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Delivering a smoke-free future

PMI SCIENCE
PHILIP MORRIS INTERNATIONAL

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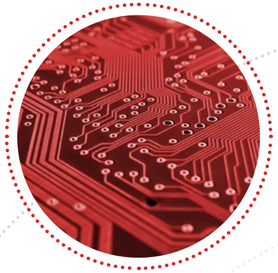

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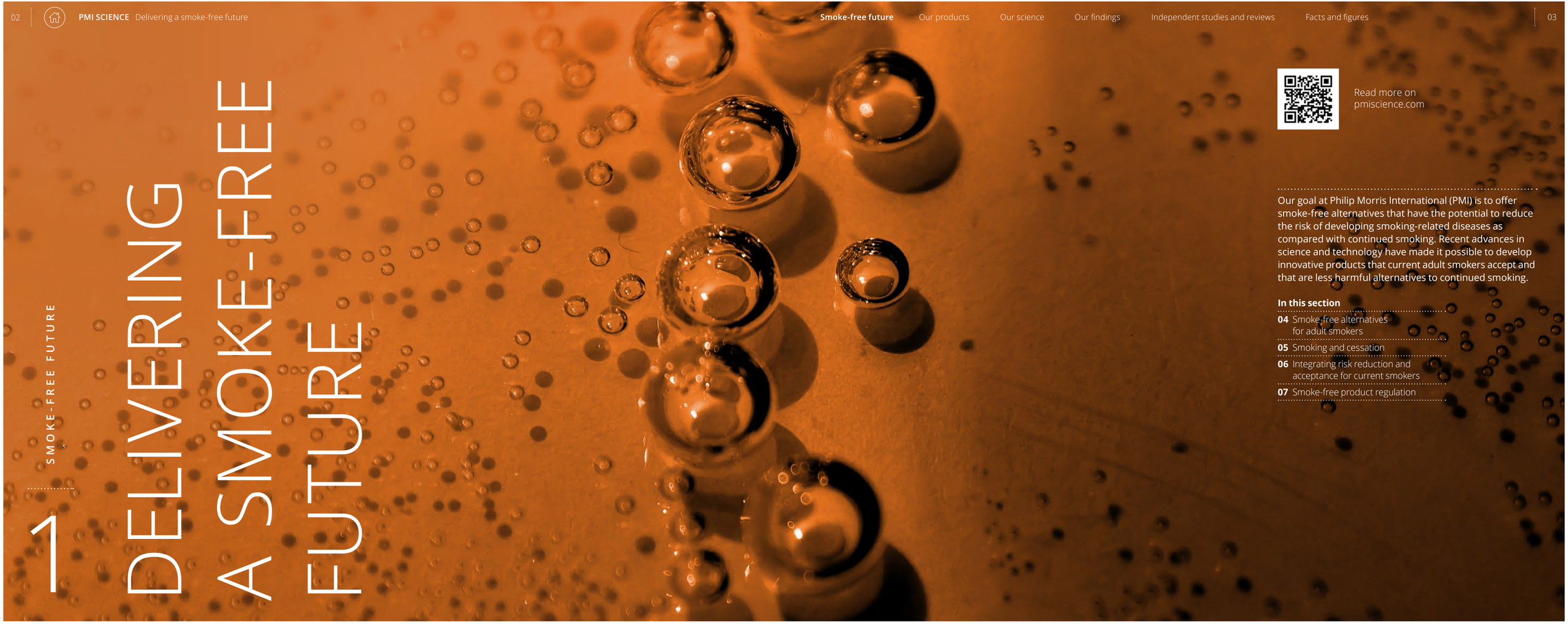

SMOKE-FREE FUTURE

1 DELIVERING A SMOKE-FREE FUTURE

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Our goal at Philip Morris International (PMI) is to offer smoke-free alternatives that have the potential to reduce the risk of developing smoking-related diseases as compared with continued smoking. Recent advances in science and technology have made it possible to develop innovative products that current adult smokers accept and that are less harmful alternatives to continued smoking.

In this section

CHAPTER 1

SMOKE-FREE ALTERNATIVES FOR ADULT SMOKERS

Smoking tobacco causes a number of serious diseases and increases the risk of early death.

Tobacco control strategies in most countries focus on supply and demand measures intended to prevent initiation, reduce consumption, and encourage cessation. These measures have resulted in a decline in smoking prevalence over the last three decades, but are unlikely to quickly eliminate smoking altogether. In fact, there are about 1 billion smokers in the world to date and, according to the World Health Organization (WHO), this number will not significantly decrease in the coming years.[1]

Given the number of smokers who will continue to smoke cigarettes, and as the technology now exists and will continue to develop, it makes sense to offer them less harmful, yet satisfying, smoke-free alternatives.

In this regard, sensible risk-based policies and regulations should allow adult smokers to access scientifically substantiated smoke-free products to help address the harm caused by smoking more effectively and rapidly than traditional policy measures alone.

"SEVEN YEARS AGO, WE SET OUT TO CREATE A NEW FUTURE FOR PMI—A FUTURE IN WHICH CIGARETTES WOULD BE OBSOLETE, REPLACED BY LESS HARMFUL, SCIENCE-BASED ALTERNATIVES."

Jacek Olczak Chief Executive Officer, Philip Morris International

SMOKING AND CESSATION

We know from epidemiology that smoking increases the risk of developing a smoking-related disease.

Epidemiology has also demonstrated that if a smoker quits, the risk of developing a smoking-related disease decreases.

Since smoking cessation is the "Gold Standard" for assessing the reduction in risk for adult smokers,[2] our goal is to develop products that have a risk profile as close as possible to that of smoking cessation, while being acceptable alternatives to cigarettes for adult smokers who would otherwise continue to smoke.

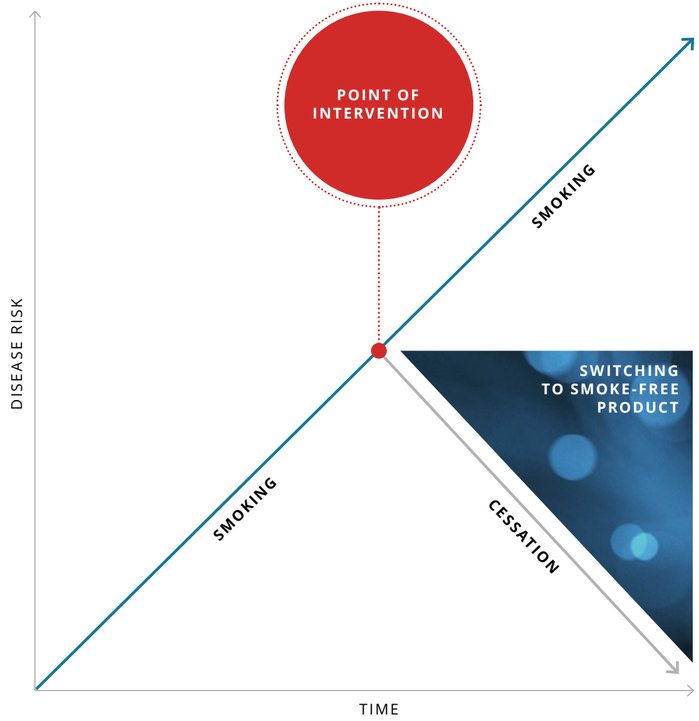


FIGURE 1

Conceptual depiction of the cumulated risk of smoking and the effect of cessation over time.[3] 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 a smoke-free product follow different trajectories for specific diseases.

CHAPTER 1

INTEGRATING RISK REDUCTION AND ACCEPTANCE FOR CURRENT SMOKERS

For any smoke-free alternative to be successful in reducing population harm, it has to fulfill two criteria: it must be scientifically proven to be significantly less harmful than cigarettes; and, it should be satisfying for current adult smokers.

In addition to taste, and other sensory aspects, a nicotine profile approaching that of cigarettes is important in achieving acceptance by adult smokers. Experts, including the U.S. Surgeon General and the U.K. Royal College of Physicians, agree that nicotine, while addictive, is not the primary cause of smoking-related diseases.

Smoking-related diseases, such as lung cancer, cardiovascular disease, and emphysema, are caused primarily by inhaling harmful compounds largely formed when tobacco is burned, not by nicotine alone.

As the U.S. Food and Drug Administration (FDA) has stated[4] "inhalation of nicotine (*i.e.*, nicotine without the products of combustion) is of less risk to the user than the inhalation of nicotine delivered by smoke from combusted tobacco products."

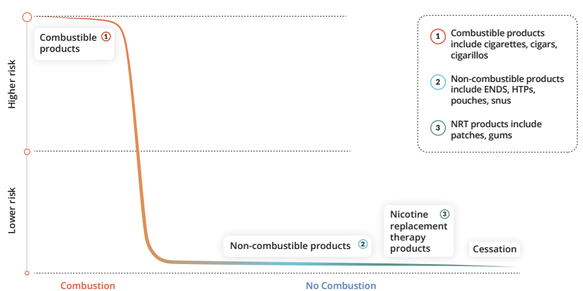
Not all tobacco products are the same. Their use exists along a continuum of risk, where smoking combusted tobacco yields the highest risk and quitting nicotine and tobacco products altogether contributes the lowest risk. The use of other tobacco products, including smoke-free products, also lie in that continuum of risk. Products that don't burn tobacco are likely to be far less harmful alternatives to continued smoking.

FIGURE 2 THE HARM REDUCTION EQUATION

Adapted from Clive Bates' presentation at the E-Cigarette Summit on 19 November 2013.

FIGURE 3

The continuum of risk shows that non-combustible products are lower risk than cigarettes.



ENDS: Electronic Nicotine Delivery Systems, HTPs: Heated Tobacco Products, NRT: Nicotine Replacement Therapy

SMOKE-FREE PRODUCT REGULATION

Advanced technological and scientific solutions require advanced regulatory tools.

Offering smoke-free alternatives to adult smokers can reduce the risk of harm. This approach should be supported by public health bodies, in addition to existing efforts to prevent smoking initiation and encourage cessation.

Progressive regulatory oversight can protect public health whilst simultaneously ensuring that adult smokers can access smoke-free products as well as accurate and non-misleading information about them.

Access to such information is a common-sense approach to public health.

Modern regulation should take into account the novel nature of smoke-free products. It should ensure that specific quality and performance standards are met. Robust scientific evidence should demonstrate their reduced-risk profile.

Our contribution so far

Our comprehensive body of scientific evidence for our leading smoke-free product, the tobacco heating system (THS), has been submitted to regulatory bodies in several countries.

