MC19-011481

# PHILIP MORRIS

AUSTRALIA NEW ZEALAND PACIFIC ISLANDS





28 June 2019

The Hon Greg Hunt MP
Minister for Health
Parliament House
CANBERRA ACT 2600

Dear Mr Hunt

Congratulations on your appointment as Minister for Health. I wish you every success in your role and look forward to working constructively with you in the future to address policy issues of mutual interest and concern.

The 46th Parliament will present you with a wide range of social and economic policy challenges to address. Few will be more important than the need to address the stagnation of smoking prevalence rates in Australia and the impact this has on the lives of Australia's almost 3 million smokers, their loved ones and public health more broadly.

Earlier this month, the Australian Institute of Health and Welfare released *Australia's health 2018*, its biennial report on the health of Australians. In relation to smoking, it highlights:

- that past declines in daily smoking have slowed;
- the significant health inequalities facing Australia's smokers; and
- the burden of disease caused by smoking.

This is even more concerning as Australia's approach to addressing smoking is now at odds with other developed nations that commonly experience declining smoking prevalence.

It is no coincidence that they embrace tobacco harm reduction policies by making less harmful products available to adult smokers in a controlled, regulated way. All OECD nations except for Australia and Turkey have now embraced this approach.

Much new evidence has emerged since the House Standing Committee on Health, Aged Care and Sport and both the Senate Economics References and Community Affairs committees each last considered this matter. While tobacco harm reduction remains controversial in Australia, it is the law overseas with bipartisan support, backed by government policy and the Department of Health in other comparable countries. In many cases, support for quitting and switching to less harmful products is proactively supported and promoted through national government advertising campaigns.

The United Kingdom, Europe and the United States have long endorsed tobacco harm reduction principles as a meaningful way to reduce smoking rates and placed vaping at the centre of their approach. Most recently, the Trudeau Government in Canada has legalised and regulated vaping, and the Ardern Government in New Zealand is in the process of doing so, and even though the law is not yet updated, they are still actively encouraging Kiwis to switch from cigarettes to less harmful, smoke-free alternatives.



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In reading this, you will likely have doubts, both about the message and the messenger. However, as Australia's progress in reducing smoking stalls, other countries are acting. With Australia due to update the National Tobacco Strategy this year, I ask you to develop your own independent understanding of the latest evidence on this important policy topic and how we can get the policy settings right.

A good starting place is the New Zealand Ministry of Health vaping website launched earlier this month (www.vapingfacts.health.nz) which sets out the facts on vaping and notably states:

*Vaping has the potential to help people quit smoking and contribute to New Zealand's Smokefree 2025 goal.*

Philip Morris is also committed to securing a Smoke-Free Future, as the greatest real-world contribution we can make to society is to replace cigarettes with smoke-free products (SFP) which are a less harmful alternative to smoking, thereby minimising the negative impact of smoking on public health.

This will seem incredible to some, however, in only a few years we have made progress in achieving this transformation. In 2018, SFPs represented 13.8% of our total net revenues, up from nothing only a few years before. In three countries, such revenues exceeded those of our combustible products and 6.6 million people have stopped smoking and switched to *IQOS*, our most advanced SFP. However, while these products remain banned in Australia, nearly 3 million smokers are without new alternatives to smoking cigarettes.

On 30 April 2019, the world's toughest and most respected regulator, the US Food and Drug Administration (FDA), finalised its rigorous science-based review through the premarket tobacco product application pathway for *IQOS*. This legislated mechanism doesn't exist in Australia, but enabled the FDA to determine that "authorizing these products for the U.S. market is appropriate for the protection of the public health because, among several key considerations, the products produce fewer or lower levels of some toxins than combustible cigarettes." The FDA also found that "few non-tobacco users would be likely to choose to start using *IQOS*, including youth."[1]

I trust you will agree that this is an important development and deserves consideration in the Australian context. Indeed, we are now presented with an enormous public health opportunity: to allow adult smokers who would otherwise continue smoking, the chance to switch to a scientifically-substantiated less harmful alternative.

To discuss this further, s 47F Manager Public Policy and I would like to arrange to meet with you in the sitting weeks commencing 22nd and 29th July 2019 or otherwise at a convenient time at your electorate office. To arrange a meeting, please contact Simon at s 47F

Best wishes for all your endeavours throughout the 46th Parliament. I look forward to speaking with you soon.

Yours sincerely

s 47F

Director External Affairs AU NZ & PI

Ps. I trust the FDA decision goes a long way in addressing your concerns.

[1] *FDA permits sale of IQOS Tobacco Heating System through premarket tobacco product application pathway*, US FDA Media Release, 30 April 2019. Available here: https://www.fda.gov/news-events/press-announcements/fda-permits-sale-iqos-tobacco-heating-system-through-premarket-tobacco-product-application-pathway

FDA NEWS RELEASE

# FDA permits sale of IQOS Tobacco Heating System through premarket tobacco product application pathway

*Agency places stringent marketing restrictions on heated tobacco products aimed at preventing youth access and exposure to the new products*

**For Immediate Release:**

April 30, 2019

The U.S. Food and Drug Administration today announced it has authorized (/tobacco-products/premarket-tobacco-product-applications/premarket-tobacco-product-marketing-orders) the marketing of new tobacco products manufactured by Philip Morris Products S.A. for the IQOS "Tobacco Heating System" – an electronic device that heats tobacco-filled sticks wrapped in paper to generate a nicotine-containing aerosol. The FDA has placed stringent marketing restrictions on the products in an effort to prevent youth access and exposure.

Following a rigorous science-based review through the premarket tobacco product application (PMTA) pathway, the agency determined that authorizing these products for the U.S. market is appropriate for the protection of the public health because, among several key considerations, the products produce fewer or lower levels of some toxins than combustible cigarettes. The products authorized for sale include the IQOS device, Marlboro Heatsticks, Marlboro Smooth Menthol Heatsticks and Marlboro Fresh Menthol Heatsticks. While today's action permits the tobacco products to be sold in the U.S., it does not mean these products are safe or "FDA approved." All tobacco products are potentially harmful and addictive and those who do not use tobacco products should continue not to. Additionally, today's action is not a decision on the separate modified risk tobacco product (MRTP) applications that the company also submitted for these products (/tobacco-products/advertising-and-promotion/philip-morris-products-sa-modified-risk-tobacco-product-mrtp-applications) to market them with claims of reduced exposure or reduced risk.

"Ensuring new tobacco products undergo a robust premarket evaluation by the FDA is a critical part of our mission to protect the public, particularly youth, and to reduce tobacco-related disease and death. While the authorization of new tobacco products doesn't mean they are safe, the review process makes certain that the marketing of the products is appropriate for the protection of the public health, taking into account the risks and benefits to the population as a whole. This includes how the products may impact youth use of nicotine and tobacco, and the potential for the products to completely move adult smokers away from use of combustible cigarettes," said Mitch Zeller, J.D., director of the FDA's Center for Tobacco Products. "Importantly, the FDA is putting in place postmarket requirements aimed at, among other things, monitoring market dynamics such as potential youth uptake. We'll be keeping a close watch on the marketplace, including how the company is marketing these products, and will take action as necessary to ensure the continued sale of these products in the U.S. remains appropriate and make certain that the company complies with the agency's marketing restrictions to prevent youth access and exposure. As other manufacturers

seek to market new tobacco products, the FDA remains committed to upholding the vital public health standards under the law and using all the tools at our disposal to ensure the efficient and appropriate oversight of tobacco products."

Under the PMTA pathway (/tobacco-products/market-and-distribute-tobacco-product/premarket-tobacco-product-applications), manufacturers must demonstrate to the agency, among other things, that marketing of the new tobacco product would be appropriate for the protection of the public health. That standard requires the FDA to consider the risks and benefits to the population as a whole, including users and non-users of tobacco products. Importantly this includes youth. The agency's evaluation includes reviewing a tobacco product's components, ingredients, additives and health risks, as well as how the product is manufactured, packaged and labeled. The review for the IQOS products took into account the increased or decreased likelihood that existing tobacco product users will stop using tobacco products, and the increased or decreased likelihood that those who do not use tobacco products will start using them.

In particular, through the FDA's scientific evaluation of the company's applications, peer-reviewed published literature and other sources, the agency found that the aerosol produced by the IQOS Tobacco Heating System contains fewer toxic chemicals than cigarette smoke, and many of the toxins identified are present at lower levels than in cigarette smoke. For example, the carbon monoxide exposure from IQOS aerosol is comparable to environmental exposure, and levels of acrolein and formaldehyde are 89% to 95% and 66% to 91% lower than from combustible cigarettes, respectively.

Additionally, IQOS delivers nicotine in levels close to combustible cigarettes suggesting a likelihood that IQOS users may be able to completely transition away from combustible cigarettes and use IQOS exclusively. Available data, while limited, also indicate that few non-tobacco users would be likely to choose to start using IQOS, including youth.

While these non-combusted cigarettes may be referred to as "heat-not-burn" or "heated" tobacco products, they meet the definition of a cigarette in the Federal Food, Drug and Cosmetic Act. Therefore, these products must adhere to existing restrictions for cigarettes under FDA regulations, as well as other federal laws that, among other things, prohibit television and radio advertising. In addition, to further limit youth access to the products and exposure to their advertising and promotion, the FDA is placing stringent restrictions on how the products are marketed – particularly via websites and through social media platforms – by including requirements that advertising be targeted to adults. The company must also give notification to the FDA of, among other things, its labeling, advertising, marketing plans, including information about specific adult target audiences, and how it plans to restrict youth access and limit youth exposure to the products' labeling, advertising, marketing and promotion. The agency has issued a document (https://www.fda.gov/media/124174/download) providing its rationale for these postmarket requirements, which highlight important considerations for reviewing the company's applications as well any potential future PMTAs for other products.

The FDA also is requiring all package labels and advertisements for these products to include a warning about the addictiveness of nicotine, in addition to other warnings required for cigarettes, to prevent consumer misperceptions about the relative addiction risk of using IQOS compared to combusted cigarettes.

With the authorization of these products, the FDA will evaluate new available data regarding the products through postmarketing records and reports required in the marketing order. The company is required to report regularly to the FDA with information regarding the products on the market, including, but not limited to, ongoing and completed consumer research studies, advertising, marketing plans, sales data, information on current and new users, manufacturing changes and adverse experiences. The FDA may withdraw a marketing order if it, among other reasons, determines that the continued marketing of a product is no longer appropriate for the protection of the public health, such as if there is an uptake of the product by youth.

The FDA is continuing its substantive scientific review of the company's MRTP applications. The company would need to receive an MRTP order from the FDA before they could market a tobacco product with any implicit or explicit claims that, among other things, a product reduces exposure to certain chemicals or that use of the product is less harmful than another tobacco product or would reduce the risk of disease. If a company markets a tobacco product as an MRTP without authorization, the company would be in violation of the law and may face FDA advisory or enforcement actions.

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## Inquiries

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240-402-9548

**Consumer:**

888-INFO-FDA

## Related Information

- Premarket Tobacco Product Marketing Orders (/tobacco-products/premarket-tobacco-product-applications/premarket-tobacco-product-marketing-orders)
- Premarket Tobacco Product Applications (/tobacco-products/market-and-distribute-tobacco-product/premarket-tobacco-product-applications)
- Modified Risk Tobacco Products (Modified Risk Tobacco Products)
- Market and Distribute a Tobacco Product (/tobacco-products/products-guidance-regulations/market-and-distribute-tobacco-product)
- Modified Risk Tobacco Products (/tobacco-products/advertising-and-promotion/modified-risk-tobacco-products)

More Press Announcements (/news-events/newsroom/press-announcements)

Abstract: Epidemiology Journal. 2019 May;30(3):396-404. doi: 10.1097/EDE.0000000000000975.

# Potential Country-level Health and Cost Impacts of Legalizing Domestic Sale of Vaporized Nicotine Products.

Petrović-van der Deen FS[1], Wilson N[1], Crothers A[2], Cleghorn CL[1], Gartner C[3], Blakely T[1,4].

