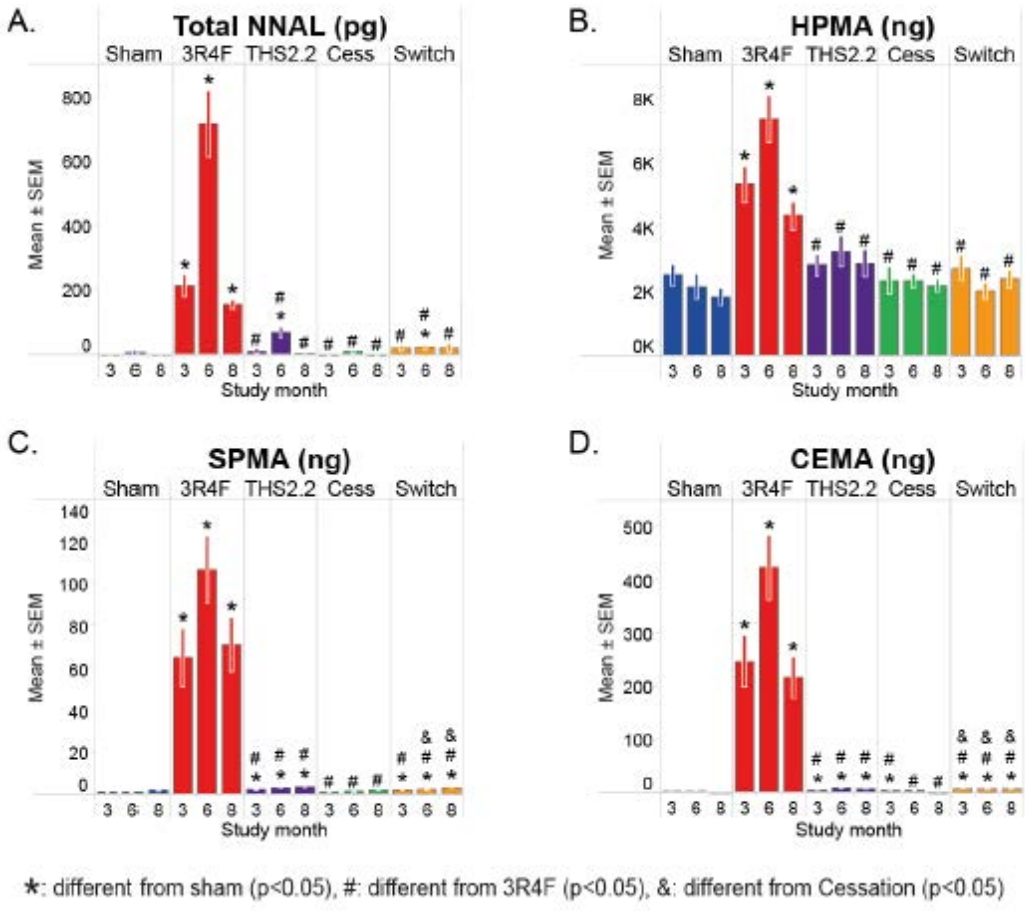


Figure 15: Urinary BoExp (non-nicotine HPHC metabolites)

Urine was collected throughout the 18-hour post-exposure period, and the respective metabolites were determined by LC-MS/MS. The measurements are expressed as the amount of metabolites excreted per mouse to account for the variable water content of the urine (physiological variations and evaporation).
A. Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (Total NNAL) B. 3-Hydroxy-1-methylpropyl-mercapturic acid (HPMA), C. S-Phenyl-mercapturic acid (SPMA), D. 2-Cyanoethylmercaturic acid (CEMA). Mean ± SEM, n=8. P-values relative to sham obtained by t-test accounting for variance heterogeneity (*) or by Wilcoxon exact MC (#). */# p< 0.05

Abbr.: CEMA: 2-Cyanoethylmercaturic acid, Cess = cessation, HPMA = 3-Hydroxy-1-methylpropyl-mercapturic acid, SPMA = S-Phenyl-mercapturic acid, THS = Tobacco Heating System, Total NNAL = Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-buranol, Switch = switching

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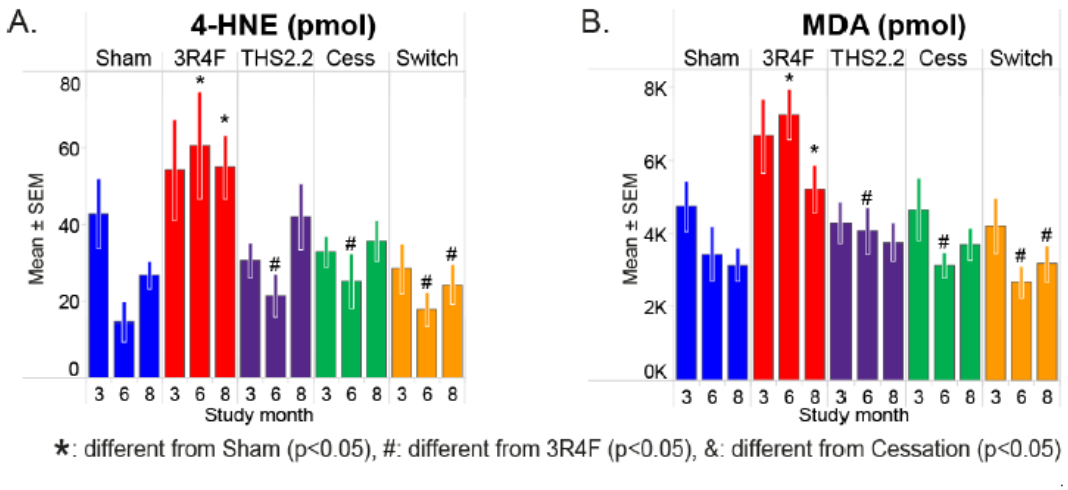


Figure 16: Urinary markers of lipid peroxidation

Urine was collected throughout the 18-hour post-exposure period, and the respective biomarkers were determined by GC-NCI-MS (A, B). The measurements are expressed as the amount of biomarker excreted per mouse to account for the variable water content of the urine (physiological variations & evaporation). A. 4-hydroxynonenal (4-HNE), B. malondialdehyde (MDA). Mean ± SEM, n=8. P-values relative to sham obtained by t-test accounting for variance heterogeneity (*) or by Wilcoxon exact MC (#). */# p<0.05.

Abbr.: Cess = cessation, GC-NCI-MS = negative ion chemical ionization capillary gas chromatography-mass spectrometry, THS, THS = Tobacco Heating System, Switch = switching

Molecular changes and biological network perturbations

In this study, classical toxicological endpoints were combined with a systems toxicology approach using transcriptomics, proteomics and lipidomics profiles. The systems toxicology analysis showed that a very broad spectrum of biological networks in the lung was significantly impacted by cigarette smoke exposure. These biological networks include Inflammation, Cell Stress, Cell Proliferation, Tissue Repair and Angiogenesis, and Cell Fate (Figure 17) along with adaptive changes in lung surfactant lipid composition and metabolism, increases in pro-inflammatory eicosanoids and ceramides and their metabolic enzymes (Titz 2016). In the liver, no clear signs of hepatotoxicity were observed in response to cigarette smoke exposure. However, integrative analysis of transcriptomics and proteomics data was indicative of perturbations in lipid metabolism, xenobiotic metabolism and iron hemostasis that likely contributed to exacerbating oxidative stress (Lo Sasso 2016b).

In contrast to the changes seen in cigarette smoke exposed Apoe$^{-/-}$ mice, the biological impact of continuous THS aerosol exposure was minimal. For instance, the systems toxicology analysis of the lungs of THS aerosol exposed animals showed significantly reduced perturbations of all biological networks affected by cigarette smoke exposure (Figure 17) (Phillips 2016), which was corroborated by a significant reduction in inflammatory mediators and proteolytic enzymes in BALF. Moreover, proteomics analysis of the lungs revealed that exposure to THS aerosol had no significant effect on protein abundance during the entire 8-month exposure period.

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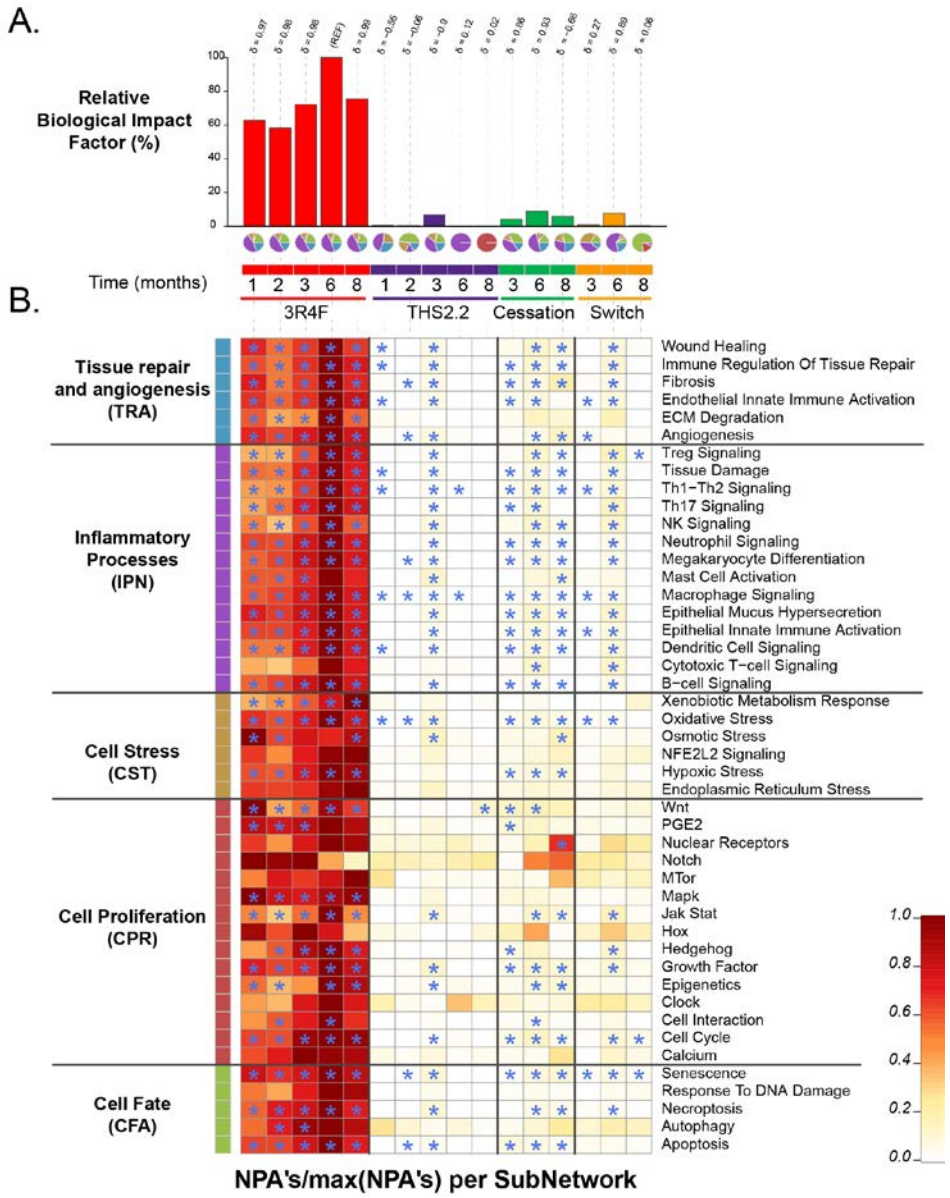


Figure 17: Network-based relative biological impact factor (RBIF) and network perturbation amplitude (NPA) analysis from the lung

(A) RBIF for treatment vs sham, the percentages show the relative biological impact which is derived from the cumulated network perturbations caused by the treatment relative to the reference (defined as the treatment comparison showing the highest perturbation, i.e., at the 6-month time-point). For each treatment comparison, the δ value (−1 to 1) indicates how similar the underlying network perturbations are with respect to the reference (i.e., 3R4F at 6 months). A δ value of 1 indicates that all networks are perturbed by the same mechanisms. The small pie charts underneath the RBIF bars demonstrates the relative contributions by the Network Perturbation Amplitudes (NPAs) of the five underlying network models (indicated by the segment colors) which are shown in greater detail in Fig. 14B.

(B) Heatmap of NPA Scores summarizing subnetwork NPAs relative to the maximum NPA in each subnetwork. Stars indicate significant perturbations.

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Finally, switching to THS aerosol and cessation showed very similar results across all molecular changes (transcriptomics, proteomics and lipidomics). For instance, the analysis of BALF showed that cessation and switching to THS aerosol reduced the secretion of inflammatory mediators and proteolytic enzymes to a similar extent (Phillips 2016). The systems toxicology analysis of the lung showed that the perturbations of all biological networks affected by cigarette smoke were attenuated similarly in both THS switching and smoking cessation groups (Figure 17). Moreover, the integrative analysis of liver transcriptomics and proteomics data indicated that the perturbations in lipid metabolism, xenobiotic metabolism and iron hemostasis were attenuated similarly in both THS switching and smoking cessation groups (Lo Sasso 2016b).

In conclusion, these results show that the overall biological impact of THS aerosol on the lung is very low compared to that of 3R4F smoke and that the effects switching to THS aerosol exposure approach those of cessation (Section 6.1.4.4.1.2.2.1).

Cellular changes

In line with the molecular changes observed in BALF, the total number of free lung cells in BALF increased and remained elevated in the 3R4F smoke exposed animals, primarily due to infiltration of neutrophils. In contrast, prolonged exposure to the THS aerosol did not affect free lung cell count. Both cessation and switching to THS aerosol exposure resulted in a rapid decline in the number of free lung cells, nearly reaching those seen in sham or in THS aerosol exposed mice already after one month (85% decrease in free lung cell count following switch/cessation) (Section 6.1.4.4.1.2.2.1).

Tissue changes

3R4F smoke exposure had significant adverse impacts at cellular and tissue levels. The histopathological evaluation of respiratory tract organs, at multiple time points, displayed typical cigarette smoke exposure-related changes including adaptive changes of epithelia (nasal, laryngeal and tracheal), infiltration of inflammatory cells and emphysematous lesions. The degree of inflammation and inflammatory cell infiltrates was much reduced in THS aerosol exposed animals and, importantly, the THS aerosol exposed lungs were indistinguishable from sham in terms of histologic appearance. Both cessation and switching to THS aerosol exposure resulted in very similar histopathological findings.

Digitalized, 4-µm serial sections of the lung were evaluated for pulmonary emphysema by semi-quantitative scoring of histopathological findings and quantitative morphometry. Morphometric parameters investigated were mean chord length (MCL), bronchiolar attachments (BAs), and destructive index (DI). In addition, several morphometric endpoints were evaluated using a design-based stereological approach. Figure 18 represents the data from the histopathological emphysema assessment, comparing all study groups over the 8-month study period (Phillips et. al, 2016).

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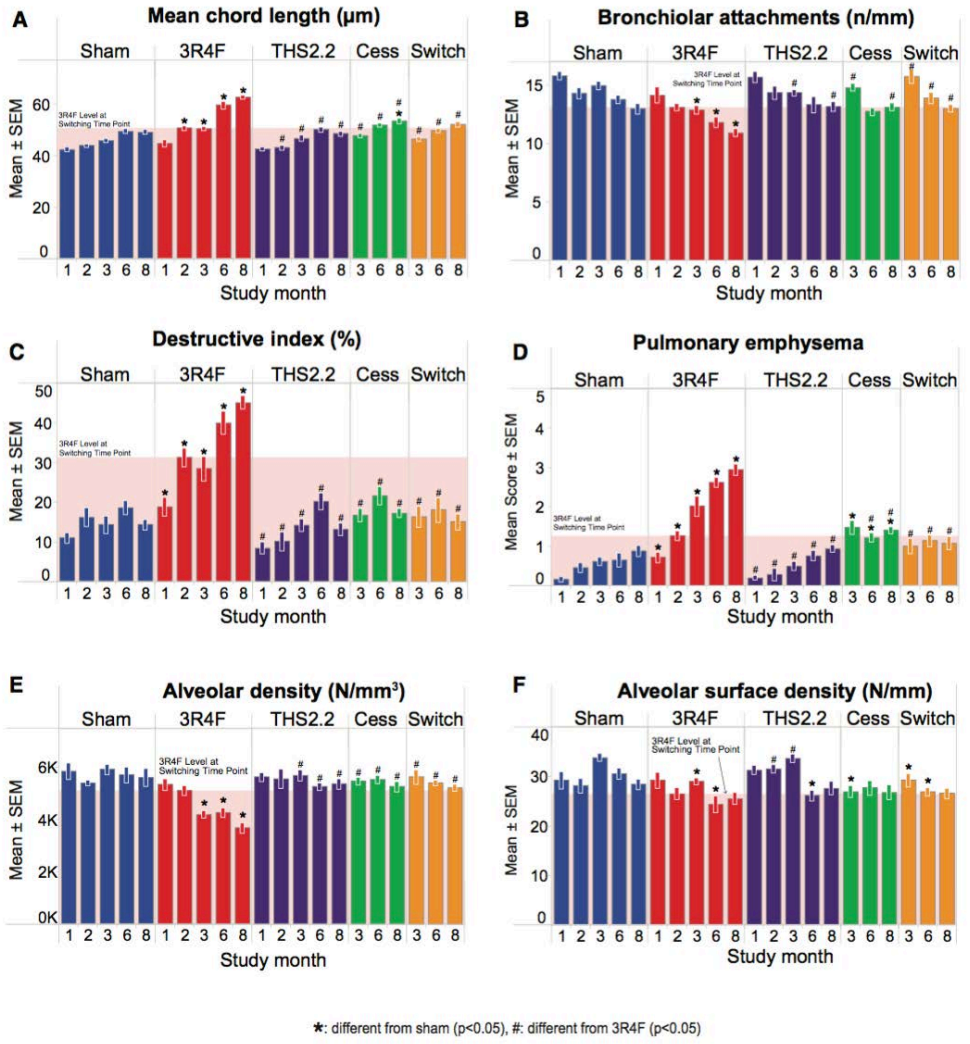


Figure 18: Emphysema assessment by morphometry and histopathological evaluation of lung sections

A-C, Morphometric assessment, classical parameters, A, mean chord length, B bronchiolar attachments, C, destructive index. D, Semi-quantitative histopathological scoring. E and F., Volume-independent morphometric parameters, E, Alveolar Density, F, alveolar surface density. Mean ± SEM, n=10. The shaded area indicates the 3R4F value at the switching/cessation time point (month 2)

Abbr.: 3R4F = Reference Cigarette 3R4F, Cess = cessation, THS = Tobacco Heating System, Switch = switching

Atherosclerotic plaque formation

An essential disease endpoint for cardiovascular disease is atherosclerotic plaque formation. While exposure to 3R4F smoke accelerated the growth of the atherosclerotic plaque in the aortic arch of continuously exposed animals, exposure to THS aerosols resulted in plaque areas that did not differ significantly from those seen in sham exposed mice. The morphometric results were confirmed by micro-computed tomography measurements of *in situ* aortic arch plaques at month 7. As seen in Figure 19, cessation

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and switching from 3R4F smoke to THS aerosol halted the atherosclerotic plaque growth that occurred in mice exposed to 3R4F smoke.

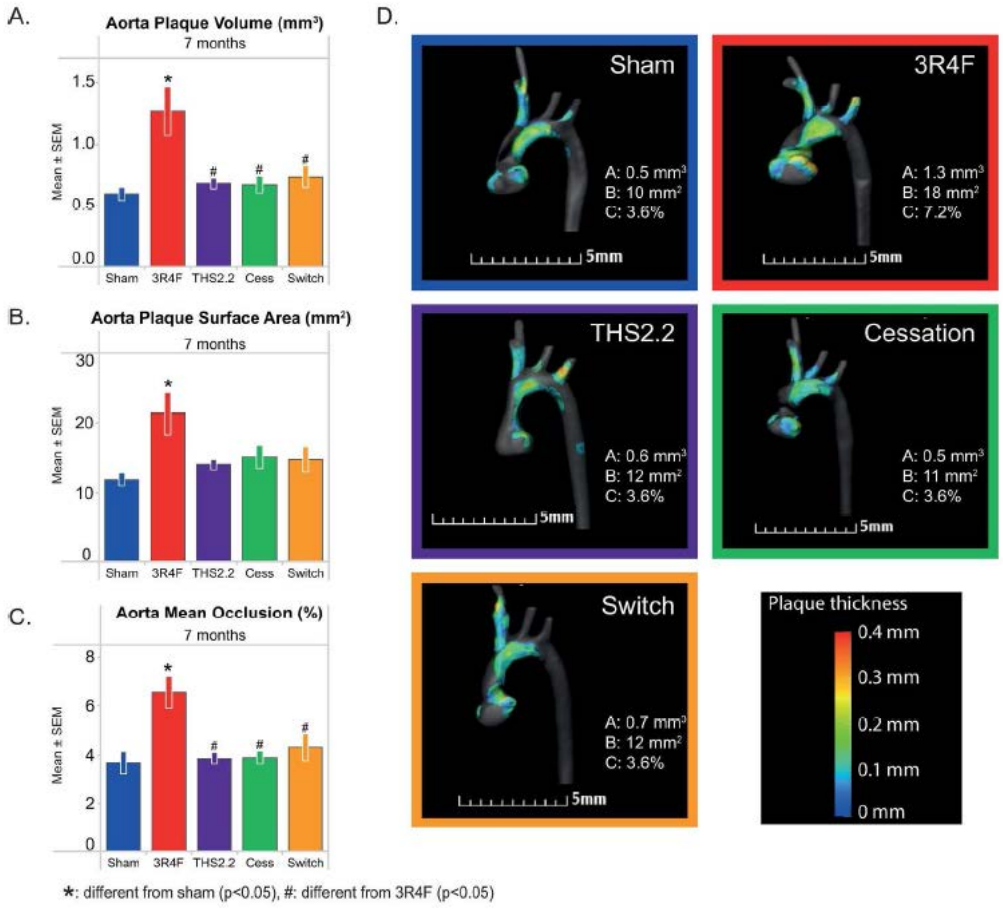


Figure 19: Evidence supporting the reduction in risk of CVD in the included non-clinical *in vivo* study – MicroCT *in situ* aortic arch plaque measurements

Abbr.: 3R4F = Reference Cigarette 3R4F, Cess = cessation, THS = Tobacco Heating System, Switch = switching

Lung function

An essential disease endpoint for COPD is the progressive deterioration of lung function. In the Apoe$^{-/-}$ mouse switching study, lung function was assessed by capturing pressure, flow, and volume relationships in the respiratory system of selected animals.

As indicated above, the histopathological evaluation of the lungs from the *Apoe*$^{-/-}$ mouse switching study indicated that THS aerosol exposed groups showed significantly reduced accumulation of pigmented alveolar macrophages compared with the 3R4F smoke exposed group. Alveolar macrophages play a pathogenic role in COPD by expressing potent elastases, cathepsins and matrix metalloproteases (MMP) (Abboud 2008). MMPs

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are elastin degrading proteinases and affect the elastin content in alveolar and airway walls (Merrilees 2008). These proteolytic enzymes play an important role in the destruction of the lung structure, as measured by histopathology, and the subsequent remodeling processes in the airway wall (Belvisi 2003). The decreasing content of elastin, gradual loss of lung structure integrity and subsequent repair mechanisms lead to a decrease of pulmonary function.

These changes have a significant impact on lung function over time, which can also be measured in pressure-volume (PV) loops in animals. In the *Apoe*$^{-/-}$ mouse switching study, lung function was assessed through quantitative pressure, flow, and volume relationships in the respiratory tract. As seen in Figure 20, cigarette smoke exposed animals showed an upward/leftward shift in PV loops from the sham curve, indicative of emphysematous changes. THS aerosol exposed animals did not show any effect on lung function (PV loop), even compared with the sham mice at any of the time points of evaluation. Switching from 3R4F smoke exposure to THS aerosol or cessation resulted in stabilization of the values, while continued 3R4F smoke exposure led to further impairment in lung function.

Other lung function parameters, such as single compartment "snapshot perturbation" measurements of dynamic lung resistance (R), dynamic elastance (E), and dynamic compliance (C), also demonstrated 3R4F smoke exposure related changes, indicating a loss of elastic recoil in the smoke exposed lungs, which was evident after 1 month of 3R4F smoke exposure. Although R changed only slightly with increasing age/study duration, age-related changes in E and C were more prominent. This leads to a gradual convergence of the sham group with the 3R4F smoke exposed group values from month 3 onwards. In THS aerosol exposed mice, the snapshot perturbation parameters did not differ significantly from those observed in the sham group ($P>0.05$). These results reflect previous PMI research findings in C57BL/6 wild type mice (Phillips 2015b).

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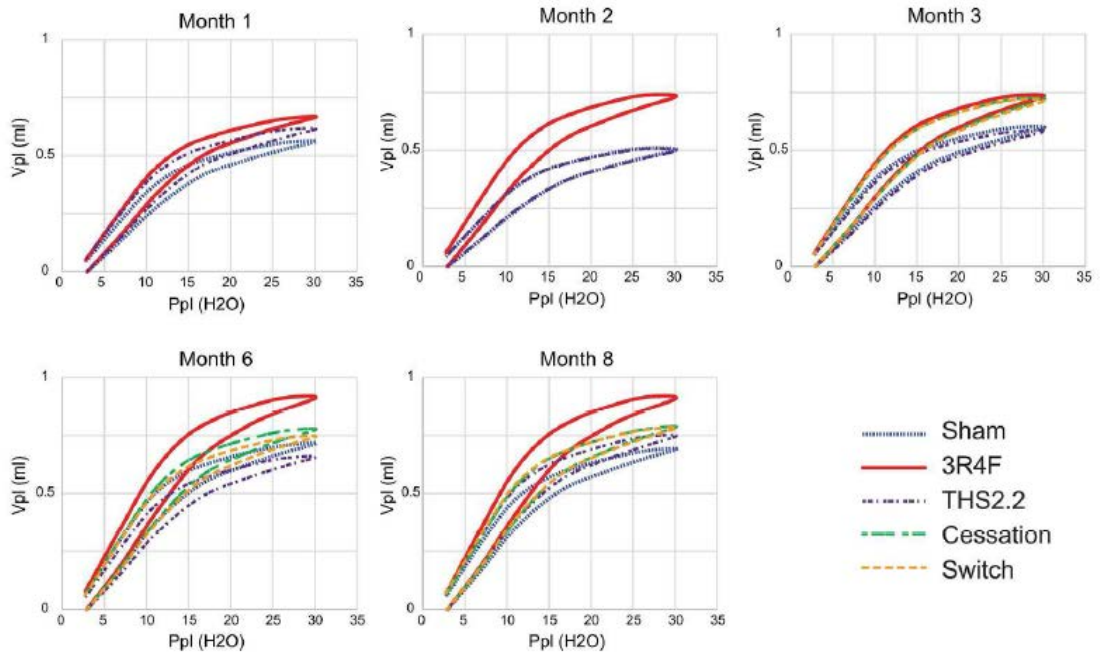


Figure 20: Lung function measurements in the Apoe$^{-/-}$ mouse switching study – PV loops

Abbr.: 3R4F = Reference Cigarette 3R4F, THS = Tobacco Heating System

Summary of systems toxicology assessment (Step 4)

In summary, PMI conducted multiple *in vitro* systems toxicology studies using a range of relevant biological test systems as well as a systems toxicology study in an animal model of disease. Taken together, the results of Step 4 of the assessment have demonstrated that THS aerosol, compared with cigarette smoke, has a reduced impact on biological mechanisms linked to disease. Furthermore, the results have demonstrated that switching from cigarette smoke to THS aerosol exposure leads to favorable changes that approach those of cessation across all levels of biological organization (from molecular changes to organ-level changes). Finally, PMI has demonstrated that by effectively reducing the exposure to HPHCs, the first step in the High Level AOP of cigarette smoking (Figure 3), the changes in subsequent steps of the AOP are concomitantly attenuated/reduced, leading to a reduction in disease endpoints. Therefore, PMI has met its objectives for Evidence Level III (Reduced Risk in Laboratory Models).

Overall Summary of Non-Clinical Assessment (Steps 3 and 4)

All classical and systems toxicology endpoints, across all non-clinical studies, have produced a coherent demonstration that reduced formation of HPHCs leads to reduced exposure to HPHCs, which in turn results in reduced toxicity and reduced harm across multiple levels of biological organization (molecular, cellular, tissue and organ-level changes), in full alignment with the AOP described in 2.7.3 (Figure 3). Furthermore, the results of the Apoe$^{-/-}$ switching study consistently showed that the biological impact of switching from smoke to THS aerosol exposure approaches that of cessation, and halted

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the development of both CVD and COPD disease endpoints. The study results were very consistent across biologically plausible and relevant mechanisms of disease causation (Inflammation, Cell Stress, Cell Proliferation, Tissue Repair and Angiogenesis, and Cell Fate). Furthermore, the mechanistic findings were remarkably consistent across animal studies conducted *in vivo* and studies conducted with human-derived cells and organotypic tissues *in vitro*. The totality of the non-clinical evidence is therefore consistent with the hypothesis that reduced exposure, as seen with switching from cigarette smoke to THS aerosol, leads to reduced toxicity, which, in turn, leads to reduced risk of harm and tobacco-related disease. Furthermore, PMI has not detected any new toxicological effect with THS, in either classical or systems toxicology studies.

Clinical Studies (Step 5)

The assessment steps 1-4 have shown that THS aerosol contains significantly less HPHCs than cigarette smoke and that, consequently, exposure to THS aerosol has a significantly reduced adverse biological impact than cigarette smoke across many biologically plausible and relevant mechanisms of disease causation and disease endpoints. This reduction in exposure and the ensuing generalized reduction in biological impact has been consistent across *in vitro* and *in vivo* systems.

The first objective of Step 5 of the assessment was to determine whether the reduced formation of HPHCs by THS leads to a reduced exposure of adult smokers who switch from cigarette smoking to THS use. The second objective was to determine whether a reduced exposure caused by switching to THS use is correlated with favorable changes in clinical risk endpoints. The third objective was to evaluate how close these changes were to those caused by smoking cessation/abstinence. Towards this end, PMI conducted clinical studies designed to compare the effects of switching to THS with continued cigarettes smoking and to smoking abstinence. Furthermore, the studies were designed to determine whether the THS product has the potential to be an acceptable alternative to cigarettes for smokers who did not have the intention to quit smoking.

PMI conducted eight clinical studies (see Table 5) to provide data to support claims under Section 911(g)(1) and Section 911(g)(2) of the of the FD&C Act:

- Four PK/PD studies were conducted to compare the nicotine uptake profile when using a THS with that of smoking a cigarette. These studies aimed to assess whether THS delivers nicotine in a manner similar to cigarettes and hence would likely satisfy a cigarette smoker. These studies are described in Section 2.7.5 Part B.
- Four clinical studies were conducted to determine the comparative reduction in exposure to HPHCs as described hereafter.

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Table 5: THS clinical assessment

Study code and Clinicaltrials.gov ID	Study Type	Investigational product	Comparators groups	Duration of exposure
ZRHR-**PK-01-EU** NCT01967732	PK/PD	THS	CC; NRT (NNS)	Single use
ZRHR-**PK-02-JP** NCT01959607	PK/PD	THS	CC, NRT (nicotine gum)	Single use
ZRHM-**PK-05-JP** NCT01967706	PK/PD	mTHS	mCC, NRT (nicotine gum)	Single use
ZRHM-**PK-06-US** NCT01967719	PK/PD	mTHS	mCC, NRT (NNS)	Single use
ZRHR-**REXC-03-EU** NCT01959932	Reduced Exposure	THS	CC; SA	5 days in confinement
ZRHR-**REXC-04-JP** NCT01970982	Reduced Exposure	THS	CC, SA	5 days in confinement
ZRHM-**REXA-07-JP** NCT01970995	Reduced Exposure	mTHS	mCC, SA	90 days (5 days confinement and 85 days ambulatory)
ZRHM-**REXA-08-US** NCT01989156	Reduced Exposure	mTHS	mCC; SA	90 days (5 days confinement and 86 days ambulatory)

Abbr.: CC = Conventional Cigarette, EU = European Union, ID = Identification, JP = Japan, mCC= mentholated conventional cigarette, NNS = Nicotine Nasal Spray, NRT = Nicotine Replacement Therapy, PD = Pharmacodynamic, PK = Pharmacokinetic, SA = Smoking Abstinence, THS = Tobacco Heating System, mTHS = menthol version of THS, US = United States of America

All clinical studies were conducted according to ICH/GCP guidelines and registered on the U.S. government's publicly available website www.clinicaltrials.gov.

Reduced exposure studies and clinical risk endpoints

PMI conducted four reduced exposure studies to determine whether the use of THS reduces exposure to HPHCs, and whether THS-related reductions in exposure were correlated with favorable changes in clinical risk endpoints. The THS data were compared to those obtained with smoking abstinence.

Two of the studies were conducted in a confined clinical setting with five days of exposure in the EU (ZRHR-EXC-03-EU) (Haziza 2016b) and Japan (Haziza 2016a) (ZRHR-REXC-04-JP). The other two studies were conducted in Japan and the US over three months with an initial confined clinical setting (5 day exposure) followed by 85 days in an ambulatory setting (ZRHM-REXA-07-JP, ZRHM-REXA-08-US). The purpose of the additional 85 days was to demonstrate whether the initial reduction in HPHC exposure observed in confinement would be sustained for a longer period in a near real-world setting. All studies were randomized, controlled, open-label, 3-arm parallel group study designs.

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In the two 5-day reduced exposure studies (ZRHR-REXC-03-EU and ZRHR-REXC-04-JP), THS was tested and compared with cigarette smoking. In the 90-day studies (ZRHM-REXA-07-JP and ZRHM-REXA-08-US), THS menthol (mTHS) was tested and compared to menthol cigarettes (mCC). This combination of studies allows comparing (i) the exposure reduction achieved by THS and mTHS after 5 days of switching, and (ii) the exposure reduction achieved by mTHS in two very different study populations. As part of PMI's ongoing efforts to build the understanding of MRTPs, PMI is conducting a longer-term exposure response study with THS in the U.S. (Clinicaltrials.gov IDs: NCT02396381 and NCT02649556) and an international multi-center smoking cessation response study (Clinicaltrials.gov ID: NCT02432729); The study protocol and results will be shared with the FDA upon completion of the study.

The study populations were healthy, adult smokers who self-reported the use of at least 10 commercially available cigarettes per day for the last 3 years prior to enrollment in the study and who did not plan to quit smoking in the next 3 months. Study participants were randomized into three study groups:

1. adult smokers who continued to smoke cigarettes,
2. adult smokers who switched to smoking abstinence and
3. adult smokers who switched from cigarettes to THS.

Product use was controlled by study staff and participating adult smokers were controlled for product compliance during the in-clinic period of the studies. During the ambulatory period of the two 90-day studies, product use was monitored based on the self-reporting by the subject on an electronic diary. Adult smokers used THS without restriction (*ad libitum*) but dual use of cigarettes and THS was not allowed during the confinement period and discouraged during the ambulatory period of the study. During the ambulatory period, the compliance to the product/regimen allocation in the ZRHM-REXA-07-JP study was particularly high in all three arms, while the compliance in the smoking abstinence (SA) group of the ZRHM-REXA-08-US study was poor (7 to 9 out of 41 subjects) as outlined in Section 6.1.3.2.3.19.

The main specific objectives of these studies were:

- To demonstrate the reduction of S-PMA, 3-HPMA, MHBMA, and COHb after 5 days of exposure in confinement, (other than total NNAL) (Section 6.1.3.2),
- To demonstrate the reduction of total NNAL in an ambulatory setting (Section 6.1.3.2),
- To determine the reduction of other BoExp in a confinement setting and in an ambulatory setting
- To describe the change in cytochrome P450 1A2 (CYP1A2) enzymatic activity (Section 6.1.3.2 for results),
- To describe the change in Urine Mutagenicity (Section 6.1.3.2),
- To monitor selected Clinical Risk Endpoints (Section 6.1.4),
- To evaluate nicotine/tobacco product use including dual use (Section 6.2.2),

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- To monitor the exposure to nicotine by measuring its urinary metabolites (free nicotine, nicotine glucuronide, free cotinine, cotinine glucuronide, free trans-3'-hydroxycotinine and trans-3'-hydroxycotinine-glucuronide (Section 6.2.2),
- To monitor the safety profiles during the studies (Section 6.1.5).

Reduction of biomarkers of exposure to HPHCs

BoExp are either a chemical, its metabolite, or the product of an interaction between the chemical and some target molecule or cell that is measured in a compartment of an organism (IOM 2010).

The biomarkers in Table 6 were selected for THS assessment using the following criteria (Section 6.1.3.1):

1. The HPHCs selected are representative of a variety of chemical classes and organ toxicity classes as defined by the FDA (carcinogen, cardiovascular toxicant, respiratory toxicant, reproductive and development toxicant, addiction potential)
2. The HPHC reflects a specific toxic exposure or is a reliable surrogate of exposure to HPHCs
3. The HPHCs assessed cover a broad range of formation temperatures
4. The HPHC is specific to smoking with other sources being minor or non-existent
5. The BoExp to a HPHC is reliably detectable using validated, reproducible, precise analytical methods
6. The BoExp to a HPHC has a half-life that is suitable with the schedule of assessments

In these studies, PMI measured 16 BoExp to HPHCs as well as nicotine and its metabolites (Table 6). These included BoExp for 14 of the 18 HPHCs currently mandated for reporting to the FDA (Table 2) (4 not included due to criterion #5 above are: acetaldehyde, ammonia, formaldehyde and isoprene) (Justification detailed in Section 6.1.3.1). These 14 HPHCs were reduced by over 95% in THS and mTHS aerosols compared with 3R4F smoke. The PMI selection included 7 of the 9 toxicants (2 not included due to criterion #5 above are: acetaldehyde and formaldehyde) recommended by World Health Organization (Table 2) (WHO 2008) for lowering in mainstream cigarette smoke are covered in the PMI exposure assessment. These 7 HPHCs were reduced by over 95% in THS and mTHS aerosols compared with 3R4F smoke.

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Table 6: Overview of the measured HPHCs and BoExp

HPHC		Constituent list	Biomarker [Matrix]	Phase	Organ class toxicity
1	1,3-butadiene	FDA, WHO	Monohydroxybutenyl-mercapturic acid (MHBMA) [Urine[1]]	Gas	CA, RT, RDT
2	1-aminonaphtalene	FDA	1-Aminonaphtalene (1-NA) [Urine[1]]	Particulate	CA
3	2-aminonaphthalene	FDA, WHO	2-Aminonaphtalene (2-NA) [Urine[1]]	Particulate	CA
4	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)	FDA, WHO	Total 4-(methylnitrosamino)- 1-(3-pyridyl)-1-butanol (total NNAL) [Urine[1]]	Particulate	CA
5	4-aminobiphenyl	FDA, WHO	4-Aminobiphenyl (4-ABP) [Urine[1]]	Particulate	CA
6	Acrolein	FDA, WHO	3-Hydroxypropyl- mercapturic acid (3-HPMA) [Urine[1]]	Gas	RT, CT
7	Acrylonitrile	FDA, WHO	2-Cyanoethylmercaturic acid (CEMA) [Urine[1]]	Gas	CA, RT
8	Benzene	FDA, WHO	S-Phenyl-mercapturic acid (S-PMA) [Urine[1]]	Gas	CA, CT, RDT
9	Benzo[a]pyrene	FDA, WHO	Total 3-Hydroxybenzopyrene (3-OH-B[a]P)[Urine[1]]	Particulate	CA
10	Carbon monoxide	FDA, WHO	Carboxyhemoglobin (COHb) [Blood[2]]	Gas	RDT, CT
11	Crotonaldehyde	FDA, WHO	3-Hydroxy-1-methylpropyl-mercapturic acid (3-HMPMA) [Urine[1]]	Gas	CA
12	Ethylene oxide	FDA	2-Hydroxyethyl-mercapturic acid (HEMA) [Urine[(1)]]	Gas	CA, RT, RDT
13	Nicotine	FDA	Nicotine (NIC-P) [Plasma[1]] Cotinine (COT-P) 3-OH-Cotinine (3OHCOTP) [Plasma[1]] Nicotine equivalents (NEq) [Urine[1]]	Particulate	RDT, AD
14	N-nitrosonornicotine (NNN)	FDA, WHO	Total N-nitrosonornicotine (total NNN) [Urine[1]]	Particulate	CA
15	*o*-toluidine	FDA	o-Toluidine (o-tol) [Urine[1]]	Gas	CA
16	Pyrene	PMI-58	Total 1-hydroxypyrene (1-OHP) [Urine[1]]	Particulate	Nontoxic
17	Toluene	FDA, PMI-58, WHO	S-benzyl-mercapturic acid (S-BMA) [Urine[1]]	Gas	RT, RDT

Abbr.: AD = addictive, CA = carcinogen, CT = cardiovascular toxicant, FDA = Food and Drug Administration, PMI = Philip Morris International, RT = respiratory toxicant, RDT = reproductive and developmental toxicant, WHO =World Health Organization
[1]Analytical methods: liquid chromatography-tandem mass spectrometry (LC-MS/MS)

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Reduced exposure studies in confined settings (REXC)

The REXC studies in Japan and the EU were conducted to investigate reduced exposure. The studies were randomized, open-label, parallel group reduced exposure studies conducted in confinement. A smoking abstinence (SA) group was included to provide the benchmark for the observed reduction in exposure to HPHCs. The smokers used the THS without restriction (*ad libitum*) during an extended daily time window (16 hours), and dual use of cigarettes and THS was not permitted. In both studies, the non-menthol product variant of THS was tested.

Both exposure studies demonstrated that smokers who switched to either THS or smoking abstinence had decreased levels of exposure to the measured HPHCs. The time course of the decrease in S-PMA, MHBMA, 3-HPMA, and COHb tested in the primary objective from the 5-day exposure study in the EU (ZRHR-REXC-03-EU) is shown in Figure 21. The drop in exposure levels to HPHCs with THS use was rapid and of a magnitude that approached the reductions seen in the group that abstained from smoking during the same period.

Similar patterns of change were seen for CEMA, 4-ABP, total 3-OH-B[a]P, 3-HMPMA, HEMA, 1-NA, 2-NA, total NNAL, total NNN, o-toluidine and total 1-OHP. The reductions in BoExp levels were of a similar magnitude in both the THS and SA groups. S-BMA levels did not show any difference in levels across all study arms. These data are summarized in Section 6.1.3.2.

