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Tobacco Heating System (IQOS)

Briefing Document

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Prepared by Philip Morris Products S.A. for the January 24-25, 2018
Tobacco Products Scientific Advisory Committee Meeting

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EXECUTIVE SUMMARY

Philip Morris International (PMI)[1] submitted modified risk tobacco product applications (MRTPAs) to the U.S. Food and Drug Administration (FDA) in December 2016 under Section 911(g) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), requesting marketing orders for IQOS[2] with three different variants of *Marlboro HeatSticks*, one regular and two menthol.[3] This briefing document presents a summary of the data and information included in the MRTPA that provides the necessary evidence to support a marketing order for a Modified Risk Tobacco Product (MRTP) with the following claims:

- Claim #1: "Switching completely from cigarettes to the IQOS system can reduce the risks of tobacco-related diseases."
- Claim #2: "Switching completely to IQOS presents less risk of harm than continuing to smoke cigarettes."
- Claim #3: "Switching completely from cigarettes to the IQOS system significantly reduces your body's exposure to harmful and potentially harmful chemicals."[4]

Although smoking prevalence in the United States has declined from 21% to 17% over the last decade, an estimated 40 million people in the U.S. continue to smoke cigarettes (CDC 2015). Cigarette smoking is the leading cause of preventable disease in the U.S., 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 a need for additional methods to reduce harm and tobacco-related disease for the 40 million American smokers who continue to smoke (IOM 2012).

Based on the principle that it is "the inhalation of the complex chemical mixture of combustion compounds in tobacco smoke that causes adverse health outcomes" (HHS 2010), PMI developed IQOS. IQOS 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 adult smokers find acceptable.

IQOS was subject to the comprehensive assessment program described below. The findings from the scientific studies demonstrate that the IQOS aerosol has much lower

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[1] We refer to Philip Morris International ("PMI") throughout this application. The following entities are included within "PMI": (1) Philip Morris International Inc., the parent entity; (2) Philip Morris Products S.A., the MRTP applicant, responsible for nonclinical, clinical trials and post marketing studies and surveillance, (3) Philip Morris International Management S.A., responsible for market research and management services, (4) Philip Morris International Research Laboratories Pte. Ltd., responsible for nonclinical *in vivo* studies, and (5) Philip Morris Manufacturing & Technology Bologna S.p.A., responsible for the manufacture of *HeatSticks*.

[2] For simplicity, we use IQOS in this document to refer to the IQOS system, consisting of the tobacco sticks, holder and charger. IQOS is in places also referred to as the Tobacco Heating System, or THS.

[3] PMI has filed an MRTPA for each variant. Throughout this document we will refer to an MRPTA, but the available data support all three MRTPAs.

[4] PMI has submitted a reduced exposure claim and included it in the MRTPA. However, PMI believes that the totality of the evidence submitted in the MRTPA supports a marketing order under section 911 (g)(1) of the FCDA and, as such, the focus of this briefing document is on the showings required by section 911(g)(1). The reduced exposure claim accurately communicates the relationship between reduced exposure to harmful toxicants/carcinogens and the reduced risk of harm and tobacco-related disease and is appropriate under a risk modification order from FDA.

levels of toxicants compared with cigarette smoke. As a result, a smoker who switches from cigarettes to IQOS will be exposed to significantly lower levels of toxicants, leading to a significant reduction in harm and the risk of tobacco-related diseases. While IQOS is not risk-free and contains nicotine, which is addictive, our data show that it is a much better choice than continuing to smoke.

The 2009 Family Smoking Prevention and Tobacco Control Act ("Tobacco Control Act") gives FDA the mandate to verify whether products that claim to reduce harm and the risk of tobacco-related disease actually do and, if so, permit those products to be marketed with accurate statements to adult smokers. Among the purposes of the Tobacco Control Act is to provide FDA with "new and flexible enforcement authority to ensure that there is effective oversight of the tobacco industry's efforts to develop, introduce, and promote less harmful tobacco products."[5]

In particular, section 911(g)(1) of the FD&C Act provides FDA authority to issue a modified-risk marketing order for a tobacco product if the agency determines that the applicant has demonstrated 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.

Determining whether this standard is met is a decision particularly within the expertise of the FDA; as Congress found in connection with its passage of the Tobacco Control Act, "[i]n connection with its mandate to promote health and reduce the risk of harm, the Food and Drug Administration routinely makes decisions about whether and how products may be marketed in the United States."[6]

PMI conducted extensive research consisting of 17 nonclinical, nine clinical, and nine perception and behavior studies, as well as a population health impact model, to assess the health effects of IQOS to the individual user and the likely impact of IQOS on the health of the population as a whole. The totality of the evidence provided in the MRTPA establishes that IQOS meets the requirements for a modified-risk tobacco product marketing order under Section 911(g) of the FD&C Act.

Part A: IQOS Significantly Reduces Harm and the Risk of Tobacco-Related Disease to Individual Tobacco Users.

Smoking-related harm and disease are directly caused by long-term exposure to the toxicants found in combusted tobacco smoke (HHS 2010). Consequently, smoking cessation is the most effective way to reduce harm and the risk of tobacco-related disease. This is because cessation eliminates the exposure to the harmful and potentially harmful constituents (HPHCs) contained in the smoke. The closer the effects of switching to an MRTP are to smoking cessation in terms of reduced exposure to HPHCs and reduced toxicity, the higher the reduced-harm and risk reduction potential of the MRTP.

[5] Family Smoking Prevention and Tobacco Control Act, 21 U.S.C. § 387.3(4) (2009).
[6] Family Smoking Prevention and Tobacco Control Act, 21 U.S.C. § 387.2(44) (2009).

To satisfy Part A of the statute, PMI designed a multi-step assessment program for IQOS that includes and shows the following:

- The chemical analysis of the aerosol generated by IQOS, which confirmed that IQOS aerosol contains substantially reduced levels of HPHCs (on average, >90% reduction in the levels of HPHCs compared with 3R4F[7] cigarette smoke).
- Six *in vitro* and two *in vivo* studies using standard methods in toxicology, conducted to compare the effects of IQOS aerosol with those of cigarette smoke. These studies showed a consistent and substantial reduction in cytotoxicity, genotoxicity, inflammation, respiratory organ toxicity and systemic toxicity of IQOS aerosol compared with cigarette smoke.

  Furthermore, lung inflammation, emphysema, and lung function measurements assessed in a chronic toxicity study in A/J mice showed significantly lower effects in IQOS aerosol-exposed mice than in smoke-exposed animals. The pulmonary outcomes in IQOS aerosol exposed mice were not different from those obtained in air exposed animals.
- Advanced nonclinical systems toxicology studies that enabled the detailed comparison of the effects of cigarette smoke and IQOS aerosol on biological mechanisms related to the causation of smoking-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).

The systems toxicology assessment included:

i. Seven *in vitro* studies, covering a variety of human-derived systems, conducted to compare the impact of IQOS aerosol with that of cigarette smoke on vascular inflammation, endothelial dysfunction and airway epithelium toxicity. These studies showed that IQOS aerosol exposure leads to significantly and consistently reduced perturbations of all biological mechanisms affected by cigarette smoke exposure, such as oxidative stress, inflammation, response to DNA damage, xenobiotic metabolism and apoptosis.

ii. One systems toxicology study, 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 IQOS aerosol exposure showed significant and consistent reductions of molecular changes, mechanistic perturbations and significant improvement in 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 IQOS aerosol exposure approached those measured in

[7]3R4F refers to the reference cigarette developed by the University of Kentucky that serves as an international standard for research purposes and was approved by representatives of commercial manufacturers, the University of Kentucky College of Agriculture, and the Kentucky Tobacco Research & Development Center.

animals in the smoking cessation group (animals switched from cigarette smoke to fresh air exposure).

- Clinical studies conducted with adult smokers to evaluate the effects of switching from cigarette smoking to IQOS use. In these four studies, conducted in the U.S., Europe and Japan, volunteer adult smokers were randomized to either continue smoking their usual cigarettes, completely switch to IQOS use, or switch to 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 IQOS showed a reduction in 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 IQOS 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 IQOS leads to a reduced exposure in adult smokers, which in turn leads to an improvement of clinical risk markers.

Across all nonclinical studies, whether conducted *in vitro* or *in vivo,* the results were consistent and showed that IQOS aerosol exposure causes significantly less toxicity and overall adverse biological effects than exposure to cigarette smoke. These studies also confirmed that IQOS 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 IQOS aerosol was directionally aligned with, and of similar magnitude to, smoking cessation.

All study results are consistent with those found in the published literature, i.e. for published studies on the plausible mechanisms of disease causation, including oxidative stress, inflammation, DNA damage response, xenobiotic metabolism and apoptosis as well as results reported in clinical and epidemiological studies on smoking cessation. 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.

In summary, the evidence demonstrates that IQOS emits significantly lower levels of HPHCs than cigarettes and that the IQOS aerosol has significantly reduced toxicity compared to cigarette smoke. In all studies, switching to IQOS led to a significant reduction in exposure to HPHCs compared to continued smoking. The evidence shows that this reduction in exposure results in a significant reduction in biological effects and harm. Further, in all experimental studies, the effects of switching to IQOS were similar in direction and magnitude to those of smoking cessation, which the IOM referred to as the "gold standard" (IOM 2012) for reducing the risk of harm and tobacco-related disease. The totality of the evidence generated from the PMI assessment program shows that IQOS satisfies Part A of the statutory standard for a MRTP.

Part B: Introducing IQOS Will Benefit the Health of the Population as a Whole.

In addition to significantly reducing harm and the risk of tobacco-related disease to individual tobacco users, IQOS 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.

PMI developed a Perception and Behavior Assessment (PBA) program, conducted in the U.S., consisting of nine studies.

1. PMI developed and tested three scientifically accurate communications (proposed claims with associated warnings). Two communications were developed to convey that IQOS, while not risk free, is a lower risk alternative for smokers.[8] The assessment of these two reduced-risk communications demonstrated that over two thirds of the consumers understood correctly that using IQOS is not risk free but presents less risk than cigarettes and only 1-2% misunderstood that IQOS presents no risk of harm. The assessment of this communication showed that approximately two thirds of the consumers were able to comprehend that using IQOS would reduce their exposure to HPHCs. Consistently, findings from the risk perception studies demonstrated that the perceived risk associated with IQOS is lower than cigarettes, the most hazardous tobacco product, and higher than nicotine replacement therapies (NRTs) and cessation.
2. A series of PBA studies assessed the likelihood of initiation among non-users of tobacco products. Overall, these studies demonstrated that IQOS is not attractive to adult never smokers and is only minimally attractive to adult former smokers. Between 0% and 1.1% of never smokers and 1.0% and 6.4% of adult former smokers expressed an intention to use IQOS.
3. The same PBA studies also showed that the IQOS communication will not increase the likelihood that persons who would otherwise stop using cigarettes will instead switch to IQOS. Instead, the studies showed that the communications did not appear to reverse the stated intention to quit smoking and all tobacco use among adult smokers who had previously expressed an intention to quit smoking. Additionally, these smokers understood that IQOS is not a substitute for cessation.
4. A combination of clinical and PBA studies showed that IQOS is an acceptable alternative to cigarettes for adult smokers. While PK/PD studies indicated that the nicotine delivery profile of IQOS is similar to that of cigarettes, the short-term (in confinement) and longer-term (in ambulatory mode) clinical studies showed that IQOS and cigarettes deliver nicotine at comparable levels and that IQOS effectively reduces the urge-to-smoke in a manner similar to cigarettes. These studies also indicated that, after 90 days, IQOS reached 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 six weeks, approximately 15% of the study participants had switched from cigarettes to either exclusive or predominant use of IQOS. Finally, providing IQOS to smokers in human studies did not lead to an increase in their total tobacco product

[8] PMI developed a separate set of warnings to test in parallel with the mandated Surgeon General's warnings for cigarettes. The evidence suggests that some of the language of the customized warnings conveys a more accurate representation of the absolute and relative risks of IQOS compared with cigarettes and aspects of these warnings may be appropriate for FDA to consider as alternative warning messages in the context of a reduced-risk tobacco product. PMI does not believe that both sets should be used on IQOS but FDA should consider which of the warning sets should be used.

consumption, including for those smokers who combined the use of IQOS with their usual cigarettes.

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

FDA has encouraged the use of computational models to estimate the potential changes (positive or negative) in public health caused by the market introduction of an MRTP. To address the effect that marketing of IQOS may have on the health of the U.S. population as a whole, PMI developed and tested a Population Health Impact Model (PHIM) using well-established methods in mathematical modeling and simulation analysis. Using hypothetical scenarios based on product-use transition probabilities, combined with changes in relative disease risk estimates based on the nonclinical and clinical data,[9] PMI conducted multiple simulations to evaluate the impact on smoking attributable deaths of introducing IQOS in the U.S. market. The results of these simulations show that the introduction of IQOS would result in a positive population health impact.

Finally, PMI developed a Post-Market Assessment program that consists of post-market studies as well as passive and active surveillance. This program may be further refined, following discussions with the FDA, and is intended to enable the identification and collection of adverse events that occur in relation to the use of IQOS after an MRTP market order is granted and the product is introduced into the U.S. 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.

Conclusion

The scientific evidence generated for this application demonstrates that IQOS meets the two-part basis for a marketing order under Section 911(g)(1) of the FD&C Act. PMI believes that IQOS represents a significant opportunity to encourage the transition of adult U.S. smokers to less harmful products, thereby reducing over time the overall smoking-related morbidity and mortality in the U.S. population.

[9] i.e., reduction in probability of smoking-related disease when switching from cigarette smoking to IQOS use.

INTRODUCTION

The Context

The FDA has stated that the modified-risk tobacco product provisions under Section 911 of the FD&C Act "may be valuable tools in the effort to promote public health by reducing 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, either the toxicity or addictiveness of tobacco products, or both." In the U.S., an estimated 40 million smokers currently continue to use the most hazardous form of tobacco consumption, the cigarette. Cigarette smoking is the leading cause of preventable disease in the U.S., 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).

Each year, nearly 70% of those smokers express a desire to quit smoking and nearly 40% will attempt to quit that year. Quitting is attempted "cold turkey" or supported by over-the-counter drug products such as nicotine-delivery technologies (patches, gums) or prescription drug products (e.g., varenicline, bupropion). Despite the high rate of quit attempts, the overall rate of successful cessation is quite low, around 6% over the subsequent 12 months for most smokers (Rigotti 2012). Recognizing that the majority of the current smokers will not quit smoking, there is an ongoing need to explore alternative methods to reduce harm for those tens of millions of American smokers, their families, and society as a whole.

Many smokers have also tried newer forms of nicotine delivery, such as electronic cigarettes (e-cigarettes). These products have resulted in many smokers switching completely from cigarettes to presumably lower risk nicotine delivery products. A recent study published in the British Medical Journal concluded that smokers who used e-cigarettes were more likely to attempt to quit smoking and more likely to succeed in quitting (Zhu 2017). Overall, the authors concluded that the increase in e-cigarettes use among U.S. adult smokers was associated with a statistically significant increase in smoking cessation rate at the population level. However, e-cigarettes have not proven universally popular with adult smokers and are rejected by most adult smokers who try them, as they lack the fundamental sensory attributes such as the flavor of tobacco, sufficient nicotine delivery, and the familiar feel of the tobacco stick.

The Description of the Product

PMI has developed a lower risk alternative to the cigarette, the Tobacco Heating System, to be marketed as "IQOS". In contrast to e-cigarettes that aerosolize a nicotine-containing liquid (e-liquid), IQOS heats a specially-designed tobacco stick, delivers an aerosol with similar nicotine delivery characteristics to a cigarette, and has flavors and aromas that are more familiar to smokers. IQOS consists of a device that heats, but does not burn, a proprietary tobacco stick ("*HeatSticks*"). IQOS, a patented novel tobacco product described more fully in Section 3.1 of the MRTPA,[10] consists of three main components (Figure 1A):

[10] References to specific sections of the IQOS MRTPA.

1. The Tobacco Stick, a novel tobacco product containing uniquely processed tobacco made from tobacco powder. It is specifically designed to function with the holder to produce an aerosol. To satisfy different consumer preferences, PMI is applying for risk modification orders for IQOS with three different variants of *Marlboro HeatSticks*, one regular and two menthol (with 1.25 mg and 2.5 mg menthol per stick).[11]
2. The Holder, into which the tobacco stick is inserted, which heats the tobacco material by means of an electronically-controlled heating blade (Figure 1B).
3. The Charger used to recharge the holder after each use. The charger stores sufficient energy for the use of approximately 20 tobacco sticks and can be recharged from household power.

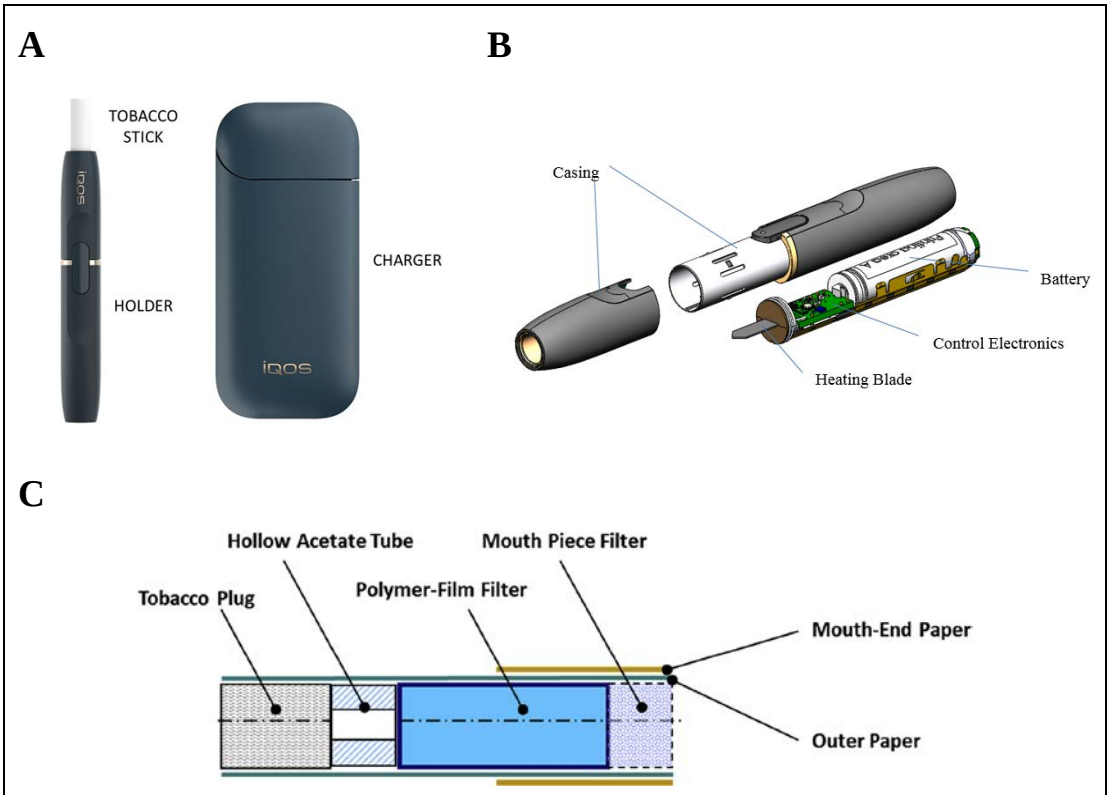


Figure 1: **IQOS components (A), a schematic exploded view drawing of the Holder (B), and a schematic cross-sectional view of the Tobacco Stick (C)**

The tobacco stick differs from a cigarette in significant ways. Unlike a cigarette that contains tobacco cut-filler (tobacco leaf cut in small pieces found in cigarettes), the tobacco stick contains specially processed tobacco that has been reconstituted into sheets (termed cast-leaf) following the addition of water, glycerin, guar gum (hemi-cellulose), and cellulose fibers. The tobacco stick (Figure 1C) contains much smaller amounts of tobacco compared with a cigarette (~320 mg compared to 550-700 mg). Unlike a cigarette, the

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

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 this aspect of a cigarette. A hollow acetate tube separates the tobacco plug and the polymer-film filter.

To operate IQOS, the user inserts a tobacco stick into the holder and turns on the device by means of a switch. This action initiates the heating of the tobacco via the heating blade inserted into the tobacco plug. The electronically controlled heating, combined with the uniquely processed tobacco, prevents combustion from occurring (Section 2.7.6 pp 40-42 of the MRTPA). The holder supplies heat to the tobacco stick through the heating blade for a period of approximately six minutes and allows up to 14 puffs to be taken during that time. The temperature of the heating blade is carefully controlled (Section 3.1 of the MRTPA) and the energy supply to the blade is cut if its operating temperature exceeds 350° C. The temperature measured in the tobacco never gets to this temperature and in fact, most of the tobacco remains below 250° C as shown in Figure 2 below and in (Section 3.2.1 of the MRTPA).