**Author information**

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2. Centre for Applied Health Economics (CAHE), School of Medicine, Griffith University, Nathan, Queensland, Australia.
3. School of Public Health, The University of Queensland, Herston, Queensland, Australia.
4. Melbourne School of Population and Global Health, University of Melbourne, Melbourne, Australia.

## Abstract

### BACKGROUND:

The net impact on population health and health system costs of vaporized nicotine products is uncertain. We modeled, with uncertainty, the health and cost impacts of liberalizing the vaporized nicotine market for a high-income country, New Zealand (NZ).

### METHODS:

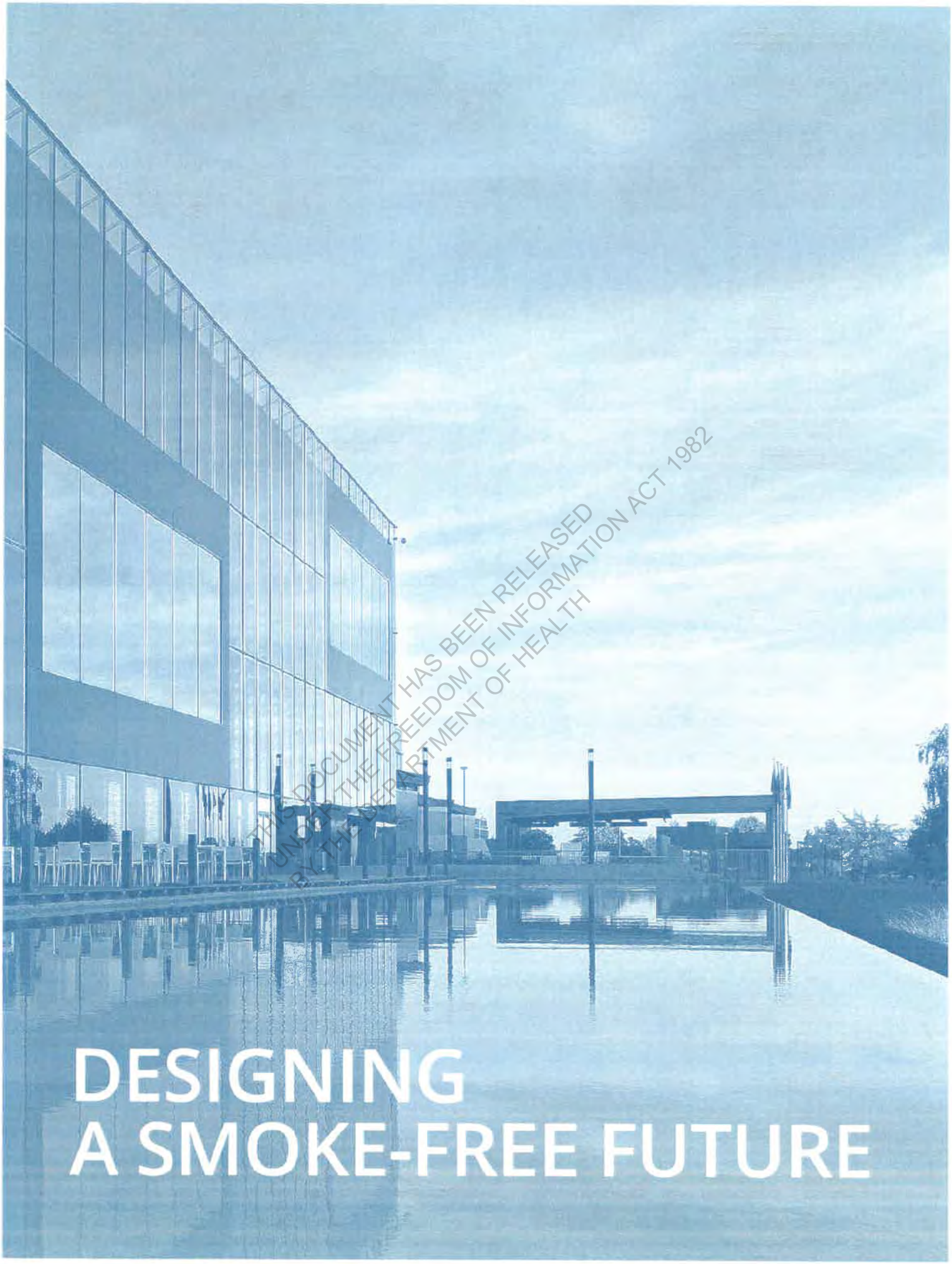
We used a multistate life-table model of 16 tobacco-related diseases to simulate lifetime quality-adjusted life-years (QALYs) and health system costs at a 0% discount rate. We incorporated transitions from never, former, and current smoker states to, and from, regularly using vaporized nicotine and literature estimates for relative risk of disease incidence for vaping compared with smoking.

### RESULTS:

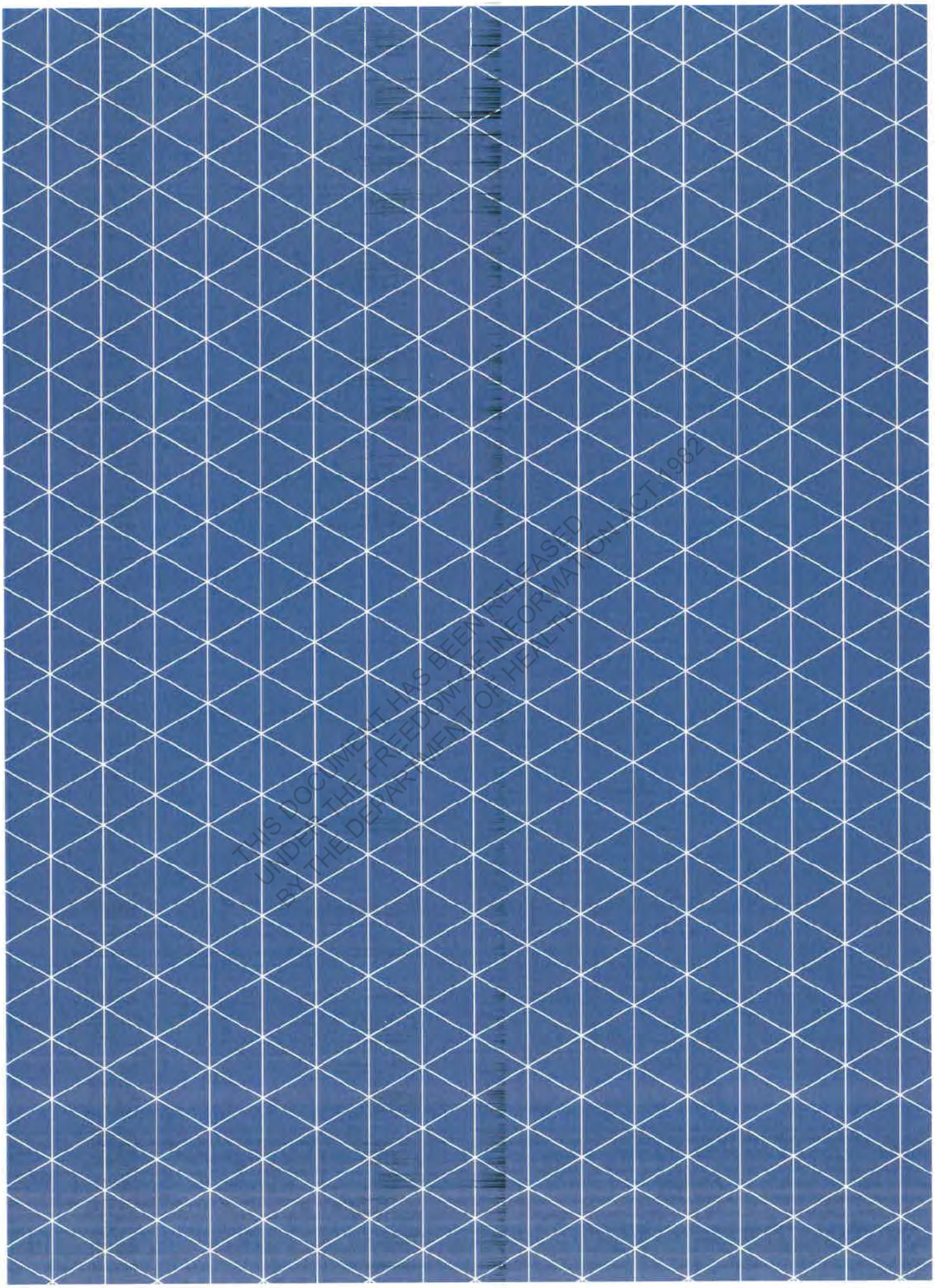
Compared with continuation of baseline trends in smoking uptake and cessation rates and negligible vaporized nicotine use, we projected liberalizing the market for these products to gain 236,000 QALYs (95% uncertainty interval [UI] = 27,000 to 457,000) and save NZ$3.4 billion (2011 NZ$) (95% UI = NZ$370 million to NZ$7.1 billion) or US$2.5 billion (2017 NZ$). However, estimates of net health gains for 0- to 14-year olds and 65+ year olds had 95% UIs including the null. Uncertainty around QALYs gained was mainly driven by uncertainty around the impact of vaporized nicotine products on population-wide cessation rates and the relative health risk of vaping compared with smoking.

### CONCLUSIONS:

This modeling suggested that a fairly permissive regulatory environment around vaporized nicotine products achieves net health gain and cost savings, albeit with wide uncertainty. Our results suggest that optimal strategies will also be influenced by targeted smoking cessation advice, regulations around chemical constituents of these products, and marketing and age limits to prevent youth uptake of vaping.



# DESIGNING A SMOKE-FREE FUTURE



# OUR GOALS.
# OUR APPROACH.
# OUR SCIENCE.

OUR FUTURE



OUR SCIENCE

# DESIGNING A SMOKE-FREE FUTURE

Our goal is to offer smoke-free alternatives that have the potential to reduce the risk of developing smoking-related diseases as compared with continued smoking. We create these products to be satisfying to current adult smokers, so that they can fully switch.



*"Our stated ambition is to convince all current adult smokers who would otherwise continue smoking to switch to smoke-free products as soon as possible."*

