SCIENTIFIC UPDATE

PMI SCIENCE – PHILIP MORRIS INTERNATIONAL

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Science under Scrutiny

NAVIGATING EVIDENCE, UNCERTAINTY, AND REAL-WORLD OUTCOMES



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Rigor, Bias, and the Limits of Certainty: Reflections from PMI's Chief Medical Officer

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Addressing the Global Burden of Smoking

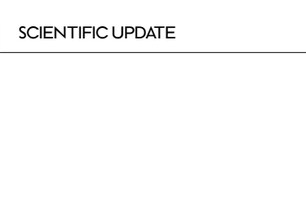
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Sweden: A Real-World Case Study in Smoking Decline and Adult Substitution

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INTRODUCTION

Smoking remains one of the leading causes of preventable disease worldwide, driven largely by chronic exposure to toxicants generated through tobacco combustion. While complete cessation offers the greatest health benefit, many adults continue to smoke despite access to quitting support and treatment. As a result, the potential role of smoke-free alternatives in reducing smoking-related harm is closely examined and actively debated.

This issue addresses the challenges of generating and interpreting evidence in a highly scrutinized field. In an interview with the Chief Medical Officer of Philip Morris International (PMI), these challenges are explored further, including how scientific rigor, bias, and uncertainty are acknowledged and managed in practice.

We also highlight several recent additions to PMI's scientific evidence base across smoke-free product categories. The update opens with a broader look at the global burden of smoking and the rationale for approaches that complement prevention and cessation, including consideration of Sweden as a real-world example where smoking has declined alongside long-standing adult use of noncombusted oral nicotine and tobacco products. It then brings together our research across heated tobacco, e-vapor, and oral smokeless product categories, examined through toxicological, clinical, and epidemiological lenses. Together, they highlight areas of consistency, important limitations, and ongoing uncertainty, reinforcing why product-specific assessment remains essential.

We invite you to explore this issue and consider the evidence presented.



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RIGOR, BIAS, AND THE LIMITS OF CERTAINTY

REFLECTIONS FROM PMI'S CHIEF MEDICAL OFFICER



What does responsible science look like when certainty is elusive and evidence is contested? In this interview, the Chief Medical Officer of Philip Morris International (PMI) discusses rigor, bias, and decision-making across medicine, public health, and smoke-free product research.

Q1.

As Chief Medical Officer at PMI, how do you define your role at the intersection of medicine, science, and consumer products?

I see my role as an opportunity to contribute to a better understanding of the potential impact smoke-free products can have for individual consumers and for public health. It is a complex task, and we do it with a highly skilled team whose expertise extends beyond my own.

That evidence-focused role reflects what PMI is trying to achieve as a consumer company. In our industry, adult consumers seek products that provide certain values to them, and our aim is to offer a substitute for those values with a lower long-term price, i.e., the health consequences of continued cigarette smoking.

However, claims of reduced burden need substance behind them. From a medical standpoint, my team is not involved in developing products. We generate, evaluate, and deliver data to assess the risk reduction potential of our products, helping build robust evidence that withstands rigorous scrutiny.

Q2.

Your career spans clinical medicine, academic research, and industry. How has that shaped the way you think about evidence and public health today?

It's been shaped by a combination of experiences, from clinical medicine and academic research at the Karolinska Institutet in Sweden, to various roles in the pharmaceutical industry, then at Swedish Match, and now at PMI.

As a physician, I treated individuals by prescribing a drug to treat a disease they have. Over time, working in nicotine and tobacco science has strengthened my public-health perspective. I could see more clearly how lifestyle choices shape disease risk.

What helped me bring these perspectives together was my scientific training. It provides a common framework for asking questions, testing assumptions, and evaluating evidence, whether you're working in a hospital, academic research, or industry.

Q3.

What have your clinical experiences taught you about evaluating smoke-free products?

From my time as a physician, I am often reminded of an example from Sweden. When biological medicines began to be used more broadly, there was strong nonclinical evidence, but limited clinical experience in wider patient populations such as inflammation-related diseases. Early case reports of complications drew a lot of attention, raising the risk that isolated anecdotal observations could halt progress altogether.

To understand the bigger picture, my colleagues and I worked with gastroenterology clinics across Stockholm County, contacted other clinics prescribing treatments for inflammatory bowel disease, and collected follow-up data on the first 217 treated patients in the region. Looking at the totality of available evidence, a very different picture emerged, one which ultimately improved how the therapy was viewed and contributed to changes in treatment guidelines.

Working now in tobacco harm reduction, that experience emphasizes the importance of stepping back from isolated signals, looking at the total body of evidence, and working to reduce uncertainty over time.

Q4.

From a medical perspective, how should nicotine be understood when considered separately from smoking?

Smoking is associated with a significantly increased risk of serious diseases, with strong evidence of causality for several outcomes and, in some cases, evidence of dose-response relationships between the number of cigarettes smoked and disease risk.

We also know that cigarette smoke contains a multitude of harmful chemicals, largely generated by burning tobacco, as well as nicotine which is addictive and not risk free.

What has not been demonstrated is a clear link between nicotine itself and the smoking-related diseases we observe. For example, cardiovascular disease (CVD) is strongly linked to smoking, but we do not see a similar risk pattern in populations using oral tobacco products such as Swedish snus, despite comparable nicotine exposure. For respiratory disease, we also see no direct link to nicotine.

This does not mean nicotine is risk free. It means long-term disease risk from nicotine alone has not been defined or quantified based on the available evidence, and that is unlikely to change in the foreseeable future.

Q5.

How do you think about bias, both PMI's own and bias in the wider scientific and public health debate?

In my opinion, medical and public-health research is often funded because we want to improve lives and prevent or treat disease, so some degree of bias is unavoidable.

The important distinction is not whether bias exists, but whether the science is rigorous. If you apply fit-for-purpose methods, follow good scientific practice, and are transparent about how the work is done, the results are scientifically valid. In principle, independent researchers using the same methods should be able to arrive at the same results, regardless of the initial motivation.

I see a real problem when studies are both biased and methodologically weak. Those findings are harder to replicate, and the conclusions can go beyond what the data actually show.

While rigor is nonnegotiable, bias should be acknowledged and managed, not denied.



Q6.

What responsibility comes with your role in a field as consequential and contested as tobacco harm reduction?

The responsibility ultimately comes down to scientific integrity and maintaining it regardless of who you are talking to. In science, there's always a risk that your study produces no results, or that results challenge your expectations, and it's my job to ensure this is accepted in the company.

Even more important is taking new evidence seriously, whether it's our own evidence or independent, and being prepared to adjust our position if new research calls for it. So far, I have not been challenged on these principles, which I take as a sign that scientific integrity is understood and supported across the organization.

Ultimately, in tobacco harm reduction, if rigorous and transparent science is allowed to speak over time, then history will tell us whether our approach truly contributes to reducing the harm caused by smoking. And on that, I'm confident it does.

ADDRESSING THE GLOBAL BURDEN OF SMOKING



Smoking is a leading cause of preventable disease, raising the question of whether traditional tobacco control measures like prevention and cessation could be complemented by other strategies to benefit public health.

In this article

01.

SMOKING-RELATED DISEASE BURDEN



02.

CESSATION IS THE BEST OPTION—YET IT IS NOT ACHIEVED AT SCALE



03.

WHAT TOBACCO HARM REDUCTION MEANS



04.

POPULATION IMPACT: WHY PRODUCT-LEVEL SUBSTANTIATION MATTERS



SMOKING-RELATED DISEASE BURDEN

Beyond its contribution to overall mortality, smoking affects multiple organ systems.

Cigarette smoking remains a major driver of preventable disease and death worldwide.

A Global Burden of Disease (GBD) analysis estimated 7.69 million deaths globally attributable to combustible tobacco use in 2019. They also estimated that ischemic heart disease (IHD), chronic obstructive pulmonary disease (COPD), stroke, and tracheal, bronchus, and lung cancer accounted for 72% of smoking-attributable mortality.

Beyond its contribution to mortality, smoking exerts systemic effects across multiple organ systems, contributing to both fatal and nonfatal cardiovascular, respiratory, and oncologic conditions and driving a substantial share of the global disease burden.

According to the U.S. Centers for Disease Control and Prevention (CDC), cigarette smoke contains over 60 established carcinogens, including polycyclic aromatic hydrocarbons (PAHs), tobacco-specific nitrosamines (TSNAs), aromatic amines, and volatile compounds. These agents can form DNA adducts, promote mutations, and disrupt cellular processes linked to cancer development. Other toxicants contribute to cardiovascular disease (CVD) by acting on the vascular endothelium, altering lipid metabolism, and promoting blood clotting. Several smoke constituents are also harmful to lung function, driving inflammation, oxidative stress, and damage to airway defenses associated with bronchitis and COPD (including emphysema), while also worsening asthma.