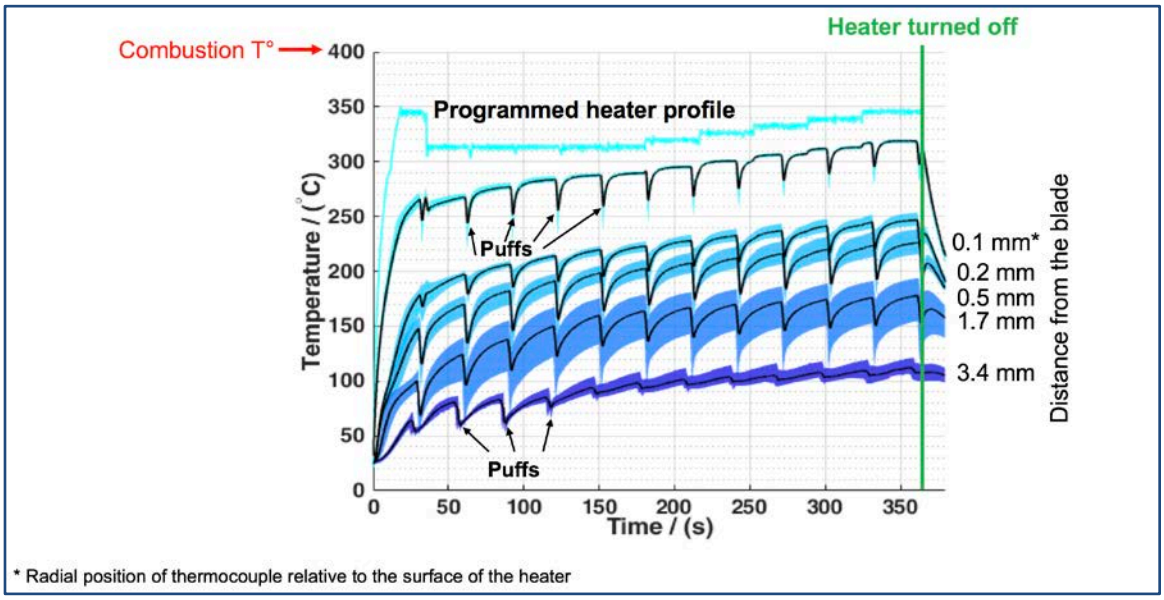


Figure 2: IQOS Temperature Profile

The tight temperature control of the heating blade, combined with its limitations in operating time and puff number, ensure that IQOS generates a consistent aerosol across a broad range of conditions of use (including extreme ones), resulting in a consistent reduction in HPHC formation.

As IQOS has been designed to heat tobacco below the level of combustion, IQOS produces an aerosol that has a very different composition than cigarette smoke. The IQOS aerosol contains significantly reduced levels of HPHCs compared with cigarette smoke and is composed mainly of water, glycerin and nicotine. As shown in Figure 3, cigarette smoke has a brown color when captured on a laboratory filter pad, which contrast with the aerosol generated by IQOS.

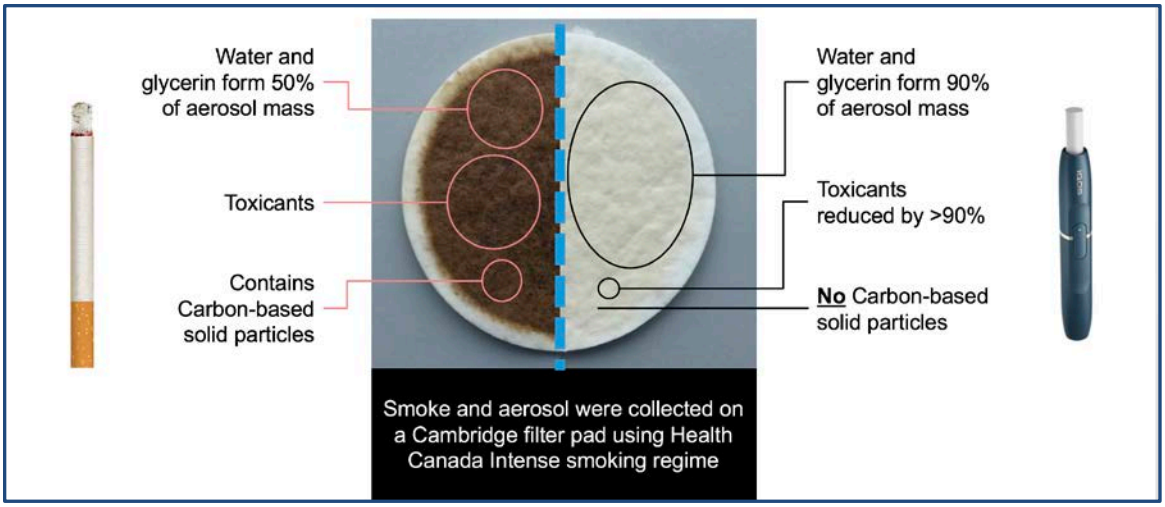


Figure 3: Differences Between IQOS Aerosol and Cigarette Smoke

This "heat-not-burn" concept is not new, and has been extensively researched by the industry and PMI for many years. However, recent advances in battery technology and miniaturization of electronics have now made it possible to develop a heating device that works reliably, controls the heating of the tobacco to yield a consistent aerosol, and is at the same time acceptable to adult smokers.

The Statutory Requirements for a Risk Modification Order

Section 911(g) of the FD&C Act provides a pathway for the marketing of lower risk tobacco products. Successful MRTP applications (MRTPA) will allow companies to communicate modified-risk claims that will inform consumers in a manner that is complete, accurate, and relates to the overall disease risk of the product. Two conditions must be met for FDA to allow a modified-risk tobacco product to carry modified-risk claims; in particular that the product, as actually used by consumers, will:

- Part A: significantly reduce harm and the risk of tobacco-related disease to individual tobacco users; and
- Part B: benefit the population as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products.

The PMI MRTP assessment program was developed to demonstrate that IQOS meets both conditions for a modified-risk tobacco product marketing order. PMI conducted numerous scientific studies across a wide range of biological systems (e.g. molecular, cellular, animal and human studies) to demonstrate that the IQOS aerosol is significantly less hazardous than cigarette smoke and that smokers who switch to IQOS will significantly reduce their risk of harm and of tobacco-related disease. PMI also conducted premarket perception and behavior (PBA) studies to assess the likelihood that users and nonusers would adopt the product, whether the modified-risk claims were understood, and whether consumers understood that IQOS, although reduced risk compared to cigarettes, was not risk free and is addictive. Overall, the totality of the evidence demonstrates that IQOS will significantly reduce harm and the risk of tobacco-related disease for smokers who switch from cigarettes to IQOS, and have a positive net benefit to the public health taking into account the factors listed in Section 911(g)(4) of the FD&C Act.

As TPSAC and FDA consider these factors, PMI believes that two central considerations should drive the decision to issue the risk modification order. First, the evidence and data submitted in this MRTPA demonstrate that a significant proportion of adult smokers will find IQOS to be a suitable alternative to their cigarettes, and switching to IQOS will significantly reduce their risk of harm compared to continued smoking. Second, although there may be some unintended use by non-smokers and use by smokers who may have otherwise quit tobacco, the available data discussed below and provided in the MRTPA indicate that these numbers are likely to be small. Overall, the key question is whether the likely benefit to the public health, through the switching of smokers to a less harmful product, is greater than the likely adverse effect on the health of the population through the initiation of nonsmokers or the interruption of smoking cessation. It is this important overall probability of population benefit that should form the basis for discussion and approval of IQOS as a modified-risk tobacco product.

The Submitted Claims

Consistent with the statutory intent of the Tobacco Control Act, the claims and product messages submitted in the MRTPA were developed based on the totality of the data from its clinical and nonclinical assessment programs to ensure that statements about IQOS are complete, accurate, and relate to the overall disease risk of the product.[12] PMI developed and tested the claims to ensure that consumers receive and understand accurate information about the relative risk of IQOS compared with cigarette smoke and the intrinsic risk of IQOS.

Each claim (underlined below) was tested along with (a) other clarifying information that will appear on the label and labeling material; (b) the mandated Federal Cigarette Labeling and Advertising Act (FCLAA) cigarette warnings;[13] and (c) PMI Important Warnings.[14] PMI is not asking FDA to substitute the mandated warnings with the PMI Important Warning at this time but believes that FDA has the discretion to determine which warnings will be most appropriate to inform the consumer and drive a successful switching outcome from cigarettes to IQOS.

Claim #1 – "Reduced Risk of Tobacco-Related Diseases"

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

[12] Family Smoking Prevention and Tobacco Control Act, 2009: Sec.2. Findings (40)

[13] The mandated cigarette warning labels are:

- 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.

[14] PMI Important Warnings were developed to clarify important aspects of absolute and relative risk compared with cigarettes. PMI believes that it is within FDA's discretion to determine whether the PMI warnings should be used in lieu of the mandated FCLAA warnings since they may result in more accurate consumer understanding and use of THS as a modified-risk tobacco product.

The **PMI Important Warning** associated with this claim was the following:

- 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 – "Reduced Harm"

- Switching completely to IQOS presents less risk of harm than continuing to smoke cigarettes.

The **PMI Important Warning** associated with Claim #2 was the following:

- 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.

Claim #3 – "Reduced Exposure"

- The IQOS system heats tobacco but does not burn it. (Clarifying information)
- This significantly reduces the production of harmful and potentially harmful chemicals. (Clarifying information)
- 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.

The **PMI Important Warning** associated with Claim #3 is the following:

- 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.

PART A: IQOS SIGNIFICANTLY REDUCES HARM AND THE RISK OF TOBACCO-RELATED DISEASE TO INDIVIDUAL TOBACCO USERS.

PMI's MRTP Assessment Program was developed to demonstrate that IQOS will meet the statutory standards for a marketing order for an MRTP. Towards this end, PMI conducted many scientific studies across a wide range of biological systems (cellular, organotypic tissue cultures, animal models and human studies) to demonstrate that IQOS aerosol is significantly less hazardous than cigarette smoke and that smokers who switch to IQOS will significantly reduce their exposure to HPHCs and thereby reduce their risk of harm and tobacco-related disease. As outlined below in the discussion of Part B of the statute, PMI also conducted premarket Perception and Behavior Assessment (PBA) studies to assess the likelihood that users and nonusers would adopt the product, whether the modified-risk claims were understood, and whether consumers understood that IQOS, although reduced risk compared to cigarettes, is not risk free and is addictive.

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 4) (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 can be quantified on each of these causally-linked events using methods such as analytical chemistry, toxicity, advanced –omics technologies (e.g., transcriptomics, proteomics, and metabolomics), cytology, histopathology, physiological measurement and, eventually, in a long-term post-market setting, through epidemiology.

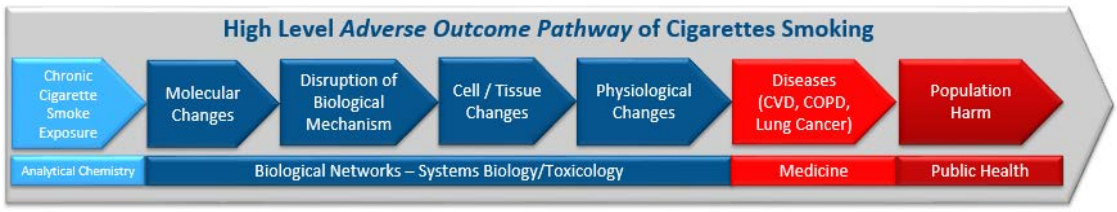


Figure 4: High Level Adverse Outcome Pathway (AOP) of Cigarette Smoking

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

Smoking Cessation – the Gold Standard for Risk Reduction

The harm and risk of smoking-related disease is caused by the exposure to HPHCs emitted by cigarettes. Epidemiological studies have provided overwhelming evidence that the risk of smoking-related disease rises in a dose and time dependent manner with continued exposure to HPHCs, as illustrated conceptually by the red line in Figure 5.

Epidemiological studies have also provided overwhelming evidence that harm and the risk of tobacco-related disease can be dramatically reduced by smoking cessation (green line in Figure 5). Smoking cessation eliminates the first step in the AOP (exposure to HPHCs)

and thereby effectively removes the chronic stimulus leading to disease development and progression. This allows for a normalization of all molecular, cellular, and tissue functions over time. Therefore, smoking cessation is the best way for a smoker to reduce the risk of harm and smoking-related disease; as the IOM has noted, it is the "gold standard", or highest potential, for risk reduction (IOM 2012).

A significant reduction in harm and disease risk should be achieved by products that significantly reduce or eliminate exposure to HPHCs (yellow lines in Figure 5). Furthermore, the closer the biological effects of a product are to cessation, the higher its potential to reduce harm and risk of tobacco-related disease.

A hypothetical MRTP that is completely devoid of HPHCs and nicotine should, if substituted for smoking, reduce harm and the risk of tobacco-related disease in the same manner as smoking cessation. PMI designed a research framework to compare a 100% reduction in exposure (cessation) and a 90% reduction in exposure (IQOS) in terms of toxicity, exposure and biological impact on cellular and mammalian systems. In the case of IQOS, the same logic as the hypothetical example applies. Disease is caused by exposure. Significant reductions in exposure should lead to significantly reduced toxicity, allowing the demonstration of reduced toxicity and adverse biological impact across multiple biological models and systems.

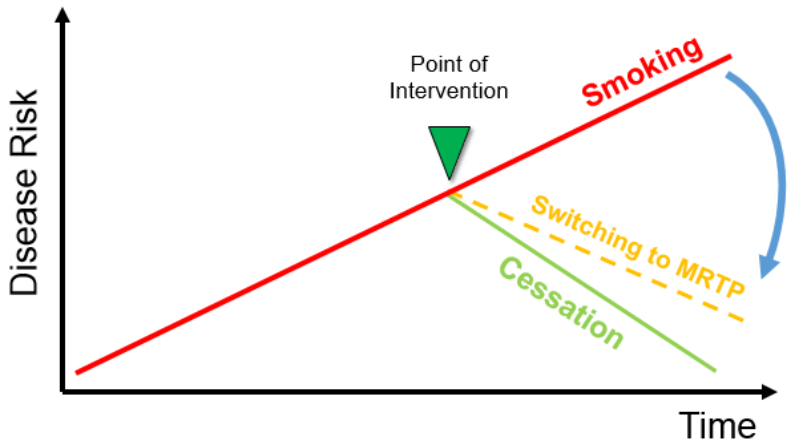


Figure 5: Risk framework for MRTP assessment

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. 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

Linking Reduced Formation of HPHCs to Reduced Risk of Harm and Disease

While a large reduction in a small number of HPHCs or a small reduction in a larger number of HPHCs may not be significant in terms of reduction of harm and risk of disease, an average reduction of 90% or more in the levels of HPHCs may lead to a significant reduction in risk, perhaps approaching that seen with a complete, or 100%, reduction in

exposure. The underlying mechanism by which cessation produces a significant reduction in risk is the withdrawal of the adverse impact caused by the HPHCs on critical biological mechanisms of disease causation such as Inflammation, Cell Stress (incl. oxidative stress and xenobiotic metabolism), Cell Proliferation, Cell Fate (incl. senescence and apoptosis) and Tissue Repair and Angiogenesis. Once exposure to HPHCs is removed, the body has restorative/reparative mechanisms that often, over time, returns normal function to cells, tissue and organ systems. Therefore, the two questions of interest are:

1. whether an average 90% reduction in exposure to HPHCs leads to a significant reduction of the effects caused by cigarette smoke, and
2. whether these reductions in biological effect approach those of smoking cessation.

Tobacco smoke is toxic and has profound effects on biological systems. These adverse effects can be quantified using a wide range of analytical technologies applied to biological models and clinical studies. For example, cigarette smoke is cytotoxic and mutagenic in cell-based *in vitro* assays. Cigarette smoke activates a broad range of molecular pathways related to disease causation and its toxicity can be quantified in animal exposure studies. In human studies, there are established biomarkers of exposure (BoExp) and clinical risk markers that are affected by cigarette smoking. When smokers quit smoking, these changes can be seen to reverse over time. It is therefore possible to build a picture of the biological effects of cigarette smoke and smoking abstinence.

The same approach can be used to evaluate the impact of IQOS aerosol compared with the effects of cigarette smoke in standard *in vivo* and *in vitro* models of toxicity. It is also possible to use experimental animal models of disease to demonstrate how smoking accelerates disease, how smoking cessation slows disease progression and how switching to IQOS impacts disease progression in comparison to both continued smoking and cessation.

The following sections will examine each of four layers of evidence to link reduced formation and emission of HPHCs to reduced harm and risk of smoking-related disease.

As explained below, these evidentiary layers establish that:

- IQOS aerosol contains significantly lower levels of HPHCs than cigarette smoke
- IQOS aerosol does not contain the ultra-fine solid carbon-based particles found in cigarette smoke
- IQOS aerosol is significantly less toxic than cigarette smoke
- IQOS aerosol significantly reduces harm and the risk of disease compared with cigarette smoke in laboratory models
- There are significant reductions in exposure to HPHCs in human studies that approach those of smoking abstinence; and
- There are favorable changes in clinical risk markers directionally similar to smoking abstinence.

IQOS *aerosol contains significantly lower levels of HPHCs than cigarette smoke*

The IQOS aerosol was analyzed to characterize its HPHC profile compared with that of cigarette smoke (Section 6.1.1, Chapter 2.7 pp 34-45 of the MRTPA) (Schaller 2016a). This comparison was based on 58 analytes that fulfilled the following criteria:

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

Altogether, PMI quantified 58 analytes, which included 54 HPHCs, water, nicotine, Total Particulate Matter (TPM), and Nicotine Free Dry Particulate Matter (NFDPM).

Table 1 lists the 58 analytes quantified by PMI, along with their health risks by category (e.g. carcinogenic, cardiovascular toxicants, etc.).

Table 1: 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

(table continues)

Analyte/Constituent	Health risk	Analyte/Constituent	Health risk
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.

The quantification of the 58 analytes listed in Table 1 was performed in compliance with published international standards and practices. All aerosols and smoke samples were generated according to international standards, using the Health Canada parameters (Health Canada 2012). The levels of HPHCs found in the aerosols generated with the three IQOS *HeatStick* variants were compared with the levels in the 3R4F reference cigarette smoke. The 3R4F reference cigarette is supplied to all tobacco manufacturers by the University of Kentucky, and is a long-established standard for cigarette smoke chemistry.

First, PMI measured the nicotine content in 3R4F smoke and the IQOS aerosols. While the nicotine content of 3R4F smoke is on average 1.8 mg/stick, the IQOS aerosols contain between 1.2 and 1.3 mg 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 1.25 mg/stick and 2.5 mg/stick respectively. The latter corresponds to the menthol in aerosol of the *HeatSticks* used in the nonclinical and clinical studies reported in this application (later called mTHS).

Third, PMI compared the constituent yields of 3R4F with those of the three *HeatStick* variants to demonstrate that IQOS aerosols contain significantly reduced levels of HPHCs.

On a per-stick basis, the majority of measured constituents was reduced by 90% to 99% (Figure 4). 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 of the MRTPA.

As shown in Table 1, each HPHC is associated with one or more health risks, the majority being known or probable human *carcinogens*. On a per-stick (as well as a per-mg nicotine) basis, these carcinogenic HPHCs were reduced on average by more than 90% in the aerosols of all *HeatStick* variants. Among them, TSNAs are of special interest as they are not generated by combustion but directly transferred from tobacco to smoke in cigarettes or to aerosol in THS. For instance, NNN and NNK are reduced by >95% in all aerosols compared with 3R4F smoke (Schaller 2016b).

The HPHCs classified as *cardiovascular*, *respiratory*, or *reproductive or developmental* toxicants (except nicotine) were reduced by more than 90% in all aerosols on a per-stick

basis. All these classes of toxicants were reduced by over 87% in in all aerosols on a per-mg nicotine basis.

The results of the aerosol characterization are summarized in Figure 6, which shows the relative reductions in each HPHC compared with its level found in tobacco smoke, i.e. 100% (with exception of 6 HPHCs that were below the LOD/LOQ for both IQOS and 3R4F – see the comment box in Figure 4).

PMI has demonstrated that IQOS generates aerosols with significantly reduced levels of HPHCs (Schaller 2016a); the differences between the Regular and the Fresh Menthol *HeatSticks* aerosols are ≤ 6% on a per-stick basis. This was a significant first step towards demonstrating that switching from cigarettes to IQOS reduces harm and the risk of tobacco-related diseases, particularly as many of these 58 analytes and constituents are linked to the most serious health effects of tobacco use.

IQOS *aerosol does not contain ultra-fine particles*

Combustion of tobacco in cigarettes generates solid ultra-fine carbon-based particles (<100 nm in diameter) (Pratte 2017), which have been shown to be cytotoxic (Fariss 2013). Whereas smoke of the reference cigarette 3R4F contains approximately 10^{12} ultra-fine particles per cigarette, IQOS aerosol does not (Pratte 2017, Section 2.7.6 pp 41-42 of the MRTPA). This eliminates the ultra-fine particles-associated toxicity from the IQOS aerosol.

