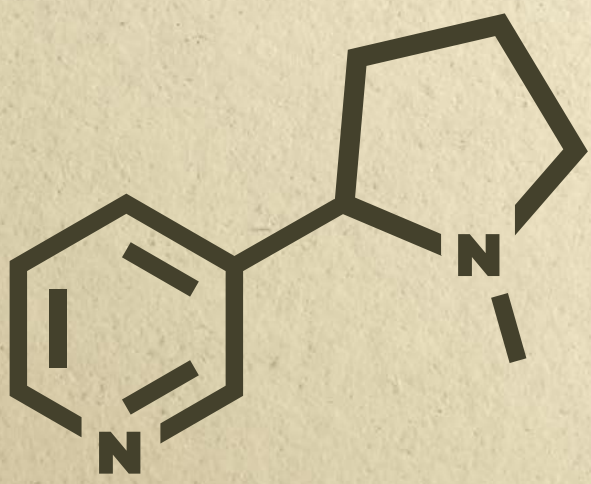
SCIENTIFIC UPDATE
PMI SCIENCE – PHILIP MORRIS INTERNATIONAL
JUNE 2024 | ISSUE 19

EXPLORING NICOTINE



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INTRODUCTION

In the past, nicotine, tobacco, and smoking were terms that all referred to the same thing: cigarettes and other combusted tobacco products. Today, that's no longer the case thanks to technological improvements and continued scientific research in the area of tobacco harm reduction.

Despite this progress, there are still many misperceptions about nicotine. Dr. Matthew Holman, VP and Chief Scientific and Strategy Officer, U.S., describes how the general public, and even physicians, often misunderstand the risks of nicotine in his article on the benefits of knowing the facts about nicotine. Also in this issue, we'll dive into the history of tobacco plant research, identifying the critical role that *Nicotiana tabacum* has played in plant biology, virology, and tobacco harm reduction.

And finally, we'll examine the role that nicotine has to play in tobacco harm reduction. Nicotine is addictive and is not risk free, but it is not the primary cause of smoking-related diseases. Nicotine can be an important factor in motivating smokers to change their habits. Ideally, this means quitting, perhaps with the help of cessation aids if necessary. Or it can mean switching to a smoke-free product for those who won't quit altogether.

We hope you enjoy reading this issue and find it informative and useful. We welcome your feedback and suggestions for future topics.

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EVENTS

You Ask, We Answer

Online

November 20-22, 2023

In this Open Science event, revisiting past Open Science highlights, we hosted an extended Q&A and received questions live on LinkedIn®. Since our launch in 2020, Open Science has grown from a simple webcast to a must-see, award-winning series, reaching an audience of over 10,000 viewers in over 50 countries. The heart of the event took place in the LinkedIn® comments section, where we invited our viewers to ask their questions and to fact-check the information that exists around our smoke-free products. There is no shortage of misconceptions, misunderstandings, and misinformation about smoke-free products and their role in tobacco harm reduction. In our 11 previous Open Science events, we've shared a wealth of information with the aim to bring clarity to the topic. In this event, we invited attendees to ask questions directly to our experts, who continued to answer questions over the following days.

Watch the replay here

Science and Sustainability

Online

December 14, 2023

For our last Open Science event of the year, we heard from Dr. Gizelle Baker, Vice President Global Scientific Engagement, and Jennifer Motles, Chief Sustainability Officer, about how science and sustainability share a common ground in fostering positive changes in society and the environment. No conversation on our dedication to sustainable business practices would be complete without remembering that, while PMI is widely known as a cigarette company, in 2016 we announced our new purpose: to deliver a smoke-free future by focusing our resources on developing, scientifically substantiating, and responsibly commercializing smoke-free products that are less harmful than smoking, with the aim of completely replacing cigarettes as soon as possible.

Watch the replay here

SCIENTIST PROFILE

Dr. Emilija Veljkovic

Emilija joined PMI in 2007 and is currently Manager of Scientific & Medical Affairs. She is a molecular biologist with a PhD in molecular biology and physiology from the Medical Faculty of the University of Zurich in Switzerland.