ESTIMATED



MILLION DEATHS
IS ATTRIBUTED TO COMBUSTIBLE TOBACCO USE[1]

SYSTEMIC EFFECTS OF SMOKING

CARDIOVASCULAR SYSTEM

- Cardiovascular disease (CVD)
- Ischemic heart disease (IHD)
- Stroke

Some toxicants contribute to CVD by altering lipid metabolism and promoting blood clotting.

RESPIRATORY SYSTEM

- Chronic obstructive pulmonary disease (COPD), including emphysema
- Bronchitis
- Asthma
- Tracheal and lower respiratory infections
- Lung cancer

Some smoke constituents harm lung function, driving inflammation, oxidative stress, and damage to airway defenses.

ONCOLOGIC EFFECTS

- Cancer development

Carcinogens in cigarette smoke can form DNA adducts, promote mutations, and disrupt cellular processes linked to cancer development.

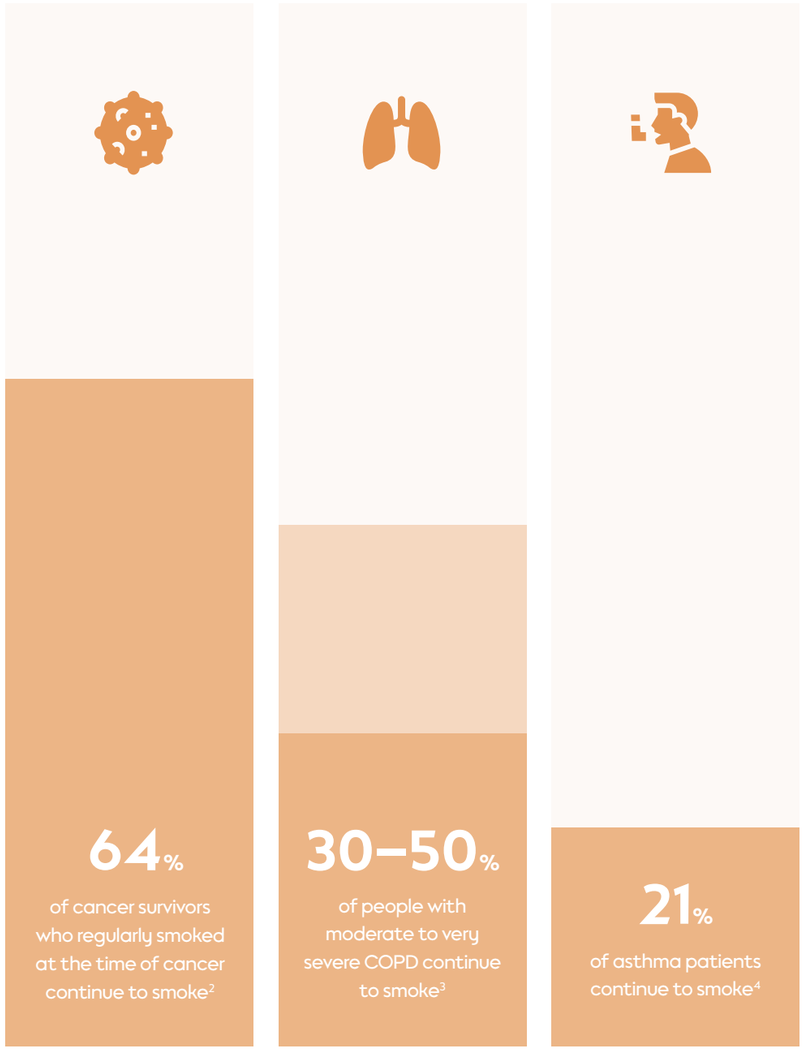
Source: 1) Global Burden of Disease 2019 Tobacco Collaborators. 2021. Lancet 397(10292), 2337-2360.

CESSATION IS THE BEST OPTION

YET IT IS NOT ACHIEVED AT SCALE

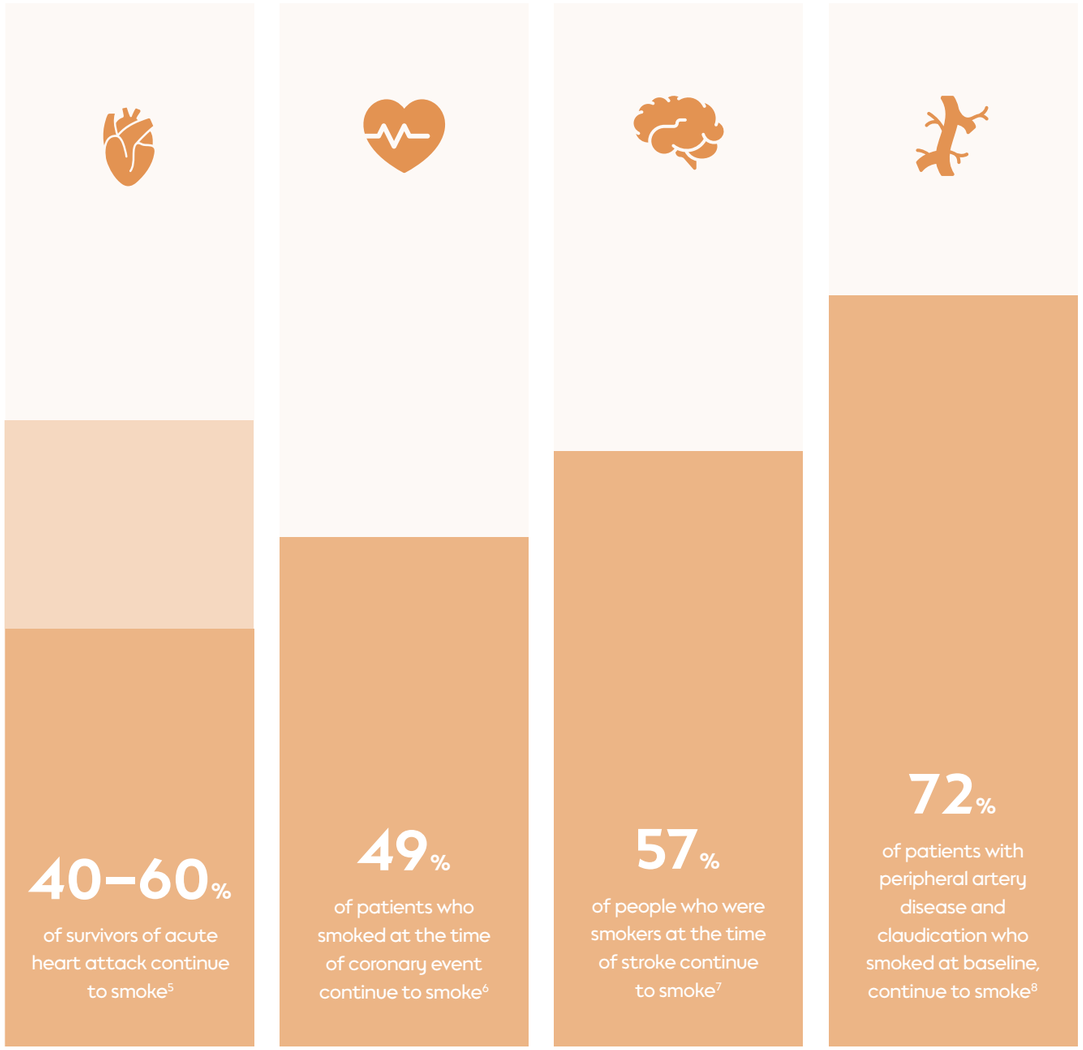
Complete cessation of tobacco and nicotine use remains the best option for health.

However, long-term abstinence for many is difficult to reach in the real world. The World Health Organization (WHO) reports that 4% of quit attempts are successful without cessation assistance. Even after serious disease events, many adults continue to smoke. Studies across the U.S. and Europe show substantial persistence of smoking following cancer diagnosis, COPD exacerbations, heart attack, and stroke.



STATISTICS OF SMOKERS WHO CONTINUE TO SMOKE AFTER A DIAGNOSIS OR WORSENING OF THEIR CONDITION

This observation does not diminish the importance of cessation. Rather, it underscores the challenge faced by population-level strategies that rely solely on cessation while ignoring the potential impact that smoke-free alternatives could have on accelerating the end of smoking.



Sources: 2) Tseng et al. 2012. BMC Public Health 12, 784. 3) Tashkin. 2021. Intern. Emerg. Med. 16, 545-547. 4) U.S. Centers for Disease Control and Prevention. 2013. Percentage of people with asthma who smoke. (Accessed August 27, 2026) 5) Höpner et al. 2020. BMC Cardiovasc. Disord. 20, 384. 6) Kotseva et al. 2016. Eur. J. Prev. Cardiol. 23(6), 636-648. 7) Sauerbeck et al. 2005. J. Neurosci. Nurs. 37(6), 316-319. 8) Patel et al. 2018. J. Am. Heart Assoc. 7(20), e010076.

