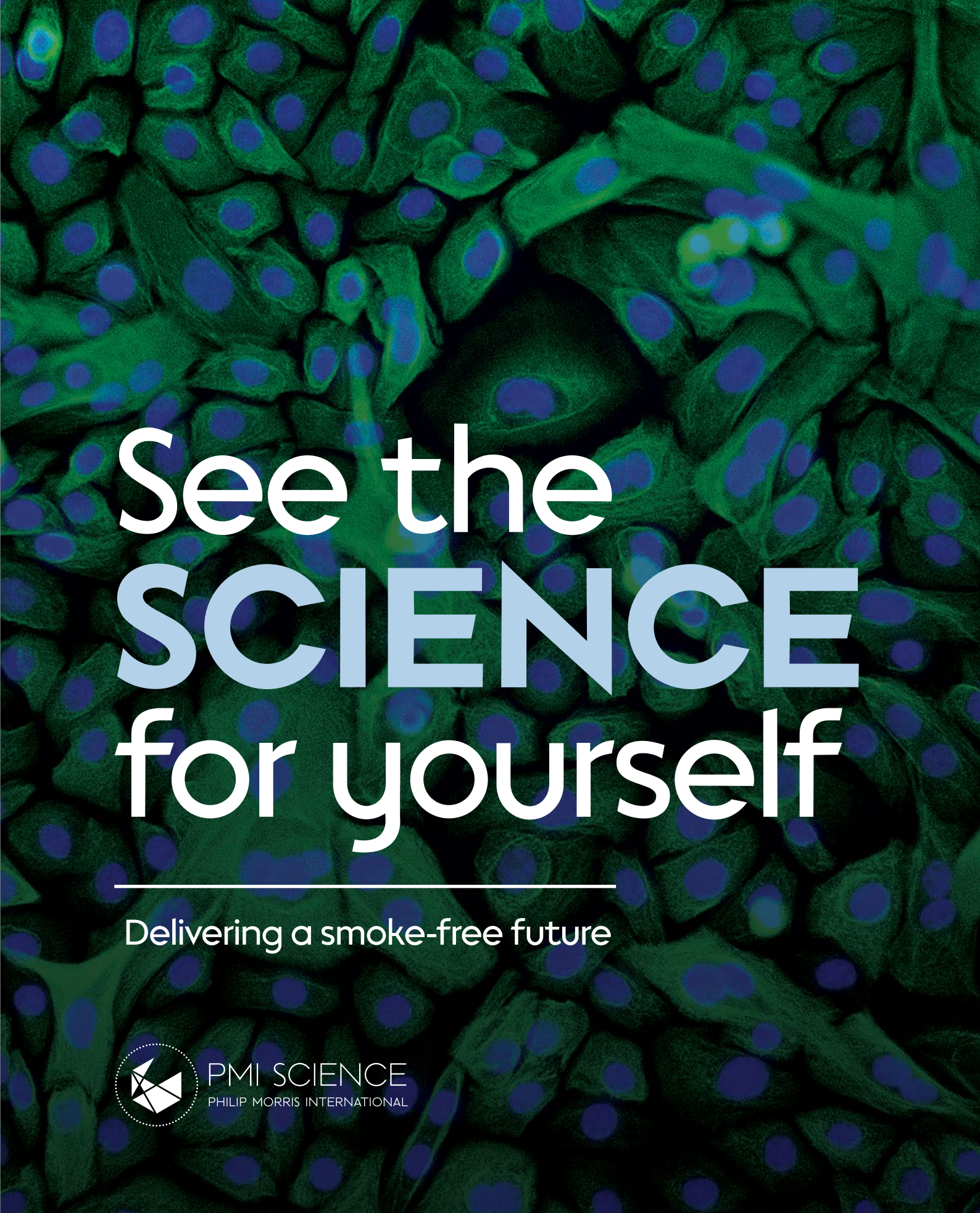
See the
SCIENCE
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Delivering a smoke-free future
PMI SCIENCE
PHILIP MORRIS INTERNATIONAL

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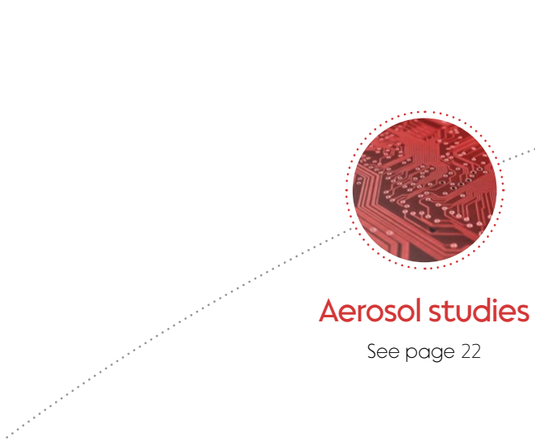
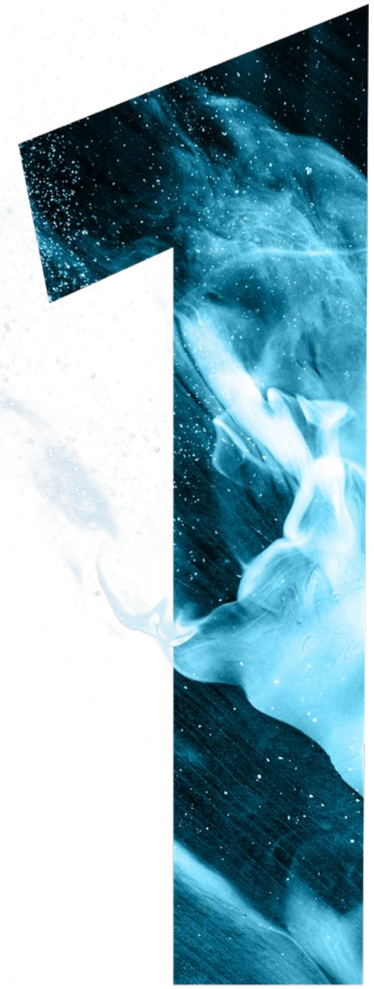


DELIVERING A **SMOKE-FREE FUTURE**



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

Read more on
PMIScience.com

"The evidence is clear: smoke-free alternatives can accelerate the end of smoking. The world has to move now to help smokers move to better alternatives. It's time to make smoking history."

JACEK OLCZAK

Chief Executive Officer,
Philip Morris International

Smoke-free alternatives for adult smokers

Cigarette smoking causes serious diseases and is addictive.

We know that smoking-related diseases, such as chronic obstructive pulmonary disease (COPD), cardiovascular disease (CVD), and lung cancer, are caused primarily by inhaling harmful compounds largely formed when tobacco is burned. We also know from epidemiology that if a smoker quits, the risk of developing a smoking-related disease decreases over time.

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, we need to keep working to help address the harm caused by smoking more effectively and rapidly than traditional policy measures alone. Cigarettes need to be replaced with alternatives that are scientifically substantiated to be less harmful compared with continued smoking.

Nicotine is a well-known component of tobacco and tobacco-containing products, and it is one of the reasons why people smoke cigarettes.

Yet, experts, including the U.S. Surgeon General and the U.K. Royal College of Physicians, agree that nicotine, while addictive and not risk free, is not the primary cause of smoking-related diseases.

As the U.S. Food and Drug Administration (FDA) has stated[2] "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."

Therefore, products that do not burn tobacco, but still provide nicotine, are likely to be far less harmful alternatives to continued smoking.

The technology to provide such alternatives exists. These alternatives are called smoke-free products.

~ 1 billion

SMOKERS GLOBALLY

We have a vision of replacing cigarettes with scientifically substantiated better products for adult smokers who do not quit.

To achieve our vision, we have developed smoke-free products that either eliminate the burning of tobacco or do not use tobacco at all.

We recognize that no single product will be acceptable to all adult smokers in order to fully switch. Therefore, our approach is to provide a wide range of smoke-free alternatives, so that adults who would otherwise continue to smoke can find a suitable alternative that allows them to fully switch.

Integrating risk reduction and acceptance for current adult smokers

Population harm in the context of smoking refers to the negative health effects that smoking has on a population as a whole.

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.

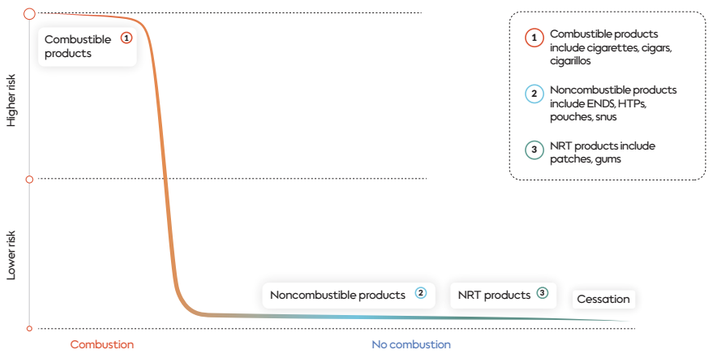
Not all tobacco products are the same. Their use exists along a continuum of risk, where smoking combusted tobacco yields the highest risk and quitting nicotine and tobacco products altogether (cessation) contributes to the lowest risk. The use of other tobacco products, including smoke-free products,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

FIGURE 1: THE HARM REDUCTION EQUATION

Successful harm reduction requires that adult smokers be offered a range of less harmful alternatives so that acceptance by the users can be best fulfilled.

FIGURE 2:

The continuum of risk shows that noncombustible products are lower risk than cigarettes.



ENDS: electronic nicotine delivery systems; HTPs: heated tobacco products; NRT: nicotine replacement therapy.