Previously, she led a team of scientists responsible for the design and data interpretation of *in vivo* product assessment studies in Singapore and is the lead author on many publications and book chapters. Emilija was a leading author of the book Nicotine and other tobacco compounds in neurodegenerative and psychiatric diseases published in 2018. The book provides a summary of the epidemiological data on smoking and several neurological disorders, describing the complex relationships between smoking and neurological disease and the bioactive compounds found in tobacco.

COULD NICOTINE PLAY A ROLE IN HARM REDUCTION?

In this article, we discuss nicotine, and its role in smoke-free products and tobacco harm reduction.

Nicotine is not the primary cause of smoking-related diseases

Nicotine is an alkaloid produced by many plants of the *Solanaceae* family. Within this family of plants, tobacco contains by far the highest levels of nicotine. It is present in cigarettes , e-cigarettes, other smoke-free alternatives as well as in nicotine replacement therapies. Nicotine is addictive and not risk free, but it is not the primary cause of smoking-related diseases.

The Commissioner of the U.S. Food and Drug Administration (FDA) and Director of the FDA's Center for Tobacco Products wrote in 2017:

> *Nicotine, though not benign, is not directly responsible for the tobacco-caused cancer, lung disease, and heart disease that kill hundreds of thousands of Americans each year.*

Tobacco smoke contains more than 6,000 chemicals, nearly 100 of which have been classified by public health agencies as harmful or potentially harmful constituents. Chronic exposure to high levels of those toxic substances emitted in the smoke when tobacco is burned is causally linked to smoking-related diseases such as cardiovascular and respiratory diseases, and lung cancer.

Our heated tobacco products heat tobacco without burning, at temperatures below the ignition temperature of tobacco. At these lower temperatures, nicotine and flavors are released from tobacco while generating on average about 90% to 95% lower levels of chemicals that are harmful or potentially harmful compared with cigarette smoke.

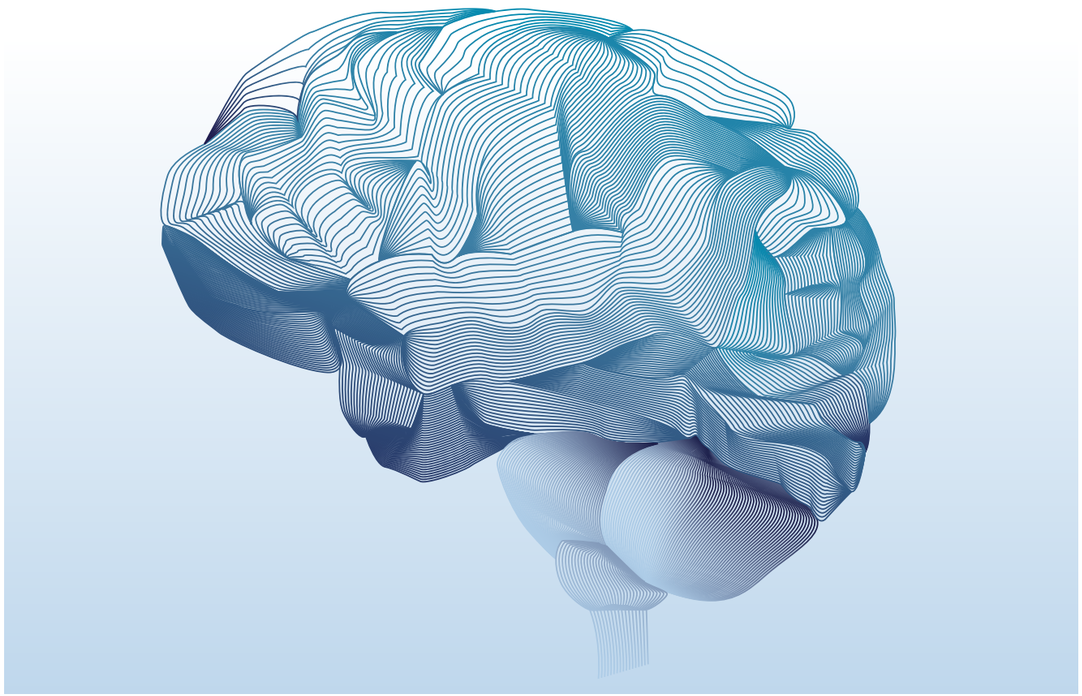
Since the regulatory focus is shifting from the harms of cigarettes to health effects of nicotine, more research is needed on how nicotine affects the body and the brain, and how this varies according to route of administration. PMI is dedicated to substantiating the risk profile of our smoke-free products, and having a better understanding of nicotine and its role in tobacco harm reduction is part of that.