Disclaimer: Differences in study design, populations, and timeframes may limit direct comparisons.

WHAT TOBACCO HARM REDUCTION MEANS

Harm reduction is commonly defined as a practical approach to reducing negative health, social, or legal consequences associated with behaviors that are difficult to stop.

It is explicitly compatible with the principle that abstinence is not the only measure of success. Applied to smoking, harm reduction complements prevention and cessation by shifting adult smokers, who do not quit, away from the high risk of combustible products toward potentially lower-risk alternatives.

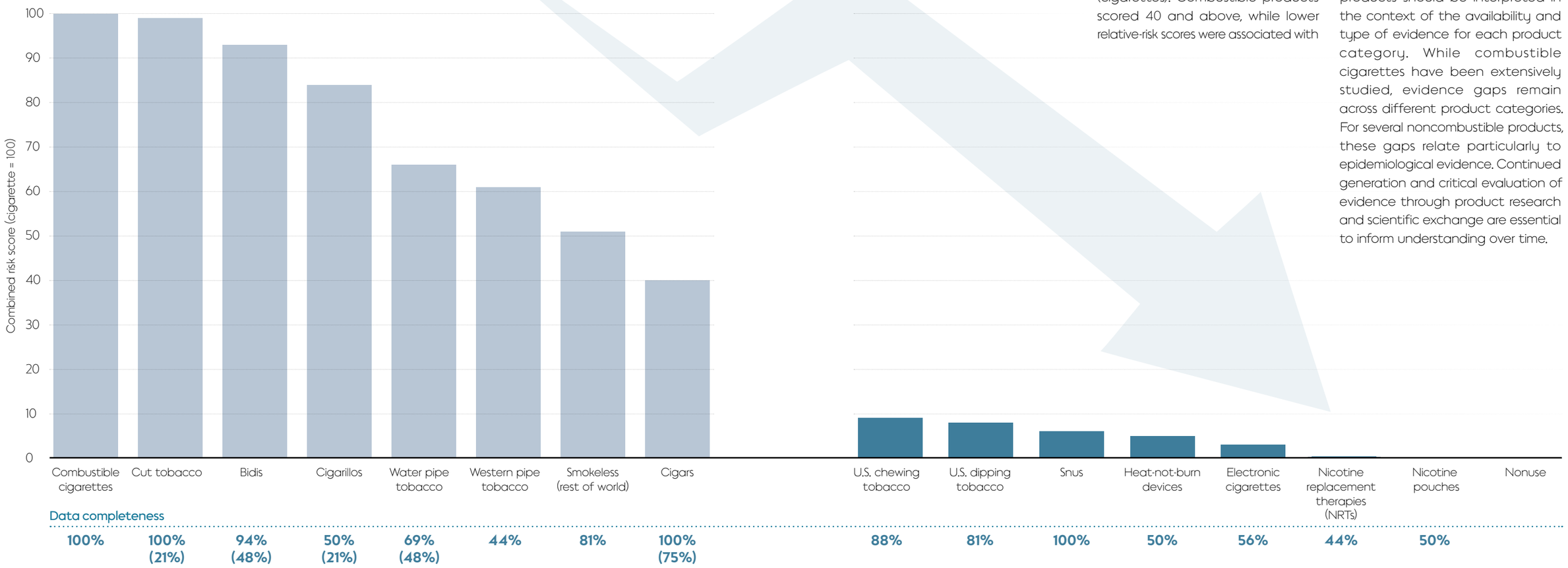
But what would be a lower-risk form of tobacco or nicotine consumption? A meta-analysis of 123 studies assessed the relative risk across product types. Based on available epidemiological evidence and emissions data in the literature, they assigned a relative-risk score from 0 (nonuse) to 100 (cigarettes). Combustible products scored 40 and above, while lower relative-risk scores were associated with noncombustible alternatives, including heated tobacco (or heat-not-burn), oral tobacco, e-cigarettes, nicotine pouches, and nicotine replacement therapies (NRTs).

Importantly, noncombustible alternatives are not risk free, and many contain nicotine, which is addictive.

Differences in the completeness of the evidence base between combustible and noncombustible products should be interpreted in the context of the availability and type of evidence for each product category. While combustible cigarettes have been extensively studied, evidence gaps remain across different product categories. For several noncombustible products, these gaps relate particularly to epidemiological evidence. Continued generation and critical evaluation of evidence through product research and scientific exchange are essential to inform understanding over time.

THE RELATIVE RISK HIERARCHY OF 15 CATEGORIES OF NICOTINE PRODUCTS

Adapted from Murkett et al. 2022. F1000Res. 9, 1225. CC BY 4.0.



Data completeness shows the proportion of the evidence sought in the study's analysis that was available for each product (100% = all planned data points available). Lower percentages indicate larger evidence gaps. Numbers in parentheses show the completeness without data assumed from another product.

POPULATION IMPACT

WHY PRODUCT-LEVEL SUBSTANTIATION MATTERS

From a population health perspective, potential benefits depend not only on relative risk, but also on how products are used in real-world settings.

Impact is shaped by whether people who smoke quit, switch to a different product, sustain use over time, engage in dual use, or relapse to smoking. Accessibility, acceptability, and patterns of use all influence whether alternatives are acceptable enough to meaningfully displace cigarettes.

For this reason, category-level evidence alone cannot predict population-level benefits. Product-level substantiation remains essential to ensure individual products are rigorously assessed, their limitations clearly characterized, and their real-world impact monitored through independent postmarket surveillance. Without this, category comparisons risk overstating benefits or obscuring meaningful differences between products.



CONCLUSIONS

Smoking remains a leading and preventable cause of disease and death, driven largely by chronic exposure to combustion-related toxicants.

While cessation offers the greatest health benefit, evidence shows that many adults continue to smoke despite serious disease and access to cessation support. Noncombustible nicotine and tobacco products potentially present lower risk than cigarettes due to the absence of combustion, but they are not risk free and contain nicotine, which is addictive. Regulatory and scientific evaluation therefore requires product-level assessment, transparent characterization of uncertainty, and ongoing independent surveillance to determine real-world health impact.

SWEDEN

A REAL-WORLD CASE STUDY IN SMOKING DECLINE AND ADULT SUBSTITUTION



In this article

01.

HOW ADULT SWITCHING TO SMOKE-FREE ALTERNATIVES HAS SHAPED SWEDEN'S SMOKING TRENDS

02.

POPULATION-LEVEL HEALTH IMPACT IN SWEDEN

03.

THE ROLE OF ORAL NICOTINE PRODUCTS IN SWEDEN'S REDUCED SMOKING PREVALENCE





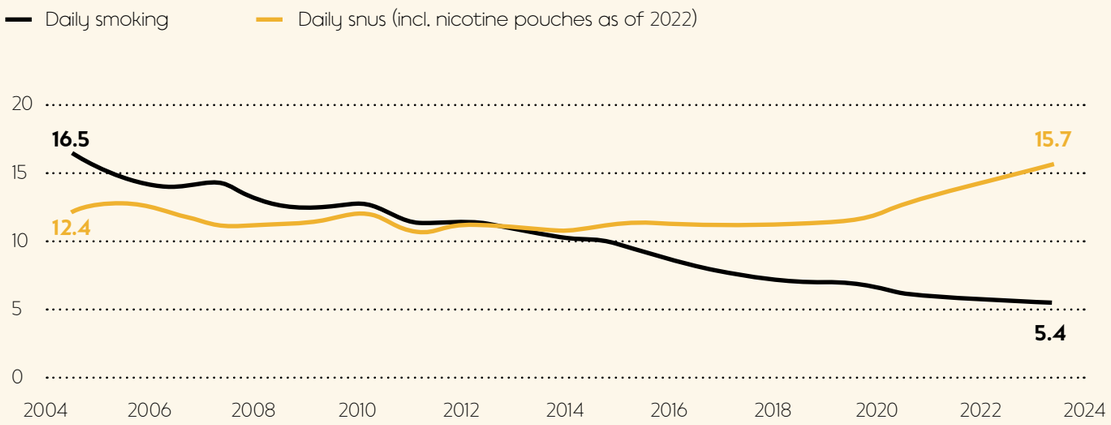


HOW ADULT SWITCHING TO SMOKE-FREE ALTERNATIVES HAS SHAPED SWEDEN'S SMOKING TRENDS

Sweden has kept smoking among the lowest in the EU for decades, where smoking prevalence dropped by 27% from 2014 to 2023.

In 2024, daily smoking was at 5.4%, placing the country less than one percentage point from the "*smoke-free*" threshold. The smoking prevalence patterns seem to align with a long-term pattern of adult substitution from cigarettes to regulated oral tobacco and nicotine products, particularly snus and, more recently, nicotine pouches. Sweden's experience therefore is a real-world case study for examining how shifts in product use patterns are associated with population-level health outcomes.