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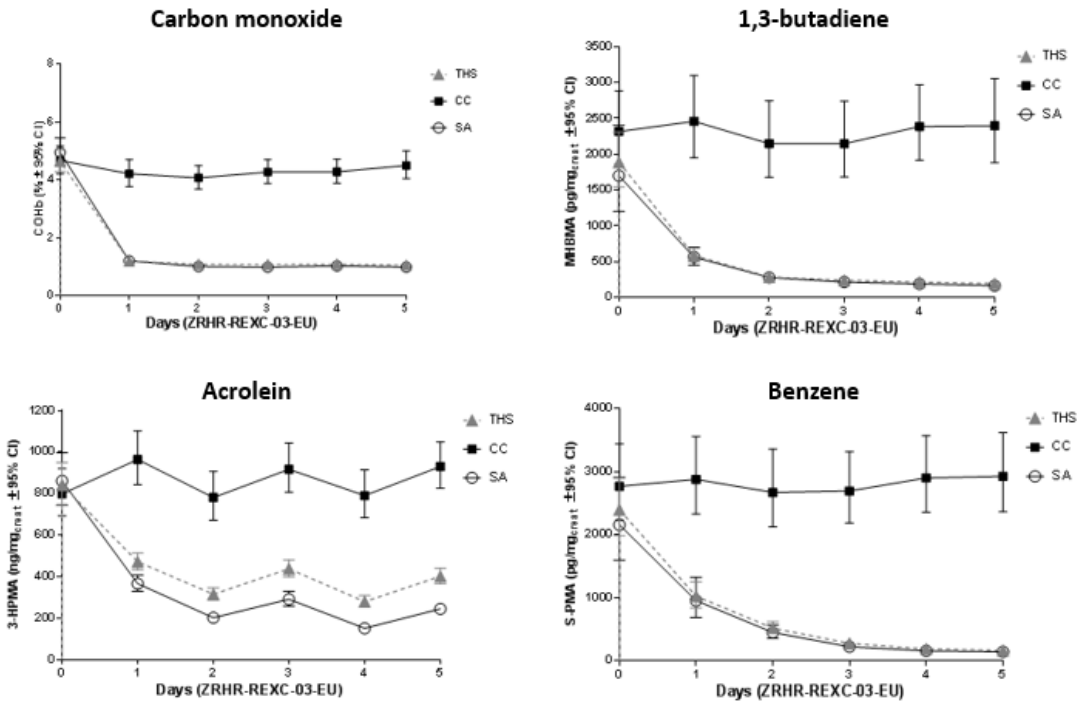


Figure 21: Concentrations of the BoExp to four HPHCs at baseline and throughout five days *ad libitum* use of THS, CC and smoking abstinence; ZRHR-REXC-03-EU

Abbr.: CC = Conventional Cigarettes, SA = Smoking Abstinence, THS = Tobacco Heating System, Switch = switching

As in the EU study, the Japanese study (ZRHR-REXC-04-JP) showed a similar pattern of reduction in the levels of BoExp (Section 6.1.3.2). Both THS and SA groups showed comparable reductions in S-PMA, MHBMA, 3-HPMA, and COHb (Table 7). S-BMA did also not show any difference in levels across all study arms.

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Table 7: Summary of 5-Day Reduced Exposure Study Results: BoExp [100-(THS:CC) ratio and 100-(SA:CC) ratio in %] in studies ZRHR-REXC-03-EU and ZRHR-REXC-04-JP at Day 5

BoExp	HPHCs [aerosol phase]	Comparison	ZRHR-REXC-03-EU Reduction (%) (95% CI)	ZRHR-REXC-04-JP Reduction (%) (95% CI)
COHb (%)	CO [gas]	THS:CC	-77% (-75.0 ; -78.0)	-53% (-49.9 ; -55.7)
		SA:CC	-78% (-76.7 ; -79.9)	-54% (-50.4 ; -57.0)
MHBMA (pg/mg creat)	1,3-Butadiene [gas]	THS:CC	-92% (-89.8 ; -93.1)	-77% (-71.1 ; -81.6)
		SA:CC	-93% (-94.2 ; -90.9)	-80% (-84.7 ; -74.0)
3-HPMA (ng/mg creat)	Acrolein [gas]	THS:CC	-58% (-54.1 ; -62.2)	-47% (-38.8 ; -54.3)
		SA:CC	-75% (-71.6 ; -77.4)	-65% (-58.9 ; -70.8)
S-PMA (pg/mg creat)	Benzene [gas]	THS:CC	-94% (-93.1 ; -94.8)	-84% (-81.2 ; -86.9)
		SA:CC	-94% (-93.4 ; -95.2)	-87% (-83.4 ; -89.1)

Abbr.: BoExp: biomarkers of exposure; CC: conventional cigarette; CI: confidence interval; CO: carbon monoxide; COHb: carboxyhemoglobin; HPHCs: harmful and potentially harmful constituents; 3-HPMA: 3-hydroxypropylmercapturic acid; MHBMA: monohydroxybutenyl- mercapturic acid; SA: smoking abstinence; S-PMA: S-phenyl mercapturic acid; THS: Tobacco Heating System.

Source: Study Reports: ZRHR-REXC-03-EU, ZRHR-REXC-04-JP

Reduced exposure studies in ambulatory settings (REXA)

PMI conducted two three-month randomized, controlled, open-label, 3-arm parallel group Reduced Exposure studies. Each study included a confinement period (5 days of exposure) followed by an ambulatory period (85 or 86 days of exposure). The studies were conducted in Japan and in the US and included THS (*ad libitum* use), cigarettes (*ad libitum* use), and smoking abstinence (SA) arms. In both studies, the menthol product variant of THS (mTHS) was tested. BoExp to HPHCs were measured as the subjects switched from menthol cigarettes to menthol THS or SA.

There were three advantages offered by conducting the study over three months. First, the study was conducted in near real-world conditions. Second, the study duration allowed the demonstration of changes to BoExp with longer half-lives, such as total NNAL. Third, given the duration of the ambulatory exposure period, the study was long enough

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to assess the initial changes in some of the clinical risk markers that have been shown to be reversible within 2 weeks to 3 months.

The results following the first 5 days were comparable across both REXA studies and to the results from REXC studies. All four primary BoExp were significantly reduced in both mTHS and SA groups and by a similar magnitude (Table 8). These reductions in BoExp were similar across the two REXA studies, which were conducted in Japan and the US with different demographics.

The results after 90 days were also consistent between the two REXA studies conducted in an ambulatory setting. In the Japanese study, nearly all of the reduction in primary BoExp seen at five days was preserved at 90 days (Table 8). In the US study, the findings were again similar to the results seen with smoking abstinence (Table 8). Both mTHS and SA groups had a significant reduction in BoExp compared with the smoking group. These findings reinforce the overall theme that switching to mTHS aerosol results in a reduced exposure to HPHCs that is similar to smoking abstinence.

The overall comparison of reduction in exposure for mTHS and smoking abstinence is presented in Figure 22, which outlines all of the primary and secondary BoExp results at 90 days. It is readily apparent that the reductions across all biomarkers is of similar direction and magnitude when comparing mTHS to SA.

In summary, the clinical studies demonstrated a consistent reduction in exposure to BoExp in smokers who switched to THS and smoking abstinence. These changes were evident as early as 5 days following the switch and were preserved throughout the 90-day duration of the REXA studies. The reductions seen in the THS group were similar in both magnitude and direction to those seen with smoking abstinence. This is plausible, given that THS aerosol contains levels of HPHCs that are reduced by 90% compared with cigarette smoke. These findings provide evidence to substantiate both a reduced risk claim, according to Section 911(g)(1), and a reduced exposure claim according to Section 911(g)(2) of the FD&C Act.

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Table 8: Summary of 90-Day Reduced Exposure Studies: Reduction of the Primary BoExp at Day 5 and Day 90 [100-(THS:CC) ratio and 100-(SA:CC) ratio in %]

BoExp	HPHCs [aerosol phase]	Comparison	Day 5		Day 90	
			ZRHM-REXA-07-JP Reduction (%) (95% CI)	ZRHM-REXA-08-US Reduction (%) (95% CI)	ZRHM-REXA-07-JP Reduction (%) (95% CI)	ZRHM-REXA-08-US Reduction (%) (95% CI)
COHb (%)	CO [gas]	mTHS mCC	-55% (-52.0 ; -57.9)	-62% (-57.5 ; -65.8)	-48% (-44.4 ; -51.9)	-53% (-45.0 ; -60.2)
		SA:mCC			-47% (-42.0; -51.0)	-48% (-32.6 ; -60.4)
MHBMA (pg/mg creat)	1,3-Butadiene [gas]	mTHS mCC	-87% (-83.4 ; -89.0)	-87% (-83.0 ; -90.7)	-81% (-75.4 ; -85.3)	-81% (-73.3 ; -87.1)
		SA:mCC			-81% (-74.7 ; -86.1)	-71% (-49.4 ; -83.8)
3-HPMA (ng/mg creat)	Acrolein [gas]	mTHS mCC	-49% (-42.8 ; -55.1)	-54% (-46.6 ; -60.8)	-46% (-37.7 ; -53.1)	-48% (-33.7 ; -59.2)
		SA:mCC			-61% (-54.0 ; -66.8)	-65% (-47.9 ; -76.1)
S-PMA (pg/mg creat)	Benzene [gas]	mTHS mCC	-89% (-87.0 ; -90.7)	-87% (-83.4 ; -90.5)	-87% (-83.4 ; -90.1)	-78% (-63.9 ; -86.5)
		SA:mCC			-87% (-82.6 ; -90.4)	-81% (-59.0 ; -91.4)

Abbr.: BoExp: biomarkers of exposure; CC: conventional cigarette; CI: confidence interval; CO: carbon monoxide; COHb: carboxyhemoglobin; HPHCs: harmful and potentially harmful constituents; 3-HPMA: 3-hydroxypropylmercapturic acid; mCC: menthol conventional cigarette; MHBMA: monohydroxybutenyl mercapturic acid; SA: smoking abstinence; S-PMA: S-phenylmercapturic acid; THS: Tobacco Heating System.
Source: Study Reports: ZRHM-REXA-07-JP, ZRHM-REXA-08-US

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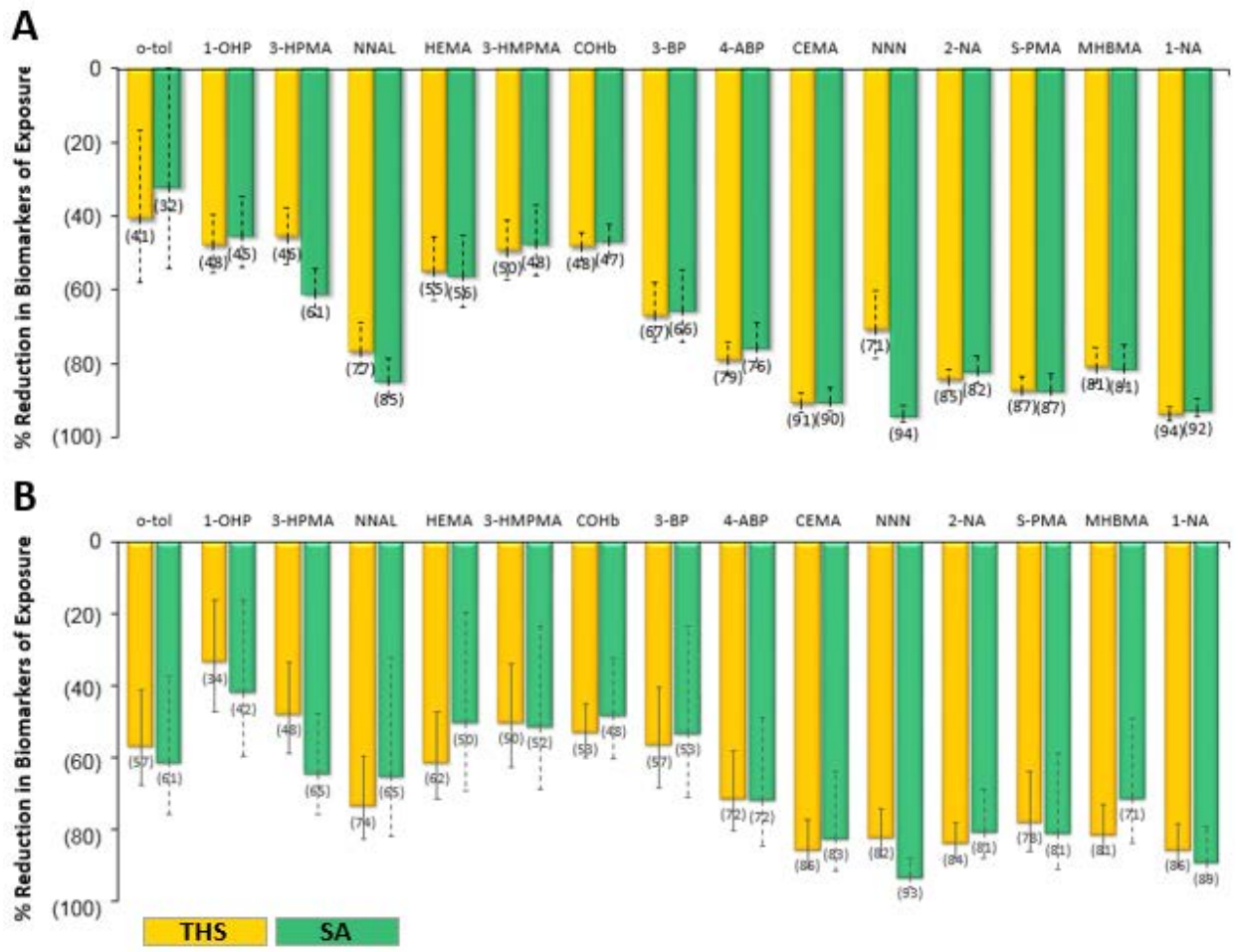


Figure 22: Percent reduction (geometric means at Day 90) in biomarkers of exposure after switching to THS (orange bars) and abstinence (green bars) after three months. A: Study conducted in Japan, B: Study conducted in the US

Abbr.: o-tol: o-Toluidine; 1-OHP: Total 1-hydroxypyrene; 3-HPMA: 3-hydroxypropylmercapturic acid; NNAL: Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-buranol; HEMA: 2-Hydroxyethyl-mercapturic acid; 3-HMPMA: 3-Hydroxy-1-methylpropyl-mercapturic acid; COHb: carboxyhemoglobin; 3-BP: 3-Hydroxybenzopyrene; 4-ABP: 4-Aminobiphenyl; CEMA: 2-Cyanoethylmercaturic acid; NNN: Total N-nitrosonornicotine; 2-NA: 2-Aminonaphtalene; S-PMA: S-phenylmercapturic acid; MHBMA: monohydroxybutenyl mercapturic acid; 1-NA: 1-Aminonaphtalene.

Source: Study Reports: ZRHM-REXA-07-JP, ZRHM-REXA-08-US

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Nicotine exposure levels during the confinement and ambulatory periods

The urinary nicotine equivalent (NEq) concentrations at baseline varied across studies, with the lowest levels found in the two Japanese studies (5.00 mg/g_{creat} in (ZRHR-REXC-04-JP) and 5.40 mg/g_{creat} in (ZRHM-REXA-07-JP) and the highest in the European (ZRHR-REXC-03-EU) and (ZRHM-REXA-08-US) studies (9.53 and 8.30 mg/g_{creat}, respectively) across arms.

The NEq concentrations were comparable between the THS and cigarette arms within studies and remained close to baseline values, with the exception of a decrease in THS during the confinement period in (ZRHM-REXA-08-US) (Figure 23). The percent changes from baseline on Day 5 were ranged from -2% to +23% and from -15% to +9% in the THS and cigarette arms, respectively.

In the 2 REXA studies, levels of urinary NEq concentrations at Day 90 were generally maintained and comparable in the THS and CC arms with percent changes from baseline in study (ZRHM-REXA-08-US) of about +4% in both the THS and cigarette arms and +37% and +25% in the THS and cigarette arms in the study (ZRHM-REXA-07-JP), respectively.

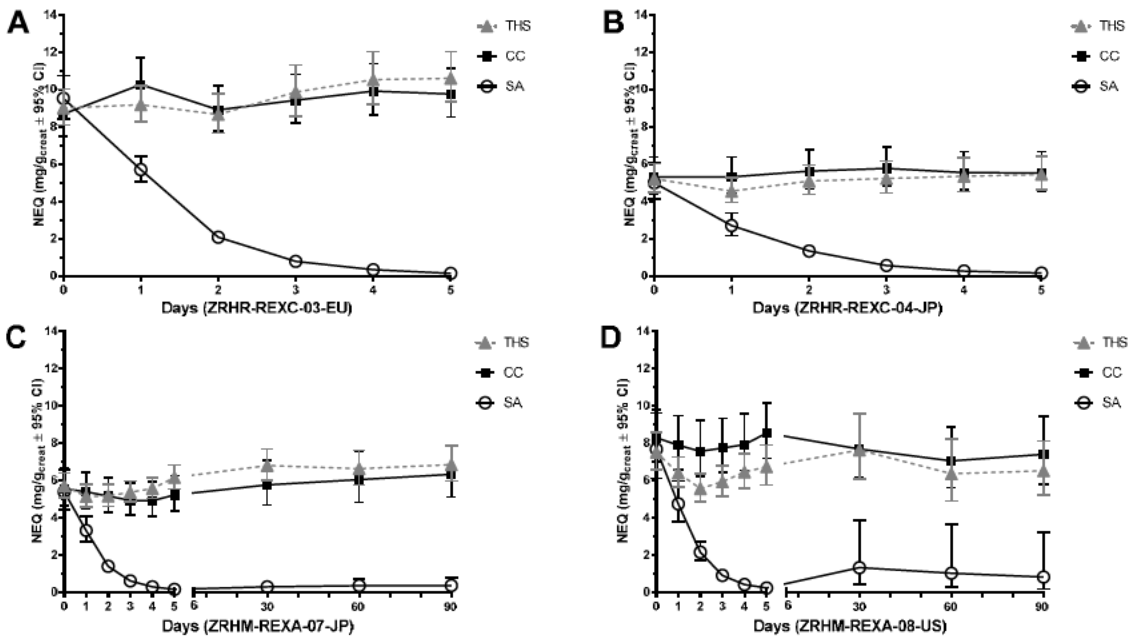


Figure 23: Geometric Mean and 95% CIs of Urinary NEq Concentrations (mg/gcreat), During the Course of: A) ZRHR-REXC-03-EU; B) ZRHR-REXC-04-JP; C) ZRHM-REXA-07-JP; D) ZRHM-REXA-08-US

Abbr.: CC = Conventional Cigarettes, SA = Smoking Abstinence, THS = Tobacco Heating System, Switch = switching
Source: Study Reports ZRHR-REXC-03-EU, ZRHR-REXC-04-JP, ZRHM-REXA-07-JP, ZRHM-REXA-08-US

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Reduction of Total NNN (biomarker for NNN) and Total NNAL (biomarker for NNK)

The tobacco-specific nitrosamines NNN (N-nitrosonornicotine) and NNK (nicotine-derived nitrosamine ketone) are constituents of tobacco and tobacco smoke and are classified as IARC Group 1 carcinogens (Table 2). As outlined earlier in this section, these two HPHCs are reduced by >95% in mTHS aerosols compared with 3R4F smoke, which is most likely due to a reduced level of evaporation in THS compared with 3R4F. NNK is rapidly reduced to its metabolite NNAL (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanonol). Since NNN and NNK are known carcinogenic constituents of tobacco, reduction of NNN and NNK levels in MRTPs should reduce the cancer risk for consumers (FDA 2016b, Xue 2014). As acknowledged by FDA during its Technical Review of a new tobacco product application (FDA 2016b), one of the most meaningful measures to substantiate reduced harm and the risk of tobacco-related disease is to demonstrate that switching to an MRTP results in substantially reduced exposure to NNN and NNK.

In all exposure assessment studies, the levels of urinary total NNN decreased substantially in the THS and smoking abstinence arms compared to baseline cigarette use (Figure 24) (Section 6.1.3.2.3.7). At the end of all four confinement studies/periods (Day 5), the percent changes from baseline of urinary total NNN levels ranged from -60% to -80% for the THS arms and from -94% to -97% for the smoking abstinence arms. At the end of the two ambulatory periods (Day 90), these changes were largely conserved with percent change from baseline ranging from -54% to -82% in the THS arms, and from -81% to -86% in the smoking abstinence arms.

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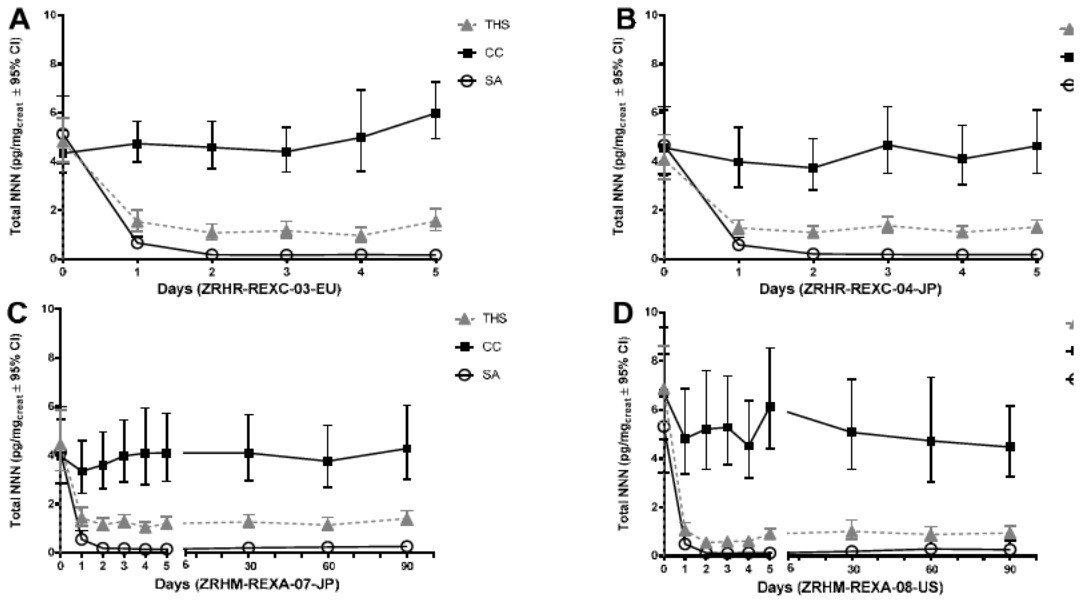


Figure 24: Geometric Mean Urinary and 95% CIs of Total NNN_{adjC} Concentrations (pg/mgcreat)

Abbr.: CC = conventional cigarettes; CI = confidence interval; NNN = N-Nitrosonornicotine; SA = smoking abstinence; THS = Tobacco Heating System

Source: Study Reports ZRHR-REXC-03-EU, ZRHR-REXC-04-JP, ZRHM-REXA-07-JP, ZRHM-REXA-08-US

Similar findings were observed across all clinical studies for NNK (Section 6.1.3.2.3.5). Total NNAL levels were reduced by over 48% at Day 5 and by over 67% at Day 90 across both REXA studies. The total NNAL levels for smokers who switched to THS approached those in the abstinence group (Figure 25).

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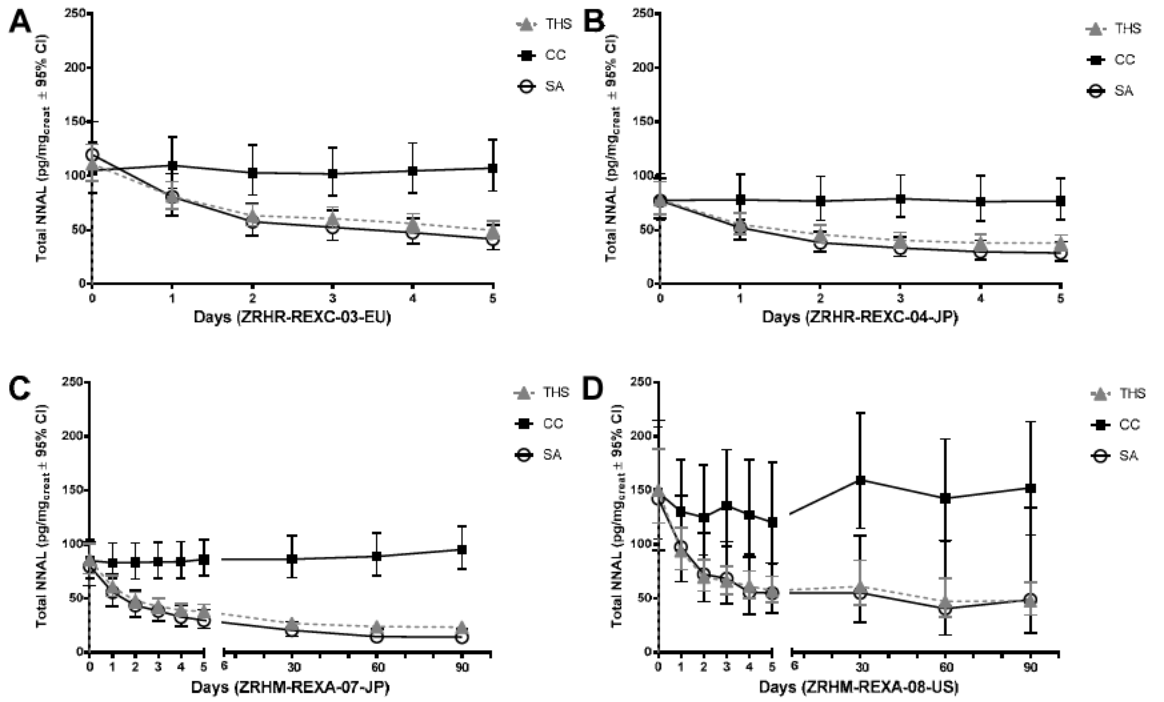


Figure 25: Geometric Mean and 95% CIs of Urinary Total $NNAL_{adjC}$ Concentrations (pg/mgcreat), During the Course of: A) ZRHR-REXC-03-EU; B) ZRHR-REXC-04-JP; C) ZRHM-REXA-07-JP; D) ZRHM-REXA-08-US

Abbr.: conventional cigarette (CC); confidence interval (CI), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL), smoking abstinence (SA), Tobacco Heating System (THS)

Source: Study Reports ZRHR-REXC-03-EU, ZRHR-REXC-04-JP, ZRHM-REXA-07-JP, ZRHM-REXA-08-US

Reduction of exposure in THS and mTHS

To compare the effect of menthol on exposure reduction, PMI compared the results of the two studies conducted in Japan with either THS (ZRHR-REXC-04-JP) or mTHS (ZRHM-REXA-07-JP) at Day 5. As indicated by Table 9, the presence of menthol in mTHS does not substantially affect the exposure to HPHCs, including NNK and NNN (further details of the analysis across studies is available in Section 6.1.3.2.3).

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Table 9: Adjusted Geometric Least Square Means of THS to CC ratios of the Primary BoExp, NNN and total NNK at Day 5 in two studies conducted in Japan.

BoExp		Study	ZRHR-REXC-04-JP	ZRHM-REXA-07-JP
		Product	THS	mTHS
COHb	THS:CC Ratio	Mean	47.10%	44.94%
		95% CI	44.30; 50.08	42.11; 47.97
		p Value	<0.001	<0.001
MHBMA	THS:CC Ratio	Mean	23.09%	13.49%
		95% CI	18.41; 28.95	10.96; 16.60
		p Value	<0.001	<0.001
3-HPMA	THS:CC Ratio	Mean	52.86%	50.67%
		95% CI	45.67; 61.17	44.88; 57.20
		p Value	<0.001	<0.001
S-PMA	THS:CC Ratio	Mean	15.68%	10.97%
		95% CI	13.09; 18.78	9.26; 12.99
		p Value	<0.001	<0.001
NNN	THS:CC Ratio	Mean	30.06%	27.02%
		95% CI	23.74; 38.06	21.75; 33.55
		p Value	<0.001	<0.001
Total NNAL	THS:CC Ratio	Mean	49.03%	43.69%
		95% CI	41.95; 57.30	39.62; 48.17
		p Value	<0.001	<0.001

Abbr.: BoExp: biomarkers of exposure; CC: conventional cigarette; CI: confidence interval; COHb: carboxyhemoglobin; 3-HPMA: 3-hydroxypropylmercapturic acid; NNAL: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; NNN: N-Nitrosonornicotine; MHBMA: monohydroxybutenyl mercapturic acid; S-PMA: S-phenylmercapturic acid; THS: Tobacco Heating System; mTHS: Menthol variant of THS.
Source: Study Reports: ZRHR-REXC-04-JP, ZRHM-REXA-07-JP

Summary of reduced exposure studies

Taken together, the results of all the exposure studies PMI has conducted show that switching from cigarette smoking to THS use significantly reduces the exposure to HPHCs, including important tobacco-specific carcinogens, while maintaining nicotine exposure at near to Baseline levels. Furthermore, the results of the two studies conducted in Japan show that switching to either THS or mTHS use for 5 days leads to similar reductions in exposure to HPHCs.

Clinical Risk Endpoints

The clinical and non-clinical MRTP assessment programs were based on the Adverse Outcome Pathway depicted in Figure 3. The fundamental objective was to demonstrate that for smokers who switch to THS, the risk of developing smoking-related diseases is reduced, and approaches that of smoking cessation. The scientific framework was developed using the

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available scientific literature on the epidemiology of smoking-related diseases as well as the mechanistic understanding of the impact of smoking and smoking cessation.

Chronic exposure to cigarette smoke leads to the multifaceted perturbation of many biological networks, which trigger multiple adverse effects causally linked to smoking–related diseases. Therefore, a single clinical risk endpoint/marker is not sufficient as a surrogate measure for the multiple adverse health effects caused by smoking, and hence is insufficient to demonstrate risk reduction. Consequently, the evaluation of the effects of THS aerosol exposure needs to be based on an assessment that integrates multiple sources of evidence. This enables the demonstration that THS significantly reduces the risk of smoking-related diseases for smokers who completely switch to THS compared with smokers who continue to smoke cigarettes.

As previously outlined in Assessment Steps 1-4, there are a number of parameters associated with perturbations of key biological mechanisms, which in turn, are causally linked with tobacco-related diseases. The major risk parameters that were evaluated across the non-clinical studies included exposure to HPHCs, genotoxicity, oxidative stress and inflammation. The non-clinical findings from the assessment of these risk parameters can be evaluated in clinical studies by incorporating BoExp, genotoxicity (BoExp, Urine Ames, CYP1A2 activity), markers of oxidative stress and platelet activation (8-epi-$PGF_{2\alpha}$ and 11-DTX-B2), markers of inflammation and endothelial function (WBC and s-ICAM-1) and alterations in lipid metabolism (HDL-C). In addition, there are a number of disease specific biomarkers that have been associated with cardiovascular risk (e.g. COHb, HDL-C, total cholesterol, triglycerides), risk of pulmonary disease (FEV_1). These biomarkers were incorporated into the PMI clinical studies to assess whether smokers who switched to THS could exhibit changes across a panel of clinical risk endpoints that aligned, in terms of direction and magnitude, with the favorable changes seen in smokers who abstained from smoking for the duration of the studies.

While the 90-day reduced exposure studies (ZRHM-REXA-07-JP and ZRHM-REXA-08-US) were primarily conducted to assess reductions in levels of BoExp to HPHCs (and powered accordingly), both studies also collected data on a number of clinical risk endpoints to assess the impact of reduced HPHC exposure on clinical risk endpoints. The full rationale for the selection of endpoints is provided in Section 6.1.4. The compliance with to product/regimen allocation in the three arms of these studies is discussed in Section 6.1.3.2.3.19.

The clinical risk endpoints were selected based on the following criteria:

- Evidence on association with smoking
- Evidence on relationship with ≥1 smoking-related health outcome
- Evidence on reversibility upon smoking cessation
- Biological plausibility
- Dose-response/temporality

The studies collected data on the following clinical risk endpoints:

- 8-epi-PGF2α, as a measure of oxidative stress
- 11-DTX-B2, as a measure of platelet activation

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- FEV_1, as a measure of airway function
- High-density lipoproteins (HDL-C), as a measure of lipid metabolism
- Total white blood cell (WBC) count, as a measure of inflammation
- sICAM-1, as a measure of endothelial dysfunction

Oxidative stress

The oxidation of lipids, proteins, and nucleic acids has been implicated in the pathogenesis of many diseases, including atherosclerosis. Isoprostanes are prostaglandin-like compounds formed from the peroxidation of arachidonic acid, which is a ubiquitous polyunsaturated fatty acid. Unlike prostaglandins, which are formed by cyclooxygenase, F2-IsoPs, including 8-epi-PGF2α, are generated by free radical-mediated peroxidation of arachidonic acid. Considering that the circulating F2-IsoP concentrations predominantly reflect its production, rather than its metabolism and excretion, it is important to measure the extent of oxidative stress in vivo (Morrow 2005). F2-IsoP is elevated in atherosclerosis and other cardiovascular diseases, supporting its use as risk marker for smoking-related CVD (Davis 2011). Prior studies demonstrated that the plasma concentration and urinary excretion of F2-IsoP and its metabolites were greater in healthy smokers than in healthy nonsmokers (Calapai 2009, Frost-Pineda 2011, Luedicke 2016). Several studies have also shown that the 8-epi-PGF2α concentration decreases rapidly after smoking cessation, within 1–2 weeks, to the concentrations observed in nonsmokers (Oguogho 2000, Pilz 2000, Reilly 1996).

Adult smokers who switched to mTHS showed a more than 12% reduction in 8-epi-PGF2α levels compared with smokers who continued to smoke (Table 10). This reduction approached that observed with smoking abstinence. The direction of the changes was consistent across the two studies (Section 6.1.4.4.4).

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Table 10: 8-epi-PGF2α Measured at the Day 90 Visit in the Reduced Exposure - Ambulatory Studies

Clinical Risk Endpoint	ZRHR-REXA-07-JP		ZRHM-REXA-08-US	
8-epi-PGF2α	CC (n=41)	221.74 pg/mg CRE (203.07, 242.12)	CC (n=32)	305.75 pg/mg CRE (277.98, 336.31)
	THS (n=70)	193.56 pg/mg CRE (181.00, 206.99)	THS (n=45)	264.61pg/mg CRE (244.14, 286.79)
	SA (n=37)	208.62 pg/mg CRE (190.24, 228.78)	SA (n=9)	279.73 pg/mg CRE (233.63, 334.92)
	THS:CC % Reduction	12.71% ↓ (2.55, 21.81)	THS:CC % Reduction	13.46% ↓ (-1.95, 23.61)

Abbr.: 8-epi-PGF2α = prostaglandin F2 alpha; THS = Tobacco Heating System; CC = conventional cigarettes; SA=smoking abstinence; CRE=creatinine (results were adjusted for creatinine); n = number of study subjects who complied with product allocation.

Note: Values are the adjusted least square means and 95% confidence intervals from the ANCOVA model conducted with baseline value, product exposure, sex and baseline CC consumption as fixed effect factors.

Source: Study Reports: ZRHM-REXA-07-JP, ZRHM-REXA-08-US

Platelet activation

Platelet activation and enhanced coagulation are causally related to cardiovascular events and can exacerbate hypertension and hypercholesterolemia (Davi 2007). Multiple cross-sectional studies have demonstrated that 11-DTX-B2 concentrations are 29–40% higher in smokers than in nonsmokers (Calapai 2009, Frost-Pineda 2011). 11-DTX-B2 concentrations were reported to be 60% higher in people who smoked ≥20 cigarettes per day with a tar content of 10 mg (Lowe 2009). In another study, urinary nicotine equivalent concentrations (in mg/24 h) were the strongest predictor of 11-DTX-B2 concentrations in adult smokers compared with nonsmokers (Frost-Pineda 2011). To date, although very few studies have examined the impact of smoking cessation on 11-DTX-B2 concentrations, it appears that its concentrations decrease quickly after stopping smoking (Rangemark 1993, Saareks 2001).

Consistent reduction was demonstrated for 11-DTX-B2 levels for smokers who switched to mTHS compared with smokers who continued to smoke across two studies (5% in ZRHM-REXA-07-JP and 4% in ZRHM-REXA-08-US). The shifts in the 11-DTX-B2 levels for smokers who switched to mTHS were in the same direction as those seen with smoking abstinence, as shown in Table 11, although the magnitude of the change was smaller than expected, especially in the US study (Section 6.1.4.4.4).

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Table 11: 11-DTX-B2 Measured at the Day 90 Visit in the Reduced Exposure - Ambulatory Studies

Clinical Risk Endpoint	ZRHR-REXA-07-JP		ZRHM-REXA-08-US	
11-DTX-B2	CC (n=41)	549.90 pg/mg CRE (498.48, 606.63)	CC (n=32)	444.47 pg/mg CRE (368.57, 536.00)
	THS (n=70)	500.52 pg/mg CRE (464.53, 539.29)	THS (n=45)	428.66 pg/mg CRE (365.22, 503.13)
	SA (n=37)	443.37 pg/mg CRE (399.99, 491.45)	SA (n=9)	412.67 pg/mg CRE (288.89, 589.47)
	THS:CC % Reduction	5.42% ↓ (-1.80, 12.13)	THS:CC % Reduction	3.56% ↓ (-23.31, 24.57)

Abbr.: 11-DTX-B2 = 11-dehydro-thromboxane B2; THS = Tobacco Heating System; CC = conventional cigarettes; SA=smoking abstinence; CRE=creatinine (results were adjusted for creatinine); n = number of study subjects who complied with product allocation.
Note: Values are the adjusted least square means and 95% confidence intervals from the ANCOVA model conducted with baseline value, product exposure, sex and baseline CC consumption as fixed effect factors.
Source: Study Reports: ZRHM-REXA-07-JP, ZRHM-REXA-08-US

Forced expiratory volume in 1 second (FEV1)

Lung function is defined by ventilation capacity, airway resistance and gas exchange capacity and influenced by lung elasticity and lung surface tension. A main characteristic of chronic pulmonary diseases such as COPD is the loss of lung elasticity, which develops gradually as a consequence of increased inflammatory responses and structural abnormalities such as increased thickness of the airway walls. Airway resistance and a reduction in lung elasticity eventually lead to expiratory airflow limitation, the hallmark and earliest sign of COPD, resulting in delayed emptying and hyperinflation of the lung characterized by an increased residual volume (RV), ultimately resulting in a decrease in vital capacity and FEV1.

Several studies have shown that subclinical inflammatory changes in small airways exist years before the advanced stages of COPD. Although relatively few longitudinal studies have assessed the effects of smoking cessation on inflammation in smokers without chronic respiratory symptoms, these studies demonstrated that the inflammatory response decreased rapidly within the first few months after smoking cessation. Considering these earlier findings, it seems likely that the favorable changes in lung function as assessed by FEV1 in the ambulatory Reduced Exposure studies can be explained by a decrease in the inflammatory state of the lung when switching from menthol cigarettes to menthol THS, similar to the changes observed following smoking cessation.

In the Japanese study (ZRHM-REXA-07-JP), smokers who switched to THS had an increase of 1.91 percent of predicted value (%Pred) in their FEV_1 as compared with smokers who continued to smoke cigarettes, with no notable differences between those switching to THS

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and with smoking abstinence. These data were promising but studies of longer duration will be required to assess fully the impact of the exposures on FEV_1.

In the US study (ZRHM-REXA-08-US), the difference in FEV_1 values between smokers who switched to THS and those who continued to smoke was smaller in magnitude as compared with in the Japanese study. Nonetheless, the results were consistent and trended in the expected direction following smoking abstinence (Table 12) (Section 6.1.4.4.6).

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Table 12: FEV_1 Measured at the Day 90 Visit in the Reduced Exposure - Ambulatory Studies

Clinical Risk Endpoint [1]	ZRHR-REXA-07-JP		ZRHM-REXA-08-US	
FEV_1	CC (n=41)	93.45 %Pred (91.81, 95.09)	CC (n=30)	90.64 %Pred (88.05, 93.24)
	THS (n=70)	95.36 %Pred (94.11, 96.62)	THS (n=47)	91.18 %Pred (89.08, 93.27)
	SA (n=37)	95.38 %Pred (93.66, 97.11)	SA (n=9)	92.64 % Pred (87.87, 97.41)
	Diff THS-CC	1.91 %Pred (-0.14, 3.97)	Diff THS-CC	0.53 % Pred (-2.09, 3.00)

Abbr.: THS = Tobacco Heating System; CC = conventional cigarettes; SA=smoking abstinence; %Pred = percent of predicted value (%Pred); n = number of study subjects who complied with product allocation.
(1) Spirometry measures in the ZRHM-REXA-07-JP study (FEV_1) were conducted pre-bronchodilator while those the in the ZRHM-REXA-08-US study were conducted post-bronchodilator
Note: Values are the adjusted least square means and 95% confidence intervals from the ANCOVA model conducted with baseline value, product exposure, sex and baseline CC consumption as fixed effect factors.
Source: Study Reports: ZRHM-REXA-07-JP, ZRHM-REXA-08-US

Lipids

The beneficial effects of HDL-cholesterol (HDL-C) on the cardiovascular system have been attributed to its ability to remove cellular cholesterol via reverse cholesterol transport. HDL-C also exerts anti-inflammatory, antioxidant, and antithrombotic effects, which act in concert to improve endothelial function and limit atherosclerosis progression, thereby reducing cardiovascular risk. Numerous studies have shown that smoking decreases HDL-C (Allen 1994, Eliasson 2001, Moffatt 2000, Ohsawa 2005). HDL-C levels increase relatively quickly after stopping smoking, but decrease again upon resumption of smoking (Allen 1994, Eliasson 2001, Frost-Pineda 2011, Yasue 2006). The effect of smoking cessation on HDL-C was eloquently demonstrated in a meta-analysis of 45 studies with a total of 94 estimates of HDL-C based on within-subject changes. For the unweighted analysis, the overall pooled increase in HDL-C following smoking cessation was 4.13 mg/dL (Forey 2013).

In the ambulatory Reduced Exposure studies, smokers who switched to THS had higher HDL-C levels compared with smokers who continued to smoke. In the Japanese study (ZRHM-REXA-07-JP), the HDL-C levels in smokers following the switch to THS were similar to those following smoking abstinence, after adjusting for baseline HDL-C levels, sex and cigarette consumption at baseline. In the Japanese study, the mean HDL-C concentration on Day 90 was 4.5 mg/dL higher in the mTHS group than in the mCC group.

In the US study (ZRHM-REXA-08-US) the HDL-C levels in smokers switching to THS were greater than those in smokers that continued to smoke. However, the results for the HDL-C levels in smokers continuing to smoke cigarettes were very similar to those in

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smokers who switched to smoking abstinence. In the US ambulatory Reduced Exposure study, only 9 of the 40 subjects randomized to the SA group reported adherence with smoking abstinence during the 3-month follow-up period, thereby limiting the ability to interpret the smoking abstinence findings in that study (Table 13) (Section 6.1.4.4.5).