For more information on this topic, see the presentation by Dr. Badrul Chowdhury, PMI's Chief Life Sciences Officer, Smoke-Free Products, at our 2023 Investor Day and the PMI Integrated Report 2023.

Nicotine has a variety of effects

Nicotine binds to nicotinic acetylcholine receptors in the central and peripheral nervous system to elicit a variety of physiological responses, for example, a transient increased heart rate and blood pressure. These effects can be influenced by the route of administration, such as via the lungs, mouth, or skin. Each of these routes affects the rate and amount of nicotine taken up into the body.

Many people who smoke cigarettes indicate that they do so for the perceived benefits, including enjoyment, stress management, and relaxation. Additionally, some studies report that nicotine can enhance cognitive processes such as improving attention, memory, and fine motor function.



Sustained nicotine use can also induce changes in the brain's reward and stress systems, leading to withdrawal symptoms, although the effects are transitory and reversible once people quit and successfully abstain from using tobacco and nicotine products. It is well understood that nicotine is addictive and not risk free. However, whilst it can be difficult for some, anyone can quit tobacco and nicotine altogether with sufficient motivation. Some studies have found that nicotine may have adverse effects on fetal development such as low birth weight. For these reasons, some populations should avoid nicotine-containing products altogether, including minors, women who are pregnant or breastfeeding, and people with pre-existing conditions, including heart disease, high blood pressure, diabetes, or epilepsy.

The scientific community continues to explore ways in which nicotine and other alkaloids present in the tobacco plant can be isolated and potentially used as therapeutic compounds. For instance, scientists are studying nicotine as a possible active ingredient in pharmaceutical applications for treating schizophrenia, depression, and other anxiety disorders. Scientists are also examining the potential effects of nicotine on treating conditions such as Tourette's, Alzheimer's, Parkinson's, attention deficit hyperactivity disorder (ADHD), and other diseases. Cellular, animal, and human studies have yielded some promising results, yet existing data are still not conclusive, and nicotine's addictiveness could be a limiting adverse effect for its development as a therapeutic compound for human health.

The role of nicotine in smoke-free products

PMI has developed smoke-free products that deliver nicotine with significantly lower levels of the harmful chemicals found in tobacco smoke. The presence of nicotine in smoke-free products is an important factor among others, including ritual, sensory, and taste, to successfully move adults away from cigarettes through adoption of smoke-free products.

These products have the potential to reduce the health harm of cigarette smoking. PMI continues to conduct scientific programs to demonstrate the reduced-risk profile of these products when used by adult smokers who would otherwise continue to smoke.

Nicotine research supports regulators and policymakers

At PMI, research and development is the catalyst for our business transformation. The rigor with which we conduct our research—and the openness with which we share our methodologies and findings—builds confidence in our science among the scientific community, regulators, and our consumers.

Scientific research from any corporation may be met with skepticism. Sharing our science and listening to feedback are critical to both encouraging debate with experts and the broader public and building trust. We produce a regular briefing through our Scientific Update publication, which complements what we share throughout the year via articles in peer-reviewed journals, presentations at conferences, and the PMI Science website. From 2008 through 2023, we have published over 532 papers on smoke-free products and related science in peer-reviewed publications. As more and more new products emerge that separate nicotine from some or all of the aspects of the smoking ritual, much more research is needed to fully understand these new products as well as the role of nicotine itself.