DAILY SMOKING AND DAILY USE OF SNUS/NICOTINE POUCHES IN SWEDEN, 2004–2024.



Source: Public Health Agency of Sweden. National Public Health Survey 2004-2024.



LOWER SMOKING PREVALENCE IN SWEDEN

SWEDEN'S DECLINE IN SMOKING

Snus has seen significant use among Swedish men since the 1970s.

Over time, Sweden has shifted away from cigarettes, with smoking rates and cigarette sales declining alongside continued use of oral smokeless products, particularly snus.

This long-term shift has helped Sweden maintain one of the lowest smoking rates in the EU, distinguishing it from many countries in the region.

In 1992, the EU banned tobacco for oral use following concerns raised by the introduction of a U.S. smokeless tobacco product that was marketed in several EU countries. Although the definition also covered Swedish snus, Sweden was not an EU member at the time. When Sweden joined the EU in 1995, it was granted a permanent exemption from the snus ban. This allowed adult consumers to continue accessing the product, while Sweden's cigarette control measures remained broadly similar to those in other EU countries.

According to the Eurobarometer survey, smoking prevalence in Sweden declined by 27% from 2014 to 2023, far outpacing the EU's 11% decline over the same period. The Swedish National Public Health Survey shows that by 2024, daily smoking reached 5.4%, placing Sweden less than one percentage point away from achieving "*smoke-free*" status. Recent survey data suggest that this milestone may already have been achieved.

Taken together, Sweden's long-term trajectory shows how access to regulated alternatives, proportionate regulation, and adult adoption of scientifically substantiated, lower-risk alternatives can align with sustained declines in cigarette smoking. It also illustrates how harm reduction can complement, rather than replace conventional tobacco control measures.

POPULATION-LEVEL HEALTH IMPACT

IN SWEDEN

Epidemiological data indicate that Swedish men have the lowest incidence of lung and oral cancers in the EU, a pattern linked to historically lower smoking, as many men moved from cigarettes to snus decades ago. In contrast, because cigarette smoking remained more prevalent among Swedish women until recently, women's smoking-related cancer indicators have tended to look closer to EU norms.

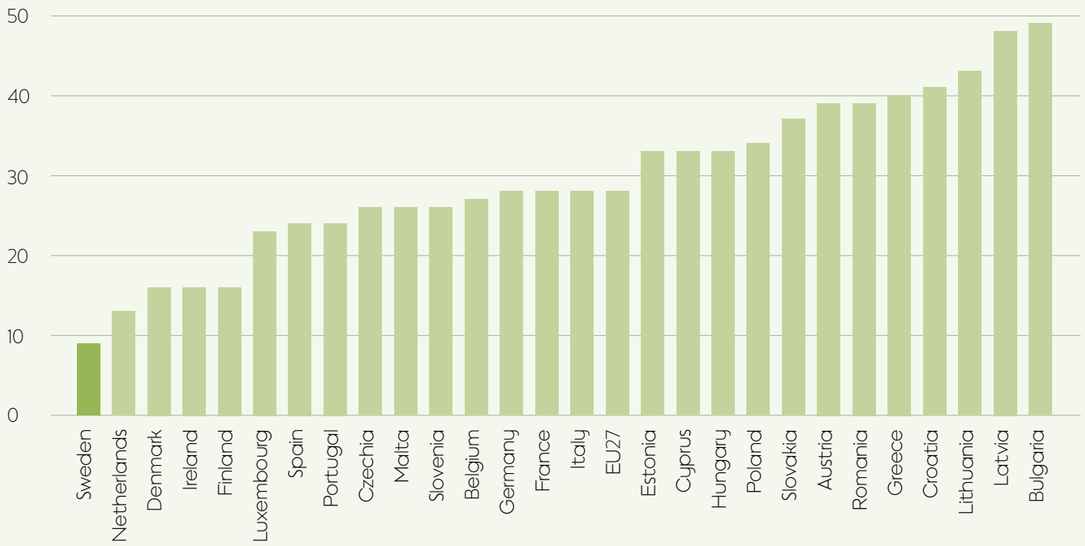
National data show that this pattern is also reflected in selected mortality indicators. According to Eurostat, in 2022, Swedish men had about 36 deaths from lung and oral cancers per 100,000 men, compared with nearly 78 deaths per 100,000 across the EU. At the population level, evidence from Sweden shows that longstanding use of snus has been associated with adults moving away from cigarettes and with favorable trends in smoking-related health outcomes. These epidemiological observations have informed regulatory decisions, including Modified Risk Tobacco Product (MRTP) authorizations granted by the U.S. Food and Drug Administration (FDA) for selected *General Snus* products.



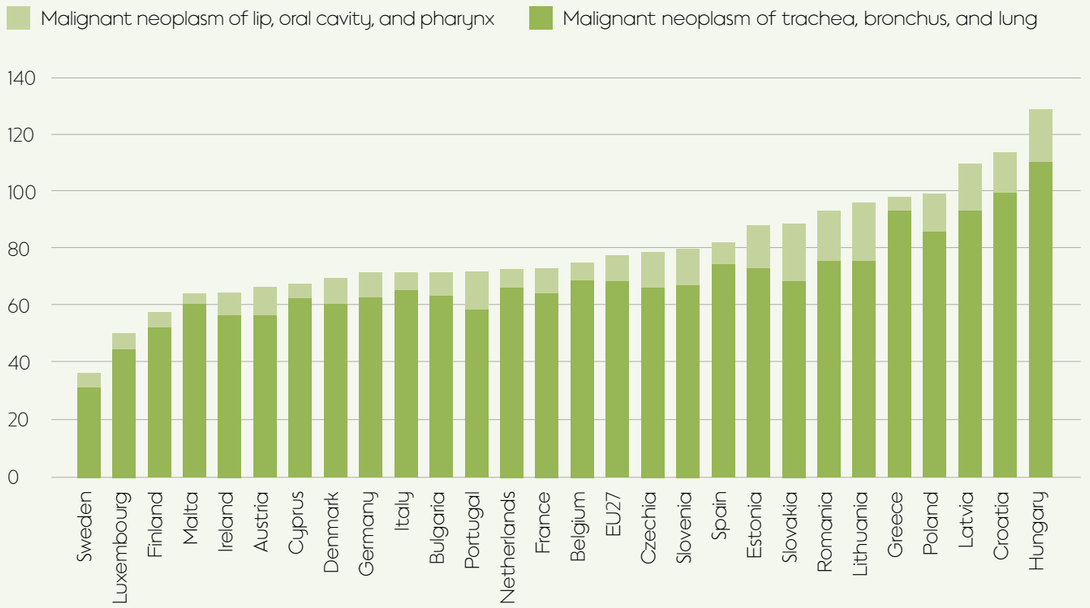
SMOKING PREVALENCE AND SELECTED SMOKING-RELATED DISEASE INDICATORS AMONG MEN IN SWEDEN AND OTHER EU COUNTRIES.

Sources: European Commission. 2024. Eurobarometer. (Accessed August 27, 2026)
Eurostat. 2022. Causes of death - standardized death rate. (Accessed August 27, 2026)

Male smoking prevalence in the European Union in 2023 (Eurobarometer, age 15 and above)



Male standardized lung and oral cancer death rate in 2022 (Eurostat)



THE ROLE OF ORAL NICOTINE PRODUCTS

IN SWEDEN'S REDUCED SMOKING PREVALENCE

Sweden's experience shows how long-term access to regulated, noncombusted alternatives can support sustained declines in smoking and reductions in smoking-related mortality.

Oral tobacco and nicotine products have supported Sweden's long-term shift away from cigarettes, with snus now widely used and nicotine pouches emerging more recently as an additional noncombusted option for adults who use tobacco and nicotine products.

Sweden is frequently cited as an example where the availability of oral smokeless products has been associated with shifts in adult tobacco and nicotine use patterns over time. Public health data show that daily smoking prevalence declined substantially over time, while daily snus use remained relatively stable. Since 2022, nicotine pouch use has increased following its introduction as a separately measured category. Taken together, these observations suggest that, in Sweden, oral smokeless products have become an important option for adult users of tobacco and nicotine products, following decades of snus use and the more recent introduction of nicotine pouches.



LESSONS FROM SWEDEN FOR RISK-PROPORTIONATE TOBACCO CONTROL

Sweden's experience shows how long-term access to regulated, noncombusted alternatives can support sustained declines in smoking and reductions in smoking-related mortality.

Evidence from Sweden and other Nordic countries suggests that similar patterns may emerge in other populations when adult smokers can access acceptable and regulated alternatives.



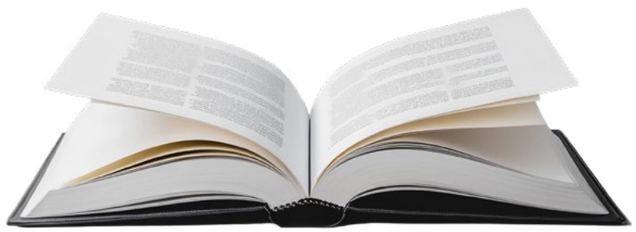
DISCLAIMER

The smoking prevalence and mortality data presented in this article originate from different sources with distinct objectives, study populations, and definitions. Consequently, these estimates are not directly comparable and should be interpreted as complementary lines of evidence.