Table 13: HDL-Cholesterol Measured at the Day 90 Visit in the Reduced Exposure - Ambulatory Studies

Clinical Risk Endpoint	ZRHR-REXA-07-JP		ZRHM-REXA-08-US	
HDL-C	CC (n=41)	57.09 mg/dL (54.42, 59.77)	CC (n=32)	53.3 mg/dL (50.5, 56.1)
	THS (n=70)	61.62 mg/dL (59.58, 63.65)	THS (n=47)	54.7 mg/dL (52.3, 57.0)
	SA (n=37)	63.45 mg/dL (60.66, 66.25)	SA (n=9)	53.3 mg/dL (48.1, 58.6)
	Diff THS-CC	4.53 mg/dL (1.17, 7.88)	Diff THS-CC	1.4 mg/dL (-2.3, 5.0)

Abbr.: HDL-C = high density lipoprotein-cholesterol; THS = Tobacco Heating System; CC = conventional cigarettes; SA=smoking abstinence; Diff THS-CC = the difference between THS and CC; n = number of study subjects who complied with product allocation.
Note: Values are the adjusted least square means and 95% confidence intervals from the ANCOVA model conducted with baseline value, product exposure, sex and baseline CC consumption as fixed effect factors.
Source: Study Reports: ZRHM-REXA-07-JP, ZRHM-REXA-08-US

Inflammation

An increased WBC count is seen as a marker of chronic, subclinical, and low-grade inflammation which is associated with an increased risk of CVD, including hypertension, atherosclerosis, 6-month mortality risk, stroke, peripheral arterial disease, and mortality following myocardial infarction (Bonaterra 2010). Cigarette smoking is consistently associated with an increased WBC count, and increased smoking intensity with a more pronounced elevation in WBC count (Asthana 2010). The mean WBC count was reported to be 7–20% higher in smokers than in nonsmokers (Frost-Pineda 2011, Ishizaka 2007, Wannamethee 2005). A meta-analysis of 24 studies quantified the within-subject changes of WBC count after quitting for <13 weeks (26 estimates), 13 to <52 weeks (7 estimates) and ≥52 weeks (3 estimates). The decreases in total WBC count (10^9/L [95% confidence interval) for these three time periods were 0.98 (0.74–1.22), 0.78 (0.58–0.98), and 0.64 (0.35–0.92), respectively (Lee 2014).

WBC counts were assessed in the two ambulatory Reduced Exposure studies. In both studies, there was a reduction in WBC counts over the course of the study. The reductions were generally largest in the SA group, but there were consistent reductions in the mTHS users, which approached the levels in the SA group. In the Japanese study, WBC decreased in the

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mTHS group and increased in the menthol cigarette group, resulting in a LS mean difference of −0.57 GI/L at Day 90 (Table 14). The reduction in WBC was slightly smaller in the mTHS group than in the SA group. mTHS exposure resulted in reduced WBC counts, as early as Day 30, to levels similar to those seen with smoking abstinence. In the 90-day US study, there was a minimal but not statistically significant difference observed in the WBC counts between subjects who switched to mTHS use and subjects who continued to smoke menthol cigarettes (Section 6.1.4.4.3).

Table 14: WBC Counts at the Day 90 Visit in the Reduced Exposure - Ambulatory Studies

Clinical Risk Endpoint	ZRHR-REXA-07-JP		ZRHM-REXA-08-US	
WBC Count	CC (n=41)	6.14 GI/L (5.76, 6.52)	CC (n=32)	7.09 GI/L (6.59, 7.59)
	THS (n=71)	5.57 GI/L (5.28, 5.86)	THS (n=47)	7.26 GI/L (6.84, 7.68)
	SA (n=37)	5.73 GI/L (5.34, 6.13)	SA (n=9)	6.15 GI/L (5.19, 7.11)
	Diff THS-CC	-0.57 GI/L (-1.04, -0.10)	Diff THS-CC	0.17 GI/L (-0.47, 0.81)

Abbr.: WBC count = white blood cell count; THS = Tobacco Heating System; CC = conventional cigarettes; SA=smoking abstinence; Diff THS-CC = the difference between THS and CC; GI/L = gills/liter; n = number of study subjects who complied with product allocation.
Note: Values are the adjusted least square means and 95% confidence intervals from the ANCOVA model conducted with baseline value, product exposure, sex and baseline CC consumption as fixed effect factors.
Source: Study Reports: ZRHM-REXA-07-JP, ZRHM-REXA-08-US

Endothelial function

Adhesion molecules facilitate the adhesion and transmigration of leukocytes into the vascular endothelium and then the sub-endothelial space, a critical event in the initiation of atherosclerosis (Kaperonis 2006). Elevated plasma sICAM-1 concentrations were reported to reflect endothelial dysfunction and ongoing atherosclerosis (Ross, 1999). A number of epidemiologic studies have suggested that elevated sICAM-1 concentrations may be an early biomarker of atherosclerosis (Gross 2012, Hsu 2009), and the significant associations between cell adhesion molecules and CVD risk factors highlight their usefulness as clinical risk marker. Current smoking increases the circulating concentrations of sICAM-1 by about 20–70% (Atikçan 2004, Bergmann 1998, Bermudez 2002, Blann 1998, Blann 1997). It was also reported that sICAM-1 concentrations are positively correlated with pack-years of smoking (Demerath 2001, Miller 2003) and increased in a dose-dependent manner with the amount of tobacco smoked per day (Demerath 2001, Lain 2006, Scott 2000, Takeuchi 2002). These effects of smoking on sICAM-1 are reversible following smoking cessation (Bermudez 2002, Halvorsen 2007, Palmer 2002, Scott 2000). Consistent with these earlier studies, we found that sICAM-1 concentrations were upregulated in smokers compared with

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nonsmokers, which might reflect endothelial dysfunction and ongoing atherosclerosis in these cigarette smokers (Luedicke 2016).

In both ambulatory Reduced Exposure studies, smokers who switched to mTHS had lower sICAM-1 levels than did subjects who continued to smoke. These sICAM-1 levels (approximately 8.5–10.5% reduced) agreed with those in subjects who abstained from smoking. These changes were generally seen within the first 30 days of exposure and were maintained throughout the ambulatory period at Day 90 (Table 15) (Section 6.1.4.4.3).

Table 15: sICAM-1 Measured at the Day 90 Visit in the Reduced Exposure - Ambulatory Studies

Clinical Risk Endpoint	ZRHR-REXA-07-JP		ZRHM-REXA-08-US	
sICAM-1	CC (n=41)	198.55 ng/mL (187.71, 210.01)	CC (n=32)	257.07 ng/mL (243.58, 271.30)
	THS (n=70)	181.23 ng/mL (173.63, 189.17)	THS (n=45)	229.84 ng/mL (219.48, 240.68)
	SA (n=37)	176.97 ng/mL (166.87, 187.68)	SA (n=9)	231.60 ng/mL (208.89, 256.79)
	THS:CC % Reduction	8.72% ↓ (2.05, 14.94)	THS:CC % Reduction	10.59% ↓ (4.03, 16.71)

Abbr.: sICAM-1 = soluble intercellular adhesion molecule 1; THS = Tobacco Heating System; CC = conventional cigarettes; SA=smoking abstinence; n = number of study subjects who complied with product allocation.
Note: Values are the adjusted least square means and 95% confidence intervals from the ANCOVA model conducted with baseline value, product exposure, sex and baseline CC consumption as fixed effect factors.
Source: Study Reports: ZRHM-REXA-07-JP, ZRHM-REXA-08-US

Summary of Clinical Risk Endpoints

In summary, 90 days after switching from menthol cigarette smoking to menthol THS use, there was a shift in the same direction for all (except WBC in the US study) of the clinical risk endpoints. The shifts in the clinical risk endpoints of smokers who switched to mTHS were of a similar magnitude (except WBC in the US study) to those seen following 90 days of smoking abstinence. The data from the clinical risk endpoints further contributes to the substantiation of a reduced risk claim according to Section 911(g)(1) of FD&C Act and a reduced exposure claim under Section 911(g)(2).

Overall Summary of Clinical Studies (Steps 5)

In summary, the clinical studies demonstrated a consistent reduction in exposure to BoExp in smokers who switched from cigarette smoking to THS use or smoking abstinence. These changes were evident as early as five days following the switch and were preserved throughout the 90-day duration of the REXA studies. The reductions seen in the THS group

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were similar in both magnitude and direction to those seen with smoking abstinence. Furthermore, in both longer-term reduced exposure studies, 90 days after switching from cigarette smoking to mTHS use, there was a shift in clinical risk endpoints in the same direction as smoking abstinence. The shifts in the clinical risk endpoints of smokers who switched to mTHS were of similar magnitude to those seen following 90 days of smoking abstinence. Therefore, PMI has met its objectives for Evidence Level IV (Reduced Exposure and Risk).

THS Reduces the Risk of Tobacco-Related Disease to Individual Tobacco Users

The scientific case that switching to THS reduces the risk of tobacco-related disease can be examined in the context of specific tobacco-related diseases such as CVD, COPD and lung cancer. The evidence that using THS instead of smoking cigarettes presents a reduced risk of tobacco-related diseases comes from a broad range of studies conducted in relevant biological systems including cell cultures, organotypic tissue cultures, *in vivo* models as well as human clinical studies. Both standard and systems-based approaches were used to collect a very diverse, detailed and comprehensive dataset that was analyzed in the context of biologically plausible disease-relevant mechanisms. As noted in the following sections, all biological systems exposed *de novo* to THS or mTHS aerosol showed consistent, dramatic and compelling reductions in biological perturbations when compared with cigarette smoke**.** Studies conducted in animals and human subjects switched from cigarette smoke to either THS/mTHS aerosol or air (smoking cessation/abstinence) showed remarkably similar reductions in BoExp, xenobiotic metabolism activation, oxidative stress, inflammation as well as lipid dysfunction. They also showed a significant reduction in the progression of aortic plaque formation, pulmonary dysfunction and emphysema in an animal model of disease. The significance of these findings will be discussed for the three main diseases caused by cigarette smoking.

Cardiovascular disease

Cigarette smoke triggers mechanisms that increase the risk of CVD

Cigarette smoking is a major risk factor for the development of CVD (Messner 2014). Cigarette smoke contains HPHCs that cross the alveolar barrier into the blood stream and elicit systemic oxidative stress and inflammatory responses that can affect normal vascular functions. These changes favor and accelerate the appearance of atherosclerotic plaque, leading to an increased risk of CVD. The consistent and biologically plausible results obtained from non-clinical as well as clinical studies outlined below lead to the conclusion that switching from cigarette smoking to THS use reduces the risk of cardiovascular disease.

Oxidative stress in vitro and in vivo

In the non-clinical assessment of THS, oxidative stress was evaluated *in vitro* by measuring multiple parameters of oxidative stress and oxidative cellular damage using high-content screening (Gonzalez-Suarez 2016), and *in vivo* by quantifying markers of lipid peroxidation in urine (Figure 16) (Phillips 2016). Moreover, systems toxicology applied to the non-clinical studies conducted *in vitro* and *in vivo* included extensive molecular profiles that were analyzed with a biological network model of oxidative stress (Schlage 2011, Boue 2015).

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Overall, the extent of oxidative stress and oxidative cellular damage was substantially lower in THS aerosol than 3R4F smoke exposed cells, tissues and animals as indicated by an array of specific markers and biological network perturbations. Furthermore, in the Apoe$^{-/-}$ mouse switching study, switching from 3R4F exposure to THS aerosol exposure lead to a reduction in oxidative stress that was similar in magnitude to the reduction seen with smoking cessation.

Inflammation in vitro and in vivo

Vascular inflammatory processes are central to all stages of atherogenesis. Oxidative stress of circulating WBC and the vascular endothelium causes a pro-inflammatory response that promotes the adhesion of circulating monocytes to endothelial cells and affects their transmigration into the vascular wall. Subsequently, the monocytes differentiate into inflammatory macrophages that phagocytose oxidized lipids (elevated in smokers) and develop into lipid-laden foam cells, eventually forming the fatty streaks that are the first visible signs of atherosclerosis (Galkina 2009, Libby 2012, Yamaguchi 2005).

In the non-clinical assessment, the effects of THS aerosol and cigarette smoke exposure on inflammatory processes were compared in several *in vivo* and *in vitro* studies using a detailed systems toxicology-based approach.

In all studies, exposure to cigarette smoke elicited a broad inflammatory response and massively perturbed the biological networks of tissue-specific and common inflammation. In contrast, exposure to THS aerosol caused markedly attenuated inflammatory responses and perturbations of the associated networks. Furthermore, in the Apoe$^{-/-}$ mouse switching study, switching to THS aerosol exposure lead to a reduction in inflammation that was similar in magnitude to the reduction seen with smoking cessation.

Lipid metabolism in vivo

Altered lipids and their metabolism are essential contributors to cardiovascular disease mechanisms. They can modulate systemic inflammatory processes such as the expression of pro-inflammatory thromboxanes and prostaglandins. Moreover, changes in lipoprotein metabolism have been causally linked to atherosclerotic plaque formation, which may lead to cardiovascular disease.

The lipid classes investigated and described in the non-clinical THS assessment focused on the role of lipids in the context of cigarette smoke-related oxidative stress and inflammatory processes that are causally involved in the pathogenesis of cardiovascular disease (De Leon 2015, Titz 2016). The lipid changes observed in rodent models of disease following cigarette smoke exposure are indicative of an altered surfactant metabolism, an imbalance between pro- and anti-inflammatory lipids in the lung, a pro-atherosclerotic milieu in the vascular wall, and an increase in systemic abundance of lipid peroxidation products. In Apoe$^{-/-}$ mice exposed to cigarette smoke, many lipid species were increased in the aortic wall, similar to those that are enriched in human aortic plaques. In contrast, most of these lipid profiles and metabolic changes were substantially attenuated or absent in THS aerosol exposed animals (Phillips 2016). Furthermore, switching to THS aerosol exposure resulted in a marked reduction of cigarette smoke-related lipid changes similar to the effect of smoking abstinence. For instance, compared to sham exposure, cigarette smoke exposed mice

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displayed increased total cholesterol (TC) at months 1 and 3, with a decrease to sham levels one month after both cessation and switching to THS aerosol exposure. Accompanying the increase in TC was a similar increase in HDL-C (Phillips 2016).

Monocyte adhesion to endothelial cells in vitro

Monocyte adhesion to vascular endothelium is an early event in atherogenesis and a hallmark of vascular inflammation. It is caused by an increase in adhesion molecules expression by endothelial cells, in response to pro-inflammatory cytokines. Using a functional assay *in vitro*, PMI has demonstrated that exposure to cigarette smoke caused a significant increase in the expression of the pro-inflammatory cytokine TNFα in exposed monocytes (MM6 cells). This triggered the upregulation of the adhesion molecule ICAM-1 on endothelial cells, which contributes to the increased adhesion of MM6 cells to the endothelial layer. In contrast, THS aerosol exposure induces significantly (10-20 fold) less MM6 adhesion and associated network perturbations than cigarette smoke.

Atherosclerotic plaque growth in vivo

The Apoe$^{-/-}$ mouse model is useful to study human cardiovascular disease and allows for the quantitative analysis of aortic arch plaque development using *in situ* plaque measurements as well as micro computed tomography. Exposure to cigarette smoke has been shown to accelerate the development of atherosclerotic plaque in this animal model. The results of the PMI 8-month Apoe$^{-/-}$ mouse switching study showed that exposure to THS aerosols resulted in plaque area measurements similar to sham exposed mice (Figure 19) (Phillips 2016). Switching from cigarette smoke to THS aerosol also slowed plaque progression in a manner similar to smoking cessation. The reduction in plaque progression, upon switching and cessation, was in direct correlation with the reduced perturbation of biological networks of oxidative stress and inflammation including that of monocyte-endothelial cell interaction. As expected, exposure to cigarette smoke caused significant perturbation of these networks, which are causally linked to accelerated plaque growth. In contrast, exposure to THS aerosol caused little to no perturbation of these networks.

Clinical markers associated with CVD risk

Exposure to cardiovascular toxicants: As listed in Table 2, several HPHCs have been recognized as cardiovascular toxicants and are significantly reduced in THS aerosol compared with cigarette smoke. The REXC and REXA studies confirmed that adult smokers who switch to THS use were exposed to significantly reduced levels of HPHCs, including cardiovascular toxicants, compared with smokers who continued to smoke (Section 6.1.6 Table 1). These reductions in exposure approached the reductions seen with smoking abstinence (Section 6.1.6 Table 1).

Oxidative stress: 8-epi-PGF2α, the marker for oxidative stress, was reduced in smokers who switched from smoking to mTHS use compared to those who continued smoking. The 8-epi-PGF2α levels were consistently reduced in both REXA studies, to levels similar to those observed in the respective SA groups.

Inflammation: In the study conducted in Japan, WBC counts were reduced in both the THS and the SA groups compared with those who continued smoking.

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Endothelial function: Smokers who switched to mTHS use had lower levels of sICAM-1 than did subjects who continued to smoke. These sICAM-1 levels agreed with those in subjects who abstained from smoking.

Smokers who switched to THS use had higher levels of HDL-C compared to those who continued to smoke. In the Japanese REXA study, the HDL-C levels in smokers who switched to THS were similar to those in smokers who abstained for the duration of the study, after adjusting for baseline HDL-C levels, sex and cigarette consumption at baseline. In the US study, the levels of HDL-C were greater in smokers who switched to THS than in smokers who continued to smoke. However, the HDL-C levels in smokers who abstained in the US study were similar to those in smokers who continued to smoke cigarettes. In the US study, only 9 of the 40 subjects randomized to the SA group reported adherence with smoking abstinence during the 3-month ambulatory period, thereby limiting the ability to interpret the smoking abstinence findings in that study.

Platelet activation: Consistent reductions in 11-DTX-B2 levels were observed in smokers who switched to mTHS use compared with smokers who continued to smoke across both REXA studies. The shifts in 11-DTX-B2 levels for smokers who switched to mTHS were in the same direction as those seen with smoking abstinence.

Summary for CVD

Smoking-related cardiovascular diseases develop because of chronic exposure to HPHCs, which causes oxidative stress and inflammation. These mechanisms, in turn, cause perturbations of biological networks linked to endothelial dysfunction, lipid metabolism and platelet activation. These changes lead to atherosclerotic plaque formation and increased cardiovascular risk.

PMI has presented multiple lines of evidence that switching from cigarette smoking to THS use would be accompanied by a lower risk of CVD.

First, THS significantly reduces the formation of HPHCs compared with cigarettes. Reduced exposure clinical studies have demonstrated that this reduced formation of HPHCs results in a reduced exposure to HPHCs, including cardiovascular toxicants.

Second, this reduced exposure to HPHCs has been shown across multiple *in vitro* and *in vivo* studies to result in a significantly reduced biological impact compared with cigarette smoke. This reduced impact is evidenced by the reduced perturbations of biological networks associated with the causation of CVD (e.g. oxidative stress, inflammation, monocyte-endothelial cell interaction) and the reduced monocyte adhesion to endothelial cells *in vitro*. Human clinical studies have confirmed that clinical markers of oxidative stress, inflammation, endothelial function, lipid metabolism and platelet activation show positive changes, similar to those seen following smoking abstinence.

Third, the $Apoe^{-/-}$ mouse switching study demonstrated that animals that were initially exposed to cigarette smoke and subsequently switched to either THS aerosol or fresh air exposure showed very similar reductions in atherosclerotic plaque growth rates.

Overall, the scientific data is remarkably consistent across all biological systems that were studied. Compared with cigarette smoke, THS aerosol had significantly reduced effects on

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mechanisms causally linked to atherosclerotic plaque formation in human-derived *in vitro* systems. Switching from smoke to THS aerosol exposure caused positive changes in clinical risk markers associated with cardiovascular risk and reduced atherosclerotic plaque growth in an animal model of disease. THS aerosol exposure performs in a manner similar to smoking cessation/abstinence when examined in both animal and human switching studies. The congruence of scientific findings indicates that smokers who switch to THS would have a lower risk of CVD compared with continued smoking.

Chronic obstructive pulmonary disease (copd)

Cigarette smoking contributes to the risk of COPD

Chronic exposure of the lung to cigarette smoke, which is the major risk factor for COPD, results in oxidative stress and inflammation. Oxidative stress and chronic inflammation, in turn, cause changes in alveolar and airway tissues. Cigarette smoke can trigger and enhance pulmonary inflammation via several distinct yet partially overlapping mechanisms involving many different cell types. Over time, the persistence of these mechanisms in the lung lead to goblet cell metaplasia/hyperplasia, mucus hypersecretion, airway remodeling, and alveolar destruction that are characteristic of COPD (Barnes 2004; Rogers, 2007). These changes have an adverse impact on the overall pulmonary structure and function, leading to COPD.

Oxidative stress and inflammation in vitro

Multiple *in vitro* studies were conducted in human-derived systems to compare the effects of THS aerosol with 3R4F smoke exposure.

First, PMI compared the overall oxidative stress impact of THS aerosol extracts with that of cigarette smoke extracts on normal human bronchial epithelial cells (NHBE) (Gonzalez-Suarez 2016). In this study, PMI measured the intracellular glutathione (GSH) content and the intracellular reactive oxygen species (ROS) load of cells exposed to either THS aerosol or 3R4F smoke. The combined results of this study demonstrated that the oxidative stress induced by THS aerosol was significantly reduced compared with that induced by cigarette smoke.

Second, PMI conducted studies in human organotypic airway tissue cultures (nasal and bronchial epithelia) grown at the air-liquid interface to compare the effects of whole 3R4F smoke exposure with those of whole THS aerosol exposure on cytotoxicity, release of inflammatory mediators and gene expression changes.

In the study conducted with organotypic nasal epithelium tissue cultures, 3R4F smoke exposure induced substantial cytotoxicity whereas exposure to THS aerosol did not. Cultures exposed to THS aerosol secreted lower levels of various inflammatory mediators compared with those exposed to 3R4F smoke (e.g. 53% reduction in CXCL-8 and 81% reduction of sICAM-1). Furthermore, the cilia beating frequency (and power) was strongly reduced by 3R4F smoke exposure while THS aerosol exposure did not affect this functional parameter (Section 6.1.4.4.1.1.4) (Iskandar 2016).

The study conducted with organotypic bronchial epithelium tissue cultures showed that, in contrast to 3R4F smoke, THS aerosol did not cause cytotoxicity. While 3R4F smoke

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exposure induced a strong inflammatory response in these cultures, the response to THS aerosol was significantly attenuated (Section 6.1.4.4.1.1.5).

Taken together, these results demonstrated that, compared with 3R4F smoke exposure, THS aerosol exposure caused little to no cytotoxicity and substantially less inflammation in these organotypic tissue cultures.

Lung inflammation in vivo

The effects of THS aerosol inhalation was assessed on pulmonary cells and function in two 90-day sub-chronic inhalation studies conducted in rats according to OECD Test Guideline 413. In the first study, PMI compared the effects of THS with those of 3R4F, while the second study compared the effects of a mentholated variant of THS (mTHS) with a specially manufactured mentholated reference cigarettes (MRC) (3R4F analogue). The purpose of the studies was to compare the toxicity of both THS and mTHS aerosols with that of cigarette smoke. In addition to the standard toxicology endpoints, the studies also assessed pulmonary inflammation (BALF analysis) and molecular changes using transcriptomics, proteomics and lipidomics analyses (Section 6.1.4.4.1.2.1).

In both studies, exposure to reference cigarette smoke over 90 days resulted in moderate to marked reserve cell hyperplasia, marked squamous metaplasia and loss of goblet cells in the rat respiratory nasal epithelium. Both THS and mTHS aerosols caused reduced levels of reserve cell hyperplasia and squamous metaplasia, and considerably less cornification and loss of goblet cells, even at the highest aerosol concentration.

The BALF analysis (Sections 6.1.4.4.1.2.1.1 and 6.1.4.4.1.2.1.2) showed that exposure to reference cigarette smoke was accompanied by an increase in total free lung cells, driven primarily by increased macrophage and neutrophil counts. In contrast, exposure to THS and mTHS aerosol did not affect the total number of free lung cells, even at the highest aerosol concentration. Levels of inflammatory mediators in BALF, including several cytokines, chemokines and growth factors, were significantly increased in reference cigarette smoke exposed rats, whereas THS and mTHS aerosol exposure caused only very limited changes, even at the highest exposure concentration. (Section 6.1.4.4.1.2.1.1).

Animal models of emphysema

Many cellular and molecular mechanisms involved in the pathogenesis of human COPD are also observed in murine pulmonary emphysema models (Brusselle 2006). Several features are shared between human early stage disease and mouse disease development, which primarily recapitulates the emphysema component (Churg 2011). Lesions in mice caused by chronic cigarette smoke exposure resemble mild centrilobular human emphysema, both morphologically and physiologically (Churg 2008). Small airway remodeling, an important cause of airflow obstruction in cigarette smokers with COPD (Hogg 2004), is also observed in cigarette smoke exposed mice (Churg 2008). In addition, exposure activates the innate immune response cascade in mice, leading to protease/anti-protease imbalances in lung tissue and eventually to alveolar destruction, suggesting that murine models can also replicate these features of human COPD (Yoshida 2007). Finally, as observed in humans, the small airways of cigarette smoke exposed C57BL/6 mice exhibit persistent up-regulation of type I pro-

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collagen and pro-fibrotic cytokine gene expression, which would be expected to contribute to airway remodeling (Churg 2006).

Previous studies have shown that chronic exposure of mice to cigarette smoke results in reduced lung function, sustained pulmonary inflammation and emphysema with features resembling those underlying human COPD pathophysiology (Awji 2015, Churg 2009, Kang 2007, March 2006, Phillips 2015b, Sato 2008, Stinn 2013).

Apoe-/- mouse switching study

Apolipoprotein E-deficient (*Apoe*$^{-/-}$) mice are commonly used as a model for atherogenesis (Veniant 2001) and have been valuable tools for investigating smoking-related atherosclerosis (Boue 2012, Chan 2012, Lietz 2013, von Holt 2009). This mouse model has also been used to study cigarette smoke-induced lung inflammation and emphysema (Arunachalam 2010, Boue 2013, Han 2012). PMI conducted an 8-month exposure study in *Apoe*$^{-/-}$ mice to compare the impact of THS aerosol exposure with 3R4F smoke exposure on the development and progression of emphysema and atherosclerotic plaque formation (Phillips 2016) (Section 6.1.4.4.1.2.2).

The objective of the study (relevant to COPD) was to compare the molecular changes, biological network perturbations, cellular and tissue changes as well as the lung function changes induced by exposure to THS aerosol with those caused by 3R4F smoke exposure (full description of study methodology and findings can be found in Section 7.5).

Molecular changes and biological network perturbations

Most inflammatory mediators measured in BALF were significantly elevated in 3R4F smoke exposed animals, showing a rapid increase following one month of exposure. However, inflammatory mediator as well as proteolytic enzyme concentrations in the BALF of THS aerosol exposed mice were very similar to those in sham exposed animals. Furthermore, animals switched from cigarette smoke to THS aerosol exposure or smoking cessation showed attenuations of these changes to almost normal values (Phillips 2016). The analysis of the lung proteome across all study groups showed a pattern that is entirely consistent with these observations (Phillips 2016).

Using a systems toxicology approach, PMI analyzed the biological network perturbations underlying the toxicological impact of 3R4F smoke exposure. This analysis encompassed a very broad range of mechanisms including Tissue Repair and Angiogenesis, Inflammatory Processes, Cell Stress, Cell Proliferation, Tissue repair and Angiogenesis and Cell Fate. 3R4F smoke exposure caused a sustained and generalized activation of all these mechanisms (Figure 17). While most of the networks affected by the initial 3R4F smoke exposure remained perturbed throughout the cessation period, the extent of these perturbations was significantly attenuated. In contrast, the lungs of animals exposed from the beginning to THS aerosol exhibited only a few significant network perturbations. Furthermore, the effects of switching from 3R4F smoke to THS aerosol exposure were similar to those of cessation. These results show that the overall biological impact of THS on the lung is very low compared to that of 3R4F and that the effects switching to THS aerosol exposure approach those of cessation.

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Cellular and tissue changes

The total number of free lung cells in the BALF increased and remained elevated in the 3R4F smoke exposed animals, primarily due to infiltration of neutrophils. In contrast, prolonged exposure to the THS aerosol had no effect on free lung cell count. Both cessation and switching to THS aerosol exposure resulted in a rapid decline in the number of free lung cells, nearly reaching those seen in sham or in THS aerosol exposed mice already after one month (Section 6.1.4.4.1.2.2.1). The histopathological evaluation of respiratory tract organs, at multiple time points, displayed typical cigarette smoke exposure-related changes including adaptive changes of epithelia (nasal, laryngeal and tracheal), infiltration of inflammatory cells and emphysematous lesions. The degree of inflammation and inflammatory cell infiltrates was much reduced in THS aerosol exposed animals and, importantly, the THS aerosol exposed lungs were indistinguishable from sham in terms of histologic appearance. Both cessation and switching to THS aerosol exposure resulted in very similar histopathological findings (Figure 18) (Phillips 2016).

Lung function

3R4F smoke exposure lead to a gradual reduction in lung function (Figure 20). In contrast, there was no detectable effect of THS aerosol exposure on lung function compared with the sham exposed mice at any time-point. Switching and cessation resulted in stabilization of the values while continued 3R4F smoke exposure led to further decline in lung function.

The results from the 8-month *Apoe*$^{-/-}$ mouse switching study provide very strong and consistent evidence that THS aerosol has a significantly reduced adverse biological impact at the molecular, cellular, tissue and functional level of the lung compared with 3R4F smoke. Moreover, the study results show that smoke exposed animals switched to either THS aerosol or smoking cessation present a very similar global recovery of the broad molecular changes, multi-facetted biological network perturbations, cellular changes, tissue changes and functional changes induced by smoke exposure.

A/J mouse inhalation study

The preliminary results of the A/J mouse inhalation study have demonstrated that exposure to THS aerosol has a substantially reduced impact on respiratory tract inflammation, and histopathological changes compared with cigarette smoke. These findings are in direct correlation with the observation that THS aerosol exposed animals did not show any effect on lung function (PV loop) compared with the sham exposed mice at both time points of evaluation (1 and 5 months), irrespective of the exposure dose (Figure 13). These results reflect PMI's previous findings in Apoe-/- mice (Figure 20) (Phillips 2016) and C57BL/6 mice (Phillips 2015b).

Clinical markers associated with COPD risk

Exposure to respiratory toxicants: As listed in Table 2, several HPHCs have been recognized as respiratory toxicants, and are significantly reduced in THS aerosol compared with cigarette smoke. The REXC and REXA studies confirmed that adult smokers who switch to THS are exposed to significantly reduced levels of HPHCs, including respiratory toxicants, compared with smokers who continued to smoke (Section 6.1.6 Table 1). These reductions in exposure approach the reductions seen with smoking abstinence (Section 6.1.6 Table 1).

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Oxidative stress and inflammation: Clinical markers of oxidative stress and inflammation have already been discussed in the CVD section.

Forced expiratory volume: In the Japanese REXA study, smokers who switched to THS had an increase of 1.91 percent of predicted value (%Pred) in their FEV_1 as compared with smokers who continued to smoke cigarettes, with no notable differences between those switching to THS and with smoking abstinence. In the US REXA study, the difference in FEV_1 values between smokers who switched to THS and those who continued to smoke was smaller in magnitude than in the Japanese study. Nonetheless, the results were consistent and trended in the expected direction following smoking abstinence.

Summary of COPD

Chronic obstructive pulmonary disease (COPD) in smokers is triggered by exposure to cigarette smoke constituents resulting in oxidative stress and inflammation. Oxidative stress and chronic inflammation, in turn, cause perturbations of biological networks and changes in alveolar and airway tissues. These changes in alveolar/airway cell functioning have an adverse impact on overall pulmonary function, leading to COPD.

PMI has presented multiple lines of evidence that switching from cigarette smoking to THS use would be accompanied by a lower risk of COPD.

First, THS significantly reduces the formation of HPHCs compared with cigarettes. Reduced exposure clinical studies have demonstrated that this reduced formation of HPHCs results in a reduced exposure to HPHCs, including respiratory toxicants.

Second, this reduced exposure to HPHCs has been shown across multiple *in vitro* and *in vivo* studies to result in a significantly reduced biological impact compared with cigarette smoke. This reduction in impact is evidenced by the reduced perturbations of biological networks associated with the causation of COPD (incl. inflammation, oxidative stress, apoptosis), less severe adaptive histopathological changes, the lack of alveolar destruction (emphysema), and by reduced pulmonary dysfunction in animal models of emphysema. Human clinical studies have confirmed that clinical markers of oxidative stress and inflammation show positive changes, similar to those seen following smoking abstinence. Furthermore, measurements of FEV_1, although studied only over 3 months, indicated that lung function in smokers who switched to THS improved in the same manner as was seen in smokers who abstained for the duration of the study.

Third, the *Apoe*$^{-/-}$ mouse switching study demonstrated that animals that were initially exposed to cigarette smoke and subsequently switched to either THS aerosol or fresh air exposure showed very similar reductions in pulmonary inflammation and a stabilization of emphysema progression.

Overall, the scientific data is remarkably consistent across all biological systems that were studied. Compared with cigarette smoke, THS aerosol had significantly reduced effects on mechanisms causally linked to lung inflammation and COPD in human-derived *in vitro* systems. Switching from smoke to THS aerosol exposure caused positive changes in clinical risk markers associated with COPD and reduced emphysema progression as well as lung function loss in an animal model of disease. THS aerosol exposure performs in a manner similar to smoking cessation/abstinence when examined in both animal and human switching

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studies. The congruence of scientific findings indicates that smokers who switch to THS would have a lower risk of COPD compared with continued smoking.

Lung cancer

The 2010 US Surgeon General's Report (HHS 2010) presents an overview of the probable causative mechanisms linking tobacco smoke and lung cancer. Regular cigarette smoking leads to an uptake of over 60 known carcinogens in smoke. Many of these mutagenic electrophilic carcinogens can bind DNA directly or after activation through enzymatic pathways, forming so-called DNA adducts. Over time, the binding of carcinogens to DNA can overwhelm normal restorative pathways leading to DNA damage, mutations, cellular proliferation and cancer. DNA can also be adversely impacted by oxidative damage induced by ROS and reactive nitrogen species (RNS) which originate from cigarette smoke or from tissues and immune cells that are exposed to cigarette smoke constituents. This oxidative damage can affect DNA, proteins and lipids.

The pathogenesis of lung cancer originates from chronic exposure to chemical carcinogens and other chemicals that induce, e.g. gene mutations, chromosomal instability, loss of normal cellular growth control mechanisms, altered signal transduction, hypermethylation, escape from immune-surveillance (Tomida 2005, Nakata 2006, Yang 2011, Scrimini 2015). In particular, ROS-mediated inflammatory processes (which are also found in COPD) can promote a microenvironment favoring tumor formation by mediating processes such as proliferation, cell survival, angiogenesis and cell transformation. It is critical to understand that all of these pathways to cancer causation are initiated and exacerbated by chronic exposure to carcinogens, pro-inflammatory chemicals and other HPHCs found in tobacco smoke.

It is well understood that the risk of lung cancer increases with the dose of cigarette smoke inhaled (Lee 2013, Doll 1978, Flanders 2003, Knoke 2004, Pope 2011) and with the duration of smoking. It is also known that the risk of lung cancer decreases upon cessation (Warren 2013). The decrease in risk seen with smoking cessation is attributed to the lack of continued exposure to the HPHCs found in cigarette smoke. Taken together, these facts lead to the conclusion that reduced exposure to HPHCs would lead to a reduced risk of lung cancer. As previously described, the reduction in exposure to HPHCs seen in smokers who switch to THS approaches that of those who stop smoking. It is therefore reasonable to anticipate that switching to THS would reduce the risk of lung cancer.

Given the latency of lung cancer disease manifestation (decades), clinical studies to confirm this reduction are impractical within any regulatory framework and require other demonstrations to show that the reductions in risk are significant and likely to occur. The PMI scientific framework offers multiple demonstrations that switching to THS aerosol would result in a reduced risk of lung cancer. First, the aerosol of THS was analyzed for its carcinogen content in comparison with cigarette smoke. Second, the exposure reduction to HPHCs, including known carcinogens, was measured in adult smoker who switched from cigarette smoking to THS use. Third, the genotoxicity of the THS aerosol was characterized and compared with that of cigarette smoke.

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Formation of carcinogens

The THS aerosol composition was extensively characterized by quantifying 58 analytes (Table 2), 32 of which are known carcinogens also present in cigarette smoke. The average reduction over the 32 tested carcinogens is 92% (on a per-stick basis). Eighteen of those carcinogens were reduced by over 95%, and 5 more were reduced by over 90%.

Exposure to carcinogens

Smokers who were switched from smoking to THS use in either of the 5-day or 90-day reduced exposure clinical studies showed substantial reductions in BoExp levels to 15 selected HPHCs, while maintaining comparable levels of nicotine (see Section 6.1.3.2). The reduction in exposure to carcinogenic HPHCs, including N-nitrosonornicotine (NNN), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), 1,3-butadiene, benzene, benzo[a]pyrene, acrylonitrile, 1- and 2-aminonaphthalene, 4-aminobiphenyl (ABP) and o-toluidine, was demonstrated unequivocally by these studies. Indeed, the exposure to every carcinogenic HPHCs measured in the clinical studies was reduced by 20% to92% in smokers who switched to THS for 90 days compared with those who continued smoking cigarettes during that period (Section 6.1.6 Table 1). Moreover, these reductions approached the reductions observed in subjects who abstained from smoking for the duration of the study (26% to 86%, Section 6.1.6 Table 1). Similarly, in animals (rats and mice) exposed to THS aerosol, urinary BoExp to the three measured carcinogens – benzene, acrylonitrile and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) – were significantly lower than in cigarette smoke exposed animals (see Section 6.1.3.2.4) (Phillips 2016). This data is consistent with the clinical study results.

Xenobiotic metabolism response

A major role of xenobiotic metabolism enzymes is to allow detoxification and clearance of chemicals. The activation and/or upregulation of many xenobiotic metabolism enzymes is driven by exposure to chemicals. Polycyclic aromatic hydrocarbons (PAH) are such a group of chemicals. Several of the HPHCs in smoke are PAHs. These PAHs are for instance driving the upregulation of enzymes belonging to the Cytochrome P450 1A (CYP1A) and 1B (CYP1B) families. Therefore, members of these families are useful markers of exposure response. In particular, CYP1A2, which is important for the elimination of environmental chemicals, is strongly induced by PAHs (Benowitz 2008). Importantly, in the context of cancer, CYP1A2 is involved in the activation of carcinogenic heterocyclic and aromatic amines (Eaton 1995) that are found in cigarette smoke. These heterocyclic and aromatic amines are initially N-oxidized to reactive metabolites by the action of cytochrome CYP1A2 in the liver (MacLeod 1997). These reactive metabolites can react with DNA to form covalent heterocyclic amine-DNA adducts (MacLeod 1997), which can in turn lead to tumor induction. The amount of DNA adducts produced from these heterocyclic and aromatic amines depends on the quantity and activity of the enzymes involved in the formation, including CYP1A2.

The PMI clinical studies showed that switching to THS use resulted in reduced levels of CYP1A2 activity similar to those observed in the SA groups (see Section 6.1.3.2.3.17). These clinical data are consistent with findings from the Apoe$^{-/-}$ mouse switching study (Lo Sasso 2016b) which showed that cigarette smoke exposure caused an upregulation of

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CYP1A2 in the liver, whereas THS aerosol exposure did not. Cigarette smoke exposed animals subsequently switched to THS aerosol exposure showed a resolution of the CYP1A2 upregulation approaching that of the animals switched to fresh air.

In many extra-hepatic tissues, including the respiratory tract, xenobiotic metabolism background activity is low but is strongly inducible by exposure to cigarette smoke constituents (Guengerich 2000, Bartsch 1995, McLemore 1990, Nakajima 1995, Rojas 1992, Ding 2003).

In the non-clinical evaluation of THS, the expression profile of major respiratory tract xenobiotic metabolism genes (Anttila 1993, Zhang 2010) was analyzed using a xenobiotic metabolism response (XMR) network model (Schlage 2011, Iskandar 2013). Across all studies where these genes were analyzed, THS aerosol had a significantly reduced impact on the XMR network compared with cigarette smoke. For instance, in the Apoe$^{-/-}$ mouse switching study (Phillips 2016), the XMR network perturbation in the lung of mice switched from cigarette smoke to THS aerosol exposure was significantly reduced compared with the perturbation in those continuously exposed to cigarette smoke (Figure 17). This reduction approached that of mice switched from 3R4F smoke to fresh air exposure. Similarly, in the 90-days rat inhalation studies, cigarette smoke exposure caused the differential expression of several xenobiotic metabolism genes whereas THS aerosol did not induce similar changes. Furthermore, in the PMI studies conducted with human organotypic tissue cultures of airway epithelia, THS aerosol induced significantly fewer and less significant changes in xenobiotic gene expression.

Genotoxicity

THS aerosol has been shown to have a significantly lower impact on genotoxicity in two different *in vitro* assays. The THS aerosol did not show any mutagenic activity in the Ames study. In the MLA assay, THS aerosol was 8-14 fold less (GVP and TPM respectively) mutagenic than cigarette smoke (Table 3). These findings are in line with the significantly reduced amounts of carcinogenic HPHCs in the THS aerosol. These results indicate that THS aerosol is less mutagenic than cigarette smoke. Moreover, THS aerosol fractions caused significantly less DNA damage in normal human bronchial epithelial cells – measured as phospho-H2AX activity and DNA damage-response network perturbation – than cigarette smoke fractions (Gonzalez-Suarez 2016). The DNA damage-response network were also significantly less perturbed in organotypic epithelial cultures exposed to THS aerosol compared with smoke exposed cultures (Iskandar 2016, Zanetti 2016). Finally, the same DNA damage-response network was also significantly less perturbed in the lung of animals exposed to THS aerosol than in those exposed to cigarette smoke (Figure 17) (Phillips 2016).

Moreover, in addition to reduced carcinogen exposure, the PMI clinical studies also showed that switching to THS use resulted in reduced urine mutagenicity similar to those observed in the SA groups (see Section 6.1.3.2.3.18). These clinical data are consistent with the strongly reduced mutagenicity of the THS aerosol fractions observed in the genotoxicity assays *in vitro* (see Sections 6.1.2.2.2 and 6.1.2.2.3).

