PMI SCIENCE
PHILIP MORRIS INTERNATIONAL

SCIENTIFIC UPDATE FOR SMOKE-FREE PRODUCTS

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Past issues can be found here.

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.

WHAT'S INSIDE:

INTRODUCTION

Nicotine is the most well-known molecule in tobacco. Because it is so well-known, it is tempting for people to wrongly associate all the dangers of smoking with nicotine. Nicotine is addictive and not risk-free, but it is not the primary cause of smoking-related diseases. It is the key ingredient of nicotine replacement therapies designed to help smokers quit smoking. It's also in smoke-free products to make them acceptable to smokers who would otherwise continue smoking cigarettes.

Smokers should have access to accurate information about nicotine-containing products. That information should include the fact that nicotine is not the primary cause of harm in cigarettes. That quitting is always the best option. That nicotine replacement products can help them quit smoking. And that, for those who want to continue using nicotine, there are also smoke-free products they can completely switch to. Considering that more than 1 billion people will keep smoking for the foreseeable future, it is imperative that current adult smokers be provided the information – clear, accurate, and not misleading – that will empower them to make a better choice.

It is wrong to tell smokers that all nicotine-containing products are equally dangerous, because they're not. It is wrong to tell them that if they don't quit, it's not worth the effort of switching to a better product. This couldn't be further from the truth.

To straighten out a few more threads of the conversation: **Nicotine is not a primary cause** of smoking-related diseases, it's the other harmful chemicals in cigarette smoke that are the primary cause of smoking-related diseases. **It's never too late to stop smoking cigarettes.** For those adult smokers who wouldn't otherwise quit smoking, **there are better alternatives than cigarettes. Nicotine is not the only reason** people smoke cigarettes. It's often not just the symptoms of withdrawal, but also the rituals and sensations associated with smoking that make it hard to quit. But **it is possible to quit, and millions of smokers successfully quit every year.** For those who don't quit, alternative products that contain nicotine but offer a reduced-risk profile could serve as a tipping point to convince a greater number of smokers to **make the switch.**

This issue of the Scientific Update summarizes the current scientific understanding of nicotine. Where it comes from, how it works in the body, and how people think about nicotine and tobacco products. We hope you learn something you didn't know before, and use it to start your own discussions about nicotine.

Prof. Manuel C. Peitsch
Chief Scientific Officer

Dr. Julia Hoeng
Director System Toxicology

Dr. Annie Heremans
Chief Medical Officer

ASSESSMENT PROGRESS OF OUR PRODUCT PORTFOLIO

HEATED TOBACCO PRODUCTS

One approach to significantly reducing the levels of emitted and inhaled toxicants is to heat tobacco to temperatures well below 400°C – the temperature where combustion can occur – instead of burning it. These products closely approximate the taste, sensory satisfaction, and ritual of cigarettes and therefore have the potential to be acceptable for people who would otherwise continue to smoke but are interested in switching to a better alternative.

PLATFORM 1
ELECTRICALLY HEATED TOBACCO SYSTEM (EHTS, REFERRED TO AS TOBACCO HEATING SYSTEM [THS] IN RESEARCH)

DESCRIPTION

An electronically controlled heating blade precisely heats a specially designed tobacco stick to temperatures below 350°C. The experience lasts six minutes or 14 puffs, whichever comes first, similar to that of a cigarette. This device also exists in a version supporting 10 consecutive uses without recharging between experiences.

ASSESSMENT PROGRESS

We have conducted 18 non-clinical and 10 clinical studies for this platform, with results consistently showing that the EHTS, while not risk-free, presents less risk of harm compared with continuing to smoke. Analysis of the results of the second six-month term of the exposure response clinical study is in progress. In April of this year, the U.S. Food and Drug Administration (FDA) announced its decision on our Premarket Tobacco Product Application following a comprehensive and rigorous two-year assessment, authorizing the sale of EHTS in the US.[1]

PLATFORM 2
CARBON-HEATED TOBACCO PRODUCT (CHTP)

DESCRIPTION

A carbon heat source heats the tobacco to temperatures below 350°C. The heat source is fully separated from the tobacco by a proprietary design to prevent the tobacco from burning.

ASSESSMENT PROGRESS

Our nonclinical assessment is well advanced and the combined study results show that CHTP aerosol is less toxic than cigarette smoke and causes less disease than cigarette smoke in an animal model of heart and lung disease. Our reduced exposure study showed a substantial reduction in relevant biomarkers of exposure to the measured harmful chemicals in those who switched to CHTP compared with those who continued to smoke. We are sharing the conclusions in scientific forums and have submitted them for publication in peer-reviewed journals in 2019.

PRODUCTS WITHOUT TOBACCO

Another approach to reduce the levels of toxicants emitted by novel products is to produce a nicotine-containing aerosol without the use of tobacco. We precisely design the composition of the aerosol-producing components and the conditions of the aerosol generation. This provides control over the resulting aerosol in terms of quality and consistency. These platforms may be best suited for people who smoke but are not necessarily looking for the taste and sensory experience of tobacco or are already using e-vapor products.

PLATFORM 3
E-VAPOR PRODUCT USING NICOTINE SALT

DESCRIPTION

Includes products in which nicotine is mixed with a weak organic acid to generate an inhalable nicotine aerosol. We have explored two routes for this platform: one with electronics and one without.

ASSESSMENT PROGRESS

We finished the clinical phase of a nicotine pharmacokinetic study for the version without electronics, and the associated report was finalized in 2018 and the results have been published. The results indicate that this platform has the potential to be an acceptable alternative to continued cigarette smoking in terms of product satisfaction. We have also launched a product use and adaptation study in adult smokers earlier this year.

PLATFORM 4
E-VAPOR PRODUCTS (COMMERCIALIZED UNDER VARIOUS TRADEMARKS)

DESCRIPTION

Battery-powered devices that vaporize a liquid nicotine solution (also known as e-cigarettes). Included among our Platform 4 products is our proprietary *MESH*® technology, designed to improve the quality and consistency of the generated aerosol and increase the content delivery while avoiding "dry puffing".

ASSESSMENT PROGRESS

Our nonclinical assessment is progressing well and already shows the very low toxicity of non-flavored e-liquid aerosols while we are now focusing on the assessment of flavored e-liquids. In March this year, we completed a six-month nonclinical study demonstrating that e-vapors induce significantly lower biological responses associated with heart and lung diseases compared with cigarette smoke. We will also initiate a clinical study to measure selected biomarkers of exposure to harmful chemicals and assess changes in clinical risk markers.

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

OTHER DEVELOPMENTS

We continue to search for new technologies in the smoke-free product space. PMI's *venture fund* invests in entrepreneurs and growth companies with new solutions for products that have the potential to present less risk of harm than continuing to smoke. Our *Idea Submission Portal* offers innovators an opportunity to provide technical solutions that can enhance our product portfolio.

PMI STEP BY STEP ASSESSMENT PROGRAM

To learn more about the steps of our assessment program, please visit pmiscience.com

Colored blocks indicate progress completed.

1. Our Modified Risk Tobacco Product Application is still under review.

NICOTINE:
FROM PLANTS TO PEOPLE

Quitting smoking is the best way to reduce the risk of smoking-related diseases, which include the development of certain types of cancer, cardiovascular diseases, and emphysema. Cigarette smoke also stains the teeth, causes bad breath, and ages the skin. **Despite being a well-known component of tobacco, nicotine is not a primary cause of these harms.** It's many of the other harmful and potentially harmful constituents (HPHCs) in smoke that are the major cause of the health risks of smoking.

Unsurprisingly, there are many misconceptions about nicotine. How much do you really know about nicotine, and how much of that information is accurate? Read on to discover facts you may not have known about nicotine, as well as its role in tobacco harm reduction research.