SCIENCE IN FOCUS

EVIDENCE AT A GLANCE

Scientific substantiation of smoke-free products plays an important role in building evidence on their potential health impact compared with cigarettes. The following pages summarize key research findings to date and highlight studies that have contributed to the evidence across PMI's smoke-free product categories.



They form part of a broader body of research developed over more than a decade, during which PMI has invested over USD 16 billion in the research, development, and scientific substantiation of smoke-free products, supported by a multidisciplinary organization of more than 1,600 scientists, engineers and technicians working in PMI's R&D*. This work has contributed to an expanding evidence base, including more than 550 peer-reviewed publications and hundreds of completed studies across product categories spanning aerosol chemistry, toxicology, clinical research, and behavioral science.

The studies highlighted in this section include recent clinical and observational research across different PMI smoke-free products, examining outcomes ranging from exposure to biological response.

Collectively, the studies summarized here provide a concise overview of current research across clinical, nonclinical, and analytical areas, while underscoring the importance of assessing evidence at the product level.

*Data includes Swedish Match and Wellness business.

In this article

01. KEY FINDINGS

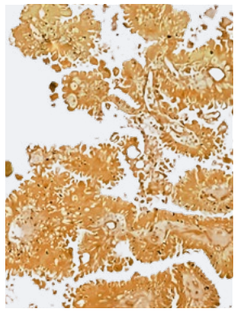


02. STUDY HIGHLIGHTS

TOBACCO HEATING SYSTEM



E-VAPOR PRODUCTS

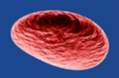


ORAL PRODUCTS



KEY FINDINGS

KEY HIGHLIGHTS TO DATE FROM PMI'S EXTENSIVE SCIENTIFIC RESEARCH ACROSS TOBACCO HEATING SYSTEM, E-VAPOR PRODUCTS, AND ORAL SMOKELESS PRODUCTS.





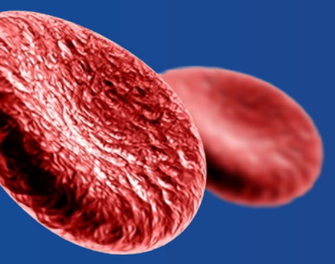
TOBACCO HEATING SYSTEM

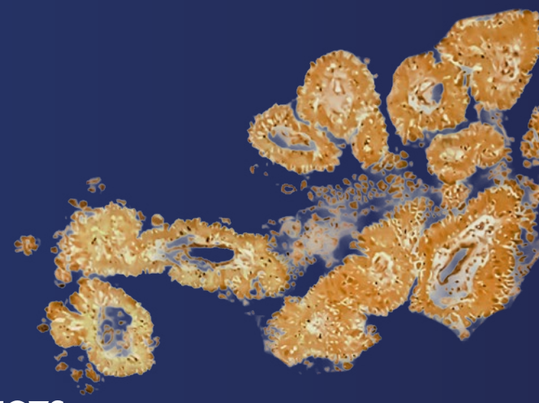
Switching completely from cigarettes to our Tobacco Heating System (THS) resulted in reduced exposure to selected harmful chemicals compared with continued smoking.

Switching to THS for 6 months was associated with favorable changes across selected health measures, with these changes maintained during a 6-month extension.

THS users for at least 2 years showed reduced exposure to selected toxicants compared with current smokers, with results approaching those from former smokers.

THS aerosol extract showed lower potential for tooth discoloration than cigarette smoke extract *in vitro*.





E-VAPOR PRODUCTS

Replacing exposure to cigarette smoke with exposure to aerosols from the tested PMI e-vapor products resulted in lower levels of inflammatory and respiratory-related responses in animal models.

Long-term exposure to tested PMI's flavored e-vapor aerosols was associated with reduced toxicity and carcinogenicity in an animal model compared with cigarette smoke exposure.

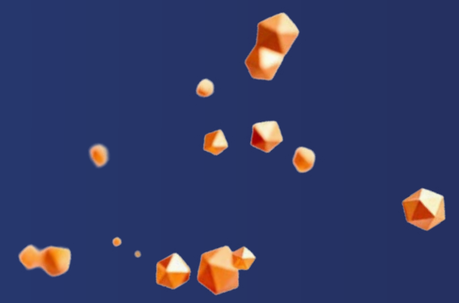
Exposure to PMI's e-vapor aerosols was associated with lower impact on bone integrity than cigarette smoke exposure in an animal model.

Exposure to PMI's e-vapor aerosols caused less and more reversible dental discoloration than cigarette smoke exposure *in vitro*.

ORAL SMOKELESS PRODUCTS

PMI's nicotine pouches showed fewer and lower levels of harmful chemicals than conventional oral tobacco products, approaching those observed in nicotine replacement therapies (NRTs).

PMI's nicotine pouch extracts did not induce cytotoxicity or reporter gene activation *in vitro* when compared with reference tobacco product extract.



TOBACCO HEATING SYSTEM



REDUCED EXPOSURE STUDY

This series of reduced-exposure studies conducted in Japan, Poland, and the U.S. evaluated whether switching from cigarettes to THS reduces exposure to harmful chemicals. All studies employed a three-arm randomized design involving approximately 160 participants, with roughly 80 switching to THS, 40 continuing to smoke, and 40 abstaining from smoking. Across two 5-day confinement studies and two 90-day studies, with an initial 5-day confinement period followed by an at-home use, researchers assessed the same panel of 15 biomarkers of exposure to harmful chemicals.

Complete switchers showed statistically significant reductions in exposure ranging from 56% to 96% within the first 5 days compared with cigarette smokers.



These reductions approached the levels seen in abstainers and were sustained over the full 90-day study periods. Nicotine uptake, however, remained broadly comparable between switchers and continued smokers. Overall, the reductions in harmful chemical exposure were consistent and reproducible across different populations and study durations.

Together, these findings indicate that switching completely to THS substantially lowers exposure to smoke-derived toxicants compared with continued smoking.

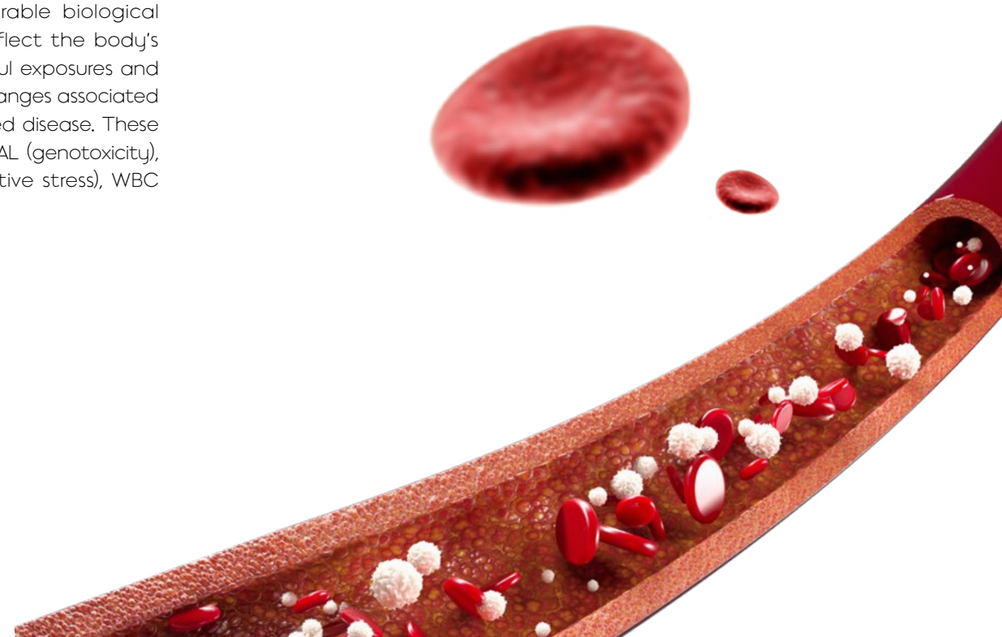
Learn more about this study

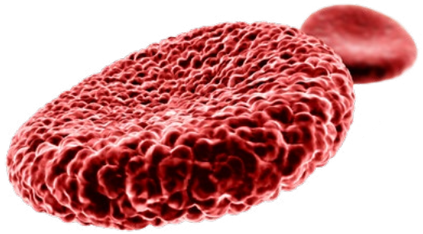
EXPOSURE RESPONSE STUDY (6 MONTHS + 6-MONTH EXTENSION)

This clinical study, conducted across 20 study sites in the U.S., was designed to verify if the reduction in exposure to harmful chemicals was associated with favorable changes in certain health measures in healthy adult smokers after they switched to THS. A total of 984 study participants were assigned to either continue smoking their own brand of cigarettes (496 people) or to switch to THS (488 people) for 6 months. Of the participants who completed the initial 6-month study, 672 continued in the extension study for an additional 6 months using their assigned product. Eight health markers were selected as the main focus for this study, serving as measurable biological indicators that reflect the body's response to harmful exposures and can signal early changes associated with smoking-related disease. These included: total NNAL (genotoxicity), 8-epi-$PGF_{2\alpha}$ (oxidative stress), WBC (inflammation), FEV^1 (lung function), COHb (oxygen delivery), sICAM-1 (endothelial function), 11-DTX-B2 (blood clotting), and HDL-C (lipid metabolism). All eight health measures in this study showed favorable changes in the same direction as with smoking cessation, with five of the eight showing statistically significant changes, even though the THS group was still allowed up to 30% continued cigarette use.