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Summary of Lung Cancer

The latency of smoking-related lung cancer appearance does not allow for clinical demonstrations of reduced risk with new MRTPs. However, there are multiple factors that make it likely that switching to THS aerosol from tobacco smoke would be accompanied by a lower risk of lung cancer. The rationale for this claim is based on the AOP depicted in Figure 3, which outlines the sequence of causally linked events leading from smoke/HPHC exposure to disease (Section 2.7.3). In the case of lung cancer, chronic exposure to high levels of HPHCs causes the perturbations in biological networks, cellular dysfunction/death, tissue injury and finally disease. Cessation is known to reduce the risk of tobacco-related disease. This corresponds to removing the first causative step in the AOP, i.e. by eliminating the exposure to HPHCs. This leads to a reduced perturbation of biological networks, reduced cell death and dysfunction, reduced tissue injury and reduced organ damage. It is reasonable to expect that an MRTP capable of reducing the risk of lung cancer would show similar biological outcomes to cessation.

PMI studies have provided several demonstrations that switching from cigarette smoke to THS aerosol would significantly reduce the risk of lung cancer. First, THS aerosol contains significantly reduced levels of carcinogenic HPHCs compared with cigarette smoke. Second, switching from cigarette smoking to THS use reduced the exposure to carcinogenic HPHCs to a level approaching the reductions induced by smoking cessation. Third, THS aerosol is significantly less genotoxic than cigarette smoke. Furthermore, THS aerosol induces significantly less DNA damage than cigarette smoke in multiple non-clinical studies conducted both *in vitro* and *in vivo*. Moreover, advanced systems toxicology studies conducted in multiple *in vitro* and *in vivo* models have demonstrated that THS aerosol is significantly less toxic and induces significantly less perturbations of all studied biological networks (incl. DNA damage-response and xenobiotic metabolism response) than cigarette smoke.

Taken together, these demonstrations offer evidence that smokers who switch from cigarette smoking to THS use would experience a significant reduction in exposure, biological impact and ultimately risk of lung cancer compared to continued smoking.

Conclusion Part A: Reduction in Individual Harm and Risk of Tobacco-Related Disease

Multiple Demonstrations of Reduced Harm and Risk of Tobacco-Related Disease

The totality-of-the-evidence presented above demonstrates that smokers who completely switch from cigarette smoking to THS should have a significant reduction in harm and the risk of tobacco-related diseases. It is acknowledged that one challenge of pre-market assessment of an MRTP is that product-specific epidemiological evidence is not available, and that clinical trial data on disease outcome is limited due to the long latency of tobacco-related disease. In this regard, the FSPTCA and FDA Draft Guidance are clear that FDA will require post-market surveillance to determine trends in use and long-term health effects to both individual users and the population as a whole (FDA 2012). At the same time, the statute is clear that sponsors will need to provide a demonstration that risk/harm will be significantly reduced and FDA must determine whether the pre-market application will stand

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up to scientific review in terms of scope, breadth, strength of evidence and biological rationale.

PMI has designed a broad-based and comprehensive scientific program to provide multiple demonstrations that switching to THS aerosol from cigarettes would offer significant reductions in risk of harm and tobacco-related disease. The PMI scientific program offers a broad base of evidence that THS aerosol is significantly less toxic than cigarette, results in less adverse biological impact than cigarette smoke and reduces the adverse impact on fundamental mechanisms of disease causation. The evidence also demonstrates that THS aerosol is able to preserve many of the effects of smoking abstinence/cessation across multiple switching studies conducted in animals and human subjects. As discussed throughout Section 2.7 and presented in detail in Section 6.1, PMI has been able to provide multiple demonstrations of reduced risk of harm and tobacco-related disease. The key outcomes, important to the overall demonstration that THS reduces the risk of harm and tobacco-related disease, enunciated in Section 2.7.4 have been addressed:

I. Evidence Level I: THS aerosol contains significantly less HPHCs than cigarette smoke.

II. Evidence Level II: THS aerosol is significantly less toxic than cigarette smoke, and, there is no evidence that THS aerosol presents any new hazard compared with cigarette smoke.

III. Evidence Level III: THS aerosol reduces the risk of harm and smoking-related diseases in laboratory models.

IV. Evidence Level IV: Switching from cigarette smoking to THS use consistently and significantly reduced the exposure to HPHCs to levels that approach the reductions caused by smoking abstinence, and, switching from cigarette smoking to THS use results in changes in clinical risk markers that are aligned with those caused by smoking abstinence. These changes are of a similar magnitude.

Strength of evidence

In evaluating the strength of evidence from this wide array of work, several considerations provide confidence in the scientific conclusion that switching to THS aerosol will reduce the risk of harm and tobacco-related disease.

First, the overall scientific studies produced coherent results that are biologically relevant and plausible. All of these studies demonstrated individually and collectively the reduced biological impact of THS aerosol compared with cigarette smoke.

Second, the data from switching studies consistently and coherently showed that the biological impact of switching to THS aerosol was directionally aligned with cessation and of similar magnitude to cessation.

Third, the scientific findings were consistent across multiple biological levels along the Adverse Outcome Pathway (Figure 3). Reduced exposure consistently reduced changes at the molecular level, which lead to reduced biological network perturbations. These in turn consistently led to reduced effects at the cellular, tissue and organ levels. There were no instances where THS exposure resulted in any new or different adverse impact when

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compared with cigarette smoke. Most notably, the changes seen across a range of studies were generally consistent with changes seen with smoking abstinence.

Fourth, the scientific findings were consistent across animal models *in vivo*, human-derived *in vitro* systems and clinical studies.

Finally, at all levels of investigation, the scientific program demonstrated findings that were consistent across known and potential pathways of disease causation (e.g. oxidative stress, inflammation, monocyte-endothelial cell interaction, DNA damage) and biologically plausible in their relevance to the risk of harm and tobacco-related diseases. While the pathways for disease causation are better described for cardiovascular disease and COPD than for lung cancer, the generalized reduction in mechanistic perturbations induced by switching from cigarette smoke to THS aerosol, are consistent with the "gold standard" of cessation, the benchmark for MRTP assessment.

In summary, the totality-of-the-evidence presented in Part A, demonstrates that THS, "*as it is actually used by consumers, will significantly reduce harm and the risk of tobacco-related disease to individual tobacco users".* Therefore, PMI believes that THS meets this criterion for approval under Section 911(g) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

B Benefit the Health of the Population as a Whole

Part B of the scientific basis for approval will present the findings to demonstrate that THS *"as it is actually used by consumers will benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products."* As outlined in Section 2.7.2, population harm reduction depends on both the availability of significantly lower risk products and a significant adult daily smoker base willing to accept and switch to these products (Figure 1). MRTPs that satisfy Part A of the scientific basis of approval will realize their maximum population harm reduction potential when they are used in lieu of more hazardous tobacco products such as cigarettes. The maximum reduction in risk will be achieved by those smokers who completely switch to THS. At the same time, to benefit the health of the population as a whole, an MRTP, like THS, should not be attractive to non-users of tobacco products, both never users and former users. The harm reduction opportunity for THS can be blunted or diminished by attracting significant numbers of never or former smokers. This may happen if consumers believe that the product is risk free based on the reduced exposure and/or risk claim(s) that accompany the product.

As outlined in Section 2.7.3, THS was developed to appeal to smokers. In order to facilitate complete switching from cigarettes, THS delivers tobacco flavors and nicotine satisfaction that are comparable to those of cigarettes, and a ritual that initially is different but to which smokers can adapt in a few days.

For individuals to make an informed decision about product use, PMI developed and tested several reduced risk and exposure claims among adult smokers and adult nonsmokers. Along with the claims, PMI developed and tested additional warning statements that further clarified the absolute (THS itself) and relative risk (compared with cigarettes). Reduced risk

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and exposure claims must be scientifically accurate and enable consumers to evaluate and understand the risk of the product in the context of other tobacco products and cessation.

PMI developed a comprehensive Perception and Behavior Assessment (PBA) program to evaluate the effect of these communication materials on (1) Intent to Use (i.e. Intention to Try and Intention to Use) and actual use of THS among adult smokers, (2) Intention to Use THS among adult never and adult former smokers and, (3) consumer understanding and risk perceptions. All studies in the PBA program were conducted within the US population to ensure that the results were directly relevant for a reduced-risk and reduced-exposure market order in the US. The PBA comprised a series of qualitative and quantitative studies (PMI Assessment Step 6). These studies, methodologies and results are summarized in the following pages and more thoroughly described in the PBA section of the application (Sections 6.2.2, 6.3.1 and 6.4).

In its 2012 Draft Guidance for MRTP applications, FDA recommended inclusion of computational models to forecast the potential change in the health of the public following the introduction of an MRTP. These models should take into account the degree of individual risk reduction, the adoption rate among populations of interest (e.g. adult smokers, adult former smokers, and adult never smokers), the degree of adoption (e.g. dual use, exclusive use, transition to more or less hazardous tobacco products) and the impact on smoking cessation. PMI has developed, validated and tested a Population Health Impact Model (PHIM) using well-established methods in mathematical modeling and simulation analysis. Using hypothetical assumptions on the likelihood of THS use, combined with estimated changes in relative disease risk, PMI has conducted multiple simulations to estimate the overall impact of THS on the health of the US population. Overall, the results of these simulations show that introduction of THS would, over time, significantly reduce the number of smoking-attributable deaths (Section 6.5).

Finally, the definitive determination of the impact of an MRTP on the health of the population as a whole will be made by post-market surveillance and studies (Section 8). Post-market studies and surveillance (Assessment Step 7) will help to determine the degree of accuracy of the model-based estimations and the consumer perception and behavioral research. PMI has developed a Post-Market Assessment Program consisting of a combination of post-market studies and data collected from passive surveillance. This program will enable the identification and collection of any unanticipated or undesired events related to the use of THS after an MRTP market order is granted and the product is introduced into the US market. PMI will submit the findings from the surveillance and studies to FDA on an annual basis.

Perception and Behavior Assessment (PBA) Framework (Step 6)

The net population benefit resulting from THS introduction in the US market will depend on whether or not consumers will adopt THS and how adult smokers who switch to THS will actually use the product. PMI developed the PBA program (Step 6) to assess the potential effect that THS and its marketing may have on population health. This broad-based approach was designed to address three key areas of investigation:

I. The effect on tobacco use behavior among current tobacco users

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a. Likelihood that current adult smokers will switch to THS (exclusively or not).

b. Likelihood that current adult smokers who switch to THS would otherwise have stopped the use of tobacco products.

c. Likelihood that current adult smokers, who switch to THS, will switch back to CC.

d. Whether consumers can and are likely to comply with any instructions for THS use and whether/how consumers might misuse the product.

II. The effect on tobacco use initiation among adult non-users of tobacco products

a. Likelihood that current adult never smokers and adult former smokers will initiate/reinitiate tobacco use with THS.

III. The effect of marketing on consumer understanding and perceptions

a. Comprehension of the information concerning modified risk claims.

b. Perception about the health risks of using THS in comparison to cigarettes, NRTs and smoking cessation.

In light of the limited publicly available, recognized and well-established methodologies to assess consumer perception and behavior associated with candidate MRTPs, PMI built its premarket PBA program leveraging on available best practice guidelines related to other categories than tobacco, such as Over-the-Counter drugs. The PBA program included a series of studies, using qualitative and quantitative methodologies under both controlled and in near real-world conditions, that were conducted in the US. These PBA program studies were organized around three key components, as outlined in Table 16.

The first component (A) was the development of validated psychometric survey instruments (PBA-01) in order to assess risk perception and intent to use THS (Scale Development).

In component (B) PMI developed and tested a series of product messages (THS-PBA-02-US and THS-PBA-03-US) to be included in the qualitative testing of label, labeling and marketing material (LLM) that contain the reduced risk and exposure claims (THS-PBA-04-US). The resulting LLM were then assessed in three quantitative studies, each of which assessed a different claim (two reduced risk and one reduced exposure claims) to determine the overall likelihood of use, risk perception, comprehension and changes in intention to quit among smokers motivated to quit (THS-PBA-05- RRC, THS-PBA-05-RRC2 and THS-PBA-05-REC studies). In addition, the THS-PBA-06-US study assessed whether adult smokers could understand and comply with the instructions for use of THS.

Finally, component (C) consisted of a single actual use study of THS usage behavior in near real-world conditions in the US (THS-PBA-07-US).

The actual use study of the PBA program was supported by Whole Offer Tests (WOT) market research studies conducted in several non-US markets including Japan, Italy, Germany, Switzerland, and South Korea.

The following section is a high-level summary of the PBA program structure and description of the study methods and findings from each of the PBA studies and WOT market research

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studies. Following this section, the data from the PBA studies will be integrated and summarized according to the effect of THS on (1) current users of tobacco products, (2), non-users of tobacco products and (3) consumer understanding and perceptions.

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Table 16: PBA Program Structure and WOT Studies

A	**Scale Development – PBA Program**		
	This component comprised a single project which involved the development and validation of psychometric instruments to assess *Risk Perception* and *Intent to Use* for tobacco products.		PBA-01
B	**I. Development of Messages – PBA Program**		
	Qualitative studies		
	Phase 1: Product message development	Multiple focus group discussions	Examined consumer reactions to potential product messages: Study THS-PBA-02-US
	Phase 2: Product message understanding	Multiple individual interviews	
	Quantitative studies		
	Randomized 5-arm parallel group experiment. The five arms corresponded to the five different THS message and smoking status.		Informed the development of the most appropriate product communication: Study THS-PBA-03-US
	II. Development of Communication Materials - PBA Program		
	Qualitative studies		
	Multiple individual interviews designed to capture participants' comments and responses when exposed to specific communication material.		Examined consumer's reactions to potential label, labeling and marketing material: Study THS-PBA-04-US
	III. Assessment of Communication Materials - PBA Program		
	Quantitative studies		
	Randomized five arm parallel group design, with subjects in each arm being presented with a separate instance of THS label, labeling and marketing material combined with either PMI Important Warning or Surgeon General's warning.		Assessed appropriateness of proposed THS labels, labeling and advertising. Studies: THS-PBA-05-RRC-US THS-PBA-05-RRC2-US THS-PBA-05-REC-US
	Single-arm study with individual interviews of adult smokers.		Assessed usability and comprehension of the proposed THS instructions for use: Study THS-PBA-06-US

(table continues)

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C	**THS usage behavior in a near to real-world conditions - PBA Program**	
	Prospective observational study to evaluate the adult smoker likelihood of switching from CC to THS in the US.	Assessed actual use in near to real-world conditions: Study THS-PBA-07-US

	THS usage behavior in a near to real-world conditions – WOT	
	Market research studies to evaluate the adult smoker likelihood of switching from CC to THS outside the US.	Assessed actual use in near to real-world conditions: Studies: Whole Offer Tests

Component A: Scale development

PBA-01

The objective of this project was to develop and validate measurement instruments for two concepts: (1) the *Perceived Risks* associated with the use of tobacco and nicotine-containing products and (2) the *Intent to Use* a tobacco product in the future (including intention to try and intention to use). These instruments were designed to quantify the levels of perceived risks associated with the use of nicotine and tobacco products and provide measures that are comparable across:

- Different sub-populations of consumers (e.g. adult smokers with no intention to quit, adult smokers with the intention to quit, adult former smokers, and adult never smokers)
- Different tobacco products and nicotine containing products
- National and cultural boundaries

PMI undertook a three-stage development process that followed best practice guidelines for self-reporting instruments. The first stage began with qualitative research to inform the development of a conceptual framework and content for a pilot version of the *Perceived Risk Instrument* (PRI). The pilot version was put through two stages of quantitative research (web surveys in US adults; N=2,020 and N=1,640, respectively) to define the final version of the instrument and assess its psychometric properties (based on Rasch Measurement Theory and traditional psychometric methods). The final conceptual framework of the PRI included two main domains: (i) health risk and (ii) addiction risk. Two independent unidimensional scales (18-item Perceived Health Risk scale; 7-item Perceived Addiction Risk scale) were constructed for these domains, complemented by two global items assessing perceived harm to others (Figure 26) (Chrea 2016).

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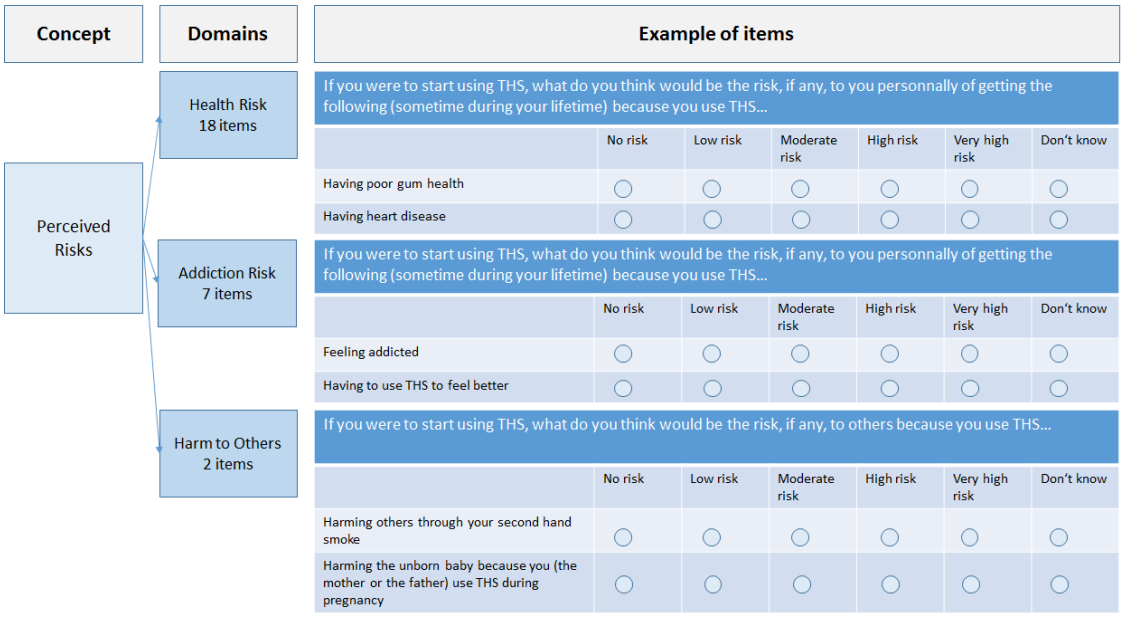


Figure 26: The Perceived Risk Instrument (PRI) to measure perceived risk associated with the use of nicotine and tobacco products

In addition to the PRI, PMI also developed the *Intent to Use Questionnaire* (ITUQ), which was designed to answer whether consumers expressed an Intention to Try and/or an Intention to Use tobacco products including cigarettes, THS, and nicotine replacement therapy (NRT). Measures of Intent to Use following exposure to product information are a well-accepted proxy to assess the extent to which consumers may adopt a tobacco product (Shiffman 2004), (Parascandola 2008). However, no questionnaire was identified as a standard and validated measure of Intent to Use in both current tobacco users and non-users. This led to the development of the ITUQ, comprised of two sets of single items assessing: (i) Intention to Try (at least once) and (ii) Intention to Use (on a regular basis). The generation of items for ITUQ was based on the interpretation of the FDA draft guidance on MRTPs (FDA 2012) and the IOM report (IOM 2012) and complemented with input from consumer focus groups and expert opinions. Even though qualitative research established content and face validities of the items constituting the ITUQ, the qualitative and quantitative evaluations of the potential instrument revealed that *Intent to Use* concept does not behave as a functional scale. Because the measure did not yield an instrument with a scale and an associated scoring, items related to *Intent to Use* were combined into the ITUQ, allowing for the administration of all items or a selection depending on study objectives.

A Research Summary Document describing key methodologies and outcomes underlying the development of the ITUQ is presented in PBA01Sum.

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Component B: Development of Messages

Development of MRTP Claims and Warnings

PMI developed a series of modified risk claims and THS product messages that were tested in a sequential manner, starting with THS-PBA-02-US and followed by THS-PBA-03-US. The intent of the product messages was three-fold:

1. Generate Intent to Use THS among adult smokers.
2. Generate low/no Intent to Use THS among adult never smokers, adult former smokers and young adult nonsmokers who are legal age of smoking to 25 years of age (LA-25).
3. Enable adult consumers (i.e. adult smokers, never smokers, former smokers and young adult LA-25 never smokers) to comprehend the THS modified risk claims and understand that THS is intended for adult smoker with no intention to quit.

Each product message consisted of a brief explanation of (i) the THS product and how it works, (ii) the intended/unintended audience, (iii) a claim (reduced exposure or reduced risk of harm/tobacco-related disease), and (iv) important warning statements to clarify absolute and relative risk. The wording of the claims, warning statements and product information were generated from the comprehensive scientific assessment of the product risk profile previously described in Part A of Section 2.7.5. Nine product messages were initially developed based on the following important considerations for the adult consumers who would be potentially exposed to the THS product:

- Accurately communicated the modified risk profile of THS compared with cigarettes.
- Accurately depicted that THS is not risk free and is addictive.
- Directly communicated intended and unintended audiences for THS (e.g. intended for smokers not intending to quit smoking; not intended for former or nonsmokers).

THS-PBA-02-US

This qualitative study was aligned with the Draft Guidance recommendation that *"when assessing consumer perception of the product, labeling, and/or marketing…[the study should assess] several variations of the proposed claim(s) on labels and/or in advertisements"* (FDA 2012). The main objective of this study was to contribute to the development of THS potential product messages that:

- Generate Intention to Use THS among adult smokers;
- Generate low Intention to Use THS among adult never smokers, adult former smokers, and adult smokers motivated to quit; and
- Enable adult smokers and adult nonsmokers to comprehend THS communicated claims and intended users.

Additionally, the study (1) assessed consumer risk perception for THS, cigarettes, NRTs, e-cigarettes, and smoking cessation, and (2) compared risk perception among these five categories. At the end of this study, as for all PBA studies, participants were debriefed to ensure that they had not acquired any false or unintended beliefs about THS.

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The study was a two-phase, sequential, qualitative study conducted at research facilities in four US cities. The study involved 154 participants in the two phases. The first phase of the research was designed to develop and refine the nine THS product messages using focus group discussions (FGD). In these FGDs, participants shared their opinions and reactions to a variety of discussion topics in an interactive group setting. The second phase of the study used individual interviews (IDI) to evaluate whether consumers understood the product messages from phase one. These IDIs were appropriate for identifying detailed perceptions, opinions, beliefs, and attitudes of participants. The design of this study followed the approach recommended by the Institute of Medicine (IOM 2012).

At the conclusion of THS-PBA-02-US, five product messages were identified based on the product message resonance with adult smokers and lack of resonance with adult nonsmokers. More details about the study can be found in Section 7.3.2.

THS-PBA-03-US

This quantitative study assessed consumer responses to five product messages to support the subsequent development of THS label, labeling and marketing material (LLM). Label refers to the display of printed text or graphical material, including branding on the pack containing *HeatSticks*, or the packaging box of the THS device. Labeling refers to printed or graphical material, which accompanies THS. For example, labeling could refer to (i) leaflets inserted into the packaging of the THS device or the pack of *HeatSticks*, and (ii) other similar text, which is not printed on the pack but is on the materials accompanying the pack. Marketing material refers to promotional material or any advertising, such as point of sale advertising and direct mail communications.

The objective of this study was to evaluate five THS messages among adults in different self-reported "smoking status" groups: (1) Adult Smokers with no Intention to Quit smoking, (2) Adult Smokers with the Intention to Quit smoking, (3) Adult Former Smokers, and (4) Adult Never Smokers. Additionally, an oversampling of Adult Never Smokers from the legal age of smoking to 25 years of age (LA-25 Never Smokers) was included in the study. The THS messages were evaluated in terms of subjects' (Table 17):

- Intent to Use THS (all groups),
- Change in Intention to Quit Smoking (only within Adult Smokers),
- Comprehension of the THS Message,
- Risk perception of THS in comparison with cigarettes, NRTs, e-cigarettes, and Cessation.

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Table 17: Assessment of consumer responses to product messages

Dimension (Assessment)	Measurement method
Intent to Use	The Intent to Use Questionnaire (ITUQ) which includes two sets of items common for all smoking status yielded descriptive measures of: • Intention to Try (i.e., to sample at least once; 2 items) • Intention to Use (i.e., for continued usage; 2 items)
Change in Intention to Quit Smoking	Closed-ended questions based on Prochaska and DiClemente's Stages of Change model (Prochaska and DiClemente 1982) measured before and after exposure to THS 2.2 message to determine change in Intention to Quit Smoking
Comprehension	Two types of comprehension were assessed: 1. "Global comprehension": overall comprehension of the THS 2.2 Message on exposure to harmful chemicals and risk of tobacco-related diseases of using THS 2.2. 2. "Specific comprehension": comprehension of three specific parts of the THS 2.2 Message: the Intended Users Statement, Evidence Statement and Warning Statement. Both types of comprehension were assessed with multiple-choice questions, 5 response options were presented, with 1 correct option, 3 incorrect options and an option for "don't know".
Risk Perception	The Perceived Risk Instrument-Personal Risk (PRI-P) comprised of two domains, each measured by a unidimensional scale: 1. Perceived Health Risk 18-item scale 2. Perceived Addiction Risk 7-item scale Additionally, there were two single items yielding descriptive measures of Perceived Harm to Others
Abbreviations: ITUQ = Intent to Use Questionnaire; PRI-P = Perceived Risk Instrument-Personal Risk; THS 2.2 = Tobacco Heating System 2.2. (THS)	

The study followed a five-arm parallel group design with a sample size of 1,713 adult subjects. The five arms corresponded to the five different THS messages tested in this study (Figure 27). Each arm included approximately equal numbers of subjects within each smoking status group. The 5 THS messages had identical THS Information Sections and Intended Users Statements but presented different combinations of Evidence Statement (modified risk claim) and Warning Sections. The study was conducted at research facilities in four US cities selected from each of the four US regions used by the United States Census Bureau.

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Message 1	Message 2	Message 3	Message 4	Message 5
Evidence Statement 1	**Evidence Statement 1**	**Evidence Statement 2**	**Evidence Statement 2**	**Evidence Statement 3**
(reduced exposure) ▪ When tobacco is burned, it produces many harmful or potentially harmful chemicals ▪ THS 2 2 heats tobacco but does not burn it ▪ With the exception of nicotine, with THS 2 2 there is a significant reduction in the production of harmful or potentially harmful chemicals	(reduced exposure) ▪ When tobacco is burned, it produces many harmful or potentially harmful chemicals ▪ THS 2 2 heats tobacco but does not burn it ▪ With the exception of nicotine, with THS 2 2 there is a significant reduction in the production of harmful or potentially harmful chemicals	(reduced exposure) ▪ THS 2 2 heats tobacco but does not burn it ▪ This significantly reduces the production of harmful or potentially harmful chemicals ▪ Scientific studies have shown that switching completely from cigarettes to THS 2 2 significantly reduces your body's exposure to harmful or potentially harmful chemicals	(reduced exposure) ▪ THS 2 2 heats tobacco but does not burn it ▪ This significantly reduces the production of harmful or potentially harmful chemicals ▪ Scientific studies have shown that switching completely from cigarettes to THS 2 2 significantly reduces your body's exposure to harmful or potentially harmful chemicals	(reduced risk) ▪ THS 2 2 heats tobacco but does not burn it ▪ This significantly reduces the production of harmful or potentially harmful chemicals ▪ Scientific studies have shown that switching completely from cigarettes to THS 2 2 can reduce the risks of tobacco-related diseases
Warning A	**Warning B1**	**Warning A**	**Warning B2**	**Warning C**
▪ **It <u>has not been demonstrated</u>** that switching to THS 2 2 reduces the risk of developing tobacco-related diseases compared to smoking cigarettes ▪ THS 2 2 tobacco sticks contain nicotine which is addictive ▪ Using THS 2 2 can harm your health	▪ A significant reduction in the production of harmful chemicals, compared to cigarettes, **<u>does not mean a reduction in the risk of developing tobacco-related diseases</u>** ▪ THS 2 2 tobacco sticks contain nicotine which is addictive ▪ Using THS 2 2 can harm your health	▪ **It has <u>not been demonstrated</u>** that switching to THS 2 2 reduces the risk of developing tobacco-related diseases compared to smoking cigarettes ▪ THS 2 2 tobacco sticks contain nicotine which is addictive ▪ Using THS 2 2 can harm your health	▪ A significant reduction in your body's exposure to harmful chemicals compared to cigarettes, **<u>does not mean a reduction in the risk of developing tobacco-related diseases</u>** ▪ THS 2 2 tobacco sticks contain nicotine which is addictive ▪ Using THS 2 2 can harm your health	▪ Reduced risk **<u>does not mean no risk</u>**. The best way to reduce your risk of tobacco-related diseases is to completely quit tobacco use ▪ THS 2 2 tobacco sticks contain nicotine which is addictive ▪ Using THS 2 2 can harm your health

Figure 27: The different combinations of Evidence Statements and Warnings included in five THS Messages (Similar message sections are represented by similar colors)

More details about the study can be found in Section 7.3.2.

The studies THS-PBA-02-US and THS-PBA-03-US yielded five potential LLM that included two reduced risk and one reduced exposure product claims for further qualitative assessment.

Development of label, labeling and marketing material

THS-PBA-04-US

The final element of the development phase was a qualitative study that assessed consumer reaction to five potential LLM and three potential product claims for THS in terms of comprehension and Intent to Use. The primary objective of this study was to guide the development of the THS LLM by:

- Understanding participants' response to different potential LLM elements in terms of comprehension and Intent to Use,
- Identifying potential LLM that can generate high Intent to Use among Adult Smokers and low Intent to Use among Adult Never Smokers and Adult Former Smokers.

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Assessing risk perception of THS in comparison with CC, e-cigarettes, NRTs and Cessation.

The research consisted of 28 individual interviews with adult smokers and adult nonsmokers (Adult Never Smokers and Adult Former Smokers). The subjects were shown several potential LLM and modified risk claims (i.e. reduced exposure or reduced risk) and asked about their responses to the materials. More details about the study can be found in Section 7.3.2.

At the end of the development phase (THS-PBA-02-US, THS-PBA-03-US and THS-PBA-04-US), three potential LLM (THS Brochure, *HeatSticks* Pack and THS Direct Mail) were selected and three potential modified risk claims were crafted:

1. A communication including Claim #1 – "Switching completely from cigarettes to the *iQOS* system can reduce the risks of tobacco-related diseases" (Table 18),
2. A communication including Claim #2 – "Switching completely to *iQOS* presents less risk of harm than continuing to smoke cigarettes" (Table 19),
3. A communication including Claim #3 – "Switching completely from cigarettes to the *iQOS* system significantly reduces your body's exposure to harmful and potentially harmful chemicals" (Table 20).

These three potential modified risk claims were alternatively associated with both PMI Important Warning and the mandated Surgeon General's warning.

Table 18: Modified risk claim and messages for Claim #1

<table>
<tr><th colspan="2">Claim #1: Reduced Risk Claim (RRC) and associated Warnings
(Tested in study THS-PBA-05-RRC-US)</th></tr>
<tr><td colspan="2">AVAILABLE EVIDENCE TO DATE:
The iQOS system heats tobacco but does not burn it.
This significantly reduces the production of harmful and potentially harmful chemicals.
Scientific studies have shown that switching completely from cigarettes to the iQOS system can reduce the risks of tobacco-related diseases.</td></tr>
<tr><td>SURGEON GENERAL'S WARNINGS:
Smoking Causes Lung Cancer, Heart Disease, Emphysema, And May Complicate Pregnancy.
Quitting Smoking Now Greatly Reduces Serious Risks to Your Health.
Smoking By Pregnant Women May Result in Fetal Injury, Premature Birth, And Low Birth Weight.
Cigarette Smoke Contains Carbon Monoxide.</td><td>PMI IMPORTANT WARNING:
Reduced risk does not mean no risk. The best way to reduce your risk of tobacco-related diseases is to completely quit tobacco use.
HeatSticks contain nicotine, which is addictive.
Using the iQOS system can harm your health.</td></tr>
</table>

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Table 19: Modified risk claim and messages for Claim #2

Claim #2: Reduced Risk Claim 2 (RRC2) and associated Warnings (Tested in study THS-PBA-05-RRC2-US)	
AVAILABLE EVIDENCE TO DATE: • Switching completely to *iQOS* presents less risk of harm than continuing to smoke cigarettes.	
SURGEON GENERAL'S WARNINGS: • Smoking Causes Lung Cancer, Heart Disease, Emphysema, And May Complicate Pregnancy. • Quitting Smoking Now Greatly Reduces Serious Risks to Your Health. • Smoking By Pregnant Women May Result in Fetal Injury, Premature Birth, And Low Birth Weight. • Cigarette Smoke Contains Carbon Monoxide.	**PMI IMPORTANT WARNING:** • Less risk of harm does not mean no risk of harm. The best way to reduce your risk of tobacco-related diseases is to completely quit tobacco use. • *HeatSticks* contain nicotine, which is addictive.

Table 20: Modified risk claim and messages for Claim #3

Claim #3: Reduced Exposure Claim (REC) and associated Warnings (Tested in study THS-PBA-05-REC-US)	
AVAILABLE EVIDENCE TO DATE: • The *iQOS* system heats tobacco but does not burn it. • This significantly reduces the production of harmful and potentially harmful chemicals. • Scientific studies have shown that switching completely from cigarettes to the *iQOS* system significantly reduces your body's exposure to harmful or potentially harmful chemicals.	
SURGEON GENERAL'S WARNINGS: • Smoking Causes Lung Cancer, Heart Disease, Emphysema, And May Complicate Pregnancy. • Quitting Smoking Now Greatly Reduces Serious Risks to Your Health. • Smoking By Pregnant Women May Result in Fetal Injury, Premature Birth, And Low Birth Weight. • Cigarette Smoke Contains Carbon Monoxide.	**PMI IMPORTANT WARNING:** • It has not been demonstrated that switching to the *iQOS* system reduces the risk of developing tobacco-related diseases compared to smoking cigarettes. • *HeatSticks* contain nicotine, which is addictive. • Using the *iQOS* system can harm your health.

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Assessment of Communication Materials

THS-PBA-05-US

Following the development phase, the assessment phase consisted of three quantitative studies to test the product messages and claims, which were combined into LLM. Each study followed the design and methodology of the preceding THS-PBA-03-US, including five randomized arms (Table 21), each based on a unique LLM in combination with either a reduced risk claim (THS-PBA-05-RRC-US and THS-PBA-05-RRC2-US) or the reduced exposure claim (THS-PBA-05-REC-US).

The objectives of each study were to describe, for each instance of THS LLM:

1. **Intent to Use**
   a. **THS** (separately within all subject groups),
   b. **Any nicotine products** (separately within Adult Former Smokers and Adult Never Smokers),
   c. **Cigarettes** (separately within Adult Former Smokers and Adult Never Smokers), and
   d. **E-cigarettes** (separately within Adult Former Smokers and Adult Never Smokers).
2. **Change in Intention to Quit** (*smoking* and *all tobacco*), after exposure to the THS material among Adult Smokers with the Intention to Quit smoking
3. **Comprehension**: for each instance of THS label, labeling and marketing material global comprehension and comprehension of specific parts.
4. **Risk Perception** for THS and for the comparators cigarette, e-cigarettes, NRTs and smoking cessation (separately within all subject groups).

LLM were given to the subjects in form of actual mock-ups. Versions of branded THS Brochures, *HeatStick* packs and THS Direct Mail (*iQOS* for THS and Marlboro for the *HeatStick* pack) were presented with a hypothetical price for the THS Device ($79.99) and for a pack of 20 *HeatSticks* (price of a Marlboro pack of cigarettes in the specific city of the research).

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Table 21: THS Communication Materials, Warning Type and Study Arms in THS-PBA-05-US Studies

		Type of Material		
		THS Brochure	**THS *HeatStick* Pack**	**THS Direct Mail**
Warning Type	**Surgeon General**[a]	Arm 1	Arm 3	NA
	PMI[b]	Arm 2	Arm 4	Arm 5

Abbr.: NA = not assessed.

[a] The Surgeon General (SG) warnings currently mandated for CC include: 1) "Smoking Causes Lung Cancer, Heart Disease, Emphysema, And May Complicate Pregnancy."; 2) "Quitting Smoking Now Greatly Reduces Serious Risks to Your Health." ; 3) "Smoking by Pregnant Women May Result in Fetal Injury, Premature Birth, and Low Birth Weight."; 4) "Cigarette Smoke Contains Carbon Monoxide." Note: Subjects randomized to the Surgeon General warning were assigned 1 of the 4 warnings.

[b] The PMI Important Warning statements were adapted for each study to present a coherent set of information between the claim and the warning concerning the modified risk

In addition to Adult Smokers[5] (with and with no intention to quit smoking), the main study samples included Adult Never Smokers and Adult Former Smokers. In total, four user groups were investigated according to their smoking status:

- Adult Smokers with no Intention to Quit Smoking
- Adult Smokers with the Intention to Quit cigarettes
- Adult Never Smokers
- Adult Former Smokers

In all the three THS-PBA-05-US (THS-PBA-05-RRC-US, THS-PBA-05-RRC2-US and THS-PBA-05-REC-US) studies, PMI included an oversampling of young Adult Never Smokers - young adults between legal smoking age and 25 years of age (LA-25). PMI internal policy prohibits the conducting of studies relating to tobacco products, which involves under legal age of smoking, a policy that is consistent with recommendations from the FDA[6].

For each of the three THS-PBA-05-US studies, the full sample was approximately of 2,200 subjects and the studies were conducted at research facilities in four US cities selected from each of the four US regions used by the United States Census Bureau. More details about the three THS-PBA-05-US studies can be found in Section 7.3.2.

[5] Including Regular Daily Smokers (smoke at least 1 CC a day) and Intermittent Smokers (between 4 and 27 days per month, with no restrictions on total number of CC smoked over that period

[6] MRTP Draft Guidance 2012, VI (C)

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THS-PBA-06-US

THS-PBA-06-US was a usability and comprehension study of the THS instructions for use and was conducted among adult smokers. The study focused on addressing the recommendations from the Draft Guidance (FDA 2012) that the applicant should provide data concerning instructions for use of the candidate MRTP, with respect to:

- *"Whether consumers can and are likely to comply with any instructions for product use";*
- *"Consumer understanding of the product's instructions for use".*

This study was a single-arm usability and comprehension assessment and conducted during individual interviews with adult smokers. Interviews were conducted at research facilities in four US cities, strategically selected to provide a geographically diverse sample, such that each city was within each of the four regions defined by the United States Census Bureau.

The purpose of the study was to assess the ability of adult smokers to understand and correctly comply with the instructions of use for THS. The instructions for use included directions for charging, cleaning and troubleshooting common issues with the product. The study assessed whether consumers were able to perform specific "use" tasks necessary to operate THS properly and understand the key messages of the THS instructions for use. More details about the study can be found in Section 7.3.2.

Component C: Assessment of Actual Use

PMI assessed the actual use of THS in the THS-PBA-07-US study and market research studies referred to as the WOT. Those WOTs were conducted in multiple non-US markets: Japan, Italy, Germany, Switzerland, and South Korea.

THS-PBA-07-US

The THS-PBA-07-US study assessed adult smokers' actual use of THS in near real-world conditions. This was a single group prospective observational study. It was conducted to assess the daily use behavior of adult smokers who had the opportunity to use THS along with their own brand of cigarette and other nicotine-containing products. Participants received THS free of charge and were able to consume THS, cigarettes and other nicotine-containing products on an *ad libitum* basis.

This study, which involved more than a 1,000 US adult daily smokers (N = 1,106), consisted of a one-week baseline period to establish the level of normal cigarette consumption, a subsequent six-week observational period during which consumers were given access to THS, and a one-week close out period. Participants were requested to make an entry into an electronic diary every time they consumed a cigarette during the baseline period and every time they consumed either a *HeatStick* or a cigarette during the observational period. Participants were also requested to make daily diary entries about whether or not they used other nicotine-containing products.

The overall study design was intended to allow product use among adult daily smokers that would simulate near real-world conditions without any specific restrictions:

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- The study was conducted in eight metropolitan areas geographically diverse and spread out across the U.S.
- The sampling method was designed to approximate the adult smoker distribution contained in the report published by the Centers for Disease Control and Prevention in 2012.
- The length of the study allowed enough time for the participant to try, experiment and use the investigational product over a 6 week period.
- The participants were able to receive and/or order *HeatSticks* through multiple channels (i.e., by going to the study facilities, by calling the hotline), making the product easily available throughout the entire observational period.
- The participants had access to both regular and menthol *HeatSticks* depending on their personal choice, closely reflecting the situation of both variants being available in the market.

Usage patterns were described per week according to three product usage categories:

- THS use (≥ 70% of total tobacco products used were HeatSticks)
- Combined use (>30% and <70% of total tobacco products used were HeatSticks)
- Cigarette use (≤ 30% of total tobacco products used were HeatSticks)

Additional information related to "product assessment" (ease of use, sensorial experience, occasion of use, and potential misuse) was collected during follow-up interviews, either by phone or face-to-face, every two weeks during the observational period. More details about the study can be found in Section 7.3.2.

Whole Offer Test (WOT)

PMI conducted WOT consumer market research studies for THS in 5 countries: Japan (JP), Italy (IT), Germany (DE), Switzerland (CH) and South Korea (KR). The WOT was undertaken to evaluate the adult smoker response to different elements of the THS offer and the likelihood of switching from cigarettes to THS. Given the very large total population of participants (N=2,809) in the five studies, this market research contributes to the understanding of the likelihood of THS use in near real-world conditions.

The target population was adult smokers living in the country in which the study was conducted. Each study included a quota sample of smokers aged between one year above the national legal smoking age and 64 years. The sample was frequency matched to the adult smoker population in terms of four characteristics: age, gender[7], social status, and main cigarette brand.

Similar to the THS-PBA-07-US study, participants had access to THS during the four-week observational period and were requested to make an entry into a paper-and-pencil diary every time they consumed either a *HeatStick* or a cigarette. Participants received THS free of

[7] The South Korean study consisted of only male participants.

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charge (either regular or menthol *HeatSticks*) and were able to consume THS, cigarettes and other nicotine-containing products on an *ad libitum* basis.

Usage patterns were described per week according to three product usage categories:

- THS use (≥ 70% of total tobacco products used are HeatSticks)
- Combined use (>30% and <70% of total tobacco products used are HeatSticks)
- Cigarette use (≤ 30% of total tobacco products used are HeatSticks)

The description of the WOT market research studies method can be found in Section 7.3.3.