Smoking and cessation

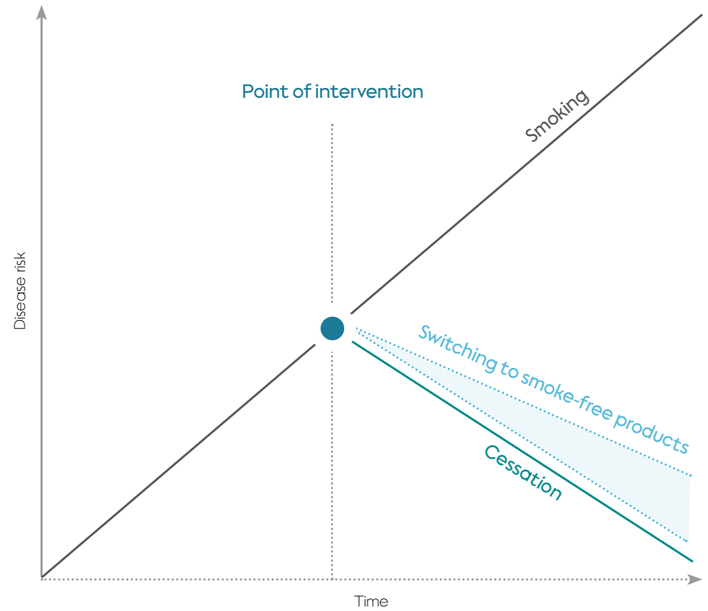
The best way to avoid the harm of smoking is to not start in the first place. For those who already smoke, quitting tobacco and nicotine altogether is the single best thing they can do to reduce their risk.

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 over time.

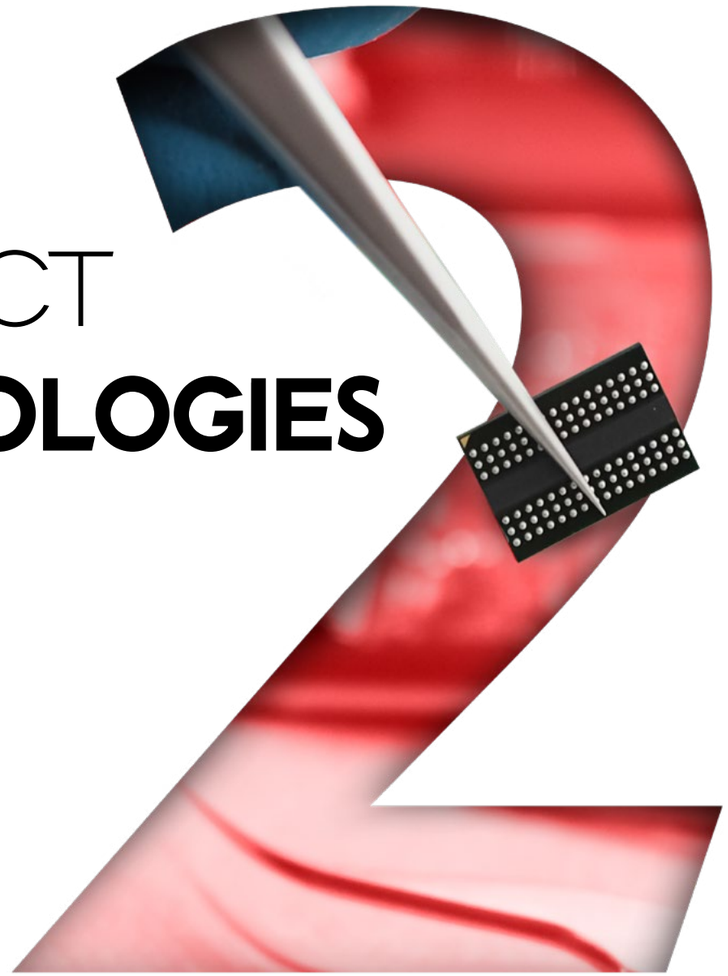
Since smoking cessation is the "gold standard" for assessing the reduction in risk for adult smokers,[3] our goal is to develop smoke-free products that have a risk profile as close as possible to that of smoking cessation, while being acceptable alternatives to cigarettes for adult smokers who would otherwise continue to smoke.

FIGURE 3:

Conceptual depiction of the cumulated risk of smoking and the effect of cessation over time.[4] 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.



OUR PRODUCT **TECHNOLOGIES**



IN THIS SECTION

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Smoke-free products

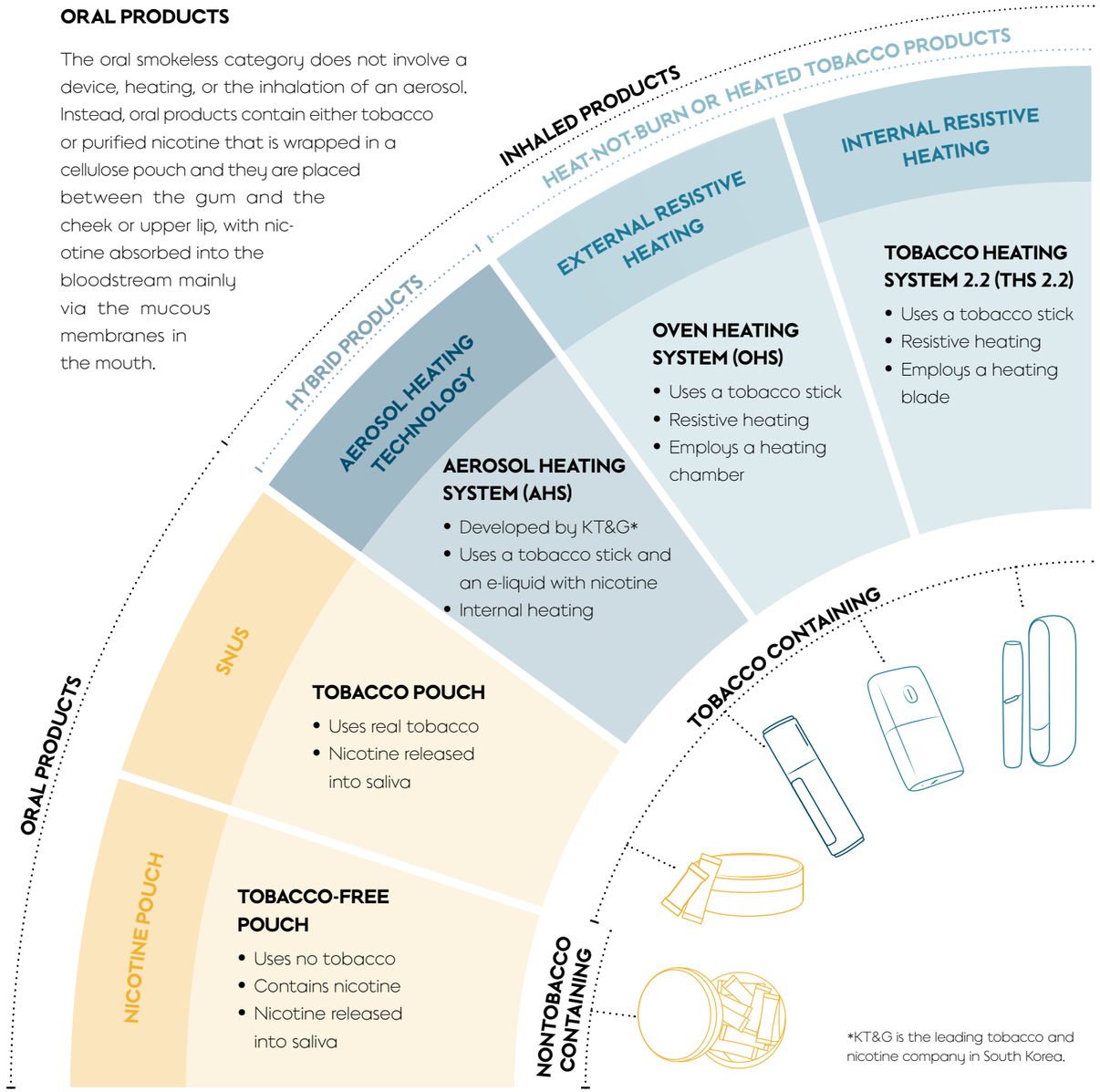
Smoke-free product is the term PMI uses to refer to products that provide nicotine without combusting tobacco. These products either release nicotine or emit aerosols that contain reduced levels of harmful and potentially harmful constituents (HPHCs) than found in cigarette smoke and therefore have the potential to present less risk of harm to smokers who switch to these products versus continued smoking. Central to this are heated tobacco products (HTPs) or heat-not-burn (HnB) products, e-vapor products, and oral products, each employing distinct methodologies to reduce harm.

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

The technologies behind our smoke-free products

ORAL PRODUCTS

The oral smokeless category does not involve a device, heating, or the inhalation of an aerosol. Instead, oral products contain either tobacco or purified nicotine that is wrapped in a cellulose pouch and they are placed between the gum and the cheek or upper lip, with nicotine absorbed into the bloodstream mainly via the mucous membranes in the mouth.



