



# SCIENTIFIC UPDATE

PMI SCIENCE – PHILIP MORRIS INTERNATIONAL

AUGUST 2021 | ISSUE 13

## HARM REDUCTION

PUTTING THE PIECES TOGETHER



06  
PRODUCT USE  
PATTERNS

10  
EFFECTS OF  
SWITCHING  
ON HEALTH

14  
WHAT IS  
RELATIVE RISK?



# CONTENTS

## 06

**A closer look at the measurement of product use patterns**



## 04

Events

## 18

Independent studies

## 19

PMI publications

## 10

**Short-term effects of switching from cigarettes to our heated tobacco product**



## 14

**Relative risk – providing critical context for a better understanding**



# INTRODUCTION

Many activities carry some level of risk of harm. Applying harm reduction to these activities reduces the risk of harm to individuals who participate in these activities. If enough individuals benefit from harm reduction, then the population as a whole benefits. And the impact of that benefit is determined by how several key factors fit together: the product, how it is commercialized, who uses it, and how it is used.

In the context of tobacco harm reduction specifically, the impact on public health is determined by:

- a scientifically substantiated reduced risk alternative to continued smoking,
- sound and robust ongoing measurements of tobacco prevalence and use patterns to have a view of potential unintended consequences and
- accurate and non-misleading communication about the risks and benefits associated with using the product to encourage adult smokers to switch to such alternatives rather than continuing to smoke.

We hope you find that this issue of the Scientific Update on tobacco harm reduction helps to put all these pieces together.



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# SCIENTIFIC UPDATE EVENTS

## Global Forum on Nicotine (GFN)

📍 Liverpool, Online 📅 June 17, 2021

Five PMI scientists participated in this year's GFN by submitting GFN Fives – 5-minute pre-recorded multimedia presentations. The theme was “The future for nicotine.” Ondrej Koumal discussed “Considerations when using sales volume data to estimate tobacco product substitution effects.” Anca Haiduc's presentation was titled “Scientific substantiation of the absence of combustion in a novel heated tobacco product” and Gerhard Lang focused on the “Comprehensive chemical characterization of the aerosol generated by a heated tobacco product.” Jennifer Motles discussed “Can increased transparency of the tobacco companies' reporting on their business contribute to greater acceptance of their role in reducing smoking-related harm?” And David Rodrigues presented on the “Quantitative assessment of intent to use IQOS among adults in Brazil.” The Forum was held in Liverpool, England, and online viewers were also able to attend remotely.

[Watch the presentations from PMI Science at GFN](#)

## Metabolomics Society Conference

📍 Online 📅 June 22-24, 2021

This conference focused on metabolomics research and was held online this year, opening with a series of workshops, followed by scientific sessions and talks selected from submitted abstracts. The term metabolomics refers to the systematic identification and quantification of the small molecule metabolic products of a biological system at a specific point in time. Three PMI scientists took part in the event. Alexandre Bergounioux discussed “Untargeted metabolomics of human fecal samples using ultra-high-pressure liquid chromatography coupled to high-resolution mass spectrometry.” Tanja Zivkovic Semren presented on the “Targeted metabolomics approach for carbonyl measurement in exhaled breath.” And Maria Fatarova focused on the “Development of a quantitative and qualitative assay for mercapturic acids in urine.”

Key themes at this year's conference included “Metabolomics in Health and Disease”, “Environmental, Plant, Animal, Agriculture, Food and Model Organisms”, and “Technology, Systems Biology and Advancing the Field.”

[Read more about this conference](#)

## OPEN SCIENCE

📍 Online 📅 June 10, 2021

In June this year, we hosted our fourth Open Science, an online webinar where four of our scientific experts, Andrea Costantini, Gizelle Baker, Pierpaolo Magnani, and Antonio Ramazzotti, took part in a recorded panel discussion and a question and answer session on the challenge of measuring the use of nicotine-containing products. The panel discussion highlighted the importance of assessing if smoke-free products are used exclusively or together with other products, as well as how frequently.

With over 660 people registered for the online event and some excellent questions during the question and answer sessions, we're looking forward to hosting more Open Science events in the future.

[Learn more about Open Science](#)

## Are your scientific studies available as open source?

Open source and sharing our data is a very key aspect of our transformation. Transparency helps building trust and it is very important for us not only to allow access to our study results but also to methods, protocols and data, and we make an effort to publish them in an open-source manner. We've had over four hundred publications on our science that we have completed here at PMI and they're all available online.

We also have a forum, INTERVALS, where we share not just the results of the study in publications, but also the raw data, the

methodology, the protocols, in a way that people can query the data and do their own analysis and draw the conclusions for themselves.

We have also submitted an extensive data set to the U.S. Food and Drug Administration as part of our Modified Risk Tobacco Product (MRTTP) applications, which was made available on their website together with the programs that were run and the study reports. So, it is very much out there and open for people to see, people to query, and people to do their own research and draw their own conclusions.

## QUESTION & ANSWER OPEN SCIENCE JUNE 2021





# A CLOSER LOOK AT THE MEASUREMENT OF PRODUCT USE PATTERNS

Measuring tobacco and nicotine-containing product (TNP) use patterns is a challenge for many reasons, such as the increasing number of new products being commercialized, the absence of commonly agreed standards, terminologies or definitions, and the limitations of self-reported measures. Despite these complexities, understanding how adults use TNPs is crucial to determining the impact those products may have on public health. So how can we improve that understanding?

## Reducing risk of harm

The best way for adult smokers to reduce their risks associated with smoking is to quit tobacco and nicotine altogether. However, evidence has shown that [many smokers don't quit](#).