IT STARTS WITH PLANTS

Where does nicotine come from? The simple answer is: plants. More specifically: the Solanaceae family, commonly known as nightshade. This family includes tomatoes (~332 ng of nicotine each on average), potatoes (~675 ng), and eggplants/aubergines (~525 ng).[2] To put that into perspective, a single cigarette contains ~12 mg of nicotine[3] – around 18 thousand times more nicotine than a potato, by mass. But only a fraction (<2 mg) of that nicotine is transferred into the smoke of a cigarette.

What does this mean? Nicotine is present in our diet in small doses. Research estimates that people eat about 1400 ng of nicotine every day in ordinary food.[3] But that doesn't explain why tobacco and other plants contain nicotine in the first place.

Nicotine is created in the plant's roots when two chemical compounds – pyridine and pyrrolidine – are joined together before being transported to the leaves. The genes behind this combination exists in all plants, but genetic duplications in the nightshade family are believed to have led to nicotine production.[4]

Wild tobacco plants of the *Nicotiana* genus with higher concentrations of nicotine survived longer than sibling plants with lower concentrations.[4] In other words: evolution. The chemical exists in these plants at greater concentrations because it benefits them. Although the primary purpose of the chemical in plants isn't definitively known,[4] studies have shown that at least one of its functions is to defend against attacking insects.[5]

However, nicotine's effects in people are different from its role in plants. Since prehistorical times, people have recognized the stimulating effects of the smoke created by burning dried tobacco leaves.[6] Since then, smoking has become the most common form of nicotine uptake from tobacco.

INTO THE BRAIN

Commercially available products, including cigarettes, nicotine replacement therapies (NRTs), smoke-free products, and others, contain high enough levels of nicotine to temporarily affect a person's brain function in a reversible way. But how does it get to the brain in the first place?

Nicotine from various sources can be absorbed through the lungs, through the mouth, or through the skin. The route of uptake determines the speed and intensity of nicotine delivery. Once absorbed, nicotine enters the bloodstream and is distributed, at various concentrations, to all tissues and organs, including the brain.

It takes little time after starting to use a nicotine-containing product for nicotine to reach the brain with a sufficient concentration to cause an effect. That time ranges from approximately 10 seconds as with smoking or may take an hour with the nicotine patch. Nicotine is also constantly being cleared from the body. It's metabolized mainly by the liver, at approximately 70% with each pass through the liver, and the metabolites are excreted via the kidneys.[7]

Once inside the brain, nicotine binds to nicotinic acetylcholine receptors (nAChRs), such as those located on the brain's nerve cells. These nAChRs are crucial receptors, involved in most communications between neurons in the brain but also outside the nervous system, such as between neurons and muscle cells. The natural signaling molecule for nAChRs is acetylcholine, which nicotine can imitate as it binds to these receptors. When it does, it causes the release of dopamine, GABA, glutamate, acetylcholine, and noradrenaline. As a result, nicotine may stimulate and ultimately affect short-term brain functions such as emotion, learning, and memory.

The action of nicotine in the brain can also trigger physiological effects outside the brain. For example, the messenger epinephrine is released into the bloodstream, leading to temporary narrowing of blood vessels, higher blood pressure, and increased heart rate.

After repeated nicotine stimulation, the brain adapts to the presence of nicotine, a process that is reversible when a person stops using nicotine-containing products. This process of nicotine stimulation can ultimately lead to difficulty quitting.

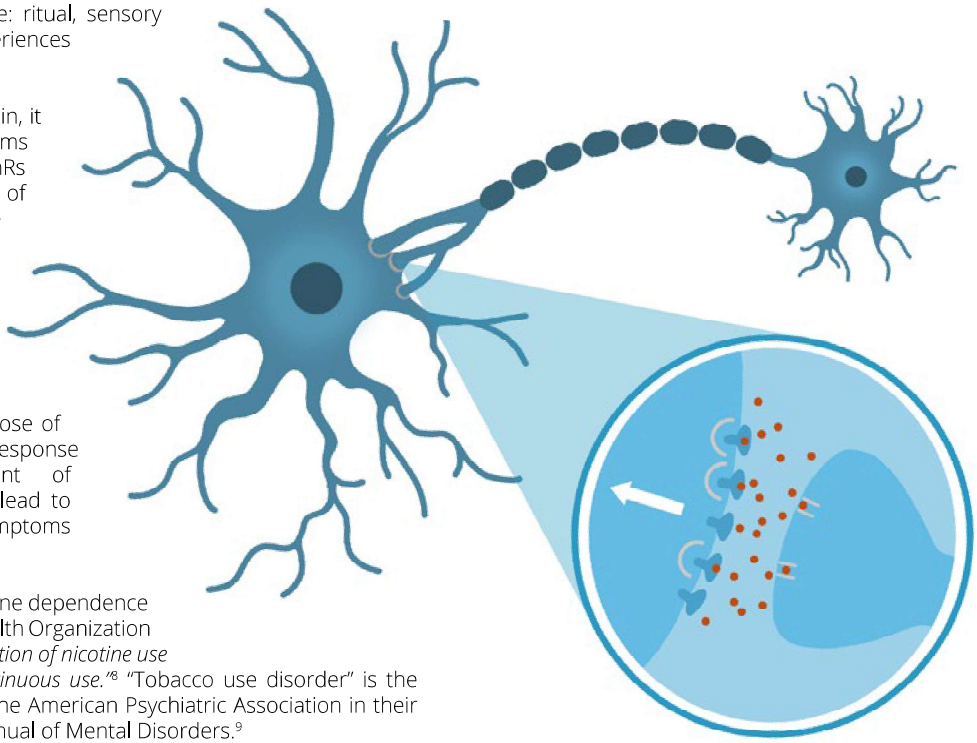
NICOTINE AND ADDICTION

It has been recognized that the addictive properties of cigarette smoking are caused by a complex interaction of factors that enhance the action that would be caused by nicotine alone. Exposure to nicotine and the extent of its effects can also be influenced by individual differences in smoking behavior, metabolism, body mass index (BMI), and genetic differences. While

2. Siegmund, B. et al. Determination of the nicotine content of various edible nightshades (Solanaceae) and their products and estimation of the associated dietary nicotine intake. *Journal of Agricultural and Food Chemistry.* 1999;46:3113-3120. (Link).
3. Alkam, T., Nabeshima, T. Molecular mechanisms for nicotine intoxication. *Neurochemistry International.* 2019;125:117-126. (Link)
4. Xu, S. et al. Wild tobacco genomes reveal the evolution of nicotine biosynthesis. *PNAS.* 2017;114(23):6133-6138. (Link)
5. Steppuhn, A. et al. Nicotine's defensive function in nature. *PLoS Biol.* 2004;2(8);e217. (Link)
6. Castaldelli-Maia, JM, et al. Tobacco smoking: From 'glamour' to 'stigma'. A comprehensive review. *Psychiatry and Clinical Neurosciences.* 2016;70:24-33. (Link)
7. Benowitz, NL., Hukkanen, J., Jacob, P. 3rd Nicotine chemistry, metabolism, kinetics and biomarkers. *Handbook of Experimental Pharmacology.* 2009;29-60. (Link)

nicotine is the focus of this review, other factors also make smoking addictive: ritual, sensory experience, and social experiences all play a significant role.

Once nicotine enters the brain, it modulates the reward systems via its binding to specific nAChRs distributed in certain regions of the brain. A chronic exposure to nicotine results in tolerance, a *decreased* response of some kind to the same dose of nicotine. It also results in sensitization, which is an *increased* response of some kind to the same dose of nicotine. These changes in response underlie the development of dependence, and they can lead to temporary withdrawal symptoms when one tries to quit.