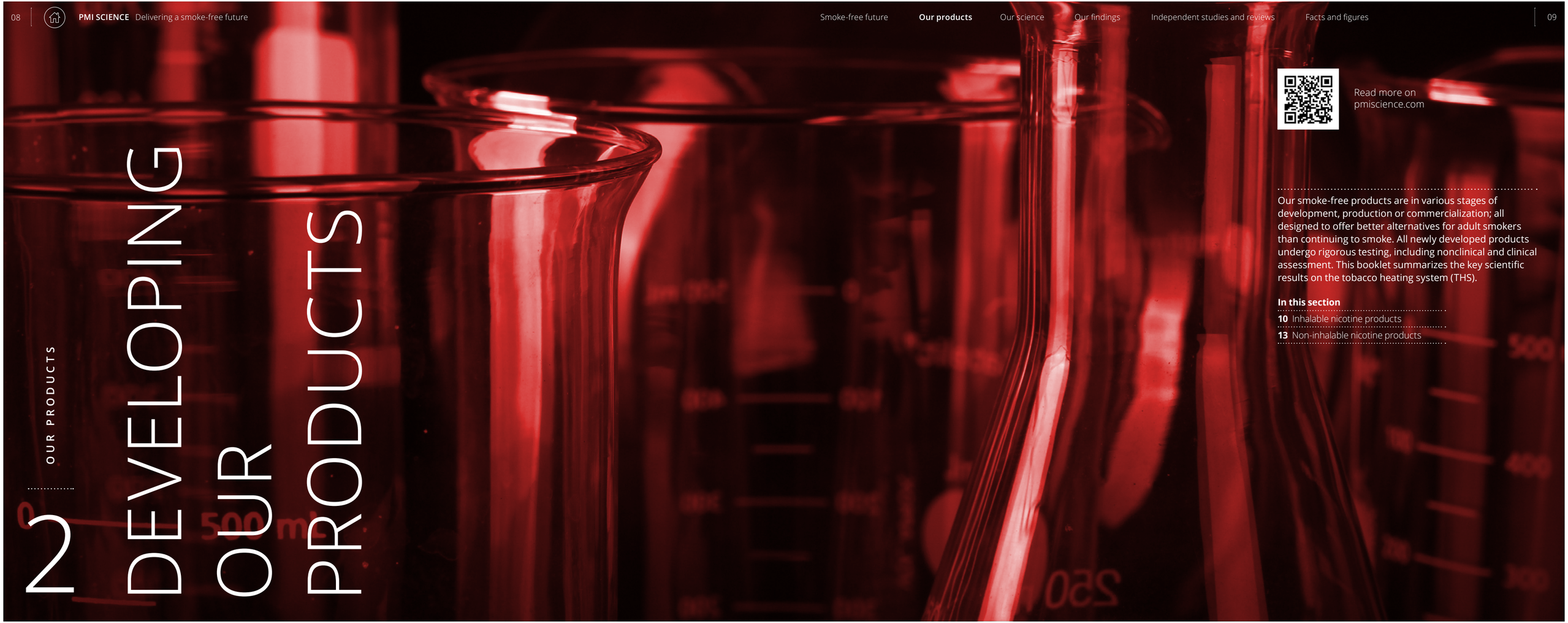
We submitted Modified Risk Tobacco Applications (MRTPAs) in December 2016 and Premarket Tobacco Product Applications (PMTAs) in March 2017 to the U.S. FDA.

We also submitted technical and scientific dossiers to regulatory authorities in several EU member states.

In April 2019, following a rigorous science-based review through the PMTA pathway, the U.S. FDA determined that authorizing THS for the U.S. market is appropriate for the protection of the public health.[5]

IN JULY 2020, THE U.S. FDA AUTHORIZED THE MARKETING OF THE TOBACCO HEATING SYSTEM AS A MODIFIED RISK TOBACCO PRODUCT WITH REDUCED EXPOSURE INFORMATION.[6]

THE AGENCY FOUND THAT THE ISSUANCE OF THE MODIFIED RISK TOBACCO PRODUCT ORDERS WITH REDUCED EXPOSURE INFORMATION WOULD BE "APPROPRIATE TO PROMOTE THE PUBLIC HEALTH AND IS EXPECTED TO BENEFIT THE HEALTH OF THE POPULATION AS A WHOLE."



OUR PRODUCTS

2 DEVELOPING OUR PRODUCTS

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Our smoke-free products are in various stages of development, production or commercialization; all designed to offer better alternatives for adult smokers than continuing to smoke. All newly developed products undergo rigorous testing, including nonclinical and clinical assessment. This booklet summarizes the key scientific results on the tobacco heating system (THS).

In this section

CHAPTER 2

INHALABLE NICOTINE PRODUCTS

All of these products avoid burning tobacco or producing smoke, each in its own way. They are designed to deliver a nicotine-containing aerosol with a reduced level of harmful and potentially harmful toxicants compared with cigarette smoke.

The products depicted are subject to ongoing development and therefore visuals are illustrative and do not necessarily represent the latest stages of product development.

HEATED TOBACCO PRODUCTS

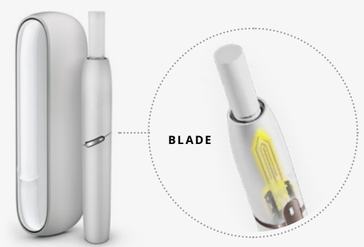
Tobacco heating system (THS)

THS heating technologies include blade and induction heating.

THS uses an electronic heat-control technology to heat tobacco within a specific temperature range. Extensive laboratory and clinical data are available supporting its potential for risk reduction compared with continued cigarette smoking. Standard THS consists of three components: a pocket charger, a holder, and a heated tobacco unit.

THS 2.2
BLADE/RESISTIVE HEATING

A heating blade that heats the tobacco plug in the consumable radially outwards from the center of the tobacco plug.



THS 3.0
INDUCTION HEATING

The induction THS uses the same internal tobacco heating principle as the blade THS, but without the blade. This means there is no direct contact between the electronics and the heating element. The tobacco is heated from within the tobacco stick through energy transfer to a heating element via a magnetic field.

Pin-based heating system (PHS)

PHS electrically heats the tobacco using either inductive or resistive heating. Developed by KT&G.*

*KT&G is the leading tobacco and nicotine company in South Korea.

Oven Heating System (OHS)

OHS uses resistive external heating, with no blade, via the ROUNDHEAT TOBACCO SYSTEM™, to heat the tobacco across the external surface of the tobacco stick instead of burning it like a cigarette does.

AEROSOL HEATED TOBACCO PRODUCTS

Aerosol heating system (AHS)

AHS combines elements of e-cigarettes and heated tobacco products into a single hybrid system. Developed by KT&G.

INHALABLE NICOTINE PRODUCTS

E-VAPOR PRODUCTS

Ceramic Vaping System (CVS)

CVS represents our latest advancement in the e-vapor category. The heating technology utilized in CVS is founded on an innovative H-shaped ceramic heater, which features a ceramic microporous substrate with a printed metallic heating track.

Disposable Vaping System (DVS)

Our ergonomically designed all-in-one pocket-sized DVS requires no charging, no cleaning, and no refilling. Unlike our THS, which heats real tobacco, these single-use e-cigarettes are battery-powered devices that vaporize a nicotine-containing liquid to create an inhalable aerosol.

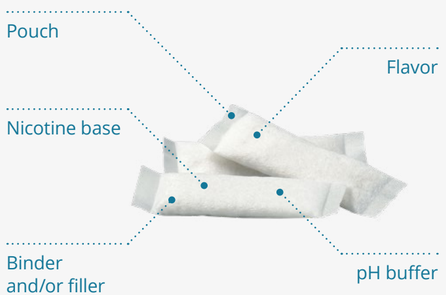
NON-INHALABLE NICOTINE PRODUCTS

Instead of producing an aerosol that is inhaled, these products are placed under the lip so that nicotine can be absorbed via the mouth. Our non-inhalable products include oral tobacco products and oral nicotine products.

ORAL SMOKELESS POUCHES

Nicotine pouches

The oral smokeless category doesn't involve a device, heating, or the inhalation of an aerosol. Instead, a teabag-like pre-portioned pouch that contains nicotine (but not tobacco), is placed between the gum and lip and removed after use. The nicotine is extracted through the action of saliva and is absorbed mainly via the mucous membranes in the mouth before entering the bloodstream. Some nicotine can also reach the gastrointestinal tract if saliva is swallowed.



03 OUR SCIENCE

INNOVATING OUR SCIENCE

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Our scientific assessment is built on a collaborative approach and expertise in the fields of chemistry, toxicology, biology, informatics, medicine, and perception and behavior. Our practices are inspired by the pharmaceutical industry and aligned with U.S. FDA's Draft Guidance for Modified Risk Tobacco Product Applications (2012).[7]

In this section

CHAPTER 3

OUR SCIENTIFIC APPROACH

PLATFORM DEVELOPMENT

The assessment of a smoke-free product's risk reduction potential relies on the quality of the initial product design and on strict manufacturing controls to ensure that the product delivers a consistent aerosol.

The products are specifically designed with the aim to eliminate or reduce the levels of Harmful and Potentially Harmful Constituents (HPHCs) found in their aerosol compared with those found in cigarette smoke.

In this initial phase of designing a product, it is verified that the product's design does not pose any additional risks to those already known for combustible cigarettes. Only then can we begin to conduct further research.

TOXICOLOGICAL ASSESSMENT

Toxicological assessment aims to confirm whether the reduced formation of HPHCs leads to reduced toxicity and shows the potential for reduced risk of smoking-related diseases in laboratory models.

PMI conducts a series of *in vitro* and *in vivo* studies on smoke-free products, following Good Laboratory Practice (GLP), to determine whether the reduced levels of HPHCs lead to a reduced toxicity compared with cigarette smoke.

We take toxicological assessment one step further by using a new area of science known as systems toxicology. Systems toxicology helps to show the potential for reduced risk of smoking-related diseases in laboratory models.

CLINICAL ASSESSMENT

Clinical studies are a cornerstone of our assessment program to demonstrate the reduced-risk potential of our smoke-free products.

They help determine the extent to which adult smokers would find the product an acceptable alternative to cigarettes.

They assess whether a reduction in the formation of HPHCs measured in the laboratory leads to a reduction in HPHC exposure under real-world conditions when an adult smoker switches to the product.

And they also investigate whether switching from cigarettes to a smoke-free product has a beneficial effect on a smoker's health profile by reducing the risk of smoking-related diseases as compared with continued smoking.

1 **PHARMACOKINETICS / PHARMACODYNAMICS**

Measures

- Smoking behavior
- Nicotine uptake
- Subjective effects

2 **REDUCED EXPOSURE**

Measures

- Exposure to harmful chemicals

3 **EXPOSURE RESPONSE**

Measures

- Changes in blood chemistry
- Functional health and symptoms

PERCEPTION AND BEHAVIOR

Perception and behavior studies help us evaluate risk perceptions and patterns of use of smoke-free products among various adult consumer groups.

For smoke-free products to have an overall positive impact on public health, it is important that adult smokers use them, that those intending to quit tobacco and nicotine altogether are not dissuaded by these products, and that nonsmokers do not use them.