André Calantzopoulos
CEO Philip Morris International

# REDUCING RISK COMPARED WITH CONTINUED SMOKING

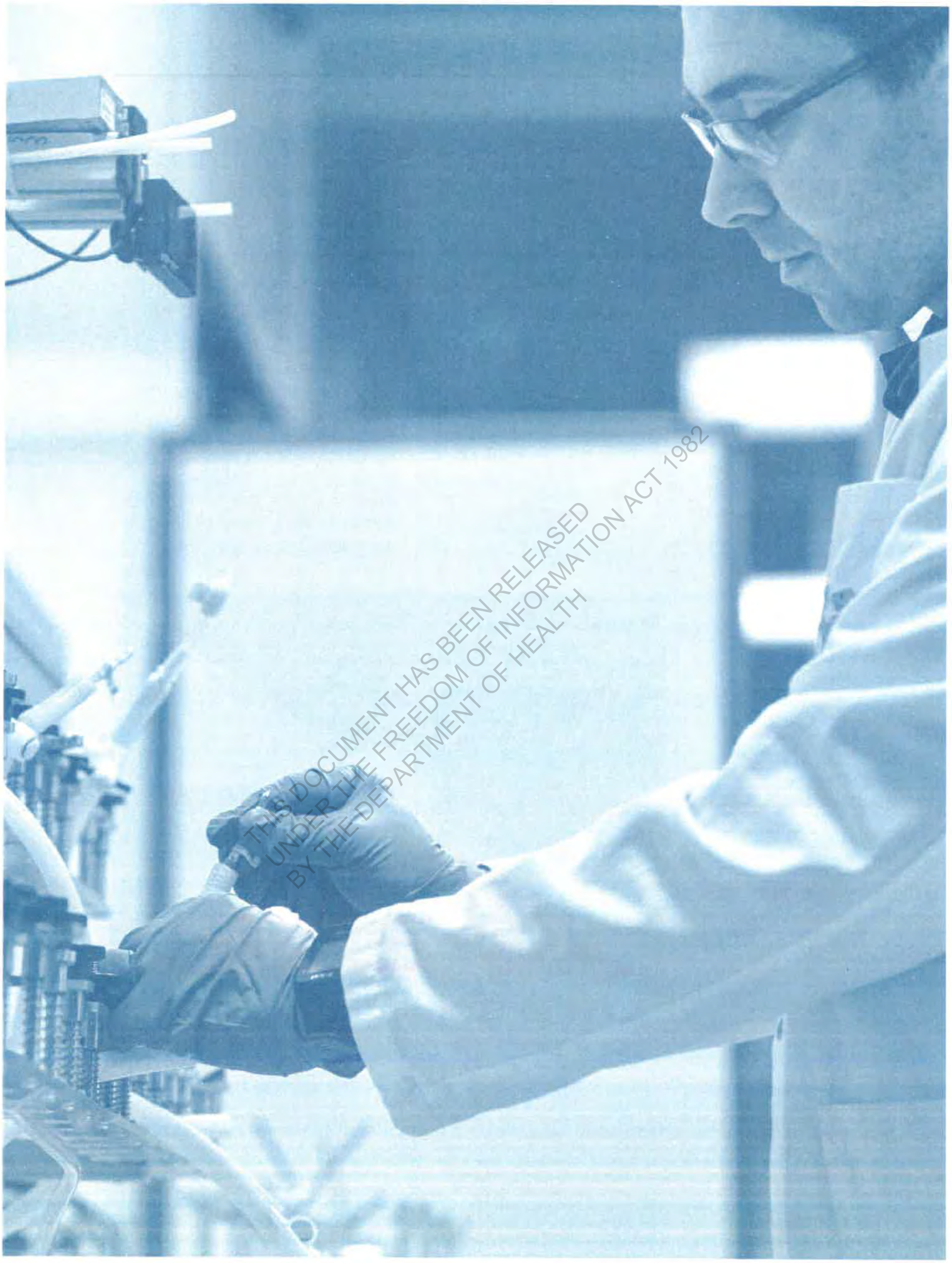
## Smoke-free alternatives for adult smokers

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, based on population trends, it is estimated that there will be more than 1 billion smokers by 2025, about the same number as today.

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.

*In fact, based on population trends, it is estimated that there will be more than 1 billion smokers by 2025, about the same number as today.*

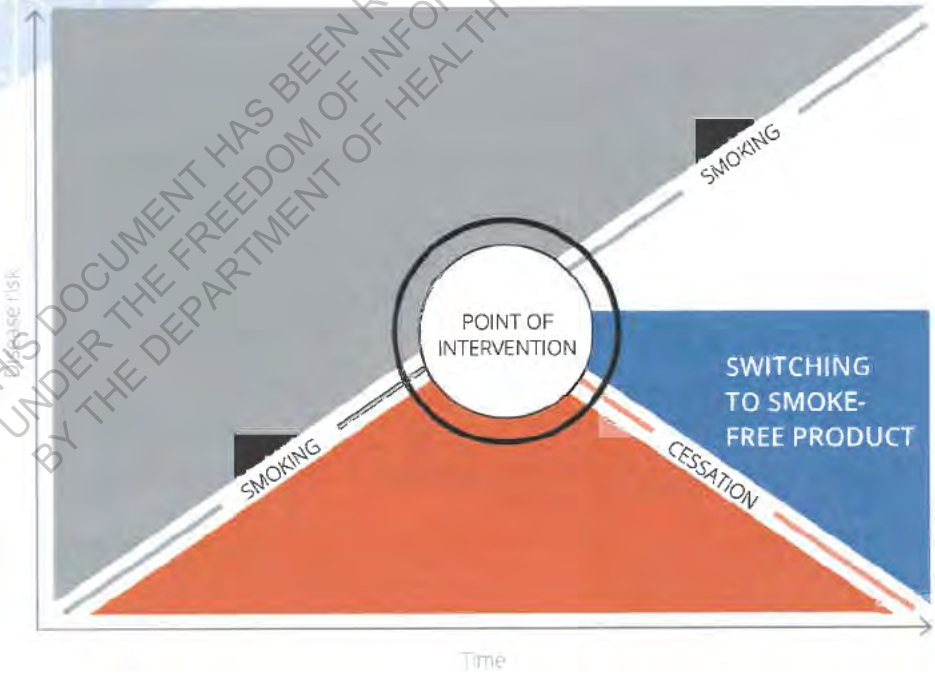


# Smoking and cessation

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, 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.






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

# Integrating risk reduction and acceptance for current smokers

For any smoke-free alternative to be successful in reducing population harm, it has to fulfil 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*, "inhalation of nicotine (i.e., nicotine without the production of combustion) is of less risk to a user than the inhalation of nicotine delivered by smoke from combusted tobacco products."



* https://www.federalregister.gov/d/2015-10685/p-677

# OUR SMOKE-FREE PRODUCTS

**Four smoke-free product platforms* are in various stages of development, production or commercialization; all designed to offer better alternatives for adult smokers than continuing to smoke. Two of our platforms are heated tobacco products, and two are nicotine-containing vapor products. All newly developed platforms undergo rigorous testing, including non-clinical and clinical assessment. This booklet summarizes the key scientific results on Platform 1. Our rigorous scientific assessment of Platforms 2, 3 and 4 progresses according to plan.**

## Heated tobacco products



### PLATFORM 1

Platform 1 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. Platform 1 consists of three components: a pocket charger, a holder, and a heated tobacco unit.

### PLATFORM 2

Platform 2 re ies on its product de sign to control the heating of tobacco within a specific temperature range. A carbon heat source at the tip generates heat which is transferred to the tobacco without the use of electronics.

# Nicotine-containing vapor products

**PLATFORM 3**

A r ove p atform de ivering an aeroso of nicotine sa t.

**PLATFORM 4**

Battery powered devices that va porize a nicotine containing iquid, scientifically engineered to give a consistent use experience, without the limitations of a coil and wick system.

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

# OUR SCIENCE

**Rigorous, robust, and transparent science is at the core of the development and assessment of our smoke-free products.**

## Our scientific approach

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 FDA's Draft Guidance for Modified Risk Tobacco Product Applications (2012).




### PLATFORM DEVELOPMENT

Our platform development process follows the principle of "Quality by Design". This means that the platforms are specifically designed with the aim to eliminate or reduce the levels of Harmful and Potentially Harmful Constituents (HPHCs) found in their aerosol compared to those found in cigarette smoke.

### TOXICOLOGICAL ASSESSMENT

Toxicological assessment aims to confirm whether the reduced formation of HPHCs leads to reduced toxicity and reduced risk in laboratory models.




### CLINICAL ASSESSMENT

Our clinical studies provide human data on the use and acceptance of our smoke-free products, as well as their potential to (1) reduce exposure to harmful chemicals and (2) reduce the risk of smoking-related diseases as compared to continued smoking.

### PERCEPTION AND BEHAVIOR

Perception and behavior studies help us understand how our smoke-free products will be perceived and actually used.

### LONG-TERM ASSESSMENT

We run long-term studies and monitor events linked to consumer use in order to track the long-term effects of smokers switching to our products.

# PLATFORM DEVELOPMENT

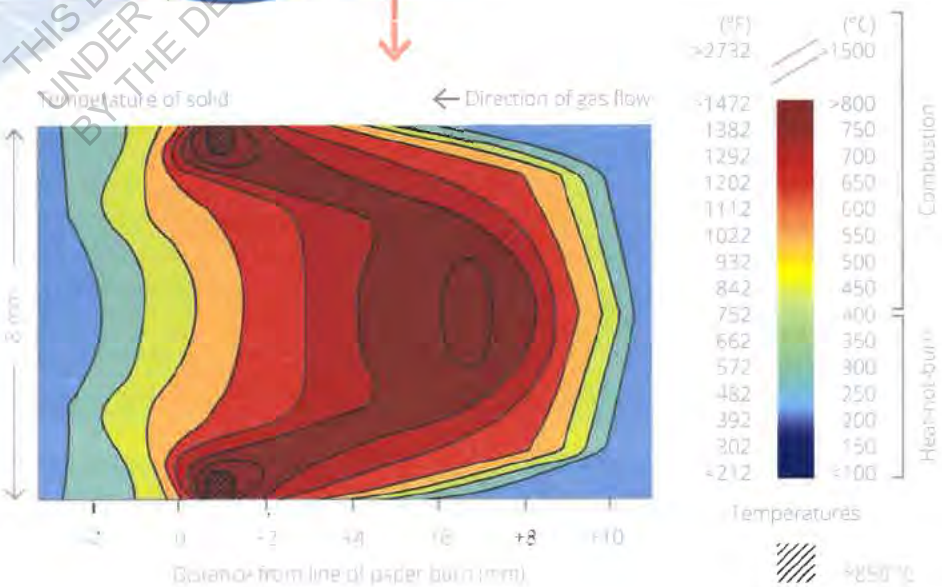
**Our platform development process follows the principle of "Quality by Design". This means that the platforms are specifically designed with the aim to eliminate or reduce the levels of Harmful and Potentially Harmful Constituents (HPHCs) found in their aerosol compared to those found in cigarette smoke.**

## It is combustion that causes the production of the majority of harmful chemicals detected in cigarette smoke

Decades of scientific research show that the primary cause of smoking-related disease is the HPHCs formed by the combustion of tobacco.

During a puff of a cigarette, the temperature increases to more than 800 °C at the tip.

The combustion of tobacco results in the formation of smoke, heat, ash, and high levels of HPHCs. The images below show a typical temperature profile in a lit cigarette during the self-sustaining combustion of tobacco (left), compared with the temperature profile for Platform 1 (right).

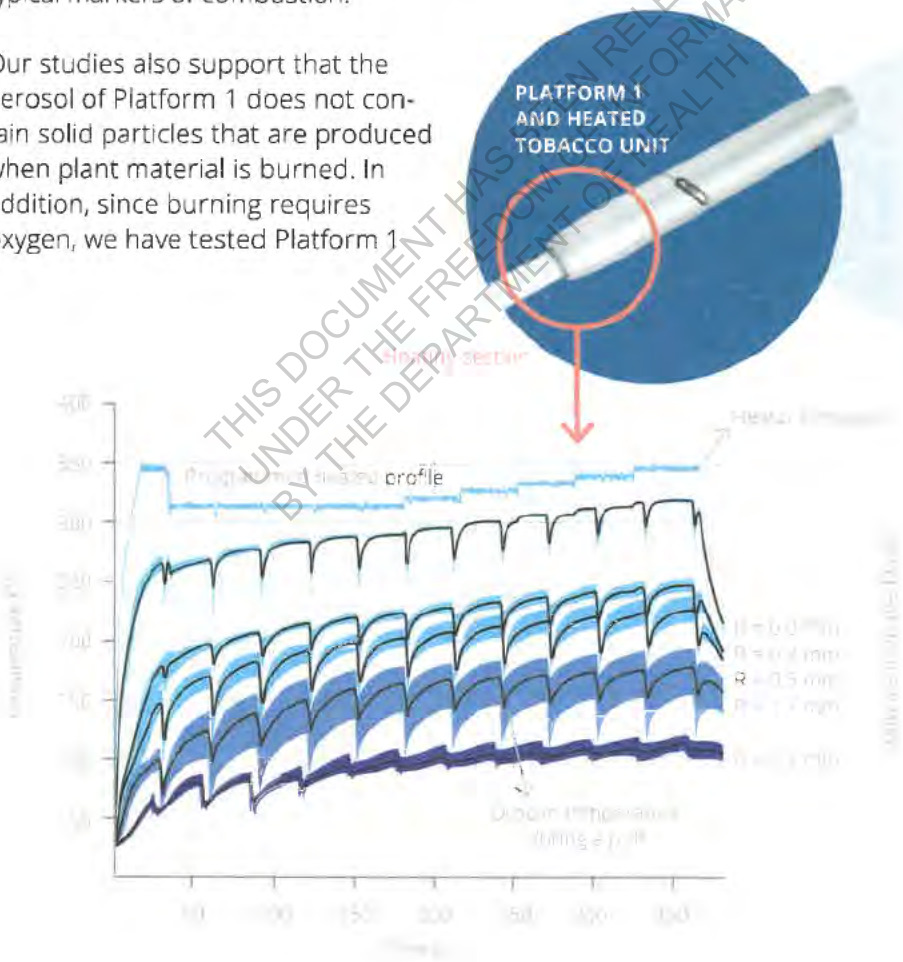




Baker, R. R. (5 of 5) Temperature variation within a cigarette combustion coal during the smoking cycle. High Temp Sci 7: 235-247

# Absence of combustion in Platform 1

We have conducted several studies to demonstrate the absence of combustion in Platform 1, including temperature measurements, experiments demonstrating the absence of exothermic processes, and measurements of constituents that represent typical markers of combustion.