Overall, the results of this study confirm that based on the positive biological effects, switching to THS likely presents less risk of harm than continued smoking.

Learn more about this study







HEALTH MEASURES AFTER 2+ YEARS OF SWITCHING VERSUS QUITTING

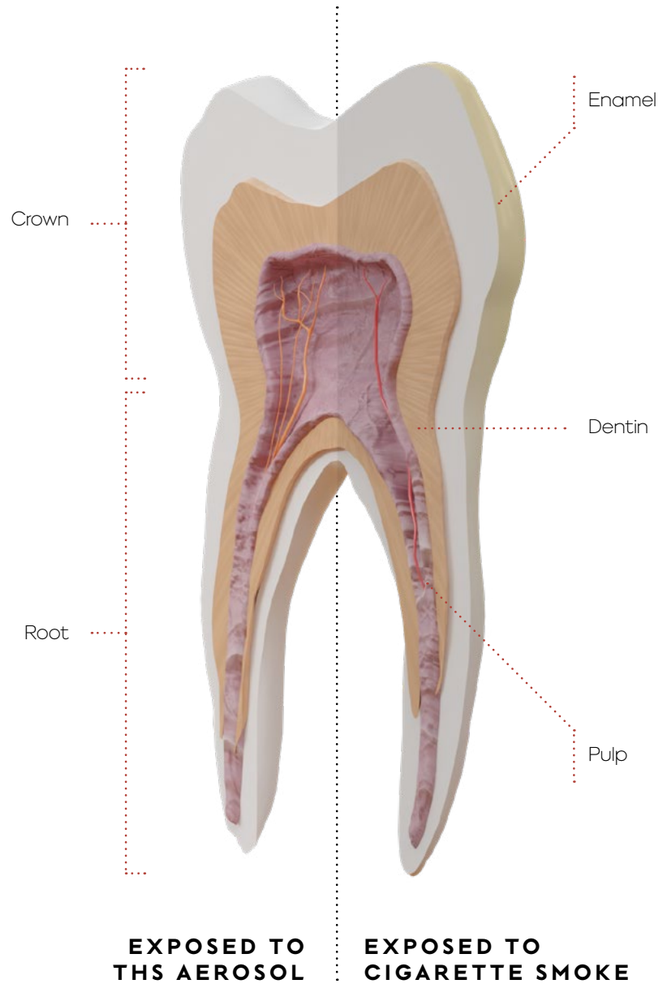
This cross-sectional study, conducted across multiple regions in Asia and the EU, evaluated whether individuals who had switched completely to THS for at least 2 years showed favorable differences in selected health measures compared with current and former smokers. Blood and urine samples from 982 healthy adults were assessed for nine biomarkers representing pathways known to improve after smoking cessation. These included: total NNAL (genotoxicity), COHb (oxygen delivery), WBC (inflammation), 8-epi-$PGF_{2\alpha}$ (oxidative stress), sICAM-1 (endothelial function), HDL-C (lipid metabolism), 11-DTX-B2 (blood clotting), FEV_1 (lung function) and AIx (central vascular augmentation index; arterial stiffness). Long-term THS users showed favorable differences across all nine biomarkers compared with current smokers, with levels closely resembling those of former smokers.

Overall, the findings indicate that switching completely to THS for 2 or more years is associated with biological improvements consistent with quitting, supporting its potential for reduced harm compared with continued cigarette smoking.

Learn more about this study

DENTAL STAINING STUDY ON THS AEROSOL

This *in vitro study* characterized and compared the chemical substances deposited on tooth enamel after exposure to extracts from cigarette smoke and THS aerosol, and identified the compounds associated with tooth discoloration. To achieve this, bovine enamel samples were exposed for 2 weeks to extracts from cigarette smoke, THS aerosol, or artificial saliva, followed by weekly brushing, color assessment, and advanced chemical analysis using GC-TOF-MS (gas chromatography coupled to time-of-flight mass spectrometry). Results showed pronounced and visually detectable enamel discoloration after exposure to cigarette smoke extract, whereas discoloration following exposure to THS aerosol was not distinguishable to the eye and appeared similar to the saliva control. Consistent with these visual findings, chemical analysis revealed that discoloration-linked compounds, mainly terpenoids, were deposited at much lower levels on enamel exposed to THS aerosol compared with cigarette smoke.



Colors depicted in this figure are only representative

Overall, the findings demonstrate that THS aerosol leads to markedly reduced deposition of color-forming chemicals on tooth enamel than cigarette smoke, suggesting a lower potential for tooth staining and related aesthetic effects for smokers who switch to THS.

Learn more about this study

E-VAPOR PRODUCTS

Microscopic changes were mainly limited to the nose and larynx, occurred primarily at higher flavor concentrations, and were less severe than those observed in the cigarette smoke group.

INHALATION STUDIES ON THE EFFECTS OF E-VAPOR AEROSOLS ON THE RESPIRATORY SYSTEM OF ANIMAL MODELS

These two long-term chronic inhalation studies in mouse models assessed whether, under defined exposure conditions, replacing cigarette smoke with e-vapor aerosols reduces inflammation and respiratory-related responses, and whether switching after prior smoke exposure mitigates smoke-induced damage. In C57BL/6 mice followed for 7 months, switching to e-vapor after 3 months of cigarette smoke exposure produced biological changes similar to smoking cessation and reduced smoke-associated gene changes in lung and nasal tissues.

Across the full 7-month period, continuous e-vapor exposure led to no or minimal increases in pulmonary inflammation, whereas continuous cigarette smoke impaired lung function, increased lung inflammation, and caused emphysematous changes.

In a separate 6-month study in ApoE−/− mice, prolonged exposure to cigarette smoke impaired lung function and led to lung inflammation and emphysema. In contrast, exposure to e-vapor aerosols resulted in lower biological changes in the lungs. At the molecular level, cigarette smoke disrupted multiple biological processes, whereas these changes were less pronounced with e-vapor aerosols. Together, these studies indicate that complete switching from smoke to e-vapor reduces respiratory injury in these models, with switching outcomes approximating cessation on key endpoints, adding to the totality of evidence suggesting a potential harm-reduction benefit of scientifically substantiated e-vapor products.

Read more about our research here and here.

TOXICITY AND CARCINOGENICITY OF E-VAPOR AEROSOLS IN ANIMAL MODELS

This inhalation study in A/J mice examined the long-term toxicity and carcinogenicity of flavored e-vapor aerosols compared with cigarette smoke. Mice were exposed for up to 18 months to several aerosol formulations and outcomes were compared with cigarette smoke and filtered air groups. Across all e-vapor groups, chronic exposure did not affect survival, lung function, clinical pathology, nor cause macroscopic changes. Microscopic changes were mainly limited to the nose and larynx, occurred primarily at higher flavor concentrations, and were less severe than those observed in the cigarette smoke group. In contrast, cigarette smoke exposure produced the most pronounced adverse effects, including lung impairment and inflammation, emphysema, increased lung tumors and laryngeal papillomas, and marked histopathological and toxicological changes.

Overall, these findings show that even with high levels of added flavors, long-term exposure to e-vapor aerosols resulted in reduced toxicity and carcinogenicity compared with cigarette smoke.

This adds to the scientific findings supporting a potential reduced-risk profile for flavored e-vapor products compared with continued smoking.

Learn more about this study



INHALATION STUDY EXAMINING EFFECTS OF E-VAPOR AEROSOLS ON BONE INTEGRITY IN ANIMAL MODELS

This 6-month inhalation study in ApoE−/− mice evaluated whether chronic exposure to e-vapor aerosols affects bone health compared with cigarette smoke. Mice were exposed to aerosols from three e-vapor formulations or to nicotine-matched cigarette smoke, with control groups exposed to fresh air, and their bone morphology, structure, and strength were assessed.



Cigarette smoke exposure caused clear detrimental effects, including reduction in bone volume, density, load, and stiffness, whereas e-vapor aerosols exposure did not produce comparable adverse effects on bone health.