Moreover, smokers should understand that quitting is the best way to reduce smoking-related health risks, and that these products are only for smokers who would otherwise continue to smoke.

LONG-TERM ASSESSMENT

The assessment of our smoke-free products continues after the products are placed on the market.

Long-term assessment, including post-market studies, will confirm whether these products reduce the risk of smoking-related diseases such as chronic obstructive pulmonary disease, cardiovascular disease, and lung cancer.

We combine a number of approaches, including safety surveillance, clinical studies, and epidemiological studies, in order to obtain a progressively clearer picture of the risk-reduction potential of our products.

1 **SAFETY REPORTS**

- Feedback from consumers
- Through scientific literature

2 **COHORT STUDIES**

- Defined group of people
- Followed through time

3 **CROSS-SECTIONAL SURVEYS**

- Defined groups of people
- Snapshots in time

CHAPTER 3

HOW DOES PMI CONDUCT ITS SCIENTIFIC ASSESSMENTS?

QUALITY PRINCIPLES

At each step, scientific rigor is applied to generate data that may support a claim that smoke-free products reduce exposure to harmful and potentially harmful constituents and present less risk of harm than continued smoking.

A risk-based Quality Management System has been conceived for smoke-free products to coordinate and guide activities with the aim of ensuring quality and integrity of the product during its complete lifecycle, from the conception through to commercialization.

ENSURING QUALITY AND INTEGRITY OF THE PRODUCT DURING ITS COMPLETE LIFECYCLE, FROM THE CONCEPTION THROUGH TO COMMERCIALIZATION.

PLATFORM DEVELOPMENT		**PRODUCT DESIGN AND CONTROL** Quality by Design (QbD)[8]	**AEROSOL CHEMISTRY** OECD GLP[9]; ISO[10] 17025; ICH Q2 (R1)[11]; ISO 3308*, 3402, 4387*, 8454, 10315:2013, 10362-1*, 13110, 19290, 20768, 20778	**INDOOR AIR QUALITY** ISO 17025; EN 15251[12]; ISO 15593, 18144, 18145, 16814, 16000-6, 11454
TOXICOLOGICAL ASSESSMENT		**NONCLINICAL STUDIES** OECD Test Guidelines; ICH Guidelines; FDA Guidelines; Applicable National Regulations; GLP; ISO 17025		
CLINICAL ASSESSMENT		**CLINICAL STUDIES** WMA Declaration of Helsinki[13]; Based on ICH-GCP E6 (R2)[14]; Applicable Local Regulations		
PERCEPTION AND BEHAVIOR		**PERCEPTION AND BEHAVIOR ASSESSMENT** Based on GEP-DGEpi[15]; Based on FDA Guidance on TPPI; FDA Guidance on PRO[16]; Applicable National Regulations; Declaration of Helsinki		
LONG-TERM ASSESSMENT		**OBSERVATIONAL STUDIES** IEA GEP[17]; Applicable National Regulations		

* With slight modifications needed to adapt to smoke-free products.

OUR FINDINGS

4 DIVING INTO OUR FINDINGS

THE TOTALITY OF EVIDENCE GATHERED SO FAR DEMONSTRATES THAT THE TOBACCO HEATING SYSTEM (THS) IS A BETTER CHOICE FOR ADULT SMOKERS WHO WOULD OTHERWISE CONTINUE SMOKING CIGARETTES AND THAT SWITCHING COMPLETELY TO THS PRESENTS LESS RISK OF HARM THAN CONTINUED SMOKING.

HIGHLIGHTS

Read more on pmiscience.com

In the following section we dive into many of our key findings. From the vital discovery that there is no burning in THS (version 2.2) through to the findings around positive impact on smokers' health up to the usage pattern of THS when the product is launched.

PLATFORM DEVELOPMENT

TOXICOLOGICAL ASSESSMENT

CLINICAL ASSESSMENT

PERCEPTION AND BEHAVIOR

LONG-TERM ASSESSMENT

CHAPTER 4: PLATFORM DEVELOPMENT

THERE IS NO BURNING IN THS

Decades of scientific research show that the primary cause of smoking-related disease is the high levels of Harmful and Potentially Harmful Constituents (HPHCs) in smoke formed during the combustion of tobacco.

During a puff of a cigarette, the temperature increases to more than 800 °C at the tip.[18] The combustion of tobacco results in the formation of smoke (containing high levels of HPHCs), heat, and ash.

We have conducted several studies to demonstrate the absence of combustion in THS, including temperature measurements, experiments demonstrating the absence of net exothermic processes, and measurements of constituents that represent typical markers of combustion.[19]

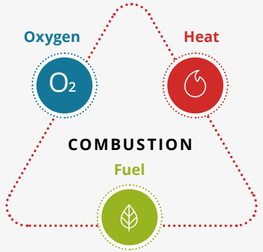
Our studies also support that the aerosol of THS does not contain solid particles that are produced when tobacco is burned.[20] In addition, since burning requires oxygen, we have tested THS in an oxygen-free atmosphere.

The results showed that oxygen does not play a major role in the thermochemical degradation of the THS tobacco or the aerosol formation. Combustion does not occur during THS use.

COMBUSTION DOES NOT OCCUR DURING THE USE OF THE TOBACCO HEATING SYSTEM.

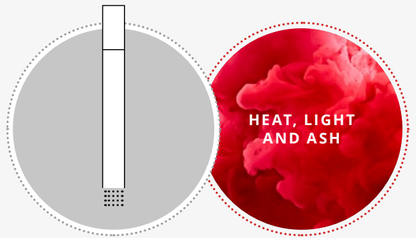
DID YOU KNOW?

Smoke is a result of combustion



For combustion to occur, three things need to be present: a fuel to be burned, a source of oxygen, and a source of heat.

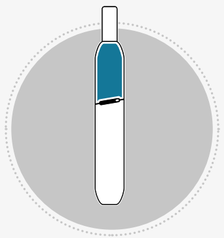
CIGARETTES SMOKE



During the puff of a cigarette, the temperature increases to more than 800 °C at the tip. The combustion of tobacco results in the formation of ash, heat and light (energy), and smoke.

Smoke contains high levels of harmful chemicals, most of which are formed during combustion, also known as burning.

HEATED TOBACCO



Heated tobacco products do not combust tobacco and therefore produce an aerosol that is not smoke.

CHAPTER 4: PLATFORM DEVELOPMENT CONTINUED

REDUCED EMISSIONS OF HARMFUL CHEMICALS

BY ELIMINATING COMBUSTION, THE LEVELS OF HARMFUL CHEMICALS ARE REDUCED ON AVERAGE BY 95% IN THE AEROSOL OF THE TOBACCO HEATING SYSTEM COMPARED WITH THOSE IN CIGARETTE SMOKE.

Aerosol chemistry: Targeted analysis

We measured a number of harmful chemicals in the aerosol of THS and compared them with the levels found in the smoke of a standard reference cigarette (3R4F). On average, a 95% reduction in the levels of these HPHCs in THS aerosol was observed.[21]

FIGURE 4

Reduced emissions of HPHCs from THS use. The average level of HPHCs in THS aerosol is shown by the red bar and is compared with the average level of HPHCs in smoke from the 3R4F reference cigarette marked as 100% in the graphic.

* Average reductions in levels of a range of harmful chemicals (excluding nicotine) compared with the smoke of a reference cigarette (3R4F). Based on the FDA 18,[22] IARC,[23] and WHO 9[24] lists of HPHCs.

Aerosol chemistry: Untargeted analytical screening

The comprehensive chemical characterization of THS aerosol using untargeted analytical screening methods revealed that a total of 532 chemical constituents (including water, glycerin, and nicotine, which were measured using different methods) were present at concentrations ≥ 100 ng/heated tobacco unit.[25]

The identities for 80% of all chemical constituents measured using untargeted screening, representing > 96% of the total determined mass, were confirmed with purchased reference chemicals. All compounds that were detected in THS aerosol ≥ 100 ng/heated tobacco unit were also found to be present in smoke from the standard reference cigarette 3R4F.

Only a minority of compounds in THS aerosol were present at concentrations exceeding those measured in cigarette smoke.

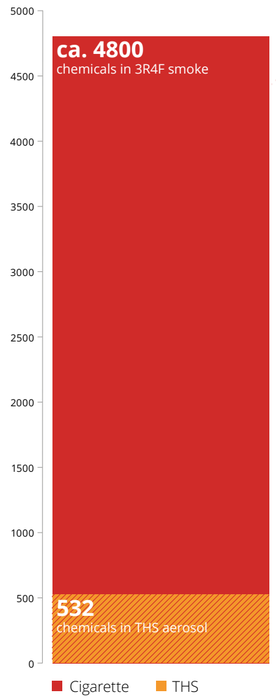
To identify any potential new hazards presented by exposure to THS aerosol, untargeted differential screening was also performed, which only looked for chemicals that were significantly more concentrated in THS aerosol compared with cigarette smoke.

The compounds that were found to be significantly higher in THS aerosol compared with cigarette smoke, including three compounds that were unique to THS aerosol (all with concentrations < 100 ng/heated tobacco unit), were submitted for toxicological evaluation. Four compounds were subsequently highlighted to be of potential toxicological concern.

The levels of these four compounds were very low and the U.S. FDA concluded that "Although some of the chemicals are genotoxic or cytotoxic, these chemicals are present in very low levels and potential effects are outweighed by the substantial decrease in the number and levels of HPHCs found in CC [combusted cigarettes]."[26]

FIGURE 5

This graph presents the untargeted characterization results of the regular variant of the THS heated tobacco unit. The 532 chemicals present in THS aerosol are also present in 3R4F cigarette smoke (≥ 100 ng/heated tobacco unit).



To the best of our knowledge, this is the first time that such a comprehensive in-depth chemical characterization of the aerosol composition of a heated tobacco product has been reported. This work represents several years of effort in the field of analytical method development and advanced structural identification techniques, which have been applied to the THS aerosol.

CHAPTER 4: PLATFORM DEVELOPMENT CONTINUED

DID YOU KNOW?

People have been talking about tar in cigarettes for a long time, yet 'What is tar?' is a question often asked today, and there are many myths surrounding the topic.

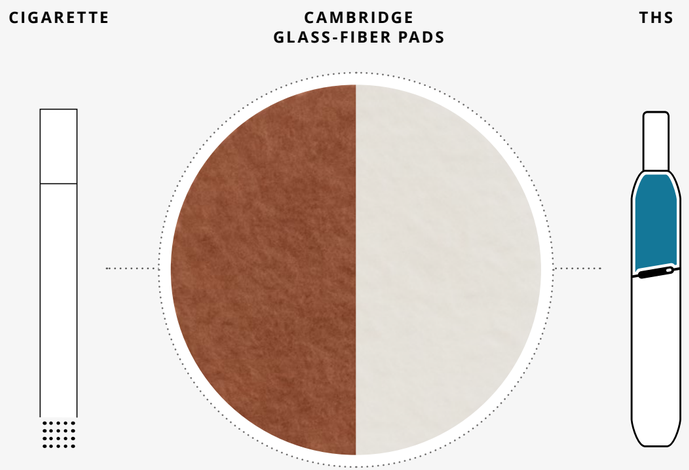
Tar is the weight of solid and liquid residue in cigarette smoke, after nicotine and water have been removed. It's not an added chemical nor the material used to pave roads, it's simply a weight measurement. So, is tar measurement useful? If we only take the weight into account, no it's not.