What next for nicotine?

Many questions remain about nicotine, including its long-term effects, separate from the effects of smoking and the addiction potential of different types of products. Steps should be taken by academia and industry to fully understand the short- and long-term impacts of nicotine use. We plan to contribute to this understanding by conducting and publishing dedicated research focusing on understanding the effects of nicotine. As such, our website PMIScience will remain up-to-date with our latest findings.

TOBACCO PLANT RESEARCH, YESTERDAY, TODAY, AND TOMORROW

Tobacco (*Nicotiana tabacum*) is one of world's most widely cultivated non-food crops. We review here some of the history behind the tobacco plant, its role as a model organism in scientific studies, and the potential future of tobacco research.

The *Nicotiana* family tree

The tobacco plant belongs to the *Nicotiana* genus, a member of the *Solanaceae* (nightshade) family which includes tomato, bell pepper, and potato. Most commercial tobaccos belong to the species *N. tabacum*, of which there are over 1,600 varieties, sometimes classified into commercial types.

The genomes of the three most cultivated types of tobacco plants, namely Virginia (or Flue-cured), Burley, and Oriental, have been sequenced by PMI researchers.

N. tabacum has a large complex genome which is allotetraploid, meaning it comprises four sets of chromosomes from two different species (as opposed to most animals which inherit their chromosomes from two parents of the same species). Indeed, *N. tabacum* is known to have evolved through the hybridization of two ancestral species, *N. sylvestris* and *N. tomentosiformis*, about 200,000 years ago. This makes tobacco a relatively young plant in terms of evolution.

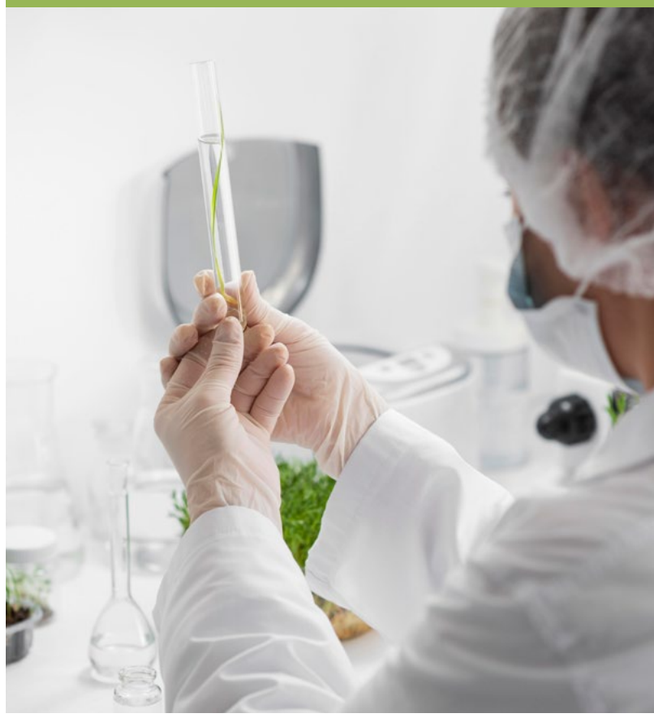
Nicotiana Rustica
AZTEC TOBACCO

The impact of humans on tobacco genetics

Tobacco cultivation first began in the Americas around 6,000 BCE. The arrival of Europeans in 1492 led to a significant growth in the use of tobacco, and by the 19th century, it had become a global industry. Over time, plants were bred to survive on different soils, in different environments, to resist different pests and predators, and to be used in different agricultural practices.

For example, Virginia and Burley were developed in the 19th century in the U.S., while Oriental is a divergent type developed over 300 years in isolated, stressful environments across what is now Greece, North Macedonia, and Turkey (tobacco was introduced to the Ottoman empire in the 16th century). This might explain differences in how they assimilate nitrogen and other compounds. Notably, Burley stands out with its relatively high nitrogen requirement.