Regarding terminology, nicotine dependence is described by the World Health Organization (WHO) as *"a disorder of regulation of nicotine use arising from repeated or continuous use."*[8] "Tobacco use disorder" is the relevant term described by the American Psychiatric Association in their Diagnostic and Statistical Manual of Mental Disorders.[9]

Withdrawal symptoms are another concern for about half of smokers when they initially quit smoking, including difficulty concentrating, anxiety, and dysphoria (meaning distress or discomfort with life).[10] While quitting smoking can be difficult, it is very much possible, and millions of smokers quit every year. NRTs and other cessation products can help address withdrawal symptoms if they occur.

One critical factor in nicotine dependence is the dose and rate of nicotine delivery. Because smoking delivers nicotine to the brain very efficiently, products that rapidly deliver peak doses of nicotine, like sprays and inhalers, are more satisfying to smokers than those that slowly deliver nicotine at much lower doses like gums and patches.[12]

LEVELS OF NICOTINE IN THE BLOOD: NOT ALL PRODUCTS ARE EQUAL

Many people assign most of the addictive power of cigarettes to the rapid absorption of nicotine through the lungs. When someone smokes a cigarette, their blood nicotine levels peak in about six to ten minutes. Then, the level of nicotine in the blood drops by about half every two hours on average, as the body naturally clears the nicotine from its system.[13] **Most NRTs don't provide the same pharmacokinetic profile as cigarettes,[14] making them less likely to satisfy a smoker.**

Our EHTS product, on the other hand, creates a nicotine profile like that of a cigarette.[15] In two studies in Japan, the peak concentration of nicotine in the blood occurred about six minutes after starting product use and reached more than 88% of the level reached with cigarettes. This likely comes even closer to 100% as the user becomes more familiar with the product, while participants in this study had only used the product during a product trial at the start of the study and during the assessment of the nicotine uptake. Subjectively, the people who used EHTS instead of a cigarette also found that the product reduced their urge to smoke similarly to cigarettes. We have also completed a pharmacokinetic study for CHTP, but the results are not yet publicly available.

We've also tested the pharmacokinetics for two versions of our nicotine salt e-vapor product. In one version, the peak nicotine concentration occurred about seven minutes after the start of product use.[16] This is much closer to the nicotine pharmacokinetics profile of a cigarette than the nicotine inhalator, which peaked at about 30 minutes. Another variant was found to cause the nicotine peak between 15 and 22 minutes during a single use of the e-vapor product. The level of nicotine depended on how the user puffed on the product.[17] This is unlike EHTS or cigarettes, which both provide a peak nicotine concentration within 6 to 10 minutes after product use begins.

The pharmacokinetic profile for *MESH* is very similar to the profile created by smoking a cigarette and the study subjects' preferred e-cigarette. Further, participants who used *MESH* rather than their own brand of e-cigarettes had a reduced nicotine craving over the next few hours after product use, comparable to that achieved with the study subjects' preferred e-cigarette.[18]

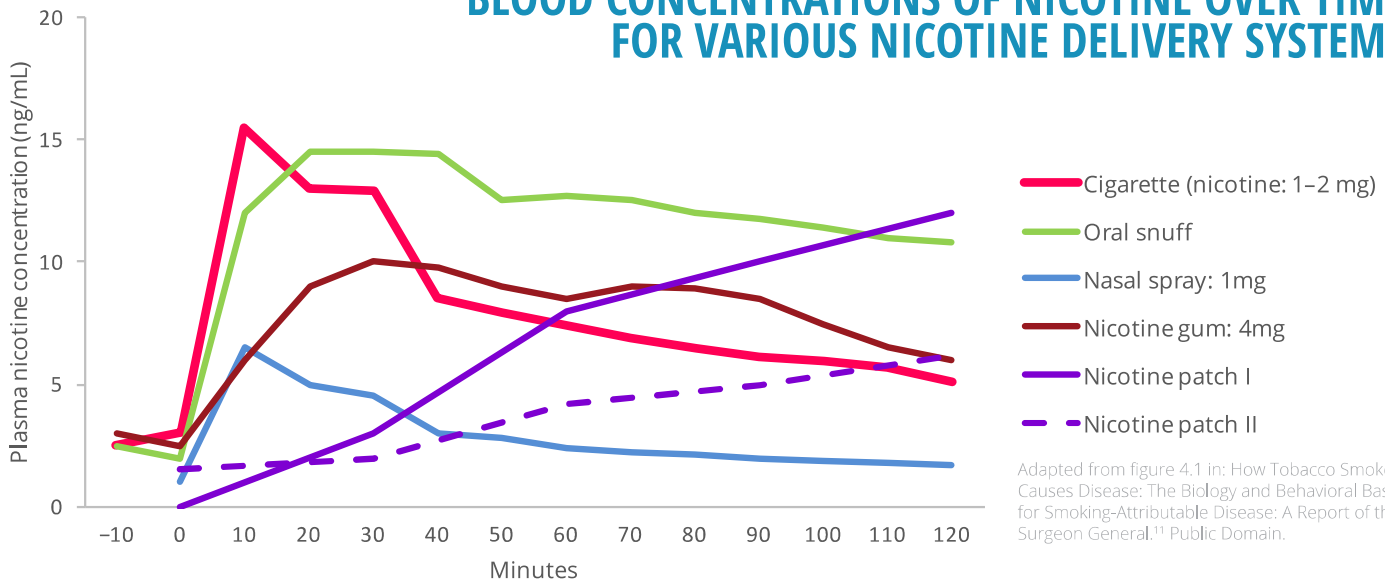
COMPARING PRODUCTS WHILE MATCHING NICOTINE LEVELS

It's important for us to have a quantitative way to compare the effects of smoke-free product aerosols and cigarette smoke. For example, we know from our laboratory studies that EHTS aerosol is significantly less toxic than cigarette smoke. This statement really means that **the same level of exposure of EHTS aerosol and cigarette smoke cause different levels of toxicity.** But in our laboratory studies, how can we know we are exposing our samples to the same levels of smoke and aerosol?

One approach is to focus on a single chemical present in both. Nicotine is an important part of why people use tobacco products, so it serves as a meaningful point of comparison. The FDA has also stated that comparing emissions on a nicotine basis is more likely to reflect human exposure levels than a per-stick basis.[19] This approach helps us to report our results in a way that other researchers can replicate.

8. World Health Organization. International Classification of Diseases (Link)
9. American Psychiatric Association: Diagnostic And Statistical Manual of Mental Disorders, Fifth Edition; American Psychiatric Association (2013) ("DSM-5"), at 485 (Link).
10. Bruijnzeel, AW. et al. Neuropeptide systems and new treatments for nicotine addiction. *Psychopharmacology*. 2017;234(9-10):1419-1437. (Link)
11. Office of the Surgeon General. How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General. Atlanta, GA, US. Centers for Disease Control and Prevention. 2010. (Link)
12. Tobacco Advisory Group of the Royal College of Physicians. Nicotine without smoke – tobacco harm reduction. Royal College of Physicians. 2016. (Link)
13. Benowitz, NL. et al. Interindividual variability in the metabolism and cardiovascular effects of nicotine in man. *The Journal of Pharmacology and Experimental Therapeutics*. 1982;221(2):368-372. (Link)
14. Centers for Disease Control and Prevention (US). How tobacco smoke causes disease: The biology and behavioral basis for smoking-attributable disease: A report of the Surgeon General. 2010. (Link)
15. Brossard, P. et al. Nicotine pharmacokinetic profiles of the Tobacco Heating System 2.2, cigarettes and nicotine gum in Japanese smokers. *Regulatory Toxicology Pharmacology*. 2017;89:193-199. (Link)
16. Teichert, A. et al. Evaluation of nicotine pharmacokinetics and subjective effects following use of a novel nicotine delivery system. *Nicotine & Tobacco Research*. 2018;20(4):458-465. (Link)
17. Bolsilkovska, M. et al. Nicotine pharmacokinetics and subjective effects following use of a novel nicotine-containing powder product. Poster presented at SRNT 2019. (Link)
18. Fredersdorf, S. et al. Nicotine pharmacokinetics and pharmacodynamic effects of P4M3 compared with subjects' own electronic cigarette. Poster presented at SRNT 2019. (Link)
19. U.S. Food & Drug Administration. 2019 Premarket Tobacco Product Marketing Order. Decision Summary PM0000479. Page 33. (Link)

BLOOD CONCENTRATIONS OF NICOTINE OVER TIME FOR VARIOUS NICOTINE DELIVERY SYSTEMS



Adapted from figure 4.1 in: How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General.[11] Public Domain.