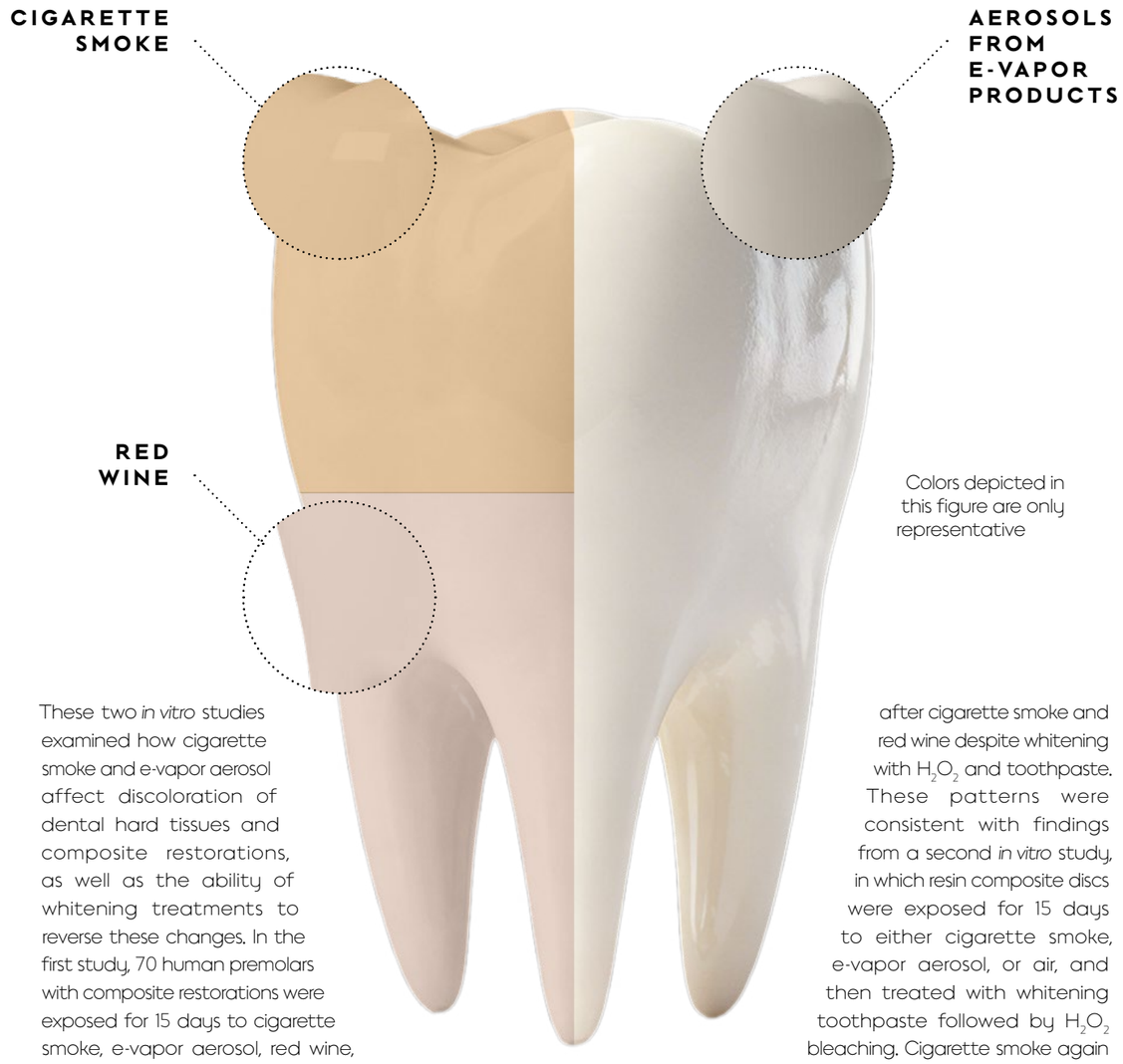
Consistent with these findings, micro-computed tomography imaging, biomechanical testing, and histological analyses showed that bone parameters in all e-vapor groups remained comparable to fresh air controls and were better than those in cigarette smoke-exposed mice.

Overall, the findings indicate that chronic inhalation of e-vapor aerosols exerted a lower impact on skeletal integrity than cigarette smoke in the animal model.



Learn more about this study

TOOTH AND DENTAL RESIN COMPOSITE STAINING STUDY WITH CIGARETTES AND E-VAPOR PRODUCTS



Colors depicted in this figure are only representative

These two *in vitro* studies examined how cigarette smoke and e-vapor aerosol affect discoloration of dental hard tissues and composite restorations, as well as the ability of whitening treatments to reverse these changes. In the first study, 70 human premolars with composite restorations were exposed for 15 days to cigarette smoke, e-vapor aerosol, red wine, coffee, or soy sauce, followed by two whitening treatments with hydrogen peroxide (H_2O_2). Teeth in the cigarette smoke and electronic vapor groups also underwent 3 weeks of brushing with whitening toothpaste. Results showed a clear ranking of staining severity, with red wine and cigarette smoke producing the most pronounced tooth discoloration and the only visible color mismatch between enamel and resin restorations. Discoloration from e-vapor aerosol was minimal and removable with whitening toothpaste, whereas color mismatch persisted after cigarette smoke and red wine despite whitening with H_2O_2 and toothpaste. These patterns were consistent with findings from a second *in vitro* study, in which resin composite discs were exposed for 15 days to either cigarette smoke, e-vapor aerosol, or air, and then treated with whitening toothpaste followed by H_2O_2 bleaching. Cigarette smoke again caused pronounced discoloration, while e-vapor produced only minimal color change. Whitening toothpaste restored the color of e-vapor-exposed composites, but neither whitening toothpaste nor bleaching reversed the discoloration caused by cigarette smoke. Together, these studies demonstrate that e-vapor aerosol induces smaller, readily reversible discoloration, while cigarette smoke causes severe and whitening-resistant staining that may result in persistent aesthetic mismatch. Read more about our research here and here.

ORAL PRODUCTS

The findings indicate that the measured harmful chemical profile of PMI's nicotine pouches was broadly similar to NRTs and lower than conventional oral tobacco products.



HPHCS STUDIED IN NICOTINE POUCH PRODUCTS

The study aimed to chemically characterize tobacco-free nicotine pouches (*ZYN* dry and moist) and to compare their harmful and potentially harmful constituents (HPHCs) content with other oral tobacco-based products (snus and moist snuff) and pharmaceutical nicotine replacement therapies (NRTs). The authors screened 43 target compounds, including 36 listed by the FDA-CTP (Center for Tobacco Products at the U.S. Food and Drug Administration) as harmful chemicals, across seven products to assess the presence and levels of selected constituents. Results showed that *ZYN* and NRT products contained no quantifiable nitrosamines or polycyclic aromatic hydrocarbons (PAHs), while only low levels of ammonia, chromium, formaldehyde, and nickel were detected. In contrast, moist snuff contained the largest number and generally highest levels of measured harmful chemicals, including multiple PAHs and nitrosamines, whereas snus contained more quantified constituents than *ZYN*/NRTs but fewer than moist snuff. Overall, the findings indicate that the measured harmful chemical profile of PMI's nicotine pouches was broadly similar to NRTs and lower than conventional oral tobacco products, supporting their potential as a lower-exposure alternative for adult nicotine users compared with tobacco-based oral products.

Learn more about this study

COMPARATIVE TOXICITY OF NICOTINE POUCHES

This comparative *in vitro* study assessed the toxicological profiles of tobacco-free oral nicotine pouches and snus relative to reference tobacco products, as part of evaluating their harm reduction potential. Extracts from five *ZYN* nicotine pouches and four snus products were tested against reference American-style loose moist snuff and cigarettes using the ToxTracker® reporter assay to monitor various cellular responses. Results showed that cigarette smoke total particulate matter (TPM) induced cytotoxicity and activated multiple stress response pathways (including oxidative stress and protein damage), while moist snuff triggered responses without cytotoxicity. Snus showed a similar pattern to moist snuff but with lower protein-damage responses.

In contrast, none of the nicotine pouch extracts induced cytotoxicity or reporter gene activation, regardless of extraction method, making them the least biologically active of all products tested.

Overall, the findings indicate that tobacco-free nicotine pouches exhibit lower *in vitro* toxicological profile than cigarettes, supporting their harm reduction potential.

Learn more about this study

To explore the full set of study findings and supporting publications, visit PMIScience.com.



DEFINITIONS

1

Tobacco Heating System (THS)

A smoke-free product that heats a tobacco or nontobacco substrate instead of burning it, producing an aerosol that is different from cigarette smoke.

2

White blood cell (WBC) count

White blood cells are an important part of the immune system. WBC count is a commonly used biomarker of inflammation.

3

Cardiovascular disease (CVD)

Includes a range of diseases affecting the heart and blood vessels, such as stroke, heart failure, and arterial disease.