Out of context, the weight gives no indication of residue content nor the risk of harm because the level of toxicants within that weight are unknown, and the WHO agrees, "While several Parties include tar in their regulatory policies, it is not on the priority list of toxicants in tobacco smoke emissions, as the composition of tar varies qualitatively and quantitatively in each type of product, limiting the possibility for validated testing and measurement."[27]

Put another way, the WHO says, "Tar need not be measured, as it is not a sound basis for regulation, and the levels can be misleading."

When people consider the risk of harm of a product in relation to tar it's more important to look at the content of the residue rather than its weight. When we look at the content of cigarette smoke, there are thousands of chemicals released and of those the U.S. FDA has listed 93 known toxicants. It is the presence of and exposure to these chemicals that plays a role in the development of smoking-related diseases, not the tar measurement.

FIGURE 6
The picture shows the visual difference between the particulate matter of standard reference cigarette smoke (1R6F, left) and the particulate matter of THS aerosol (right) after collection on Cambridge glass-fiber pads (1 stick per product, aerosol regime ISO 20778:2018).



TAR NEED NOT BE MEASURED, AS IT IS NOT A SOUND BASIS FOR REGULATION, AND THE LEVELS CAN BE MISLEADING.

World Health Organization

CHAPTER 4: PLATFORM DEVELOPMENT CONTINUED

NO ADVERSE EFFECT ON THE OVERALL INDOOR AIR QUALITY

Measuring air quality markers in accordance with international guidelines allows to assess the quality of indoor air.

We measured 24 compounds including carbonyls, tobacco-specific nitrosamines, and volatile organic compounds under simulated residential conditions.

When using THS, the levels of 21 of these compounds did not increase beyond the levels already present as background in our dedicated Indoor Air Quality room. Only the nicotine, acetaldehyde, and glycerin were measurably higher than the background, although well below the exposure limits established in air quality guidelines.[28, 29, 30]

THE USE OF THE TOBACCO HEATING SYSTEM IN AN INDOOR ENVIRONMENT, WHERE REGULATORY NORMS OF ADEQUATE VENTILATION ARE RESPECTED, DOES NOT ADVERSELY AFFECT THE OVERALL INDOOR AIR QUALITY.

THS USE HAS NO ADVERSE EFFECT ON THE OVERALL INDOOR AIR QUALITY (IAQ)

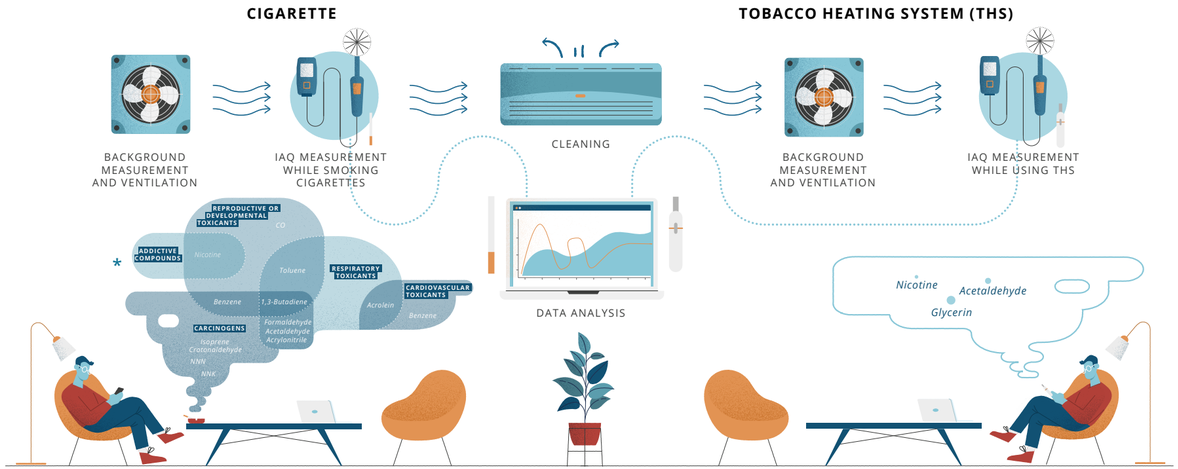
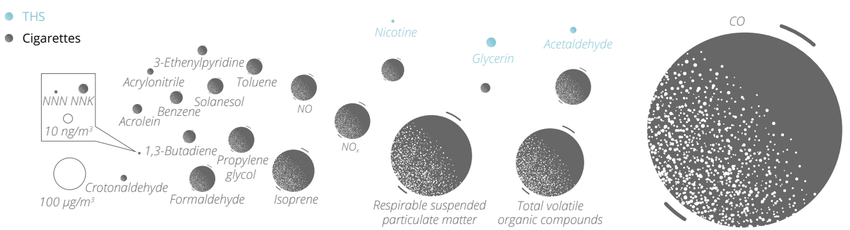


FIGURE 7

When THS was used indoors, out of 24 measured compounds, only nicotine, acetaldehyde, and glycerin were measured at levels higher than the background, although well below the exposure limits established in air quality guidelines. The use of THS in an indoor environment, where regulatory norms of adequate ventilation are respected, does not adversely affect the overall indoor air quality.



* The classification of toxicants was based on the list of the International Agency for Research on Cancer [23] and the U.S. FDA's established list of Harmful and Potentially Harmful Constituents (HPHCs).[31] In addition, other compounds were measured too.

CHAPTER 4: TOXICOLOGICAL ASSESSMENT

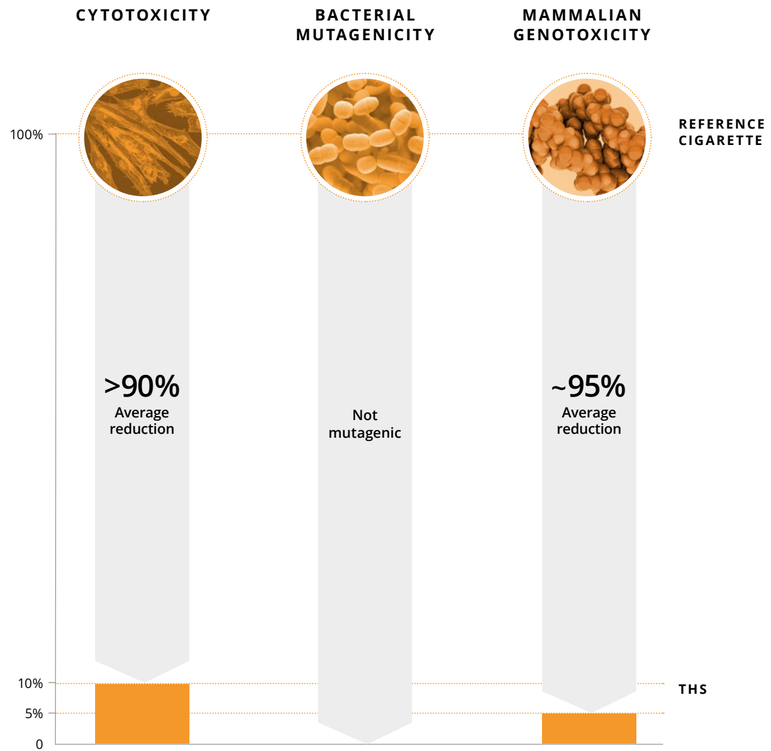
REDUCED TOXICITY

We have conducted a series of regulatory toxicology tests to compare the toxicity of THS aerosol with that of the smoke from a standard reference cigarette (3R4F).

In our laboratories, we observed a substantial reduction in toxicity of the THS aerosol compared with cigarette smoke.[21]

STUDIES SHOW A SUBSTANTIAL REDUCTION IN TOXICITY OF THE AEROSOL OF THE TOBACCO HEATING SYSTEM COMPARED WITH CIGARETTE SMOKE.

FIGURE 8
The chart shows our findings concerning the relative *in vitro* toxicity of THS aerosol compared with the smoke from the 3R4F reference cigarette using three *in vitro* assays (Neutral Red Uptake, Ames and Mouse Lymphoma) commonly used to assess cytotoxicity and genotoxicity.



CHAPTER 4: TOXICOLOGICAL ASSESSMENT CONTINUED

EFFECTS ON THE RISK OF COPD AND CVD

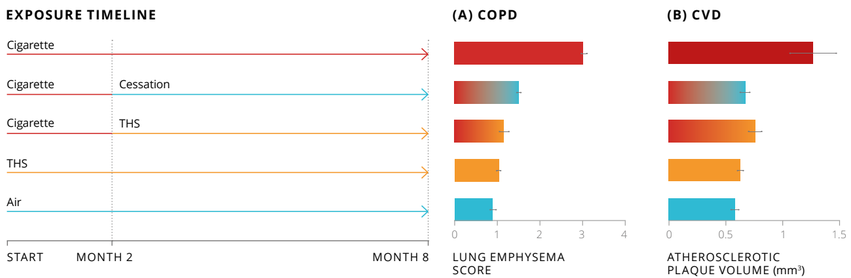
PMI conducted a systems toxicology study in an animal model (Apoe$^{-/-}$ mouse) that develops atherosclerotic plaques and emphysema when exposed to cigarette smoke.

In this study, mice were exposed to either the smoke of a standard reference cigarette (3R4F) or THS aerosol for 8 months. A group of mice was first exposed for 2 months to 3R4F smoke and then randomized to either THS aerosol (switching) or fresh air (cessation). Switching to THS aerosol following 2 months of cigarette smoke led to reduced impact on biological mechanisms and disease endpoints associated with COPD and CVD in a manner similar to smoking cessation.[32]

FIGURE 9
The charts are showing the findings for the disease endpoints COPD and CVD in a mouse switching study. Lung emphysema (A) and atherosclerotic plaque volume (B) were measured in Apoe$^{-/-}$ mice that were exposed for 8 months to either 3R4F smoke or THS aerosol. A group of mice was first exposed for 2 months to 3R4F smoke and then switching to either THS aerosol or fresh air. The fresh air control is also depicted here. Lung emphysema scores were assessed by histopathology after 8 months of exposure, atherosclerotic plaque volumes were measured by micro-CT after 7 months of exposure.