Comparisons can also be made between EHTS and cigarettes on a per-stick or per-cigarette basis. We do use this comparison in some cases where it makes sense, such as where participants in our clinical studies are using the product. But it's necessary to use equivalent nicotine dose in our cell culture and other toxicity studies, for example.[20] A cell culture is exposed to a liquid containing the extract of cigarette smoke or smoke-free product aerosol at multiple matched nicotine levels. In other studies, cell cultures may be exposed to the smoke or aerosol directly, but again at matched nicotine levels. Doing so provides a clear way to compare the effects of different products at the same exposure level, and it makes the experiment and results easier for other scientists to confirm independently. It also makes it easier to extrapolate the results to what a user of the product might experience.

Because a major part of that experience is the nicotine, smokers may compensate for the nicotine level in their blood for a while after they first switch from cigarettes to our Platform 1 product or other smoke-free products. This may be achieved by using more of the product per day or by intensifying the frequency and volume of puffs taken. However, over long-term use of Platform 1, the compensation often remains incomplete. In other words, they end up maintaining a lower nicotine level in their blood.[21]

In a recent PMI study, switching from mentholated cigarettes to the menthol EHTS resulted in an almost complete compensation (measured as urinary nicotine equivalents) within a period of 90 days.[22] Based on these observations, comparing products on the basis of their nicotine content seems like the right approach.

Such comparisons can be made using automated smoking machines that collect cigarette smoke by puffing on the product. The smoke volume inhaled in a puff and how much time comes between puffs are some of the parameters that can be quantified. Under the ISO smoking regime, we measure 0.672 mg nicotine per reference cigarette.[23] The Health Canada Intense smoking regime, with deeper puffs repeated more often, yields 1.86 mg of nicotine per reference cigarette. These or other smoking regimes can be used to compare the levels of constituents in smoke-free product aerosols with cigarette smoke repeatably in a laboratory setting, though they don't accurately mimic real smoking behaviors.

EXPLORING THE RISKS OF NICOTINE

Nicotine is not risk free and is addictive. However, nicotine is not the primary cause of smoking related diseases.

Nicotine alone is clearly less harmful than the cigarette smoke that contains it, as can be seen in many studies on nicotine-containing products that aren't cigarettes. For example, even the U.S. Surgeon General concluded that *"there is insufficient data to conclude that nicotine causes or contributes to cancer in humans."*[24] While the Surgeon General has acknowledged the possibility that nicotine might be a tumor promoter based on animal and mechanistic studies, the current scientific consensus appears to be that nicotine does not initiate cancer and is far less harmful than many of the harmful and potentially harmful chemicals found in cigarette smoke.[25,26]

The Lung Health Study on the natural history and safety of prolonged use of medicinal nicotine gum indicated no evidence for an effect of NRT use on overall cancer[27] or COPD risk.[28] Available evidence to date suggests that nicotine also likely does not increase the risk of cardiovascular events: five out of six epidemiological studies did not detect any increased cardiovascular risk for snus users compared to never tobacco users.[29] Certain people, including those with heart disease or severe high blood pressure, should not use tobacco or nicotine-containing products.

WHAT DO PUBLIC HEALTH REPRESENTATIVES SAY?

"Nicotine is the very same compound FDA has approved for over 30 years as a safe and effective medication. People are dying from the tobacco-related diseases from the smoke particles, not the nicotine... Can we start to take a

20. Schaller JP. et al. Evaluation of the tobacco heating system 2.2. Part 2: Chemical composition, genotoxicity, cytotoxicity, and physical properties of the aerosol. *Regulatory Toxicology and Pharmacology.* 2016;81(S2):S27-S47. (Link)
21. Scherer, G. and Lee, PN. Smoking Behavior and Compensation: A review of the literature with meta-analysis. *Regulatory Toxicology and Pharmacology.* 2014;70(3):615-628. (Link)
22. Lüdicke, F. et al. Effects of switching to 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 & Tobacco Research.* 2018;20(2):161-172. (Link)
23. "Platform 1's mainstream aerosol compared to reference cigarette smoke". PMIScience.com. (Link)
24. Office of the Surgeon General. The Health Consequences of Smoking – 50 Years of Progress: A Report of the Surgeon General. Atlanta, GA, US. 2014. Centers for Disease Control and Prevention. (Link)
25. IARC Working Group on the Evaluation of Carcinogenic Risk to Humans. Smokeless Tobacco and some Tobacco-specific N-Nitrosamines. 2007;89. Lyon: International Agency for Research on Cancer. (Link)
26. National Academies of Sciences Engineering and Medicine. Public Health Consequences of E-Cigarettes. Washington, DC. 2018. The National Academies Press. (Link)
27. Murray RP, et al. Does nicotine replacement therapy cause cancer? Evidence from the Lung Health Study. *Nicotine & Tobacco Research.* 2009;11: 1076 – 1082. (Link)
28. Tønnesen P. Smoking cessation and COPD. *European Respiratory Review.* 2013;22:37-43. (Link)
29. Tobacco Advisory Group of the Royal College of Physicians. Harm reduction for nicotine addiction. 2007. Royal College of Physicians, London.

different look at this?" [30] That's according to Mitch Zeller, director of the U.S. FDA's Center for Tobacco Products back in 2014.

The Royal College of Physicians have said: *"Nicotine is not, however, in itself a highly hazardous drug ... it is inherently unlikely that nicotine inhalation itself contributes significantly to the mortality or morbidity caused by smoking. The main culprit is smoke and, if nicotine could be delivered effectively and acceptably to smokers without smoke, most if not all of the harm of smoking could probably be avoided."* [31]

We agree that the burning of tobacco, not the nicotine, is the biggest problem with cigarettes. This is why we develop and research a portfolio of smoke-free nicotine-containing products that are a better choice for adult smokers than continuing to smoke cigarettes. Independent studies have shown how important it is to make better alternatives like these available to adult smokers who would otherwise continue to smoke.[32,33,34]

Among the leaders of public change are public health organizations and regulatory bodies, whose opinions and decisions affect everyone involved. Many of these leaders agree that tobacco harm reduction is the right route to take. However, opinions still vary about what role alternative products should play in tobacco harm reduction.

Institutes like Public Health England (PHE)[35] and the U.S. FDA[36] see the potential of nicotine-containing products as smoking alternatives. For example, PHE states that *"e-cigarettes could be contributing to at least 20,000 successful new quits per year and possibly many more".*[37] However, regions like Australia carry heavier restrictions on nicotine. Under Australian Commonwealth law, nicotine-containing products are categorized as prescription-only (with nicotine patches, gums, or sprays as exceptions) or dangerous poisons (with the exception of its use in therapeutics or cigarettes).