Integrated Summary of Empirical Findings on the Impact of THS on the Health of the Population as a Whole

The integrated summary of findings uses the totality-of-the-evidence from the PBA program, along with supportive evidence from WOTs and insights obtained in Clinical Studies to address the subsequent three key topics that directly influence the impact of an MRTP on the health of the population as a whole:

- Effect of THS on "Tobacco use behavior among current tobacco users"
- Effect of THS on "Tobacco use initiation among nonusers (both never users and former users)"
- Effect of THS LLM on "Consumer understanding and perceptions"

I Effects of THS LLM on tobacco use behavior among current tobacco users

In accordance with the MRTP draft guidance (FDA 2012), the assessment of an MRTP should address the effect that an MRTP and its marketing might have on tobacco use behavior among current tobacco users (FDA 2012), specifically addressing:

- The likelihood that current tobacco product users will start using the MRTP
- The likelihood that tobacco users who adopt the MRTP will switch back to cigarettes or other tobacco products that present higher levels of individual health risk than THS
- The likelihood that consumers will use the product in conjunction with other tobacco products
- The likelihood that tobacco product users who may have otherwise quit using tobacco products will instead use THS
- The likelihood that consumers will use the product as intended or designed and not misuse/abuse the product.

The assessment of the effects of THS label, labeling and marketing materials is based on data from a wide array of studies including the clinical assessment program, the PBA program and market research studies (WOT) conducted in five different countries. Across the studies shown in Table 22, three major dimensions relating to product usage were studied to assess:

1 **Behavioral intention** including (i) Intent to Use THS (overarching concept including Intention to Try and Intention to Use) and (ii) change in intention to quit smoking based on exposure to THS communication materials

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2 **Product usability** including (i) ability to understand and correctly comply with the instruction of use THS and (ii) potential misuse

3 **Product use behavior** including (i) nicotine uptake, (ii) level of consumption, (iii) patterns of use (e.g., predominant use, combined use), (iv) human puffing topography (e.g., puff volume, puff duration, number of puffs), and (v) product acceptance (subjective reinforcing effects and sensorial experience)

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Table 22: Overview of studies conducted on product use

Study Code	Setting	Population	Outcome Measure
ZRHR-REXC-03-EU	Confinement	S-NITQ	Level of consumption, nicotine uptake, subjective effects, puffing topography
ZRHR-REXC-04-JP	Confinement	S-NITQ	Level of consumption, nicotine uptake, subjective effects, puffing topography
ZRHM-REXA-07-JP	Confinement and ambulatory	S-NITQ	Level of consumption, patterns of use, nicotine uptake, subjective effects, puffing topography
ZRHM-REXA-08-US	Confinement and ambulatory	S-NITQ	Level of consumption, patterns of use, nicotine uptake, subjective effects, puffing topography, intention to quit smoking
THS-PBA-07-US	Observational	S-NITQ	Patterns of use, level of consumption, sensorial experience, misuse
Whole Offer Test (WOT) Study	Observational	S-NITQ	Patterns of use, level of consumption
THS-PBA-02-US	FGD, IDIs	S-NITQ, S-ITQ, FS, NS	Intent to Use
THS-PBA-03-US	CASI in central location	S-NITQ, S-ITQ, FS, NS	Intent to Use, Change in Intention to Quit Smoking
THS-PBA-04-US	IDIs	AS, FS, NS	Intent to Use
THS-PBA-05-RRC-US	CASI in central location	S-NITQ, S-ITQ, FS, NS	Intent to Use, Change in Intention to Quit Smoking and All Tobacco
THS-PBA-05-RRC2-US	CASI in central location	S-NITQ, S-ITQ, FS, NS	Intent to Use, Change in Intention to Quit Smoking and All Tobacco
THS-PBA-05-REC-US	CASI in central location	S-NITQ, S-ITQ, FS, NS	Intent to Use, Change in Intention to Quit Smoking and All Tobacco
THS-PBA-06-US	IDIs	AS	Ability to understand and correctly comply with the instruction of use

Abbr.: FGD: Focus Group Discussion; IDIs: Individual Interviews; CASI: Computer-Assisted Self-Interview; AS: Adult Smokers; CC: Conventional cigarettes; S-NITQ: Adult Smoker with No Intention to Quit CC; S-ITQ: Adult Smoker with Intention to Quit CC; FS: Adult Former Smokers; NS: Adult Never Smokers, SA: Smoking abstinence; THS: Tobacco Heating System

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Behavioral intention among Current Tobacco Users

Assessing Intention to Use among Current Smokers

Intention to Try/Use THS in Adult Smokers with No Intention to Quit Cigarettes (S-NITQ)

The following section summarizes the results of quantitative PBA studies (i.e., THS-PBA-03-US, THS-PBA-05-RRC-US, THS-PBA-05-RRC2-US and THS-PBA-05-REC-US) and differentiates between current smokers with and without the intention to quit smoking. Results from the two qualitative studies (THS-PBA-02-US and THS-PBA-04-US) are presented in details in Section 6.2.2.

Study THS-PBA-03-US

Prior to the selection of the "final" three MRTP claims, PMI conducted the quantitative THS-PBA-03-US study designed to guide the final selection process for modified risk and exposure claims and messages. In this study, 1,713 adult subjects were asked about their Intention to Try/Use THS based on "plain text" THS messages (see Section 6.2.2). Five different messages were tested, presenting combinations of three claims and different warnings.

Table 23 summarizes the numbers of Adult Smokers with No Intention to Quit who reported a positive Intention to Try[8] THS and a positive Intention to Use[9] THS regularly. Within this group, the positive Intention to Try THS ranged from 38.4% to 56.9%. With regards to the likelihood that they would use THS regularly, between 51.4% to 65.3% of subjects stated a positive Intention to use THS regularly.

[8] Positive Intention to Try THS was operationalized as the sum of % Very Likely and % Definitely responses for each item of Intention to Try by study arm and smoking status group.

[9] Positive Intention to Use THS was operationalized as the sum of % Very Likely and % Definitely responses for the first item of Intention to Use by study arm and smoking status group.

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Table 23: Proportion of Subjects with Positive Intention to Try and Intention to Use THS- Adult Smokers with No Intention to Quit in THS-PBA-03-US

		Message				
	Statistics	**1 (N=72)**	**2 (N=72)**	**3 (N=73)**	**4 (N=72)**	**5 (N=70)**
Positive Intention to Try THS						
	n (%)	36 (50.0)	41 (56.9)	28 (38.4)	37 (51.4)	34 (48.6)
	95% CI	(38.0, 62.0)	(44.7, 68.6)	(27.2, 50.5)	(39.3, 63.3)	(36.4, 60.8)
Positive Intention to Use THS regularly						
	n (%)	40 (55.6)	37 (51.4)	39 (53.4)	47 (65.3)	44 (62.9)
	95% CI	(43.4, 67.3)	(39.3, 63.3)	(41.4, 65.2)	(53.1, 76.1)	(50.5, 74.1)

N=total sample size; n=number of values reported.
Abbr.: CI, confidence interval; THS, Tobacco Heating System 2.2.
Note: the 95% confidence intervals are calculated using the exact Clopper-Pearson method
Source Study report THS-PBA-03-US Table 15.2.2.1

THS-PBA-05-US STUDIES

As previously described, three identical quantitative studies were conducted in the US to test consumer responses to three different communications, each of which included either a reduced risk claim or a reduced exposure claim:

1. "Reduced risks of tobacco-related diseases" (THS-PBA-05-RRC-US, N = 2,255)
2. "Reduced risk of harm" (THS-PBA-05-RRC2-US, N = 2,247)
3. "Reduced body's exposure to harmful and potentially harmful chemicals" (THS-PBA-05-REC-US, N = 2,272)

The study data showed that among Adult Smokers with No Intention to Quit, there were very similar results across all three studies. On average, between 30-50% of Adult Smokers with No Intention to Quit indicated an interested in trying the product and 25-30% indicated that they were likely to use the product on a regular basis. As shown in Table 24, Adult Smokers with No Intention to Quit consistently indicated a positive Intention to Try that was greater than positive Intention to Use, a result not unexpected based on the uncertainty of product characteristics and experience.

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Table 24: Proportion of Adult Smokers with No Intention to Quit CC with Positive Intention to Try THS and Positive Intention to Use THS in THS-PBA-05 Studies

	Positive Intention to Try[1]		Positive Intention to Use[2]	
	Min.	Max.	Min.	Max.
THS-PBA-05-RRC	34.4%	47.4%	28.4%	38.9%
THS-PBA-05-RRC2	30.9%	54.3%	20.2%	37.9%
THS-PBA-05-REC	30.2%	49.5%	20.8%	36.8%

[1] Positive *Intention to Try* refers to the proportion of subjects whose response to the single item assessing intention to try THS was either *Very Likely* or *Definitely*.

[2] Positive *Intention to Use* refers to the proportion of subjects whose response to the single item assessing intention to use THS was either *Very Likely* or *Definitely*.

Intention to Try/Use THS in Adult Smokers with Intention to Quit Cigarettes (S-ITQ)

It is important within the context of an MRTP application to understand whether the introduction of a new tobacco product could potentially change the intention of subjects to quit the use of cigarettes or all tobacco products. In the following analysis, Adult Smokers with Intention to Quit smoking were asked about their Intention to Try and Intention to Use THS as well as asked specifically about their overall intention to quit smoking following exposure to THS messages.

THS-PBA-03-US

Table 25 summarizes the numbers of Adult Smokers with the Intention to Quit smoking who reported a positive Intention to Try/Use THS. Within this group, positive Intention to Try THS ranged from 35.7% to 53.6%. The number of subjects who expressed a positive Intention to Use THS regularly ranged from 44.4% to 61.1%. These numbers were, overall, similar to the results from the group of Adult Smokers with No Intention to Quit smoking.

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Table 25: Proportion of Subjects with Positive Intention to Try and Intention to Use THS Adult Smokers With the Intention to Quit Smoking in THS-PBA-03-US

		Message				
	Statistics	**1 (N=75)**	**2 (N=72)**	**3 (N=71)**	**4 (N=69)**	**5 (N=68)**
Positive Intention to Try THS						
	n (%)	34 (45.3)	29 (40.3)	25 (35.7)	37 (53.6)	31 (45.6)
	95% CI	(33.8, 57.3)	(28.9, 52.5)	(24.6, 48.1)	(41.2, 65.7)	(33.5, 58.1)
Positive Intention to Use THS regularly						
	n (%)	46 (61.3)	32 (44.4)	33 (47.1)	37 (53.6)	38 (55.9)
	95% CI	(49.4, 72.4)	(32.7, 56.6)	(35.1, 59.4)	(41.2, 65.7)	(43.3, 67.9)

Abbr.: CI = confidence interval; N=total sample size; n=number of values reported; THS = Tobacco Heating System 2.2.
Note: the 95% confidence intervals are calculated using the exact Clopper-Pearson method.

Source Study Report THS-PBA-03-US

THS-PBA-05-US STUDIES

As shown in Table 26, there was a positive Intention to Try and positive Intention to Use among the group of Adult Smokers with the Intention to Quit smoking, regardless of the claims or overall messages. Adult Smokers with the Intention to Quit smoking expressed a positive Intention to Try across all arms of the study (32.6% to 51.6%) and a positive Intention to Use (21.3% to 35.1%) across study arms. These numbers were similar to those generated by the groups of Adult Smokers with No Intention to Quit smoking (Figure 28, Figure 29 and Figure 30). There was no evidence of an association between the type of claim and either Intention to Try or Intention to Use, which suggests that all three claims would be suitable to market THS in the US.

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Table 26: Proportion of Adult Smokers With the Intention to Quit Smoking with Positive Intention to Try THS and Positive Intention to Use THS in THS-PBA-05-US Studies

	Positive Intention to Try[1]		Positive Intention to Use[2]	
	Min.	Max.	Min.	Max.
THS-PBA-05-RRC-US	33.0%	50.0%	23.2%	34.0%
THS-PBA-05-RRC2-US	40.9%	51.6%	21.3%	35.1%
THS-PBA-05-REC-US	32.6%	39.6%	22.3%	29.2%

[1] Positive *Intention to Try* refers to the proportion of subjects whose response to the single item assessing intention to try THS was either *Very Likely* or *Definitely*.

[2] Positive *Intention to Use* refers to the proportion of subjects whose response to the single item assessing intention to use THS was either *Very Likely* or *Definitely*.

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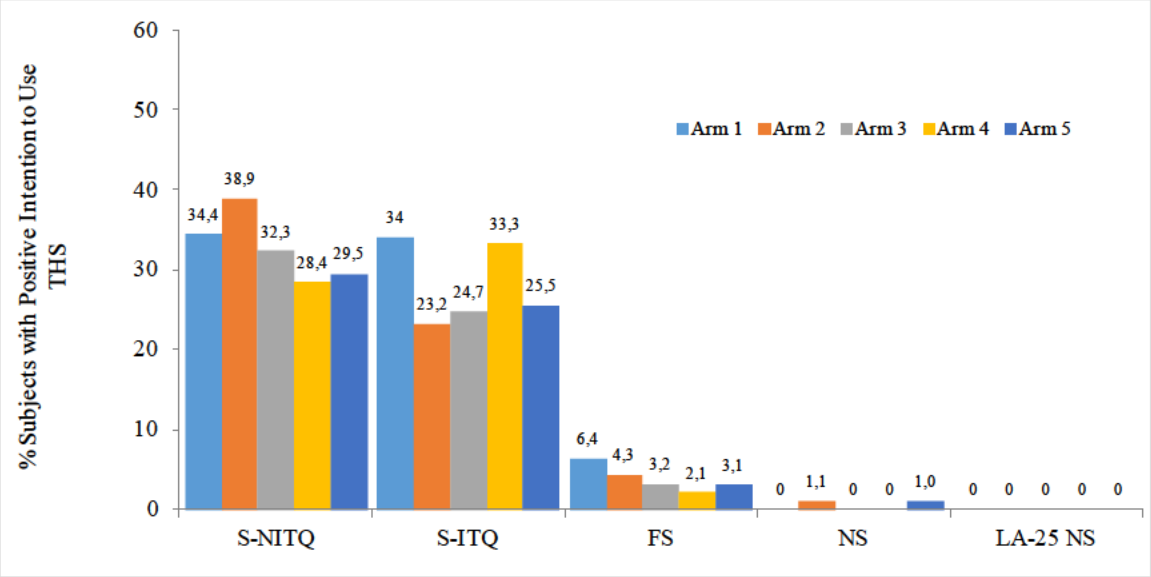


Figure 28: Positive Intention to Use THS (very likely/definitely), THS-PBA-05-RRC-US

Abbr.: FS = Adult Former Smokers; LA-25 NS = Adult Never Smokers from legal smoking age to 25 years; NS = Adult Never Smokers; S-ITQ = Adult Smokers With the Intention to Quit; S-NITQ = Adult Smokers with No Intention to Quit;

Arm 1: THS brochure in combination with one of four possible Surgeon General's warnings in a rotating fashion; Arm 2: THS brochure in combination with the "Important Warning" developed by PMI; Arm 3: *HeatSticks* pack and diagram card in combination with one of four possible Surgeon General's warnings in a rotating fashion; Arm 4: *HeatSticks* pack and diagram card in combination with the "Important Warning" developed by PMI; Arm 5: THS Direct Mail communication in combination with the "Important Warning" developed by PMI.

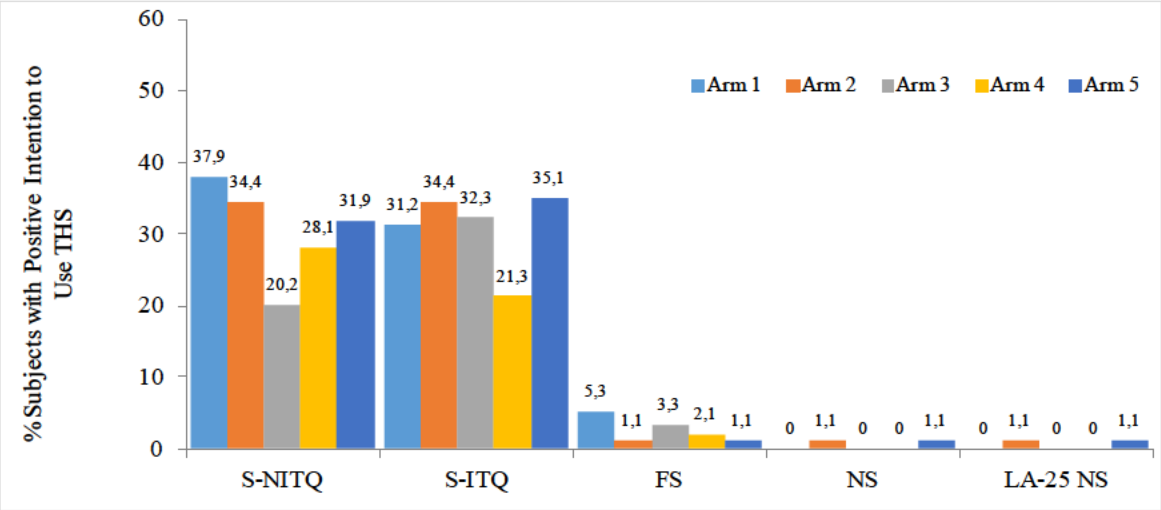


Figure 29: Positive Intention to Use THS (very likely/definitely), THS-PBA-05-RRC2-US

Abbr.: FS = Adult Former Smokers; LA-25 NS = Adult Never Smokers from legal smoking age to 25 years; NS = Adult Never Smokers; S-ITQ = Adult Smokers With the Intention to Quit; S-NITQ = Adult Smokers with No

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Intention to Quit;

Arm 1: THS brochure in combination with one of four possible Surgeon General's warnings in a rotating fashion; Arm 2: THS brochure in combination with the "Important Warning" developed by PMI; Arm 3: *HeatSticks* pack and diagram card in combination with one of four possible Surgeon General's warnings in a rotating fashion; Arm 4: *HeatSticks* pack and diagram card in combination with the "Important Warning" developed by PMI; Arm 5: THS Direct Mail communication in combination with the "Important Warning" developed by PMI.

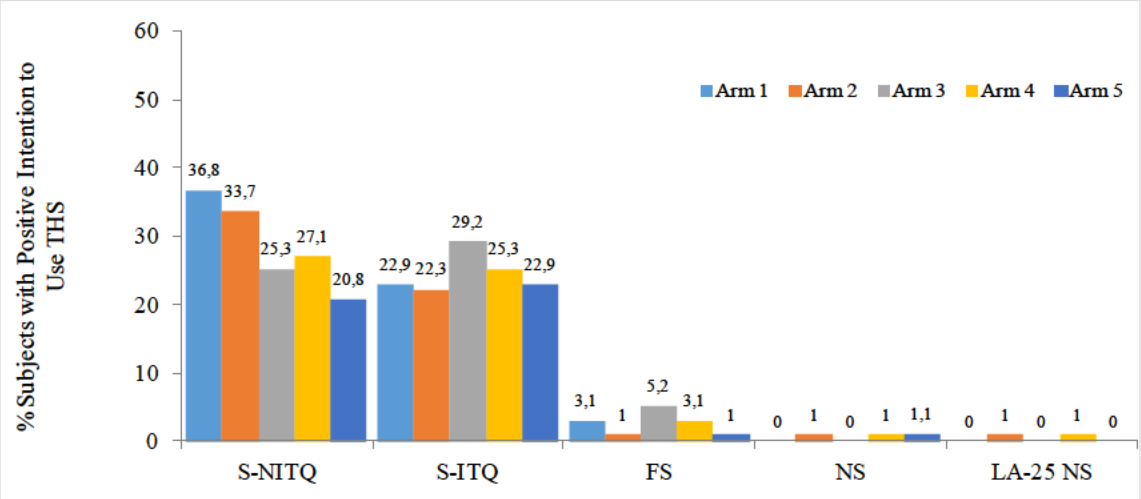


Figure 30: Positive Intention to Use THS (very likely/definitely), THS-PBA-05-REC-US

Abbr.: FS = Adult Former Smokers; LA-25 NS = Adult Never Smokers from legal smoking age to 25 years; NS = Adult Never Smokers; S-ITQ = Adult Smokers With the Intention to Quit; S-NITQ = Adult Smokers with No Intention to Quit;

Arm 1: THS brochure in combination with one of four possible Surgeon General's warnings in a rotating fashion; Arm 2: THS brochure in combination with the "Important Warning" developed by PMI; Arm 3: *HeatSticks* pack and diagram card in combination with one of four possible Surgeon General's warnings in a rotating fashion; Arm 4: *HeatSticks* pack and diagram card in combination with the "Important Warning" developed by PMI; Arm 5: THS Direct Mail communication in combination with the "Important Warning" developed by PMI.

Change in Intention to Quit among Adult Smokers with Intention to Quit Smoking

THS-PBA-03-US

Adult Smokers with Intention to Quit smoking were asked about their Intention to Quit after being exposed to the THS messages. Although these smokers expressed interest in THS trial and use, most smokers did not change their Intentions to Quit, maintaining positive responses to quitting in a range of 83% to 97% across all arms of the study.

THS-PBA-05-US Studies

Although groups of Adult Smokers with Intention to Quit smoking in all three THS-PBA-05-US (THS-PBA-05-RRC-US, THS-PBA-05-RRC2-US and THS-PBA-05-REC-US) studies

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expressed a substantial interest in using THS, they did not appreciably change their stated intentions to quit smoking and all tobacco as reflected in Table 27. In the THS-PBA-05-RRC2-US study, some Adult Smokers with Intention to Quit smoking actually indicated an increased desire to quit smoking although this finding was isolated to one of three studies.

Table 27: Proportion of Adult Smokers with Intention to Quit Smoking Who Stated a Change in Intention to Quit Smoking or All Tobacco in THS-PBA-05-US Studies

	Change in Intention to Quit Smoking		Change in Intention to Quit All Tobacco	
	Min.	Max.	Min.	Max.
THS-PBA-05-RRC-US	5.3%	11.6%	1.1%	11.6%
THS-PBA-05-RRC2-US	1.1%	11.8%	-3.2[1]%	9.7%
THS-PBA-05-REC-US	4.2%	9.6%	1.0%	5.2%

[1] Note: This change in Intention to Quit is negative indicating an increase from baseline, whereas most changes were decreases from baseline.

Overall, the results on change in Intention to Quit were variable between the studies. There was no obvious pattern associating claims with changes in Intentions to Quit, although the THS-PBA-05-RRC2-US results showed that smokers expressed less likelihood of changing their Intention to Quit smoking. For this group, these data on change in Intention to Quit, when read in association with the data on Intention to Try/Use THS, highlight the need for post-market surveillance/studies to determine the actual change in quitting intentions.

Conclusions on Behavioral Intention among Current Smokers

Across all of the PBA studies on adult smokers, there were very consistent findings that are summarized as follows:

- THS communication materials tested in all studies generated a substantial Intent to Use among the intended population, i.e. adult smokers with no intention to quit smoking
- Across all of the THS-PBA-05-US quantitative studies, adult smokers indicated a consistent positive Intention to Try and positive Intention to Use after being exposed to any of the three claims and associated communications materials that are the subject of this MRTPA
- These levels of Intent to Use THS are in line with similar data that have been reported on e-cigarettes (Wackowski 2016, Zhu 2013)
- Intent to Use was broadly similar between Adult Smokers with and without the Intention to Quit Smoking

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- Adult Smokers with the Intention to Quit smoking did not substantially change their intention to quit smoking and the use of tobacco products even though they expressed interest in trial and use of THS
- The type of communication materials (i.e. THS Brochure, *HeatSticks* Pack and THS Direct Mail) did not seem to have a notable influence on Intent to Use among adult smokers.

Product Usability: Correct Use and Potential for Misuse

Ability to Understand and Correctly Comply with Instruction for Use

The main purpose of the THS-PBA-06-US study was to evaluate the usability and the comprehension of THS instruction for use in 258 adult cigarette smokers in the US. The majority of use tasks (e.g. charging the THS Holder, how to consume the THS Tobacco Stick, how to remove a stuck THS Tobacco Stick from the THS Holder) were executed correctly by more than two-thirds of the participants. A few tasks (how to insert the THS Tobacco Stick into the THS Holder, how to remove the THS Tobacco Stick, how to heat-clean the THS Holder, how to use the THS Cleaning Tool) were less well executed.

Generally, consumers understood the three key messages after reviewing the instructions, with 85% expressing the correct understanding for not using THS with cigarettes, 95% understanding not to use *HeatSticks* as a cigarette and 67% of consumers understanding that the THS Holder should be fully charged prior to cleaning.

Overall, the results of the THS-PBA-06-US study indicated that the THS instructions for use seem to be adequate in explaining the various tasks required to normally operate THS and suggest that THS is likely to be used as designed and intended by adult smokers. Subjects' understanding and demonstration of certain parts of the instructions for use were more difficult and were improved either through the revision of the instruction for use or the way tasks are to be executed in an improved version of the THS Device (see Section 3.5 for more details).

Potential Misuse of THS

The potential for misuse was also assessed during the Actual Use Study, THS-PBA-07-US. Misuse of THS was characterized by two different situations that were reported by study participants: (1) "*HeatSticks* consumed without THS Device" and (2) "THS Device used with a product other than *HeatSticks*". For each situation, the kind of misuse was collected using two predefined response options:

(1) "I lit up the *HeatSticks* (like a cigarette)" or "others"

(2) "I used THS device with cigarettes" or "others"

A total of 47 out of 985 participants (4.8%) reported using *HeatSticks* without the THS Device. Of those, 23 reported 1 occasion of misuse, 14 reported 2 to 4 occasions, 7 reported 5 to 9 occasions, and 3 reported misuse 10 times or more.

Two participants used the THS Device with a product other than THS Tobacco Sticks.

Overall, these results suggest a low level of misuse potential and that THS is likely to be used as designed and intended by adult smokers. Events of unintended use are taken seriously by

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PMI and will be further monitored and addressed as part of the post-market assessment program.

Product use behavior: Level and pattern of consumption

The net benefit for the public health from the market introduction of THS as an MRTP will depend, in part, on the actual use level of the product. When assessing the product use behavior, PMI studied whether adult smokers used THS exclusively or in combination with cigarettes or other tobacco products. In order to generate robust data on use behavior, PMI collected data on levels of consumption and patterns of use in both clinical settings and near real-world conditions.

The FDA Draft Guidance on Modified Risk Tobacco Product Applications (FDA 2012) recommends that sponsors provide data on the use of the candidate MRTP alone and in conjunction with other tobacco products. This data is important to determine the extent to which adult smokers find a novel tobacco product acceptable as a cigarette substitute. PMI conducted numerous human studies involving actual use of THS, including four *ad libitum* use clinical studies and one actual use study in the US. This data was complemented with data from a market research WOT study conducted in Europe and Asia. In all these studies, daily product consumption (number of cigarettes or *HeatSticks* used per day) and the patterns of use (e.g., dual or combined use with other tobacco or nicotine-containing products) were assessed to provide insight into how THS would be used after introduction in the market. Daily consumption was recorded either (i) by the study personnel when subjects were in confinement or (ii) by the subjects (self-reporting) in an ambulatory/observational setting.

To describe patterns of product use across the different studies, product use categories were defined based on the percentage of *HeatSticks* used in a predefined period compared to the number of total tobacco products used. THS use was defined as the proportion of *HeatSticks* use representing 70-100% of the total number of cigarettes and *HeatSticks* used. Combined use of THS and cigarettes use was defined as the proportion of *HeatSticks* used being between 30-70% of the total number of tobacco products used and Cigarette Use was defined as *HeatSticks* use being less than 30% of the total number of THS and cigarette products being used (Figure 31). Usage categories were further split into sub-categories in order to describe product use patterns with more granularity (exclusive use, predominant use, combined mostly, combined balanced, see Figure 31.

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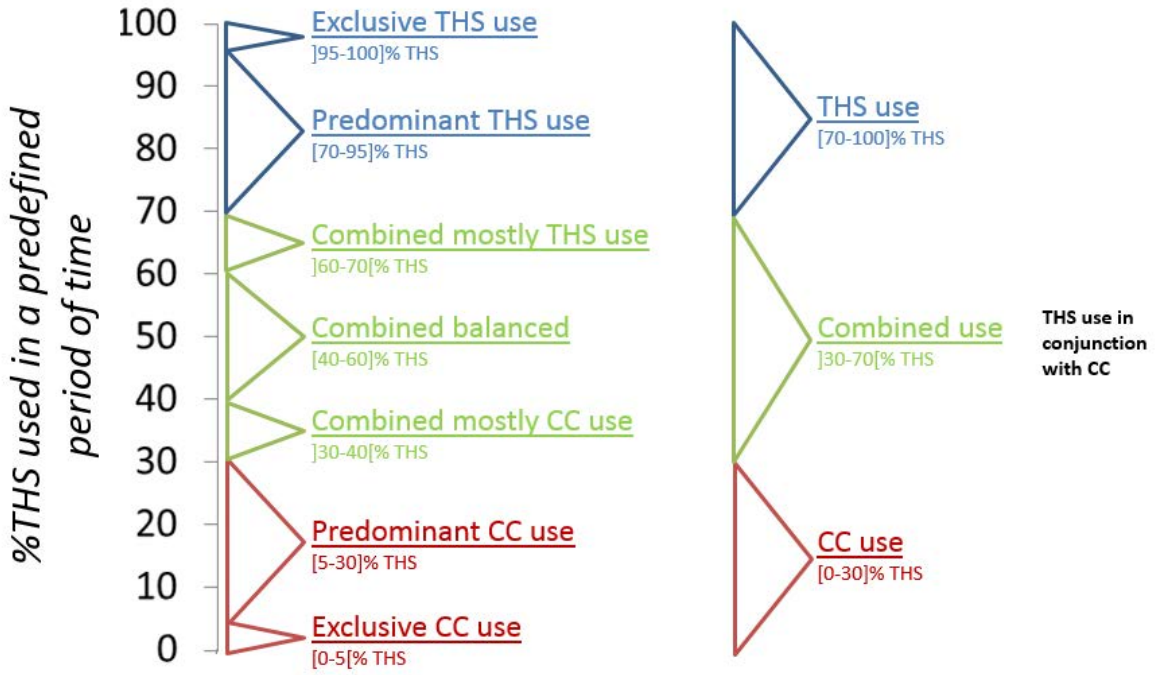


Figure 31: Product Use Categories

Abbr.: CC = Conventional cigarettes; THS = Tobacco heating system

Level and pattern of THS consumption in controlled environments

The REXA and REXC clinical studies provided the opportunity to assess THS (REXC studies) and mTHS (REXA studies) use in both controlled and ambulatory settings. During the 5-day confinement period of each study, product access was directed and product use was monitored by the study staff to ensure product use compliance per the study protocol. Subjects were allowed to use either THS or mTHS without restriction (*ad libitum*) during an extended daily time window (16 hours). Dual use of cigarettes and THS or any other nicotine-containing product was not permitted to allow an accurate assessment of the exposure reduction achieved when switching from cigarettes to THS.

During the 5-day confinement periods of the REXC studies (ZRHR-REXC-04-JP and ZRHR-REXC-03-EU) and the five-day confinement period of the 90-day REXA studies (ZRHM-REXA-07-JP and ZRHM-REXA-08-US), subjects exclusively used their assigned product. For all four clinical studies, the baseline consumption of cigarettes (own brand) ranged from 10.3 cigarettes/day to 16.2 cigarettes/day. For the subjects who were switched to THS, the overall consumption level remained fairly constant with the exception of the 5-day European study (ZRHR-REXC-03-EU) where the daily consumption of THS exceeded baseline by approximately 4 sticks per day at the end of the five day study (Figure 32).

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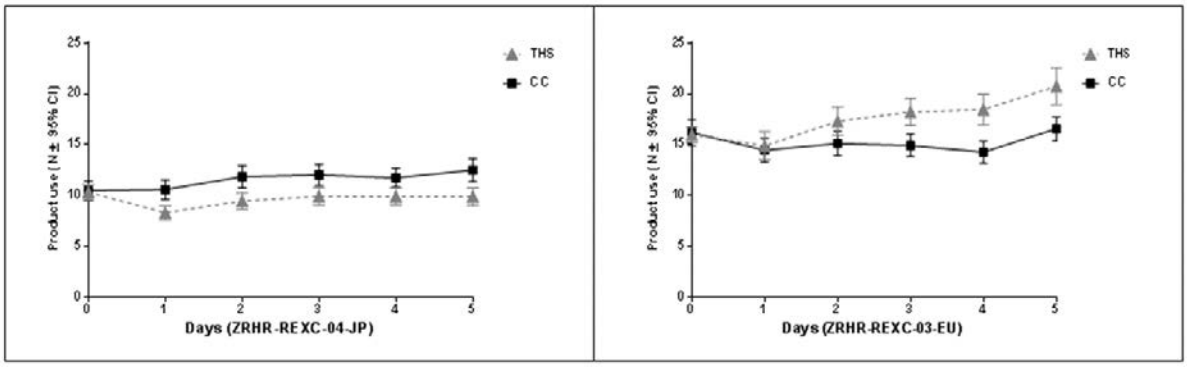


Figure 32: Product Consumption (Number of products used) between baseline and Day 5

(Left panel: ZRHR-REXC-04-JP and right panel: ZRHR-REXC-03-EU).

Abbr.: CC = Conventional Cigarettes, THS = Tobacco Heating System

In the longer-term REXA studies, the level of consumption at 90 days was lower than the baseline level by approximately 1-2 sticks per day (Figure 33). Collectively, these observations indicate that switching from cigarettes smoking to mTHS use did not increase the overall consumption of tobacco products over a 90-day period.

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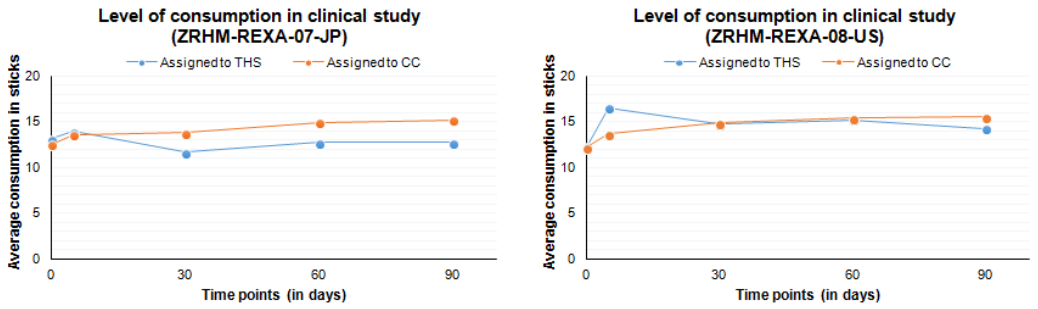


Figure 33: Level of THS and cigarette consumption in near to real-world condition.

Sources: ZRHM-REXA-07-JP and ZRHM-REXA-08-US

Abbr.: CC = Conventional Cigarettes, THS = Tobacco Heating System

Consumption of cigarettes further increased during the ambulatory period in both studies, remaining higher compared to baseline, and higher compared to the number of *HeatSticks* consumed at Day 30, Day 60 and Day 90.

Patterns of Use in Clinical Studies

The patterns of use in the clinical studies were comparable between the confinement period and ambulatory period. In the Japanese study, subjects were highly compliant to their assigned product. In the confinement period, nearly 100% of the subjects in the mTHS group were compliant and used exclusively their mTHS (in clinical settings, exclusive use was defined as 100%). During the ambulatory period, 91% of the subjects used mTHS. Eighty-two percent of these subjects used mTHS 100% of the time throughout the 85 days of the ambulatory period.

The US study was different in terms of compliance. Similar to the Japanese study, subjects were highly compliant during the confinement period. However, during the 85-day ambulatory period, 42.5% of the subjects in the THS group used mTHS 100% of the time and 58.8% of these subjects met the criteria for >95% of THS use.

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

Patterns of product consumption were different between the study population in Japan and in the U.S. In Japan, the levels of compliance with the allocated product were higher than in the US and almost no dual-use with cigarettes or other nicotine-containing products occurred. It is also important to consider other product use parameters such as puffing topography, nicotine uptake and subjective effects, as they may be affected by differences in nicotine

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yield, taste, sensorial and ritual experience between the new product and one's own brand of cigarettes. More importantly, the variations in product consumption observed with mTHS between different users did not affect the observed reduction in exposure to HPHCs.

Pharmacokinetic/Pharmacodynamics studies

Sufficient delivery of nicotine is an important attribute of an effective alternative product for smokers (IOM 2012). FDA has also recommended that MRTP applications provide an assessment of the product's "speed and efficiency of nicotine delivery"[10]. The PK/PD studies were designed to assess the nicotine uptake profile in adult smokers who use THS compared to cigarettes and NRT.

PMI conducted four PK/PD studies, two in Japan, one in the UK and one in the US. In these studies, the extent and rate of nicotine absorption during single stick *ad libitum* use of THS was measured and compared with cigarettes and NRTs (for the results with NRTs see Sections 6.2.1 and 6.2.3). The studies also evaluated the relationship between plasma nicotine concentration and the suppression of the urge to smoke in adult smokers. The studies also provided initial safety data on product usage (e.g. vital signs, clinical biochemistry, hematology, spirometry, electrocardiogram and adverse events).

As seen in Figure 34, all four PK/PD studies showed a similar profile (e.g. time to maximum nicotine concentration (T_{max}) maximum nicotine concentration (C_{max})) of nicotine uptake in smokers who used THS compared with cigarettes. The US study, using mTHS, differed from the other three studies, with mTHS users achieving a reduced C_{max} compared with menthol cigarettes. These results could reflect a lack of preference for this mTHS (high menthol content) among these particular study participants. The study findings are discussed more completely in Section 6.2.1. However, when taken together, the studies demonstrated that THS provided nicotine in similar amounts (i.e. AUC) and at a similar rate (T_{max} and C_{max}) as cigarettes for most participants.

[10] MRTP Draft Guidance, Section VI(B)(3)

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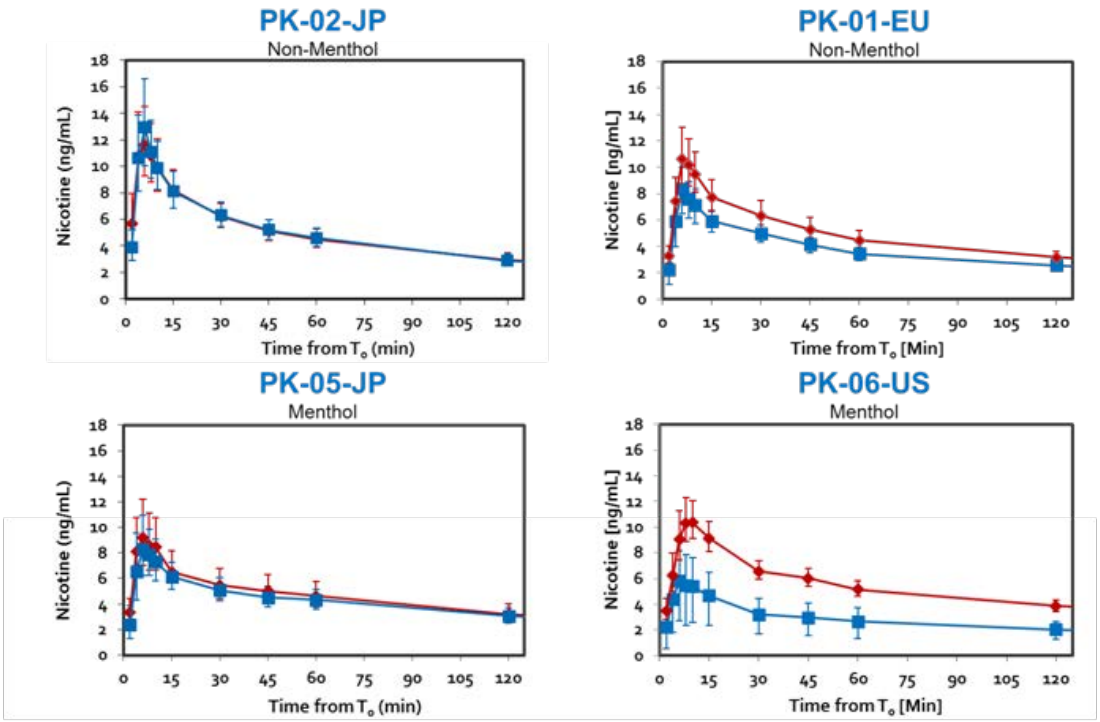


Figure 34: Geometric means and 95% confidence intervals of nicotine concentrations over 120 minutes with a single use of the THS or cigarette

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 THS;

Abbr.: CC = Conventional Cigarette, EU = European Union, JP = Japan, Min = Minutes, PK = Pharmacokinetic, T_0 = Start of product use, THS = Tobacco Heating System

Source: Study ZRHR-PK-01-EU, ZRHR-PK-02-JP, ZRHM-PK-05-JP and ZRHM-PK-06-US

All data refer to menthol variant 1

In addition to the 4 PK/PD studies, PMI assessed overall nicotine exposure over both the 5-Day exposure studies (REXC) and the 90-Day exposure studies (REXA). Nicotine exposure was assessed by measuring urinary nicotine equivalents (NEQ), plasma nicotine levels and plasma cotinine levels at Baseline, on Day 5 and Day 90 (REXA only) to determine whether smokers who switched to THS were able to maintain the desired levels of nicotine when using THS *ad libitum*. The full description of findings on nicotine exposure across the confinement (REXC) and ambulatory (REXA) clinical studies is provided in Section 6.2.2.4.1.2.1. The profiles of urinary NEQ, plasma nicotine and plasma cotinine through the 4 reduced exposure studies were comparable between the THS and cigarette arms, indicating that THS delivers nicotine to the users at comparable levels compared with cigarettes. This provides additional support that THS has a high potential to be accepted by current adult smokers as an alternative to cigarettes.

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Taken together, the results of the PK/PD and reduced exposure studies do not indicate a higher risk of abuse liability in smokers switching to THS compared with cigarettes. The full description of PMI's assessment of abuse liability is found in Section 6.2.3.

Level and pattern of THS consumption in Observational Studies

THS-PBA-07-US (Actual Use) Study

In the observational study THS-PBA-07-US, the pattern of use was described per week according to three product usage categories:

1. THS use (≥70% of total tobacco products used are *HeatSticks*)
2. Combined use (>30% and <70% of total tobacco products used are *HeatSticks*)
3. Cigarette use (≤30% of total tobacco products used are *HeatSticks*)

This study showed that 14.6% of adult daily smokers reported *HeatSticks* use at the end of a 6-week usage period (Figure 35). The proportion was relatively constant during the observational period of the study. This was further confirmed by the fact that 63% of participants, who adopted THS at the end of the observational period, had already done it in the first three weeks of the observational period.