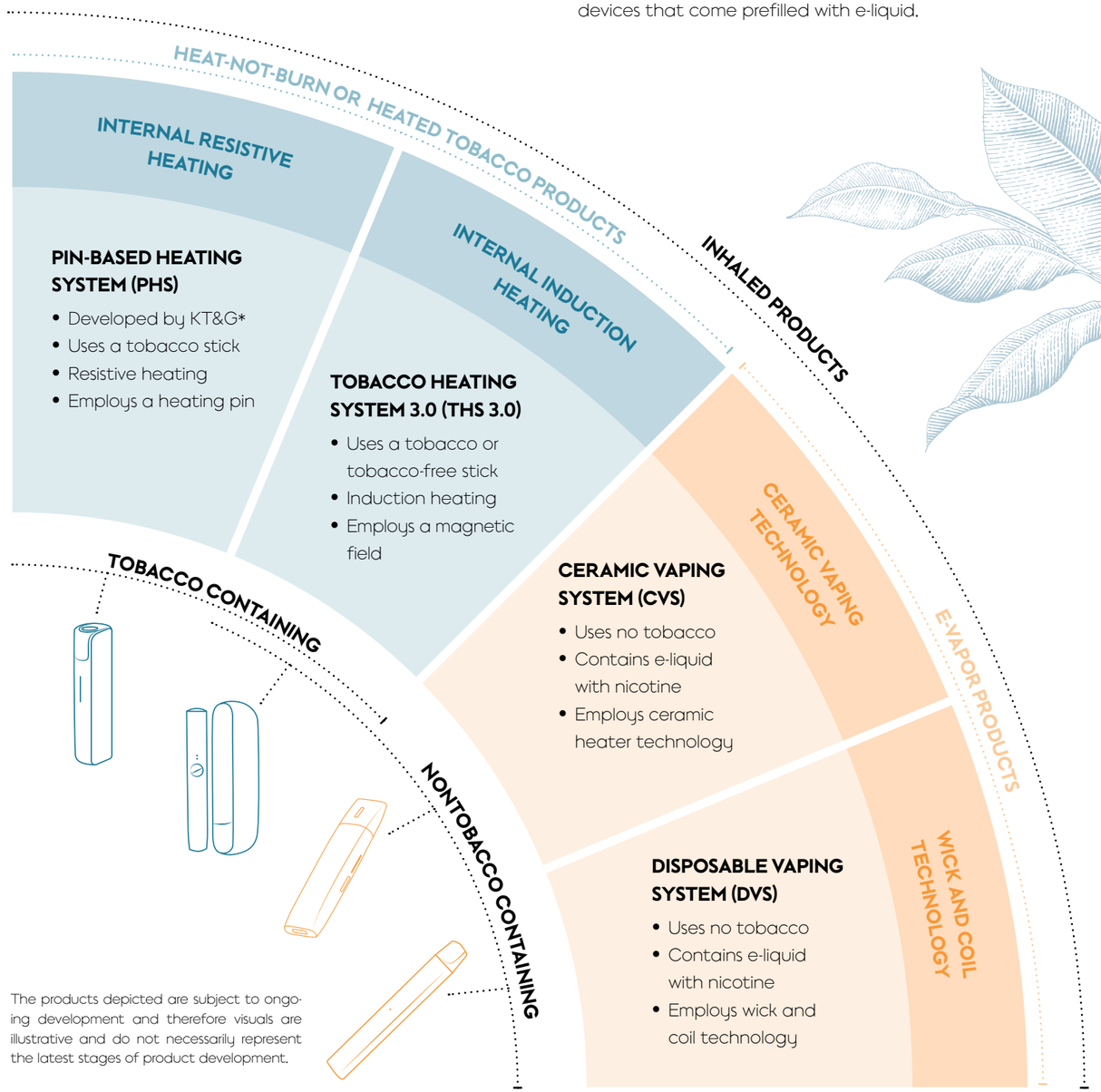
*KT&G is the leading tobacco and nicotine company in South Korea.

HEAT-NOT-BURN OR HEATED TOBACCO PRODUCTS

Our HTPs, also known as HnB products, electrically heat tobacco or a nicotine substrate, using either inductive or resistive heating, just enough to release a nicotine-containing aerosol without burning.

E-VAPOR PRODUCTS

E-vapor products are battery-powered devices, commonly known as e-cigarettes, that vaporize a liquid solution containing nicotine and flavors to create an inhalable aerosol. While traditional e-vapor products come with rechargeable batteries and replaceable or refillable cartridges, disposable e-vapor products are single-use devices that come prefilled with e-liquid.



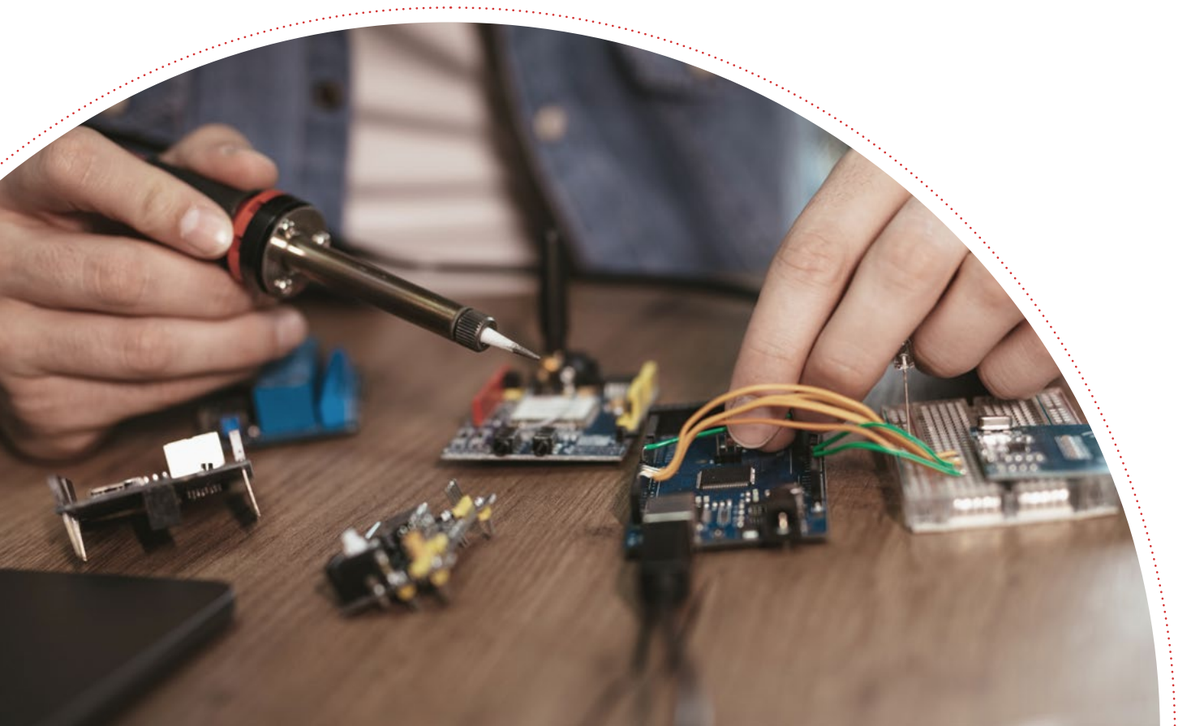
The products depicted are subject to ongoing development and therefore visuals are illustrative and do not necessarily represent the latest stages of product development.

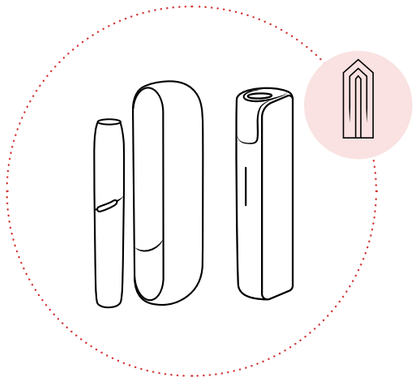
The technologies behind our smoke-free products

HEATED TOBACCO TECHNOLOGIES

HTPs, or HnB products, are a category of products that heat the tobacco instead of burning it.

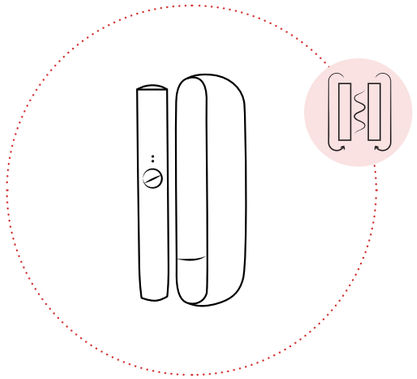
HTPs aim to significantly reduce the emission of harmful chemicals that are associated with combustion compared with cigarettes. HTPs typically consist of an electronic device and a consumable unit that contains a tobacco plug made from ground and reconstituted tobacco leaves to form a crimped sheet, or a nontobacco substrate infused with nicotine. This innovative and evolving category includes products that vary with respect to temperature profile, heating source, the way the tobacco is processed (e.g., dry, moist, or liquid tobacco ingredients) or even the presence of tobacco itself.





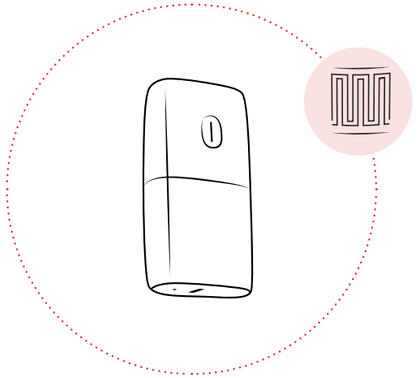
INTERNAL RESISTIVE HEATING TECHNOLOGY *

Uses a heating blade or pin which is inserted directly into the tobacco plug of the consumable unit. Once turned on, the heating blade heats the tobacco radially outwards from the center of the tobacco plug while also monitoring its temperature to ensure consistent taste and avoid burning.



INTERNAL INDUCTION HEATING TECHNOLOGY **

Employs a magnetic field to heat the tobacco plug or tobacco-free*** substrate in the consumable unit. When the consumable unit is inserted inside the heating device, an electric current flows through a coil, creating a magnetic field that transfers energy in form of heat to a heating element, known as susceptor, which is located in the center of the tobacco plug or the substrate, and heats them from the inside.



EXTERNAL RESISTIVE HEATING TECHNOLOGY ****

Employs a resistive heater which surrounds the tobacco stick and heats its external surface. The external heater is made of flexible polyimide stainless-steel tracks wrapped around a stainless-steel tube, with an insulated thermal casing around it.

* The products developed with blade technology include THS 2.2, also known commercially as *IQOS 3* or *Originals*.
** The product developed with induction technology is THS 3.0, also known commercially as *IQOS ILUMA*.
*** In addition to tobacco sticks specially designed to be used with induction technology, we have developed nicotine-containing sticks that do not contain tobacco. When heated, they provide a nicotine-containing aerosol. These tobacco-free sticks are known commercially as *LEVIA*.
**** The product developed with external heating technology is *BONDS by IQOS*.

E-VAPOR TECHNOLOGIES

Within our portfolio of smoke-free products, we offer a range of e-vapor or vaping products, also known as e-cigarettes.

E-cigarettes are handheld battery-operated devices that generate an inhalable aerosol by heating a liquid solution containing nicotine and flavors.

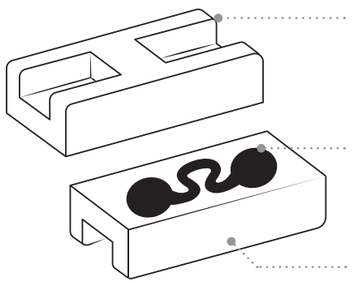
WICK AND COIL TECHNOLOGY*

The wick is a strip of porous material made up of organic cotton which uses capillarity to draw an e-liquid onto a coil-heating element. The coil heats the e-liquid until all its chemical compounds evaporate into the gas phase. The gas phase then rapidly cools down, leading to the condensation of vapor into liquid droplets forming the aerosol.