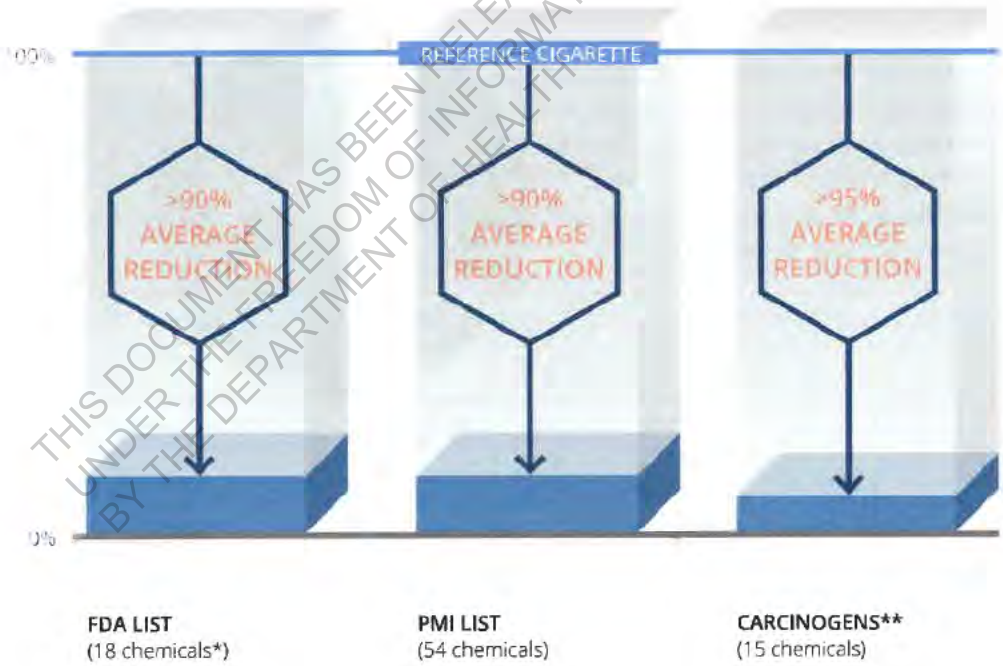
Our studies also support that the aerosol of Platform 1 does not contain solid particles that are produced when plant material is burned. In addition, since burning requires oxygen, we have tested Platform 1 in an oxygen-free atmosphere and the results showed that the aerosol generated by Platform 1 was equivalent under both atmospheres, supporting the view that combustion does not occur during Platform 1 use.



# Platform 1 aerosol contains significantly lower levels of harmful chemicals than smoke from a standard reference cigarette (3R4F)

We measured a number of harmful chemicals in the aerosol of Platform 1 and compared them to the levels found in the smoke of a standard reference cigarette (3R4F). An average of 90-95% reduction in the levels of these HPHCs in Platform 1 aerosol was observed.



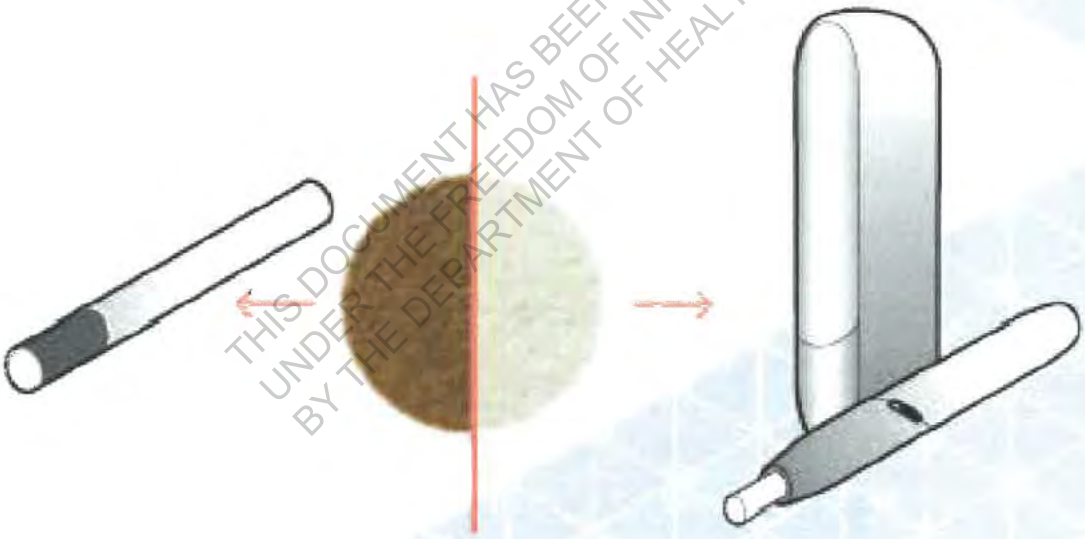



The chart shows the reduced formation of HPHCs by Platform 1. The level of HPHCs in Platform 1 aerosol is shown by the blue bars and is compared with the 100% in smoke from the 3R4F reference cigarette. The level of reduction for each group of HPHCs is shown.

* Not reduction calculation excludes nicotine
** IARC Group 1 carcinogens

The picture below shows the visual difference between the particulate matter of cigarette smoke (left) and the particulate matter of Platform 1 aerosol (right) after collection on Cambridge glass-fiber pads (5 sticks per product).






Schaller, J. P., et al. (2016). Evaluation of the Tobacco Heating System 2.2. Part 2: Chemical composition, genotoxicity, cytotoxicity, and physical properties of the aerosol. Regul Toxicol Pharmacol 81 Suppl2: S27-S47.

# No negative impact on indoor air quality

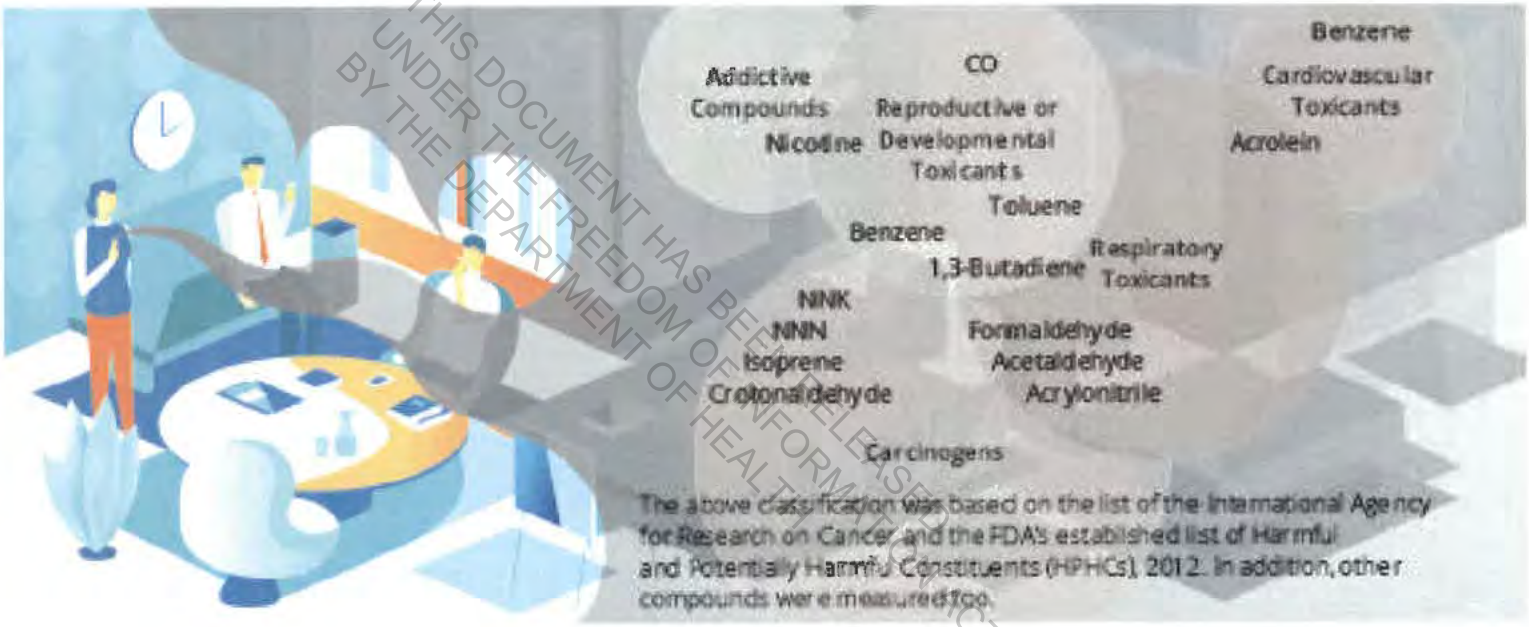
The quality of indoor air can be evaluated by measuring air quality markers in accordance with international guidelines. We measured 22 air pollutants as well as glycerin in our studies. When using Platform 1, the levels of 20 of these pollutants did not increase beyond the levels already present as background in our dedicated Indoor Air Quality room. The levels of nicotine and acetaldehyde were measurably higher, although well below the EU guidelines for exposure limits; more than 250 times lower for nicotine and 40 times lower for acetaldehyde.



**Out of 22 measured air pollutants, the levels of 20 did not increase beyond background with Platform 1. Nicotine and acetaldehyde were detectable, although at levels well below those set in the EU guidelines.**

## INDOOR AIR QUALITY AND TOBACCO SMOKE

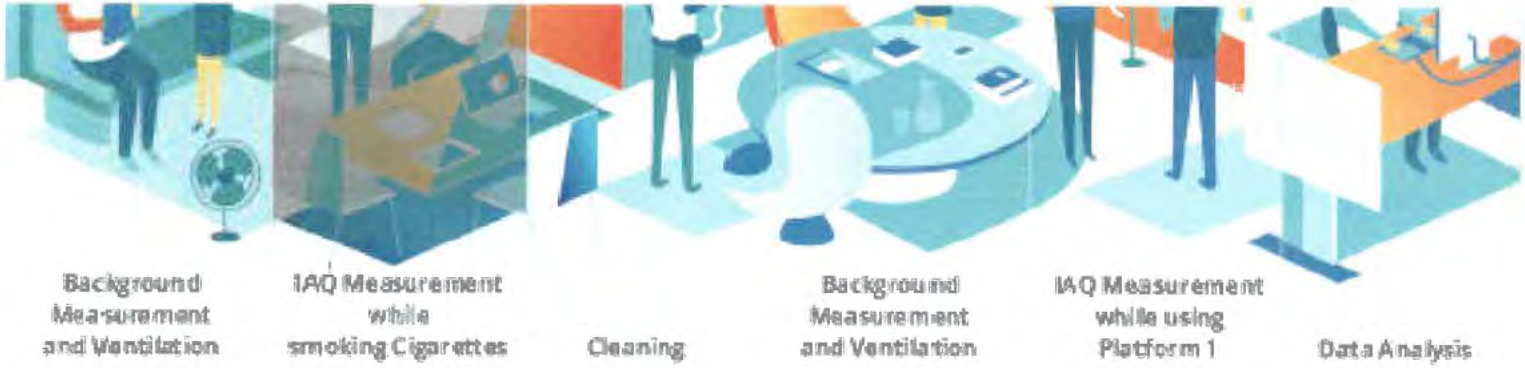
Environmental tobacco smoke is a major indoor air pollutant. It contains thousands of compounds, many of which are harmful. PMI has studied the levels of such compounds and representative markers of environmental tobacco smoke after using cigarettes or Platform 1 indoors.