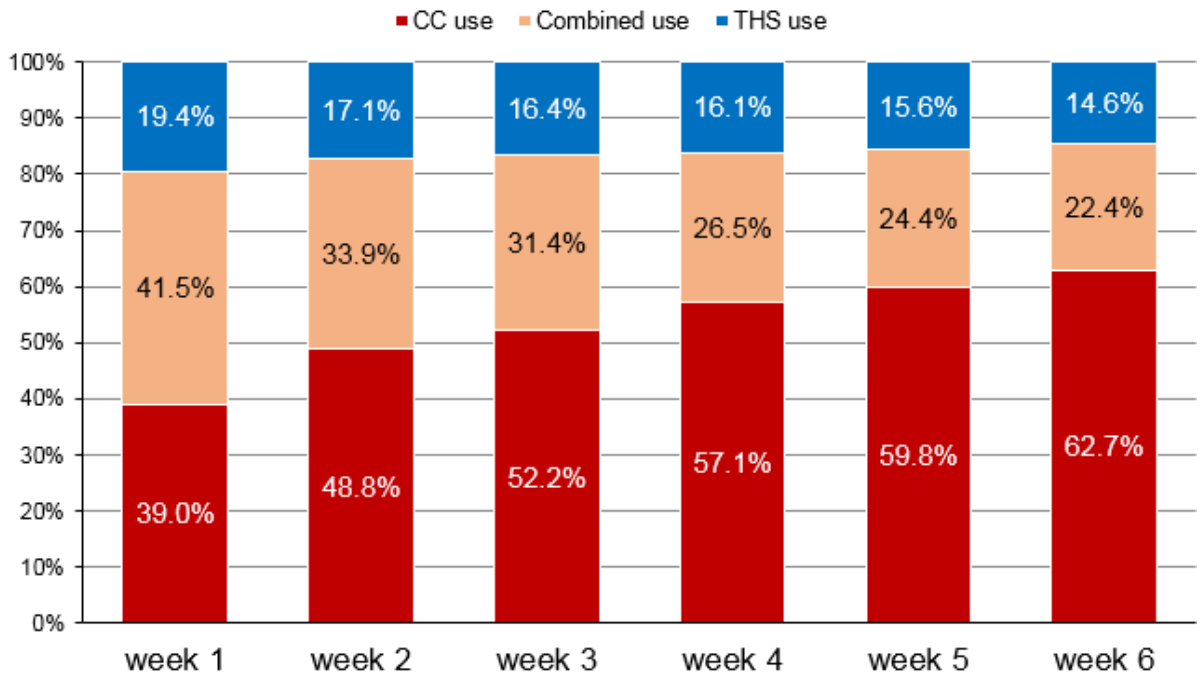


Figure 35: Percent Product Use by Usage Category during Continued Use and by Week for the FAS Population in THS-PBA-07-US

Abbr.: CC = Conventional Cigarettes, FAS = Full Analysis Set, THS = Tobacco Heating System

Sources: Study Report THS-PBA-07-US

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As can be deduced from Figure 35, switching back from predominant/exclusive THS use in Week 1 to *Combined use* or cigarettes was less frequent (-4.8%) than going from *Combined use* to cigarettes (-19.1%) by week 6.

A certain proportion of participants reported *Combined use* over the course of the observational period. However, this proportion decreased over time. Additionally, there was no increase in the total use of tobacco products (*HeatSticks* and cigarettes), with cigarette consumption reduced on average by half, for participants with *Combined use* at Week 6 compared to baseline (cigarettes consumption only).

Assessment of ease to use THS and sensorial experience during the observational period showed that participants who adopted a "THS use" usage pattern at the end of the observational period liked the taste (60.9%), smell (47.8%) and aftertaste (46.4%)[11] and found the product easy to use (81.9%)[12].

In summary, this study showed that approximately 15% of the participants were able to switch from cigarettes to THS and to adopt it as a substitute for cigarettes. There was no overall increase in the use of tobacco products for consumers who used THS exclusively or in combination with cigarettes. Adult daily smokers did not often switch back from THS to cigarettes. A demographic analysis revealed that THS was slightly more attractive to adult smokers who were males above 25 years of age, Black or African American, Hispanic or Latino, who consume between one and ten cigarettes per day and who favor menthol cigarettes.

[11] The taste, smell, and aftertaste of the product were assessed using a 7-point rating scale ranging from "1=I don't like it at all" to "7=I like it very much". Rating of 5-7 response categories provided in the text.

[12] Ease of use of THS was assessed using a 7-point rating scale ranging from "1=not easy to use at all" to "7=very easy to use". Rating of 5-7 response categories provided in the text.

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Whole Offer Tests (WOTs)

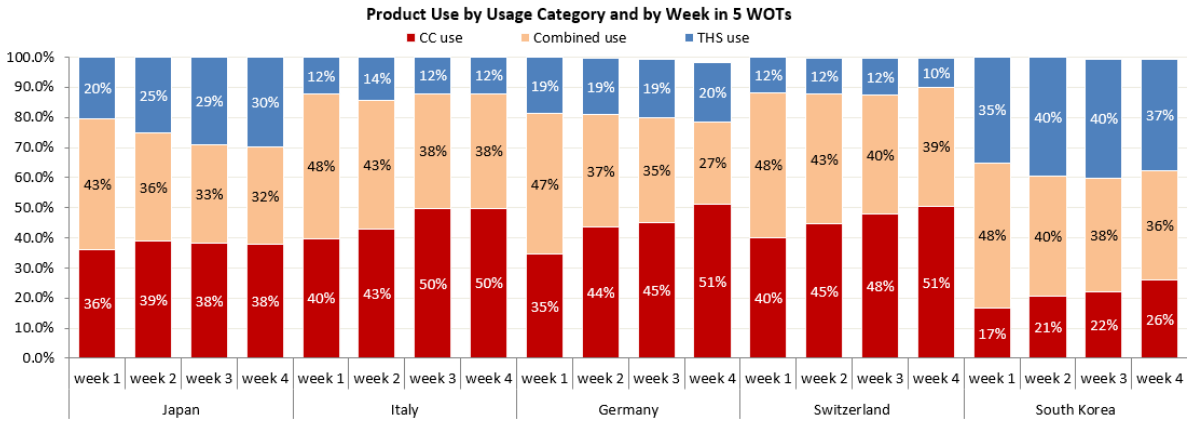


Figure 36: Percent Product Use by Usage Category of participants over four weeks in 5 countries for FAS Population in Whole Offer Test

Abbr.: CC = Conventional Cigarettes, FAS = Full Analysis Set, THS = Tobacco Heating System

Source: Study Report Whole Offer Tests

The results of the WOTs show that between 10% and 37% of adult daily smokers, depending of the country, were able to adopt THS as a substitute to their cigarettes. For those who switched to THS by Week 1, the likelihood of switching back to cigarettes was low (see Figure 36 for THS use during the observational period). The data from the WOT studies indicate that a certain proportion of adult daily smokers used both cigarettes and THS together but their overall daily average tobacco consumption was actually lower by an average of two sticks per day. The data on the combined use group indicates that the proportion of smokers decreased over time, with smokers returning to either cigarette use by the end of the observational period, to a lesser extent, transitioning to THS.

Insights from Post Market Research outside the US

THS is commercially available (under the brand name of *iQOS* for the THS device and *HeatSticks* for the THS Tobacco Sticks) nationwide in Japan and in selected areas of several countries including Italy, Switzerland, Germany, Portugal, Russia and Romania.

Market research combined with in-market performance data provides valuable information on product use patterns. Product use patterns are influenced by several factors that cannot be replicated and accounted for in pre-market studies. For instance, adult tobacco consumers are likely to be affected by factors such as repeated exposure to product communications, peer-to-peer information sharing ("word of mouth") and gradually increasing familiarity and acceptability of an alternative behavior (i.e., using *iQOS*). The influence on tobacco use behavior of these factors become evident over time. *iQOS* has been available in Japan since November 2014 when the product was test marketed in the city of Nagoya and has achieved significant levels of penetration and adoption among adult smokers. Data from the Japanese market offers valuable insights into the influence of the aforementioned factors on tobacco

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use behavior in Japan, notwithstanding that the data are evolving and represent a snapshot at a specific moment in time.

As shown in Figure 37, the market share of *HeatSticks* (i.e., the total *HeatSticks* sales volume as a percentage of the total estimated sales volume for cigarettes and *HeatSticks*) has increased steadily since the national rollout in April 2016. By mid-September, market share had reached an estimated 4.1%. Over the same period, the "penetration ratio" for the *iQOS* devices (i.e., the ratio between the number of *iQOS* devices sold in Japan and the estimated number of Japanese adult smokers) has reached 9.5%.

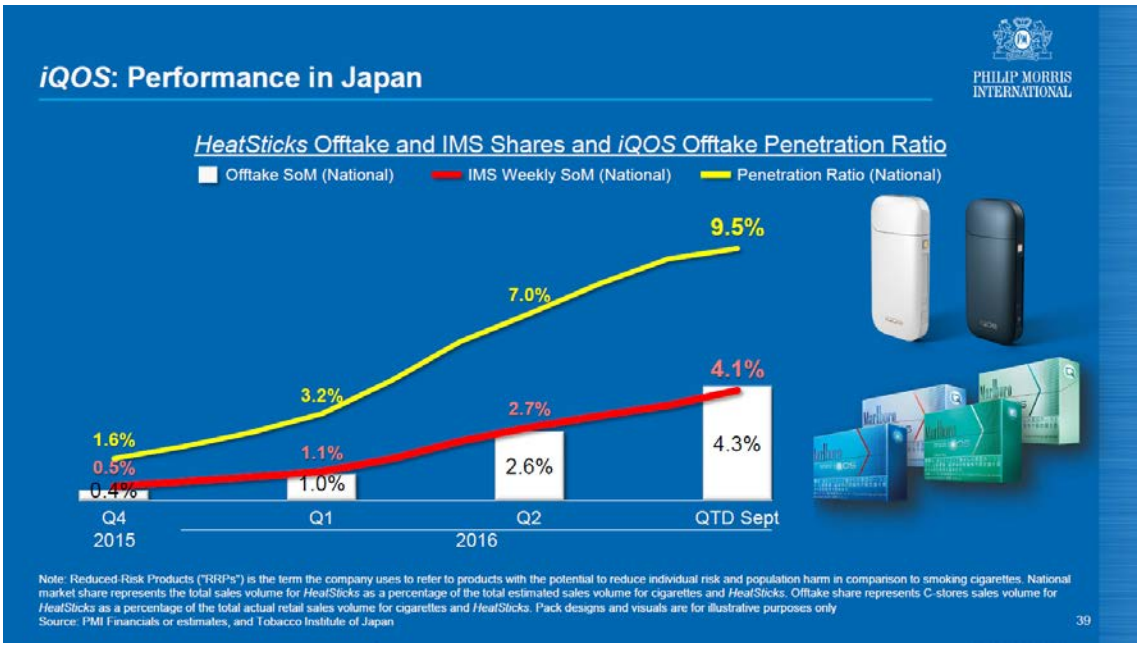


Figure 37: *HeatSticks* Offtake, IMS Shares and *iQOS* Offtake Penetration Ratio - Japan

Abbr.: Q1 = 1st Quarter, Q2 = 2nd Quarter, Q4 = 4th Quarter, QTD Sept = Quarter till September, IMS = In-Market Sales

These data provide a measure of the penetration of *iQOS* and the *HeatSticks* in relation to conventional cigarettes. However, they do not provide insights about *iQOS* users or the extent to which *iQOS* users have switched from other tobacco products. To provide a more detailed understanding of these important questions, PMI has established sizable continuous Market Research Panels of adult *iQOS* purchasers in many markets including Japan. These panels include only adult *iQOS* purchasers who registered their device in a PMI database, and who agree to participate. Due to this potential selection bias, the panel presents some limitations in the generalizability of the findings. However, the panel allows the collection of valuable insights into the *iQOS* purchaser population. The minimum size of the panel is set at 1,500 participants, in order to attain a sufficient precision in conducting defined analyses. The Japanese panel comprises more than 11,000 members. For the first 3 months, the panelists respond to online surveys administered with a weekly frequency. As of the fourth month, participants are interviewed on a monthly basis. The information collected using

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online surveys includes, but is not limited to, self-reported use of *IOQS* and conventional cigarettes, the way *iQOS* owners receive and provide information about the product, their attitudes toward the product and their socio-demographic profile.

In order to assess the extent to which smokers have switched from cigarettes to *iQOS* and *HeatSticks*, PMI has defined four usage categories defined as follows:

1. "Exclusive": >95% of tobacco use is *iQOS*;
2. "Predominant": ≥70% and ≤95% of tobacco use is *iQOS*;
3. "Situational": ≥5% and <70% of tobacco use is *iQOS*;
4. "CC": <5% of tobacco use is *iQOS*.

Figure 38 shows the evolution on a monthly basis of the *iQOS* use categories in the Japanese *iQOS* panel. The proportion of Exclusive *iQOS* users has grown from 52% in January 2016 to 65% in July 2016.

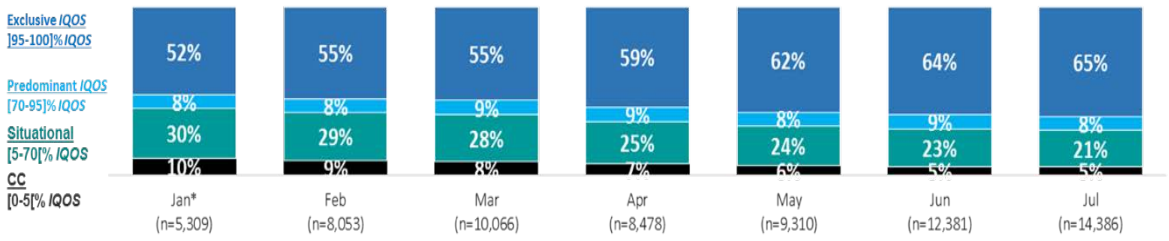


Figure 38: Percent product use by usage category - Japanese *iQOS* panel

Source: Japanese Market Research Panel

This effect of the factors described above is confirmed when the data are analyzed clustering the panelists according to the month in which they purchased *IOQS*, i.e., defining cohorts of *iQOS* users by date of purchase (Figure 39).

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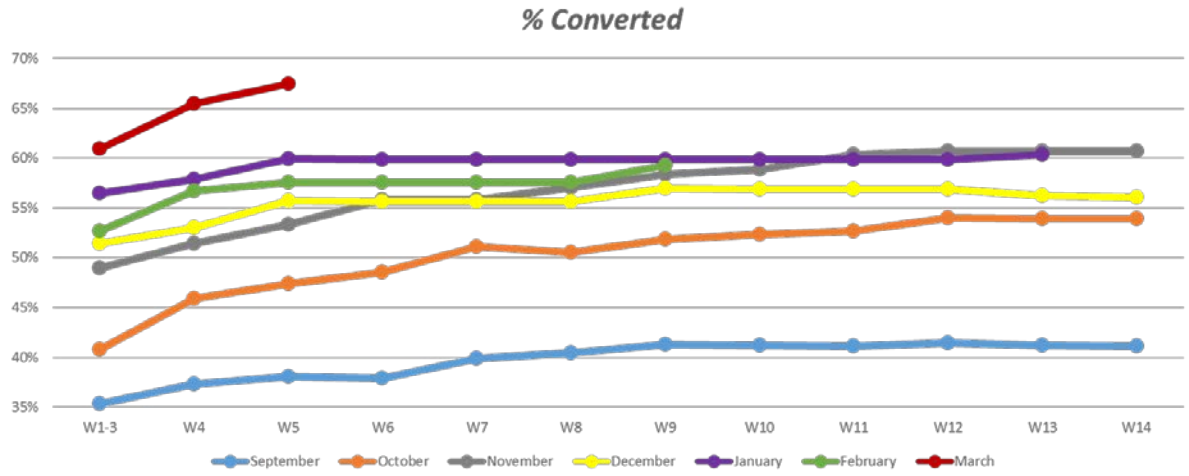


Figure 39: Evolution of conversion rate over time according to month of *iQOS* purchase

Note: % of converted is calculated as the proportion of panel participants who used *iQOS* exclusively (> 95%)

Source: Japanese Market Research Panel

For example, the blue line in Figure 39 shows the conversion trajectory of adults who bought *iQOS* in September 2015; the violet line represents the conversion trajectory of those who bought *iQOS* four months later, in January 2016. The data indicate that those who purchased *iQOS* later tend to convert faster and in greater numbers than those who bought *iQOS* in the first months of launch. In addition to communication and guided trials (i.e., counseling adult smokers by explaining how to use *iQOS*), the increasing popularity of *iQOS* makes adult consumers feel increasingly comfortable using *iQOS* in presence of others. Also, "word of mouth" becomes a major contributing factor in raising awareness. The repeated exposure to various forms of communication facilitates adoption among adult smokers, not only by those who are usually the first to try innovative products ("innovators") but also by those who tend to adopt products when they have become more generally acceptable. Taken together, these factors support the need to communicate and encourage adult smokers in their "conversion journey" (the process to reach exclusive use of *iQOS*) during the first weeks following purchase. This is achieved by using appropriate communication, an extensive customer care program designed to address questions about the device and resolve technical problems (if any) and by reinforcing that *iQOS* use is an acceptable alternative to cigarette smoking.

Statistical analysis of the *iQOS* panel data can predict likely future tobacco use behaviors. For instance, a Markov model applied to the Japanese Market Research Panel data provided an understanding of the likely evolution of *iQOS* use categories based on information collected at the beginning of the conversion journey.

A transition probability matrix is generated by applying the Markov model to two cohorts of *iQOS* purchasers (September 2015 and May 2016) (Figure 40). The transition probability

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matrix indicates the likely evolution of *IOQS* use among the panelists according to three use categories.

Transition Probability Matrix – September 2015 Cohort

	Converted	Situational	Abandoners
Converted	52.3%	30.1%	17.6%
Situational	43.0%	29.8%	27.1%
Abandoners	24.8%	27.5%	47.7%

Transition Probability Matrix – May 2016 Cohort

	Converted	Situational	Abandoners
Converted	89.7%	9.7%	0.6%
Situational	51.9%	41.6%	6.5%
Abandoners	2.6%	11.9%	85.5%

Figure 40: Markov Model - Cohort Transition Probability Matrix

Note:

1. Converted = >95% of tobacco use is *iQOS*
2. Situational = all other % of *iQOS* not included in "converted" or "abandoners"; or *iQOS* users who showed an increasing trend towards "converted" or decreased trend towards "unconverted"
3. Abandoners = <5% of total tobacco use is *iQOS;* or <30% total tobacco use is *iQOS* and showed a decreasing trend with *iQOS* use < 5% for two consecutive weeks

Source: Japanese Market Research Panel

Specifically, *iQOS* purchasers who have already fully converted to *iQOS* have a very high and growing probability to remain in the same category (89.7% for May 2016 vs 52.3% for September 2015). This suggests that, once converted and *iQOS* use becomes familiar, the adoption of the new ritual and satisfactory experience seems to prevent *iQOS* users from switching back to other tobacco products. *iQOS* users who are in a "situational" status have a similar probability to either convert or remain in the same category and continue to use *iQOS* in conjunction with other tobacco products (51.9% and 41.6% respectively for May 2016 cohort). These observations reinforce the importance of continuously encouraging adult smokers in their "conversion journey", while they are in a transitional status in order to minimize dual use. Finally, the application of the Markov model indicates that the "abandoners" (when *iQOS* represents less than 5% of the weekly tobacco consumption) who are struggling to get used to the new product, are very unlikely to convert to *iQOS* (the probability to remain abandoners is 85.5% for May 2016 cohort). As a result, the May 2016 *iQOS* purchasers' cohort is likely to evolve towards an increasing proportion of converted

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iQOS users (75.7%), a smaller group of situational *iQOS* users (14.5%) and a percentage of abandoners close to 10% (see Figure 41).

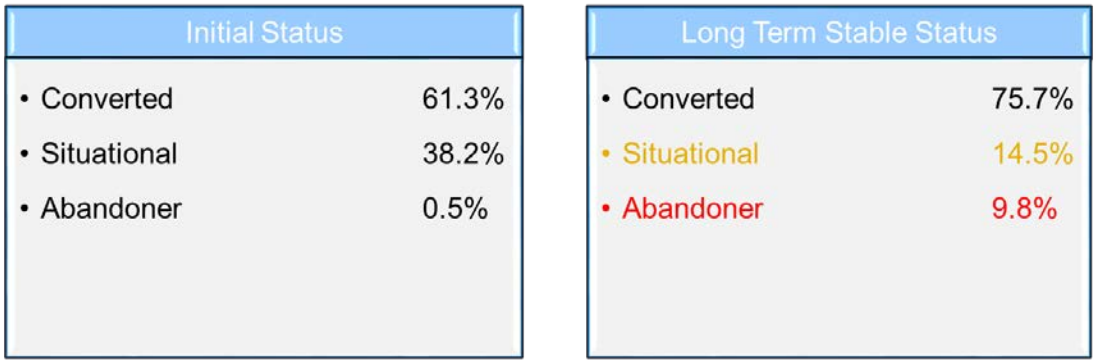


Figure 41: Markov Model - Long term status estimate

1. Note: Converted = >95% of tobacco use is *iQOS*
2. Situational = all other % of *iQOS* not included in "converted" or "abandoners"; or *iQOS* users who showed an increasing trend towards "converted" or decreased trend towards "unconverted"
3. Abandoners = <5% of total tobacco use is *iQOS;* or <30% total tobacco use is *iQOS* and showed a decreasing trend with *iQOS* use < 5% for two consecutive weeks

Source: Japanese Market Research Panel

Although data from these panels are helpful in understanding the behaviors and likely behaviors of the *iQOS* users, other studies are needed to monitor the potential effect on tobacco use behavior once *iQOS* is introduced in the market. Therefore, PMI is implementing a program to (i) monitor the use of *iQOS* and other selected tobacco products at the population-level, and (ii) determine other related tobacco use behaviors.

PMI has also conducted two initial online cross-sectional studies to evaluate the effects that *iQOS* could have on tobacco use initiation among adult nonsmokers. The first was conducted in Nagoya in March 2015 (where *iQOS* was initially test launched), and the second was conducted in September 2016 and covered the entire Japanese market. Although, it is not yet known whether these results are generalizable to the entire adult population, the studies showed less than 1.2% initiation among adult never smokers and less than 1.5% relapse among adult former smokers.

Taken together, the data from Japan show that a significant proportion of adult smokers bought and exclusively use *iQOS*. The proportion of exclusive users is increasing over time. This indicates that the growing popularity of *iQOS*, and the repeated exposure of adult smokers to various forms of product communication including "word of mouth", facilitate adoption among different types of adult smokers. Moreover, successful conversion to exclusive *iQOS* use is maximized when smokers switch fully in the first weeks of *iQOS* use.

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Finally, early studies on the adult population seem to indicate that the rate of initiation and relapse associated with *iQOS* commercial availability are very low.

Although the Japanese market data and insights do not necessarily extrapolate to the US market, they do provide a valuable perspective on the effect of *iQOS* commercialization on tobacco use behavior and the need to supplement LLM with guided trials (counseling) and after-sale support to effectively convert adult smokers and make *iQOS* use an accepted alternative to smoking cigarettes.

Determining product acceptance

Tobacco product acceptance partly depends on subjective effects such as relief from urge-to-smoke, cigarette craving and cigarette withdrawal symptoms among other measures of product acceptance. These subjective effects can be reinforced positively or negatively for the particular behavior. In the context of smoking, an example of positive reinforcement would be the strengthening of a certain product use behavior due to the rewarding effects of the product such as pleasurable sensory cues, euphoria, etc. Withdrawal symptoms are an example of a negative reinforcement stimulus, which can lead to smoking in order to alleviate this aversive state. Aversive stimuli such as craving and withdrawal have been characterized as motivating negative reinforcing effects of tobacco products.

Modified Cigarette Evaluation Questionnaire (mCEQ)

In the context of the assessment of THS, the mCEQ (Cappelleri 2007) was used to evaluate how closely THS approximated the profile of reinforcing and aversive effects observed for cigarettes, allowing some estimation of adoption and future use of the new product.

Five sub-scales were included in the assessment; (i) smoking satisfaction (satisfying, tastes good and enjoys smoking), (ii) psychological rewards (calms down, more awake, less irritable, helps concentrate, reduces hunger), (iii) aversion (dizziness, nauseous), and two single items, (iv) enjoyment of respiratory tract sensations (single-item assessment), and (v) craving reduction (single-item assessment) (Cappelleri 2007).

The results from the REXA and REXC studies showed that THS and cigarettes were very similar when evaluated at multiple time points across multiple studies in differing populations. The following diagrams illustrate the results on the five sub-scales of the mCEQ across the 5-day confinement studies (REXC) and the 90-day confinement/ambulatory studies (REXA). The data (Figure 42, Figure 43) shows that cigarettes and THS were very similar in terms of subscale scores for aversion, craving reduction, respiratory tract sensation, psychological reward and smoking satisfaction.

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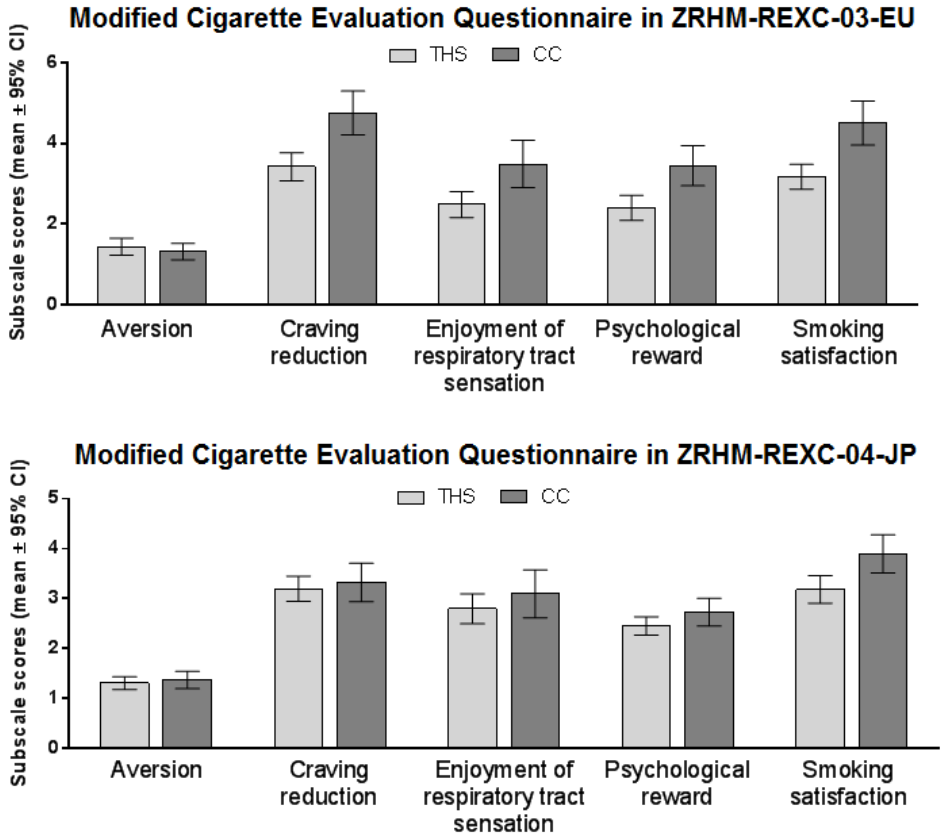


Figure 42: Comparison of subscales in the Modified Cigarette Evaluation Questionnaire (aversion, craving reduction, enjoyment of respiratory tract sensation, psychological reward, and smoking satisfaction) in the clinical studies ZRHM-REXC-03-EU and ZRHM-REXC-04-JP

Abbr.: CC = Conventional Cigarettes, FAS = Full Analysis Set, THS = Tobacco Heating System

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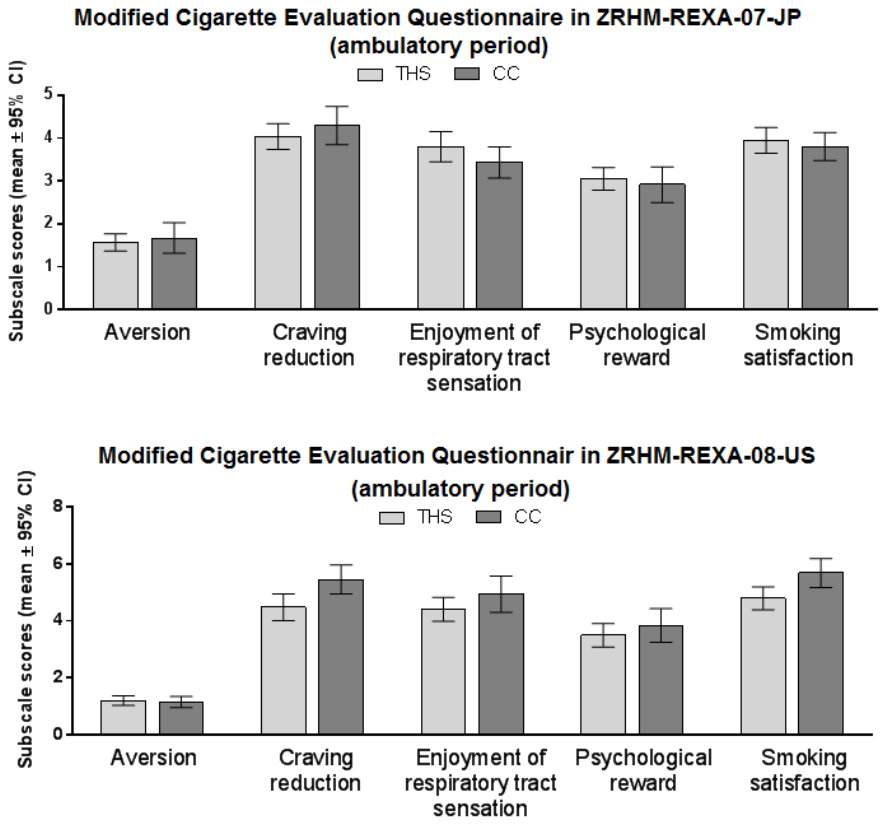


Figure 43: Comparison of subscales in the Modified Cigarette Evaluation Questionnaire (aversion, craving reduction, enjoyment of respiratory tract sensation, psychological reward, and smoking satisfaction) in the clinical studies ZRHM-REXA-07-JP and ZRHM-REXA-08-US on day 90

Abbr.: CC = Conventional Cigarettes, FAS = Full Analysis Set, THS = Tobacco Heating System

Urges-to-Smoke

The urge-to-smoke is a subjective motivational state, which, among other aversive effects, contributes to either maintenance or relapse of cigarette use. In the context of assessing an MRTP, the evaluation of urge-to-smoke has been recommended as a key outcome measure to prove that an MRTP can reduce the adverse effects of cigarette smoking "*through the ability of the MRTP to quell tobacco withdrawal (especially urges) and to reduce motivation to smoke conventional cigarettes due to preloading with the MRTP"* (IOM 2012).

The questionnaire of smoking urges (QSU) brief, which originates from the initial QSU 32-items questionnaire (Tiffany 1991), provides a multidimensional measure to assess the urge to smoke with 2 factor scores and a total score derived from the 10-item questionnaire:

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1. Factor 1: a positive reinforcement factor reflecting intention and desire to smoke and anticipation of pleasure from smoking
2. Factor 2: a negative reinforcement factor reflecting the anticipation of relief from negative affect and nicotine withdrawal, and urgent and overwhelming desire to smoke.

THS effectively reduces the urge-to-smoke in a manner similar to cigarettes, a finding that would be expected given the similarity of the nicotine pharmacokinetic curve of THS compared with cigarettes. An example of this result is illustrated in the Figure 44, which was taken from the 5-day REXC study in the EU. As seen in the figure, the urge-to-smoke score increases above baseline in the SA group but THS and cigarettes remain essentially the same.

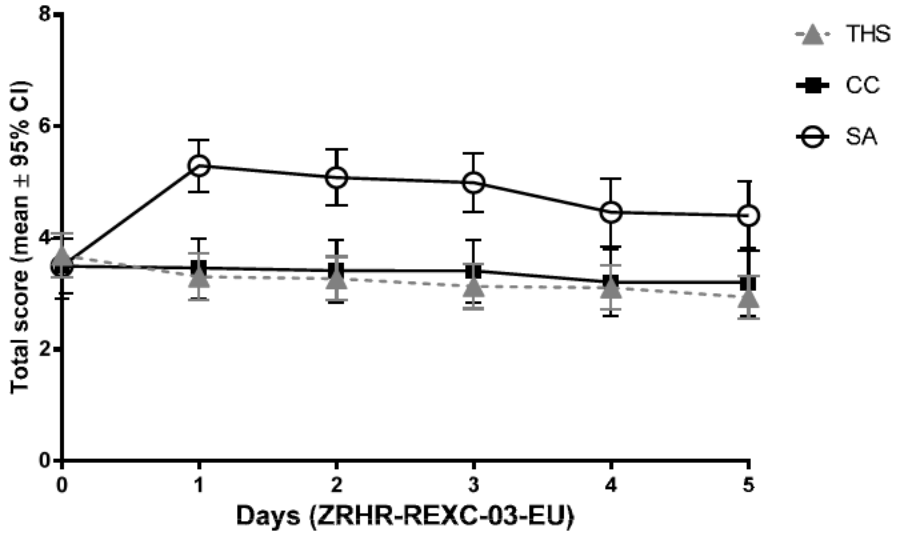


Figure 44: Total Score – Questionnaire of Smoking Urges During the Course of the Study

Abbr.: Tobacco Heating System (THS), Conventional Cigarette (CC), Smoking Abstinence (SA), confidence intervals (CI)

A second example of the urge-to-smoke scores is taken from the REXA 90-day study in Japan. As seen in Figure 45, for the mTHS and mCC arms, the mean urge-to-smoke total scores remained stable over the five days of the confinement period as well as during the ambulatory period, with Day 90 urge-to-smoke total scores of 3.25 and 2.83, respectively. In the smoking abstinence arm, the mean urge-to-smoke total score increased from baseline to Day 1 (score: 5.01 corresponding to a mean increase of 52%). From Day 2 to 5, total score values continously decreased until Day 5 (score: 4.47) and further decreased until Day 90 (score: 2.19).

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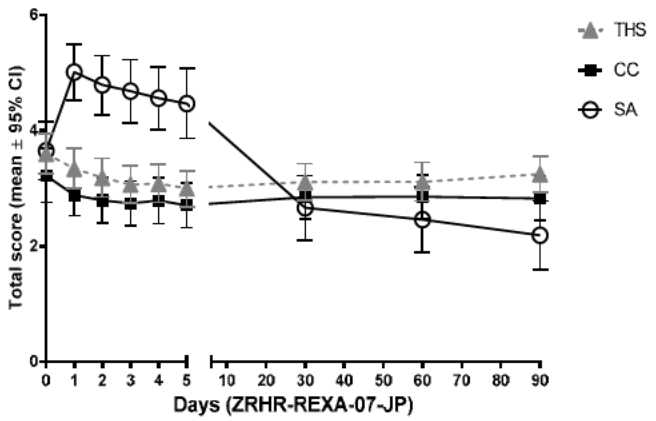


Figure 45: Total Score – Questionnaire of Smoking Urges During the Course of the Study

Abbr.: Tobacco Heating System (THS), Conventional Cigarette (CC), Smoking Abstinence (SA), confidence intervals (CI)

Abuse Liability Assessment

PMI conducted an abuse liability assessment to compare THS with cigarettes, using information regarding product design and content, aerosol chemistry and human clinical and behavioral studies. First, THS is designed to limit the temperature of the heating blade and the number of puffs that can be taken from a Tobacco Stick. Second, THS does not deliver additional addictive substances compared with cigarettes. Third, *HeatSticks* deliver nicotine in a manner that is broadly similar to cigarettes when assessed by aerosol chemistry, single use PK/PD studies and reduced-exposure clinical studies in both confined and ambulatory settings. For instance, the reduced-exposure clinical studies confirmed that the overall *HeatSticks* consumption and nicotine exposure are similar between the THS and CC arms of the studies, indicating that THS and cigarettes have a similar abuse liability. Taken together these facts do not provide evidence of any additional risk of abuse liability when comparing THS with cigarettes.

Based on the totality of the available evidence, THS has a similar abuse liability than cigarettes and there is no significant evidence that THS is attractive to non-users of tobacco. The full description of methodology and scientific findings can be found in Section 6.2.3.

Integrated Summary of Product Use Behavior

The results summarized in this section covered various dimensions of product usage, from product use behavior, behavioral intention and product usability. Overall, the combined results pertaining to each of these dimensions consistently point toward THS as a product that is attractive to some adult smokers as an alternative to cigarettes.

Sensorial experience, taste, ritual and nicotine delivery are among the attributes that contribute to the acceptance of a new product by a current adult smoker and are likely to significantly influence product use behavior. The four PK/PD studies (ZRHR-PK-01-EU,

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ZRHR-PK-02-JP, ZRHM-PK-05-JP, ZRHM-PK-06-US) demonstrated that smokers who used THS *ad libitum* were able to reach nicotine levels similar to cigarette smoking. Similarly, across all studies, the measures of subjective effects (e.g., urge-to smoke, withdrawal symptoms, product evaluation) demonstrated that THS provided similar scores/ratings to what was experienced by smokers when smoking cigarettes. For many smokers, the product satisfaction for THS, as measured by nicotine uptake and subjective effects, is comparable to a cigarette, which allows some smokers to completely transition away from the most hazardous form of tobacco consumption, the cigarette.

Results on product consumption and use patterns, both in controlled as well as in near real-world conditions, suggest that THS is likely to be adopted by current cigarette smokers. Furthermore, smokers who switch to THS do not increase their overall tobacco consumption, and most studies demonstrated that total tobacco consumption actually decreased in those smokers who completely switched to THS. It should also be pointed out that the product consumption and use patterns were achieved in smokers who did not have the benefit of regular exposure to advertising and product information that informed them of the reduced risk of THS compared with cigarettes. In fact, across all of the studies, smokers had only one opportunity, at enrollment, to be told of the potential for reduced exposure and risk. It is therefore likely that these overall patterns of use and switching represent a conservative estimate for an MRTP, i.e. testing performed without the exposure to product information that would be expected in the market place.

At the same time, an adaptation process is expected and was indeed observed within the first month of product use in most of the PMI studies assessing product use behavior (e.g., variation in product consumption, puffing behavior, or use patterns). Over a prolonged product exposure, the level of THS consumption tended to stabilize to reach levels comparable to what was reported at baseline for cigarettes. Patterns of product consumption and product satisfaction differed across study populations with differences between Japan and the US populations consistently observed, regardless of the type of studies. Product satisfaction was initially higher and adoption of THS was faster in Japan compared to the US, with eventually marginal differences only towards the end of the 3-months exposure studies. Cultural differences in taste preferences, difference in the products used prior to switching to THS, or more generally in the propensity to try new tobacco products may likely explain the differences observed on THS product use behavior across the different PMI studies. These cultural differences may also explain why complete switch was higher in some countries while combined/dual use of THS and cigarettes was the predominant pattern in other countries in observational studies.

The PBA study data on the THS messages consistently demonstrated that the product messages generated substantial Intent to Use THS among adult smokers including smokers with the intention to quit smoking. However, the data also shows that nine out of ten smokers who expressed an intention to quit stated that THS did not change their overall intentions.

Finally, data on product usability suggested that the instruction for use seem adequate in explaining the majority of the tasks required to operate THS. Based on findings from the THS-PBA-06-US study, improvements were subsequently made to the instruction for use. These results, put in perspective with the very low level of misuses observed in near real-

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world conditions such as in the THS-PBA-07-US study, suggest that THS is likely to be used as designed and intended by adult smokers.

In conclusion, based on the totality of the available evidence on product usage, THS offers an experience that is close to cigarettes and provides a satisfying experience for many adult smokers, and enabling them to either predominantly or fully switch to THS. Furthermore, PMI expects a more significant post-market appeal to adult smokers based on the ability to communicate the reduced-risk and exposure potential of the product.

II Effect of THS on tobacco use initiation among non-users (never users and former users)

A critical population health consideration under Sections 911(g)(1)(B) and 911(g)(2)(B)(iv) of the FD&C Act is the effect that an MRTP and its marketing will have on tobacco use initiation among non-users (never users and former users). The product's LLM must be designed in a way that does not encourage non-users to initiate (never users) or reinitiate (former users) tobacco product use. One of the objectives of the PMI PBA program was to develop communications for THS that generate substantial interest in the intended consumer group, i.e. adult smokers with no intention to quit smoking, while generating low Intent to Use among those for whom THS is not intended, such as adult never smokers and adult former smokers. A detailed description of the PBA work related to non-users can be found in Section 6.3.1.

Behavioral Intention among non-users

Assessing Intent to Use among Adult Non-users

Overall, adult nonsmokers showed very low or no Intention to Try or Intention to Use across all the PBA studies in which the Intention to Use among adult nonsmokers was assessed.

The first study to demonstrate the lack of Intention to Use was THS-PBA-02-US in which 30 Adult Former Smokers and 6 Adult Never Smokers were shown nine product messages and asked about their Intention to Use the product (Section 6.3.2). As shown in Table 28, which summarizes the results of this study, these consumers strongly rejected THS because they were aware that THS contained tobacco, understood that the product was not intended for them, and understood that THS could be "addictive and harmful to health".

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Table 28: THS Product Messages and Intent to Use in Study THS-PBA-02-US

			Adult smokers with no intention to quit	Adult smokers motivated to quit	Never and former adult smokers
REDUCED EXPOSURE	GENERAL	**Product Message C** Switching to THS 2.2 significantly reduces your body's exposure to many harmful chemicals found in cigarette smoke which are identified as likely causes of tobacco-related diseases	Some	Low	No
	SPECIFIC	**Product Message L** THS 2.2 significantly reduces the production of harmful chemicals, such as carbon monoxide which is reduced by 95%, found in cigarette smoke	Some	Low	No
		Product Message B THS 2.2 does not produce smoke or second-hand smoke	Some	Low	No
REDUCED RISK	GENERAL	**Product Message H** Switching to THS 2.2 can lower several risk factors that could lead to tobacco-related diseases	Low	No	No
		Product Message J Switching to THS 2.2 can reduce risks of tobacco related diseases	Some	Low	No
	SPECIFIC	**Product Message E** Switching to THS 2.2 can lower your cardiovascular disease risks	Low	No	No
		Product Message K Switching to THS 2.2 can improve lung function	No	No	No

Note: SOME = Some Intent to Use based on THS product message; LOW = Low Intent to Use based on THS product message; NO= No Intent to Use based on THS product message.

Abbr.: THS 2.2 = Tobacco Heating System (THS)

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A subsequent quantitative study, THS-PBA-03-US, showed very similar results in terms of lack of Intent to Use THS among adult nonsmokers. Subjects were shown five THS messages and asked about their Intention to Try and Intention to Use the product.

Among Adult Former Smokers, across all *THS Messages*, positive Intention to Try ranged from 0% to 4.2% and positive Intention to Use[13] from 4.1% to 15.7%. Very few Adult Never Smokers expressed a positive Intention to Use THS (≤3% for each of the 5 THS Messages for both positive Intention to Try and positive Intention to Use). Similarly, level of Intention to Use THS was low among LA-25 Never Smokers (≤6% for each of the 5 THS Messages for both positive Intention to Try and positive Intention to Use) (see Section 6.3.2).