CERAMIC VAPING TECHNOLOGY**

The heater in this vaping technology features a ceramic microporous substrate with a printed metallic heating track.

The innovative H-shape design of the heater increases the e-liquid supply surface area, allowing a sustained feed of e-liquid to the metallic heating track during the heating process.



CERAMIC BODY
H-shape structure on the heater front side in contact with the e-liquid formulation.

HEATING TRACK
Printed on the back side of the ceramic body.

CERAMIC BODY

* The product developed with wick and coil technology is the Disposable Vaping System (DVS), commercialized as *VEEV* NOW.
** The product developed with this vaping technology is the Ceramic Vaping System (CVS), commercialized as *VEEV* ONE.

ORAL PRODUCTS TECHNOLOGY

Our oral products are pouches that do not involve a device, heating, or the inhalation of an aerosol.

Instead, these pouches are designed to be placed between the gum and the cheek or upper lip, allowing nicotine absorption through oral mucous membranes before entering the bloodstream.

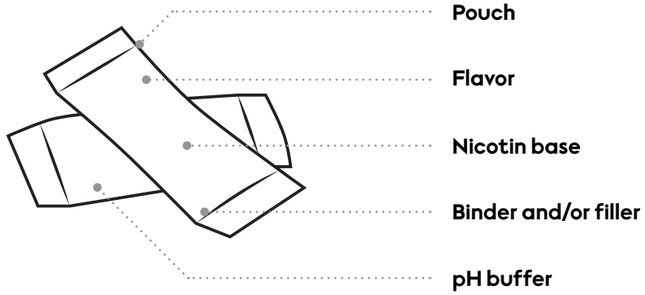
SNUS*

A type of moist tobacco, containing finely ground tobacco, salt, water, and flavorings.

NICOTINE POUCH**

It does not contain tobacco.

It is typically made from organic cellulose compounds, and it contains pharmaceutical-grade nicotine, pH buffer, water, flavorings, and plant-based fibers (fillers).



* Snus are commercialized under various affiliate brands, such as *General*.
** Nicotine pouches are commercialized under our affiliate brand *ZYN*.

DIVING INTO OUR **FINDINGS**

The totality of evidence gathered so far demonstrates that the 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.

Read more on PMIScience.com

In the following section we dive into many of our key findings for THS (version 2.2); from the absence of combustion to the positive impact on smokers' health. We also explore usage patterns after product launches.

Our scientific approach

At PMI, our scientific assessment is built on a collaborative approach and expertise in multiple fields, such as chemistry, biology, clinical, medical, behavioral, and data sciences.

Our practices are inspired by the pharmaceutical industry and are aligned to the draft guidance for modified risk tobacco product (MRTP) applications issued by the U.S. Food and Drug Administration's Center for Tobacco Products in 2012.[5] Learn more about how we conduct our smoke-free product research and explore the results of our studies.

Aerosol studies

Aerosol research is a foundational part of our smoke-free product assessment.

Our smoke-free products are developed to avoid tobacco combustion. The aerosol chemistry and physics studies we conduct aim to confirm that combustion does not take place and to confirm for each product that the resulting aerosol contains lower levels of HPHCs compared with cigarette smoke. Aerosol research also includes studies on the effects of smoke-free products on indoor air quality.

Toxicology studies

After a product has been shown to generate lower levels of HPHCs compared with levels found in cigarette smoke, we conduct toxicology research.

This helps translate the aerosol assessment into an estimate of the risk reduction potential for a smoke-free product. Some toxicology studies are necessary before clinical studies can begin. Toxicology answers the question of whether smoke-free product emissions or releases are toxic to cells and other model systems compared with cigarettes and allows scientists to understand the biological processes that lead from exposure to the onset of smoking-related diseases.

Clinical studies

Once a product has been demonstrated to be less toxic in laboratory studies, we can begin clinical studies.

Clinical studies provide human data on the use and acceptance of our smoke-free products as well as their potential to reduce exposure to HPHCs, and the potential to reduce the risk of smoking-related diseases as compared with continued smoking.

Perception and behavior studies

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 not enough to know whether a smoke-free product has a reduced-risk profile compared with cigarettes.

It is equally important that these products are used by the right audience: adult smokers who would otherwise continue to smoke.

Moreover, smokers should understand that quitting is the best way to reduce smoking-related health risks.

Long-term studies

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

This area of research includes post-market studies, safety surveillance, clinical studies, and epidemiological studies to continually refine our understanding of the risk reduction potential of our products.

Long-term assessment, including post-market studies, will confirm whether these products reduce the risk of smoking-related diseases such as COPD, CVD, and lung cancer.

Guidance on assessment methods used by PMI can be found in the annex (page 57).

QUALITY PRINCIPLES

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

A risk-based quality management system (QMS) 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.

There is no burning in THS

Scientific data show that the primary cause of smoking-related disease is the high levels of 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.[6] The combustion of tobacco results in the formation of smoke (containing high levels of HPHCs), heat, and ash.

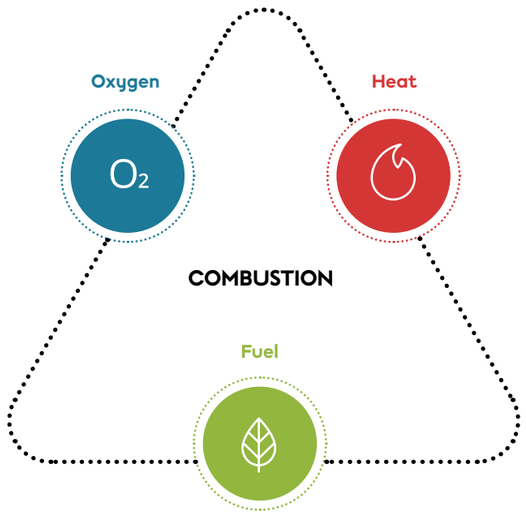
We have conducted several studies to demonstrate the absence of combustion in THS, including temperature measurements, experiments demonstrating the absence of net exothermic processes, and measurements of constituents that represent typical markers of combustion.[7]

Our studies also support that the aerosol of THS does not contain solid particles that are produced when tobacco is burned.[8] 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.

FIGURE 4:

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



Combustion does not occur during the use of the THS.

DID YOU KNOW?

Tar is the weight of solid and liquid residue in cigarette smoke, after nicotine and water have been removed. It is not an added chemical, nor the material used to pave roads, it is simply a weight measurement. Is tar measurement useful?

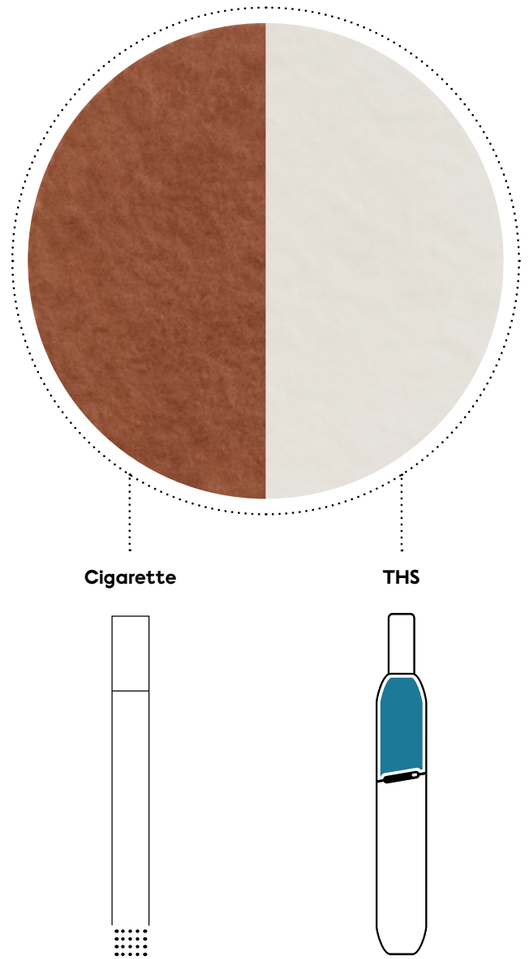
If we only take the weight into account, it is not. Out of context, the weight gives no indication of residue content nor the risk of harm because the level of toxicants within that weight are unknown, and the WHO agrees, "While several Parties include tar in their regulatory policies, it is not on the 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." [9]

Additionally, 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 is 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 HPHCs. 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.

Scan to learn about the difference between cigarette smoke and THS aerosol.

FIGURE 5:

The picture shows the visual difference between the particulate matter of standard reference cigarette smoke (IR6F, left) and the particulate matter of THS aerosol (right) after collection on laboratory filter pads (1 stick per product, aerosol regime ISO 20778:2018).



Reduced emissions of harmful chemicals

Aerosol chemistry: targeted analysis

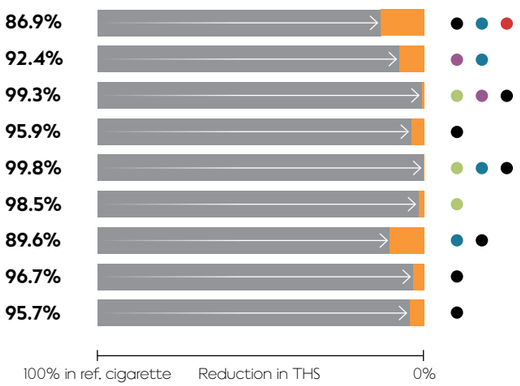
We measured a number of HPHCs in the aerosol of THS and compared their levels with the levels found in the smoke of a standard reference cigarette (3R4F).[10] On average, we observed a 95% reduction in the levels of HPHCs based on recognized HPHC lists.

*By eliminating combustion, the levels of HPHCs are reduced on average by 95% in the aerosol of THS compared with those in cigarette smoke.**

FIGURE 6:

This figure illustrates the reductions of HPHCs, as listed in the WHO 9 list,[11] present in the THS aerosol compared with cigarette smoke.