For these adult smokers who would otherwise continue to smoke cigarettes, switching to a scientifically substantiated smoke-free alternative could reduce their risk of smoking-related harm, such as lung cancer, chronic obstructive pulmonary disease (COPD), and cardiovascular diseases, compared to continued smoking. These products could, indeed, complement existing tobacco control efforts and be part of an overall harm reduction strategy to benefit public health.

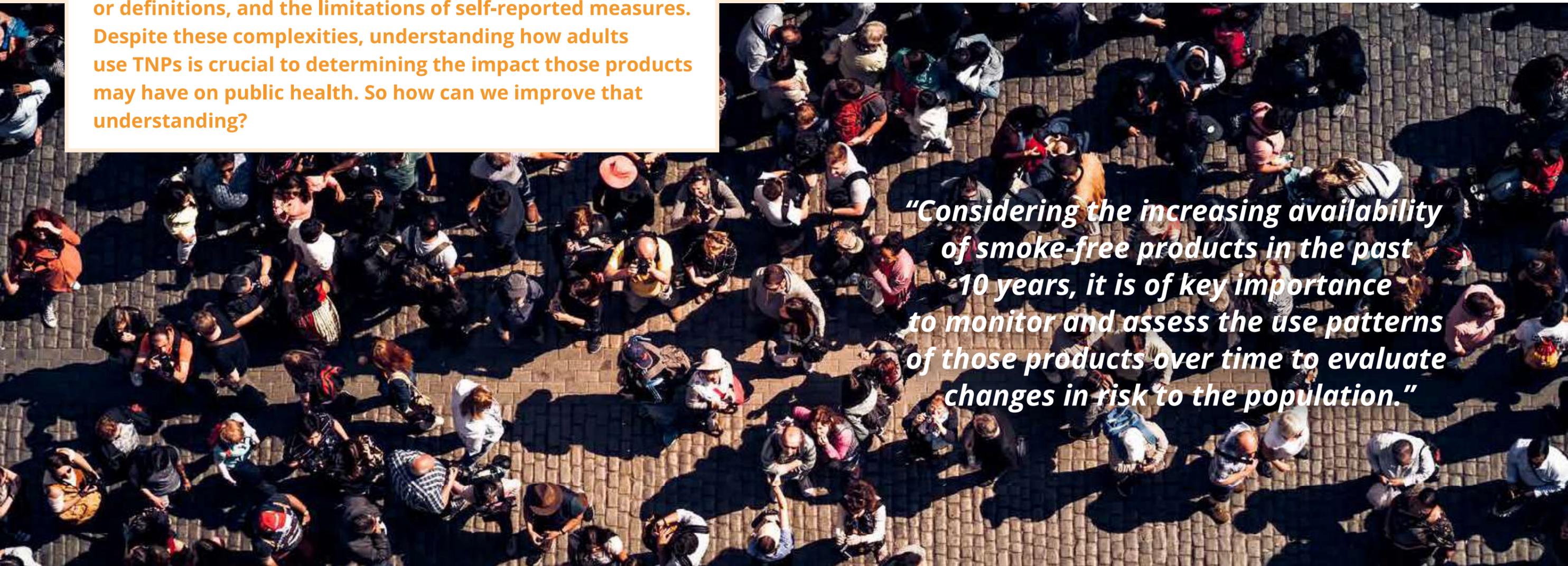
In recent years, an increasing number of smokers have switched from cigarettes to smoke-free alternatives such as e-cigarettes, heated tobacco, or oral tobacco products to reduce the risk of harm to their health compared to continued smoking. Many have stopped smoking cigarettes to completely switch to one of these smoke-free products, while some are using those smoke-free products in combination with other TNPs, including cigarettes. Measuring the extent to which those smoke-free products are used exclusively or together with one or more other products is an important factor to determine

the impact that those smoke-free products may have on the individual and on the population as a whole.

Considering the increasing availability of smoke-free products in the past 10 years, it is of key importance to monitor and assess the use patterns of those products over time to evaluate changes in risk to the population. To do that, it is necessary to set standards for how to categorize product use patterns. For example, does smoking a cigarette once per month make the person a smoker? If so, in this scenario shouldn't the definition be the same for smoke-free products in order to properly compare them?

## Why does measuring product use patterns matter?

Product use patterns are important to measure as they impact public health. For instance, for adult smokers who would otherwise continue to smoke, replacing their cigarettes with scientifically substantiated smoke-free alternatives can be a way to reduce the risk of harm to their health compared to continued smoking. This is because these products, while not risk-free and still containing nicotine, which is addictive, expose users to fewer and lower levels of toxicants compared to cigarettes.



*“Considering the increasing availability of smoke-free products in the past 10 years, it is of key importance to monitor and assess the use patterns of those products over time to evaluate changes in risk to the population.”*