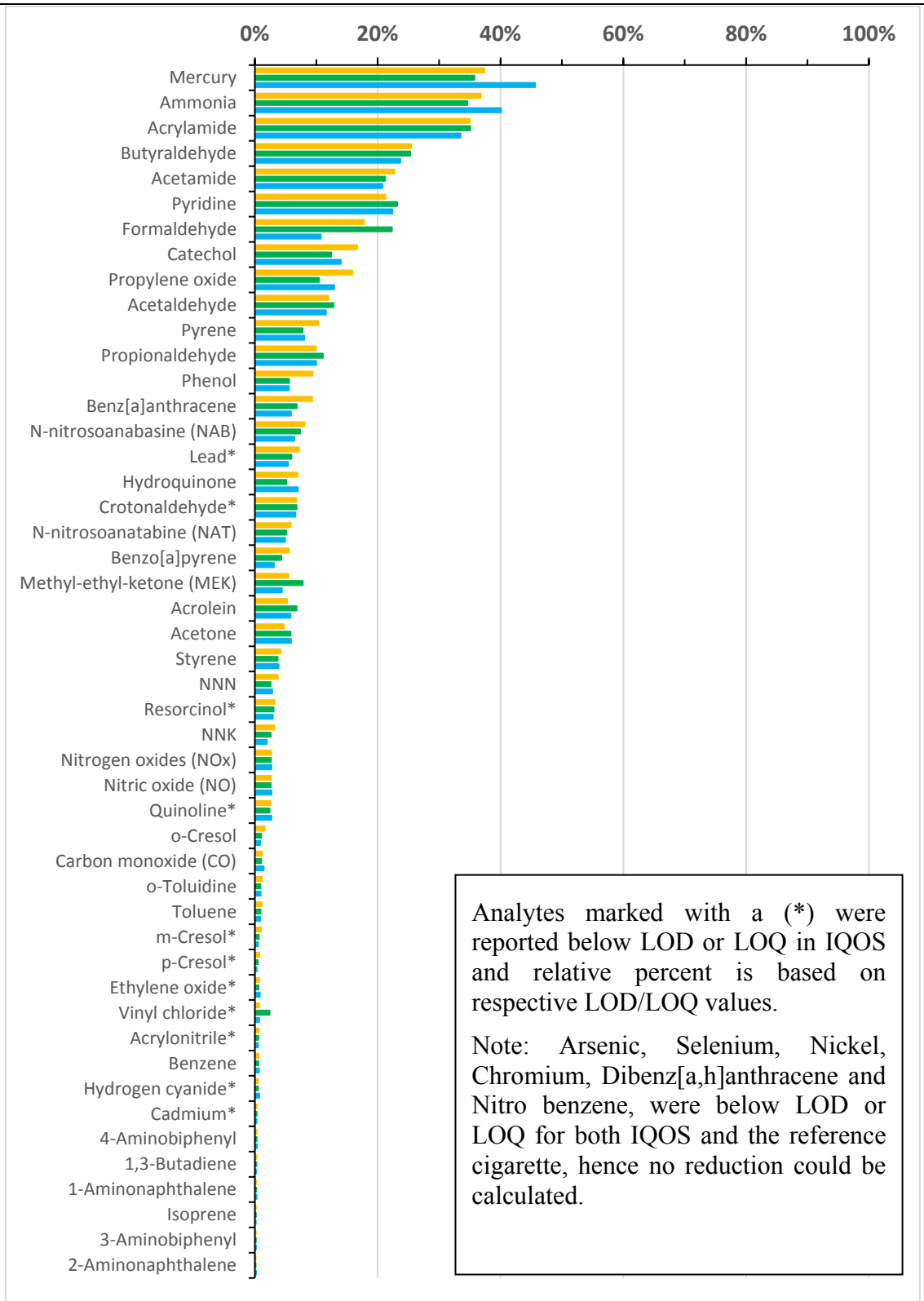


Figure 6: Percent constituent yields in IQOS Regular (yellow), Smooth Menthol (green) and Fresh Menthol (blue) aerosols compared with 3R4F (=100%) smoke on a per tobacco stick basis

IQOS *aerosol is significantly less toxic than cigarette smoke*

PMI conducted a series of *in vitro* and *in vivo* studies, following Good Laboratory Practices (GLP), to determine whether the reduced levels of HPHCs in IQOS aerosol led to a reduced toxicity compared with cigarette smoke.

In Vitro Toxicity of IQOS Aerosol vs. Cigarette Smoke

Six *in vitro* studies, using standard assays of cellular toxicity (Neutral Red Uptake Assay, Section 6.1.2.2.1 of the MRTPA) and mutagenicity (AMES assay - Section 6.1.2.2.2 of the MRTPA, Mouse Lymphoma Assay - Section 6.1.2.2. of the MRTPA), showed that reduction in HPHC levels delivered by the Regular and Fresh Menthol *HeatStick* variants resulted in a similar reduction in toxicity, a prerequisite for reduced risk of harm and smoking-related disease (Detailed summary in Section 2.7.6 pp 45-48 of the MRTPA, Schaller et al 2016a).

In Vivo Toxicity of IQOS Aerosol vs. Cigarette Smoke

Two 90-day rat *in vivo* inhalation studies were conducted according to the OECD Testing Guideline 413 to compare the effects of the Regular *HeatStick* variant (THS) (Wong 2016) and the Fresh Menthol *HeatStick* variant (mTHS) (Oviedo 2016) aerosols with those of cigarette smoke (Section 6.1.2.3.1 of the MRTPA). The objective of these studies was to compare the systemic toxicity and respiratory tract effects of the THS aerosols and cigarette smoke in rats. The data obtained across all endpoints (e.g., in-life observations, clinical pathology, histopathology, and lung inflammation) demonstrate that the THS aerosol is significantly less toxic than 3R4F smoke. THS aerosol exposure, when 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 2015). Similar results have been obtained when exposing rats to mTHS aerosol, showing a lower toxicity than both 3R4F and mentholated reference cigarette smoke (Detailed summary in Section 2.7.6 pp 49-56 of the MRTPA).

Furthermore, a chronic exposure study in A/J mice was conducted following the OECD Test Guideline 453 to assess the combined chronic toxicity and carcinogenicity upon exposure of mice to THS aerosol, compared with 3R4F smoke (Section 6.1.2.3.2 of the MRTPA). While the analysis of the 18 months dissection time point is ongoing, key data about lung inflammation, emphysema and lung function from the interim dissections at months 1, 5 and 10 are part of this application. The results showed that THS aerosol exposed mice had (1) significantly lower lung inflammation than cigarette smoke exposed animals and that (2) lung function and emphysema endpoints were not different from those of air exposed animals (Detailed summary in Section 2.7.6 pp 56-58 of the MRTPA).

THS aerosol reduces harm and the risk of disease compared to cigarette smoke in laboratory models

Smoking-related diseases are caused by chronic exposure to toxicants found in tobacco smoke. Exposure to these toxicants has an adverse impact on the biology of an exposed organism. The causal chain of adverse biological effects (Figure 4) begins with changes at the molecular level that can be quantified using –omics technologies (e.g. proteomics, transcriptomics, lipidomics). These molecular changes affect the normal function of biological mechanisms including Cell Stress (incl. oxidative stress and xenobiotic metabolism), Inflammation, Cell Fate (incl. senescence and apoptosis), Cell Proliferation

and Tissue Repair and Angiogenesis. In fact, the normal function of each of these broad biological mechanisms is affected by hundreds of changes induced by cigarette smoke at the molecular level. These disruptions in biological mechanisms cause quantifiable changes at the cell and tissue level, which in turn lead to quantifiable disease endpoints.

These changes can be followed, over time, and used to compare the effects of THS aerosol exposure with those of cigarette smoke exposure at each step of the Adverse Outcome Pathway depicted in Figure 4. This integrated approach, enabled by advanced computational data analysis, is known as systems toxicology (Hoeng 2012, Sturla 2014, Section 2.7.6 pp 58-60 of the MRTPA).

Using the systems toxicology approach, it was possible to compare the biological effects of THS aerosol exposure with those of cigarette smoke exposure at every step along the causal chain of events linking exposure to disease (Figure 4) across a wide variety of human cell *in vitro* systems (e.g. organotypic tissue cultures of the respiratory tract) and animal models of disease (the Apoe-/- and A/J mouse). In addition, systems toxicology was used to elucidate mechanisms leading to the changes in systemic toxicity and respiratory endpoints in the two 90-day rat inhalation toxicity studies (Section 2.7.6 pp 62-63 of the MRTPA).

Human 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 (Iskandar 2017a). 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 of the MRTPA).

A similar 3-day repeat exposure study conducted with human organotypic gingival epithelium tissue cultures (Zanetti 2017) was performed. This study also showed that exposure to THS aerosol had a lower impact on the pathophysiology of human gingival organotypic cultures than 3R4F smoke (Section 7.5 of the MRTPA).

Similar comparative exposure studies were performed in human organotypic nasal epithelium cultures (Section 6.1.4.4.1.1.4 of the MRTPA, Iskandar 2017b) and bronchial epithelium cultures (Section 6.1.4.4.1.1.5 of the MRTPA, Iskandar 2017c), which measured changes along the causal chain of events linking smoking to disease (Figure 2). Of particular interest was the cilia beating frequency, which 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. Across all endpoints, THS aerosol was shown to have a significantly reduced overall biological

impact on nasal and bronchial cultures than 3R4F smoke at equivalent nicotine concentrations (Iskandar 2017a).

A more detailed summary of the *in vitro* systems toxicology studies conducted in airway cell and organotypic tissue cultures is provided in Section 2.7.6 pp. 60-61 of the MRTPA.

Human 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 of the MRTPA). 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. 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 an 8-month switching study in Apoe$^{-/-}$ mice to compare the impact of switching to THS aerosol with continued exposure to cigarette smoke and to smoking cessation. 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). In this switching study, Apoe$^{-/-}$ mice were exposed to either smoke from the 3R4F reference cigarette, the aerosol from THS or fresh air (Phillips 2016). After two months of exposure to 3R4F smoke, designated animals were switched to THS aerosol exposure (switching group) or to fresh air (cessation group) for up to six months. At designated time points multiple endpoints 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) (Section 2.7.6 pp 62-72 of the MRTPA).

This 8-month study demonstrated that animals switched from cigarette smoke to THS aerosol exposure showed significant and consistent reductions of molecular changes, mechanistic disruptions, cellular and tissue changes as well as 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 from cigarette smoke to fresh air exposure).

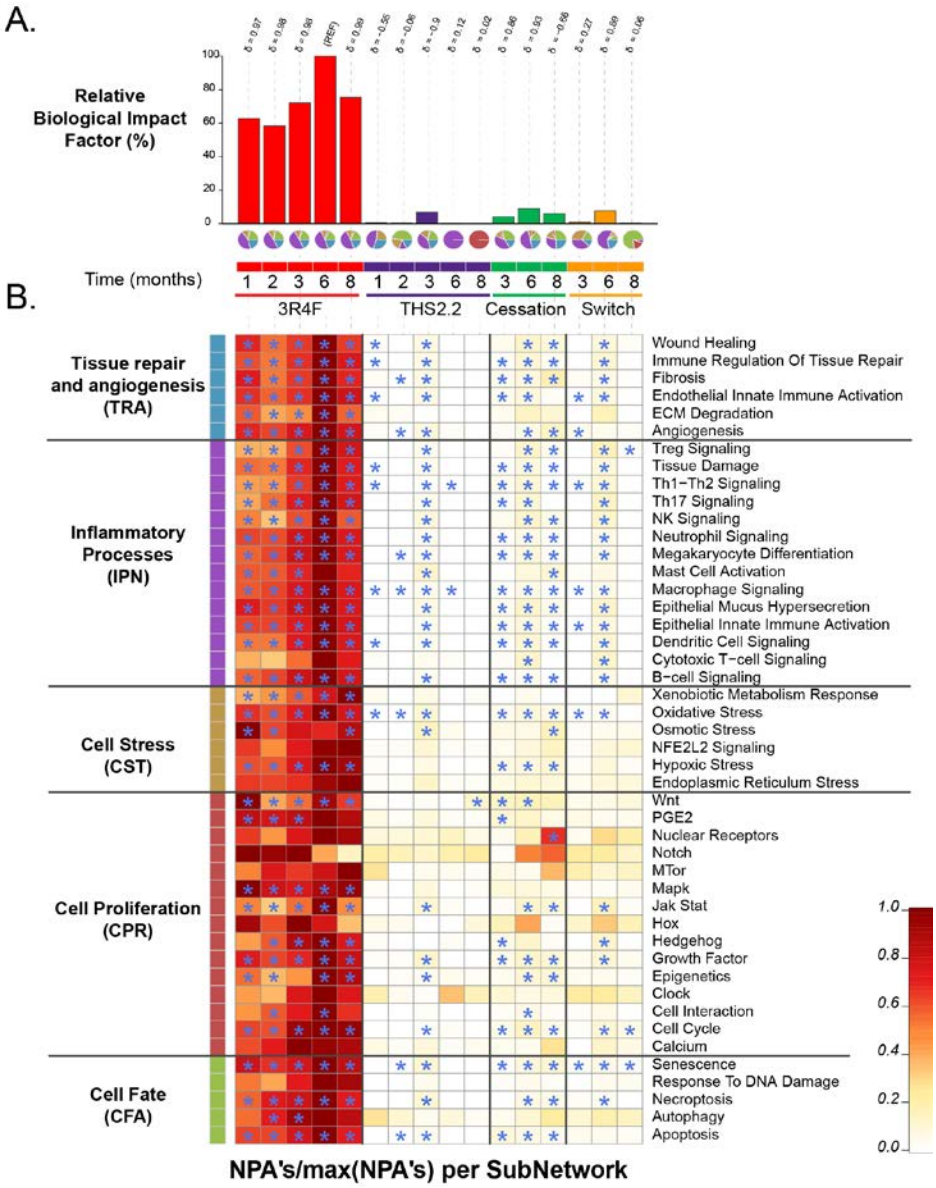


Figure 7: Network-based relative biological impact factor (RBIF) and network perturbation amplitude (NPA) analysis from the lung

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.
Abbr.: THS 2.2 = THS

In addition, the study also showed that the relative biological impact of THS aerosol exposure was not significantly different than exposure to fresh air and was significantly less impactful than cigarette smoke exposure.

Figure 7 illustrates the pulmonary findings of the (a) relative biological impact in various exposure groups and (b) a heatmap representation of the network perturbation amplitudes (mechanistic disruptions) in various exposure groups; the affected biological networks included Inflammation, Cell Stress, Cell Proliferation, Tissue Repair and Angiogenesis, and Cell Fate.

The systems toxicology analysis of the lung showed that cigarette smoke exposure resulted in a significant adverse biological impact across many biological mechanisms and that these perturbations were attenuated similarly in both THS switching and smoking cessation groups. Additionally, exposure to THS aerosol alone did not appear to have a significant biological impact on the biological mechanisms affected by smoke exposure (Section 6.1.4.4.1.2.2.1 of the MRTPA).

The molecular changes and mechanistic disruptions in the different exposure groups correlated directly with the observations of the development of disease symptoms in this animal model. Figure 8 summarizes the effects of various exposure conditions disease endpoints. Animals exposed to 3R4F cigarette smoke showed significant progression of the emphysema score as well as the formation of atherosclerotic plaque (red bars). In contrast, animals exposed to THS aerosol showed very similar findings to animals exposed to fresh air. For those animals who were switched from cigarette smoke exposure after two months to either cessation or THS aerosol, both endpoints showed a similar reduction in disease endpoint progression.

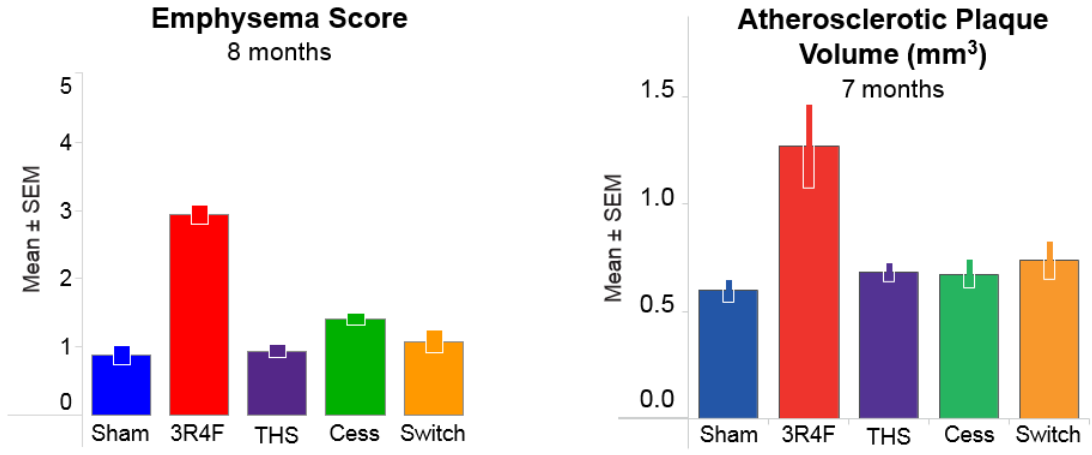


Figure 8: Disease endpoints in the Apoe-/- mouse switching study.

Left panel: lung emphysema score after 8 months of exposure determined by histopathology. Right panel: atherosclerotic plaque volume after 7 months of exposure determined by micro-computed tomography.

Summary of nonclinical research findings

All classical and systems toxicology endpoints, across all nonclinical studies, produced a consistent and 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). Furthermore, the results consistently showed that the biological impact of switching from smoke to THS aerosol exposure approaches that of cessation in both magnitude and directionality. The study results were consistent across biologically plausible and relevant mechanisms of disease causation (Inflammation, Cell Stress, Cell Proliferation, Cell Fate and Tissue Repair and Angiogenesis). Furthermore, the mechanistic findings were remarkably consistent across animal studies conducted *in vivo* and studies conducted with human-derived cells and organotypic tissue cultures *in vitro*. The totality of the nonclinical evidence is therefore consistent with the hypothesis that reduced exposure, as seen with switching from cigarette smoke to THS aerosol, leads to reduced toxicity and a reduced risk of harm and smoking-related disease.

Clinical Exposure Studies

PMI conducted 8 clinical studies listed in Table 2:

- Four Pharmacokinetic/Pharmacodynamics (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.
- Four clinical studies were conducted to determine the reduction in exposure to HPHCs relative to ongoing smoking. These studies also included a smoking abstinence arm to compare the reductions in HPHC exposure in smokers who switched to THS to the reduction in exposure induced by smoking abstinence.

Table 2: 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 International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (ICH) / Good Clinical Practice (GCP) guidelines and registered on the U.S. government's publicly available website www.clinicaltrials.gov.

Pharmacokinetic and Pharmacodynamic Studies (PK/PD)

The results of the PK/PD studies and nicotine uptake in general are discussed in Part B in the context of the determination of product use acceptance.

The REXC (5-Day) and REXA (90-Day) Reduced Exposure Studies

PMI conducted 4 clinical studies in the U.S., Europe and Japan to quantify the reduction in exposure to HPHCs after switching to THS relative to continued smoking, and to compare the exposure reductions achieved by switching to THS to those observed when subjects abstained from smoking for the duration of the studies. 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. In these randomized, controlled, open-label, 3-arm parallel group studies, adult smokers were randomized to either continue smoking their usual cigarettes, completely switch to THS use, or switch to smoking abstinence (SA).

Two of the studies were conducted in a confined clinical setting with five days of exposure in the EU (ZRHR-REXC-03-EU) (Haziza 2016b) and Japan (Haziza 2016a) (ZRHR-REXC-04-JP). The other two studies were conducted in Japan and the U.S. over three months with an initial confined clinical setting (5-day exposure) followed by 85 days in an ambulatory setting in Japan (ZRHM-REXA-07-JP) (Luedicke 2017a) and the U.S. (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. In these 90-day studies, the Fresh Menthol *HeatStick* variant (mTHS) was tested and compared with mentholated cigarettes (mCC).

Product use was controlled by study staff during the in-clinic period of the studies. During the ambulatory period of the two 90-day studies, product use was self-reported 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 Japanese study was high in all three arms, while the compliance in the smoking abstinence (SA) group of the U.S. study was poor (7 to 9 out of 41 subjects) as outlined in Section 6.1.3.2.3.19 of the MRTPA.

In all these studies, PMI quantified changes in exposure to 16 Biomarkers of Exposure (BoExp)[15] (Appendix A) which represented 14 of 18 HPHCs currently mandated for reporting to the FDA as well as toxicants recommended by the World Health Organization for lowering in mainstream cigarette smoke (WHO 2008). Furthermore, overall exposure to nicotine was assessed by measuring urinary nicotine equivalents (NEQ). A more complete summary of the study designs, rationale for selected BoExp and study results are provided in Section 2.7.6 pp 73-88 of the MRTPA, Section 6.1.3.1 of the MRTPA and Section 6.1.3.2 of the MRTPA.

The main specific objectives of these studies were:

- To determine the reduction in levels of BoExp to HPHCs in adult smokers who switch to THS in a confinement and in an ambulatory setting (Section 6.1.3.2 of the MRTPA)
- To compare the reductions in BoExp to HPHCs in smokers who switched to THS to those induced by smoking abstinence
- 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 of the MRTPA)
- To describe the change in cytochrome P450 1A2 (CYP1A2) enzymatic activity (Section 6.1.3.2.3.17 of the MRTPA)
- To describe the change in Urine Mutagenicity (Section 6.1.3.2.3.18 of the MRTPA)
- To monitor selected Clinical Risk Endpoints (Section 6.1.4 of the MRTPA)
- To evaluate product use (Section 6.2.2 of the MRTPA).
- To monitor the safety profiles during the studies (Section 6.1.5 of the MRTPA).

[15] The biomarker for toluene (S-BMA) did not show changes in any study group, most likely due to a lack of sensitivity of the analytical method. The results for the remaining 15 biomarkers are presented.

Reduced Exposure in 5-day confined setting (REXC studies)

Both 5-day reduced exposure studies demonstrated that smokers who switched to either THS or SA 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 study is shown in Figure 9.