## HOW TO MEASURE THE IMPACT ON INDOOR AIR QUALITY

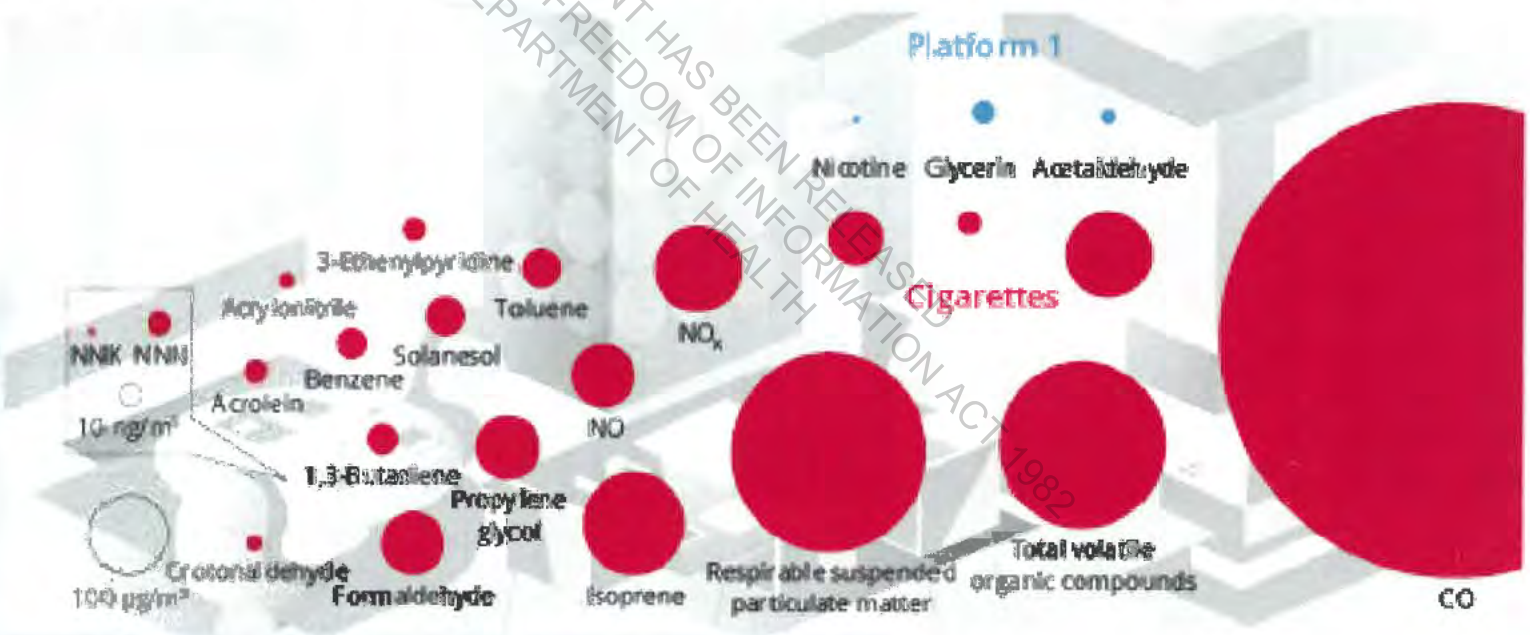
Our studies were conducted in PMI's specially equipped Indoor Air Quality (IAQ) facility. We compared IAQ data after using Platform 1 and cigarettes to the levels of background air.






**PLATFORM 1: NO NEGATIVE IMPACT ON OVERALL INDOOR AIR QUALITY**

We measured 22 air pollutants, as well as glycerin. The levels of 20 of these pollutants did not increase beyond background levels with Platform 1. Nicotine and acetaldehyde were detectable, although at levels well below those set in the EU guidelines.



# TOXICOLOGICAL ASSESSMENT

**Toxicological assessment aims to confirm whether the reduced formation of HPHCs leads to reduced toxicity and reduced risk in laboratory models.**

## Two complementary approaches

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 determine whether reduced toxicity leads to reduced risk in laboratory models. Systems toxicology allows a detailed assessment of the disease-relevant biological mechanisms affected by exposure to toxicants. It relies on state-of-the-art high-throughput experimental technologies and advanced computational sciences.

First, systems toxicology is applied to identify the biological mechanisms that are altered by cigarette smoke, capturing this knowledge in biological network models. These models are then used to analyze the datasets for product assessment, allowing comparisons between the network alterations caused by the aerosols of smoke-free products and those caused by cigarette smoke. Furthermore, the approach allows quantitative comparison of the overall biological impact of these exposures in the context of toxicological and disease endpoints.



*The aim is to demonstrate that the toxicity of the aerosol from smoke-free products is lower than that of cigarette smoke.*

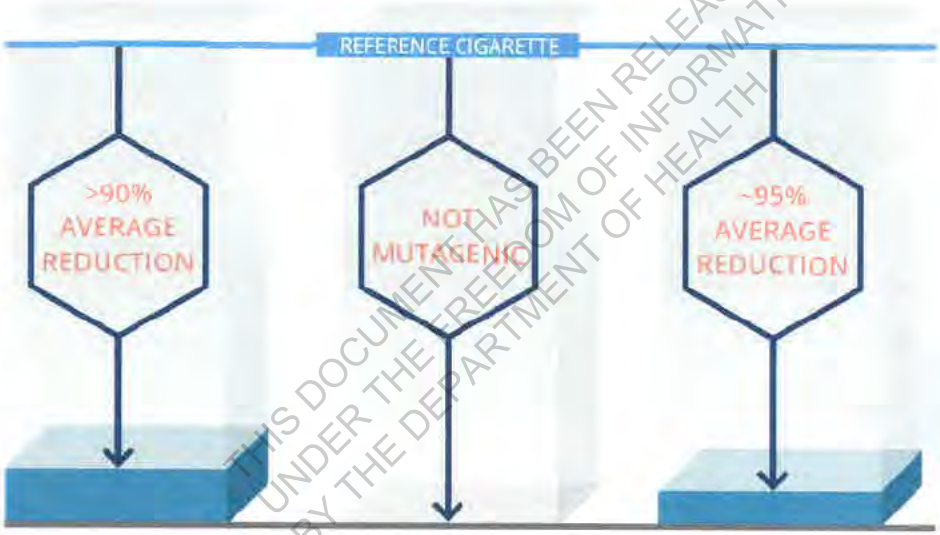
Please find our verification programs here:
www.sbromprover.com
www.intervals.science

# Reduced toxicity

We have conducted a series of tests to compare the toxicity of Platform 1 aerosol with that of the smoke from a standard reference cigarette (3R4F).

In our laboratories, we observed a substantial reduction in toxicity of the aerosol of Platform 1 compared to cigarette smoke.





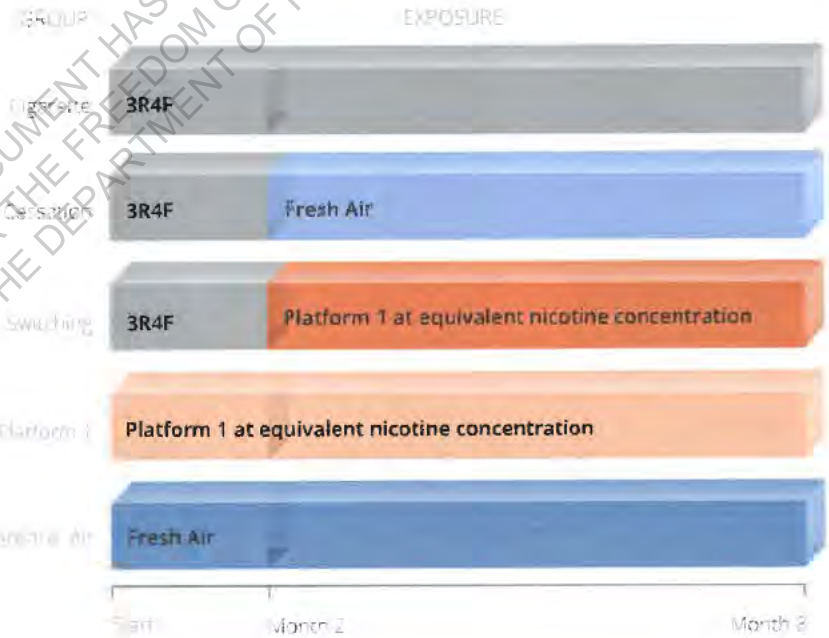

The chart shows our findings concerning the relative *in vitro* toxicity of Platform 1 aerosol compared with the smoke from the 3R4F reference cigarette using three *in vitro* assays (Neutral Red Uptake, Ames and Mouse Lymphoma) commonly used to assess cytotoxicity and genotoxicity.

# Effects of switching and cessation in mice

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 Platform 1 aerosol for 8 months. A group of mice was first exposed for two months to 3R4F smoke and then randomized to either Platform 1 aerosol (switching) or fresh air (cessation). Switching to Platform 1 aerosol following two months of cigarette smoke led to reduced impact on biological mechanisms and disease endpoints associated with chronic obstructive pulmonary disease (COPD) and cardiovascular disease (CVD) in a manner similar to smoking cessation.



## STUDY DESIGN




Phillips, B. ... et al. (2016). An 8-month systems toxicology inhalation/cessation study in Apoe$^{-/-}$ mice to investigate cardiovascular and respiratory exposure effects of a candidate Modified Risk Tobacco Product, THS 2.2, compared with conventional cigarettes. Toxicol Sci 149(2): 411–432.

**A: DISEASE ENDPOINT FOR COPD –**

**B: DISEASE ENDPOINT FOR CVD –**




The charts are showing the findings for disease endpoints 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 Platform 1 aerosol. A group of mice was first exposed for two months to 3R4F smoke and then switching to either Platform 1 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.

# CLINICAL ASSESSMENT

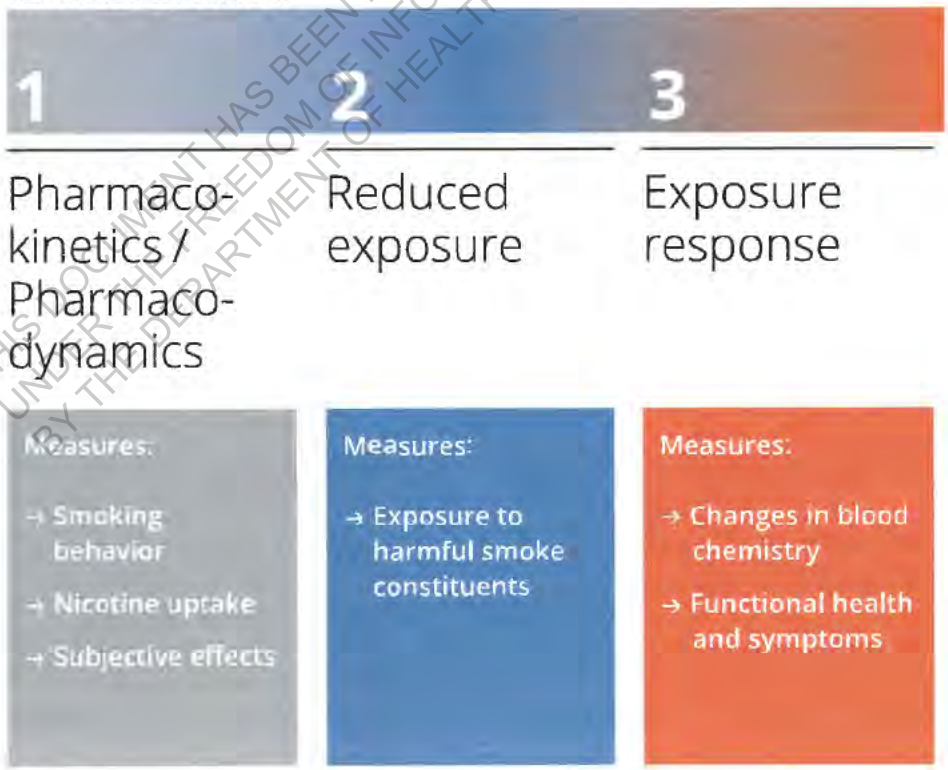
**Our clinical studies provide human data on the use and acceptance of our smoke-free products, as well as their potential to (1) reduce exposure to harmful chemicals and (2) reduce the risk of smoking-related diseases as compared to continued smoking.**

Clinical studies are a cornerstone of our assessment program.