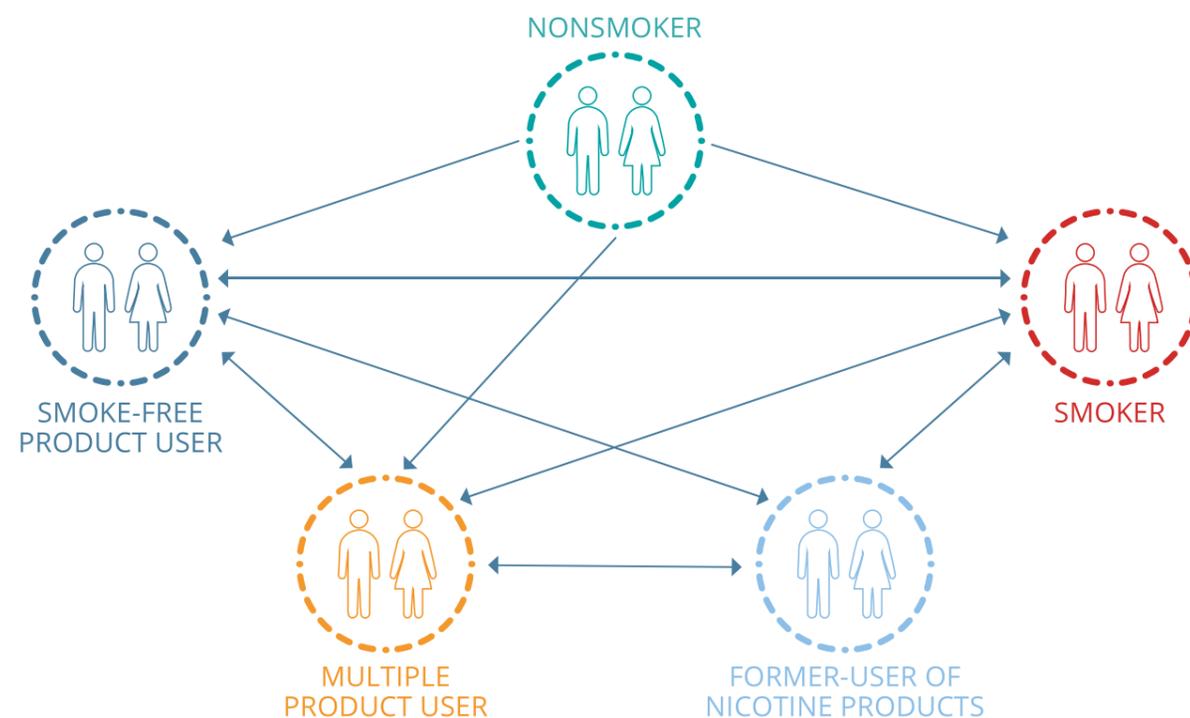
In short, to understand the potential health effects of these products on public health, we must understand how they are used. As a result, we need to answer several questions about use patterns, such as:

- Are adult smokers who switch to these products actually stopping smoking cigarettes?
- Are they continuing to smoke, perhaps while at the same time using additional tobacco products?
- Which types of nicotine-containing products are they using and how are they using them, both in terms of frequency and intensity of use?

Here are a couple of examples showing why answers to these questions are important. If an adult who smokes 20 cigarettes a day starts using one of these smoke-free products, such as an e-cigarette, this person may completely switch to this e-cigarette. Switching completely would reduce their exposure to harmful and potentially harmful chemicals and, therefore, their smoking-related health risks. But if instead that adult smoker replaces half of their cigarette consumption with e-cigarettes, in other words they are using e-cigarettes but

still smoke 10 cigarettes a day, they would not achieve the full benefits of switching.

To ensure that smokers can make informed decisions, they should be aware that smoke-free alternatives exist and have access to accurate and truthful information about the benefits, but also the risks, of these products. They should also be reminded that the absolute best choice they can make is to quit tobacco and nicotine use altogether.



## How to overcome the challenges of measuring product use patterns?

Behavior change is a complex process and for the most part these changes do not happen overnight. Therefore, measuring product use prevalence and use patterns needs to be done in a repeated and consistent manner to understand changes and trends over time. Such evidence will allow scientists and regulators to progressively assess the potential positive impact that scientifically substantiated smoke-free products may have on the individual and the population as a whole.

To reach any meaningful conclusions about the impact of new TNPs on public health, it is important that those measures provide accurate, consistent, and reliable data. Therefore, scientists, regulators and the industry should work together to establish commonly agreed standards and definitions to measure product use patterns and promote comparability across different studies. Once those practices are in place, it becomes possible to combine use prevalence and use pattern data with other information from public health impact modeling, real-world evidence, and epidemiological studies. Together, these important assessment tools can better clarify the impact of smoke-free products on population health.