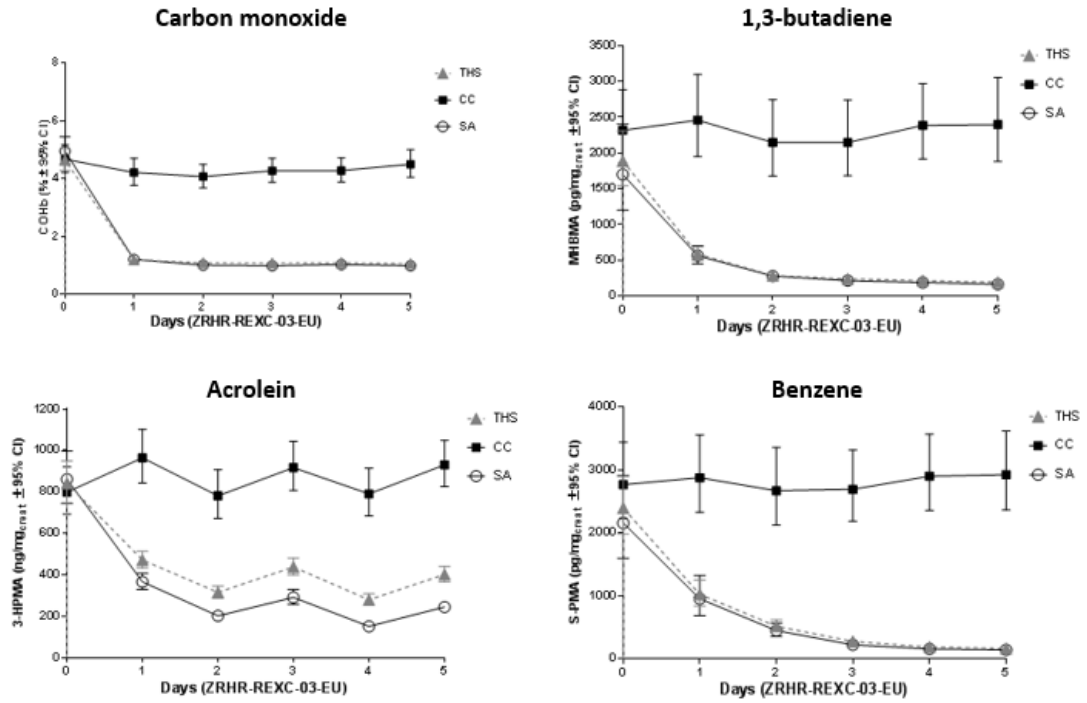


Figure 9: Concentrations of the BoExp to four HPHCs at baseline and throughout five days *ad libitum* use of THS, CC and smoking abstinence; ZRHR-REXC-03-EU

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

The reduction in exposure levels to HPHCs with THS use was rapid and of a magnitude that approached the reductions observed in the group that abstained from smoking for the duration of the study. Similar reductions in exposure were achieved for 11 additional BoExp to HPHCs also assessed in these studies.

As in the EU study (Section 6.1.3.2.2.1 of the MRTPA), the Japanese study (Section 6.1.3.2.2.2 of the MRTPA) showed a similar pattern of reduction in exposure to all assessed HPHCs, with the THS and the SA groups showing comparable reductions.

Reduced Exposure in 90-day ambulatory settings (REXA)

PMI conducted two three-month 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 U.S. and included mTHS (*ad libitum* use), mCC (*ad libitum* use), and SA arms. In both studies, the menthol product variant of THS (mTHS) was tested.

The results following the first 5 days were comparable across both REXA studies and to the results from the two REXC studies. The levels of all four BoExp to HPHCs tested as part of the primary objective were significantly reduced by a similar magnitude in both mTHS and SA groups compared to the mCC group. These reductions in levels of BoExp to HPHCs were similar across the two REXA studies, which were conducted in Japan and the U.S. with different demographics.

Furthermore, the results remained consistent between the two REXA studies at the end of the ambulatory period (Day 90) (Figure 10). Both THS and SA groups had a significant reduction in levels of BoExp to HPHCs compared with the smoking group. Furthermore, the reductions across all BoExp to HPHCs in the mTHS group were of a similar magnitude than those induced by smoking abstinence. This reinforces the overall finding that switching to THS results in a reduction in exposure to HPHCs that is similar to smoking abstinence.

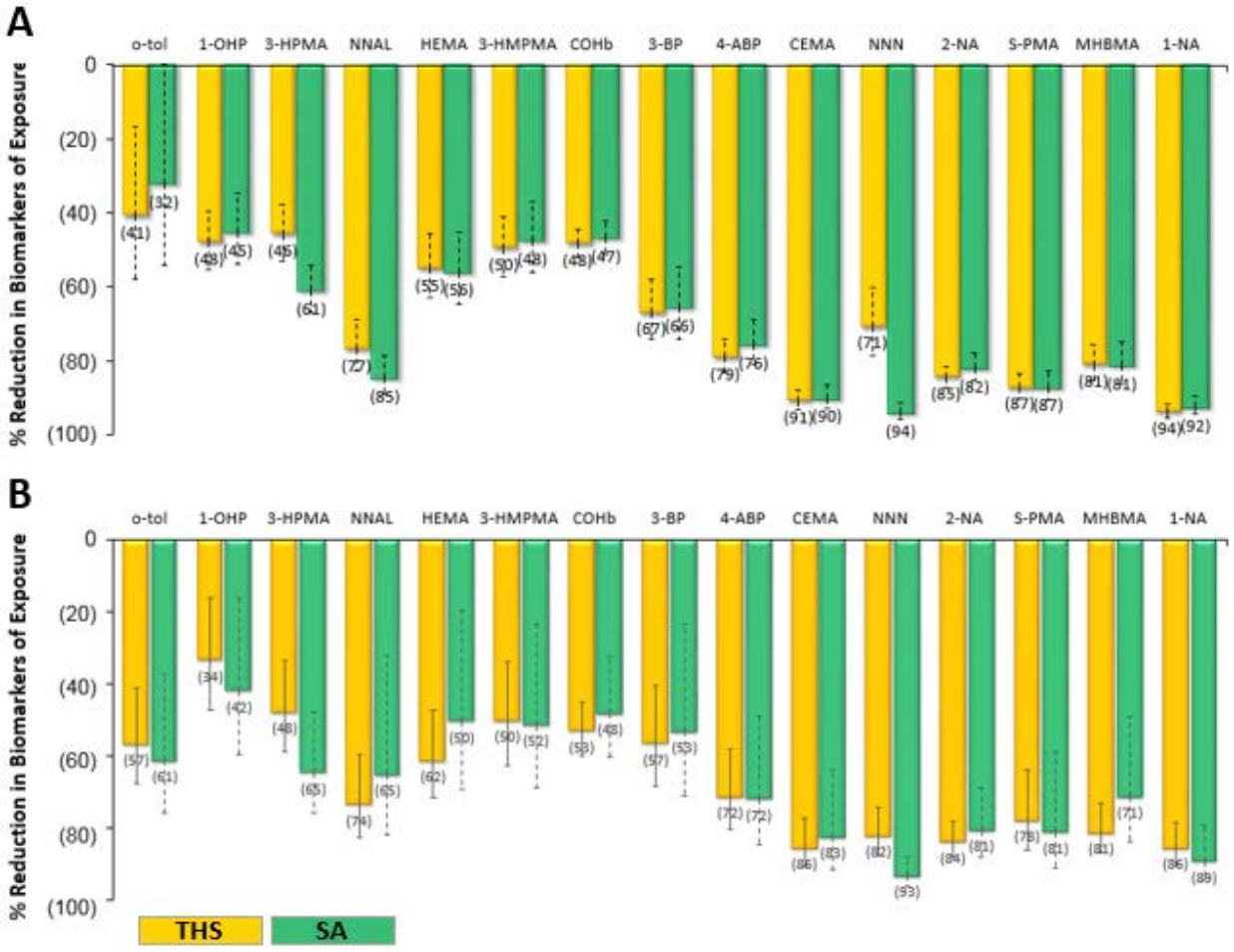


Figure 10: Percent reduction (geometric means at Day 90) in biomarkers of exposure after switching to mTHS (orange bars) and abstinence (green bars) after three months. A: Study conducted in Japan, B: Study conducted in the US

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 of the MRTPA

Reduced Exposure to Tobacco Specific Nitrosamines

The tobacco-specific nitrosamines (TSNAs) 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 1). As acknowledged by the FDA during its Technical Review of a new tobacco product application (FDA 2016), 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.

NNN and NNK are reduced by >95% in THS aerosol compared with 3R4F smoke. 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 2016, Xue 2014).

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 11) (Section 6.1.3.2.3.7 of the MRTPA). 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.

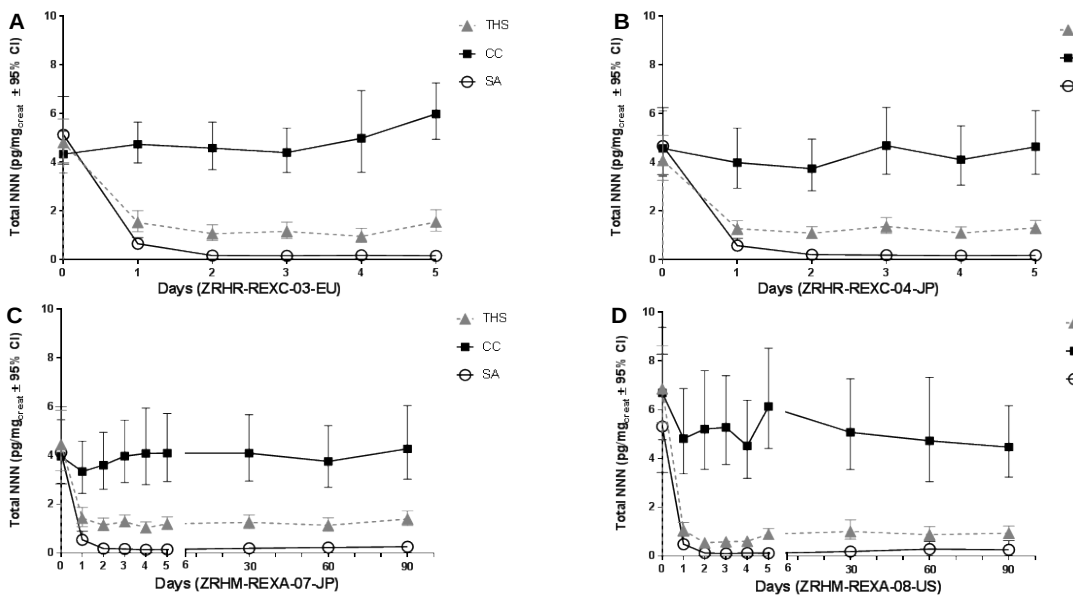


Figure 11: Geometric Mean Urinary and 95% CIs of Total NNN_{adjC} Concentrations (pg/mgcreat)

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 of the MRTPA

Similar findings were observed across all clinical studies for NNK through a quantification of its major metabolites expressed as Total NNAL (Figure 12) (Section 6.1.3.2.3.5 of the MRTPA). 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.

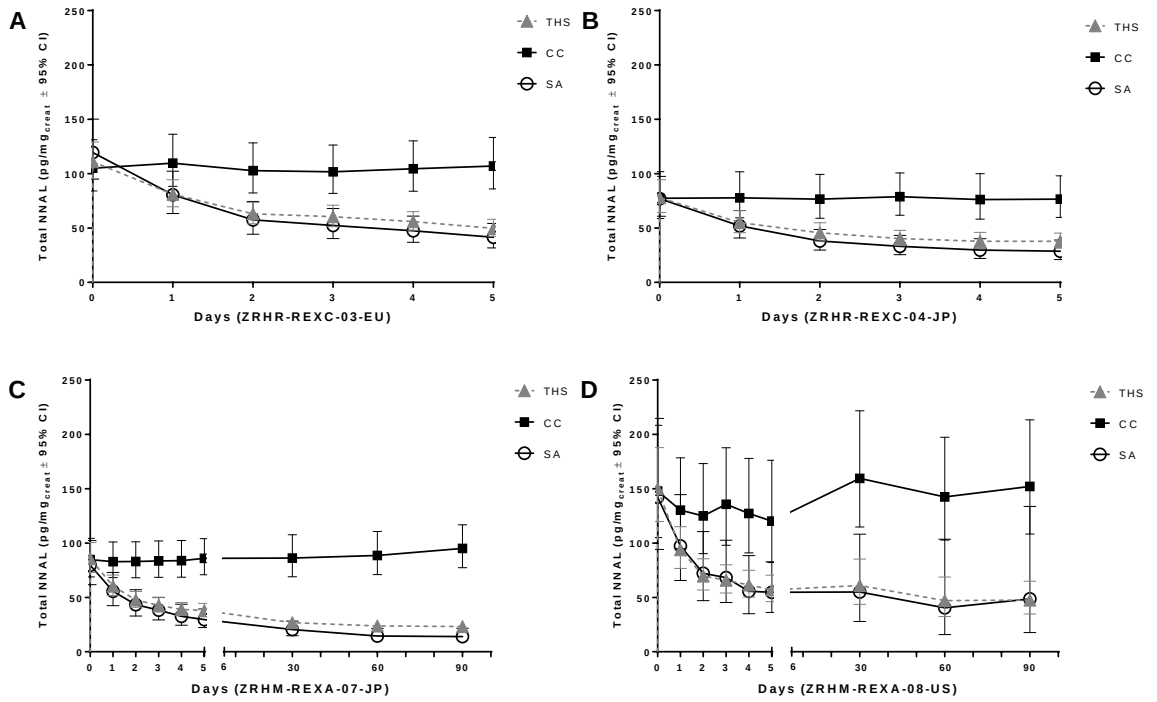


Figure 12: Geometric Mean and 95% CIs of Urinary Total $NNAL_{adjC}$ Concentrations (pg/mgcreat), During the Course of: A) ZRHR-REXC-03-EU; B) ZRHR-REXC-04-JP; C) ZRHM-REXA-07-JP; D) ZRHM-REXA-08-US

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 of the MRTPA

Additional reduced exposure markers

The P450 1A2 cytochrome (CYP1A2) is a key factor in the activation metabolism of various constituents, including carcinogens, such as heterocyclic amines, mycotoxins, TSNAs, and aryl amines, found in tobacco smoke, and can thus be indicative of exposure to tobacco smoke (Eaton 1995). In addition, CYP1A2 is induced by polycyclic aromatic hydrocarbons (PAH), which are among HPHCs generated in the smoke of CCs. Across studies, the levels of CYP1A2 activity observed with THS use were statistically significantly lower than values observed in the cigarette smoking arms at Day 5 and Day 90 and overall comparable to levels observed in the smoking abstinence arms (Section 6.1.3.2.3.17 of the MRTPA). The measured levels were

within the expected range found in the published literature from smoking cessation studies. These results are also supported by the observation that in the 8-months switching study conducted in Apoe$^{-/-}$ mice (Phillips 2016) (Section 6.1.4.1.1 of the MRTPA), cigarette smoke induced both mRNA and protein expression of CYP1A2 in the liver (the main site of CYP1A2 expression in mice), while exposure to THS aerosol did not. Furthermore, switching to THS aerosol following 2 months of cigarette smoke exposure led to a reduction in CYP1A2 mRNA and protein expression to levels approaching those of cessation (Section 6.1.3.1.2.6 of the MRTPA) (Lo Sasso 2016b).

The urine mutagenicity assay developed by Ames (Ames 1975) provides a relative assessment of the mutagenicity of urine samples from subjects exposed or not to tobacco smoke (Gregg 2013). Except for the ZRHR-REXC-04-JP study, where the levels in the cigarette smoking arm decreased to a similar extent as in the THS and smoking abstinence arms, the levels of urine mutagenicity observed with THS use were lower than values observed in the cigarette smoking arms at Day 5 and Day 90, and overall comparable to levels observed in the SA arms, as well as to published literature from smoking cessation studies (Section 6.1.3.2.3.18 of the MRTPA). These findings are consistent with the overall absence of measureable mutagenicity observed in the pre-clinical *in vitro* Ames test conducted with the total particulate matter of the THS aerosol (in presence and absence of S9) (Section 6.1.2.2.2 of the MRTPA) (Schaller 2016a).

In summary, the clinical studies demonstrated a consistent reduction in exposure to HPHCs in smokers who switched to THS or abstained from smoking for the duration of the study. These changes were evident as early as 5 days following the switch to THS 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 clinical evidence to substantiate a reduction in harm and risk of tobacco-related disease according to Section 911(g)(1) of the FD&C Act.

Clinical Risk Markers

While the 90-day reduced exposure studies were primarily conducted to assess reductions in exposure to HPHCs, both studies also collected data on multiple clinical risk endpoints to assess how the reduction in exposure achieved by switching from smoking to THS use affects these clinical risk endpoints.

As demonstrated in the nonclinical section, 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 clinical risk markers.

PMI chose clinical risk markers that (1) are responsive to smoking and are associated with at least one smoking-related disease, (2) reverse upon smoking cessation, and (3) are plausible from a biological mechanisms perspective. The clinical risk markers that were measured in the 90-day REXA studies are markers of (1) oxidative stress and platelet activation (8-epi-PGF2α

and 11-DTX-B2), (2) inflammation and endothelial dysfunction (WBC and s-ICAM-1), (3) alterations in lipid metabolism (HDL-C), and (4) risk of pulmonary disease (FEV1).

This panel of clinical risk markers was assessed in these studies to evaluate whether smokers who switched to THS could exhibit changes across this panel of clinical risk markers that are aligned, in terms of direction and magnitude, with the favorable changes seen in smokers who abstained from smoking for the duration of the studies. A more detailed explanation for the selection and use of the clinical risk markers can be found in Section 6.1.4 of the MRTPA.

The results from the two 90-day REXA studies conducted in Japan (Luedicke 2017b) and the U.S. showed that the changes in clinical risk markers in smokers who abstained for the duration of the study were positive in that they were generally aligned with the expected direction of change derived from the literature (Section 6.1.4 of the MRTPA) (Figure 13). As expected, these changes were small, yet represent the achievable magnitude of change upon abstinence in these clinical study populations of healthy smokers and given the sample size and duration of the study. In those smokers who completely switched to THS, the changes in clinical risk markers were similar to those observed in the smoking abstinence groups across both studies.

In the Japanese study (Luedicke 2017b), there were reductions in the markers for oxidative stress (8-epi), platelet activation (11-DTX-B2), inflammation (WBC) and endothelial dysfunction (s-ICAM). There was an increase in HDL-C, which is favorable in terms of cardiovascular health. At the three-month time point, small favorable changes in FEV1 were observed. Although these changes were promising, longer-term studies with a larger sample size will be required to confirm these changes.

The compliance with smoking abstinence and switching to THS was notably lower in the U.S. study than in Japanese study, which may be the cause for some differences observed between the two studies. Most notably in the U.S. study where the WBC counts decreased in the SA group but increased in the THS group. With this notable exception, the changes in the other clinical risk points were directionally comparable between the THS and SA groups and, in most cases, so was their magnitude. Overall, this data provides further evidence that switching to THS aerosol preserves much of the effects of cessation, primarily due to the >90% reduction in exposure to HPHCs. The full data set for the clinical risk endpoints can be found in Section 6.1.4 of the MRTPA and is summarized in more details in Section 2.7.6 pp 88-97 of the MRTPA.

A

Disease Pathway	Clinical Risk Marker	Abstinence Effect at 3m	Expected Direction of change	Switching to IQOS Effect at 3m
Lipid Metabolism	HDL-C	6.4 mg/dL	↑	4.5 mg/dL
Inflammation	WBC	-0.41 10^9/L	↓	-0.57 10^9/L
Airway Impairment	FEV_1	1.93 % pred	↑	1.91 % pred
Endothelial Dysfunction	sICAM-1	-10.9 %	↓	-8.7 %
Oxidative Stress	8-epi-$PGF_{2\alpha}$	-6.0 %	↓	-12.7 %
Clotting	11-DTX-B_2	-19.4 %	↓	-5.4 %

B

Disease Pathway	Clinical Risk Marker	Abstinence Effect at 3m	Expected Direction of change	Switching to IQOS Effect at 3m
Lipid Metabolism	HDL-C	0.0 mg/dL	↑	1.4 mg/dL
Inflammation	WBC	-0.94 10^9/L	↓	0.17 10^9/L
Airway Impairment	FEV1	1.95 % pred	↑	0.53 % pred
Endothelial Dysfunction	sICAM-1	-9.9 %	↓	-10.6 %
Oxidative Stress	8-epi-PGF2α	-8.5 %	↓	-13.5 %
Clotting	11-DTX-B2	-7.2 %	↓	-3.6 %

Figure 13: Relative Changes in Clinical Risk Endpoints at 90-days in the 90-day REXA studies. A: Study conducted in Japan, B: Study conducted in the US.

Abbr.: HDL-C = high density lipoprotein-cholesterol; WBC count = white blood cell count; FEV1 = Forced Expiratory Volume in 1s; sIMAC-1 = soluble intercellular adhesion molecule 1; 8-epi-PGF2α = 8-epi-prostaglandin F2 alpha; 11-DTX-B2 = 11-dehydro-thromboxane B2.
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 of the MRTPA

Summary of clinical research findings

The clinical studies demonstrated a consistent reduction in exposure to HPHCs in smokers who switched from cigarette smoking to THS use or smoking abstinence. These changes were evident within a few days of switching 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.

Furthermore, in both longer-term reduced exposure studies, 90 days after switching from cigarette smoking to THS use, there was a shift in clinical risk markers in the same direction as smoking abstinence. The shifts in the clinical risk endpoints of smokers who switched to THS were of similar magnitude to those seen following 90 days of smoking abstinence.