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



**CLINICAL ASSESSMENT**



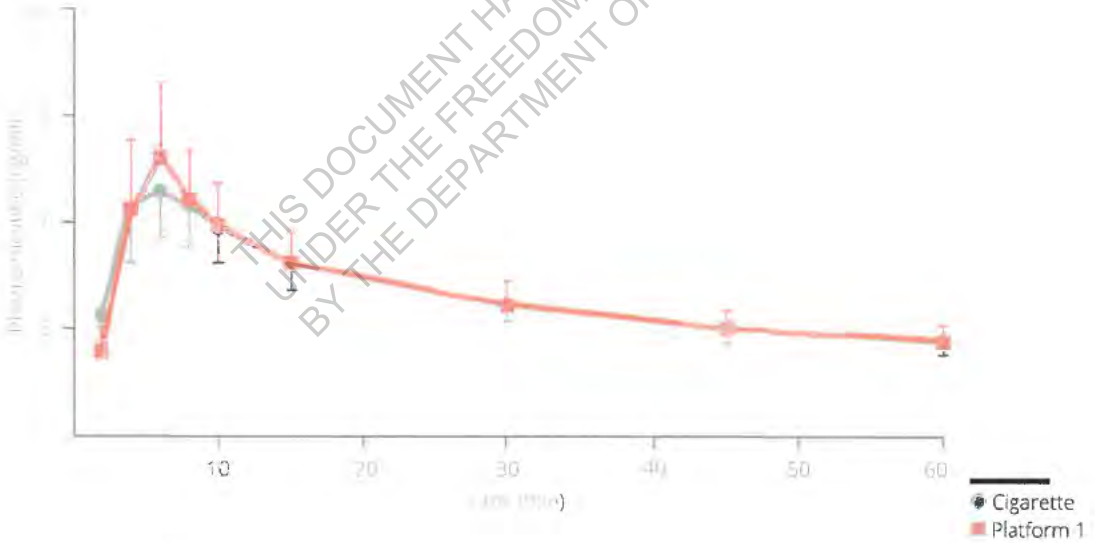
# 1

# Pharmacokinetics / Pharmacodynamics

**When switching to Platform 1, the nicotine uptake and urge-to-smoke scores were comparable to those measured in subjects who continued smoking.**

We have shown 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 Platform 1. Furthermore, the urge-to-smoke scores were similar for smokers and switchers. This suggests that switchers do not seek to use Platform 1 more frequently than smokers seek to use cigarettes, and that switchers can find Platform 1 acceptable and satisfying.





# 2

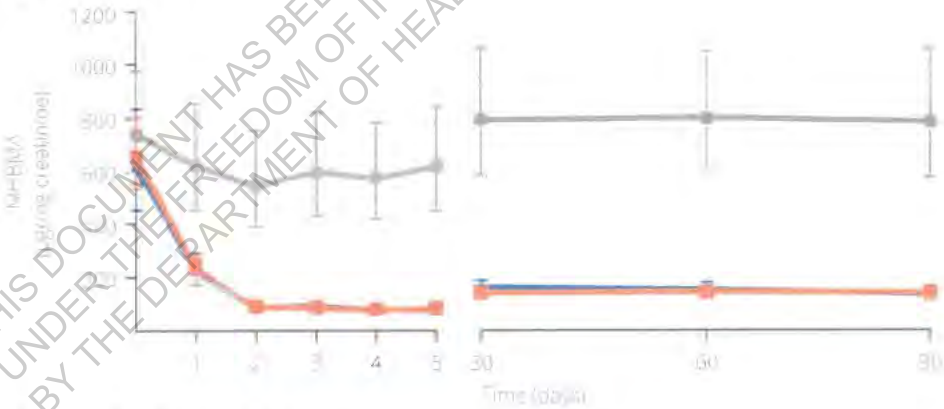
# Reduced exposure

**We found that smokers switching to Platform 1 were exposed to significantly lower levels of harmful chemicals compared to those who continued smoking during the study.**

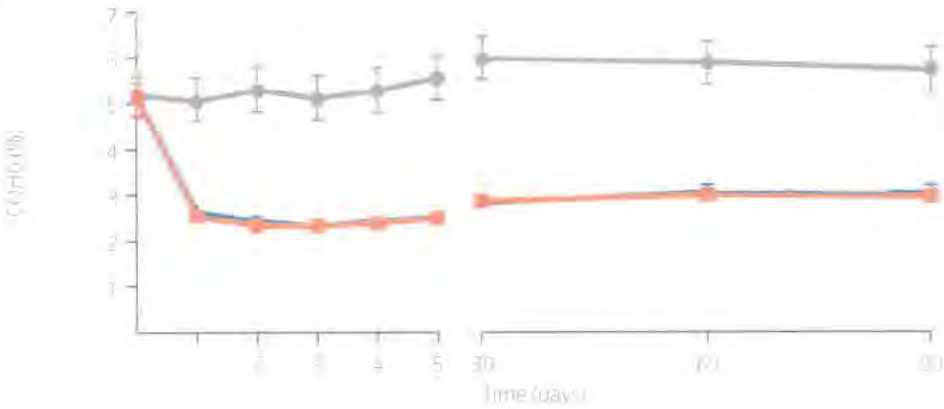
In our 5-day and 90-day clinical reduced exposure studies, we measured biomarkers in the blood and urine representing exposure to selected harmful chemicals. We found that levels of 15 biomarkers of exposure in participants switching to Platform 1 were comparable to the levels of those who quit smoking for the duration of the study. In both cases, the levels remained significantly below those observed in subjects who continued smoking during the study.



**1,3-BUTADIENE***




**CARBON MONOXIDE***

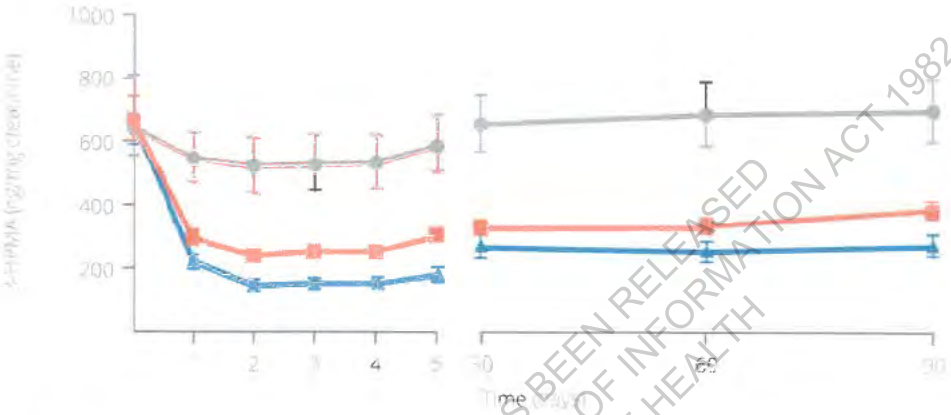



Lüdicke, F., et al. (2018) Effects of switching to the Tobacco Heating System 2.2 menthol smoking abstinence, or continued cigarette smoking on biomarkers of exposure: a randomized controlled, open-label, multicenter study in sequential confinement and ambulatory settings (Part 1). Nicotine Tob Res 20(2): 161-170.

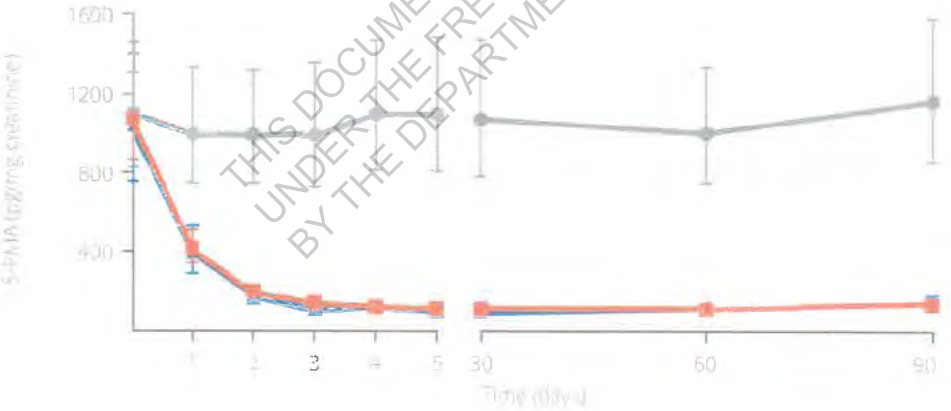
Our clinical studies are registered on **www.clinicaltrials.gov**

The ID of the presented study is **NCT01970995**

**ACROLEIN***




**BENZENE***



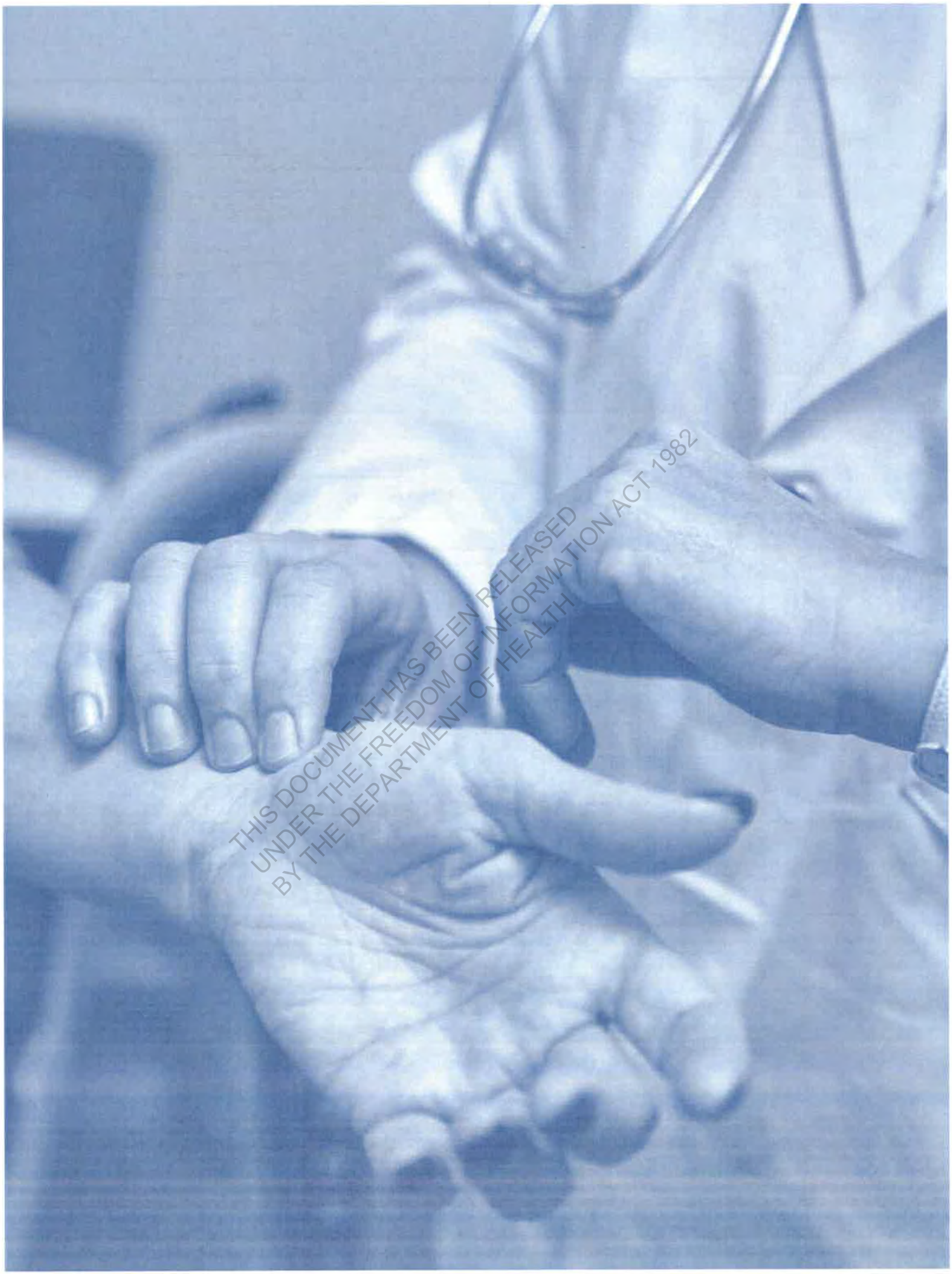



Cigarette
Cessation
Platform 1

We examined a total of 15 biomarkers, all displaying the same trend.