# SHORT-TERM EFFECTS OF SWITCHING

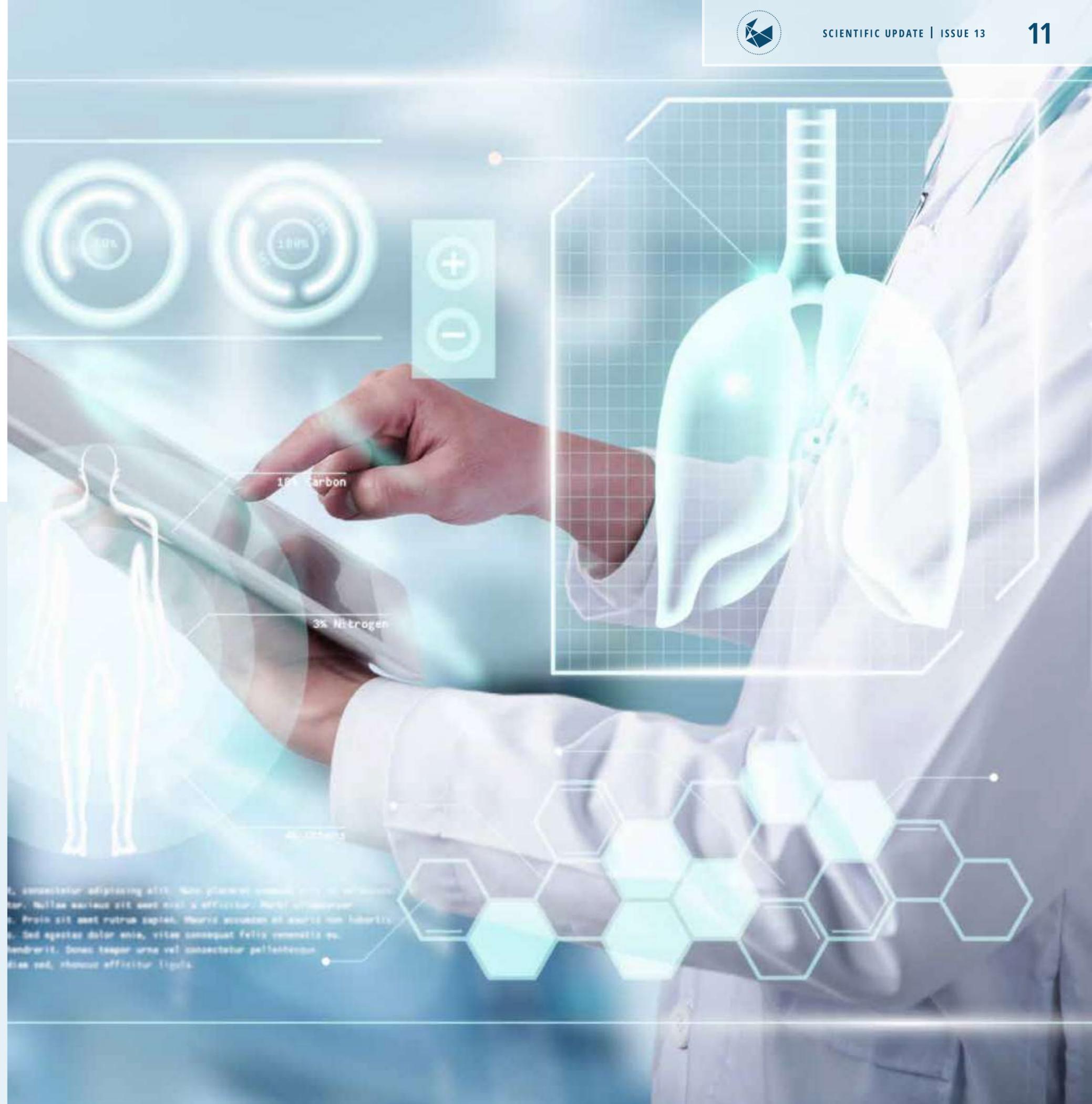
## FROM CIGARETTES TO OUR HEATED TOBACCO PRODUCT

### Quitting is the gold standard for tobacco harm reduction

The best way to avoid the harm of smoking is to not start in the first place. For someone who already smokes, quitting smoking is the single best thing they can do to reduce their risk. And if a person won't quit, then switching to a product that doesn't burn tobacco is a better choice than continuing to smoke cigarettes. This is because the vast majority of harmful chemicals found in cigarette smoke and linked to smoking-related diseases are generated by combustion.

When someone stops smoking, their risk of developing smoking-related health problems and diseases will not disappear overnight, but it will decrease with time. The longer they've smoked, and the more cigarettes they smoke during that time, the bigger their risks. This is why it's so important for a smoker to quit smoking as soon as possible. After the first few days of someone quitting cigarettes, their exposure to toxicants is greatly reduced and within three to six months they may notice a decrease in their coughing and shortness of breath.

The best choice a smoker can make is to stop smoking altogether but, unfortunately, not everyone who smokes makes that choice. In recent years, alternative products to cigarettes, for those who continue using tobacco or nicotine products, have been developed. Choosing to use these products is better than continuing to smoke because they do not burn tobacco, though it is important for each product to be scientifically verified to determine exactly how much better they really are compared to cigarettes. Here, we'll describe some of the data collected on changes smokers may observe in their body as a result of switching to Platform 1, our leading heated tobacco product (HTP). Before getting into the details of the studies, we need to emphasize that smoke-free alternatives, although potentially less harmful, contain tobacco or nicotine, and as such they are not risk-free.





## Reduced carbon monoxide in the blood

Carbon monoxide (CO) is released during the burning process, like in a cigarette. When the smoker puffs on a cigarette, CO enters the body and red blood cells that normally carry oxygen start carrying around CO instead. It reduces the amount of oxygen that is delivered throughout the body. CO is also naturally produced in the body when hemoglobin—the oxygen-carrying part of red blood cells—is broken down. But continued exposure to low levels of CO, as smokers have, can lead to reduced exercise capacity, the progression of atherosclerosis, and development of cardiovascular diseases.

Within days after switching from cigarettes to Platform 1, the body is exposed to lower levels of CO. Platform 1 produces on average 98% less CO compared to cigarettes. In PMI clinical studies by [Luedicke et al.](#) and by [Haziza et al.](#), those participants who switched from cigarettes to Platform 1 saw a significant drop of CO levels measured in the blood after just 24 hours of switching. That reduction was almost the same as the reduction observed for those who quit smoking.

## Decreased oxidative stress and inflammation

Oxidative stress occurs when there are too many highly reactive molecules (oxidants) in the cells – there is an imbalance between oxidants and antioxidants. Oxidative stress is involved in the development of cardiovascular diseases, dementia, chronic inflammation, and aging. Cigarette smoke increases oxidative stress because it has a high level of oxidants, therefore reducing antioxidant defenses. Stopping smoking helps reduce oxidative stress, as measured in our [Smoking Cessation Study](#) via the biomarker 8-epi-PGF<sub>2α</sub>, the [gold standard for the evaluation of oxidative stress in the human body](#). This biomarker was reduced in participants who quit smoking by 9.98% to 18.8%, varying by region, compared to baseline after three months.

In our [Exposure Response Study](#), after three to six months of switching completely to Platform 1, oxidative stress decreased compared to continued smoking, based on the statistically significant reduction in the levels of the biomarker 8-epi-PGF<sub>2α</sub> in the blood. The levels of this biomarker were reduced by 13.46% compared to baseline after three months. At the six-month mark in the study, the switching group had a 6.8% lower level of 8-epi-PGF<sub>2α</sub> in their blood compared to those who had continued smoking. While this measurement was not statistically significant, there was a clear trend of reduced oxidative stress compared to continued smoking.