HPHCs	Ref. cigarette mean (per stick)	THS mean (per stick)	Reduction in THS versus ref. cigarette (per stick)
Acetaldehyde	1641 µg	215 µg	**86.9%**
Acrolein	156 µg	11.8 µg	**92.4%**
Benzene	81.1 µg	0.533 µg	**99.3%**
Benzo[a]pyrene	15 ng	0.621 ng	**95.9%**
1,3-butadiene	98.5 µg	0.233 µg	**99.8%**
Carbon monoxide	30.2 mg	0.447 mg	**98.5%**
Formaldehyde	85.2 µg	8.89 µg	**89.6%**
NNK**	264 ng	8.72 ng	**96.7%**
NNN***	283 ng	12.3 ng	**95.7%**



*Based on the WHO 9 list.[1]

Tobacco-specific nitrosamines:
**NNK: 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone
***NNN: N-Nitrosonornicotine
Yields are obtained under the Health Canada Intense Testing regime.

Toxicants classification based on the established FDA list.[12]

- Carcinogen
- Respiratory toxicant
- Cardiovascular toxicant
- Reproductive or developmental toxicant
- Addictive

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.[13]

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

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 3R4F 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.

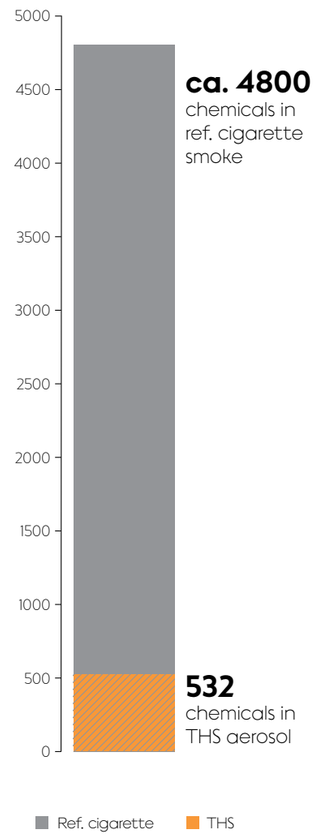
The levels of these four compounds were very low and the U.S. FDA concluded that "Although some of the chemicals are genotoxic or cytotoxic, these chemicals are present in very low levels and potential effects are outweighed by the substantial decrease in the number and levels of HPHCs found in CC [combusted cigarettes]."[14]

Additionally, to minimize differences between the test items, untargeted differential screening was conducted using the same tobacco blend structure in both THS and a cigarette. No major compounds present in THS aerosol that were absent in cigarette smoke were detected.[15]

To the best of our knowledge, this is the first time that such a comprehensive in-depth chemical characterization of the aerosol composition of an HTP 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.

FIGURE 7:

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 smoke (≥ 100 ng/heated tobacco unit).



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.

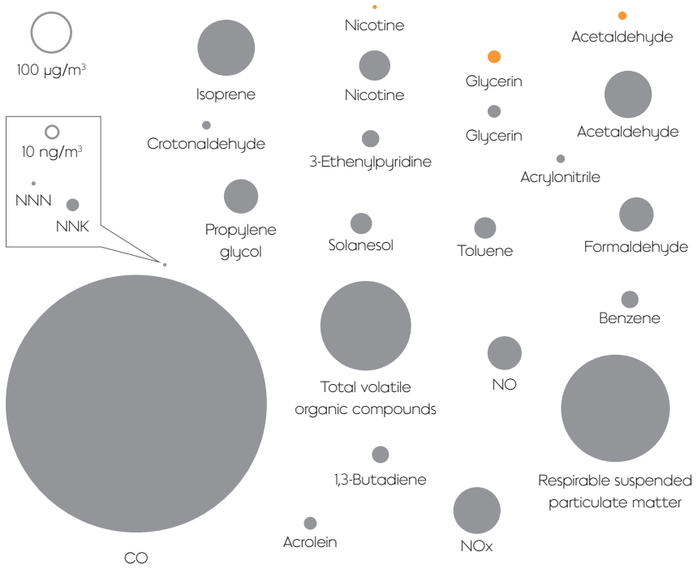
We measured 24 compounds including carbonyls, tobacco-specific nitrosamines, and volatile organic compounds under simulated residential conditions.

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.[16 17 18]

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.

FIGURE 8:

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.



- Compounds in THS aerosol measured at levels higher than the background
- Compounds in cigarette smoke measured at levels higher than the background
- Scale

Nicotine

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.

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 nonnicotine users.

Nicotine-containing products should also not be used during pregnancy or while breastfeeding. 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 COPD, CVD, and lung cancer, are caused primarily by inhaling HPHCs largely formed when tobacco is burned, not by nicotine alone.

Nicotine is a crucial factor, alongside taste, sensory experience, and ritual characteristics, in encouraging adult smokers to switch to smoke-free alternatives.

It is the thousands of chemicals contained in tobacco and tobacco smoke that make tobacco use so deadly. This toxic mix of chemicals—not nicotine—causes serious health effects, including fatal lung diseases and cancer. [19]

Reduced toxicity

Toxicological studies provide a good indication of the risk reduction potential of a smoke-free product and the confidence to move forward with clinical studies.

From a regulatory standpoint, the main purpose of certain toxicology assays, such as the neutral red uptake, Ames, and mouse lymphoma assays, is to provide data for regulatory agencies on whether our products meet the defined acceptability criteria. These criteria include requirements for manufacturing and are prerequisites to clinical studies. We also take toxicology assessment a step further by using systems toxicology, which seeks to explain the relationship, or mechanism, that connects the initial exposure to the resulting effects.

Studies show a substantial reduction in toxicity of the aerosol of THS compared with cigarette smoke.

We have conducted a series of regulatory toxicology tests to compare the toxicity of THS aerosol with that of 3R4F smoke. In our laboratories, we observed a substantial reduction in toxicity of the THS aerosol compared with cigarette smoke.[10]

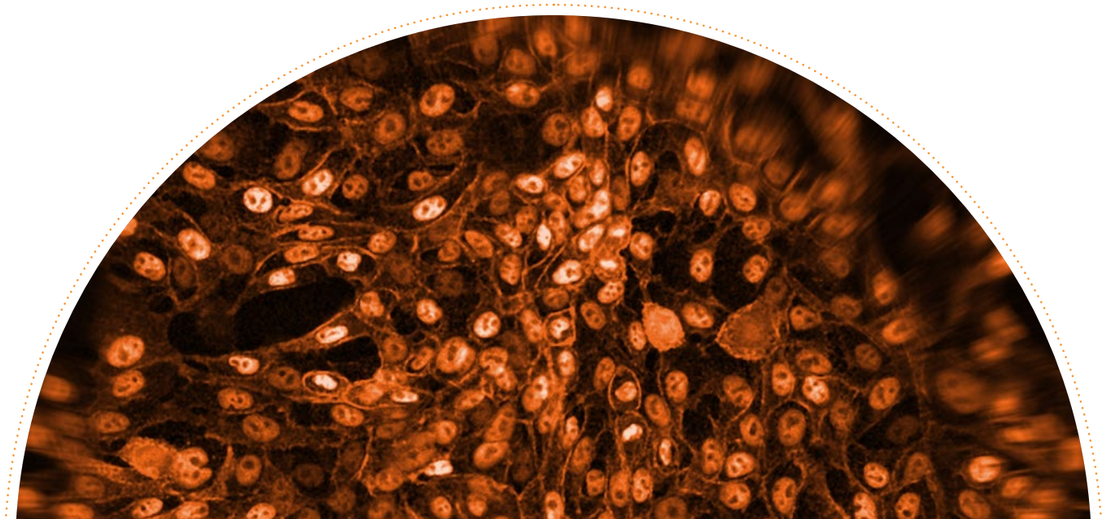
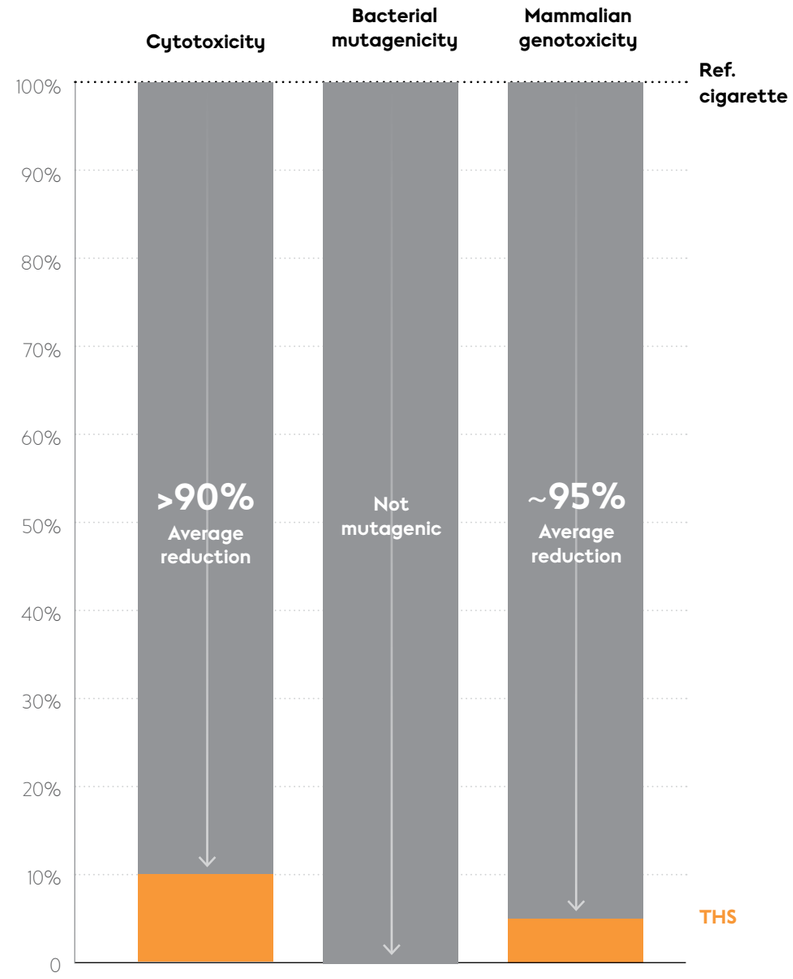


FIGURE 9:

The chart shows our findings concerning the relative *in vitro* toxicity of THS aerosol compared with 3R4F smoke using three *in vitro* assays (neutral red uptake, Ames, and mouse lymphoma) commonly used to assess cytotoxicity, mutagenicity, and genotoxicity.