The same type of study in the U.S. (NCT02396381) showed comparable results.

* Levels of Biomarkers Detected (Three-Month Study in Japan)



# 3

# Exposure response

**Clinical findings indicate that switching to Platform 1 can have a positive impact on smokers' health risk.**

In a six-month clinical study complemented with a six-month extension, we measured clinical risk markers known to be affected by smoking, and based on literature, expected to improve upon cessation. We observed that after switching from smoking to Platform 1 for six months, all these indicators changed in the same direction as expected upon smoking cessation based on literature, five of them with statistical significance. The data from the second six months of the study are currently being analyzed.



| Endpoint | Link to smoking-related disease | | Expected direction of change with smoking cessation | When switching to Platform 1, is the direction of change the same as the one expected with smoking cessation? |
|---|---|---|---|---|
| HDL-C* | Cardio-vascular | Lipid Metabolism | ↑ | Yes |
| WBC* | | Inflammation | ↓ | Yes |
| sICAM-1 | | Endothelial Dysfunction | ↓ | Yes |
| 11-DTX-$B_2$ | | Clotting | ↓ | Yes |
| 8-epi-$PGF_{2\alpha}$ | | Oxidative Stress | ↓ | Yes |
| COHb* | | Acute Effect | ↓ | Yes |
| $FEV_1$* | COPD | Airway Impairment | ↓ | Yes |
| Total NNAL* | Cancer | Genotoxicity | ↓ | Yes |

* statistically significant change compared to continued smoking

NCT02396381

# PERCEPTION AND BEHAVIOR

**Perception and behavior studies help us understand how our smoke-free products will be perceived and actually used.**

## Our studies showed a low intent to use Platform 1 among non-smokers

For smoke-free products to have an overall positive impact on public health, it is important that non-smokers do not start using them, and that smokers who intend to quit are not dissuaded by these products. In a pre-market setting, our studies conducted in the U.S. showed that low proportions of non-smokers expressed intent to use Platform 1 (up to 6.4%), in contrast to substantial proportions of current adult smokers (up to 39%). Moreover, smokers should understand that quitting is the best way to reduce tobacco-related health risks, and that these products are only for smokers who would otherwise continue to smoke.

Furthermore, we have shown that smokers correctly understand that switching to Platform 1 presents less risk of harm than continued smoking, while not being risk free.



*Smokers should understand that quitting is the best way to reduce tobacco-related health risks.*

# LONG-TERM ASSESSMENT

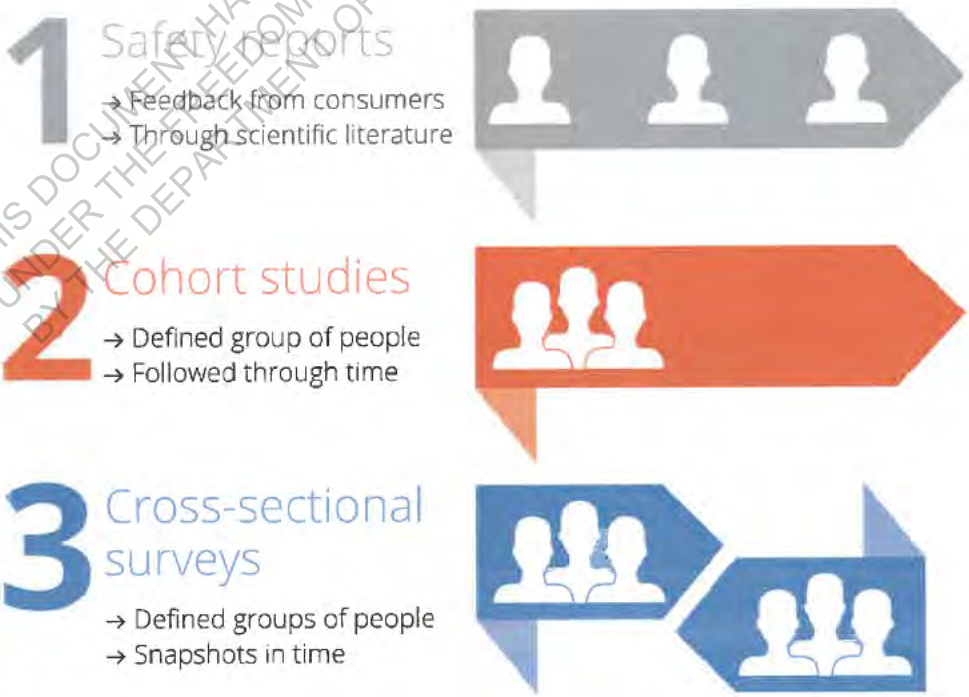
## Continued studies, reports and surveys

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.



**LONG-TERM ASSESSMENT**

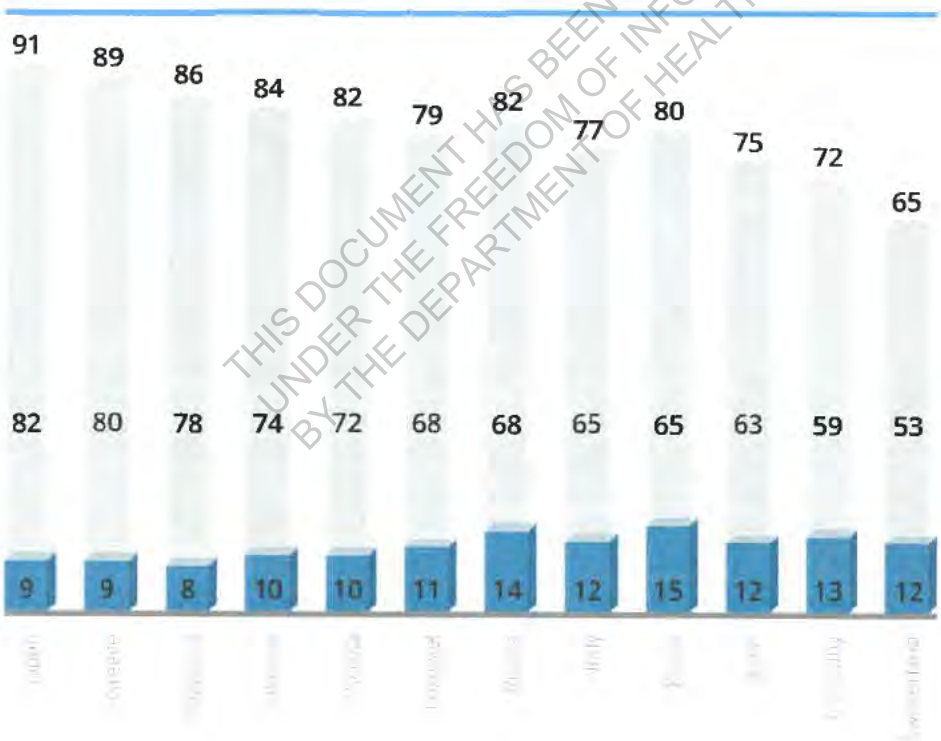


# Adoption in launched markets

Over 6.6 million adult smokers have already switched to Platform 1 as of December 2018.

The chart below shows exclusive and predominant user shares among persons who purchased Platform 1 as of December 2017.





# HOW DOES PMI CONDUCT 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 (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.



**OBSERVATIONAL STUDIES**
IEA GEP[1];
Applicable National Regulations

**PERCEPTION AND BEHAVIOR ASSESSMENT**
Based on GEP-DGEpi[2];
FDA Guidance on PRO[3];
ISPOR PGP for the TCA[4];
Applicable National Regulations

**CLINICAL STUDIES**
WMA Declaration of Helsinki[5];
Based on ICH-GCP E6 (R1)[6];
Applicable National Regulations

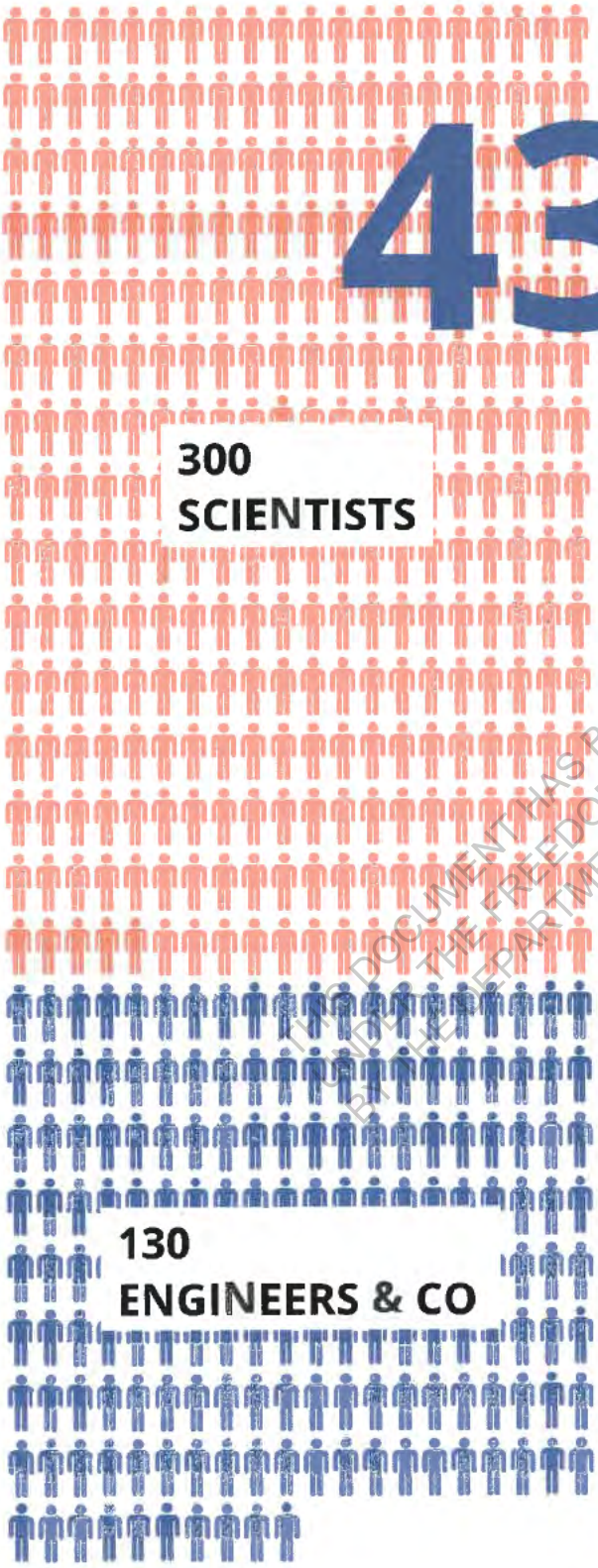
**REGULATORY TOXICOLOGY ASSESSMENT**
OECD GLP[7], INVITTOX 3A/ERGATT/FRAME; OECD Test Guidelines 412, 413, 451, 453, 471, 487, 490

**PRODUCT DESIGN AND CONTROL**
Quality by Design (QbD)[8]

**AEROSOL CHEMISTRY**
OECD GLP; ISO[9] 17025; ICH Q2 (R1)[10]; ISO 3308*, 3402, 4387*, 8454, 10315:2013, 10362-1*, 13110, 19290; CORESTA CRM81[11]

**INDOOR AIR QUALITY**
ISO 17025; EN 15251[12]; ISO 15593, 18144, 18145, 16814, 16000-6, 11454

# KEY FACTS AND FIGURES




## PMI'S R&D PEOPLE OVER

**430**

## SCIENTISTS AND ENGINEERS

R&D experts work on our smoke-free products.