Similarly, after three to six months the smoking-related inflammation decreased in those who switched completely to Platform 1 compared to those who continued smoking. This was measured using the white blood cell count, which stays high while a person continues to smoke. Study participants who switched to Platform 1 showed significantly lower white blood cell counts, 0.475 GI/L and 0.420 GI/L after three and six months respectively, compared to continued smoking.

## Better breathing and lung function decline begins to normalize

Lung function naturally declines gradually as we age, but smoking accelerates this process. With time, the toxicants in smoke can damage the lungs to the point where they can't stretch properly. The lungs can become inflamed and as a result, less air flows into and from the lungs. Quitting smoking can reduce the rate of decline compared to continued smoking. One measure of lung function is the FEV<sub>1</sub> test or forced expiratory volume test. It calculates how much air a person can exhale in one second.

After six months of switching completely to Platform 1, users can experience better breathing compared to continued smoking, due to different factors, one of them being the fact that less mucus is produced. Our studies show that lung-related benefits, such as better breathing, already begin to be apparent after three months of fully switching. In our [Exposure Response Study](#), the FEV<sub>1</sub> was measured for both people who switched to Platform 1 and those who continued to smoke cigarettes. The clinical data shows a statistically significant improvement at the six-month mark among those who switched completely compared to those who continued to smoke cigarettes.

## Improved cholesterol levels

Smoking cigarettes changes the way the body metabolizes cholesterol, generally reflected by a decrease in good cholesterol in the body. HDL (high-density lipoprotein) is known as “good cholesterol”, because this protein picks up cholesterol and other molecules in the body and transports them to the liver (and certain other organs) to be removed from the body. Higher HDL values are associated with a lower risk of atherosclerosis. In contrast, LDL (low-density lipoprotein) is known as “bad cholesterol” that contributes to the plaque buildup.

After three to six months of switching completely to Platform 1, the levels of “good” cholesterol improve compared to continued smoking. In studies by PMI and others,\* participants who switched from cigarettes to Platform 1 saw their levels of biomarkers of exposure to harmful chemicals reduce and the level of HDL increase, reducing the risk of plaque buildup. After six months, participants who switched showed an increase of 3.09 mg/dL in their HDL, which is double the change that was seen at three months. This increase approached the levels encountered after smoking cessation.

\* PMI Research and Development. [Evaluation of Biological and Functional Changes in Healthy Smokers After Switching to THS 2.2 for 26 Weeks](#) Registered on [clinicaltrials.gov](#): NCT02396381;

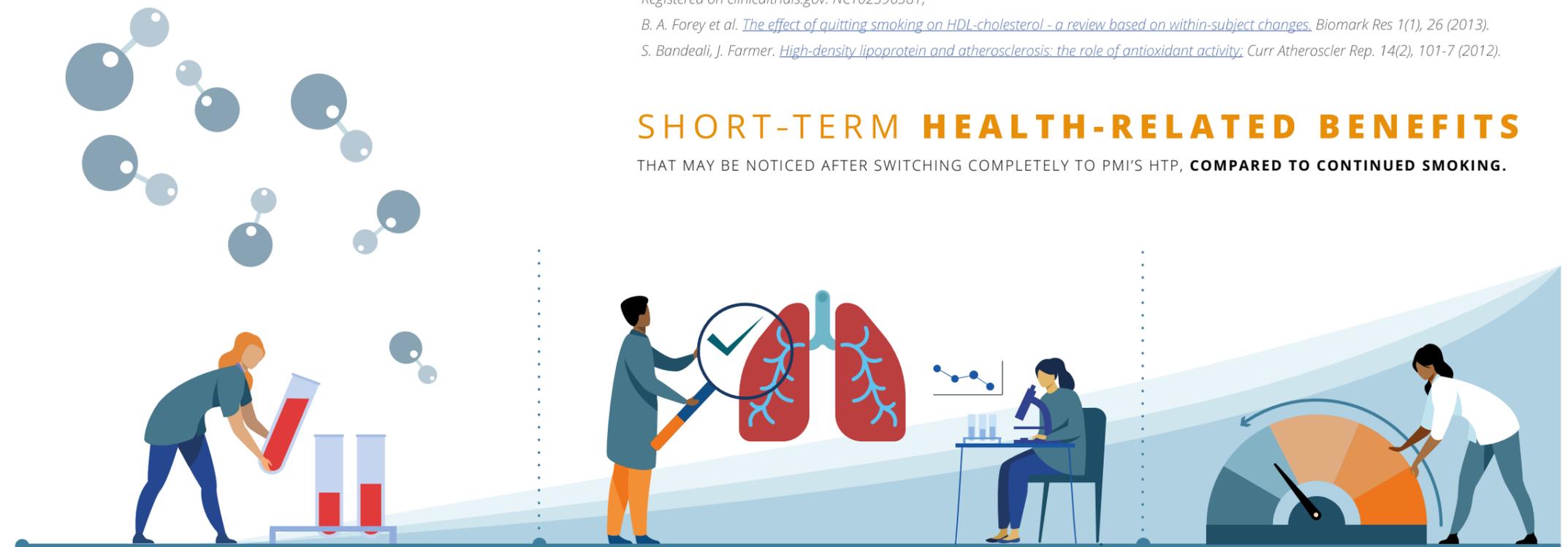
B. A. Forey et al. [The effect of quitting smoking on HDL-cholesterol - a review based on within-subject changes](#). *Biomark Res* 1(1), 26 (2013).

S. Bendeali, J. Farmer. [High-density lipoprotein and atherosclerosis: the role of antioxidant activity](#). *Curr Atheroscler Rep.* 14(2), 101-7 (2012).