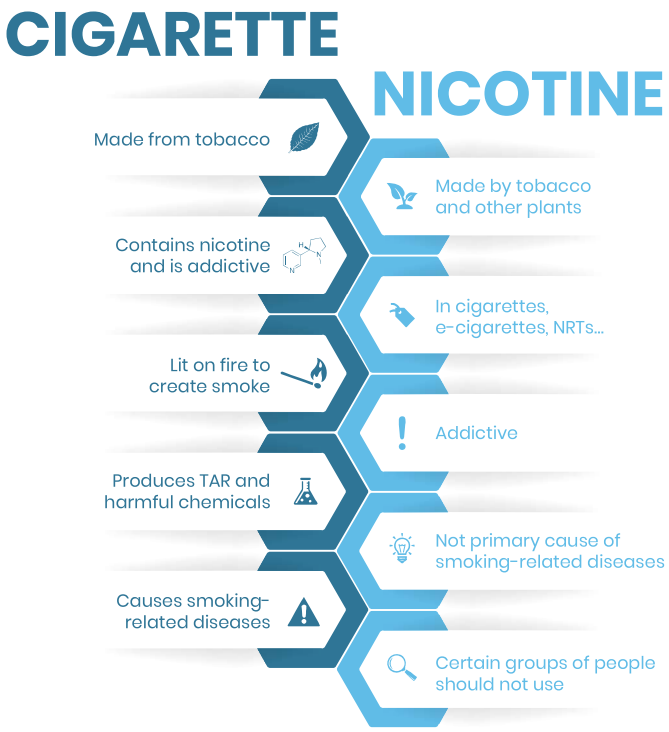
PHE also weighs in on the public awareness of nicotine, saying *"there is much public misunderstanding about nicotine (less than 10% of adults understand that most of the harms to health from smoking are not caused by nicotine)".*[38]

WHAT DO PEOPLE THINK?

People deserve accurate and non-misleading information in order to be able to make an informed decision. And choices like these add up to affect public health outcomes. This is one of the reasons why it is so important to combat public misperceptions about nicotine.

Many people still mistakenly believe that nicotine is a major cause of tobacco-related diseases. A literature review of 54 studies has shown that peoples' assumptions about nicotine vary, and are often wrong.[38] According to another review, these incorrect assumptions could alter the outcome or even the validity of smoking cessation trials.[39]

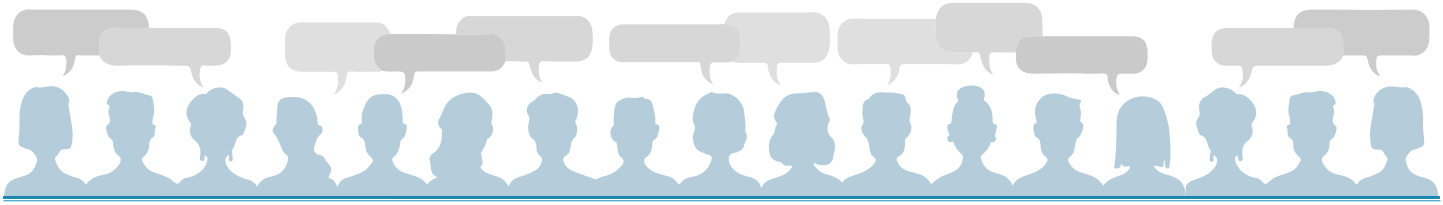
Since up to 73 percent of people mistakenly believe nicotine causes cancer according to a U.S. population study,[40] it is important to educate the public about nicotine and nicotine-containing products.



CONCLUSIONS

Clearly, it is important for people to have a balanced perspective on nicotine. On one hand, products containing nicotine should not be used by certain groups of people.[41] On the other hand, nicotine can support public health by encouraging smokers who would not otherwise quit to switch to smoke-free products.

It's time to decouple the discussions about nicotine from those on the dangers of smoking cigarettes. There is already plenty of information worth sharing about nicotine, and we look forward to seeing what new additions are made to the body of research that already exists on nicotine.



30. Zeller, M., Director of US FDA's Center for Tobacco Products; Presentation at Legacy Foundation, 11 June 2014. (Link)
31. Royal College of Physicians, Nicotine without smoke: Tobacco harm reduction, 2016. (Link)
32. Abrams, DB. Managing nicotine without smoke to save lives now: Evidence for harm minimization. *Preventive Medicine.* 2018;117:88-97. (Link)
33. Nitzkin, JL. et al. The case in favor of e-cigarettes for tobacco harm reduction. *International Journal of Environmental Research and Public Health.* 2014;11(6):6459-6471. (Link)
34. Levy, DT. A framework for evaluating the public health impact of e-cigarettes and other vaporized nicotine products. *Addiction Debate.* 2016;112(1):8-17. (Link)
35. Public Health England. PHE publishes independent expert e-cigarettes evidence review. 2018. (Link)
36. U.S. FDA. Statement from FDA Commissioner Scott Gottlieb, M.D., on actions to advance our comprehensive plan to reduce tobacco-related disease and death, through new efforts to improve the tobacco product application review process, including a newly proposed rule. 2019. (Link)
37. Public Health England. PHE publishes independent expert e-cigarettes evidence review. 2018. (Link)
38. Czoli, CD. et al. How do consumers perceive differences in risk across nicotine products? A review of relative risk perceptions across smokeless tobacco, e-cigarettes, nicotine replacement therapy and combustible cigarettes. *Tobacco Control.* 2017;26:e49-e58. (Link)
39. Schlagintweit, HE. et al. Non-pharmacological considerations in human research of nicotine and tobacco effects: A review. *Nicotine & Tobacco Research* 2019; [Epub ahead of print]. (Link)
40. O'Brien, EK. et al. U.S. adults' addiction and harm beliefs about nicotine and low nicotine cigarettes. *Preventative Medicine.* 2017;96:94-100. (Link)
41. Nicotine-containing products should not be used by people who have or are at risk of heart disease, are diabetic, are epileptic, or are experiencing seizures. Nicotine-containing products should not be used during pregnancy or while breast-feeding.

LATEST EVENTS & OTHER MILESTONES

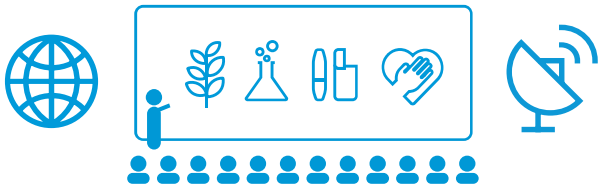
"It's time to talk about nicotine"

6TH GLOBAL FORUM ON NICOTINE (GFN)

Warsaw, Poland
13-15 June 2019

The Global Forum on Nicotine welcomes scientists, politicians, policy advocates, industry representatives and nicotine consumers and advocates to an annual public discussion on nicotine, and the role that alternative nicotine products can play to help people switch from smoking. Sessions of the conference for this year focused on topics including emerging science on nicotine, focusing on the needs of adult nicotine users, international perspectives on tobacco harm reduction, the regulation of nicotine, evidence on real world use of e-cigarettes, and much more.

More than 600 participants attended the conference this year, which also includes several satellite events. For example, one workshop introduced non-experts to computational modeling of tobacco product impacts on population health, including trainers from both academia and industry, open to all GFN attendees. ISoNTech, which stands for International Symposium on Nicotine Technology, was on June 13. This satellite symposium invites developers, manufacturers, and distributors to demonstrate their products and discuss their design and development. Our own Dr. Gizelle Baker, Director Scientific Engagement, presented the story of EHTS as part of this symposium. Other satellite events included a film festival, networking, and open discussion meetings.



We also presented three posters as part of GFN. Our poster describing our population health impact model web application was presented by Dr. Smilja Djurdjevic, Sr. Scientist – Population Modeling. The application supports exploratory research beyond that conducted by PMI, and it allows for more complete reporting of health impact modeling generated outcomes. Dr. Loyse Felber Medlin, Clinical Scientist, presented a poster on the results of our 1-year smoking cessation study, which provides clear data on how certain biological responses change favorably after a person quits smoking cigarettes. Results from the first year and a half of our repeated cross-sectional survey in Japan were presented in a poster by Dr. Baker.

Learn more about our presence at GFN on PMIScience.com

U.S. FDA ANNOUNCES DECISION ON PMTA: AUTHORIZATION TO SELL GRANTED

Washington, USA
30 April 2019

The U.S. FDA announced on April 30 that it permits the sale of EHTS, which will be marketed in the U.S. as *IQOS* by Altria Group, Inc. This landmark ruling follows a comprehensive and rigorous two-year assessment of the science in our Premarket Tobacco Product Application. The FDA's scientific evaluation included a review of the data in our application, peer-reviewed published literature, and other sources. The FDA's news release further explained that "the agency determined that authorizing these products for the U.S. market is appropriate for the protection of public health because, among several key considerations, the products produce fewer or lower levels of some toxins than combustible cigarettes."