The three THS-PBA-05-US studies were conducted among large samples that included adult former smokers as well as adult never smokers (including an oversampling of young adult never smokers who were LA-25). All three studies (THS-PBA-05-RRC-US, THS-PBA-05-RCC2-US and THS-PBA-05-REC-US) confirmed a consistent low or very low Intention to Use THS among adult nonsmokers. These findings extended consistently across all three modified risk claims, the different LLM materials tested, and both the PMI and Surgeon General's warnings.

Table 29 summarizes the Intention to Use (both Intention to Try and Intention to Use) for the three studies. Among the three adult nonsmoker groups, Adult Former Smokers expressed a positive Intention to Try in the low single digits with a maximum value of 9.6% and a minimum value of 2.1%. However, these same Adult Former Smokers, when asked about their Intention to Use, gave considerably fewer positive responses, with a maximum proportion of 5.3% and a minimum of 1.1%. This trend of slightly higher Intention to Try and lower Intention to Use was also observed in all other nonsmoker groups. The overall proportion of positive Intention to Try and Intention to Use responses for Adult Never Smokers and LA-25 Never Smokers were very small, ranging between 0 and 2% for both Intention to Try and Intention to Use.

[13] Note: Positive intention was operationalized as the proportion of subjects whose response to the single item assessing intention to try/use THS was either "*Very Likely*" or "*Definitely*".

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Table 29: Proportion of Adult Nonsmokers with Positive Intention to Try and Positive Intention to Use THS in THS-PBA-05-RRC-US, THS-PBA-05-RRC2-US and THS-PBA-05-REC-US

	Intention to Try		Intention to Use	
	Min. n/N (%)	Max. n/N (%)	Min. n/N (%)	Max. n/N (%)
THS-PBA-05-RRC-US				
Adult Former Smokers	3/94 (3.2%)	9/94 (9.6%)	2/94 (2.1%)	6/94 (6.4%)
Adult Never Smokers	0/96 (0.0%)	1/95 (1.1%)	0/96 (0.0%)	1/95 (1.1%)
LA-25 Never Smokers	0/97 (0.0%)	1/94 (1.1%)	0/97 (0.0%)	0/94 (0.0%)
THS-PBA-05-RRC2-US				
Adult Former Smokers	2/96 (2.1%)	7/92 (7.6%)	1/93 (1.1%)	5/94 (5.3%)
Adult Never Smokers	0/96 (0.0%)	1/93 (1.1%)	0/96 (0.0%)	1/92 (1.1%)
LA-25 Never Smokers	0/92 (0.0%)	3/101 (3.0%)	0/101 (0.0%)	1/92 (1.1%)
THS-PBA-05-REC-US				
Adult Former Smokers	3/96 (3.1%)	6/96 (6.3%)	1/96 (1.0%)	5/96 (5.2%)
Adult Never Smokers	0/96 (0.0%)	2/96 (2.1%)	0/96 (0.0%)	1/95 (1.1%)
LA-25 Never Smokers	0/97 (0.0%)	2/97 (2.1%)	0/97 (0.0%)	1/96 (1.0%)

Abbr.: THS = Tobacco Heating System.
Note:
[1] Positive *Intention to Try* refers to the proportion of subjects whose response to the single item assessing intention to try THS was either *Very Likely* or *Definitely*.
[2] Positive *Intention to Use* refers to the proportion of subjects whose response to the single item assessing intention to use THS was either *Very Likely* or *Definitely*.

Adult nonsmokers were also asked about their Intention to Try and Intention to Use comparator products such as cigarettes and e-cigarettes. The proportion of adult nonsmokers who indicated a positive Intention to Try or Intention to Use these comparator products were in the single digits, indicating that adult nonsmokers had no more interest in THS than in other tobacco or nicotine containing products (Section 6.3.1.4).

Across all of the PBA studies in which the Intent to Use among adult nonsmokers was assessed, the THS product messages and LLM did not appear to generate Intent to Use among adult non-users of tobacco products. Furthermore, the propensity to initate with THS is not significantly different from that of initiating with a comparator product (cigarettes or e-cigarettes). In addition, young adult LA-25 Never Smokers (LA-25) appeared to have the same or even lower interest in product trial and use than Adult Never Smokers in general. Taken together, all these results indicate that THS is not likely to increase tobacco use at the population level.

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III Effect of THS marketing on consumer understanding and perceptions

In a pre-market setting, it is important to measure consumer understanding and perception associated with the MRTP, as these may be crucial determinants of future use (IOM 2012). Whereas a commercial MRTP could be of benefit to the smokers who switch completely from cigarettes, it could also have a negative impact on the population as a whole by encouraging nonsmokers to start using a tobacco product or alter the decision of current smokers who intend to quit either smoking or the use of all tobacco products. In particular, a critical concern is ensuring that the product label, labeling and advertising material provide an accurate, balanced, and non-misleading picture of the product's characteristics that permits consumers to understand the risks of using the product compared to other tobacco products and thus allow them to make informed decisions about product use (Hatsukami 2012).

The overall evaluation of consumer understanding and perceptions of THS was based on data from six PBA studies, which provided consistent evidence on the appropriateness of the proposed claims, labeling and advertising submitted in this MRTPA. The PMI approach relied on a multistep approach using a combination of qualitative (THS-PBA-02-US and THS-PBA-04-US) and quantitative studies (THS-PBA-03-US, THS-PBA-05-RRC-US, THS-PBA-05-RRC2-US, and THS-PBA-05-REC-US) to provide (i) in depth information on how consumers understand and perceive THS communication, and (ii) precise estimates of comprehension and risk perception, using methods developed on the basis of accepted standards (FDA 2010, FDA 2009). The full details of the study methods and results can be found in Section 6.4 of this application.

Comprehension of THS Communication

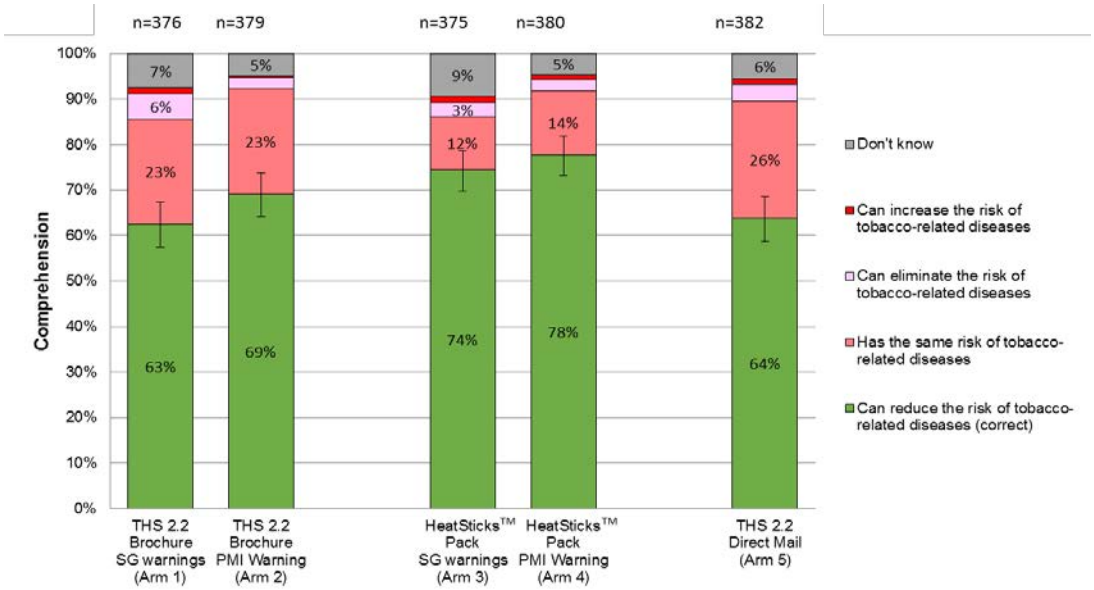
Comprehension of Reduced Risk Claims (Claims #1 and #2)

The findings of THS-PBA-05-RRC-US (testing Claim #1: "Reduced risks of tobacco-related diseases") and THS-PBA-05-RRC2-US (testing Claim #2: "Reduced risk of harm") show that most adult smokers and adult nonsmokers have an accurate understanding that THS presents less risk than cigarettes. The assessment of whether consumers were able to correctly understand the reduced risk information was based on the proportion of subjects who responded correctly that *there was a reduced risk of switching from cigarettes to THS* (Claim #1 = *reduced risks of tobacco-related diseases; Claim #2 = reduced risk of harm)*. The findings for the two reduced risk claims are summarized in Figure 46.

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A



B

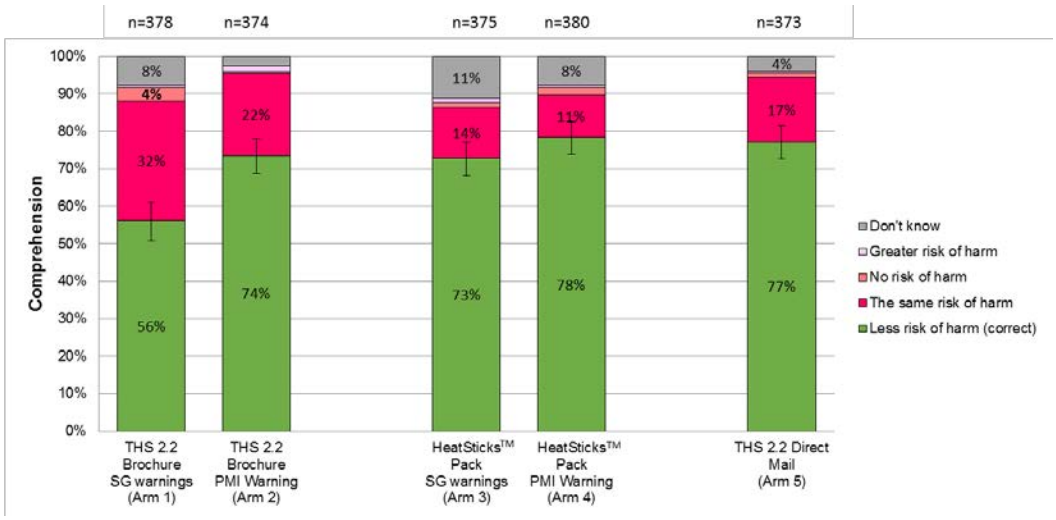


Figure 46: Comprehension of reduced risk information for THS-PBA-05-RRC-US (A) and THS-PBA-05-RRC2-US (B) within the Main Sample

Abbr.: SG=Surgeon General.
Note: Error bars presented are 95% confidence intervals of the proportion correct.

The correct consumer comprehension responses to the reduced risk claims were very similar when comparing Claim #1 (64-78% of correct responses across all five arms) and Claim #2 (56-78% correct responses). The levels of correct comprehension were broadly consistent across the two studies and across the three types of materials (i.e., THS Brochure, *HeatSticks*

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Pack, and THS Direct Mail). Consumers across both studies recognized that THS had some risk of use since only 4-6% of responses across the two studies indicated that the THS had NO risk.

Similar consumer comprehension was seen in both smokers and nonsmokers, particularly for the group of LA-25 Never Smokers, demonstrating that young adults did not have a different understanding of THS communication than older consumers. These results are consistent with providing accurate, understandable information to the public that THS is not a risk-free product and for all age cohorts to understand this message, particularly young adults who are more susceptible to trying new products and technologies.

As seen in Figure 46, the second most frequent response was that *disease/harm risk of switching from cigarettes to THS is "the same"* (between 12% and 32% across studies and communication materials). The fact that some consumers believe that THS and cigarettes have a similar risk is consistent with the literature on alternative tobacco products (e.g. smokeless tobacco products) where researchers have noted a general misconception among consumers regarding the relative harmfulness of noncombustible products (Borland 2012, Pepper 2015). Consumers do not have the necessary knowledge to discriminate the harm of each non-combustible product in comparison to cigarettes. Therefore, educating consumers about THS is essential to help convince adult smokers to switch to THS. Clearly, effective and accurate communication provided by the product manufacturer will contribute to achieving this objective. It is nevertheless important to consider how best to address this incorrect understanding of the relative risk, since some adult smokers may not be willing to switch to an MRTP if they believe that it has no benefit compared with cigarettes.

Furthermore, these studies also showed that consumers were also able to recognize that THS contains nicotine, which is addictive, providing the correct response between 87-92% of the time. Finally, consumers were also comprehending that "the best way to reduce the risk of tobacco-related diseases is to completely quit tobacco use" between 83-91% of the time.

The findings across the two reduced risk claims and the different communication materials provides consistent evidence that:

- the proposed THS communications will not mislead consumers with regards to the potential risk reduction of switching from cigarettes to THS;
- the THS communications lead to either an accurate or a conservative understanding of the risk of THS (risk of THS < risk of cigarettes or risk of THS = risk of cigarettes);
- consumers do not believe that THS is without risk;
- consumers understand that THS contains nicotine, which is addictive
- consumers understand that the best way to reduce the risk of tobacco-related disease is to completely quit tobacco use

Taken together, the results indicate that the two reduced risk communications were clearly comprehended by consumers, and provided appropriate information on risk reduction to both current smokers and nonsmokers. The communications enabled all consumer groups to understand the significance of the information regarding diseases risk and addictiveness associated with the use of THS relative to other tobacco products.

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Comprehension of Reduced Exposure Information (Claim #3)

In THS-PBA-05-REC-US, the evaluation of the ability of consumers to understand the reduced exposure information was based on the level of correct comprehension of two key communication objectives: (i) "*Exposure to HPHCs is significantly reduced"* and (ii) "*It has not been demonstrated that switching to THS reduces the risk of developing tobacco-related diseases compared to smoking cigarettes*." The second key statement was contained in the PMI Important Warning. This statement was developed to explicitly address the FDA's Draft Guidance, which states that for an Exposure Modification Order, applicants must demonstrate that labeling and marketing does not "*mislead consumers into believing that the product is or has been demonstrated to be less harmful…. than one or more other commercially marketed tobacco products*" (lines 801–804, (FDA 2012). Because this statement on risk of tobacco-related diseases occurred only in the PMI Important Warning, subjects exposed to materials with Surgeon General's warnings (Arm 1 and 3) were not presented with the second statement.

Figure 47 summarizes the results from the first key communication objective, indicating that most consumers were able to understand that upon switching from cigarettes to THS they would experience a significant reduction in exposure to HPHCs (levels of comprehension between 46% and 72%). Interestingly, the second most common response is that the overall exposure was reduced by a small amount (11% and 20% of responses across all 5 arms), which is a more conservative interpretation of exposure reduction. These results indicate that a large majority of subjects had a clear understanding that exposure to HPHCs was reduced by THS (between 66% and 83% across study arms) compared with cigarettes, although some subjects underestimated the degree of exposure reduction. Taken together, these results indicate that consumers are very likely to understand that switching to THS will result in a reduced exposure to HPHCs.

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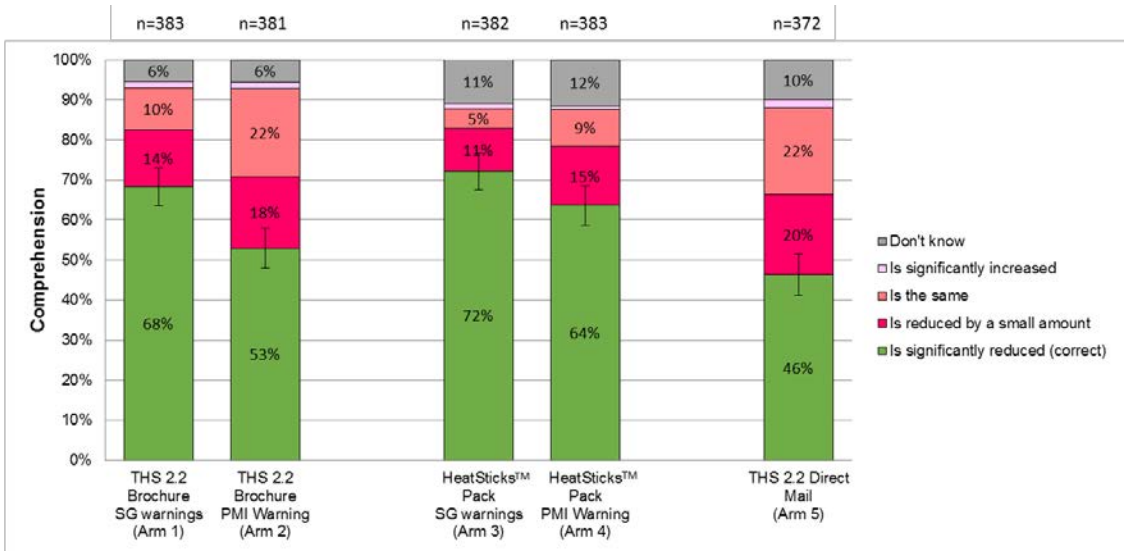


Figure 47: Comprehension of reduced exposure information within the Main Sample of THS-PBA-05-REC-US

Abbr.: SG=Surgeon General.

Note: Error bars presented are 95% confidence intervals of the proportion correct. The 5 responses options to the Global Comprehension question on reduced risk information are presented in the Figure box caption.

The ability of the consumers to understand the second communication objective was more variable and seemed to fluctuate in association with different warning statements (e.g. mandatory cigarette warnings vs. PMI warnings). As seen in Figure 48, the mandated cigarette warnings (SG in the chart) were accompanied by a lower understanding of the key communication objective with a higher percentage of consumers responding incorrectly that the product reduced the risk of disease. The percent of correct responses for the SG warnings were 27% for the *HeatSticks* Pack and 41% for the Brochure. This is in contrast to the PMI Important Warning where correct comprehension responses ranged from 60-70% for the Brochure, *HeatSticks* Pack and Direct Mail communications. The percentage of incorrect responses (i.e. percent of consumers who believed that the risk of tobacco-related disease had been demonstrated) ranged from 44-58% for consumers exposed to the SG warnings, while those for consumers exposed to the PMI warnings ranged from 26-28%. This suggests that an explicit representation in the label, i.e. that the risk of tobacco-related diseases had not been demonstrated, was able to improve consumer comprehension.

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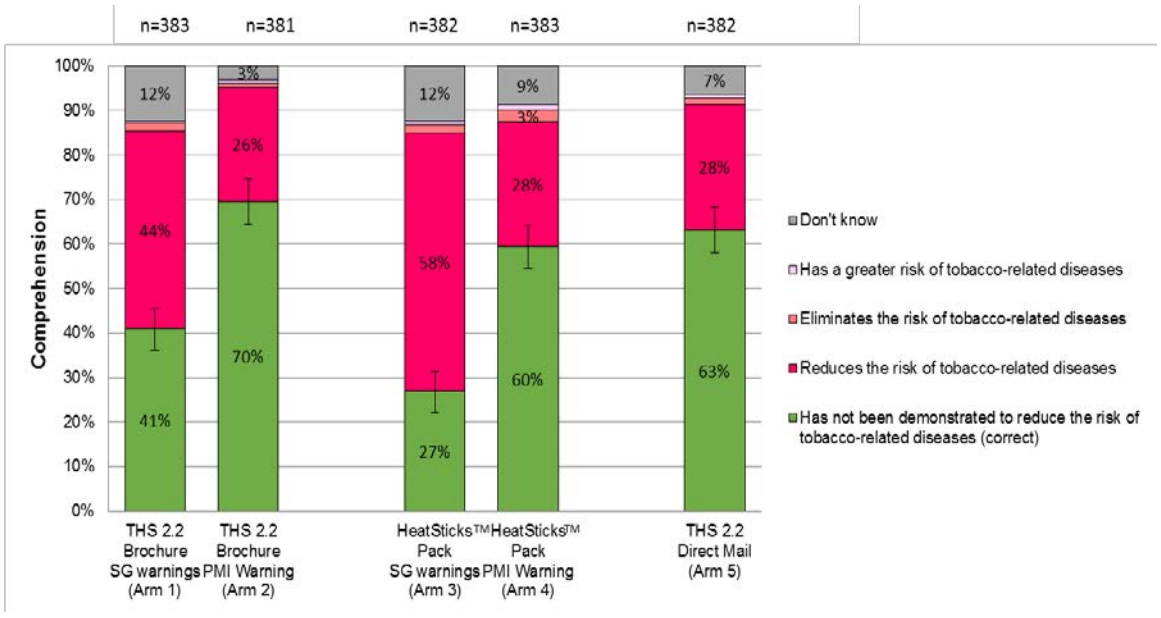


Figure 48: Comprehension of disease-risk within the Main Sample of THS-PBA-05-REC-US

Abbr.: SG, Surgeon General.

Note: Error bars presented are 95% confidence intervals of the proportion correct. The 5 responses options to the Global Comprehension question on reduced risk information are presented in the Figure box caption.

The challenge in appropriately communicating the reduced toxicity of an MRTP without conveying that the product is less harmful than other tobacco products has been acknowledged by the FDA Draft Guidance (lines 1041 to 1043, FDA 2012). Evidence from earlier generation of products, referred to as potential reduced exposure products (PREPs) by the IOM (Stratton 2001), shows that, despite the absence of explicit reduced health risk claims, consumers tend to over-interpret information on the reduced toxicity of PREPs as an indication of reduction in health risks (Hamilton 2004, O'Connor 2005, Pederson 2007, Shiffman 2004). The results of our studies support these earlier findings, and indicate that the use of appropriate warning statements improves the correct comprehension of a reduced exposure communication.

In summary for the reduced exposure claim, consumers are able to comprehend correctly that their exposure to HPHCs is reduced by using THS, although this reduction is interpreted conservatively by some smokers. The comprehension of the second communication objective was more variable and seemed to be influenced by the accompanying warning statements, which may have presented conflicting information that the consumer was not able to reconcile with the first communication objective. This indicates that an Exposure Modification Order should be accompanied by an explicit statement to clarify that reduced exposure does not imply reduced risk of tobacco-related disease. PMI anticipates that the findings from this study will be a topic of discussion with FDA to determine the appropriate

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label, labeling and marketing materials that would accompany an Exposure Modification Order under Section 911(g)(2).

Risk Perception based on THS Communication

PMI developed and validated a new measurement instrument, the Perceived Risk Instrument (PRI) which allows the comparison, on the same metric, of both Perceived Health Risk and Perceived Addition Risk across different tobacco products (e.g., cigarettes, e-cigarettes), NRTs and cessation, and across consumers with different smoking habits (e.g. current smokers, former smokers, never smokers).

The findings from the six studies conducted on risk perception of THS unambiguously showed that consumers perceive THS to be less risky than cigarettes, which are uniformly viewed as the tobacco product that presents the greatest risk to health. On average, THS was approximately between 8 and 22 points lower than cigarettes on the 0 to 100 *Perceived Health Risk Scale*, and between 5 and 30 points lower on the 0 to 100 *Perceived Addiction Risk Scale*, considering all materials (Figure 49).

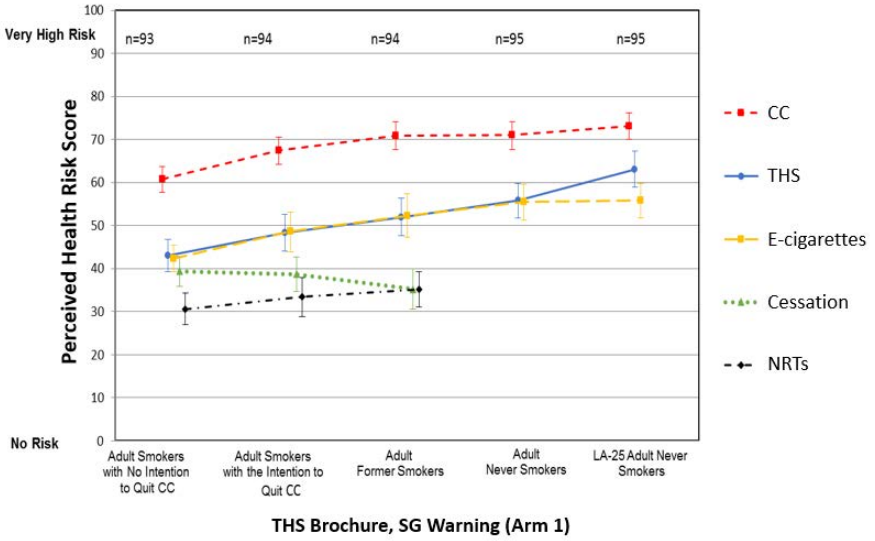
Risk perceptions of e-cigarettes and THS were very close, both on *Perceived Health Risk* and on *Perceived Addiction Risk*. On average, the absolute difference between THS and e-cigarettes varied between 1 and 5 points and between 1 and 8 points on a 0 to 100 scale for *Perceived Health Risk* and *Perceived Addiction Risk*, respectively. It is conceivable that study participants may have interpreted them as similar products due to the electronic component in both types of products. Based on qualitative findings (THS-PBA-02-US), the presence of tobacco in THS seems to be a key factor to trigger a slightly higher perception of risk than e-cigarettes. While this may be the exact reason why adult smokers are attracted to use the product, it appears also to be the reason expressed by most adult nonsmokers for having no interest to try or use THS.

When comparing different consumer groups, (i.e., current smokers, former smokers and never smokers), the study findings indicate a high degree of consistency on how THS was perceived compared to other tobacco products, namely lower in risk compared to a cigarette, and a similar risk as e-cigarettes. At the same time, perception of health risk was consistently higher in nonsmokers (former and never) compared to current smokers, regardless of the tobacco product. These results are in line with previous literature on perceived risk of tobacco products (Weinstein 2005) and provide further confidence in the external validity of our measurement instrument to measure perceived risks, not only for cigarettes but also potential MRTPs.

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A



B

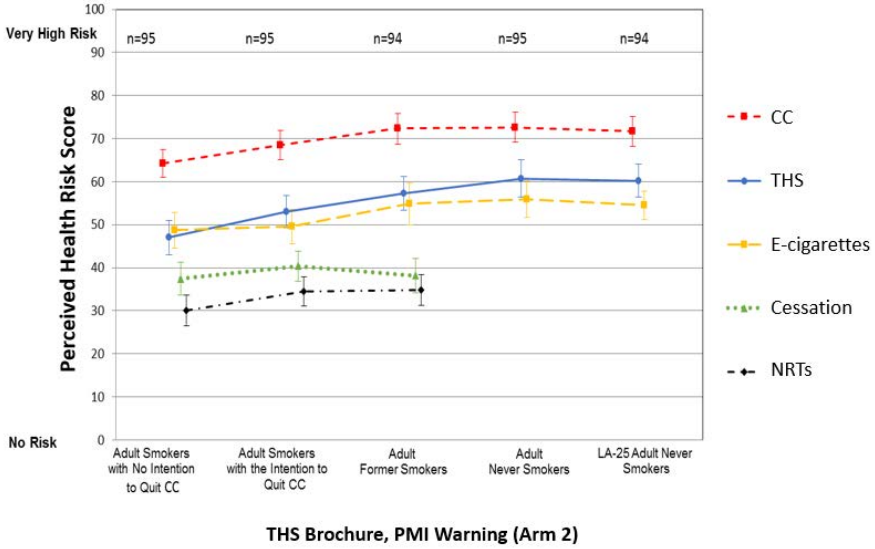


Figure 49: Perceived Health Risk – THS Brochure with SG Warnings: Arm 1(A) and with PMI Warning: Arm 2(B) from THS

Error bars are the 95% confidence intervals of the mean.
Note: Adult Never Smokers group includes only those Adult Never Smokers from the Main Sample.
Source: Study Report: THS-PBA-05-RRC-US

Perceived risks of THS compared to Cessation Aids and Quitting all Tobacco Use

Across all six PBA studies, THS was consistently rated as a higher perceived health and addiction risk than NRTs and smoking cessation. In studies using the Perceived Risk Instrument, THS was, on average, between 11 and 29 points higher than NRTs and between

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2 and 25 points higher than smoking cessation on the 0 to 100 *Perceived Health Risk Scale*. When asked about risk of addiction, consumers rated THS between 2 and 21 points higher than NRTs and 0- 41 points higher than smoking cessation on the 0 to 100 *Perceived Addiction Risk Scale*.

The higher risk perception of THS compared to NRTs is consistent with existing literature on risk perception of novel products (Overland 2013, Pepper 2015) that are compared to NRTs.

This further supports the conclusions that smokers are unlikely to perceive THS as equivalent to NRTs, though some of them may see THS as a less risky alternative to cigarettes that could help them quitting smoking. The PBA results also suggest that, if THS is marketed as proposed, smokers who would otherwise quit tobacco use would have the correct understanding and perception from THS communication that with THS they will still encounter risk for their health and a risk of nicotine addiction compared to quitting tobacco use altogether.

Summary of Risk Perception Findings

The PBA studies demonstrated that adult smokers and adult nonsmokers were able to understand and form accurate perceptions about health risks of THS, both in absolute terms and in comparison to other tobacco products, NRTs and cessation from all tobacco products. Consumers correctly perceived cigarettes as the most harmful tobacco product and rated THS lower in risk, both to themselves and to others, at a comparable level to electronic cigarettes but higher than NRTs and smoking cessation. Consumers were able to understand that, while THS has a reduced risk potential compared with cigarettes, the product is not risk free in terms of impact on health and the potential for addiction. Overall, adult nonsmokers tended to assign higher ratings for the risk of THS compared to smokers, providing further evidence that nonsmokers will not find THS attractive for trial or use.

Summary Perception and Behavior Assessment (Step 6)

The results presented on THS claims and communication materials provide additional support to the overall application for THS as an MRTP under both Section 911(g)(1) and Section 911(g)(2). Based on the modified risk claims and communication messages, all adult consumer groups that were tested (e.g. Adult Smokers with no intention to quit, Adult Smokers with intention to quit, Adult Former Smokers, Adult Never Smokers and LA-25 Never Smokers) were able to understand properly the following key points regarding THS:

- THS presents less risk to health than cigarettes
- THS is for adult smokers with no intention to quit; it is not intended for former smokers or never smokers
- THS is not risk free
- Quitting the use of all tobacco is the best way to reduce the risk of tobacco-related disease
- THS contains nicotine, which is addictive
- THS is perceived to have less risk than cigarettes, a similar risk to e-cigarettes and more risk than NRTs aids and quitting the use of tobacco

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There are some challenges presented by reduced risk versus reduced exposure claim, primarily based on the finding that consumers believe that a reduction in exposure leads to a reduction in risk of harm and tobacco-related disease. PMI has demonstrated this to be true. However, the current FSPTCA explicitly states that this could be potentially misleading to consumers and lead to undesirable product use among nonusers of tobacco products. This paradox on the part of consumers will have to be looked at carefully by FDA during its review of the application and when considering final LLM. PMI believes that the data should drive the final decision in order to maximize the use among smokers and minimize the use among nonsmokers.

The combined results of the PBA program indicate that the modified risk claims and communication materials provide scientifically accurate information that is clear and easily understandable. They allow consumers from different tobacco use experiences to make informed decisions about the use of THS in a manner that is consistent with an overall reduction in population harm and the risk of harm and tobacco-related disease.

In summary, the totality-of-the-evidence presented in step 6, combined with data from clinical studies on product use behavior, show that THS is not only an acceptable alternative to cigarettes for at least part of the adult cigarette smoker population, but is properly understood by the adult smokers and nonsmokers. Therefore, PMI has met the pre-market objectives for Evidence Level V.

Population Health Impact Model (PHIM)

The MRTP Draft Guidance refers to the use of computational models to estimate the potential impact of an MRTP on public health. The FDA has also acknowledged the inherent difficulties of such models since they require assumptions about how today's consumers, both users and non-users of tobacco products, will modify their future behavior in response to the entry of an MRTP into the market. There are a number of unknown future conditions that may highly influence consumer decisions (e.g. changes in public policy, regulation and consumer preferences) and therefore tobacco use behavior among consumers. For this reason, the ideal input parameters for population models will be derived from future data collected during post-market surveillance and studies. These will provide a real-world context to the modeling assumptions.

As outlined in Section 2.7.2, population harm reduction depends on both the availability of significantly lower risk products and a significant proportion of adult smokers who are willing to accept and switch to these products (Figure 1). To estimate the potential change in tobacco-related mortality that could occur following a US market introduction of THS as an MRTP, PMI developed a Population Health Impact Model (PHIM). The PHIM was built to reflect the two major factors that affect the overall model results: the magnitude of reduction in individual risk of disease and the population prevalence of use of THS.

PHIM Development

The PHIM was created with two major components: the "Prevalence Component" and the "Epidemiological Risk Component" (Figure 50). A detailed description of the model and the rationale for its development can be found in Section 6.5 and a recent publication (Weitkunat 2015).

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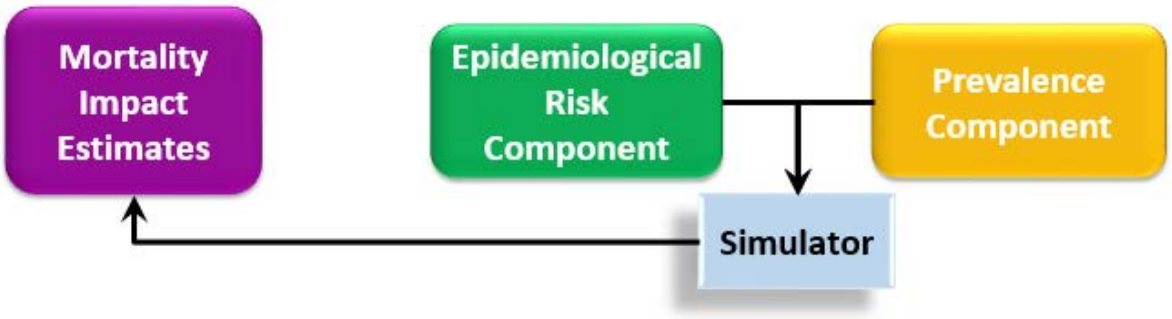


Figure 50: Approach to Assessing Population Harm.

The Population Health Impact Model (PHIM) was developed to reflect the Harm Reduction Equation presented in **Figure 1**.

Prevalence Component

The Prevalence Component established a hypothetical population of individuals, of a given sex and age, who were assigned an initial tobacco use status of "Never Smoker" (N), "Current Smoker" (C) and "Former Smoker" (F) based on smoking prevalence from publically available databases and the scientific literature. Tobacco transition probabilities (TTPs) are applied to reflect the probability of a single transition in smoking behavior within each given year and this is modeled over a twenty-year period (1990-2010).

The model considers two scenarios: (1) the Null Scenario, where the MRTP is not introduced, and (2) the "THS Scenario", where the MRTP is introduced. In the Null Scenario, only three tobacco use statuses were used (N, C and F) and only three different status transitions were possible: N-C, C-F and F-C (e.g. it is not possible to switch from C-N or N-F). The "THS Scenario" had five possible use statuses: In addition to N and F, this scenario also included Current Cigarette Smoker (C_C), Current MRTP Use (C_M) use and Current Dual Use (C_D). In this scenario, 15 different status transitions are possible as illustrated in Figure 51.

The appropriateness of the Prevalence Component under the "Null Scenario" was tested by comparing the International Smoking Statistics estimates of smoking prevalence (current and former smokers) for ages 30-34, 50-54 and 70-74 in 1995, 2000, 2005 and 2010 with those predicted from the PHIM. Although there were some small differences in estimates, overall the assumptions for the PHIM were a reasonable fit with actual smoking prevalence in the US market over the time of the model assessment.

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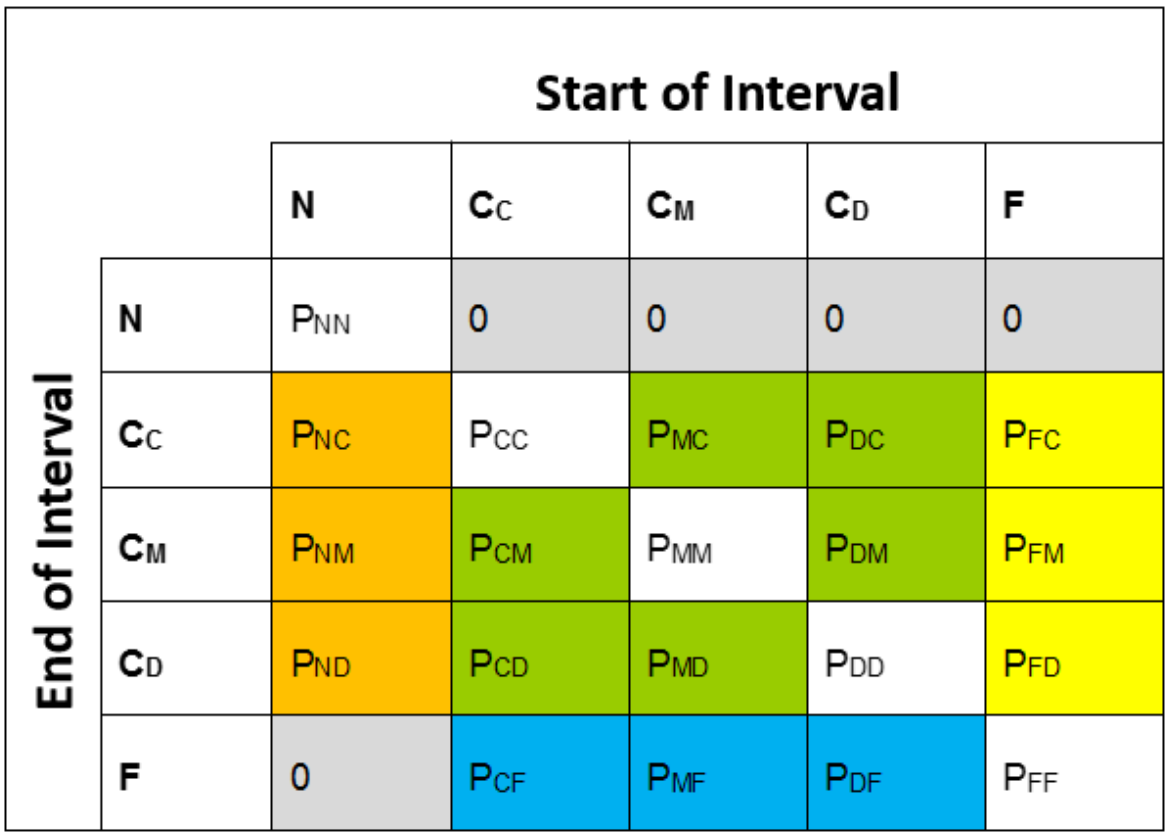


Figure 51: Matrix of Possible Tobacco Transition Probabilities (TTPs) under the THS Scenario

Where the tobacco use behaviors for the THS Scenario are defined as N=never smoker, C_C=current cigarette smoker, C_M=current MRTP user (THS user), C_D=current dual user, and F=former tobacco user. The six Tobacco Transition Probabilities are =probability of switching product use =probability of initiating, =probability of re-initiating, and =probability of cessation. Under this Scenario, the probabilities of individuals not transitioning within an interval can be calculated as the complement of the probabilities of a transition from that group.

Epidemiological Risk Component

The "Epidemiological Risk Component" used the age and sex-specific tobacco use histories generated by the Prevalence Component together with estimates of the disease-specific relative risk (RR) of smoking relative to never smoking, for each of the four major tobacco-related diseases; ischemic heart disease (IHD), lung cancer, stroke and COPD. The model uses a negative exponential function to quantify the decline in excess relative risk over time. The model also incorporated the relative risk (f-value) of using THS compared with cigarette smoking. This product-specific relative exposure is based on the assumption that the risk associated with THS use is proportional to relative exposure. For example, a product that reduces the exposure to HPHCs by, on average, 90% would have an f-value of 0.10. The

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maximum risk reduction achieved by smoking cessation (the "gold standard"), i.e., an exposure reduction of 100%, would give an *f*-value of zero. The estimation of the reduced exposure from THS relative to cigarettes was generated using the totality-of-the-evidence from the PMI scientific program described in Part A of Section 2.7.5.

For each year of the follow-up, and for each of the four diseases, the cumulative relative risk estimates for each individual were calculated. A hypothetical example of the change in relationship between relative risk and relative exposure for a given consumer over a lifetime of product use is provided in Figure 52. The individual risk profiles were used to calculate, at the population level, the numbers of smoking attributable deaths each year based on the actual national data for total US deaths.

The appropriateness of the Epidemiological Risk Component, was tested under the "Null Scenario" by comparing the smoking attributable deaths predicted from the PHIM, with published estimates from the 2014 US Surgeon General Report for 2005-2009 (HHS 2014) and the Morbidity and Mortality Weekly Report (Anonymous 1993).

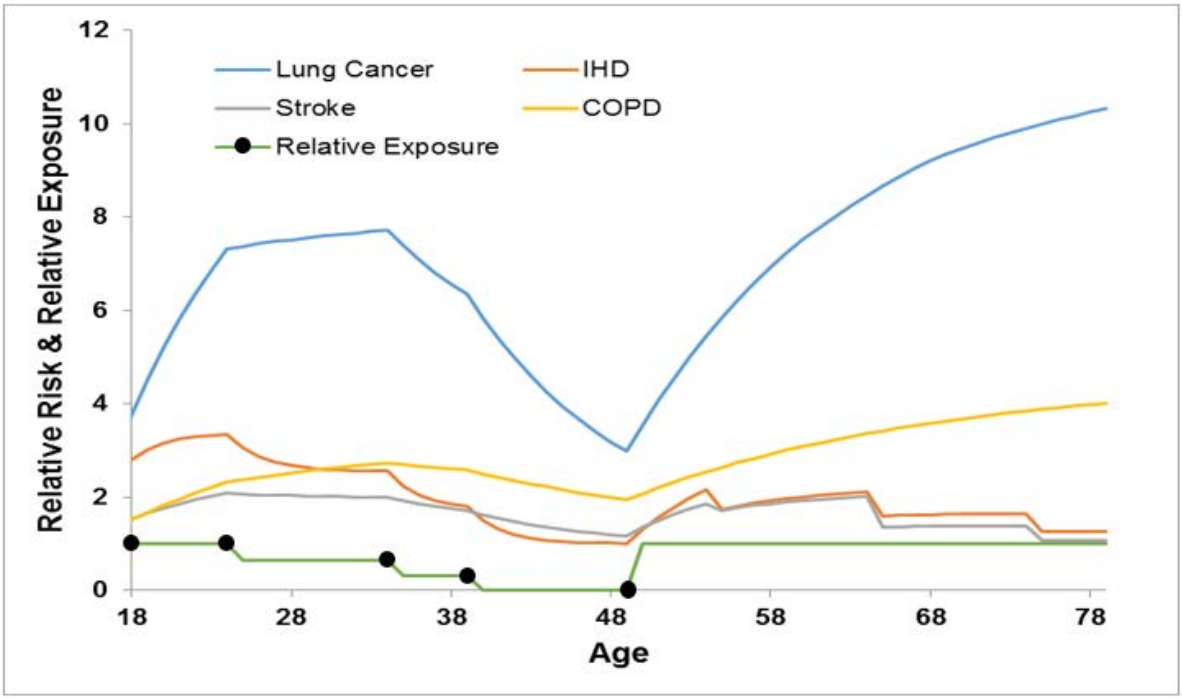


Figure 52: Illustration of the Increase and Decrease in Relative Risk by Age with Changing Tobacco Product Use Patterns

Each individual in the population will have such a curve of relative risk and exposure by age. In this example we assume an *f*-value for iQOS of 0.3 (for illustrative purposes), which results in a dual use relative exposure = 0.65. The relative exposure (green line) is expressed on a scale from 0 to 1. Every change in tobacco use behavior is highlighted by a black circle. The individual started smoking at the age of 18, switched to dual use at age 25, and then became an iQOS user at the age of 35 before quitting at the age 40 and re-initiating smoking at the age of 50.