SWITCHING TO THE TOBACCO HEATING SYSTEM LED TO REDUCED IMPACT ON BIOLOGICAL MECHANISMS AND DISEASE ENDPOINTS ASSOCIATED WITH COPD AND CVD COMPARED WITH CONTINUED SMOKING IN LABORATORY MODELS.

REDUCED RISK OF COPD AND CVD



EFFECTS ON THE RISK OF LUNG CANCER

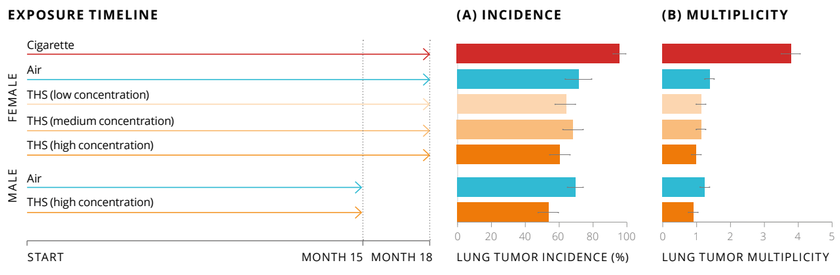
A study was conducted to compare carcinogenic effects of THS aerosol with 3R4F cigarette smoke over the lifetime (18 months) of A/J mice.

The A/J mouse spontaneously develops tumors in the lungs, but they occur more often and the number is higher in mice that are exposed to cigarette smoke. In this study, the number of mice who developed tumors (incidence) and the number of tumors per animal (multiplicity) were significantly lower in THS aerosol exposed mice than in those exposed to cigarette smoke. Incidence and multiplicity were similar in the mice exposed to fresh air and those exposed to THS aerosol.[33, 34]

FIGURE 10
Regarding the disease endpoint lung cancer, the charts are showing the findings on combined lung adenoma and/or adenocarcinoma incidence (A) and multiplicity (B) from a carcinogenicity study in A/J mice exposed to either 3R4F cigarette smoke or THS aerosol for up to 18 months. Gene analysis confirms similarities between spontaneously developed tumors and tumors developed in THS aerosol-exposed animals.

UNLIKE CIGARETTE SMOKE, THE AEROSOL OF THE TOBACCO HEATING SYSTEM DOES NOT LEAD TO INCREASED LUNG TUMOR INCIDENCE AND MULTIPLICITY IN A MOUSE MODEL.

REDUCED RISK OF LUNG CANCER

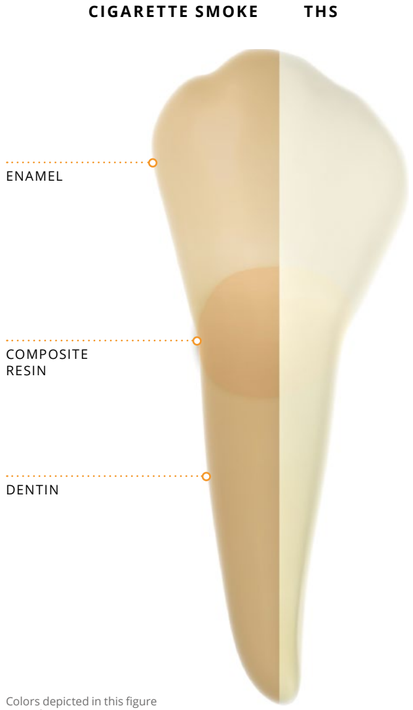


CHAPTER 4: TOXICOLOGICAL ASSESSMENT CONTINUED

LESS STAINING ON TEETH

Our studies on human teeth demonstrate the reduced discoloration effects of THS aerosol compared with the smoke of a 3R4F cigarette.

Teeth that had cavities filled with dental resins were exposed to cigarette smoke or THS aerosol for 4 days a week, followed by brushing and incubation. After 3 weeks of such exposure, cigarette smoke exposure caused an overall larger color change compared with THS aerosol exposure. Exposure to cigarette smoke also caused mismatches between the tooth and the dental resins while THS aerosol exposure did not.[35]



Colors depicted in this figure are only representative.

FIGURE 11
After 3 weeks, THS aerosol caused no obvious discoloration to the teeth and no color mismatch between the teeth and dental resins, unlike cigarette smoke.

THE AEROSOL OF THE TOBACCO HEATING SYSTEM DISCOLORS TEETH SIGNIFICANTLY LESS THAN CIGARETTE SMOKE.

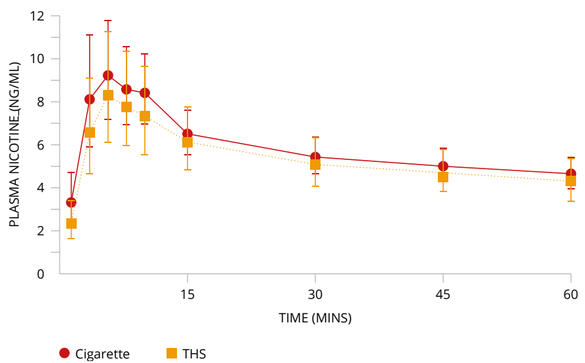
CHAPTER 4: CLINICAL ASSESSMENT

NICOTINE UPTAKE

We have shown in the pharmacokinetic and pharmacodynamic clinical studies that the level of nicotine, and the timing of its peak concentration in the blood, were comparable for smokers and for subjects who switched to THS.

Furthermore, the urge-to-smoke scores were similar for smokers and switchers. This suggests that switchers do not seek to use THS more frequently than smokers seek to use cigarettes, and that switchers can find THS acceptable and satisfying.[36]

FIGURE 12
Nicotine plasma concentration over 60 minutes for a cigarette and THS.



DID YOU KNOW?

Nicotine occurs naturally in the tobacco plant and at significantly lower levels in some other plant varieties. When tobacco is burned, nicotine is transferred to the smoke.

Nicotine can be acutely toxic when ingested or absorbed at levels much higher than what consumers are exposed to when using tobacco or nicotine-containing products, and it can increase a person's heart rate and blood pressure.

When tobacco smoke is inhaled, nicotine is absorbed through the lungs into the bloodstream, and reaches the brain in about 10-20 seconds. There, nicotine binds to specific receptor molecules, mimicking the actions of a naturally occurring brain chemical, acetylcholine. In turn, these activated receptors influence the brain's 'pleasure center', which may explain the subjective pleasurable effects associated with smoking, but also relates to the potential for dependence.

Nicotine also affects other parts of the body such as the heart and blood vessels. The physiological effects of nicotine on the brain and body are short term and reversible.

"It is primarily the toxins and carcinogens in tobacco smoke – not the nicotine – that cause illness and death."
U.K. National Institute for Health and Care Excellence (NICE).[37]

Nicotine used in pharmaceutical products (nicotine replacement therapies (NRTs)) as well as in e-cigarettes is usually extracted from tobacco. It is possible to produce synthetic nicotine, but the process is costly. Certain people should not use products that contain nicotine. Minors should not use or have access to tobacco or nicotine-containing products. Nicotine products should not be used by non-nicotine users.

Nicotine-containing products should also not be used during pregnancy or while breast-feeding. Nicotine-containing products should not be used by people who have or are at risk of heart disease, are diabetic, are epileptic or experience seizures. Experts, including the U.S. Surgeon General and the U.K. Royal College of Physicians, agree that, while nicotine is addictive and not risk free, it is not the primary cause of smoking-related diseases.

Smoking-related diseases, such as lung cancer, cardiovascular disease, and emphysema, are caused primarily by inhaling harmful chemicals largely formed when tobacco is burned, not by nicotine alone.

CHAPTER 4: CLINICAL ASSESSMENT CONTINUED

REDUCED EXPOSURE TO HARMFUL CHEMICALS

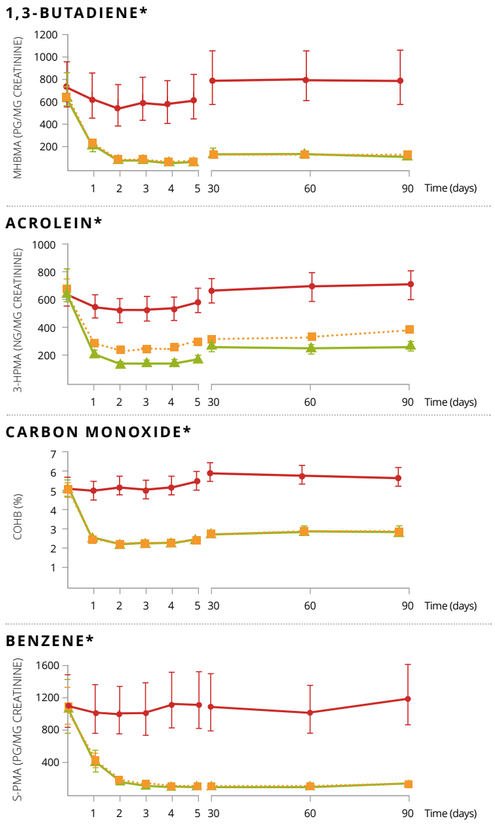
In our 5-day and 90-day clinical reduced exposure studies, we measured biomarkers in the blood and urine representing exposure to selected harmful chemicals.

We found that levels of 15 biomarkers of exposure in participants switching completely to THS were comparable with the levels of those who quit smoking for the duration of the study. In both cases, the levels remained significantly below those observed in subjects who continued smoking during the study.[38, 39]

SMOKERS SWITCHING COMPLETELY TO THE TOBACCO HEATING SYSTEM WERE EXPOSED TO SIGNIFICANTLY LOWER LEVELS OF HARMFUL CHEMICALS COMPARED WITH THOSE WHO CONTINUED SMOKING DURING THE STUDY.

FIGURE 13

The effects of switching to THS or smoking abstinence on biomarkers of exposure levels for four selected HPHCs. We examined a total of 15 biomarkers, all displaying the same trend. The same type of study in the U.S. (NCT01989156) showed comparable results.



* Levels of biomarkers detected (3-month study in Japan).

DID YOU KNOW?

FIGURE 14

In the U.S. FDA established list of harmful and potentially harmful constituents (HPHCs)[31]:

1,3-BUTADIENE
is classified as a carcinogen, respiratory toxicant, and reproductive or developmental toxicant.

Monohydroxybutenyl mercapturic acid (MHBMA) is a biomarker of 1,3-butadiene exposure.

ACROLEIN
is classified as respiratory and cardiovascular toxicant.

3-Hydroxypropylmercapturic acid (3-HPMA) is a biomarker of acrolein exposure.

CARBON MONOXIDE
is classified as a reproductive or developmental toxicant.

Carboxyhemoglobin (COHb) is a biomarker of carbon monoxide exposure.

BENZENE
is classified as a carcinogen, cardiovascular toxicant, and reproductive or developmental toxicant.