Conclusion Part A: Reduced Harm and Risk of Tobacco-Related Disease

The scientific case that switching to IQOS reduces harm and the risk of tobacco-related disease can be examined in the context of CVD, COPD and lung cancer. The evidence that using IQOS instead of smoking cigarettes presents a reduced risk of smoking-related diseases comes from a broad range of studies conducted in relevant biological systems including human cell cultures and organotypic tissue cultures, *in vivo* models as well as human clinical studies. Both standard and systems toxicology approaches were used to collect detailed and comprehensive datasets that were analyzed in the context of biologically plausible, disease-relevant mechanisms and endpoints. In addition, exposure to IQOS elicited a much lower toxicity than exposure to cigarette smoke as measured in a variety of *in vitro* and *in vivo* test systems.

While a more detailed description of the rationale is provided for each major disease in Section 2.7.6 pp 98-110 of the MRTPA, the following section summarizes the evidence in the context of the high-level AOP depicted in Figure 4.

First, the aerosol of THS contains on average >90% less toxicants classified as carcinogens and/or respiratory, cardiovascular, reproductive or developmental toxicants (Table 1) than cigarette smoke. In addition, THS aerosol does not contain carbon-based ultra-fine solid particles that are found in cigarette smoke and are known to be toxic. This reduction in emission of toxicants led to a consistent reduction in toxicant exposure in four clinical studies conducted across the U.S., Europe and Japan. Study subjects who switched entirely to THS achieved >90% of the exposure reduction achieved by the subjects who abstained from smoking for the duration of the studies. Similarly, laboratory systems, such as animal models of disease, exposed to THS aerosol and cigarette smoke at equivalent doses of nicotine also displayed a >90% reduction in toxicant exposure. Furthermore, the reduction in carcinogen exposure of study subjects who switched to THS is supported by a reduction in urinary mutagenesis and CYP1A2 activity in line with the literature on smoking cessation studies.

Second, the changes in gene, protein and lipid expression induced by cigarettes smoke exposure across all tested human and animal laboratory systems are reduced on average by >90% in systems exposed to THS aerosol. Furthermore, in an animal model of disease, switching from cigarette smoke to THS aerosol exposure led to a reduction in molecular changes approaching the reduction induced by cessation.

Third, all human and animal biological systems exposed to THS aerosol consistently showed dramatically reduced perturbations (> 90%) of all biological networks perturbed by cigarette smoke, including xenobiotic metabolism, oxidative stress, lipid dysfunction, DNA damage response, apoptosis, inflammation, cell proliferation and tissue repair**.** Furthermore, in an animal model of disease, switching from cigarette smoke to THS aerosol exposure led to a reduction in the amplitude of perturbation of all biological networks affected by cigarette smoke exposure, to a level approaching the reduction induced by cessation.

Fourth, all biological systems exposure to THS aerosol consistently showed dramatically reduced cellular changes (> 90%) than systems exposed to cigarette smoke**.** For instance, THS aerosol is >10 fold less potent than cigarette smoke in inducing human neutrophil adhesion to endothelial cells and in disrupting both chemotaxis and transmigration. In addition, THS exposure causes >90% less emphysema and infiltration of free cells in the lung than cigarette smoke *in vivo*. Furthermore, in an animal model of disease, switching from cigarette smoke to THS aerosol exposure led to a reduction in number of free lung cells and emphysema than

cigarette smoke exposure, to a level approaching the reduction induced by cessation. Finally, in line with a reduction of >95% in carcinogens, THS aerosol is >95% less potent as a mutagen across *in vitro* studies.

Fifth, animal models of disease exposed to THS aerosol show disease endpoints that are >90% less pronounced than those exposed to cigarette smoke. Furthermore, switching from cigarette smoke to THS aerosol exposure halts the progress of atherosclerotic plaque growth and emphysema to a degree that approaches the effects of cessation. Additionally, human organotypic tissue cultures of both nasal and bronchial epithelia exposed to THS aerosol do not display a reduction in cilia beating rate as do cultures exposed to matched doses of cigarette smoke.

Finally, the two 90-day clinical studies showed that the clinical risk markers displayed favorable changes (i.e. similar to those seen with cessation) in smokers who switched completely to THS after three months. The directions of these changes paralleled those observed in study participants who abstained from smoking for the duration of the study. While the changes in individual clinical risk markers are small and may therefore not by themselves be indicative of disease risk, all changes taken together are consistent with those expected from epidemiology and observed upon smoking cessation (both in terms of amplitude and direction), which is the best and most efficient way to reduce the harm and risk of smoking-related disease.

Several considerations provide confidence in the scientific conclusion that switching to THS aerosol will reduce harm and the risk of tobacco-related disease.

First, the studies conducted by PMI produced coherent results that are biologically relevant and plausible. 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 and mechanistically aligned with cessation and of similar magnitude to cessation. This consistency was noted across all switching studies conducted *in vivo* and in a clinical setting.

Third, the scientific findings were consistent across multiple biological levels along the Adverse Outcome Pathway (Figure 4). 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 compared with cigarette smoke. Most notably, the changes seen across a switching studies were generally consistent with changes seen with smoking abstinence.

Finally, at all levels of investigation, the PMI MRTP Assessment 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 harm and the risk of 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, thus demonstrating that THS, will significantly reduce harm and the risk of tobacco-related disease to individual tobacco users.

PART B: ASSESSING THE POTENTIAL TO BENEFIT THE HEALTH OF THE POPULATION AS A WHOLE

Section 911(g)(1) of the FD&C Act states that the Secretary must determine if the applicant has demonstrated that the product will benefit the health of the population as a whole taking into account both users and nonusers of tobacco products. The statute provides additional specificity to that determination in Section 911(g)(4) by providing that, in addition to evaluating the risks to individual users of the product, the Secretary must also consider the likelihood that existing smokers who would otherwise stop will switch to IQOS and the likelihood that non-smokers will start using IQOS.

Given the statutory structure to weigh the benefit to the individual with the benefit or harm to the population as a whole, it is clear that Congress was concerned that there could be a product which benefited the individual, while having a net harm on the population. As addressed above, IQOS significantly reduces the risk and harm of tobacco related diseases to the individual adult smoker. To assess the net impact on the public health, the assessment must take into account unintended use by non-smokers and smokers who would otherwise quit tobacco all together. In that regard, PMI developed a Perception and Behavior Assessment program (PBA) to assess consumer understanding of product messages, whether a meaningful proportion of American adult smokers will accept IQOS as a substitute for cigarettes and will use IQOS exclusively as well as the likelihood of unintended use.

PMI developed a Population Health Impact Model (PHIM) to evaluate the potential benefit of a U.S. market introduction of IQOS, taking into account the probabilities of both intended and unintended IQOS uses. The data from the IQOS assessment program and from the experience with IQOS in markets outside of the U.S. indicate that a meaningful proportion of American adult smokers will accept IQOS as a substitute for cigarettes and will use IQOS exclusively. Furthermore, this data indicates that the likelihood of unintended use is low. As discussed in more detail below and in the MRTPA, the simulations from the PHIM predict that introducing IQOS will result in a significant reduction in smoking-attributable deaths over a 20-year period. The predictions from the model will be further evaluated through the rigorous post-market assessment program described below and Module 6.5 of the MRTPA.

Perception and Behavior Assessment

The PBA program was developed to assess the potential population impact of the market introduction of IQOS on the health of the population as a whole. The PBA program studies were organized around three key stages detailed in Section 2.7.6 pp 113-131 of the MRTPA. The first stage of the program was the development of validated psychometric survey instruments to assess risk perception and intent to use IQOS. The second stage involved the development and testing of several potential product messages that contained reduced risk and reduced exposure claims. Along with the modified-risk and exposure claims, PMI developed and tested additional warning statements that further clarified the absolute (IQOS itself) and relative risk (compared with cigarettes). These claims and warning statements were vetted to ensure that they were scientifically accurate and enabled consumers to evaluate and understand the risk of the product in the context of other tobacco products and cessation.

The resulting communication materials were then evaluated in three large quantitative studies, each of which assessed the effect of specific modified-risk or exposure communication materials on (1) Intent to Use (i.e., Intention to Try and Intention to Use) of IQOS among adult smokers, (2) Intention to Use IQOS among adult never and adult former smokers and, (3) consumer understanding and risk perceptions to determine:

- the overall likelihood of IQOS trial and use among adult smokers and nonsmokers
- consumer comprehension of reduced risk and exposure claims
- risk perception of IQOS including its comparative risk perception to cigarettes, e-cigarettes, NRTs, and cessation.

PMI also conducted a separate study (PBA-06 of the MRTPA) to assess the comprehension of IQOS instructions for use and potential for product misuse (described in Appendix B). Finally, PMI assessed acceptance of IQOS using an actual use study (PBA-07 of the MRTPA) of IQOS usage behavior in near real-world conditions in the U.S.

All studies in the PBA program were conducted within the U.S. population to ensure that the results were directly relevant to the MRTP application. The study designs and rationale are summarized in Section 2.7.6 pp 112-131 of the MRTPA and in the PBA section of the MRTP application (Sections 6.2.2, 6.3.1 and 6.4 of the MRTPA).

Likelihood of IQOS use among adult smokers and nonsmokers

The data from the three quantitative studies on behavioral Intentions to Try and Use IQOS showed a consistent pattern of interest among smokers and lack of interest among nonsmokers. The data from the three studies has been combined into Figure 14, which represents the Intention to Use for three modified-risk claim, reduced-risk claim #1 (THS-PBA-05-RRC-US), reduced-risk claim #2 (THS-PBA-05-RRC2-US) and the reduced-exposure claim #3 (THS-PBA-05-REC-US). Among all adult smokers, there were a substantial number of smokers who responded that they would be interested in both trial and use of IQOS. The data tables for the quantitative studies can be found in Section 2.7.6 pp 132-139 of the MRTPA.

Overall, the study data showed that among Adult Smokers with No Intention to Quit, there were very similar results across all three studies. The range of positive responses to try IQOS ranged between 30% and 50% and the range of positive responses to use the product on a regular basis ranged from 20% to 38% across the three studies (Figure 14).

IQOS did not seem to have any significant appeal to nonsmokers. Less than 2% never smokers expressed an interest in trial and use. The study included an over-sampling of Legal Age – 25 years of age never smokers (LA-25) who also showed little interest in trial and/or use of IQOS across all three quantitative studies (between 0% and 3%). Among former smokers, between 1% and 6.6% of respondents expressed an interest in using IQOS

It was important to understand whether the introduction of IQOS as a MRTP could potentially change the intention of adult smokers who express the intention to quit the use of cigarettes or all tobacco products. These smokers 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.

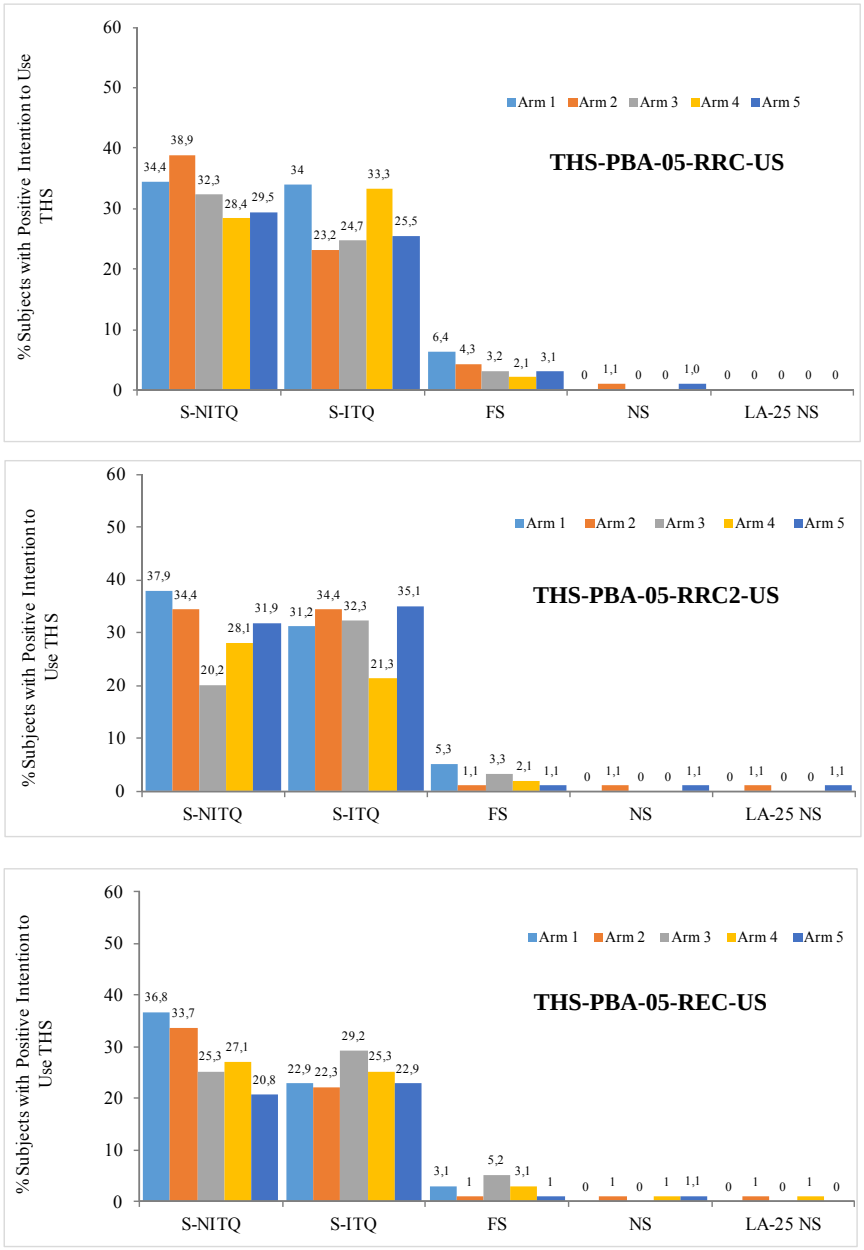


Figure 14: Positive Intention to Use IQOS (very likely/definitely) for all PBA-05-US Studies assessing IQOS Communication Materials

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: IQOS brochure in combination with one of four possible Surgeon General's warnings in a rotating fashion; Arm 2: IQOS 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: IQOS Direct Mail communication in combination with the "Important Warning" developed by PMI.

However, when asked about their intentions to quit smoking and/or the use of all tobacco products both before and after viewing the modified-risk claims and materials, they did not appreciably change their stated intentions to quit smoking or the use of all tobacco products as reflected in Table 3 below.

Table 3: Range 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.

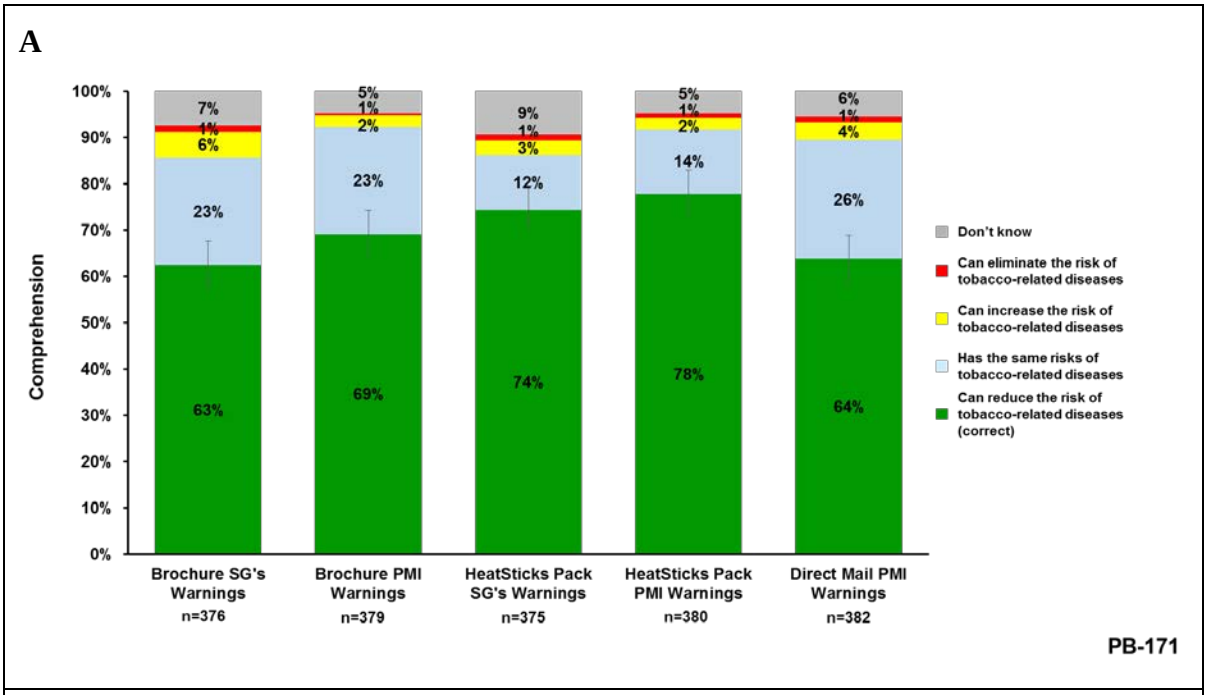
Consumer Comprehension of Proposed Claims

Comprehension of Reduced Harm and Risk Claims

The overall findings of the three quantitative PBA-05 studies show that most adult smokers and adult nonsmokers have an accurate understanding that IQOS presents less risk than cigarettes but are not risk-free. The assessment was based on the proportion of subjects who responded correctly that *there was a reduced risk of tobacco-related disease or harm by switching from cigarettes to* IQOS (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 15.

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

As shown in Figure 15, 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 IQOS 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). Many consumers do not have the necessary knowledge to discriminate the harm of each non-combustible product in comparison to cigarettes. Therefore, educating consumers about IQOS is essential to help convince adult smokers to switch to IQOS.



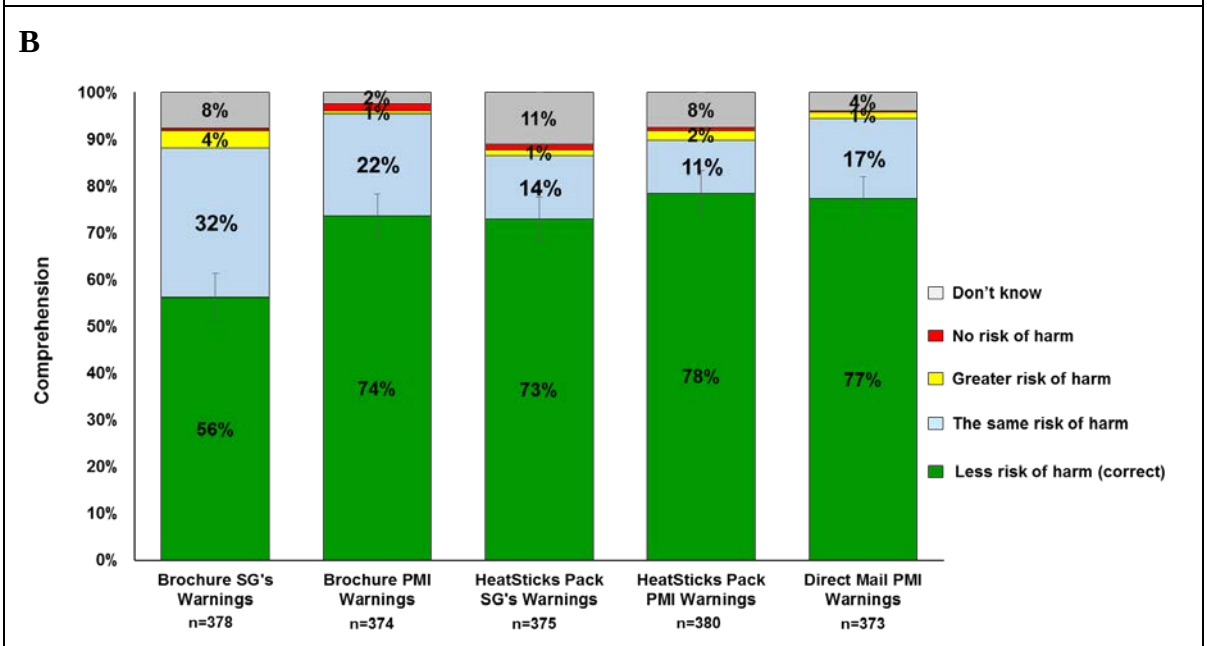


Figure 15: Comprehension of reduced risk information for THS-PBA-05-RRC-US (A) and THS-PBA-05-RRC2-US (B) within the Main Sample

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., IQOS Brochure, *HeatSticks*

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

These studies also showed that consumers were also able to recognize that IQOS contains nicotine, which is addictive, providing the correct response between 87-92% of the time. 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 IQOS communications will not mislead consumers with regards to the risk reduction of switching from cigarettes to IQOS;
- the IQOS communications lead to either an accurate or a conservative understanding of the risk of IQOS (risk of IQOS < risk of cigarettes or risk of IQOS = risk of cigarettes);
- consumers understand that IQOS is not without risk;
- consumers understand that IQOS 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

These 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.

Comprehension of the Reduced Exposure Claim (Claim #3)

The assessment of the consumer understanding of 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* IQOS *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*" (FDA 2012, lines 801–804). 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 16 summarizes the results from the first key communication objective, indicating that most consumers were able to understand that upon switching from cigarettes to IQOS they would experience a significant reduction in exposure to HPHCs (levels of comprehension between 46% and 72%). The second most common response was that the overall exposure was reduced by a small amount (11% and 20% of responses across all 5 arms), a more conservative interpretation of exposure reduction. These results indicate that a majority of subjects had a clear understanding that exposure to HPHCs was reduced by IQOS (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 IQOS will result in a reduced exposure to HPHCs.