## Overall health risk profile improves

What we can clearly see from this summary of our research is how a smoker's overall health risk profile can improve over time after switching completely to our leading heated tobacco product. We saw that carbon monoxide levels decrease, breathing becomes easier, coughing lessens, inflammation decreases, oxidative stress lessens, and cholesterol improves for those smokers who made the switch.

Switching from cigarettes to a smoke-free product will never be better for health than stopping the use of all tobacco and nicotine-containing products. The research discussed here clearly shows that switching to this particular smoke-free product can reduce the harms from smoking compared to continued cigarette use, and that the impact of switching on a person's health adds up over time. This information is why we stand behind our statement that quitting smoking is the best choice, and for those who won't quit, switching to a smoke-free product with a harm reduction profile backed by science is a better choice than continuing to smoke cigarettes.



## SHORT-TERM HEALTH-RELATED BENEFITS

THAT MAY BE NOTICED AFTER SWITCHING COMPLETELY TO PMI'S HTP, COMPARED TO CONTINUED SMOKING.

### 1-5 DAY(S)



Carbon monoxide in blood reduced

### 3 MONTHS



Better breathing and less cough



Oxidative stress decreases



Smoke-related inflammation decreases



Cholesterol level improves

### 6 MONTHS



Overall health risk profile improves



Smoking-related lung function decline begins to normalize



# RELATIVE RISK

## PROVIDING CRITICAL CONTEXT FOR A BETTER UNDERSTANDING



**Most people don't have a good grasp on the concept of risk, either over or underestimating the risk of an activity depending on how the data is presented. So, what is the best way to provide the facts and avoid confusion when it comes to heated tobacco and other alternative products?**

*Both methods of communicating risk can provide important information when they're based on scientific facts, and both have their place in scientific discussion.*

### What are absolute risk and relative risk?

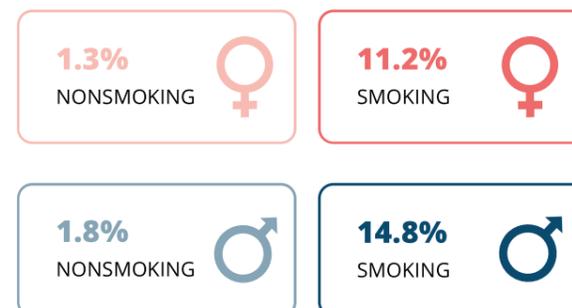
Adults who would otherwise continue to smoke should have access to accurate information about scientifically substantiated less harmful alternatives that the advance in science and technology may make available to them. Understanding the difference between relative and absolute risk is key when looking at harm reduction for smokers. Relative risk compares the risk between certain groups. For instance, stated in terms of relative risk, a 2021 study by Bruder et al. estimated that [a smoker is around eight times more likely to develop lung cancer than a nonsmoker](#). However, in absolute risk terms, a woman who smokes has an 11.2% (14.8% for men) risk of developing lung cancer, versus a nonsmoking woman's 1.3% risk (1.8% for men).

In scientific terms, absolute risk is the number of people experiencing an event in relation to the population at risk – often presented as a percentage or as a ratio, like “1 in 10 people.” Relative risk is often communicated in a similar way, but with key words added to indicate that a comparison is being made,

such as “10% higher/lower risk” or “five times more/less likely to...” Relative risk information can promote understanding of the implications of absolute risk by providing the context for how specific factors or behaviors, such as age, sex, physical activity, and diet, are estimated to impact our chances, for example, of developing a disease or health issue.

Both methods of communicating risk can provide important information when they're based on scientific facts, and both have their place in scientific discussion. Relative risk communications can be more impactful because they provide context for the reader, but they're also a bit more complex as they convey more information at once. Relative risk statements need to use the right comparator to properly convey an understanding of the estimate. When talking about tobacco harm reduction, we could consider comparing the estimated risks of a product to those estimated for cessation, continued smoking, never smoking, and even other products. What makes the most sense to best communicate about these products' risk profiles?

### ABSOLUTE RISK of developing lung cancer



### RELATIVE RISK of developing lung cancer





*The goal is to determine if the risk profile of switching to a smoke-free product is similar to continued smoking, or to smoking cessation, or somewhere in between.*

### Why relative risk is important

Switching from cigarettes to a nicotine-containing product that is avoiding combustion carries a higher risk than either abstinence or cessation, which remain the absolute best choice one can make. That is why smoke-free products are developed for and marketed to adults who would otherwise continue to smoke cigarettes, and not to youth, nonsmokers or former smokers. Adults who smoke are aware of the risks of smoking, and so learning that there are other products whose risks may be lower than that of continued cigarette smoking could encourage them to switch.

This is why it is so important to include comparisons between the use of smoke-free products and cigarettes in scientific studies. The aim is to build scientific evidence that will demonstrate the likely reduced risk profile of smokers who completely switch to smoke-free products. Other comparisons can still be informative, but leaving out this comparison means we miss out on critical context for our results. The goal is to determine if the risk profile of switching to a smoke-free product is similar to continued smoking, or to smoking cessation, or somewhere in between.

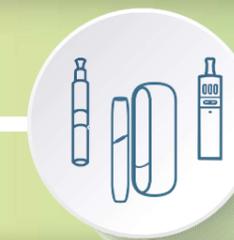
## CONTINUUM OF RISK

More Harmful

Less Harmful



Cigarettes and other tobacco-burning products



Smoke-free products



Cessation of all tobacco/nicotine-containing products

### Not all tobacco products are equal

The best way to minimize one's risk of smoking-related diseases, including lung cancer, chronic obstructive pulmonary disease (COPD) and cardiovascular diseases, is to never start smoking at all. For current smokers (about 1 billion people globally), the best single step they can take to reduce their risk of harm is to quit tobacco and nicotine use altogether. The more people who do this, the bigger the reduction in population harm that is caused by smoking cigarettes. For adult smokers who would otherwise continue smoking, switching to scientifically substantiated smoke-free alternatives has the potential to reduce their risk of developing major smoking-related diseases. However, these products are not risk free and contain nicotine, which is addictive.