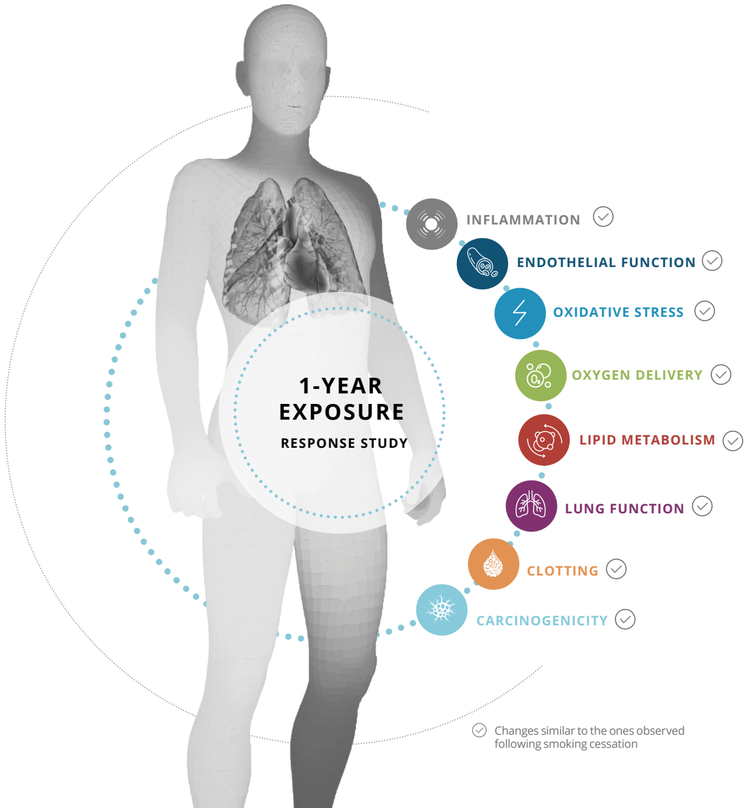
S-Phenylmercapturic acid (S-PMA) is a biomarker of benzene exposure.

CHAPTER 4: CLINICAL ASSESSMENT CONTINUED

POSITIVE IMPACT ON SMOKERS' HEALTH

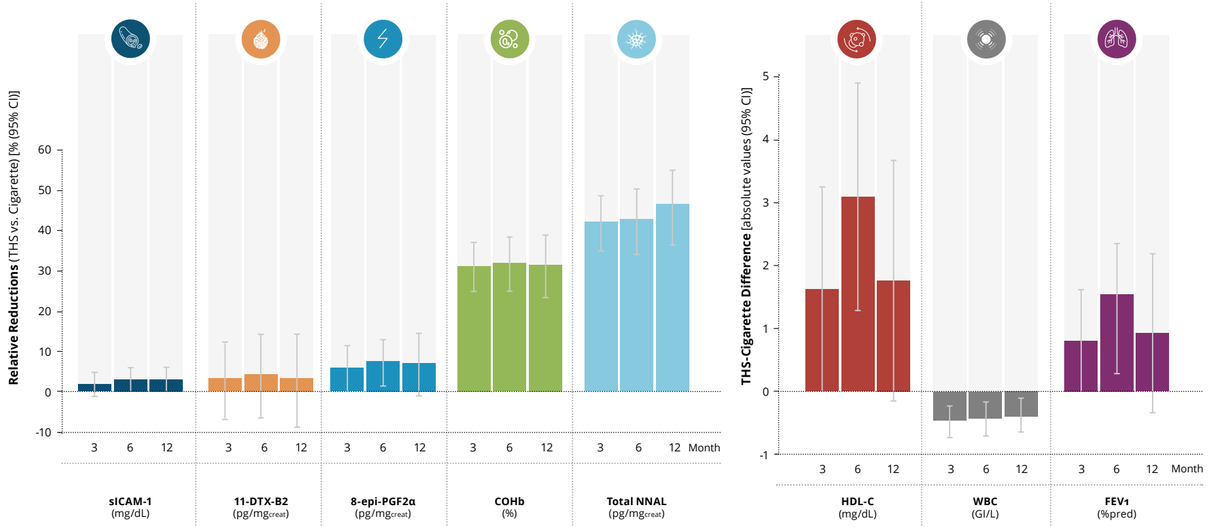
We conducted a 1-year exposure response study, which consisted of a 6-month study followed by a 6-month extension study. Eight biomarkers of potential harm (BoPH) covering different physiological pathways altered by cigarette smoking were measured with the aim to demonstrate favorable changes on all eight BoPH (as observed when stopping smoking) when switching from smoking to THS versus continued cigarette smoking. To compare the effect of switching to THS to that of smoking cessation, we conducted in parallel a 1-year smoking cessation study evaluating the same core set of eight BoPH.

Our studies showed that smokers who switched from cigarettes to THS for 12 months had favorable changes in all eight BoPH, in the same direction as upon smoking cessation. We found that in predominant THS users, the lesser the concomitant cigarette smoking the greater were the favorable effects on the BoPH. Furthermore, exclusion of the highest intensity of cigarette consumption in THS users showed that the favorable response to THS use corresponded to more than 67% of that of smoking cessation for seven of the eight BoPH.[40,41,42]



CLINICAL FINDINGS PROVIDE EVIDENCE ON THE POTENTIAL OF THE TOBACCO HEATING SYSTEM TO REDUCE THE RISK OF DEVELOPING CVD, COPD, AND CANCER COMPARED WITH CONTINUED CIGARETTE SMOKING.

FIGURE 15
Changes in BoPH related to smoking-related diseases when switching to THS.



CHAPTER 4: PERCEPTION AND BEHAVIOR

INTENTION TO USE

We conducted perception and behavior studies to investigate the effect of introducing smoke-free products on:

1. Tobacco use behavior amongst adult smokers
2. Tobacco use initiation amongst adult nonsmokers (i.e., former smokers and never smokers)
3. Consumer understanding of product messages and perception of risks

Our pre-market perception and behavior studies conducted in the U.S. showed that substantial proportions of current adult smokers (up to 39%) expressed intention to use THS. At the same time, our perception and behavior studies showed that low proportions of nonsmokers expressed intention to use THS (i.e., adult former smokers ≤ 6.4%, adult never smokers and legal age to 25-years-old never smokers ≤ 1.1%).

Moreover, we also conducted studies for THS with adults who were not consumers of tobacco or nicotine-containing products (TNPs) in several countries in 2020 and 2021. The results of those studies also show very low intention to use THS among adult former users of TNPs and adults who had never used TNPs.

The study findings also showed that adult smokers correctly understand that switching to THS presents less risk of harm than continued cigarette smoking, while not being risk free. Furthermore, our data showed a low impact of THS communication materials on the intention to quit all tobacco among adult smokers with the intention to quit smoking.

OUR PERCEPTION AND BEHAVIOR STUDIES SHOWED THAT SMOKERS CORRECTLY UNDERSTAND THAT SWITCHING TO THE TOBACCO HEATING SYSTEM PRESENTS LESS RISK OF HARM THAN CONTINUED CIGARETTE SMOKING.

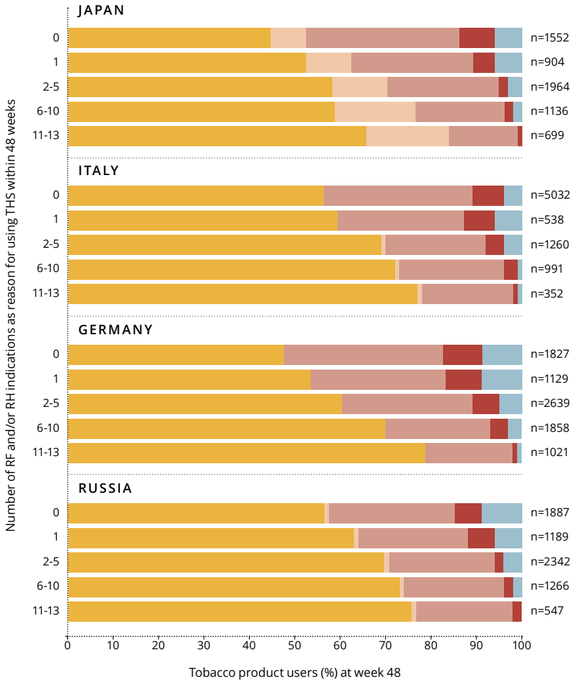
PERCEIVED RISK OF THS AND SWITCHING BEHAVIOR

To understand whether communicating risk-related information to adult consumers can help them switch completely to THS, we conducted a study across four culturally and socio-economically diverse countries: Japan, Italy, Germany, and Russia.

We examined the impact of risk-related perceptions of THS, on smokers' behavior and its impact on exclusive and stable use over time, highlighting the importance of factual and non-misleading product information capable of enabling informed decision making.

This study employed a large-scale longitudinal survey involving participants who were THS users.[43] Participants completed questionnaires assessing their perceptions and THS use patterns over a 48-week period. The results showed that individuals who identified perceived reduced formation of harmful chemicals or perceived reduced risk of harm as reasons for using THS were more likely to switch exclusively and did so more quickly than those who did not.

Factual and accurate information about the reduced-risk profiles of smoke-free products is essential for empowering adult smokers to make informed decisions and can help them transition away from cigarettes, the most harmful way of nicotine consumption. The results of the study might be of interest also for policy experts and decision makers in shaping the tobacco regulatory framework.



Abbreviations:
CC: manufactured and hand-rolled cigarettes;
HTP: heated tobacco product;
Other TP use: participants with no tobacco product use in the past 7 days and/or no intention to use tobacco products in future.

FIGURE 16
This figure shows the patterns of tobacco product use at week 48 of the study, separated by country and the number of time the reduced-formation and/or reduced risk statements were selected by participants.
RF: perceived reduced formation of harmful chemicals; RH: perceived reduced risk of harm.

CHAPTER 4: PERCEPTION AND BEHAVIOR

USE BEHAVIOR

Our pre-market, actual use perception and behavior study conducted in the U.S. aimed to measure the effect of THS on tobacco use behavior among adult daily cigarette smokers.

This 6-week observational actual use study showed that 15% of smokers switched from cigarettes to THS exclusive or predominant use.[44] The study findings also showed that the availability of THS did not lead to an increase in total tobacco product consumption (THS and cigarettes).

The U.S. actual use study findings were aligned with similar pre-market studies conducted in Germany, Italy, South Korea, Japan, and Switzerland which showed that between 10% and 37% of smokers switched from cigarettes to THS exclusive or predominant use.[45] We have conducted post-market studies after the commercialization of THS (under the brand *IQOS*) and the study results show that these pre-market actual use studies well predicted THS future use behavior.

PMI will continue to conduct perception and behavior studies as part of PMI's overall scientific assessment program for PMI's smoke-free products.

OUR ACTUAL USE PERCEPTION AND BEHAVIOR STUDIES SHOWED THAT A SIZEABLE PROPORTION OF SMOKERS WERE LIKELY TO SWITCH FROM CIGARETTES TO THE EXCLUSIVE OR PREDOMINANT USE OF THE TOBACCO HEATING SYSTEM.