In 2018, PMI was recognized as the

**58th**

## LARGEST PATENT FILER IN THE EUROPEAN UNION

and is the only tobacco company in the top 100.

## OVER

**4,600** PATENTS GRANTED

and **approximately 6,300** pending patent applications.

## INVESTMENTS OVER

# 4.5 BILLION USD INVESTED

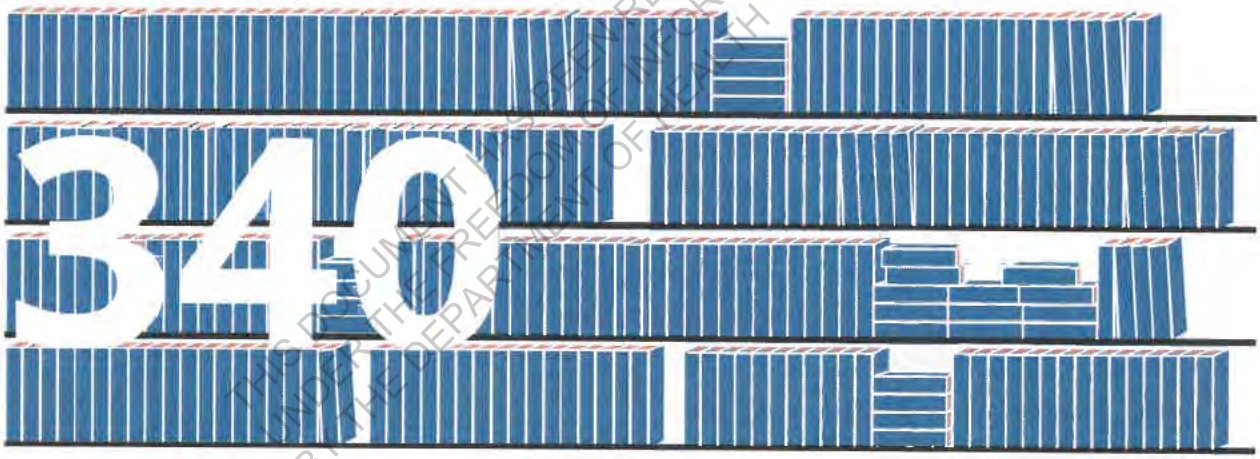
by PMI since 2008 in fundamental research, product development, scientific substantiation and manufacturing capacity of our smoke-free products.

# 120 MILLION USD INVESTED

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



## MORE THAN




## PEER-REVIEWED PUBLICATIONS

and **book chapters related to our smoke-free products since 2008;** in scientific journals such as the *American Journal of Physiology, Nature Biotechnology* and *Regulatory Toxicology and Pharmacology.*

## MOST ARE OPEN ACCESS PUBLICATIONS


Data as of September 20[illegible]

ANNEX
42

# GLOSSARY

## A

**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.

## C

**COPD**
Chronic Obstructive Pulmonary Disease

**CVD**
Cardiovascular disease

## E

**Exposure**
We can talk about exposure to chemicals because they are present in sufficient quantity and there is a possibility that they can be inhaled, absorbed or ingested by people or lab animals. Human chemical exposure is important because it may have an influence on human health.

## H

**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 non-smokers. 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.

## M

**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.

## P

**Peer-reviewed publications**
In academic publishing, the goal of peer review is to assess the quality of articles submitted for publication. The review

process ensures that the standards for a set discipline are met. Peer-reviewed articles that are accepted for publication exemplify the best research practices in a given field of science.

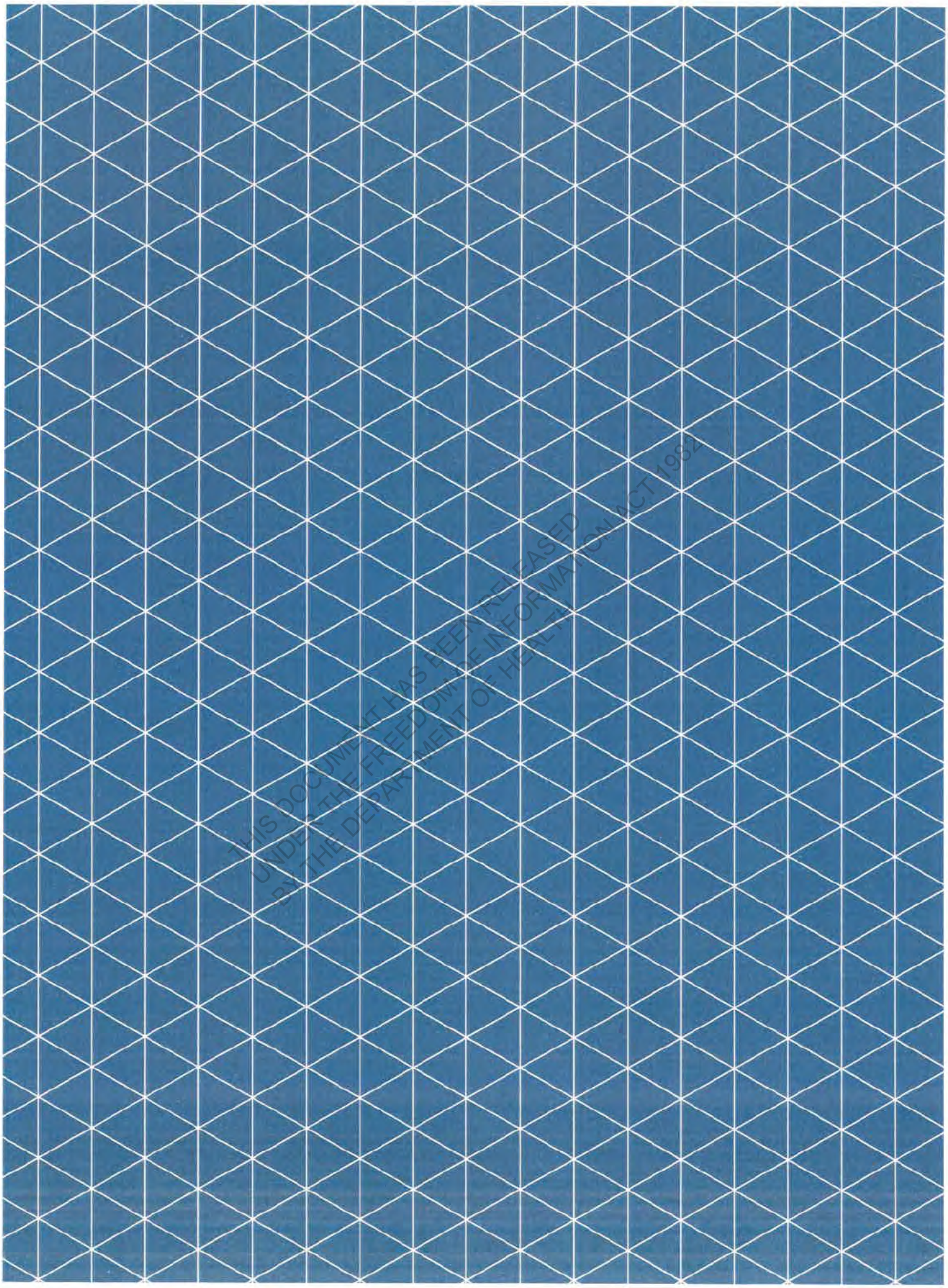
**Pharmacokinetics**
Pharmacokinetics is the study of the process by which a pharmacological compound is absorbed, distributed, metabolised and eliminated by the body.

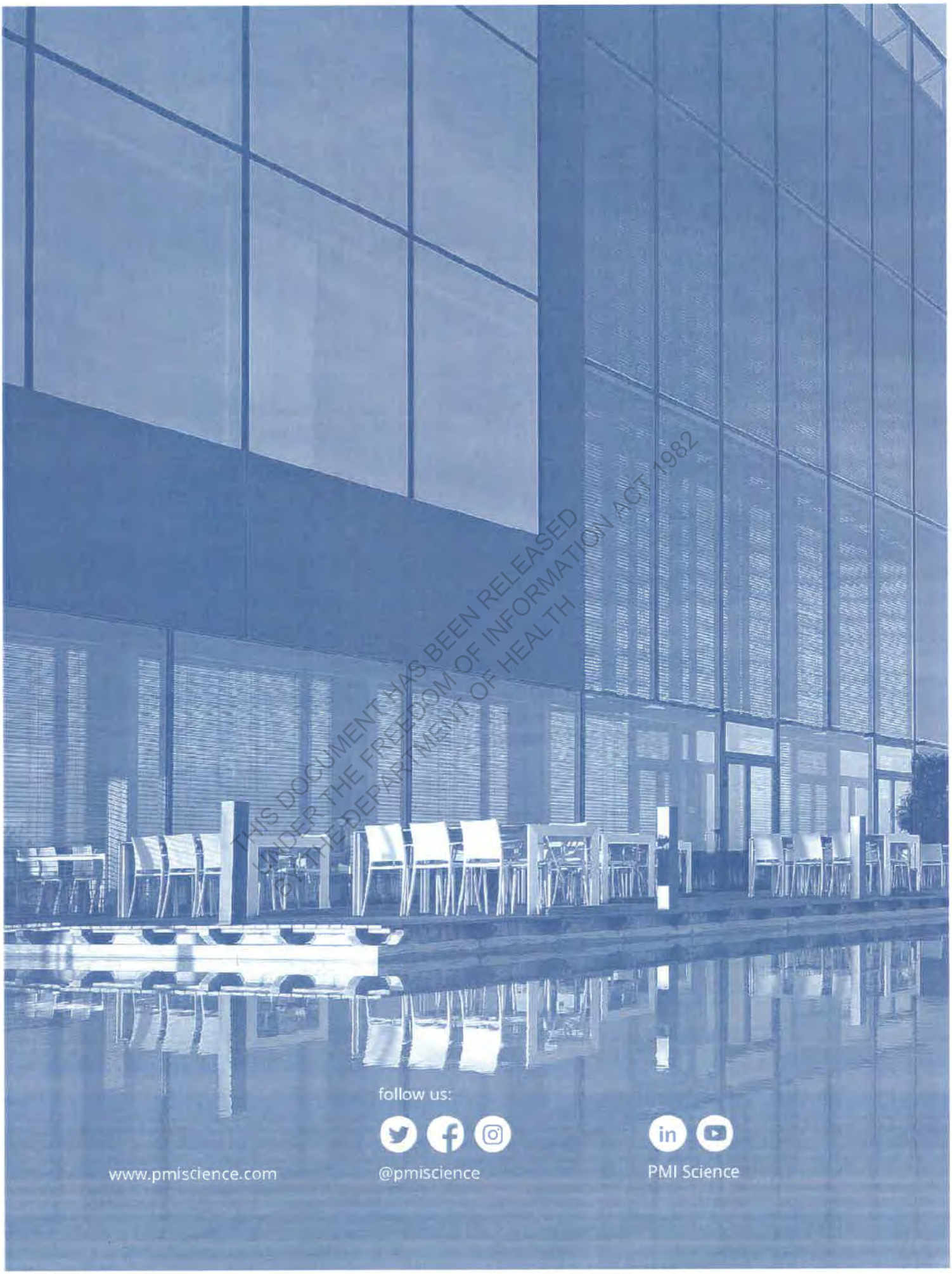
## R

**REFERENCE CIGARETTE 3R4F**
A standard cigarette for laboratory testing provided by the University of Kentucky. The current version is known as 3R4F and is used for non-clinical investigations by tobacco manufacturers, contract and government laboratories, and academic institutions.

## U

**U.S. FDA**
United States Food and Drug Adminstration





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*Official Journal of the International Society of Regulatory Toxicology and Pharmacology*





# Evaluation of the Tobacco Heating System 2.2 Supplement

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