The FDA also stated that the nicotine levels in EHTS aerosol may help smokers make a full transition away from cigarettes, and that few non-tobacco users would likely choose to start to use EHTS including youth. A parallel application for EHTS to be categorized as a "Modified Risk Tobacco Product" is still under review.

55TH CONGRESS OF THE EUROPEAN SOCIETIES OF TOXICOLOGY (EUROTOX)

Helsinki, Finland
8-11 September 2019

Eurotox is a federation of more than 40 European societies of toxicology, representing 7,500 European toxicologists, with approximately 1,500 participants. The theme of this year's congress was "Toxicology – Science Providing Solutions". The congress program included a wide range of toxicology topics dealing with new and emerging technologies, personalized medicine, and epidemiology of exposure to chemicals. PMIScience also attended the conference and reported on the wide range of toxicology topics in two articles: "Connecting the dots: conclusions across studies" and "The toxicological crystal ball".

At Eurotox, Dr. Stephanie Boué, Manager Scientific Transparency and Verification, presented a new meta-analysis of in vitro toxicology assessments of diverse smoke-free products on the INTERVALS platform. Dr. David Bovard presented his research on the characterization of a human liver spheroid model, and Dr. Filippo Zanetti presented his research that showed that our platform 3 e-cigarette *MESH* causes less biological alterations than cigarette smoke in buccal organotypic cell cultures.

RESPIRATORY DRUG DELIVERY EUROPE (RDD)

Lisbon, Portugal
7-10 May 2019

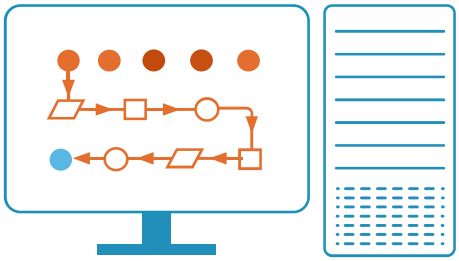
The Respiratory Drug Delivery conference in Europe is one of a series of academically organized international symposia focusing on the development and commercialization of pulmonary and nasal pharmaceutical products. The meetings are organized in partnership with academic institutions, professional organizations, and representatives from companies active in the nasal and pulmonary areas. PMI researchers presented two posters at this year's conference.

Dr. Mahdi Asgari, Postdoctoral Fellow, presented our results on the aerosol evolution and deposition in the human upper respiratory tract. This includes the creation of a computer-aided design of a 3D printed cast based on models of the human upper respiratory tract. This work was selected as one of five posters to be specially presented at the "Posters on the Podium" session. Dr. Sandro Steiner, Scientist – Cellular Labs, presented preliminary work to characterize a Vitrocell® system and its application in exposures to aerosolized Bortezomib and Ibuprofen.

A NEW SBV IMPROVER CHALLENGE: Efforts to Design AI Tools for Diagnosis

August 2019

Last year's successful sbv IMPROVER - Microbiota Composition Prediction challenge aimed at evaluating computational methodologies for their ability to predict microbiome composition. This year brings the Metagenomics for Inflammatory Bowel Disease Diagnosis challenge. Open from August 2019 through January 15 2020, the challenge addresses fundamental questions regarding the function and composition of the gut microbiome. It aims at investigating the diagnostic potential of metagenomics data to discriminate patients with inflammatory bowel diseases (IBD) – including Ulcerative Colitis and Crohn's Disease – from non-IBD subjects. These diseases can present with similar symptoms, requiring invasive tests to diagnose properly.



The challenge brings together for the first time two large, publicly available datasets, which participants will use for training their machine learning algorithms, and a third PMI dataset, obtained from an independent study, which will be used for testing the algorithms. The participants will evaluate whether metagenomics data collected from stool samples are sufficiently informative to be leveraged as a diagnostic tool for IBD, and determine which computational methods are best suited for this task. The outcome of the challenge will represent a step forward to providing healthcare professionals with tools based on Artificial Intelligence. These tools can help medical professionals to improve patients' treatment options by speeding up the diagnosis, replacing invasive medical procedures, and lowering the costs in the healthcare system.

Click here to find out more and join the challenge.

INDEPENDENT RESEARCH ON SMOKE-FREE PRODUCTS

STUDY PARTICIPANTS' BELIEFS ABOUT NICOTINE AFFECT RESEARCH RESULTS

A recent review article found that something similar to the placebo effect is happening in nicotine research: people's beliefs about nicotine and tobacco effects impact their subjective responses to the test products.[42] The authors state: *"Many smokers do not understand or are misinformed about nicotine and tobacco effects. In fact, a substantial proportion of smokers endorse beliefs that nicotine causes cancer, that longterm nicotine replacement therapy use is harmful, and that nicotine replacement therapy is ineffective in facilitating smoking cessation."* To these points, the facts are that nicotine is not a primary cause of cancer, longterm nicotine replacement therapy is not generally recognized as harmful, and using NRT can increase the likelihood that a given quit attempt will be successful.[43]

These differing beliefs mean that subjective self-reported effects of nicotine or tobacco products may not accurately reflect the true biological effects on the subjects. Most studies don't control or even consider this effect, which could compromise the study validity and applicability to real-life scenarios.

Outside of the research setting, we feel this also highlights the importance of providing accurate and non-misleading information to people, so they are equipped to make the best choices for themselves about nicotine and tobacco use.

INDEPENDENT CLINICAL STUDY: HEATED TOBACCO AND VAPING ARE BETTER CHOICES THAN CIGARETTES

Preliminary research published in March in the Journal of the American Heart Association found that using heated tobacco products and e-cigarettes causes less acute effects on several medical tests compared to smoking cigarettes.[44] This study included 20 smokers who each used all three types of products at some point during the study.

Use of any of the three products had some effect on the medical tests compared to the participants' baseline, but cigarette use caused more detrimental results than either heated tobacco or vaping products. Heated tobacco products were shown to have the lowest effect on oxidative stress and the lowest effect on blood pressure of the three. They also appeared to be more satisfying to current smokers than electronic cigarettes. This research highlights the fact that not all smoke-free products are the same, but both e-cigarettes and heated tobacco products tested in this study are better choices than cigarettes.

INTEREST IN HEATED TOBACCO GREATEST AMONG CURRENT ADULT SMOKERS

Researchers from Hong Kong conducted a survey to determine awareness and interest in heated tobacco products in Hong Kong, which has among the lowest smoking rates in the developed world and where no heated tobacco products are formally marketed.[45] In this telephone survey conducted in 2017, just over 5,000 adult respondents were asked questions about their awareness of heated tobacco products, their smoking status, and their sociodemographic characteristics. The answers given by respondents were then weighted according to the sociodemographic of the population of Hong Kong to yield the values given in the results.

The study found that, overall, 11.3% of people in Hong Kong are likely aware of heated tobacco products, with higher awareness among current smokers (27.2%). Ever use of heated tobacco products was weighted to about 1.0% of the population in Hong Kong, with higher prevalence among current smokers (8.9%) than among ex-smokers (0.6%) or never smokers (0.05%). Respondents of higher academic attainment and monthly household income were also more likely to have tried heated tobacco products.

HOW VAPING VIEWS DIFFER BETWEEN COUNTRIES

Researching the perception of e-cigarettes across different demographics and countries could provide a glimpse into how tobacco control policies can affect acceptance of these products, as well as affecting access to information about them. A cross-sectional study looked into beliefs about e-cigarettes to find out if these variations do exist across countries, smoking status, and vaping status.[46] Two main perceptions were studied: beliefs about the behavior of people using e-cigarettes, and beliefs about whether NVPs are socially acceptable.