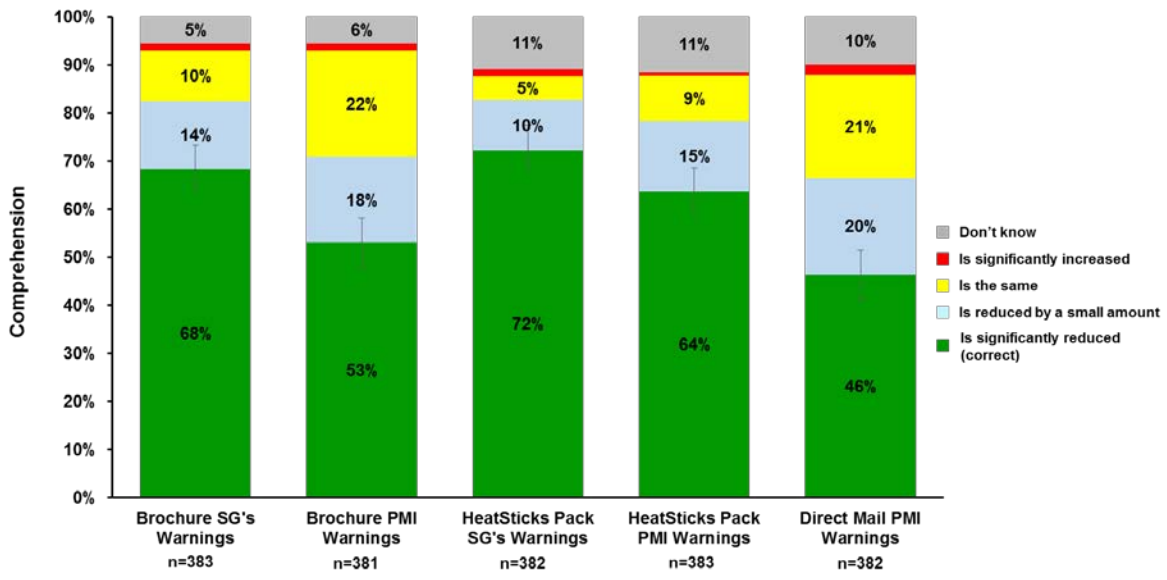


Figure 16: Comprehension of reduced exposure information within the Main Sample of THS-PBA-05-REC-US

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 consumers' understanding of the second key 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 17, the mandated cigarette warnings (SG in the chart) were accompanied by a lower understanding of the second 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 finding contrasts with 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.

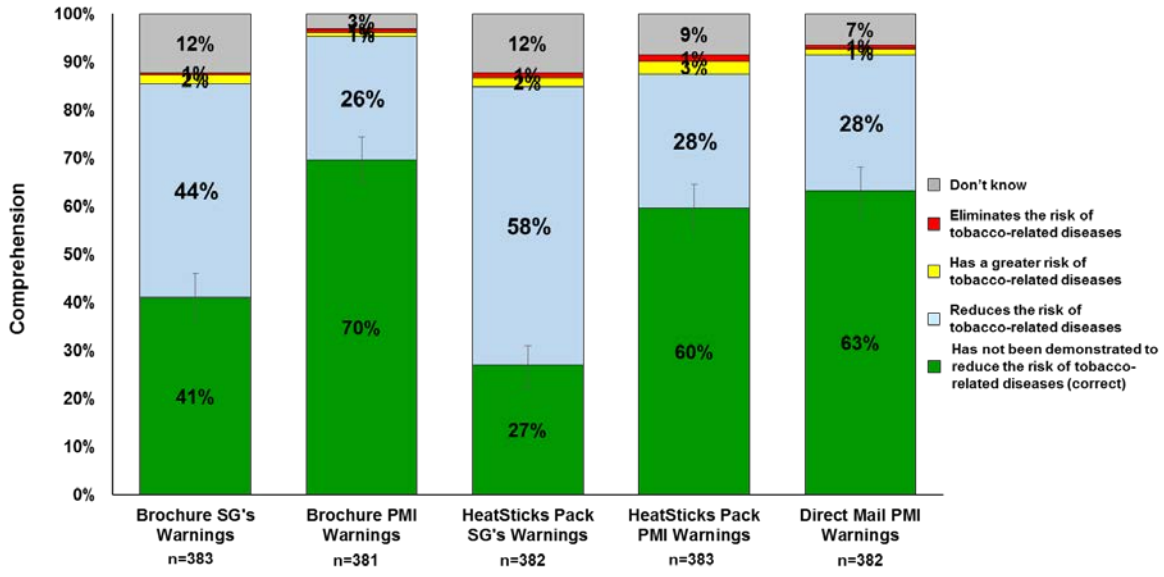


Figure 17: Comprehension of disease-risk within the Main Sample of THS-PBA-05-REC-US

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.

In summary for the reduced exposure claim, consumers are able to correctly comprehend that their exposure to HPHCs is reduced by using IQOS, although this reduction is interpreted conservatively by some smokers. The comprehension of the second key 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 the second key communication objective of the reduced exposure claim (claim #3) may be more appropriate in the event that FDA issues an exposure modification order under Section 911(g)(2).

Risk Perception of IQOS

PMI developed and validated a new measurement instrument, the Perceived Risk Instrument (PRI) to compare the Perceived Health Risk and Perceived Addition Risk across different tobacco products (e.g., cigarettes, e-cigarettes), NRTs and cessation, and among consumers with different smoking habits (e.g., current smokers, former smokers, never smokers).

The findings from the six studies conducted on risk perception of IQOS uniformly demonstrated that consumers perceive IQOS to be less risky than cigarettes which are uniformly viewed as the tobacco product that presents the greatest risk to health. On average, IQOS was approximately between 8 and 22 points lower than cigarettes on the 0 to 100 *Perceived Health Risk Scale* (Figure 18) and between 5 and 30 points lower on the 0 to 100 *Perceived Addiction Risk Scale*, considering all materials (Figure 19).

Risk perceptions of e-cigarettes and IQOS were similar for both *Perceived Health Risk* and on *Perceived Addiction Risk*. On average, the absolute difference between IQOS 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. 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 IQOS 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.

Across all PBA studies, IQOS was consistently rated as a higher perceived health and addiction risk than NRTs and cessation. IQOS was, on average, rated between 11 and 29 points higher than NRTs and between 2 and 25 points higher than cessation on the 0 to 100 *Perceived Health Risk Scale*. When asked about risk of addiction, consumers rated IQOS between 2 and 21 points higher than NRTs and 0- 41 points higher than cessation on the 0 to 100 *Perceived Addiction Risk Scale*. The higher risk perception of IQOS compared to NRTs is consistent with existing literature on risk perception of novel products (Overland 2013, Pepper 2015) that are compared to NRTs.

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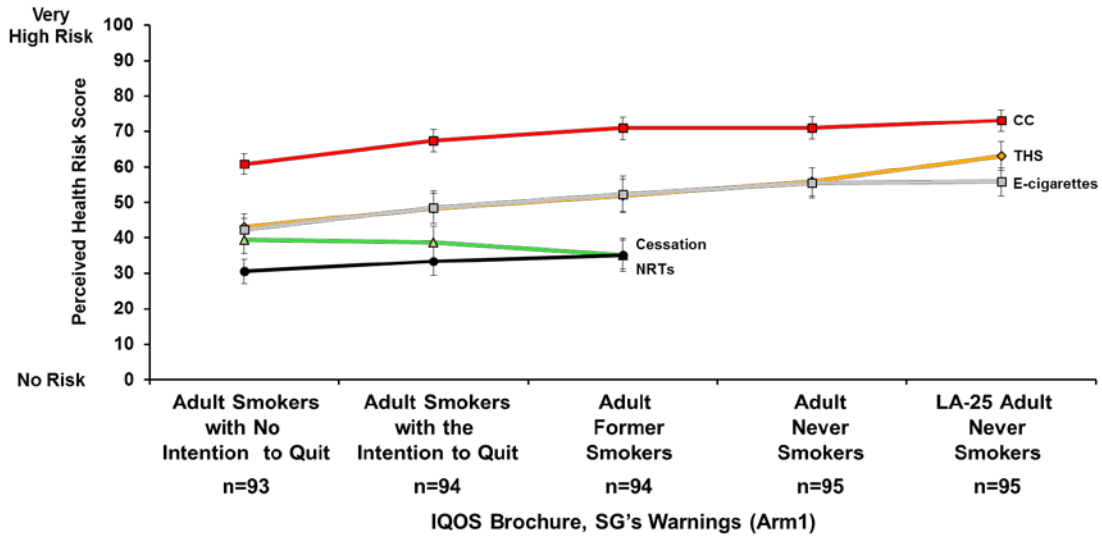

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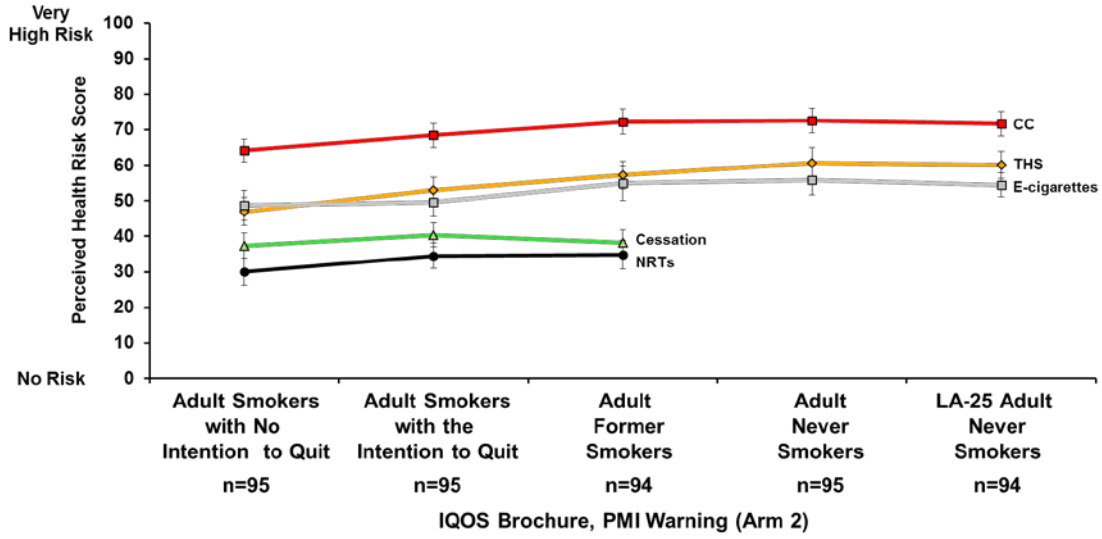
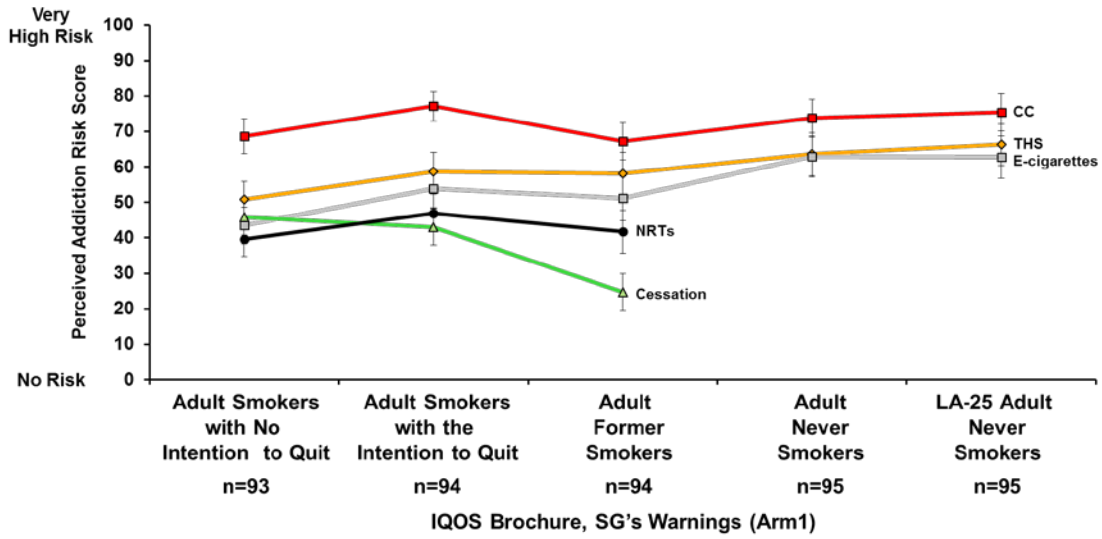


Figure 18: Perceived Health Risk – THS Brochure with SG Warnings: Arm 1(A) and with PMI Warning: Arm 2(B) from THS-PBA-05-RRC-US

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 of the MRTPA

A



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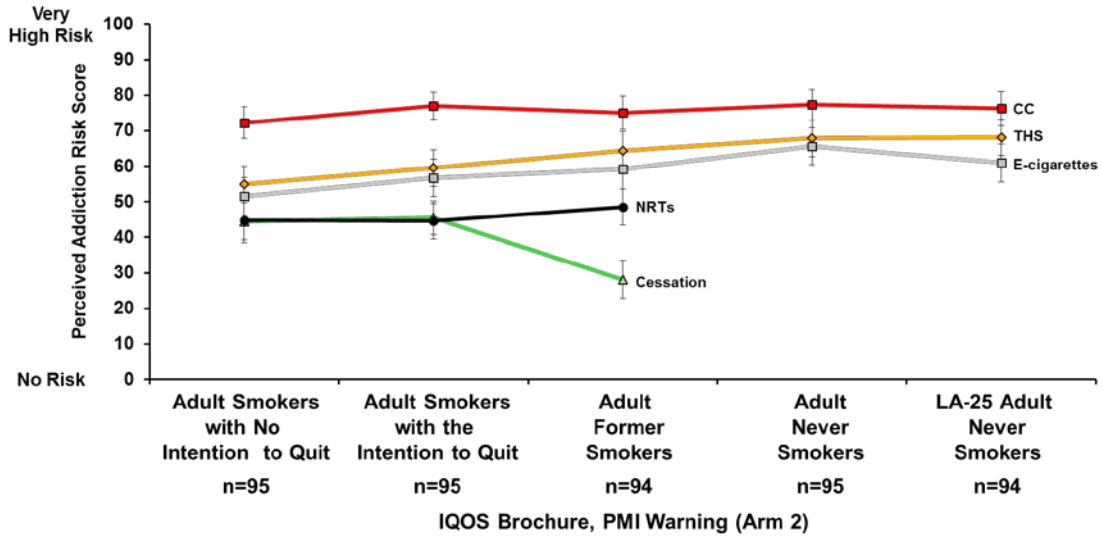


Figure 19: Perceived Addiction Risk - THS Brochure with SG Warnings: Arm 1(A) and with PMI Warning: Arm 2(B) from THS-PBA-05-RRC-US

Abbreviations: LA = legal age. Error bars are the 95% confidence intervals from the mean.
Note: Adult Never Smokers group includes only those Adult Never Smokers from the Main Sample.
Note: connecting lines are only to highlight clustering of outcomes for each comparator along the y-axis.
Source: Study Report: THS-PBA-05-RRC-US of the MRTPA

Integrated Summary of Product Understanding and Perception

Overall, the results presented on IQOS claims and communication materials provide additional support to the overall application for IQOS as an MRTP under both Section 911(g)(1) and Section 911(g)(2). Based on the reduced harm and risk claims and associated 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) could understand the following key points regarding IQOS:

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

In addition, nonsmokers expressed low levels of intention to IQOS regardless of whether they saw a reduced risk or reduced exposure claim. The combined results of the studies summarized in this section 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 IQOS in a manner that is consistent with an overall reduction in population harm and the risk of tobacco-related disease.

Studies involving Actual Product Use

PMI collected data on levels of consumption and patterns of use in both clinical settings and near real-world conditions including four *ad libitum* use clinical studies and one Actual Use Study in the U.S. This data was complemented with data from a market research Whole Offer Test (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 IQOS 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. IQOS use was defined as the proportion of *HeatSticks* use representing 70-100% of the total number of cigarettes and *HeatSticks* used. Combined use of IQOS 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 IQOS and cigarette products being used.

THS Consumption in Controlled Study Environments

The 5-day (REXC) and 90-day (REXA) reduced exposure clinical studies provided the opportunity to assess THS use in both controlled and ambulatory settings. During the 5-day confinement periods of both REXC and REXA studies, 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.

An initial decrease in product consumption from Baseline to Day 1 was observed in the THS arms in most of the Reduced Exposure studies, except in the REXA conducted in the U.S. (ZRHM-REXA-08-US of the MRTPA) where product consumption increased from Day 1 onwards.

From Day 2 onwards, THS consumption increased in all studies. THS consumption reaching levels comparable to Baseline by Day 5 in the 2 studies conducted in Japan. In the European REXC study and the U.S. REXA study, daily consumption of THS exceeded baseline by 30-35% (approximately 3-4 sticks per day) at the end of the 5-day period. Importantly, in the CC groups similar trends were observed, with a decrease in product consumption from Baseline to Day 1 observed in most of the studies, and reaching comparable or exceeding Baseline levels at Day 5.

During the Ambulatory Period, THS consumption decreased in both REXA studies by Day 30.

In the Japanese study (ZRHM-REXA-07-JP of the MRTPA), THS consumption returned to levels comparable to Baseline by Day 60 (Day 60: 12.7 THS Tobacco Sticks/day) and remained stable until Day 90.

In the U.S. study (ZRHM-REXA-08-US of the MRTPA), THS consumption remained only slightly above Baseline on Day 90 (14.2 THS Tobacco Sticks/day or 16% difference compared to Baseline).

Importantly, in the CC groups the cigarette consumption increased in both REXA studies during the ambulatory period, remained higher compared to Baseline, and higher than the number of THS consumed at Day 30, Day 60 and Day 90 by approximately 1-2 sticks per day (Figure 20).

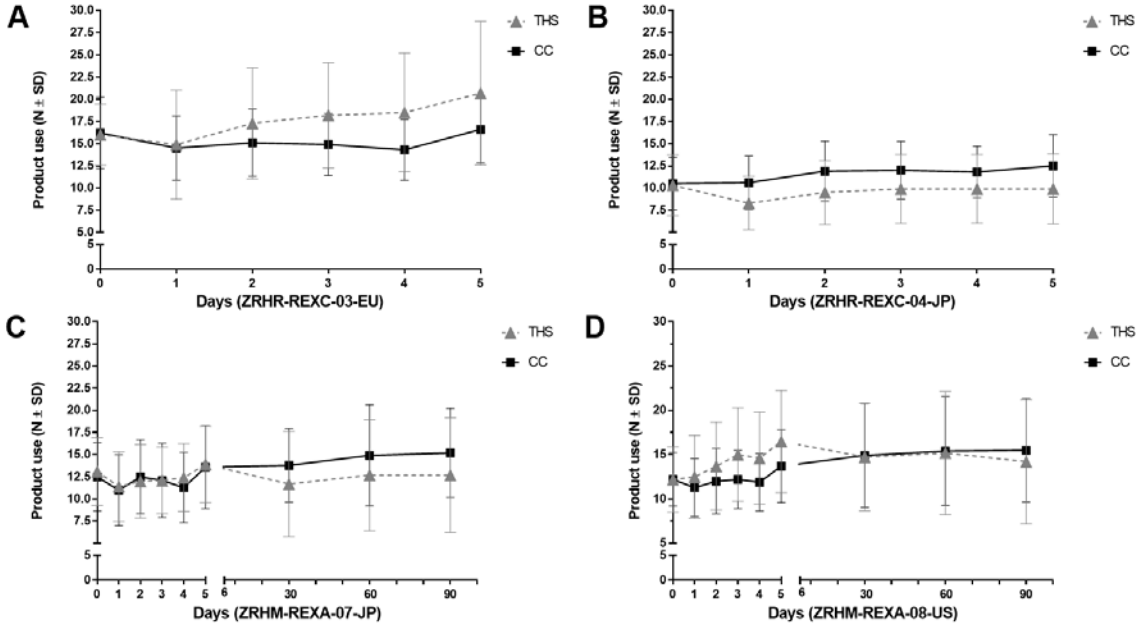


Figure 20: Product Consumption (Number of products used) between Baseline and at Day 5 (A: ZRHR-REXC03-EU and B:ZRHR-REXC04-JP) and Baseline and Day 90 (C: ZRHM-REXA07-JP and D: ZRHM-REXA08-US)

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

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

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.

Collectively, these observations indicate that switching from cigarettes smoking to THS use did not increase the overall consumption of tobacco products over a 90-day period.

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. A detailed summary is available in Section 2.7.6 pp 155-160 of the MRTPA.

Nicotine Exposure

Sufficient delivery and a comparable speed of uptake of nicotine are important attributes 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"[16].

PMI conducted four PK/PD studies, two in Japan (Brossard 2017), one in the UK and one in the U.S. The PK/PD studies were designed to assess the nicotine uptake profile in adult smokers who use THS for the first time compared to cigarettes and NRT. 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 of the MRTPA). The studies also evaluated the relationship between plasma nicotine concentration and the suppression of the urge to smoke in adult smokers. In addition, the studies provided initial safety data on product usage (e.g., vital signs, clinical biochemistry, hematology, spirometry, electrocardiogram and adverse events).