Reducing tobacco-related harm at the population level through less harmful alternatives, depends not only on the absolute risk to the individual using the product, but also its adoption by adult smokers. The biggest impact on population health occurs when as many smokers as possible

quit altogether or if adults who would otherwise continue to smoke switch to scientifically substantiated lower risk products, rather than continuing to smoke cigarettes. Not all tobacco products are the same. Their use exists along a continuum of risk, where smoking combusted tobacco yields the highest risk and quitting nicotine and tobacco products altogether contributes the lowest risk. The use of other tobacco products, including smoke-free products, also lie in that continuum of risk. Products that don't burn tobacco are likely to be far less harmful alternatives to continued smoking.

A study, for example, indicated that emissions from vaporized nicotine (e.g., e-cigarettes) and heated tobacco products, contain carcinogens but generally in lower concentrations than found in cigarette smoke. Both product categories had more than an order of magnitude lower cancer potency than cigarettes according to the study's criteria. When it comes to risk of harm, it's smokers switching completely that is important, not which lower risk product they switch to.

### The harm reduction equation

Now, reducing the risk of harm for an individual is not enough to reduce the risk of harm for an entire population. The more individuals who choose the lowest risk options instead of continuing to smoke, the bigger the impact on reducing population harm. This is known as the harm reduction equation.

Put another way, a product that is extremely low risk compared to cigarettes but is either not acceptable to smokers or is very attractive to never/ex-smokers will have little to no impact on the population harm. And a product that is roughly the same risk as cigarettes will also make no headway in reducing population harm, no matter how many smokers switch to it. For any smoke-free alternative to be successful in swiftly reducing harm compared with continued smoking, it must fulfil two criteria: it must be scientifically substantiated as significantly less harmful than cigarettes, and it should be satisfying for current adult smokers so that they completely switch.

As stated above, besides acceptability to smokers, there is one further facet of the harm reduction equation to keep in mind. If people who have never smoked cigarettes pick up the new product in appreciable numbers, or if youth or former smokers use it, then the risk of harm to the population actually gets higher. The overall goal, then, is to develop a product that presents significantly less risk than continued smoking, is acceptable to current smokers who would otherwise continue to smoke cigarettes, and which is generally not attractive to youth, nonsmokers, or former smokers.





## INDEPENDENT STUDIES

### Study evaluates the impact of switching to HTPs in patients who do not quit smoking

A [three-year study](#) conducted by researchers at the University of Catania in Italy identified long-term health effects for chronic obstructive pulmonary disease (COPD) patients who completely or substantially reduced their cigarette consumption by switching to heated tobacco products (HTPs). Changes in daily cigarette smoking, annualized disease exacerbations (meaning a worsening or “flare up” of symptoms), patient-reported outcomes (COPD assessment test scores), lung function indices, and 6-minute walk distance or 6MWD test were measured in COPD patients who were using HTPs at 12, 24 and 36 months. Results of those who switched to HTPs were then compared with those of a group of age- and sex-matched COPD patients who continued smoking.

The study found that HTP use decreased the number of acute exacerbations of COPD by approximately 40% compared to continued smoking. Consistent improvements in rate of disease exacerbations, exercise tolerance, respiratory symptoms, and quality of life were observed in patients with COPD who abstained from smoking, and in those who substantially reduced their cigarette consumption by switching to HTPs.

### Smoking cessation aids

A [retrospective study from the IASLC Tobacco Control Committee](#) published in The Journal of Thoracic Oncology analyzed the cessation aids used by 3,614 current and ex-smokers in Australia, Canada, England, and the United States at their last attempt to quit smoking.

These included nicotine vaping products (NVPs), nicotine replacement therapy (NRTs), other pharmacologic therapies (OPTs: varenicline, bupropion or cytisine), tobacco (noncombustible: heated tobacco product or smokeless tobacco), services aimed at helping smokers stop (counseling, quitline or doctors), and other cessation supports (e.g., mobile apps, websites or pamphlets).

The results showed that 28.8% of the current and ex-smokers used nicotine replacement therapy, 28.0% nicotine vaping products, 12.0% used OPTs, 7.8% used cessation service, 1.7% used tobacco products, 16.5% used other cessation supports, and 38.6% did not use any aid or assistance. For those smokers who relied on assistance, NRTs and NVPs were the most common method, causing the authors to conclude that nicotine substitution is critical for smokers attempting to quit.

### Study assessing the potential of e-cigarettes as an alternative to continued smoking

A [recent paper](#) published in the Cochrane Database of Systematic Reviews examined the effectiveness, tolerability, and safety of using electronic cigarettes (ECs) in helping people who smoke achieve long-term smoking abstinence by switching.

The Cochrane review took into consideration 56 studies, representing 12,804 adult smokers from multiple countries, mostly the UK, the U.S. and Italy, with evidence published up to February 1, 2021. The authors noted they were *“moderately confident that nicotine e-cigarettes help more people to stop smoking than nicotine replacement therapy or nicotine-free e-cigarettes. However, these results might change if further evidence becomes available.”*

**In their results, the authors noted that nicotine ECs may help more people to stop smoking than no support or behavioral support only. They found that around 10 in 100 people may stop smoking using nicotine ECs, while only six in 100 people stop smoking using nicotine-replacement therapy ECs without nicotine. And 4 in 100 quit using no support or behavioral support alone. The study concludes that more studies are needed to confirm the size of the effects of ECs, particularly the effects of newer types of ECs that have better nicotine delivery, the review concluded.**

### Impact of an HTP aerosol on denture teeth color relative to cigarette smoke

A [study published in the Journal of Prosthetic Dentistry](#) examined the level of discoloration on the color of artificial denture teeth caused by cigarette smoke and compared it with that of PMI’s Tobacco Heating System (THS) aerosol.