Using data from a 2006 International Tobacco Control Survey, the researchers analyzed 10,900 individuals from Australia, Canada, England, and the U.S, including participants with varying smoking and vaping habits. Diving into that large dataset helped them discover that vaping norms do change across countries and led them to propose reasons for those variations.

The most positive perceptions about NVP were found in England, followed by Canada and the U.S., and then Australia. The researchers found that higher e-cigarette prevalence correlated with more positive perceptions about the product. People from England were 20 times more likely to be frequently exposed to e-cigarettes in public than Australian participants. They also suggested that less restrictive regulatory environments (such as England, in this study) may lead to more opportunities for e-cigarettes use.

70+
INDEPENDENT PUBLICATIONS
ON PLATFORM 1

MANY BRANCH OUT TO
ANSWER NEW QUESTIONS

MOST INDEPENDENT RESEARCH FOCUSES ON **SMALL-SCALE CLINICAL STUDIES** AND **AEROSOL CHEMISTRY AND PHYSICS**

42. Schlagintweit, H. E. et al. Non-pharmacological considerations in human research of nicotine and tobacco effects: a Review. *Nicotine & Tobacco Research.* 2019. Accepted Manuscript. (Link)
43. Cochrane.org "Can nicotine replacement therapy (NRT) help people quit smoking?" (Link)
44. Biondi-Zoccai, G. et al. Acute effects of heat-not-burn, electronic vaping, and traditional tobacco combustion cigarettes: The Sapienza University of Rome-Vascular Assessment of Proatherosclerotic Effects of Smoking (SUR-VAPES) 2 Randomized Trial. *Journal of the American Heart Association.* 2019;8(6):e010455. (Link)
45. Wu, Y.S. et al. Heated tobacco products use in Chinese adults in Hong Kong: a population-based cross-sectional study. *Tobacco Control.* 2019. Online First. (Link)
46. Aleyan, S. et al. Differences in norms towards the use of nicotine vaping products among adult smokers, former smokers and nicotine vaping product users: Cross-sectional findings from the 2016 ITC Four Country Smoking and Vaping Survey. *Addiction.* 2019 [Epub ahead of print]. (Link)

PMI'S PEER-REVIEWED PUBLICATION HIGHLIGHTS

NEW PROTOCOLS DEVELOPED TO DETECT SPECIFIC GENES IN MULTIPLE 3D CELL CULTURES

PMI researchers have developed new protocols for the RNAscope®, an RNA (ribonucleic acid) imaging technology created by Advanced Cell Diagnostics. Until now, the RNAscope has not been used to study three-dimensional (3D) cell cultures, which are among the latest advances in cell culture technology. These protocols allow for the detection of specific genes in various human cell culture models that are organotypic, meaning they retain the 3D structure of native tissues. Tissues tested include small airway, nasal, and gingival cell cultures.

Because these are 3D cell cultures, it's key to prepare the tissues for imaging in a way that does not destroy their complex structure while allowing them to be cut into cross sections for viewing. This publication provides guidelines on optimal methods of cell preparation, staining, and handling for imaging with this technique. Further, these protocols widen the range of experiments that can be done with human cell cultures rather than animal research, improving scientists' ability to implement the 3Rs: replace, reduce, and refine animal testing.

Find more details on PMIScience.com.[47]

INDEPENDENT PANELS OF EXPERTS REVIEW PMI RESEARCH

The peer-review process is a key part of the validation of scientific results and feeds into regulatory decision making. In addition to the typical scientific peer-review process, we sponsored a two-tier peer review to gather a wider and more in-depth independent assessment of several non-clinical and clinical studies on EHTS.[48] Reviewers were generally supportive or very supportive of the study methods and results, and they support the robustness of the studies and validity of the conclusions.

In tier one, several independent panels of experts were gathered by SciPinion LLC and given access to the publications and associated data. These experts then answered questions about the design, methods, quality of data, and interpretation of results in a report, which they then discussed in an online, anonymized debate. In tier two, an additional panel of experts reviewed the Tier 1 process.

All reviewers from both tiers were given ample time to conduct their review and compensated for their time. Reviewers were selected by SciPinion LLC and remained anonymous to one another and to us. Reviewers were not told beforehand the research was conducted by PMI though they likely came to this conclusion while reading and reviewing the material.

Learn more about this study on PMIScience.com.[49]

A SIMPLE BLOOD TEST COULD TELL SMOKERS FROM NONSMOKERS

It would be easier to draw conclusions from the clinical assessment of smoke-free products, continued smoking, and cessation if there were a simple way to measure whether the participants correctly followed their assigned roles. Toward that goal, this research combined the results of four earlier clinical studies to identify a blood test that can distinguish between smokers and those who have quit smoking or switched to a smoke-free product.

Published in the Predictive Toxicology section in the journal Frontiers in Pharmacology, this work considered the levels of smoke exposure response signatures on just 11 genes drawn from the blood samples of the participants. Three groups of participants were involved in those clinical studies: people who switched from cigarettes to EHTS, those who had continued to smoke, and those who abstained from smoking. They stayed at the clinic for 5 days using their assigned product, and in two of the studies participants returned home to their normal lives for a further 85 days as the ambulatory phase of the study.

In all four studies the signature scores were consistently reduced in those who either stopped smoking or switched to EHTS compared with those who continued to smoke. In fact, the team found that the participants of the smoking abstinence arm had higher variability in signature scores during the ambulatory period, indicating that some participants may not have been compliant with their assigned role.

You can find this paper on PMIScience.com.[50]

IN THE RESEARCH LITERATURE, EHTS IS REFERRED TO AS TOBACCO HEATING SYSTEM (THS OR THS 2.2)

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50. Martin, F. et al. A meta-analysis of the performance of a blood-based exposure response gene signature across clinical studies on the Tobacco Heating System 2.2 (THS 2.2). *Frontiers in Pharmacology.* 2019;10(198):1-11.

EHTS DOESN'T NEGATIVELY AFFECT RESIDENTIAL AIR QUALITY

While a growing number of smokers are switching to smoke-free products such as EHTS, few studies have looked at how the aerosol emissions from these devices affect indoor air quality. We have previously shown that EHTS does not negatively impact indoor air quality, including under residential conditions.[51] This new study measures the impact of EHTS on air quality while simulating a residential building with natural air ventilation. Cigarette smoke's impact on air quality was used as a comparison.

It is well established that environmental tobacco smoke (ETS or secondhand smoke) contributes to air pollution. In contrast, the study found that only three chemicals nicotine, acetaldehyde, and glycerin were above background levels in the air, following EHTS use. The amounts detected were still below harmful levels, as defined by the relevant indoor air quality guidelines. The study therefore concluded that the use of EHTS in an adequately ventilated environment does not negatively affect indoor air quality.

Learn more about this study on PMIScience.com.[52]

HOW DO E-CIGARETTES COMPARE TO KNOWN TOOTH-STAINING FOOD AND DRINKS?

The reduced tooth staining effects of Platform 1 have been previously studied, showing significantly less tooth discoloration effects compared to cigarette smoke. In this study, our platform 3 e-cigarette *MESH* was compared against cigarette smoke as well as coffee, red wine, and soy sauce. 70 human teeth extracted for orthodontic reasons were collected and cavities were created and filled with a dental restoration resin. The teeth were split into exposure groups and exposed for 56 minutes a day to their assigned food, beverage, or cigarettes, or to 75 minutes of exposure to *MESH* aerosol for 15 days.

At baseline and every 5 days, the teeth were brushed with toothpaste and assessed for color. Ten teeth from each exposure group were also whitened using a commercial tooth whitening kit. Red wine caused the greatest discoloration, followed by cigarette smoke, soy sauce, and coffee, and finally *MESH* affected the color least. Of the four exposure groups, only the *MESH* exposure group showed no mismatch between the tooth and discoloration. With whitening treatments, only the *MESH* exposure group regained their original colors completely without multiple treatments of the higher strength kit.