As seen in Figure 21, 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 U.S. study, using THS menthol (mTHS), differed from the other three studies, with mTHS users achieving a reduced C_{max} compared with menthol cigarettes (mCC). This difference in C_{max} observed in the U.S. study is most likely explained by the fact that: a) the PK studies were single use studies with no possibility for subjects to adapt to the new product, b) mTHS has a significantly lower nicotine yield in IQOS vs. U.S. market brands and c) the T_{max} in the CC arm was 10.1min which suggests that the smoking duration in the U.S. for cigarette is longer than the 6 minutes of use time available with the THS.

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

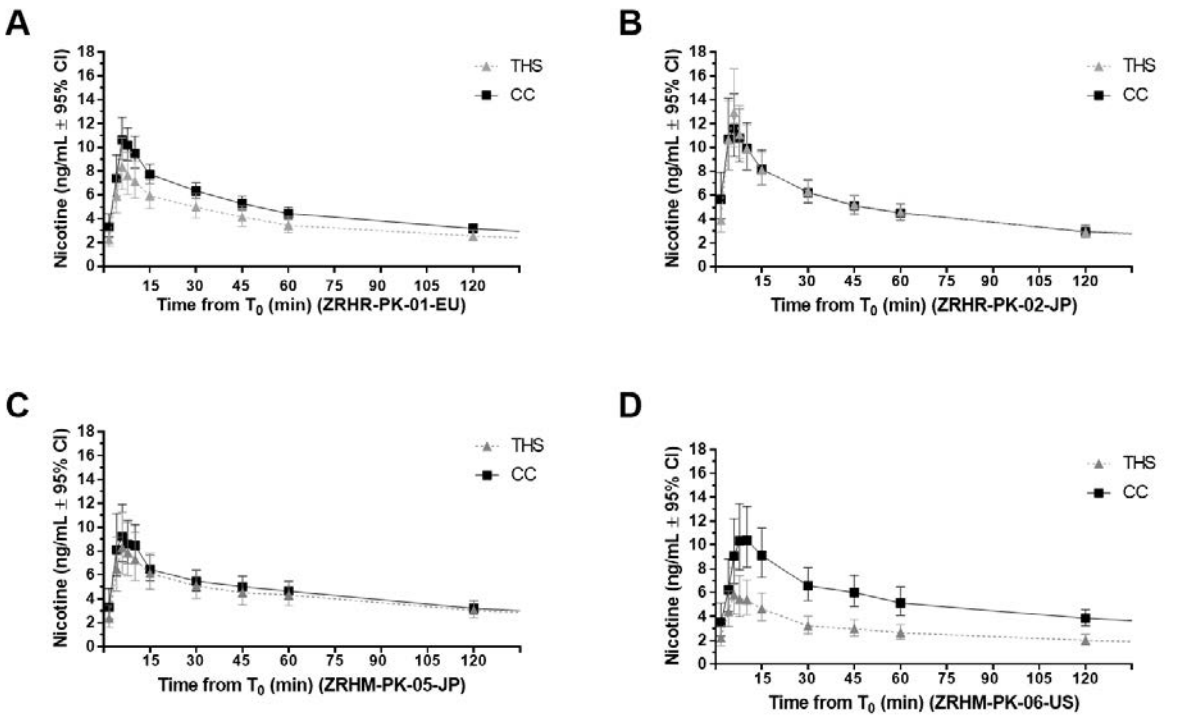


Figure 21: Geometric means and 95% confidence intervals of nicotine concentrations over 120 minutes with a single use of the THS or cigarette; During the Course of: A) ZRHR-PK-01-EU; B) ZRHR-PK-02-JP; C) ZRHM-PK05-JP; D) ZRHM-PK-06-US

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 of the MRTPA

All data refer to menthol variant 1

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 after single use. The study findings of the PK/PD studies are discussed more completely in Section 6.2.1 of the MRTPA.

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 could 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 of the MRTPA.

The overall nicotine exposure was determined by measuring the urinary nicotine equivalent at baseline and then over varying time points during the exposure studies. The 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 of the MRTPA) and 5.40 mg/g_{creat} in (ZRHM-REXA-07-JP of the MRTPA) and the highest in the European (ZRHR-REXC-03-EU of the MRTPA) and U.S. study (ZRHM-REXA-08-US of the MRTPA) (9.53 and 8.30 mg/g_{creat}, respectively) across arms.

The NEQ concentrations (Figure 22) were comparable between the THS and cigarette arms within studies and remained close to baseline values, with the exception of an increase of NEQ in THS users during the confinement period of the 5-day Reduced Exposure Study in the EU. The percent changes from baseline on Day 5 ranged from -2% to +23% and from -3% to +15% in the THS and cigarette arms, respectively. In the two 90-day Reduced Exposure studies in the U.S. and JP, levels of urinary NEQ concentrations at Day 90 were generally maintained and comparable in the THS and cigarette arms with percent changes from baseline in study (ZRHM-REXA-08-US of the MRTPA) 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 of the MRTPA), respectively.

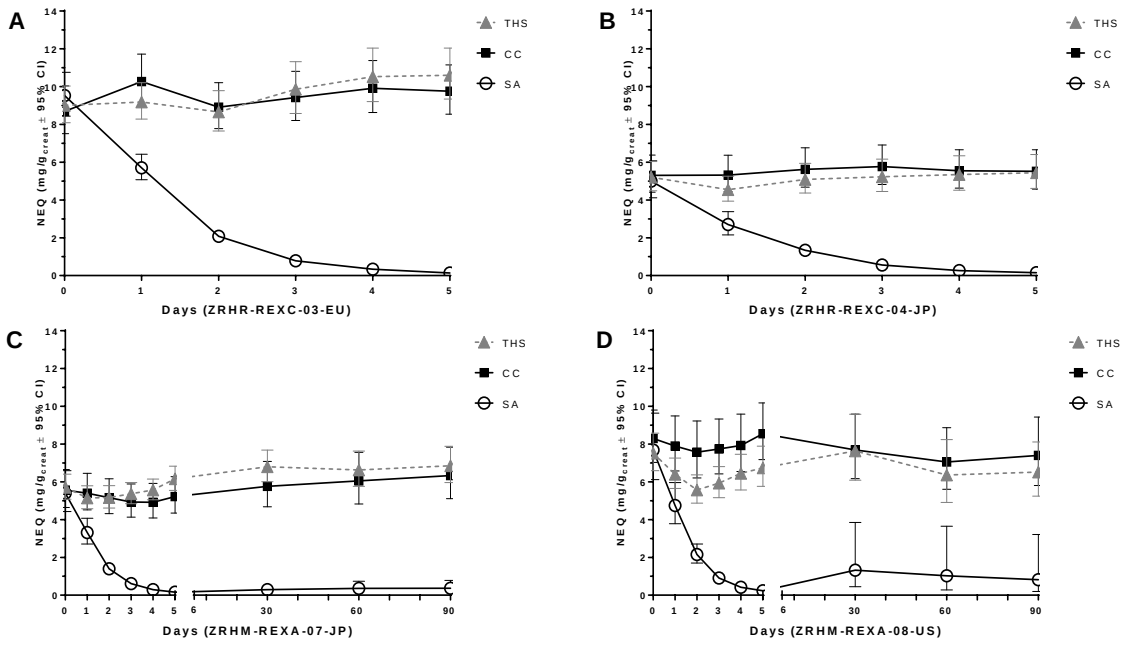


Figure 22: Geometric Mean and 95% CIs of Urinary NEQ Concentrations (mg/gcreat), During the Course of: A) ZRHR-REXC-03-EU; B) ZRHR-REXC-04-JP; C) ZRHM-REXA-07-JP; D) ZRHM-REXA-08-US

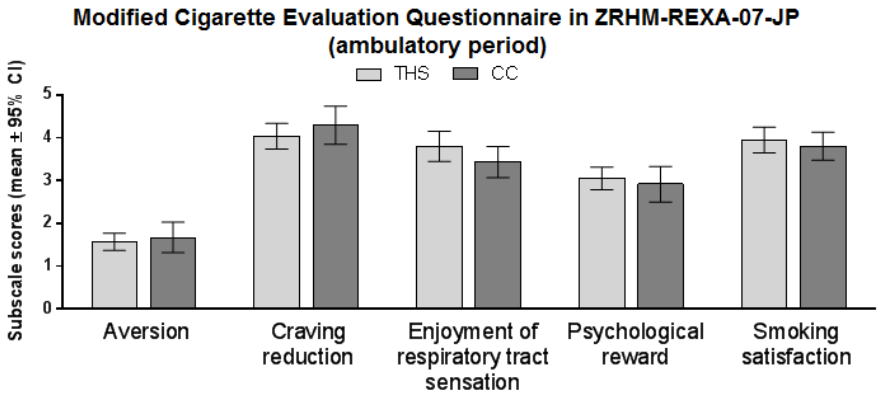
Abbr.: CC = Conventional Cigarettes, SA = Smoking Abstinence, THS = Tobacco Heating System, Switch = switching
Source: Study Reports ZRHR-REXC-03-EU, ZRHR-REXC-04-JP, ZRHM-REXA-07-JP, ZRHM-REXA-08-US of the MRTPA

In conclusion, the profiles of NEQ 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. The results for plasma nicotine and plasma cotinine were similar to those observed for the assessment of NEQ (Section 6.2.2.4.1.2.1 of the MRTPA).

Reinforcing and Aversive Effects of IQOS *compared to Cigarettes*

In addition to the taste, smell and ease of use, there are other factors that contribute to the likelihood of a successful switching from cigarettes to THS, namely the similarity in reinforcing and aversive effects of the two products. 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 THS. 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 REXC and REXA studies showed that the results for THS and cigarettes were, after an initial adaptation period, comparable in terms of subscale scores for aversion, craving reduction, respiratory tract sensation, psychological reward, and smoking satisfaction. Figure 23 illustrates the results on the five sub-scales of the mCEQ in both 90-day REXA studies conducted in Japan and the U.S.



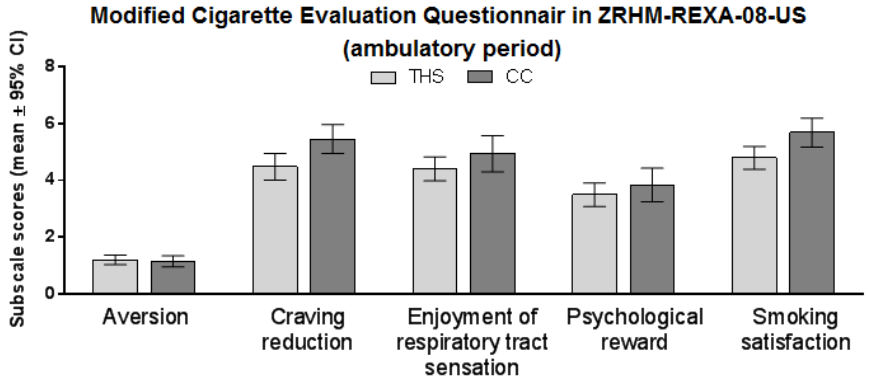


Figure 23: Comparison of subscales in the Modified Cigarette Evaluation Questionnaire (aversion, craving reduction, enjoyment of respiratory tract sensation, psychological reward, and smoking satisfaction) in the clinical studies ZRHM-REXA-07-JP and ZRHM-REXA-08-US on day 90

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. The results from the exposure studies conducted in confinement and under ambulatory conditions show that 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 urge-to-smoke score taken from the 90-day REXA study in Japan. As seen in Figure 24, the mean urge-to-smoke total scores remained stable over the 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%).

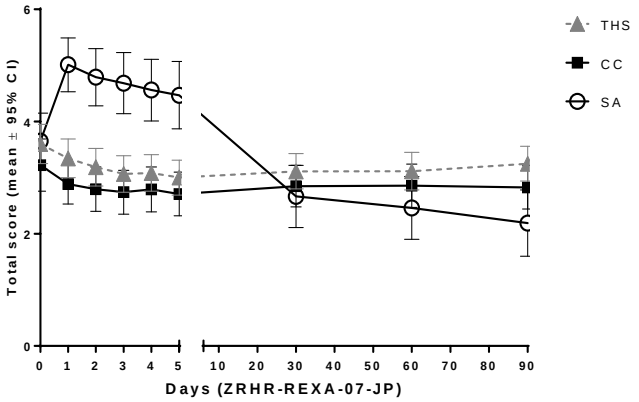


Figure 24: Total Score – Questionnaire of Smoking Urges During the Course of the Study

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

Level and pattern of IQOS consumption in observational studies

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

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

1. IQOS 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 IQOS use at the end of a 6-week usage period (Figure 25). 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 IQOS at the end of the observational period, had already adopted it in the first three weeks of the observational period.

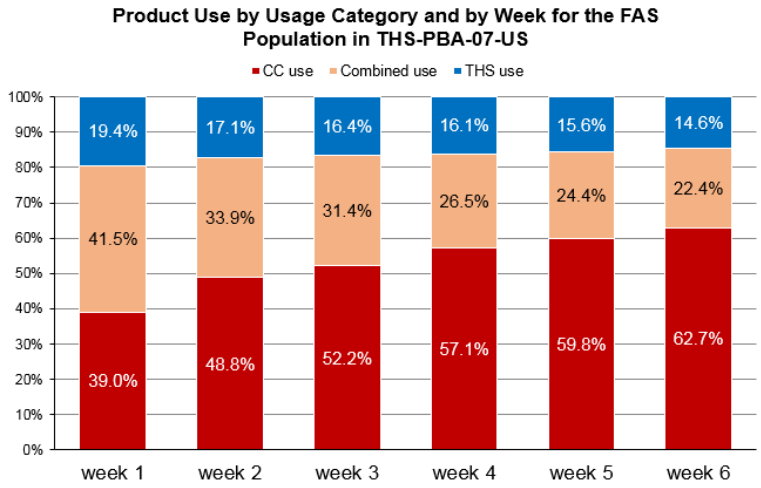


Figure 25: Percent Product Use by Usage Category during Continued Use and by Week for the FAS Population in THS-PBA-07-US

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

Sources: Study Report THS-PBA-07-US

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 (IQOS and cigarettes), with cigarette consumption reduced on average by half, for participants with *Combined use* at Week 6 compared to baseline (cigarettes consumption only). Overall, the participants who adopted a "IQOS use" usage pattern at the end of the observational period liked the taste (60.9%), smell (47.8%) and aftertaste (46.4%)[17] and found the product easy to use (81.9%)[18].

In summary, this study showed that approximately 15% of the participants were able to switch from cigarettes to IQOS and to adopt it as a substitute for cigarettes. There was no overall increase in the use of tobacco products for consumers who used IQOS exclusively or in combination with cigarettes. A demographic analysis revealed that IQOS 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.

[17] 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.

[18] 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.

The Whole Offer Tests (WOT)

The results of the WOTs (Section 2.7.6 pp 149 of the MRTPA) conducted in 5 countries show that between 10% and 37% of adult daily smokers, depending on the country, adopted IQOS as a substitute to their cigarettes. These results were very similar to the percentages of adult smokers in the Actual Use Study who switched to IQOS (see Figure 26 for IQOS use during the observational period). The data from the WOT studies indicate that a certain proportion of adult daily smokers used both cigarettes and IQOS together but their overall daily average tobacco consumption was 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 IQOS.

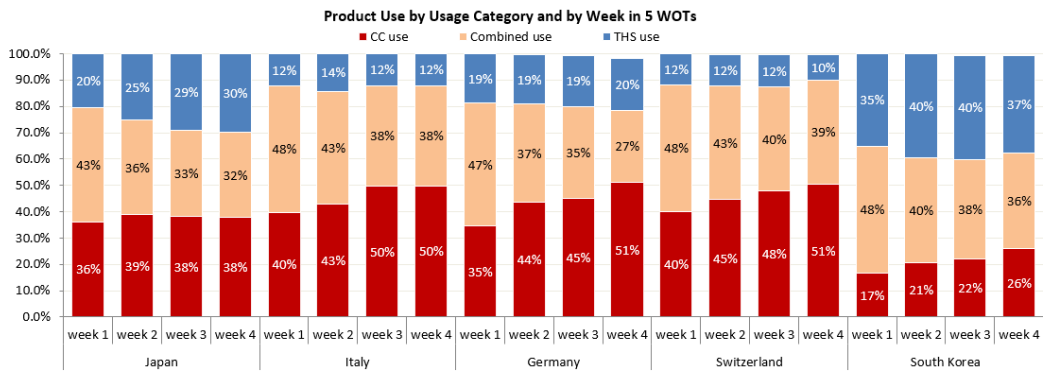


Figure 26: Percent Product Use by Usage Category of participants over four weeks in 5 countries for FAS Population in Whole Offer Test

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

Source: Study Report Whole Offer Tests MRTPA Section 6.

Abuse Liability Assessment

PMI conducted an abuse liability assessment to compare IQOS with cigarettes, using information regarding product design and content, aerosol chemistry and human clinical and behavioral studies. First, IQOS is designed to limit the temperature of the heating blade and the number of puffs that can be taken from a Tobacco Stick. Second, IQOS 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 IQOS and smoking arms of the studies, indicating that IQOS and cigarettes have a similar abuse liability. Taken together these facts do not provide evidence of any additional risk of abuse liability when comparing IQOS with cigarettes.

Based on the totality of the available evidence, IQOS has a similar abuse liability to cigarettes and there is no significant evidence that IQOS is attractive to non-users of tobacco. The full

description of methodology and scientific findings can be found in Section 6.2.3 of the MRTPA.

Integrated Summary of Product Use Behavior

The results summarized in this section show that IQOS has the potential to be accepted as an alternative to cigarettes by adult smokers and does not lead to an increase in tobacco consumption.

First, sensorial experience, taste, ritual and nicotine delivery are among the attributes that contribute to the acceptance of a new product by current adult smokers and are likely to significantly influence product use behavior. The four PK/PD studies and the assessment of nicotine exposure in the Reduced Exposure studies demonstrated that smokers who switched to IQOS 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 IQOS provided similar scores/ratings to what was experienced by smokers when smoking cigarettes. For many smokers, the product satisfaction for IQOS, 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.

Second, results from studies on actual product use suggest that IQOS is likely to be adopted by current cigarette smokers. 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 product information regarding the reduced risk of IQOS compared with cigarettes. In fact, across all studies, smokers had only one opportunity, at enrollment, to be told of the potential for reduced exposure and risk. It is therefore likely that, in the long term, 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.

Third, results on product consumption and use patterns, both in controlled as well as in near real-world conditions, show that smokers who switch to IQOS do not increase their overall tobacco consumption. In fact, over prolonged exposure to the product, IQOS consumption tended to stabilize and reach levels comparable to what was reported at baseline for cigarettes.

Fourth, data on product usability from the THS-PBA-06-US of the MRTPA study suggested that the instructions for use seem adequate in explaining the majority of the tasks required to operate IQOS. These results, combined with the very low level of misuses observed in near real-world conditions such as in the THS-PBA-07-US of the MRTPA study, suggest that IQOS is likely to be used as designed and intended by adult smokers.

Finally, while the PBA data showed that the product messages generated substantial Intent to Use IQOS among adult smokers with the intention to quit, nine out of ten did not change their intention to quit.

In conclusion, based on the totality of the available evidence on product usage, IQOS offers an experience that is close to cigarettes and provides a satisfying experience for many adult smokers, enabling them to either predominantly or fully switch to IQOS.

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 of the MRTPA, 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. To estimate the potential change in tobacco-related mortality that could occur following a U.S. market introduction of IQOS as an MRTP, PMI developed a Population Health Impact Model (PHIM). The PHIM was built to reflect the major parameters that affect the overall model results and comprises (1) a Prevalence Component which describes the transition probabilities between tobacco use states (e.g., cigarette initiation, cigarette cessation, switching between products, etc.), and (b) an epidemiological risk component which 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 smoking-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 function (based on the effective dose = f-value) of using IQOS compared with cigarette smoking.

The PHIM is based on smoking prevalence from publically available databases and the scientific literature covering a twenty-year period (1990-2010). Therefore, the model is designed to test scenarios in the context of realistic data and ask questions of the type: "what would have happened over a twenty-year period if IQOS had been introduced in 1990?"

A more detailed description of the model and the rationale for its development can be found in Section 2.7.6 pp 174-178 and Section 6.5 of the MRTPA as well as in recent publications (Weitkunat 2015, Lee 2017).

This epidemiology-based computational model can be used to estimate outcomes in smoking attributable mortality in the presence and absence of IQOS. The model was used to estimate the potential impact of IQOS on smoking attributable mortality using business case assumptions developed by PMP S.A. There are many uncertainties in the application of such models but they do provide a reasonable comparative estimate of the potential impact of IQOS on the population health.

20 Years of Cessation Model

To evaluate the estimated impact of IQOS on smoking attributable mortality, it is first necessary to consider the maximum achievable effect of smoking cessation, which is the "gold standard" for the maximum achievable risk reduction. Towards this end, the first simulation

examines a hypothetical scenario in which all current smokers would stop smoking immediately. In this scenario, 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.