Effects on the risk of COPD and CVD

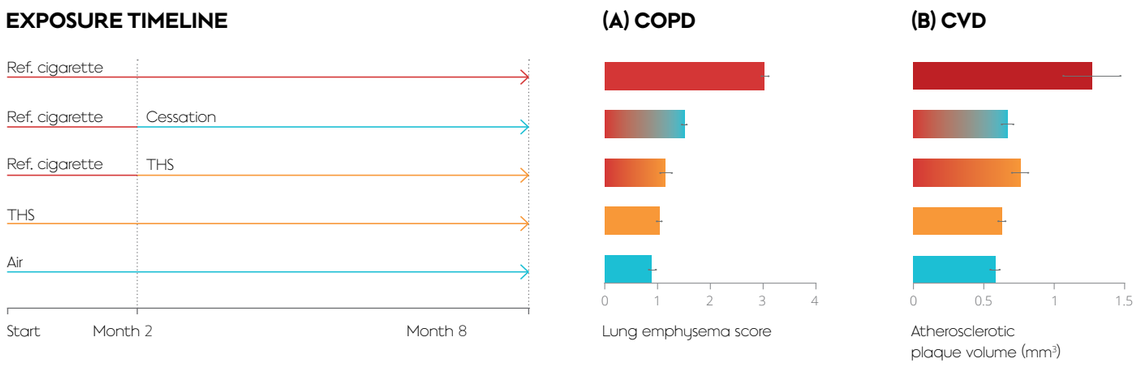
PMI conducted a systems toxicology study in an animal model (Apoe$^{-/-}$ mouse) that develops atherosclerotic plaques and emphysema when exposed to cigarette smoke.

In this study, mice were exposed to either 3R4F smoke 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.[20]

Switching to THS led to reduced impact on biological mechanisms and disease endpoints associated with COPD and CVD compared with continued smoking in a laboratory model.

FIGURE 10: REDUCED RISK OF COPD AND CVD

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.



Effects on the risk of lung cancer

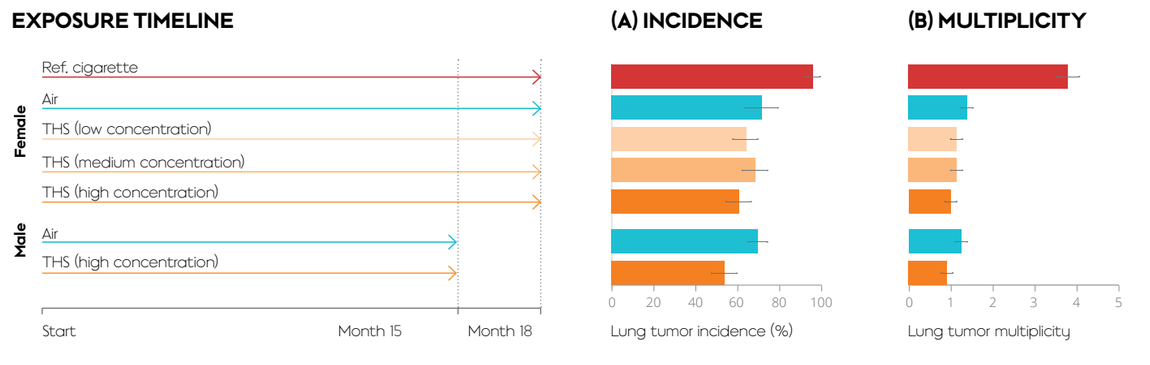
A study was conducted to compare carcinogenic effects of THS aerosol with 3R4F smoke over the lifetime (18 months) of A/J mice.

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 3R4F smoke. Incidence and multiplicity were similar in the mice exposed to fresh air and those exposed to THS aerosol.[21,22]

Unlike cigarette smoke, the aerosol of THS does not lead to increased lung tumor incidence and multiplicity in a laboratory model.

FIGURE 11: REDUCED RISK OF LUNG CANCER

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 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.



Less staining on teeth

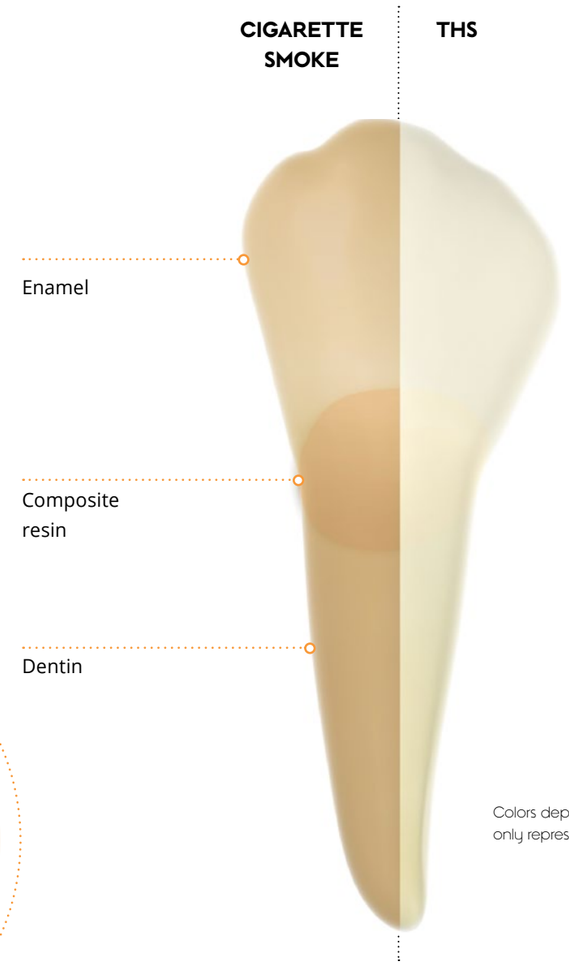
Our studies on human teeth demonstrate the reduced discoloration effects of THS aerosol compared with 3R4F smoke.

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.[23]

The aerosol of THS discolors teeth significantly less than cigarette smoke.

FIGURE 12:

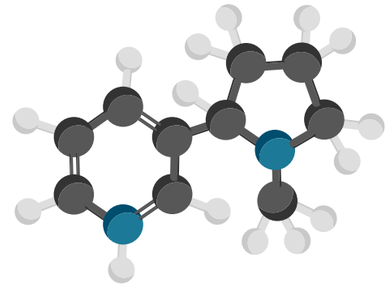
After 3 weeks, THS aerosol caused no obvious discoloration to the teeth and no color mismatch between the teeth and dental resins, unlike cigarette smoke.



Colors depicted in this figure are only representative.

Nicotine uptake

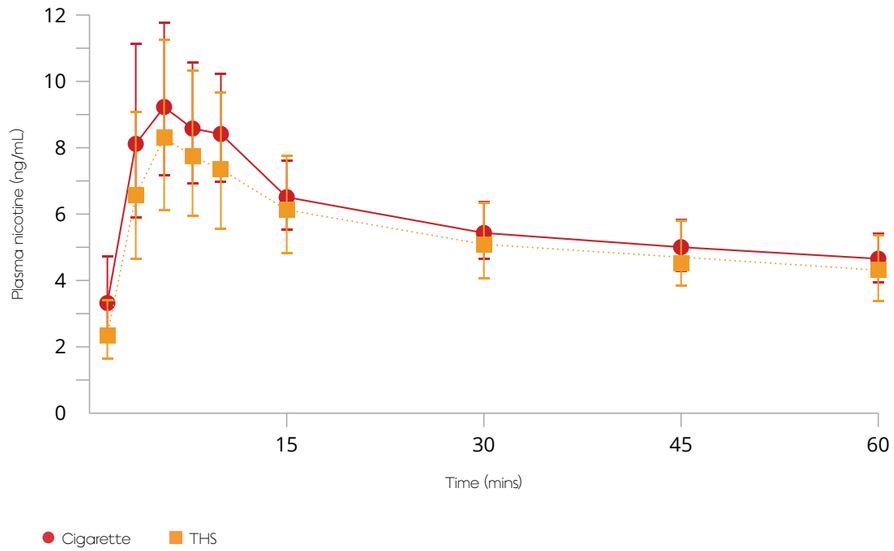
We have shown in the pharmacokinetic and pharmacodynamic clinical studies that the level of nicotine, and the timing of its peak concentration in the blood, were comparable for smokers and for subjects who switched to THS.



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.[24]

FIGURE 13:

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



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 HPHCs.

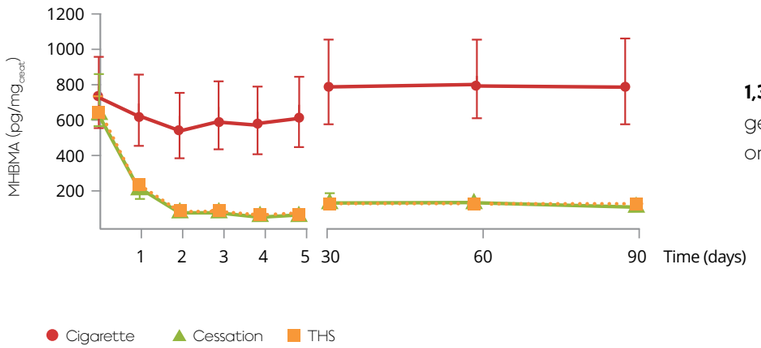
We found that levels of 15 biomarkers of exposure in participants switching completely to THS were comparable with the levels of those who quit smoking for the duration of the study. In both cases, the levels remained significantly below those observed in subjects who continued smoking during the study.[25,26]

Smokers switching completely to THS were exposed to significantly lower levels of HPHCs compared with those who continued smoking during the study.