You can find more details about this and related research on PMIScience.com.[53]

MAN-MADE MICROVESSELS ON A CHIP

Rodent studies are often used to study atherogenesis, which is the formation of fatty deposits in the arteries. In this research, we developed a 3D model of microscale blood vessels on a chip to replace rodent studies of atherogenesis. The microvessels were created by filling the channels of a commercial 96-chip OrganoPlate with a matrix of collagen. Endothelial cells then attached themselves to the inside of the matrix. Just as in the human body, the endothelial cells formed a one-layer thick barrier between the inside of the blood vessel and the surrounding area. Blood flow was simulated by filling the microvessels with a solution to mimic blood, and then gently rocked back and forth. With this system, we can measure how many white blood cells sticks to the inside of the blood vessels, and to see other molecular changes to the vessels themselves indicating for example inflammation and oxidative stress.

This study is available on PMIScience.com,[54] **as well as additional information about our organ-on-a-chip research.**

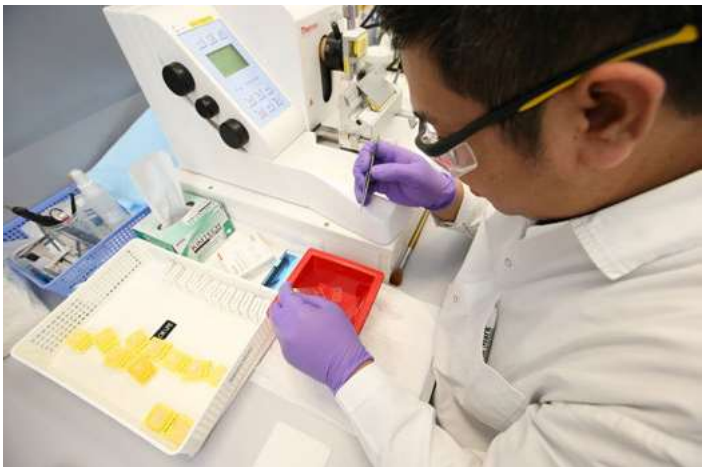
SWEDEN'S SNUS HISTORY HELPS MODEL PUBLIC HEALTH IMPACT FOR SMOKE-FREE PRODUCTS

PMI has previously developed the Population Health Impact Model, or PHIM, a model that estimates the reduction in the number of smoking-related deaths that could result from the introduction of smoke-free products. In this study, the PHIM was applied to estimate the effects of snus use on four diseases: COPD, lung cancer, ischemic heart disease, and stroke. Three hypothetical scenarios or "approaches" were created using available data on smoking prevalence and snus use.

Approach 1 compares mortality in Sweden across the selected data set. Approaches 2 and 3 both compare hypothetical mortality in Sweden across the selected data set with the hypothetical mortality if snus users had never smoked, with approach 2 disregarding history and approach 3 using our Public Health Impact Model or PHIM.

Our scientists found that the PHIM simulation provided a reasonable approximation of the available data that was used in approach 2 of the study.

Find out more about the differences between these approaches on PMIScience.com.[55]



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53. Zhao, X. et al. Effects of different discoloration challenges and whitening treatments on dental hard tissues and composite resin restorations. *Journal of Dentistry.* 2019;89:103182.
54. Poussin, C. et al. 3D human microvessel-on-a-chip model for studying monocyte-to-endothelium adhesion under flow – application in systems toxicology. *ALTEX.* 2019. Accepted.
55. Djurdjevic, S. et al. Using data on snus use in Sweden to compare different modelling approaches to estimate the population health impact of introducing a smoke-free tobacco product. *BMC Public Health.* 2019; Accepted.

GLOSSARY

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 it contains many gases, water and water-soluble constituents, and 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.

BIOMARKERS
Biomarkers can be classified into *biomarkers of exposure* and *clinical risk markers.*
- *Biomarkers of exposure:* indicate exposure to a potentially hazardous substance. In our case, the biomarker may be a cigarette smoke constituent or metabolite that is measured in a biological fluid or tissue. Biomarkers of exposure can provide a measure of internal dose, which is the amount of the constituent taken up into the body.
- *Clinical risk markers:* a measurable change in biochemical, physiological (organs, tissues, cells), or behavioral function within an organism that is known to be associated with a health impairment or disease. These biomarkers indicate the body's response to exposure to harmful chemicals. While clinical risk markers do not necessarily cause these health concerns, their presence and magnitude help identify whether a person already has or is in danger of developing a health impairment or disease.
- *Clinical risk endpoints:* clinical risk markers that have been selected for measure in a clinical study.

CLINICAL RISK MARKERS OR ENDPOINTS
See Biomarkers.

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

EXPOSURE RESPONSE STUDY
Designed to assess whether switching to a smoke-free product leads to favorable changes in clinical risk markers that are benchmarked to smoking cessation. This is a longer-term study (six months + a six month extension) conducted with adults who smoke.

MODIFIED RISK TOBACCO PRODUCT (MRTP)
The U.S. Family Smoking Prevention and Tobacco Control Act (2009) granted to the FDA authority to regulate tobacco products. MRTP is defined in that Statute as *"any tobacco product that is sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products."*

NICOTINE
A chemical compound that is produced by tobacco and other plants. When inhaled, ingested, or absorbed through the skin, nicotine enters the bloodstream and is transported to all organs including the brain, enhancing or interfering with cellular signaling processes. Nicotine is addictive and not risk-free, but is not the primary cause of smoking related diseases. It serves an important role in encouraging adult smokers to switch from cigarettes to better alternatives.

PHARMACOKINETIC STUDIES
These studies measure how a substance, such as nicotine, is absorbed, distributed, and processed by the body. This helps in determining the extent to which adults who smoke would find the alternative product an acceptable substitute for cigarettes, although other factors, such as taste and product design, are important elements in determining consumer acceptability. In addition to the kinetic profile of nicotine, we also monitor the safety of the users of the product under investigation (e.g., data on vital signs, clinical biochemistry, and adverse events).

REDUCED-RISK PRODUCT (RRP)
The term PMI uses to refer to products that present, are likely to present, or have the potential to present less risk of harm to smokers who switch to these products versus continued smoking. We have a range of RRPs in various stages of development, scientific assessment and commercialization. Our RRPs are smoke-free products that produce an aerosol that contains far lower quantities of harmful and potentially harmful constituents than found in cigarette smoke.

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.

STANDARD TOXICOLOGY
To compare whether the reduction in the levels of harmful and potentially harmful chemicals generated by our smoke-free products reduces the toxicity of their aerosol, we perform a range of standard toxicological assays. For example, we have conducted a number of widely used *in vitro* assays comparing the toxicity of our smoke-free products' aerosol to cigarette smoke.

These include, but are not limited to:
- The Neutral Red Uptake cytotoxicity assay (measuring mammalian cell toxicity)
- The Ames bacterial mutagenicity assay (measuring bacteria cell mutations)
- The Mouse Lymphoma mammalian mutagenicity assay (measuring mutations in mammalian cells)

We have also conducted *in vivo* assays of different durations, including acute and repeated dose inhalation studies in accordance with Organization for Economic Co-operation and Development (OECD) Test Guidelines.

SYSTEMS TOXICOLOGY
Systems toxicology integrates standard toxicology with advanced experimental and computational methods (including large-scale molecular measurements, imaging technologies, mathematical modeling and computational biology) to identify the biological mechanisms triggered by exposure to toxic substances and quantify their biological impact.

One example of a systems toxicology approach is to use organotypic tissues: tissue samples which behave as if they were in the body. These tissues can make the results more complex and difficult to interpret but also more relevant to effects on the human body compared to standard toxicology methods.

PMI'S PEER-REVIEWED PUBLICATIONS ON SMOKE-FREE PRODUCTS: 2019 TO-DATE

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