The researchers divided ninety incisor denture teeth into three groups. The teeth in the control group were exposed to air. The teeth in the second group were exposed to cigarette smoke, while teeth in the third group were exposed to THS.

The researchers used standard conditions from the Coresta Recommended Method N°22 to simulate smoking. A total of 105 cigarettes were used based on a smoking simulation of 15 cigarettes per day for seven days. The results of the study showed that cigarette smoke caused the greatest color change, while the THS aerosol caused significantly less discoloration. These conclusions are in line with [previous research conducted by PMI and researchers from the University of Rochester](#).

### Evaluating the toxicology of ENDPs

PMI Scientists published a book examining [the potential role of Electronic Nicotine Delivery Products \(ENDPs\) in tobacco harm reduction](#) and how they may reduce the risk of smoking-related diseases in smokers who switch to them. It provides toxicologists, health practitioners, and public health professionals with the scientific information necessary to assess the relative risk of ENDPs compared with continued cigarette smoking and smoking cessation, it being understood that smoking cessation remains the best choice a smoker can make.

**This book summarizes key concepts and results from tobacco harm reduction research from the past 15 years, focusing on PMI’s research but also including key findings from independent studies. It explains that developing new products that are scientifically substantiated to present less risk of harm compared to continued cigarette smoking is one approach to harm reduction. For an ENDP to qualify as a less harmful alternative to continued cigarette smoking, it must be scientifically proven to emit and expose users to significantly lower levels of toxicants, and to cause significantly less adverse effects than continued cigarette smoking. Scientifically substantiated ENDPs that avoid combustion of tobacco have been shown to emit significantly lower levels of toxicants than cigarettes. The extent of that reduction should, however, be scientifically assessed for each product.**

### An Intestinal Model for screening compounds with anti-inflammatory properties

This paper describes the development of [an immunocompetent in vitro triculture intestinal model](#) consisting of a differentiated intestinal epithelial layer and immunocompetent cells. Our study tested the model with the tobacco alkaloids nicotine and anatabine, which possess immunomodulating properties.

The triculture mimicked a healthy intestine with stable barrier integrity. Lipopolysaccharide treatment triggered a controlled and reversible inflammatory state, resulting in significant impairment of barrier integrity and release of pro-inflammatory cytokines and chemokines, which are known hallmarks of intestinal inflammation.

Treatment with known anti-inflammatory reference compounds prevented the induction of an inflammatory state. The two tobacco alkaloids were also tested in the *in vitro* triculture for their potential anti-inflammatory properties. One of the tobacco alkaloids, anatabine, showed anti-inflammatory effects.

The results show that our *in vitro* triculture intestinal model exhibits mucosal immune responses and is suitable for screening compounds with anti-inflammatory properties. By capturing the key features of intestinal inflammation, this *in vitro* tool provides a means to investigate immunomodulating therapeutic intervention of the inflamed intestine.



## PMI PUBLICATIONS

### Robustness of our HTP in reducing toxicants in high intensity puffing conditions

This peer-reviewed study evaluated the performance of [our Tobacco Heating System \(THS\) in significantly reducing toxicants compared to cigarette smoking over a broad range of puffing regimes](#). Puffing behavior relates to how a smoker smokes a cigarette, and it is characterized by parameters such as puff volume, puff duration, and the number of puffs. Heated tobacco products heat tobacco to a controlled temperature - below that of combustion, to produce a nicotine-containing aerosol with significantly lower levels of harmful and potentially harmful constituents (HPHCs) compared to cigarette smoke.

The study demonstrated the robustness of THS in reducing the level of HPHCs in the aerosol compared to cigarette smoke under different puffing conditions. The results showed the concentrations of the 54 HPHCs investigated were reduced on average by more than 90% under the Health Canada Intense (HCI) and more intense smoking regimes when compared with the concentrations of smoke from a standard reference cigarette (3R4F). Evaluating the chemical properties of a product’s aerosol is a key step for assessing the robustness of current and future tobacco heating systems as they continue to evolve.

### Assessing the generation, exposure, and collection of EVP aerosols

A recent review article provided a detailed description of various [experimental setups and methods for assessing e-vapor products \(EVP\)](#). EVP have become popular alternatives for cigarette smokers who would otherwise continue to smoke. However, studying these products can be challenging and complex, mostly because of the numerous and rapidly evolving technologies and designs, as well as the many e-liquids available.

This review highlighted the urgent need to standardize all stages of EVP assessment, from the production of a reference product to e-vapor generation methods and from physicochemical characterization methods to nonclinical and clinical exposure studies. The lack of manufacturing standards also adds uncertainty to the relevance of research findings because of variations in product quality. Furthermore, the absence of standardized assessments makes research data difficult to evaluate, interpret, and compare. This review aims to support further studies, objective evaluation, comparison, and verification of existing evidence, and the formulation of standardized methods for testing EVPs.



# PMI SCIENCE

PHILIP MORRIS INTERNATIONAL

## Important information

This Scientific Update provides an overview of the most recent scientific developments behind PMI's approach to achieving a smoke-free future through a range of alternatives to cigarettes that do not burn tobacco.

The following pages include our product development and assessment efforts, our initiatives to share our methodologies and results, as well as independent research and government reports.

More detailed information can be found at [www.pmiscience.com](http://www.pmiscience.com).