FIGURE 14:

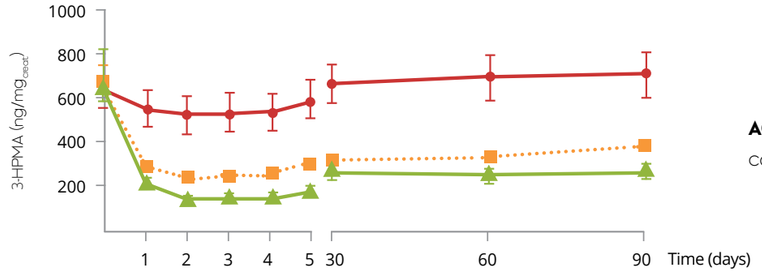
The effects of switching to THS or smoking abstinence on biomarkers of exposure levels for four selected HPHCs. We examined a total of 15 biomarkers, all displaying the same trend. The same type of study in the U.S. (NCT01989156) showed comparable results.

1,3-BUTADIENE*



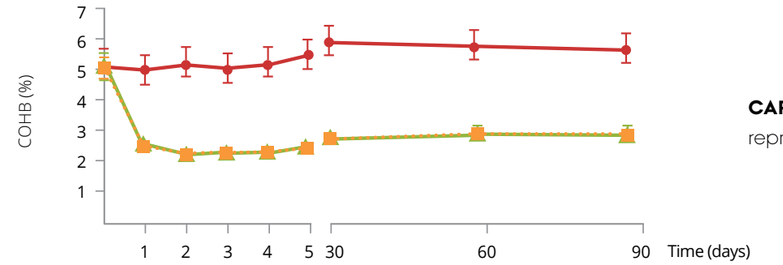
1,3-BUTADIENE is classified as a carcinogen, respiratory toxicant, and reproductive or developmental toxicant.

ACROLEIN*



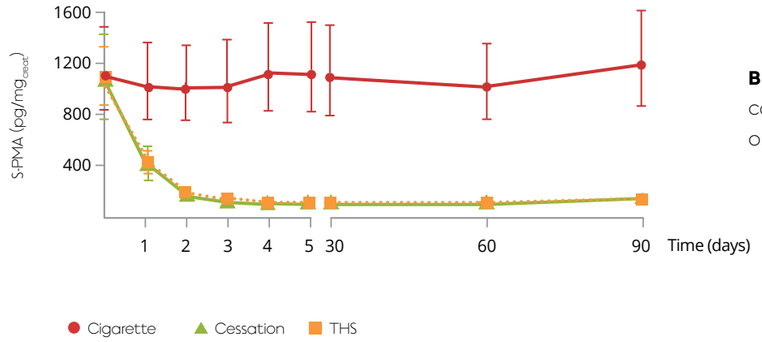
ACROLEIN is classified as a respiratory and cardiovascular toxicant.

CARBON MONOXIDE*



CARBON MONOXIDE is classified as a reproductive or developmental toxicant.

BENZENE*



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

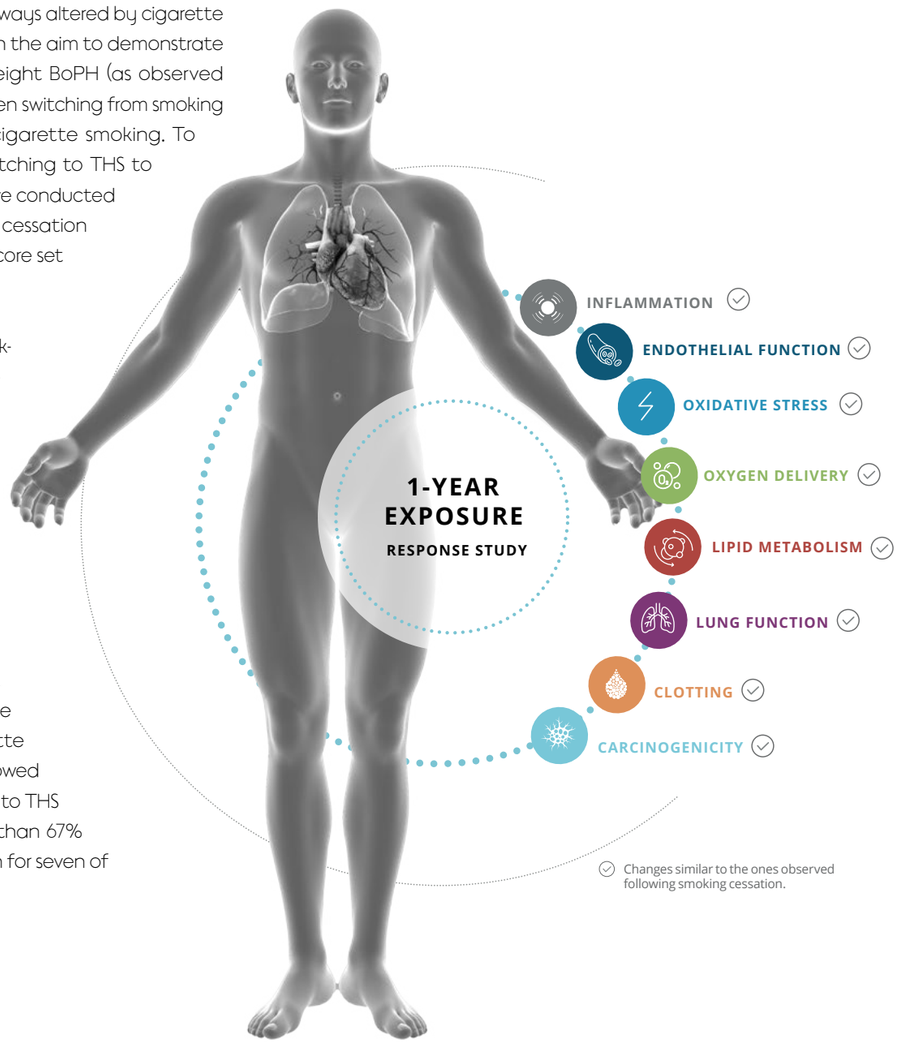
*Levels of biomarkers detected (3-month study in Japan).

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.

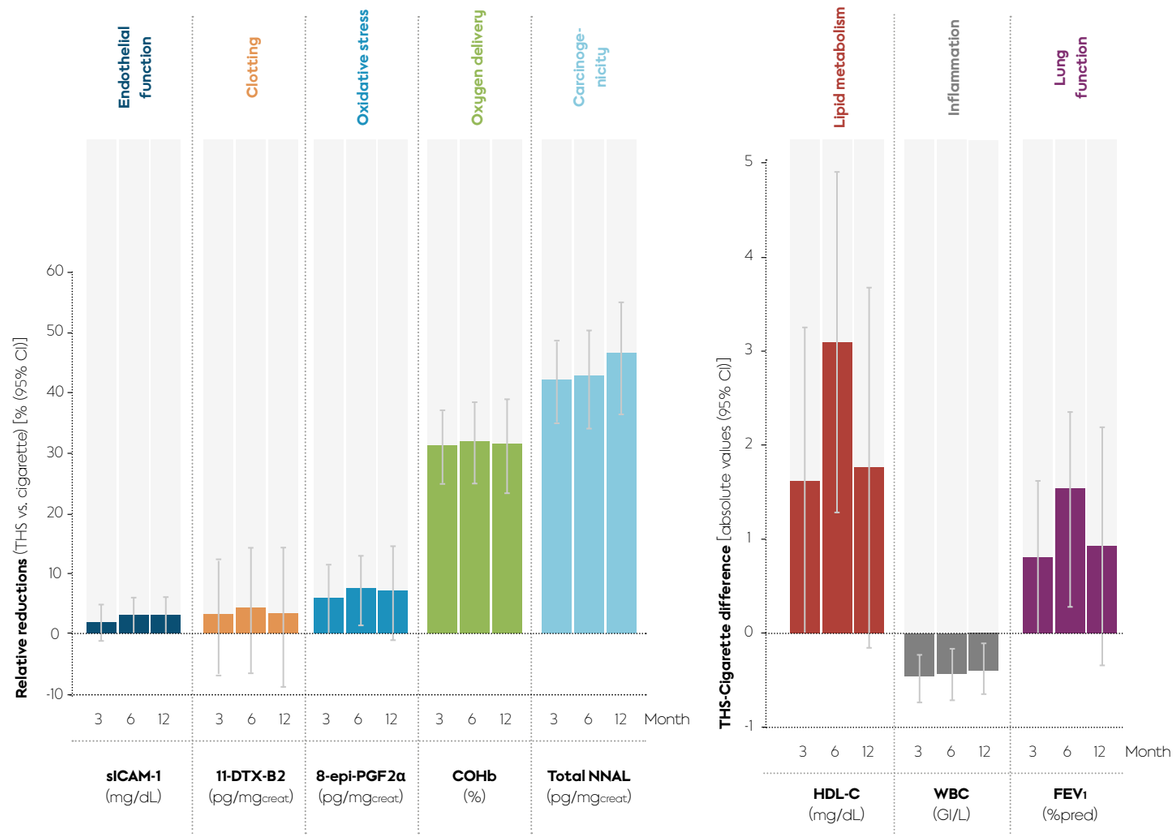
Our studies showed that smokers who switched from cigarettes to THS for 12 months had favorable changes in all eight BoPH, in the same direction as upon smoking cessation. We found that in predominant THS users, the lesser the concomitant cigarette smoking the greater were the favorable effects on the 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.[27 28 29]



Clinical findings provide evidence on the potential of THS to reduce the risk of developing COPD, CVD, and cancer compared with continued cigarette smoking.

FIGURE 15:

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



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.

In addition, the study findings 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 THS presents less risk of harm than continued cigarette smoking.

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.[30] 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.[31] 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 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 THS.

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 nonmisleading product information capable of enabling informed decision making.