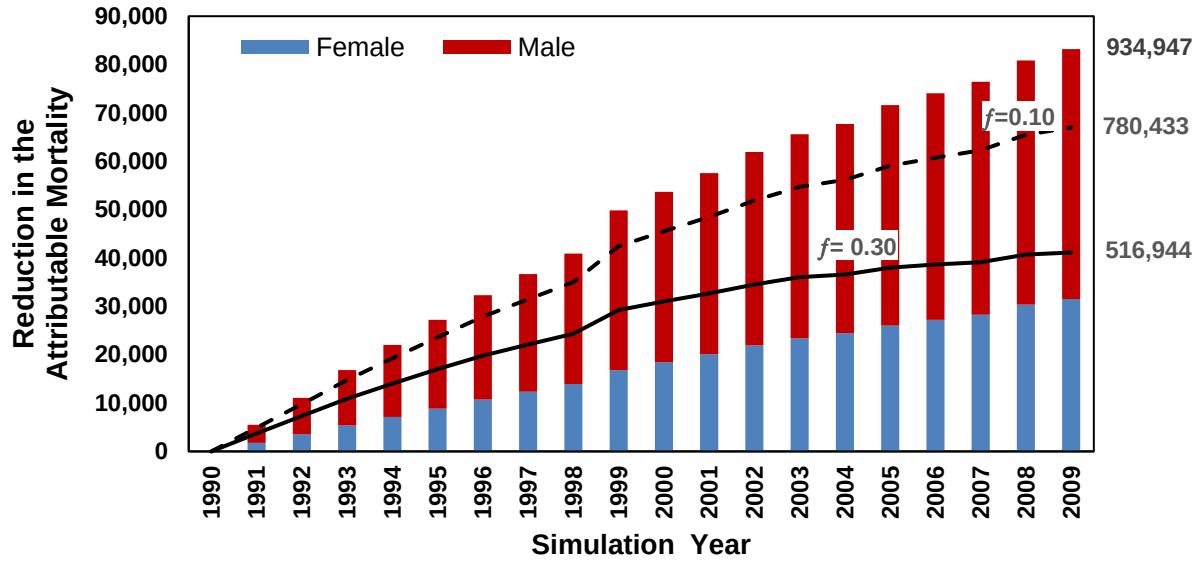


Figure 27: Reduction in the smoking attributable mortality each year (1990 to 2009) over the 20-year simulation under the hypothetical scenario where 100% of smoking is eliminated in 1990 (100% cessation)

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 but diminish gradually over time as depicted by the bar chart in Figure 27. In the initial years following the elimination of smoking, the annual reduction in smoking attributable deaths 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 would result in 934,947 fewer smoking attributable deaths (Figure 27). This number would further increase in subsequent years.

20 Years of IQOS (without cigarettes) Model

The maximal achievable impact of introducing IQOS into the U.S. market was tested in a second hypothetical scenario. In this scenario, all current smokers in 1990 immediately transitioned to IQOS, rather than cessation, assuming that cigarettes had completely disappeared from 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 IQOS instead of cigarettes.

To understand the range of the potential impact of IQOS, PMI included two relative exposure conditions for IQOS:

1. Condition 1: IQOS preserved the effects of cessation by 90% (f-value=0.10),
2. Condition 2: IQOS 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 IQOS 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 IQOS.

IQOS *Business Assumption*

In Section 6.5 of the MRTPA, PMI presents the "Business Case" for IQOS. This simulation assumed that 17% of the smoking population would be using IQOS within 10 years following its commercial launch (15% IQOS 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 (where the MRTP is not introduced) and the IQOS Scenario, as the majority of IQOS 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% IQOS users in 2009.

In the Business Case scenario, the introduction of IQOS 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).

IQOS *Business Assumption Combined with WHO 2025 Assumptions*

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 IQOS over 10 years. In this scenario, 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 IQOS -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 IQOS could provide additional reductions in smoking attributable deaths and function in a synergistic manner with efforts to reduce smoking prevalence.

PHIM *Conclusions*

The closeness of the "Null Scenario" model-based predictions to actual epidemiological and authoritative statistics from the U.S. population across the twenty-year study period provides a solid basis for assessing the potential population benefit of IQOS within the context of the MRTPA. In all but the most unlikely simulations, the introduction of IQOS resulted in fewer tobacco-related deaths. The degree to which tobacco-related deaths were reduced was primarily influenced by the prevalence of use of IQOS, 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 IQOS. This process may take time to allow for a meaningful number of smokers to convert to IQOS. 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 IQOS into the U.S. population will lead to a net public health benefit in terms of reduced cigarette-related mortality.

Post-market studies and surveillance

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 IQOS on individual consumers and the overall public health. The proposed post-market assessment 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 28. 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 IQOS.

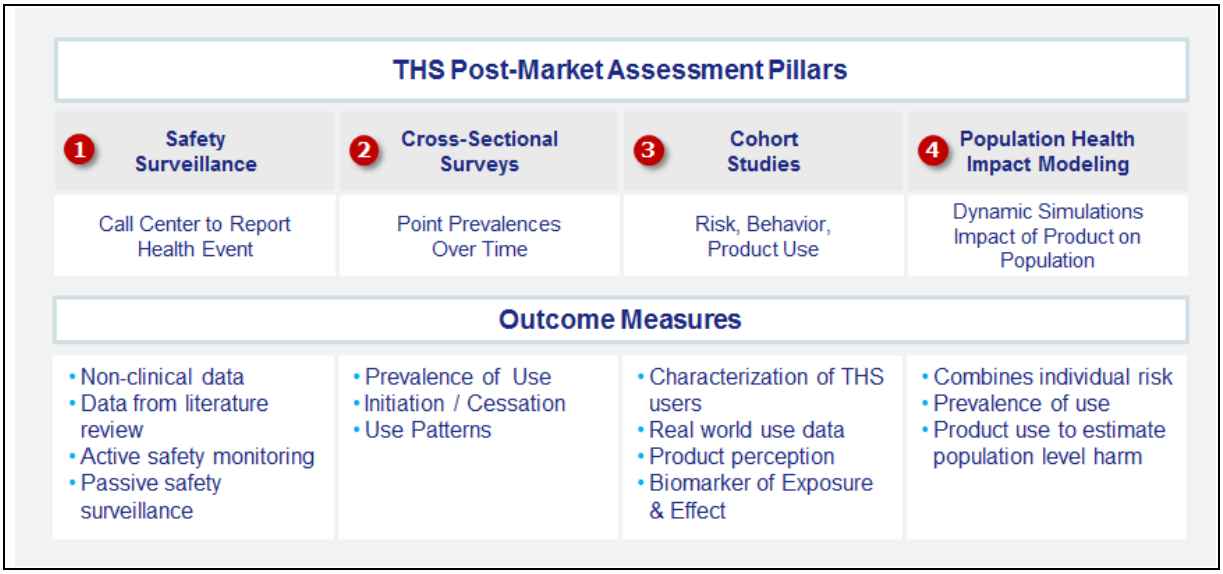


Figure 28: IQOS Post-Market Assessment Program

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 IQOS, 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 IQOS, monitoring of the use of IQOS and other tobacco products at the population-level, as well as determine the related tobacco use behaviors.

Following market authorization of IQOS, PMI[19] will submit to FDA an annual "Safety Summary Report" that will summarize the findings of all U.S. 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 U.S. report, PMI will also provide FDA with a summary safety report of IQOS in markets Outside the United States (OUS). A more detailed description of the program can be found in Chapter 2.7.6 pp 182-186 of the MRTPA.

Safety surveillance

PMI currently conducts safety surveillance activities in OUS markets to ensure that the medical safety oversight of IQOS is in line with relevant regulations in countries where IQOS 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 IQOS. PMI has the medical expertise for continuous assessment of IQOS 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 U.S. market, IQOS consumers will be able to contact and report any health-related event using ALCS's established AE collection system.

Outside the U.S., PMI has implemented a similar, but independent AE collection system for countries where IQOS 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 IQOS 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 IQOS with the National Poison Data System from the

[19] 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.

American Association of Poison Control Centers (AAPC) to allow the identification and tracking of AE reports through U.S. hospitals and emergency rooms.

All AEs regardless of their source will be consolidated into a single Safety database, coded and summarized in the IQOS *Annual Safety Report*. In addition to the AE reporting and the summary of AEs in the THS Annual Safety Summary Report, serious AEs (SAEs)[20] reported in the U.S. 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 IQOS 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 IQOS, its brand family, and product category. This infrastructure would serve as a signal detection tool to identify potential unanticipated and undesired events related to IQOS 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 IQOS 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 IQOS 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 IQOS consumers;
3. assess patterns of use such as concurrent/dual use with cigarettes; determine whether IQOS 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 IQOS.

PMI will assess the use of IQOS 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.

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

[20] 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)

market penetration for IQOS, 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 IQOS.

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. 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 harm and risk of tobacco-related disease to individual smokers who switch to IQOS and to confirm a net benefit to the population as a whole including users and non-users of tobacco products.

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 U.S. appear to be genuinely interested in both trial and use of IQOS. Adult smokers and adult nonsmokers alike understood the proposed IQOS communications and product proposition. Overall, the PMI modified-risk messages and claims generated substantial Intention to Use IQOS among adult smokers, while not encouraging adult nonsmokers to try/use IQOS. This is an important criterion in establishing the utility of IQOS as a harm reduction product.

The overall findings for current adult tobacco product users are summarized as follows:

- In all six PBA studies that looked at the effect of IQOS labeling and advertising materials, adult smokers (with no intention to quit) expressed a substantial interest in trying IQOS.
- Adult smokers expressed a consistent Intention to Use across studies with Intention to Use responses ranging between 20.2% and 38.9% of adult smokers.
- Study results indicate that the IQOS instructions for use are sufficient to explain the various tasks required to operate IQOS. The actual use study results indicate a low level of misuse potential.
- Exposure to either product messages or communication materials concerning IQOS 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 IQOS, as measured by nicotine uptake and subjective effects, is comparable to a cigarette, which is critical to adult smoker acceptance of IQOS 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 IQOS compared to cigarettes.
- Product use data collected in near real-world conditions provide evidence that adult daily smokers who consume IQOS freely with other tobacco and nicotine containing products do not increase their overall tobacco product consumption, whether they use IQOS predominantly or in combination with cigarettes.
- It is unlikely that those who rapidly and completely switch to IQOS 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. Taken together, the findings of the actual use study (U.S.) and the WOT (5 countries, not U.S.) show consistently that a sizeable proportion of adult smokers were able to adopt and continuously use IQOS 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 IQOS 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 IQOS to be of sufficient interest to start using IQOS, even in the event of significantly lower risk than cigarettes.

- Adult non-users of tobacco products did not show significant interest in IQOS 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 IQOS contains tobacco.
- There was only small Intention to Try/Use IQOS 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 IQOS 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 IQOS Brochure, nor the *HeatSticks* Pack or the IQOS Direct Mail generate Intention to Use among U.S. 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.

Comprehension and risk perception

It is likely that the use of IQOS will be substantially influenced by consumer perceptions regarding the health risks of IQOS. The IQOS communication materials are intended to convey accurate scientific information about the reduced risk of the product and to ensure that consumers evaluate/understand this risk appropriately within the context of other tobacco products and cessation and to understand that the use of IQOS is not risk free. The following points summarize key findings from the PBA studies:

- The proposed IQOS communication materials enabled the public to comprehend information concerning reduced risk and reduced exposure claims.
- Overall, consumers perceive that the health and addiction risks of using IQOS were lower than cigarettes but higher than NRTs or Cessation.
- The public perceives that IQOS is not risk free and is addictive.
- The results demonstrate that the content of the communication materials enable the public to understand the potential harm reduction benefits to substitute cigarettes with IQOS, as well as the relative risks of using IQOS compared to cigarettes, cessation aids and quitting smoking.
- A substantial portion of subjects in the reduced exposure claim study incorrectly stated that switching to IQOS 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.

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 U.S. market penetration and the relative risk of IQOS compared with cigarettes, PMI has conducted multiple simulations to model the potential impact of IQOS on the health of the U.S. population. The results of these stimulations show that introducing IQOS on the U.S. market would result in a significant reduction in smoking-attributable deaths.

Post-Market Assessment Program

The combination of the following overall findings, obtained prior to market launch of IQOS, is sufficient to expect a net reduction in harm at the population level. To confirm these overall finding, PMI has developed a Post-Market Assessment program that will enable the measurement of IQOS 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 seek to minimize, to the extent possible, any adverse and unintended population health effects that might arise.

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 IQOS has the potential to benefit the health of the population as a whole. Therefore, PMI believes that IQOS meets the second criterion for approval under Section 911(g) of the Federal Food, Drug, and Cosmetic Act (FD&C Act).

CONCLUSION

Section 911(g)(1) of the FD&C Act states that the Food and Drug Administration (FDA) shall issue a modified-risk market order for a tobacco product if the applicant demonstrates 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.

The MRTP Assessment Program Demonstrates IQOS Meets the Statutory Standard for a Marketing Order

The PMI scientific assessment program has demonstrated that IQOS will significantly reduce the harm and risk of tobacco-related disease for those for smokers who switch from cigarette smoking to IQOS use. The totality of the evidence discussed above and provided in the MRTPA establishes the following in support of this conclusion:

- IQOS produces significantly lower levels of HPHCs compared with cigarette smoke
- IQOS aerosol does not contain the carbon-based ultra-fine solid particles found in cigarette smoke
- IQOS aerosol is significantly less toxic than cigarette smoke
- IQOS aerosol causes significantly less disease-associated network perturbations *in vitro* and *in vivo*
- IQOS aerosol causes significantly less emphysema and atherosclerotic plaque in animal models of disease
- Clinical studies have shown that switching from cigarette smoking to IQOS leads to a significantly reduced exposure to HPHCs, which approaches the reductions in exposure that are seen with smoking abstinence
- Clinical studies have shown that switching from cigarette smoking to IQOS results in positive changes in clinical risk markers that are similar to those early changes that are seen following smoking cessation.

Smoking-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 4) 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 smoking-related disease.

Smoking cessation is the most effective way to reduce the subsequent risk of smoking-related disease in smokers. Smoking cessation is, by definition, the complete elimination of exposure 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.

Part A of the statutory standard requires a demonstration that harm and the risk of tobacco-related diseases is "significantly" reduced. As demonstrated by the evidence, IQOS is likely to approximate most of the reduction in risk that is seen with smoking cessation in those smokers who switch from cigarettes to IQOS. The basis for this statement is the fact that IQOS produces significantly lower (>90%) levels of HPHCs than cigarettes. As a result, IQOS aerosol has been shown to be significantly less toxic than 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 smoking-related disease causation.

The significance of these reductions in exposure were confirmed in a switching study conducted in an animal model of disease ($Apoe^{-/-}$ mouse), which confirmed that animals, switched from cigarette smoke exposure to either IQOS 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 IQOS 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 clinical findings that approach those seen with smoking abstinence. It is well understood that long-term epidemiology will provide a fuller determination on the overall impact of switching to IQOS. 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, demonstrate that switching to IQOS will result in a significant reduction in HPHC exposure, harm and risk of tobacco-related disease for the individual tobacco users. PMI submits that this evidence is sufficient to meet the requirements of a Risk Modification Order under Section 911(g)(1)) with regards to a significant benefit to individual users of tobacco products.

Part B of the statutory standard requires a demonstration of benefit to 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 reflected by the evidence discussed above and included in the MRTPA, IQOS will benefit the population as a whole. The IQOS product and the proposed claims and messages have been extensively tested across relevant populations including current adult smokers who do not intend to quit smoking, current adult 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.

Among adult smokers, IQOS 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 U.S. and in Whole Offer Tests conducted in non-U.S. markets (Japan, Italy, Germany, Switzerland, and South Korea). Across all studies, a substantial proportion of adult smokers were able to convert completely to IQOS use. The fact that a substantial proportion of adult smokers used IQOS 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 IQOS communication materials. However, this did not appreciably change their stated intention to quit smoking and all tobacco, providing sufficient evidence that IQOS would not alter the intentions of the 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 IQOS product and the reduced risk/exposure claims. Adult non-users did not seem interested in trial and use of IQOS after being exposed to the IQOS 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. Importantly, these findings extended to never smokers and young adult never smokers (LA-25) who expressed low levels of positive Intention to Try and Intention to Use.

Overall, the PMI Perception and Behavior Assessment program provides strong evidence that the IQOS 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 IQOS 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 IQOS 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 nonclinical, clinical and perception/behavioral studies. All of these studies showed coherent findings of reduced biological impact of the IQOS aerosol compared with cigarette smoke and show that the appropriate consumer groups are able to respond to the product concept and communication materials in a manner that is consistent with public health objectives. In summary, the totality of the scientific evidence generated for this application demonstrates that IQOS meets the two-part standard for a marketing order under Section 911(g)(1) of the FD&C Act and that FDA should authorize a Risk Modification Order.

The review and authorization of a marketing order for a product like IQOS, with the substantial body of data demonstrating its effect on the individual smoker and the health of the public at large, was exactly what Congress and other public health advocates had in mind when the FD&C Act was amended to provide FDA comprehensive authority over tobacco products. This comprehensive authority specifically provided for a pathway for the marketing of reduced risk products. As noted by FDA in its draft guidance on Modified Risk Tobacco Product Applications:

> The modified risk tobacco product provisions of the FD&C Act 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 either the toxicity or addictiveness of tobacco products, or both.

There are always uncertainties in a regulatory decision to authorize marketing of an innovative product based on pre-market data, regardless of the product category at issue. In the MRTP context, these uncertainties are addressed through the statutory authority provided by the Tobacco Control Act. As amended, the FD&C Act is now designed to guard against tobacco products that purport to have, but do not actually have, a reduction in the harm or risk of disease caused by cigarette smoking. It guards against consumer deception by tightly regulating statements regarding tobacco products directed to a consumer which even imply an unsubstantiated reduction in risk. And it guards against a product which might benefit the individual smoker, but result in a net harm to the public, by requiring substantiation of both individual risk reduction and a net benefit to the public. Furthermore, a marketing order does not provide unrestricted access to the market. Marketing orders are time limited, requiring sponsors to come back to FDA and submit new MRTPAs for review before being permitted to continue to market the product. FDA has substantial oversight authority, including the authority to impose post-marketing requirements, as well as the ability to modify or revoke a marketing order. FDA is uniquely suited to the task of review and regulation of modified risk tobacco product given its deep scientific expertise, sophisticated regulatory experience and focus on the protection of the public health.

The decision to authorize a risk modification order for IQOS would provide U,S, smokers access to a product that is significant improvement over conventional cigarettes and provide accurate, non-misleading statements to permit informed choices. IQOS is not a perfect solution; it contains nicotine and is not risk free. The best choice is to quit tobacco altogether, but for those that do not quit, IQOS is a better choice. Maintaining the status quo for adult smokers will result in a significant number of smokers continuing to use combustible products which will continue to lead to high rates of tobacco related diseases. IQOS meets the statutory standards and should be allowed to enter the market in a careful and deliberate manner under FDA regulation and oversight. A marketing order for IQOS is consistent with the intent of the Tobacco Control Act to advance the goals of tobacco harm reduction by providing adult smokers with lower risk alternatives and truthful and non-misleading risk information. The scientific evidence, when considered in its totality, demonstrates that IQOS has satisfied the requirements of Section 911(g)(1) of the FD&C Act and should be granted the requested marketing order.

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APPENDICES

Appendix A: Biomarkers of Exposure

Biomarkers of Exposure (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 4**.** were selected for THS assessment using the following criteria:

1. The HPHCs selected were 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 the reduced exposure studies, PMI measured 16 BoExp to HPHCs as well as nicotine and its metabolites (Table 4). These included BoExp for 14 of the 18 HPHCs currently mandated for reporting to the FDA (four not included due to criterion #5 above are: acetaldehyde, ammonia, formaldehyde and isoprene) (justification detailed in Section 6.1.3.1 of the MRTPA). 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 (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.

Table 4: 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)

S-BMA, the biomarker of exposure to toluene, did not show any difference in levels across study arms, including smoking abstinence. This is likely due to a lack of sensitivity of the analytical method. The data for all studies is summarized in Section 6.1.3.2 of the MRTPA.

Appendix B: Comprehension of IQOS instructions for use and potential for product misuse

THS-PBA-06-US was a usability and comprehension study of the IQOS instructions for use and was conducted among adult smokers. It was designed to address 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 IQOS. 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 IQOS properly and understand the key messages of the IQOS instructions for use. More details about the study can be found in Section 7.3.2 of the MRTPA.

Product Usability: Correct Use and Potential for Misuse

The THS-PBA-06-US study evaluated the usability and the comprehension of IQOS instruction for use in 258 adult cigarette smokers in the US. The majority of use tasks (e.g., charging the IQOS Holder, how to consume the IQOS Tobacco Stick, how to remove a stuck IQOS Tobacco Stick from the IQOS Holder) were executed correctly by more than two-thirds of the participants. A few tasks (how to insert the IQOS Tobacco Stick into the IQOS Holder, how to remove the IQOS Tobacco Stick, how to heat-clean the IQOS Holder, how to use the IQOS 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 IQOS with cigarettes, 95% understanding not to use *HeatSticks* as a cigarette and 67% of consumers understanding that the IQOS Holder should be fully charged prior to cleaning.

Overall, the results of the THS-PBA-06-US study indicated that the IQOS instructions for use seem to be adequate in explaining the various tasks required to normally operate IQOS and suggest that IQOS 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 IQOS Device (Section 3.5 of the MRTPA).

Potential Misuse of IQOS

The potential for misuse was also assessed during the Actual Use Study, THS-PBA-07-US. Misuse of IQOS 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 IQOS 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 IQOS Device with a product other than IQOS Tobacco Sticks.

Overall, these results suggest a low level of misuse potential and that IQOS is likely to be used as designed and intended by adult smokers. Events of unintended use are taken seriously by PMI and will be further monitored and addressed as part of the post-market assessment program.