CHAPTER 4: LONG-TERM ASSESSMENT

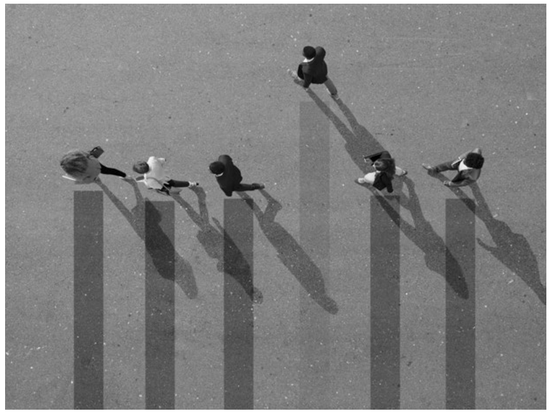
POPULATION HEALTH IMPACT MODEL

At PMI, we developed an epidemiological model relying on mathematical simulations using publicly available data, the Population Health Impact Model (PHIM), with the aim to estimate, in the absence of epidemiological data, the potential effects of introducing a smoke-free product on the public health of a whole population.

Our researchers utilize the PHIM to analyze the relative and absolute risks of smoking-related diseases for different groups, including people who have never smoked, current smokers, former smokers, and those who switch to smoke-free products. By incorporating individual choices, demographic factors, and various data sources, our model provides estimates of mortality impact and potential years-of-life saved by introducing smoke-free products.

We have conducted several studies using our PHIM for a number of countries, and one country is Japan.[46] In a Japan study, the model estimated that the introduction of a hypothetical heated tobacco product could prevent 65,000 to 87,000 deaths in Japan over 20 years, which is 24-32% of preventable smoking-attributed deaths, estimated as 270,000. The model estimated that about 12.5 years of life expectancy would be saved for smokers switching to the heated tobacco product. These simulations seem to suggest that the introduction of a smoke-free product as modeled in Japan has the possibility to substantially reduce smoking-related deaths.

PHIM studies have several limitations, but by continually refining and improving our model, we aim to provide policymakers and public health officials with valuable insights which can be taken into consideration during the decision-making process regarding the regulation of smoke-free products.



CHAPTER 4: LONG-TERM ASSESSMENT CONTINUED

MAJORITY OF THS USERS NO LONGER SMOKE CIGARETTES AND USE THS EXCLUSIVELY

As part of our ongoing long-term assessment, we have conducted repeated post-market cross-sectional surveys in a representative sample of the adult population from Japan[47,48], Italy, and Germany, to monitor the use prevalence of THS after its commercialization.

These studies show that the total use prevalence of tobacco or nicotine-containing products (TNPs) in Japan, Italy, and Germany is overall stable across time, with higher total TNP use prevalence in Italy and Germany compared with Japan. These studies also show a growing prevalence of THS use among TNP users across time with a higher prevalence of THS use in Japan (2019: 18.4%) compared to Italy (2019: 4.1%) and Germany (2019: 1.2%).

MORE THAN 99% OF CURRENT THS USERS HAVE A HISTORY OF TNP USE BEFORE SWITCHING TO THS.

ONLY 1% TO 2% OF CURRENT THS USERS RELAPSED OR RE-INITIATED TOBACCO USE WITH THS.

Moreover, these studies show that more than half of THS users no longer smoke cigarettes and use THS exclusively. This shift towards the use of smoke-free products suggests that smoke-free products, such as THS, are acceptable alternatives to cigarette smoking.

Our post-market cross-sectional surveys also show very low to non-existing TNP initiation with THS among never TNP users (<0.1%). More than 99% of current THS users have a history of TNP use before switching to THS, and only 1% to 2% of current THS users relapsed or re-initiated tobacco use with THS.

On a population level, based on the results of our post-market cross-sectional surveys, the commercialization of THS appears to be in line with the principles of tobacco harm reduction.

PMI will continue to conduct post-market studies as part of PMI's overall scientific assessment program for PMI's smoke-free products.

FIGURE 17

History of TNP use in THS users in Japan, Italy, and Germany in 2019.

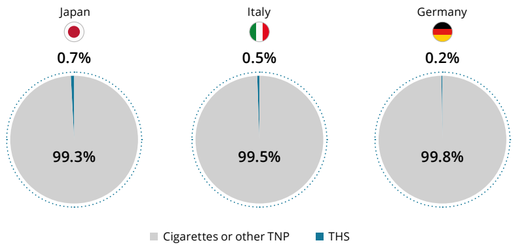
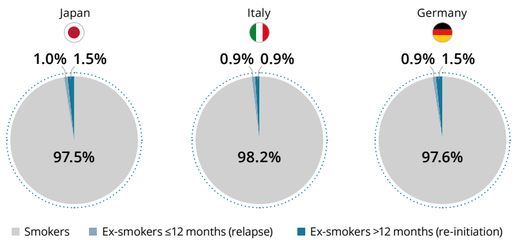


FIGURE 18

Tobacco relapse or re-initiation among current THS users with a history of TNP use in Japan, Italy, and Germany in 2019.

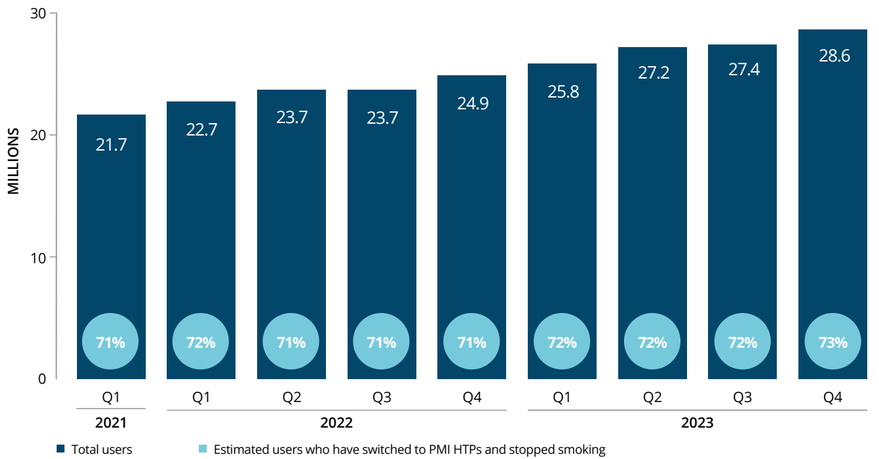


SMOKERS WHO HAVE SWITCHED TO PMI HEATED TOBACCO PRODUCTS (HTPs) WORLDWIDE

As of December 2023, there are approximately 28.6 million users of PMI HTPs globally, of which approximately 20.8 million (73%) have switched to PMI HTPs and stopped smoking.

FIGURE 19

Number of smokers who have switched to PMI HTPs worldwide.



Source: PMI Financials or estimates, THS user panels and PMI Market Research. Status as of December 2023.

INDEPENDENT STUDIES AND REVIEWS

5 VALIDATING OUR RESEARCH

INDEPENDENT STUDIES AND REVIEWS

Read more on pmiscience.com

Over the last few years, numerous independent studies have already confirmed different elements of our research on the tobacco heating system (THS).

In this section

CHAPTER 5

INDEPENDENT STUDIES AND REVIEWS

Many government bodies have conducted literature reviews or performed research on scientifically substantiated heated tobacco products, finding that they expose users to significantly lower levels of harmful chemicals.

PUBLIC HEALTH ENGLAND (PHE)[49]

2018: Public Health England (PHE) published a review of the evidence on e-cigarettes and heated tobacco products, and stated that heated tobacco products likely reduce users' and bystanders' exposure to harmful compounds compared with cigarettes.

PHE also stated available evidence suggests that heated tobacco products may be considerably less harmful than tobacco cigarettes and more harmful than e-cigarettes.

U.K. COMMITTEE ON TOXICITY (COT)[50]

2017: The U.K. Committee on Toxicity conducted a review of available evidence on two heated tobacco products, one of which is *IQOS**, and concluded that there is a "likely reduction in risk for smokers switching to heat-not-burn tobacco products."

DUTCH NATIONAL INSTITUTE FOR PUBLIC HEALTH AND THE ENVIRONMENT (RIVM)

2018: RIVM published a fact sheet on novel tobacco products that are heated and an English-language summary.

They concluded that "The use of Heatsticks with the *IQOS* is harmful to health, but probably less harmful than smoking tobacco cigarettes," based on their aerosol chemistry measurements, which are "of the same order of magnitude as in the data of Philip Morris."[51]

2020: RIVM published the findings of its research on "A Method for Comparing the Impact on Carcinogenicity of Tobacco Products: A Case Study on Heated Tobacco Versus Cigarettes."

RIVM developed a method to estimate risk – or assess the potential magnitude of the health impact – between tobacco products.

In their publication they assessed eight carcinogens to understand the likely health impact on individuals who switch to *IQOS*, compared with those who continue smoking. In their conclusions they state that – while *IQOS* is not risk free – it is associated with 10 to 25 times lower exposure to these carcinogens, and that this could translate into a substantially improved risk profile.[52]

GERMAN FEDERAL INSTITUTE FOR RISK ASSESSMENT (BfR)[53]

2018: The German Federal Institute for Risk Assessment (BfR), published laboratory studies on *IQOS* in Archives of Toxicology, finding that reductions in selected toxicants measured by the institute "are likely to reduce toxicant exposure."

SUPERIOR HEALTH COUNCIL OF BELGIUM (SHC)[54]

2020: The Superior Health Council of Belgium (SHC) published results of its inquiry into heat-not-burn products. The SHC concluded that heat-not-burn products, while not safe, have a more favorable toxicity profile than cigarettes. However, in light of the uncertainty of such products' short- and long-term impacts, the toxic effects of the dual use with cigarettes, and the existence of approved smoking cessation tools, the SHC recommended that current regulations for cigarettes should apply to heat-not-burn products.

U.S. FOOD AND DRUG ADMINISTRATION (U.S. FDA)

2018: The U.S. FDA , in a briefing document, reviewed PMI's data supporting *IQOS* and the available independent literature about *IQOS*. The briefing document included a section explaining the results of the U.S. FDA's *IQOS* aerosol chemistry measurements.[55]

2019: Following a comprehensive assessment of PMI's premarket tobacco product applications, the U.S. FDA confirmed that *IQOS* is appropriate for the protection of public health and has authorized it for sale in the United States. "Appropriate for the protection of public health" means that looking at population as a whole, new products cannot pose the same or greater harm to public health as smoking. The U.S. FDA published a detailed report describing their assessment and their conclusions including results on aerosol chemistry, toxicology and unintended use.[5]

2020: The U.S. FDA issued decisions on PMI's Modified Risk Tobacco Product (MRTP) applications for the *IQOS* tobacco heating system. In doing so, the agency found that the issuance of the modified risk tobacco product orders with reduced exposure claims would be "appropriate to promote the public health and is expected to benefit the health of the population as a whole." This decision follows a review of the extensive scientific evidence package PMI submitted to the U.S. FDA in December 2016 to support its MRTP applications.[6]

To date, over 50 studies from independent laboratories have results that are in line with our findings on THS.