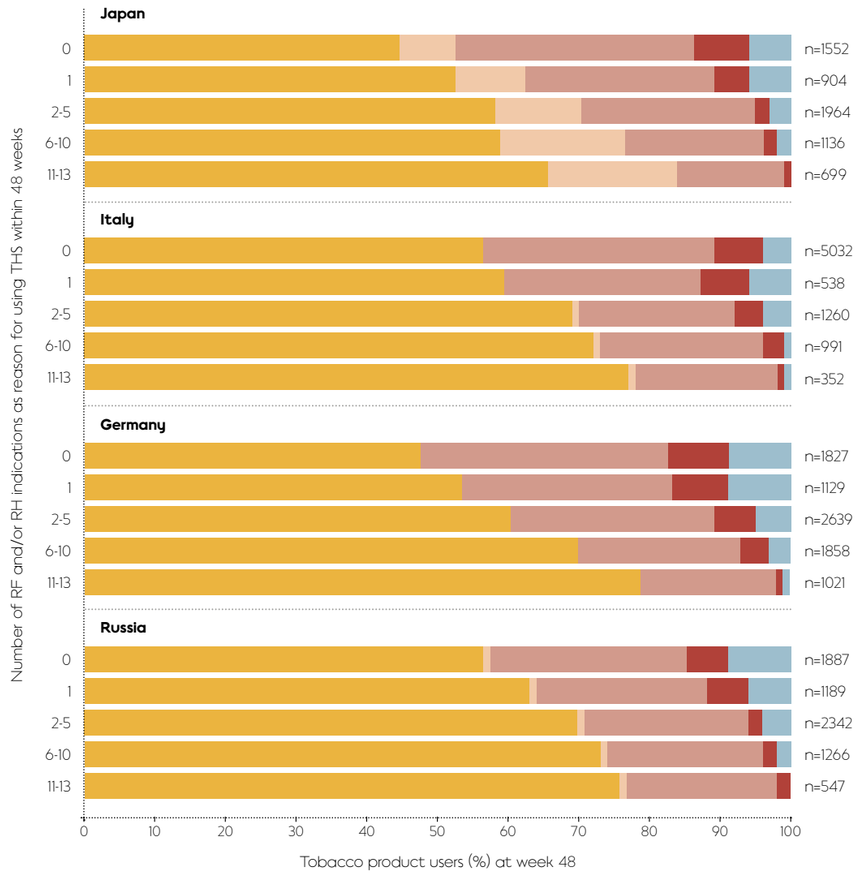
This study employed a large-scale longitudinal survey involving participants who were THS users.[32] Participants completed questionnaires assessing their perceptions and THS use patterns over a 48-week period. The results showed that individuals who identified perceived reduced formation of HPHCs or 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.

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 HPHCs;
RH: perceived reduced risk of harm.



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.

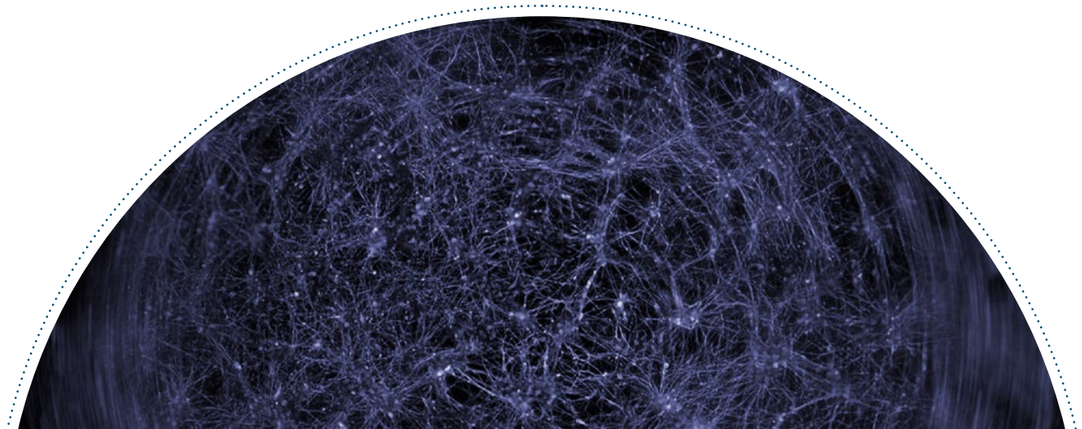
Population health impact model

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.[33] In a Japan study, the model estimated that the introduction of a hypothetical HTP 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 HTP. 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.



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[34,35], 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%).

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 nonexisting 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.

FIGURE 17:

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

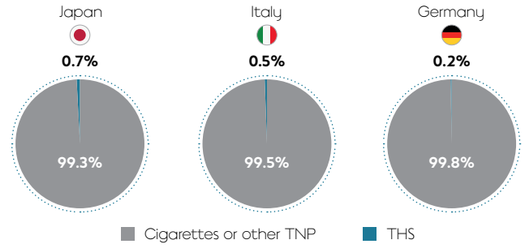
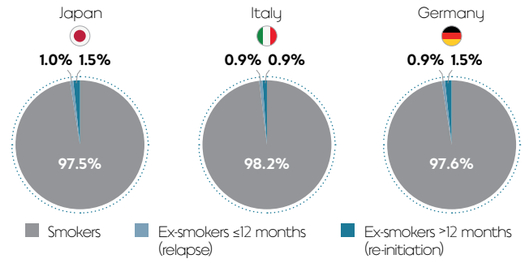


FIGURE 18:

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



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.

VALIDATING OUR RESEARCH

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

IN THIS SECTION

Read more on PMIScience.com

Governmental studies

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 nonmisleading 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. Many government bodies have conducted literature reviews or performed research on scientifically substantiated HTPs, finding that they expose users to significantly lower levels of HPHCs.

*IQOS is the commercial name for the THS.

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.[36]

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 U.S. "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.[37]

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.[38]

2022: The U.S. FDA authorized the use of reduced exposure claims for a newer version of *IQOS*.[39]

2023: The U.S. FDA has accepted PMI's MRTP renewal application for *IQOS*.[40]

U.K. COMMITTEE ON TOXICITY (COT)

2017: U.K. COT conducted a review of available evidence on two HTPs, one of which is *IQOS*, and concluded that there is a "likely reduction in risk for smokers switching to heat-not-burn tobacco products." [41]

PUBLIC HEALTH ENGLAND (PHE)

2018: PHE published a review of the evidence on e-cigarettes and HTPs, and stated that HTPs likely reduce users' and bystanders' exposure to harmful compounds compared with cigarettes. PHE also stated available evidence suggests that HTPs may be considerably less harmful than tobacco cigarettes and more harmful than e-cigarettes.[42]

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." [43]

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.[44]

GERMAN FEDERAL INSTITUTE FOR RISK ASSESSMENT (BFR)

2018: 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." [45]

2019: BfR published an article titled "Heated Tobacco Products: A Review of Current Knowledge and Initial Assessments" confirming the findings of their previous study.[46]

SUPERIOR HEALTH COUNCIL OF BELGIUM (SHC)

2020: 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.[47]

Independent reviews

Over the past several years, a growing number of organizations and institutions have initiated or completed studies on our smoke-free products or on the methodologies and results supporting them.

The number of independent studies on heated tobacco products published each year—many of them on PMI's heat-not-burn products—has significantly increased over the past years, as shown on PMIScience.com.

In general, these studies confirm important elements of our research results. There can also be differences between studies, such as different results, interpretations of data, methodological differences, and differences in how conclusions are drawn.

Individual studies, no matter how well they are designed, can only ever tell part of the story. It is the totality of evidence, built up over time, which provides the clearest understanding of the harm reduction potential of our smoke-free products.

Over the years, numerous independent studies have already confirmed different elements of our research on smoke-free products.

PMI'S EFFORTS AT A GLANCE

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.

IN THIS SECTION

Read more on PMIScience.com

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.

1,586

people including scientists, engineers, technicians, and support staff working in PMI R&D in 2023.*

USD 120 million

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

532

scientific publications by PMI from 2008 to 2023 - most open access.

USD 12.5 billion

invested by PMI to develop, scientifically substantiate, and commercialize smoke-free products since 2008.**

USD 709 million

total R&D expenditure in 2023.

30

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

99%

of total R&D expenditure was dedicated to smoke-free products in 2023.

~3,720

patents granted for smoke-free technologies by the five largest intellectual property offices in the world (IP5, cumulative from 2015 to 2023).***

* Data includes employees of Swedish Match and Vectura Fertin Pharma.
** Investments reflect research, product and commercial development, production capacity, scientific substantiation, and studies on adult smoker understanding. Figure does not include Swedish Match and Vectura Fertin Pharma.
*** IP5 jurisdictions are Europe (patents granted by the European Patent Office), China, South Korea, Japan, and the U.S.

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.

* MRTP: Modified Risk Tobacco Product
** PMTA: Premarket Tobacco Product Application

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.

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

The science on our smoke-free products does not just end here

There is much more to explore on our website PMIScience.com.

Learn more about our smoke-free product technologies.

Stay up to date on our latest science news.

Learn more about our research on smoke-free products.

Use our glossary for further clarifications.

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ANNEX

PMI's quality management system: guidelines, guidances, principles, practices, and standards

AEROSOL CHEMISTRY AND PHYSICS RESEARCH	**Product design and control** Quality by design (QbD)[48]	**Aerosol chemistry** OECD GLP[49]; ISO[50] 17025; ICH Q2 (R1)[51]; ISO 3308*, 3402, 4387*, 8454, 10315:2013, 10362-1*, 13110, 19290, 20768, 20778 **Indoor air quality** ISO 17025; EN 15251[52]; ISO 15593, 18144, 18145, 16814, 16000-6, 11454
TOXICOLOGY RESEARCH	**Nonclinical studies** OECD Test guidelines; ICH guidelines; FDA guidelines; Applicable national regulations; GLP; ISO 17025	
CLINICAL RESEARCH	**Clinical studies** WMA declaration of Helsinki[53]; Based on ICH-GCP E6 (R2)[54]; Applicable local regulations	
PERCEPTION AND BEHAVIOR RESEARCH	**Perception and behavior studies** Based on GEP-DGEpi[55]; Based on FDA guidance on TPPI; FDA guidance on PRO[56]; Applicable national regulations; WMA declaration of Helsinki	
LONG-TERM RESEARCH	**Long-term studies** IEA GEP[57]; Applicable national regulations	

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

EDITION 7.0, MAY 2024

PMIScience.com is operated by Philip Morris International for the purpose of publishing and disseminating scientific information about Philip Morris International's efforts to develop and assess products that have the potential to reduce individual risk and population harm associated with tobacco use.

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