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Simulation Results

In order to contextualize and understand the impact that the introduction of an MRTP can have on the health of a population, it is important to first understand the public health environment into which the MRTP is introduced.

20 Years of Cessation

Given that smoking cessation is the "gold standard" for the maximum risk reduction that can be achieved, the first simulation examines a scenario in which all current smokers would stop smoking immediately. In this simulation, the transition during the first year results in 0% initiation rate and 100% cessation rate in smokers. The smoking prevalence remains at zero as the population is then followed through the simulation for 20 years.

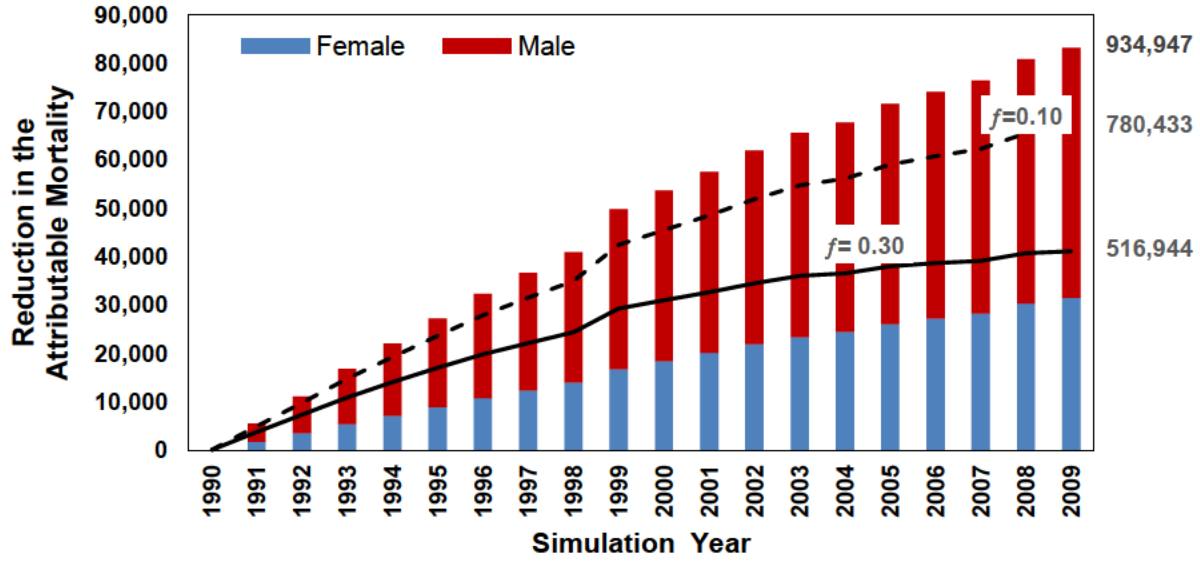


Figure 53: Reduction in the smoking attributable mortality each year (1990 to 2009) over the 20-year simulation under the hypothetical scenario where 100% of smoking is eliminated in 1990 (100% cessation)

Superimposed on the bar chart are the curves for replacing 100% of smoking with modified risk tobacco product use in 1990, considering both a relative exposure (f-value) = 0.10 (dashed line) and a relative exposure (f-value) = 0.30 (solid line).

The risks of smoking-related diseases do not diminish instantaneously following smoking cessation (f-value=0.00). Instead, the risks diminish gradually over time (the half-life of excess risk for smoking following smoking cessation is between 1.5 years for IHD and 13.3 years for COPD). In the initial years following the elimination of smoking, the initial annual reduction in smoking attributable mortality is relatively small (approximately 5,500 in 1991), but increases each subsequent year as the excess relative risk of smoking related disease declines. By the end of the simulation in 2009, the reduction in smoking attributable deaths would be over 83,000 per year. Over the 20-year simulation, a total elimination of smoking

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would result in 934,947 fewer smoking attributable deaths (Figure 53). This number would further increase in subsequent years.

20 Years of THS, with no cigarettes

PMI modeled an alternate scenario to understand the maximal impact of introducing THS into the US market. In this scenario, all current smokers in 1990 immediately transitioned to THS, rather than cessation, following THS introduction into the market. Unlike the total cessation simulation scenario in which initiation and re-initiation were eliminated, this simulation assumed that initiation and re-initiation rates did not change and all future smokers (i.e. initiators and re-initiators) used THS instead of cigarettes.

To understand the range of the potential impact of THS, PMI included two relative exposure conditions for THS:

1. Condition 1: THS preserved the effects of cessation by 90% (f-value=0.10),
2. Condition 2: THS preserved the effects of cessation by 70% (f-value=0.30).

Similar to the total cessation simulation, the initial years of the simulation show a marginal reduction in smoking attributable deaths per year (between 3,726 and 4,907 in 1991). However, by the end of the simulation period, the introduction of THS resulted in either 516,944 (f-value=0.30)*)* or 780,433 (f-value=0.10) fewer smoking attributable deaths (55-83% of the results seen for total cessation) depending upon the relative exposure of THS.

WHO 2025 Target and Projection

The 2015 World Health Organization's "Global Report on Trends in Tobacco Smoking 2000-2025" targets a 30% reduction in the prevalence of tobacco smoking between 2010 and 2025.

> *"If the 194 WHO Member States collectively achieved a 30% reduction from the 2010 level of 22.1%, they would be expected to reach a prevalence level of 15.4% in 2025. At this stage, it is projected that the prevalence level in 2025 will be 18.9%, or 3.5 percentage points above the target. This would represent a 14% relative reduction overall."*

To examine the impact that such a reduction in prevalence of smoking might have on the health of the US population, PMI used the PHIM to estimate the impact of reducing the smoking prevalence by 30% over a period of 15 years (in the model this is from 1990 and 2005). In order to compare these results with the total cessation scenario, the WHO target simulation was run over the full period (20 years), and the smoking prevalence was allowed to continue to decline over the last five years of the simulation. In addition, the simulation also included the projection of a 14% decline over the same 15-year period, which would represent the projected prevalence level in the report.

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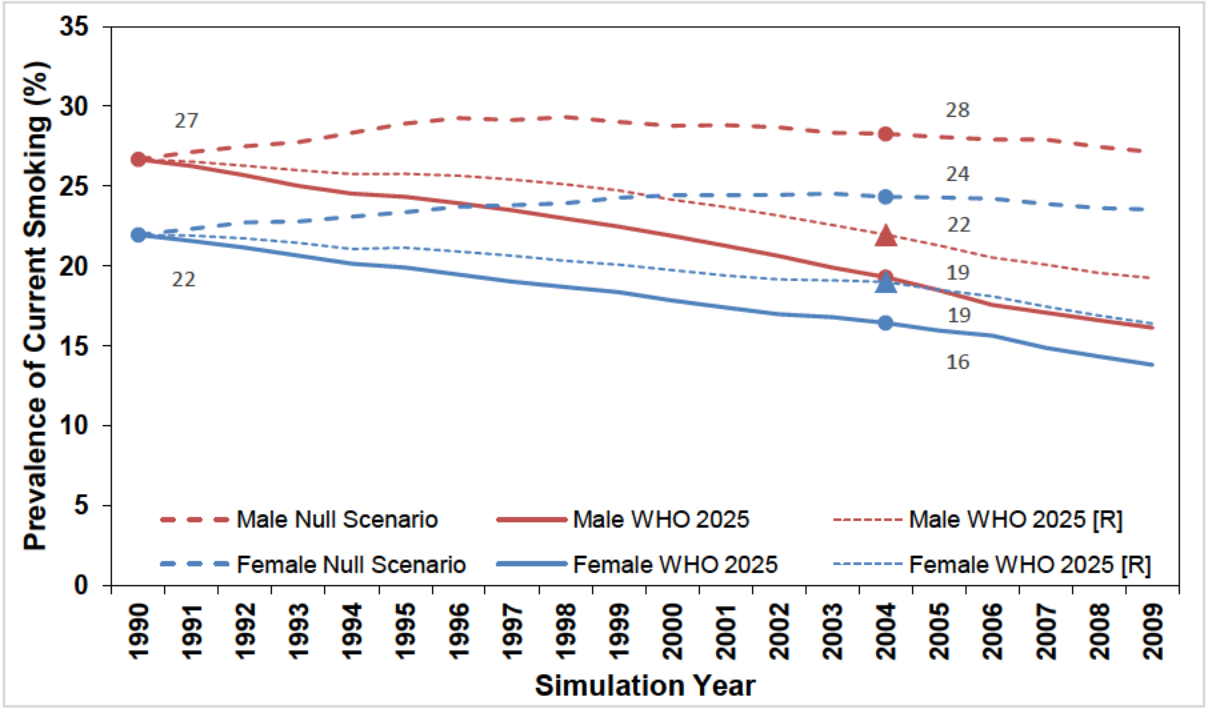


Figure 54: Reduction in Smoking Prevalence between 1990 and 2005 under the Null Scenario and the WHO 2025 projections

WHO 2025 reflects the initial estimates of a 30% reduction. WHO 2025 [R] reflects the revised projections.

For this simulation (Figure 54), PMI looked at the ingoing 1990 levels of smoking prevalence under the Null Scenario (27% in the male population and 22% in the female population). In the Null scenario, without the introduction of THS, the smoking prevalence remained somewhat constant over the 20-year simulation with approximately 27% smoking in the male population and 24% smoking in the female population in 2009. These results were compared with a simulation of the WHO 2025 target (30% reduction in the smoking prevalence) and WHO projection (14% reduction in smoking prevalence) over 15 years.

The WHO 2025 simulation resulted in a smoking prevalence of 18% in the male population (equivalent to a 30.7% reduction in the smoking prevalence) and 16% in the female population (equivalent to a 27.3% reduction in the smoking prevalence). In this scenario, the simulation results in 172,458 fewer smoking attributable deaths cumulatively over the 20-year period (108,637 in the male population and 63,820 in the female population).

The revised WHO projection (14% reduction) resulted in a smoking prevalence that was approximately 3.5 percentage points above the target, i.e. a smoking prevalence of 22% in the male population and 19% in the female population. In this case, there was a reduction of 111,102 smoking attributable deaths (69,041 in the male population and 42,060 in the female population).

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THS Business Case

In Section 6.5, PMI presents the "Business Case" for THS. This simulation assumed that 17% of the smoking population would be using THS within 10 years following its commercial launch (15% THS users and 2% dual users). In this simulation, there was very little change in the prevalence of never smokers and former smokers between the Null Scenario and the THS Scenario, as the majority of THS users and dual users were former cigarette smokers. At the end of the 20-year simulation, the initial 27% prevalence of smoking in the male population in 1990 had transitioned to 19% current cigarette smokers and 8% THS users in 2009.

In the Business Case scenario, the introduction of THS resulted in 70,274 fewer smoking attributable deaths (f-value=0.30), 90,155 (f-value=0.10) and 100,234 in the case where the same consumers were switched to smoking cessation (f-value=0).

THS Business Case in addition to the WHO 2025 Targets and Projections

PMI conducted another simulation to examine the effects of combining the WHO 2025 projection of 30% reduction in smoking prevalence with the Business Case scenario in which 17% of the remaining adult smokers would transition to THS over 10 years. In this case, the model estimated between 226,538 and 240,978 fewer smoking attributable deaths over the 20-year simulation. This simulation shows how MRTPs such as THS can complement existing efforts to reduce smoking attributable deaths.

A final scenario was modeled in which the WHO 2025 target was not met and the actual smoking prevalence was closer to the WHO 2025 projection of 14% overall reduction. In this case, the combination of tobacco prevention and THS-related harm reduction could result in a reduction of smoking attributable deaths ranging from 173,891 to 188,859. In the context of smaller overall reductions in smoking prevalence, the addition of THS could provide additional reductions in smoking attributable deaths and function in a synergistic manner with efforts to reduce smoking prevalence.

Conclusions

The closeness of the "Null Scenario" model-based predictions to actual epidemiological and authoritative statistics from the US population across the twenty-year study period provides a solid basis for assessing the potential population benefit of THS within the context of the MRTPA. In all but the most unlikely simulations, the introduction of THS resulted in fewer tobacco-related deaths. The degree to which tobacco-related deaths were reduced was primarily influenced by the prevalence of use of THS, i.e. complete switching by adult smokers and minimal influence on non-users. In the real world, consumers will need to understand the relative health benefits and the importance of completely switching to exclusive use of the THS. This process may take time to allow for a meaningful number of smokers to convert to THS. During this time, it will be important to conduct post-market surveillance and studies to provide additional insights that could encourage switching behavior among smokers. Overall, based on the scenario assumptions within the various PHIM simulations, introducing THS into the US population will lead to a net public health benefit in terms of reduced cigarette-related mortality.

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Post-market studies and surveillance (Step 7)

The ultimate determination of the impact of a modified risk tobacco product on the population health can only be established with long-term epidemiological studies. In the meantime, scientific studies and surveillance that are conducted after the commercial launch of a modified risk tobacco product will be essential to understand the actual use of the product in the market and detect any unforeseen physical effects or misuse of the product that may adversely impact the public health.

PMI has developed a post-market assessment program that will allow the collection of relevant data on safety, use patterns and product perception. The wide range of this assessment program will create essential insights into the impact of THS on individual consumers and the overall public health. The proposed post-market research program will measure product usage, both exclusive and in combination with other tobacco products including cigarettes. The combination of passive surveillance and research studies will also provide early detection of unintended population effects on either the intended audience (adult smokers) or unintended audience such as vulnerable populations.

The PMI post-market assessment framework is outlined in Figure 55. The framework is based on four assessment "pillars" that will deploy multiple and diverse methodologies to collect quantitative and qualitative data to support the post-market assessment of THS.

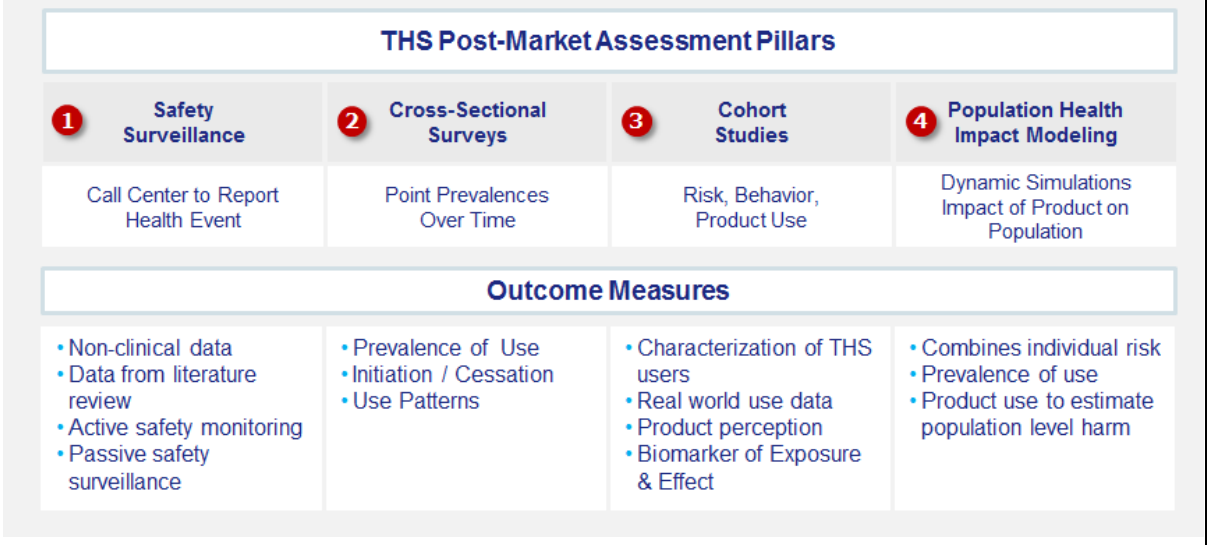


Figure 55: THS Post-Market Assessment Program

PMI designed the program to capture and evaluate the effect of the issuance of a risk reduction and/or exposure reduction order and the subsequent marketing of THS, as a reduced risk product, on consumer perception, behavior, and health over time. This program will enable the identification and collection of unanticipated and undesired health-related events associated with the use of THS, monitoring of the use of THS and other tobacco products at the population-level, as well as determine the related tobacco use behaviors.

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Following market authorization of THS, PMI[14] will submit to FDA an annual "Safety Summary Report" that will summarize the findings of all US post-market surveillance and studies. In addition to the annual report, PMI will review the status and approaches implemented in the Post-Market Assessment Program on an ongoing basis and will inform FDA of any changes that will be implemented into the assessment plan. In addition to the US report, PMI will also provide FDA with a summary safety report of THS in markets Outside the United States (OUS).

Safety surveillance

PMI currently conducts safety surveillance activities (Figure 56) in markets OUS to ensure that the medical safety oversight of THS is in line with relevant regulations in countries where THS is commercialized. The objective of this medical surveillance is to detect any safety signals pertaining to adverse events that are associated with the use of THS. PMI has the medical expertise for continuous assessment of THS safety profiles during pre-and post-market phases based on proprietary data and information from external sources.

Both PMI and ALCS have ongoing passive surveillance programs to capture spontaneous reports of adverse events (AEs) by consumers and healthcare professionals. For the US market, THS consumers will be able to contact and report any health related event using ALCS's established AE collection system.

[14] PMI has entered into an agreement with Altria Client Service LLC ("ALCS") by which ALCS and or its operating companies have a license to distribute and sell *iQOS* in the US. The ALCS operating company that will distribute and sell *iQOS* in the US, is Philip Morris USA (PM USA); but ALCS will be responsible for certain aspects of the Post-Market Assessment Program. For the purposes of this module, references to activities undertaken to support the post-market surveillance and studies in the US by PMP may ultimately be carried out by PMI, ALCS, or as a collaboration between the two parties.

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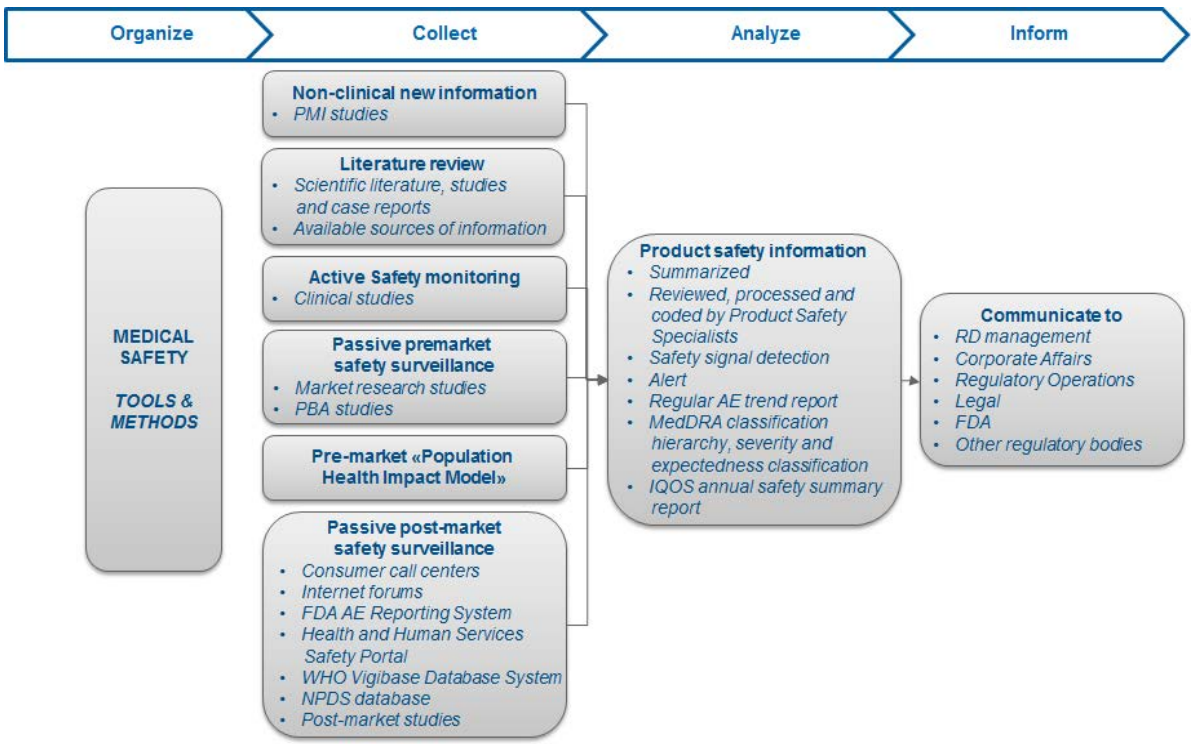


Figure 56: THS Product Safety Surveillance

Abbr.: AE = Adverse Event, FDA = Food and Drug Administration, MedDRA = Medical Dictionary for Regulatory Activities, NPDS = National Poison Data System, PBA = Perception and behavior Assessment, PMI = Philip Morris International, WHO = World Health Organization

Outside the US, PMI has implemented a similar, but independent AE collection system for countries where THS has been launched. The system is adapted to the country specific regulations, and language(s). Because of the diversity of markets OUS, there will be country-specific reporting patterns, which will be integrated into the THS Annual Safety Summary Report along with a country-specific summary of the AEs reported.

In addition to the passive surveillance through the AE collection systems, PMI plans to collect and analyze AEs identified and reported through other data sources. At present, the data sources that are proposed in this Post-Market Assessment Plan include literature reviews, internet forum monitoring, the FDA AE Reporting System, the Health and Human Services Safety Portal and the World Health Organization Vigibase Database System. PMI is also exploring the possibility of registering THS with the National Poison Data System from the American Association of Poison Control Centers (AAPC) to allow the identification and tracking of AE reports through US hospitals and emergency rooms.

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All AEs regardless of their source will be consolidated into a single Safety database, coded and summarized in the *THS Annual Safety Report*. In addition to the AE reporting and the summary of AEs in the THS Annual Safety Summary Report, serious AEs (SAEs)[15] reported in the US market will be submitted to the FDA as individual cases within 15 business days of receiving the reported events.

In addition to the passive surveillance program, PMI is working to develop and test a systematic data collection tool and analysis infrastructure for the THS Post-Market Assessment Program using Internet forum data. This infrastructure could be utilized to monitor discussions related to the use patterns, consumer perceptions (including risk perception), abuse, misuse, and product tampering as well as health-related information pertaining to THS, its brand family, and product category. This infrastructure would serve as a signal detection tool to identify potential unanticipated and undesired events related to THS once it is introduced to the market and to help contextualize observations from other sources of data.

Cross-sectional surveys

PMI has proposed the use of cross-sectional surveys to assess how THS is used by consumers in a real-world setting. These surveys are a type of observational study that involve the analysis of data collected from a population, or a representative subset at one specific point in time. They are descriptive and intended to provide data on the entire population under study, not individuals within a specific characteristic.

These studies will:

1. obtain information on whether current smokers, former smokers, or never smokers initiate or switch to THS from their usual tobacco product or non-use of a tobacco product;
2. capture the use of other tobacco and nicotine products (i.e., nicotine replacement therapy) among THS consumers;
3. assess patterns of use such as concurrent/dual use with cigarettes; determine whether THS delays/prevents those smokers who intend to quit the use of all tobacco products from quitting; and determine the extent of nonsmokers or former smokers who initiate the use of THS.

PMI will assess the use of THS among different segments of the population. The cross-sectional studies will include a broad selection of demographic items: age, sex, race, ethnicity, education, employment status, information on socio-economic status, military service, sexual orientation, whether the respondent is currently pregnant or nursing, suffers from mental health conditions or self-reported medical conditions such as lung disease (e.g., chronic obstructive pulmonary disease), or cardiovascular disease.

[15] Defined in the MRTP Draft Guidance as "…an AE that results in any of the following: death; a life-threatening condition or event; persistent or substantial disability or incapacitation; hospitalization or prolonged hospitalization; or a congenital anomaly or birth defect." (FDA 2012)

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PMI anticipates that the cross-sectional studies will initially be limited in their ability to use probability-based sampling to recruit sufficient numbers of participants due to an initially small market penetration for THS, which will grow over time. Therefore, the initial studies will rely on panel-based sampling strategies to obtain data sufficient to examine the outcomes of interest. This approach will be complemented by an ongoing, cross-sectional study designed to provide a national probability-based sample to estimate tobacco use prevalence, including use of THS as feasible.

Cohort studies

PMI proposes the use of cohort studies to recruit a group of people who share a common characteristic or experience and who are monitored over a defined period to characterize their profile and use patterns. This data will also include questions that will characterize consumer perception and switch patterns. This data will be used as input parameters to refine and better characterize the PHIM. The prospective cohort study will focus on tobacco use patterns and behaviors over time (see example of ongoing Japanese cohort study in Figure 57).

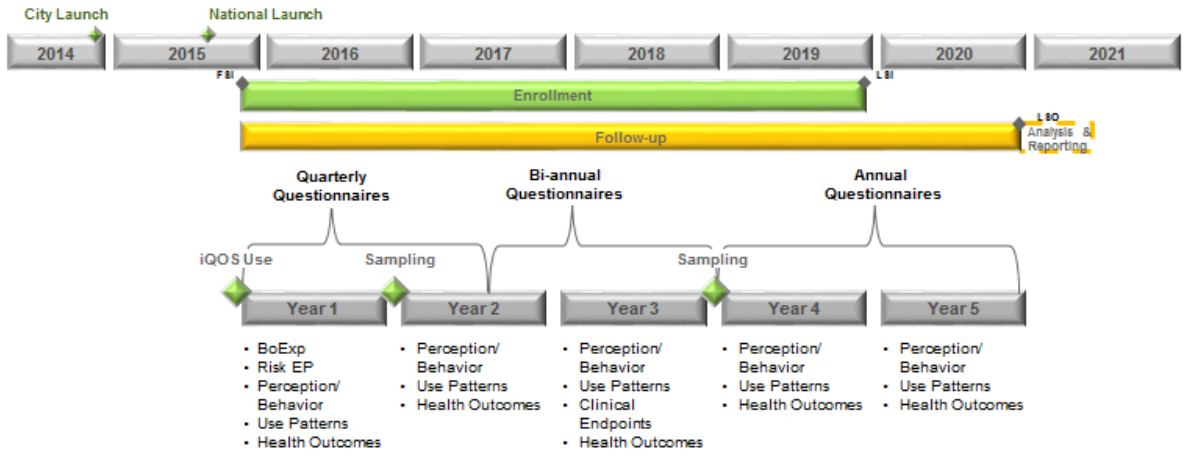


Figure 57: Example: Japanese Cohort Study

To understand fully the effect of THS on the use of tobacco product(s), specific segments of the population (recent adopters – within one year of initiating THS long-term consumers – greater than one year of THS use) may be targeted to monitor and assess how changes in the market awareness, product trial and regular use of THS affect the population over time. Health-related objectives will be limited to characterizing potential changes in self-reported, smoking-related signs and symptoms over time and assessing changes in prevalence.

In summary, the post market assessment program will allow, over time, the confirmation of a reduced risk of harm and tobacco-related disease to individual smokers who switch to THS and to confirm a net benefit to the population as a whole including users and non-users of tobacco products.

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Conclusion Part B: Benefit the Health of the Population as a Whole

Potential impact on current users of tobacco products

Overall, adult smokers in the US appear to be genuinely interested in both trial and use of THS. Adult smokers and adult nonsmokers alike understood the proposed THS communications and product proposition. Overall, the PMI modified risk messages and claims generated substantial Intention to Use THS among adult smokers, while not encouraging adult nonsmokers to try/use THS. This is an important criterion in establishing the utility of THS as a harm reduction product.

The overall findings for current adult tobacco product users are summarized as follows:

- In all six PBA studies, which looked at the effect of THS labeling and advertising materials, adult smokers (with no intention to quit) expressed a substantial interest in trying THS.
- Adult smokers expressed a consistent Intention to Use across the three THS-PBA-05-US studies with Intention to Use responses ranging between 20.2% and 38.9% of adult smokers. These percentages, when extrapolated to the current estimated US adult smoking population of 40 million, estimate that between 8-15.5 million adult smokers would be interested in using THS.
- Study results indicate that the THS instructions for use are sufficient to explain the various tasks required to operate THS. THS-PBA-07-US study results indicate a low level of misuse potential. Therefore, THS is likely to be used as designed and intended by adult smokers.
- Exposure to either product messages or LLM concerning THS does not substantially affect those adult smokers who have a stated intention to quit, i.e., the exposure slightly reduces their intention to quit smoking or all tobacco (between 1.1% and 11.8%).
- Product satisfaction for THS, as measured by nicotine uptake and subjective effects, is comparable to a cigarette, which is critical to adult smoker acceptance of THS as a suitable alternative to cigarettes.
- The results of the PK/PD studies as well as the levels of exposure to nicotine from the reduced exposure studies do not indicate a higher risk of abuse liability in smokers switching to THS compared to cigarettes.
- Product use data collected in near real-world conditions provide evidence that adult daily smokers who consume THS freely with other tobacco and nicotine containing products do not increase their overall tobacco product consumption, whether they use THS predominantly or in combination with cigarettes.
- It is unlikely that those who rapidly and completely switch to THS will switch back to cigarettes.
- The product use behaviors observed in clinical and observational settings do not raise an abuse liability concern beyond that for cigarettes.

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- Taken together, the findings of the actual use study (US) and the WOT (5 countries, not US) show consistently that a sizeable proportion of adult smokers were able to adopt and continuously use THS by the end of the study period (about 10% to 37% across the 6 countries). This suggests that a substantial proportion of adult smokers are willing to substitute almost completely their cigarette consumption by THS use.

Potential impact on persons not currently using tobacco products

PBA data demonstrated that persons not currently using tobacco products (i.e. Adult Never Smokers and Adult Former Smokers) do not find THS to be of sufficient interest to start using THS, even in the event of significantly lower risk than cigarettes.

- Adult non-users of tobacco products did not show significant interest in THS across the numerous studies, particularly when shown the complete product messages with the modified risk claim, intended and unintended audience message, clarification of risk and the fact that THS contains tobacco.
- There was only small Intention to Try/Use THS among all three examined nonsmoker groups. Adult Former Smokers expressed a slightly higher Intention to Use than Adult Never Smokers (Adult Never Smokers had a very low Intention to Use in all three assessment studies (< 2.1% positive responses). In these nonsmoker groups, the Intent to Use THS was not different from the Intent to Use e-cigarettes or cigarettes.
- Positive Intention to Try and Intention to Use responses throughout all tested materials were particularly low for LA-25 Never Smokers (no more than 3.0% of positive Intention to Try/Use).
- Results suggest that neither the THS Brochure, nor the *HeatSticks* Pack or the THS Direct Mail generate Intention to Use among US adult nonsmokers.
- Adult Former Smokers and Adult Never Smokers were not differentially attracted to a reduced risk claim versus a reduced exposure claim, having a low or very low Intention to Use irrespective of the type of claim.

Furthermore, as described in Section 2.7.5 Part A, the use of THS does not negatively impact indoor air chemistry, and reduces the risk of accidental fires.

Comprehension and risk perception

It is likely that the use of THS will be substantially influenced by consumer perceptions regarding the health risks of THS. The THS communication materials are intended to convey accurate scientific information about the reduced risk potential of the product and to ensure that consumers evaluate/understand this risk appropriately within the context of other tobacco products and smoking cessation and to understand that the use of THS is not risk free. The following points summarize key findings from the PBA studies:

- The proposed THS LLM enabled the public to comprehend information concerning reduced risk and reduced exposure claims.
- The public perceives THS as a medium risk product, lower than cigarettes but not risk free. Overall, consumers perceive that the health and addiction risks of using THS were lower than cigarettes but higher than NRTs or Cessation.

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- The results demonstrate that the content of the communication materials enable the public to understand the potential harm reduction benefits to substitute cigarettes with THS, as well as the relative risks of using THS compared to cigarettes, cessation aids and quitting smoking.
- A substantial portion of subjects in the reduced exposure claim study incorrectly stated that switching to THS would reduce the risk of developing tobacco-related diseases. Comprehension was improved when consumers were actually given an explicit statement that communicated that the significant reduction in exposure did not mean that the risk of tobacco-related disease had been proven. PMI believes that there is sufficient overall comprehension of the reduced exposure claim to warrant an Exposure Reduction Order but recognizes that there will need to be additional discussion with FDA to optimize the reduced-exposure communication to consumers.
- The results support the conclusion that the proposed claims are not misleading but rather consistent with the totality-of-the-evidence on harm reduction presented in this application.

Taken together, the results presented above on THS claims and communication materials, support the application of THS as an MRTP.

Population Health Impact Modeling

The FDA has encouraged the inclusion of computational models to forecast the potential change in the health of the public, either positive or negative, introduced by an MRTP (FDA 2012). PMI has developed, validated and tested a Population Health Impact Model (PHIM) using well-established methods in mathematical modeling and simulation analysis. Based on conservative assumptions about US market penetration and the relative risk of THS compared with cigarettes, PMI has conducted multiple simulations to model the potential impact of THS on the health of the US population. The results of these stimulations show that introducing THS on the US market would result in a significant reduction in smoking-attributable deaths.

Post-market studies

The combination of the following overall findings, obtained prior to market launch of THS, is sufficient to expect a net reduction in harm at the population level. To confirm these overall finding, PMI has developed a post-market research program that will enable the measurement of THS use prevalence along with prevalence of use of other tobacco products, both exclusively and in combination. This comprehensive program will allow PMI and FDA to monitor population-level total exposure to tobacco products and to ensure that no unintended population effects will ensue, eventually including adverse population health impacts.

In summary, the totality-of-the-evidence presented in Part B, which takes into account both users of tobacco products and persons who do not currently use of tobacco products, demonstrates that THS has the potential to benefit the health of the population as a whole. Therefore, PMI believes that THS meets the second criterion for approval under Section 911(g) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

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2.7.7 OVERALL CONCLUSION

The FDA has acknowledged that "*The modified risk tobacco product provisions of the FD&C may be valuable tools in the effort to promote public health by reducing the morbidity and mortality associated with tobacco use, particularly if companies take advantage of these provisions by making bold, innovative product changes that substantially reduce, or even eliminate altogether, the toxicity or addictiveness of tobacco products, or both*" (FDA 2012).

Section 911(g)(1) of the FD&C Act states that the Food and Drug Administration (FDA) may issue a modified risk market order for a tobacco product if the sponsor satisfies a two-part "basis for approval". As outlined in the Draft Guidance, an MRTP must meet a series of rigorous criteria that demonstrate that the product will:

A. Significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and
B. Benefit the health of the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products.

The results of the PMI scientific program presented in this application are compelling and show that THS satisfies the two-part "basis for approval" for a Risk Modification Order.

As outlined in Part A, the PMI scientific program has demonstrated that THS will significantly reduce the harm and risk of tobacco-related disease for those for smokers who switch from cigarette smoking to THS use. The basis for this conclusion rests on these pillars of evidence:

1. THS produces significantly lower levels of HPHCs compared with cigarette smoke
2. THS aerosol does not negatively impact indoor air quality; most constituents are below either baseline levels of detection or US regulatory limits for chronic exposure
3. THS aerosol is significantly less toxic than cigarette smoke
4. THS aerosol causes significantly less disease-associated network perturbations *in vitro* and *in vivo*
5. THS aerosol causes significantly less emphysema and atherosclerotic plaque in animal models of disease
6. Clinical studies have shown that switching from cigarette smoking to THS use leads to a significantly reduced exposure to HPHCs, which approaches the reductions in exposure that are seen with smoking abstinence
7. Clinical studies have shown that switching from cigarette smoking to THS results in positive changes in clinical risk markers that are similar to those seen following smoking cessation.

Tobacco-related diseases are a result of a dose- and time-dependent exposure to HPHCs found in cigarette smoke. The disease causation is explained by the High Level Adverse Outcome Pathway (Figure 3) in which exposure to HPHCs adversely affects the homeostasis of biological mechanisms, which leads to cellular and tissue damage. Over time, these perturbations and damages lead to physiological changes that are directly linked to the causation of tobacco-related disease.

Smoking cessation is the proven standard for reducing the subsequent risk of tobacco-related disease in smokers. Smoking cessation is, by definition, the complete elimination of exposure

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to HPHCs and thereby the removal of their adverse impact on molecular, cellular and tissue function. Smoking cessation is accompanied by predictable and favorable restoration of normal cellular and tissue function that can be measured across experimental *in vivo* and *in* vitro systems using standard and systems toxicology approaches. Human subjects, who quit smoking show favorable changes in clinical risk endpoints and, over time, improved physiological function.

THS is likely to approximate most of the reduction in risk that is seen with smoking cessation in those smokers who switch from cigarettes to THS. The basis for this statement is the fact that THS produces significantly fewer HPHCs than cigarettes, approaching a 90% reduction in overall HPHC levels compared with cigarette smoke. As a result, THS aerosol has been shown to be significantly less toxic, compared with cigarette smoke, across multiple *in vitro* and *in* vivo models using standard and systems toxicology approaches. The reductions in exposure to HPHCs were accompanied by reductions in biological network perturbations that are associated with tobacco-related disease causation.

The significance of these reductions in exposure were confirmed in a switching study conducted in an animal models of disease ($Apoe^{-/-}$ mouse) which confirmed that animals, switched from cigarette smoke exposure to either THS aerosol or ambient air, show similar reductions in disease progression and similar reductions in perturbations of disease-related biological networks.

Similarly, human smokers who were switched to either THS or smoking abstinence show similar patterns of reduction in biomarkers of HPHC exposure and improvements in clinical risk endpoints, suggesting that the 90% reduction in HPHC exposure results in similar clinical findings to those seen with 100% reduction in exposure. It is well understood that long-term epidemiology is necessary for a full determination on the overall impact of switching to THS. Nevertheless, the significant reductions in HPHC exposure and the improvement in clinical risk endpoints observed in smokers who switch to THS compare favorably to the reduced HPHC exposure and improvements in clinical risk endpoints observed in smoking abstinence.

The findings from the clinical studies, when combined with the totality of the laboratory-based evidence demonstrates that switching to THS will result in a significant reduction in HPHC exposure, harm and risk of tobacco-related disease for the individual tobacco users. This evidence is sufficient to meet the requirements of either a Risk Modification Order (Section 911(g)(1)) or an Exposure Modification Order (Section 911(g)(2) with regards to a benefit to individual users of tobacco products.

Part B of the two-part "basis for approval" for a Risk Modification Order or an Exposure Modification Order is that the MRTP must benefit the population as a whole, which is determined, in large part, by the impact of the MRTP on tobacco initiation and cessation. The THS product and its intended modified risk claims and messages have been extensively tested across relevant populations including current adult smokers who do not intend to quit smoking, current Adult Never Smokers who intend to quit smoking, Adult Former Smokers, Adult Never Smokers and young Adult Never Smokers who are between the minimum legal age of smoking and 25 years of age.

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Among Adult Smokers, THS and the associated claims generated interest in trial and use. The behavioral intentions for trial and use among Adult Smokers were subsequently confirmed by observing patterns of use among Adult Smokers who participated in clinical studies, an Actual Use Study in US and in Whole Offer Tests conducted in non-US markets (Japan, Italy, Germany, Switzerland, and South Korea). Across all studies, a substantial proportion of Adult Smokers were able to convert completely to THS use. The fact that a substantial proportion of Adult Smokers used THS exclusively or predominantly is an outcome that is completely aligned with providing a net benefit to public health.

Adult Smokers with an intention to quit showed an Intent to Use only slightly lower than the adult smokers with no intention to quit, after being exposed to the THS communication materials. However, this did not appreciably change their stated intention to quit smoking and all tobacco, providing sufficient evidence that THS would not alter the intentions of the vast majority of smokers who had expressed an intention to quit smoking. This finding is consistent with benefitting the public health by not interrupting the intentions of smokers who intend to quit smoking.

The impact on initiation was examined through studies on Adult Former Smokers and Adult Never Smokers who received information about the THS product and the reduced risk/exposure claims. Adult non-users did not seem interested in trial and use of THS after being exposed to the THS communication materials that included the reduced risk/exposure claims. There was a small level of expressed interest in trial and use by Adult Former Smokers, but these expressions of interest were in the single digits with the vast majority of former smokers indicating lack of interest in product trial and use. Importantly, these findings extended to young Adult Never Smokers (LA-25) who expressed very low levels (≤1%) of positive Intention to Try and Intention to Use.

Overall, the PMI Perception and Behavior Assessment program demonstrated that the THS product would benefit the population as a whole. A substantial proportion of Adult Smokers with no intention to quit were attracted to the product and were able to use the product exclusively or in a combined use pattern which significantly lowered the use of their normal cigarette. The PBA program has also demonstrated that THS will not adversely impact the overall opportunity for harm reduction in the population by reversing the decision of smokers who intend to quit smoking OR by attracting adult nonsmoker who might be influenced to begin the use of tobacco products. Finally, the PHIM model predicts that the introduction of THS into the commercial market will reduce the overall morbidity and mortality from tobacco products. Therefore, the second basis for approval, which is an overall benefit to the population as a whole, is met.

The strength of the PMI scientific assessment program resides in the totality of the scientific evidence. First, the scientific studies produced results that are coherent in terms of biological relevance and plausibility. Second, the results are consistent across numerous non-clinical, clinical and perception/behavioral studies. All of these studies showed coherent findings of reduced biological impact of THS aerosol compared with cigarette smoke and show that the appropriate consumer groups are able to respond to the product concept and LLM in a manner that is consistent with public health objectives. In summary, the totality of the scientific evidence generated for this application convincingly demonstrates that the THS

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product meets the two-part "basis" for approval" under Section 911(g)(1) of the FD&C Act and that FDA should authorize a Risk Modification Order. Furthermore, the scientific data indicates that PMI has demonstrated that an Exposure Reduction Order would also be appropriate, under Section 911(g)(2), following further discussions with FDA on the final wording of the label, labeling and marketing material.

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