Researchers working for the American Cancer Society confirm that the introduction of *IQOS* is the only likely cause of cigarette sales decline in Japan.[56]

Research by the Japanese Department of Environmental Health, National Institute of Public Health, compared selected chemicals in the aerosol generated by *IQOS* and in smoke from reference cigarettes. The research shows significant reductions in the levels of several chemicals, in line with those found by PMI's research.[57]

The China National Tobacco Quality Supervision and Test Centre, a member of the WHO Tobacco Laboratory Network, published an independent study comparing the harmful chemicals present in *IQOS* aerosol and cigarette smoke, which generally agree with PMI's results.[58]

One of Ukraine's leading research institutes conducted a 6-month clinical study on *IQOS*, which was published in prominent national medical periodical Ukrainian Health, showing no significant adverse effect on users of smoke-free products.[59]

Researchers at the University of St. Andrews, Scotland, calculated that *IQOS* aerosol has "lower cancer potencies than tobacco smoke by at least one order of magnitude, but higher potencies than e-cigarettes."[60]

The first independent study investigating levels of carbon monoxide in the exhaled breath (eCO) after use of two recently marketed heated tobacco products (HTPs) was conducted by Pasquale Caponnetto, Marilena Maglia, Gaetano Prosperini, Barbara Busà and Riccardo Polosa and was published in Respiratory Research. The aim of this randomized cross-over study was to measure the exposure levels of the combustion marker, eCO of subjects after use of two HTPs and to compare these levels with participants' own brand of cigarettes. The study found no eCO elevations during inhalational testing with HTPs under investigation in any of the study participants.[61]

Research by cardiologist and leading e-cigarette researcher Dr. K. Farsalinos on *IQOS* was published in the journal Addiction, showing that *IQOS* emits lower levels of carbonyls than a commercial cigarette, but higher levels than an e-cigarette.[62]

* *IQOS* is the brand name under which the tobacco heating system is commercialized.

FACTS AND FIGURES

6 SEEING THE EVIDENCE

Read more on pmiscience.com

Our value creation model describes what we do and how we allocate our resources to deliver long-term value for both our company and our stakeholders.

OUR MISSION

Accelerate the end of smoking.

WHAT WE DO

Replace cigarettes with less harmful tobacco and nicotine products for the benefit of adults who would otherwise continue to smoke.

In this section

+1,180
scientists, engineers, technicians, and support staff working on our smoke-free products in 2022*.

USD 120 million
invested in construction of the Cube, PMI's remarkable R&D facility in Neuchâtel (Switzerland).

USD 10.7 billion
invested by PMI from 2008 to 2022 in research, product development, production capacity, scientific substantiation, and perception and behavior studies.

30
scientific and engineering disciplines including: materials science, consumer electronics, clinical science, and systems toxicology.

USD 642 million
total R&D expenditure in 2022.

~2,500
patents granted for smoke-free technologies by the five largest intellectual property offices in the world (IP5, cumulative from 2015 to 2022)**.

99%
of total R&D expenditure was dedicated to smoke-free products in 2022.

511
scientific publications by PMI from 2008 to 2022 – most open access.

*Data does not include employees of Swedish Match or Vectura Fertin Pharma.
**IP5 jurisdictions are Europe (patents granted by the European Patent Office), China, South Korea, Japan, and the U.S.

CHAPTER 6

MILESTONES ON OUR SMOKE-FREE JOURNEY

Philip Morris International (PMI) launches the first electronically heated tobacco product, called *Accord* in the U.S. and *Oasis* in Japan.

Spin-off from Altria Group Inc., PMI enhances R&D capabilities to **research and develop smoke-free alternatives** to cigarettes.

PMI opens **The Cube**, a new R&D center in Switzerland, and **International Research Laboratories** in Singapore.

Technology for Nicotine Salts Product (NSP) is acquired.

Release of the U.S. Food and Drug Administration (FDA) draft guidance on the submission of an MRTP* application, **PMI's assessment approach** largely in line with it.

Our Tobacco Heating System (THS), commercialized as *IQOS*, is launched in selected cities in Japan and Italy.

PMI inaugurates the **Philip Morris Manufacturing & Technology Bologna (PMMTB)** in Italy – a pilot manufacturing facility for large-scale production of heated tobacco products (HTPs), and a center of excellence for staff training and prototyping.

PMIScience.com is launched to publicly share our scientific efforts, methodologies, and findings on PMI's smoke-free products.

PMI announces its vision of a smoke-free future and its ambition to *"convince all current adult smokers that intend to continue smoking to switch to smoke-free products as soon as possible."*

An MRTP application for THS is submitted to the U.S. FDA, which upon issuance of marketing orders would allow **relative risk claims** in comparison with cigarettes.

PMI enters the e-vapor category with MESH Vaping System (MVS) in the U.K.

Opening of the **PMI Science R&D Center Armenia**, specializing in data science, materials science, and the physical foundations of technological processes.

Opening of the **Electronic Product Development Center (ePDC)** in Hong Kong (and later Shenzhen in 2021), managing development, industrialization, manufacturing, and global supply of our electronic devices.

U.S. FDA grants the first-ever modified risk orders to Swedish Match USA, Inc. for snus smokeless tobacco products.

U.S. FDA **authorizes the sale of THS 2.2** (*IQOS 2.4*) as *"appropriate for the protection of public health"* pursuant to the PMTA** pathway.

U.S. FDA issues an MRTP order authorizing PMI to market THS 2.2 (*IQOS 2.4*) with **reduced exposure claim.**

The first **Open Science event** is hosted, which then became an event series dedicated to sharing openly our scientific results.

THS 3.0 using induction technology is launched, commercialized as *IQOS ILUMA*.

PMI progresses on acquisition of Fertin Pharma, Vectura, and OtiTopic to accelerate "Beyond Nicotine" vision and provide a base for **building critical respiratory and oral product development capabilities.**

PMI enters the category of **oral smokeless products** with the acquisition of AG Snus.

U.S. FDA issues an MRTP order authorizing PMI to market THS 2.2 (*IQOS 3*) with **reduced exposure claim.**

PMI acquires **Swedish Match** and expands the oral smokeless portfolio.

Oven Heating System (OHS) is launched, which uses resistive external heating, commercialized as *BONDS by IQOS*.

Disposable Vaping System (DVS) is launched, which uses wick and coil technology and closed e-liquid storage unit, commercialized as *VEEV NOW*.

Ceramic Vaping System (CVS) is launched, commercialized as *VEEV ONE*.

Greece is the first EU country to approve differentiated health claims for THS.

There are 28.6 million users of PMI HTPs globally, of which approximately 20.8 million (73%) have **switched to PMI HTPs and stopped smoking.**

By 2030, our ambition is to be a substantially smoke-free company.

* MRTP: Modified Risk Tobacco Product

** PMTA: Premarket Tobacco Product Application

GLOSSARY AND ACRONYMS

AEROSOL

An aerosol is a suspension of fine solid particles and/or liquid droplets in a gas (usually air). Cigarettes generate a smoke aerosol that is the result of the combustion (burning) of tobacco and contains carbon-based solid particles. While smoke is an aerosol, not all aerosols are smoke.

PMI's smoke-free products do not produce smoke because they do not burn tobacco. Instead, they generate a nicotine-containing aerosol, either by heating tobacco or through other technologies that do not involve combustion.

Consumers typically use the term "vapor" to refer to the aerosol generated from heated tobacco products or other nicotine-containing products.

BIOMARKER OF POTENTIAL HARM

Biomarkers of potential harm (BoPH) are a measurable change in biochemical, physiological (organs, tissues, cells), or behavioral function within an organism that is known to be associated with a health impairment or disease. These biomarkers indicate the body's response to exposure to harmful chemicals. While BoPH do not necessarily cause these health concerns, their presence and magnitude help identify whether a person already has or is in danger of developing a health impairment or disease.

BIOMARKERS OF EXPOSURE

Indicate exposure to a potentially hazardous substance. In our case, the biomarker may be a cigarette smoke constituent or metabolite that is measured in a biological fluid or tissue. Biomarkers of exposure can provide a measure of internal dose, which is the amount of the constituent taken up into the body.

COMBUSTION

Combustion is the process of burning a substance in oxygen, producing heat and often light. When a cigarette is lit, the combination of tobacco (fuel) and oxygen in the air generates a self-sustaining combustion process that consumes the tobacco. The combustion of tobacco results in the formation of smoke (that contains a range of chemical constituents), heat, and ash. The high heat associated with combustion leads to the thermal breakdown of the tobacco when it is burned, resulting in the production of many of the toxicants found in cigarette smoke.

COPD

Chronic obstructive pulmonary disease

CVD

Cardiovascular disease.

EXPOSURE

Exposure to a chemical describes how much of a chemical comes into contact with a human, laboratory animal, or cell culture so that it might be inhaled, ingested, or absorbed and how often and for how long that does happen. Exposure of humans to chemicals is important to understand because it may have an influence on human health.

HPHCs

Harmful and Potentially Harmful Constituents, HPHCs are chemicals or chemical compounds in tobacco products or tobacco smoke that cause or could cause harm to smokers or nonsmokers. The Food, Drug and Cosmetic Act (FD&C Act) requires tobacco manufacturers and importers to report the levels of HPHCs found in their tobacco products and tobacco smoke.

MODIFIED RISK TOBACCO PRODUCT (MRTP)

'Modified risk tobacco product' or 'MRTP' is the term formally used by the U.S. Food and Drug Administration to describe an alternative to cigarettes that is associated with less risk of disease.

MUTAGENIC

In genetics, a mutagen is a physical or chemical agent that changes the genetic material, usually DNA, of an organism and thus increases the frequency of mutations above the natural background level.

PHARMACODYNAMICS

Pharmacodynamics is the study of the response of the body to a pharmacological compound.

PHARMACOKINETICS

Pharmacokinetics is the study of the process by which a pharmacological compound is absorbed, distributed, metabolized, and eliminated by the body.

STANDARD REFERENCE CIGARETTE (E.G., 2R4F, 3R4F, 1R6F)

Standard reference cigarettes such as the 2R4F, 3R4F, and 1R6F reference cigarettes, are provided by the University of Kentucky for laboratory testing. A standard reference cigarette is used as a consistent and uniform test item for nonclinical investigations by tobacco manufacturers, contract and government laboratories, and academic institutions. The current version is the standard reference cigarette 1R6F.

U.S. FDA

United States Food and Drug Administration

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