4

Total particulate matter (TPM)

The total mass of solid and liquid particles collected from cigarette smoke or aerosol. In cigarette smoke research, TPM is often used as a test material in analytical and toxicological studies.

5

Polycyclic aromatic hydrocarbons (PAHs)

A group of chemicals formed during incomplete combustion of organic material, including tobacco. Several PAHs are established carcinogens and contribute to the harmful effects of cigarette smoke.

6

Ischemic heart disease (IHD)

A cardiovascular condition in which narrowed or blocked coronary arteries reduce blood flow to the heart muscle. It is one of the major causes of smoking-attributable mortality reported in population-level analyses.

7

sICAM-1

sICAM-1 is short for soluble intercellular adhesion molecule-1. It is a circulating form of ICAM-1, a cell adhesion molecule involved in inflammatory and endothelial responses. sICAM-1 is used as a biomarker associated with endothelial function.

8

11-DTX-B2

11-DTX-B2 is short for 11-Dehydro-thromboxane B2. A stable metabolite of thromboxane A2 that is used as a biomarker for blood clotting.

9

8-epi-$PGF_{2\alpha}$

8-epi-$PGF_{2\alpha}$ is short for 8-Epi-prostaglandin $F_{2\alpha}$. This compound is widely used as a biomarker of oxidative stress. It is also known as an isoprostane.

10

Mutagenicity

The ability of substances to cause permanent changes (mutations) in the DNA in a cell or organism. Mutagenicity is associated with cancer development.

11

Genotoxicity

The ability of substances to damage genetic material in a cell. Genotoxicity is associated with cancer development.

12

Cytotoxicity

The ability of a substance to damage or kill cells. Cytotoxicity is an indicator of how harmful a substance might be.

13

COHb

COHb is the abbreviation for carboxy-hemoglobin. It is formed when carbon monoxide binds to hemoglobin in red blood cells. COHb is a biomarker associated with carbon monoxide exposure and reflects the body's reduced capacity to transport oxygen.

14

FEV_1

FEV_1 is short for Forced Expiratory Volume in 1 second, or the volume of air that can be forcibly exhaled during one second after a full inhalation. FEV_1 is a biomarker of lung function and respiratory health.

15

Carcinogenicity

The ability of a substance to contribute to the development of cancer. Whether cancer occurs depends not only on the substance itself but also on the level and duration of exposure, as well as individual factors including genetics, biology, environmental influences, and lifestyle.

16

in vitro

This term means 'in glass' in Latin, referring to laboratory studies conducted on cell cultures or biological molecules outside of the body.

17

in vivo

This term means 'in the living' in Latin, referring to laboratory studies conducted on living organisms such as laboratory animals, to observe biological processes in a whole-body context.



18

Total NNAL

The sum of 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL) and its glucuronide conjugates. Total NNAL is commonly used as a biomarker of exposure to the tobacco-specific nitrosamine NNK.

19

Biomarkers

Health measures that are associated with exposure to certain chemicals or substances (biomarkers of exposure or BoE), or associated with increased risk of harm in the body (biomarkers of potential harm or BoPH).

20

Oxidative stress

Oxidative stress indicates an excess of reactive molecules that can damage cells, when not enough antioxidants are available to neutralize them. 8-epi-$PGF_{2\alpha}$ is a biomarker associated with oxidative stress.

21

Harmful and Potentially Harmful Constituents (HPHCs)

Chemicals or chemical compounds in tobacco products or tobacco smoke that cause or could cause harm to smokers or nonsmokers, as defined by the U.S. Food and Drug Administration.

22

Apolipoprotein E knockout mice (ApoE−/− mice)

A genetically modified mouse model lacking the apolipoprotein E gene. These mice are widely used in research on atherosclerosis, lipid metabolism, and related disease mechanisms.

23

High-density lipoprotein cholesterol (HDL-C)

HDL-C is commonly referred to as "good cholesterol." It is a biomarker associated with the body's ability to transport cholesterol and metabolize lipids (or fats).

24

Tobacco-specific nitrosamines (TSNAs)

A group of harmful chemicals formed from nicotine and other tobacco alkaloids during tobacco curing, processing, and use. TSNAs are among the toxicants commonly assessed in tobacco and nicotine research.

25

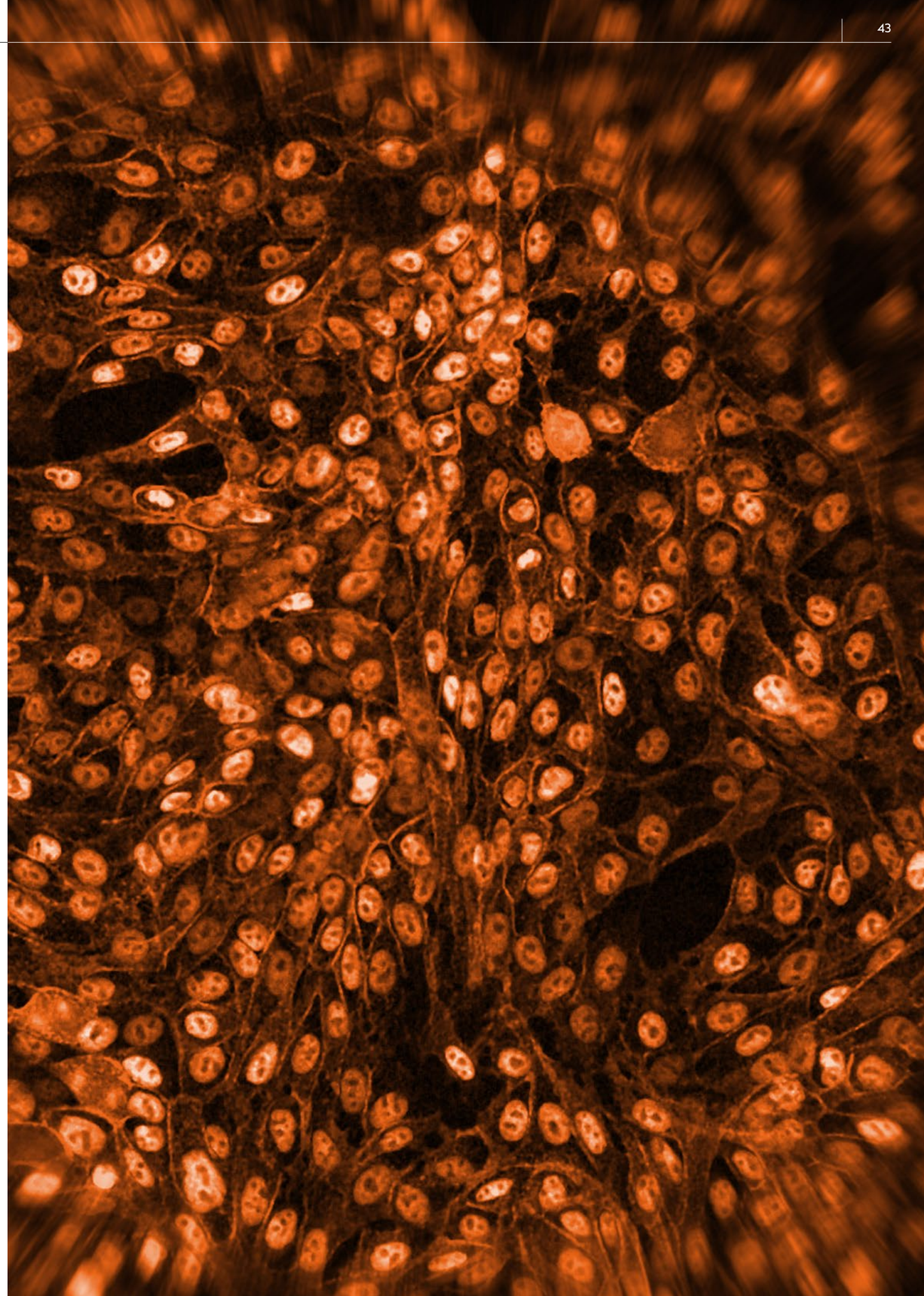
Chronic obstructive pulmonary disease (COPD)

A group of diseases that result in airflow blockage and breathing-related problems. It includes chronic bronchitis (airway inflammation) and emphysema (a lung condition that causes shortness of breath). Tobacco smoking is a risk factor for the development and progression of COPD.

26

Endothelial function

The endothelium, the layer of cells lining the inside of the blood vessels, plays a key role in regulating blood flow, clotting, and blood vessel dilation. sICAM-1 is a biomarker that indicates how well the endothelium is functioning.



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 text in these pages include our product development and assessment efforts, our initiatives to share our methodologies and results, as well as our publications.

More detailed information can be found at www.pmiscience.com.

Smoke-free products are not risk free and contain nicotine, which is addictive. The best choice any smoker can make is to quit tobacco and nicotine altogether.

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