The way *N. tabacum* has evolved to metabolize nitrogen and other compounds has been studied extensively by PMI researchers and others.



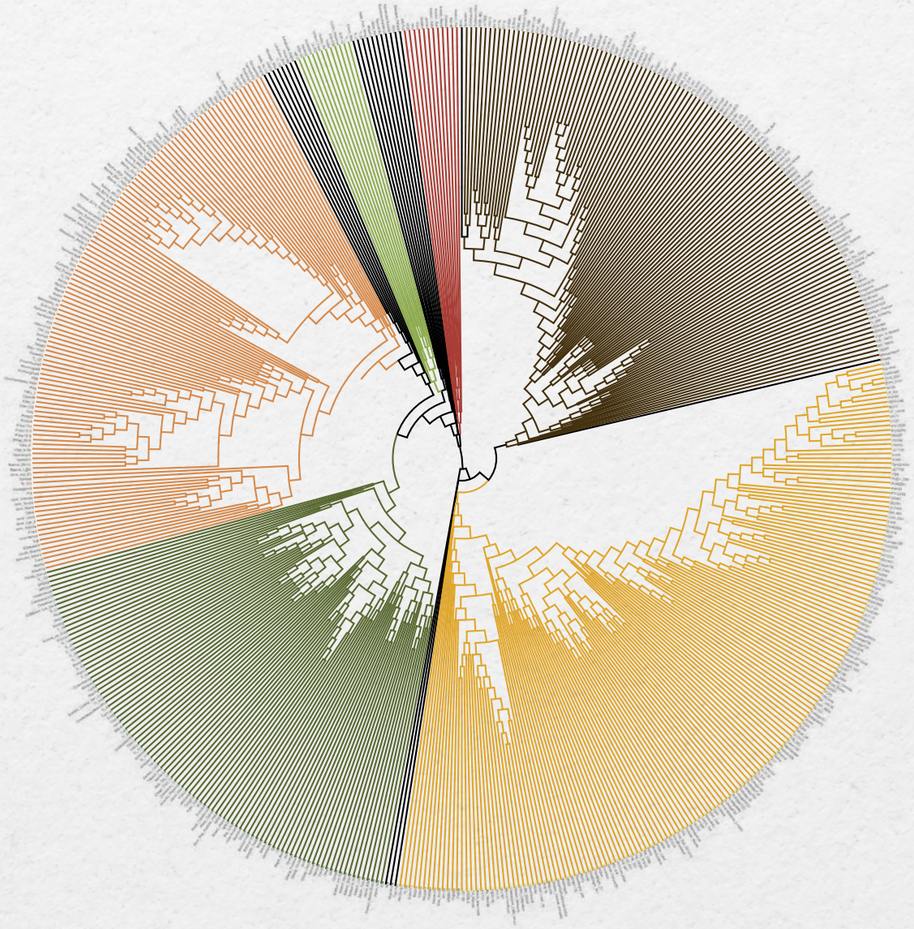
Tobacco synthesizes several organic compounds known as alkaloids, which includes nicotine, to protect the plant against insects and other pathogens.

Nicotine and other plant defense mechanisms

Tobacco synthesizes several organic compounds known as alkaloids, which includes nicotine, to protect the plant against insects and other pathogens. Mining the *N. tabacum* genome for sequences related to alkaloid biosynthesis, our researchers found evidence that the expression of genes related to nicotine biosynthesis occurs mainly in the roots, where most alkaloids are synthesized.

While nicotine defends against animal pests and numerous pathogens, it is ineffective against the destructive and widespread plant pathogen known as the tobacco mosaic virus (TMV), which causes leaf mottling, stunted growth, and reduced yield, leading to important economic impact.

TMV was the first virus ever discovered, with Martinus Beijerinck proposing in 1898 the existence of an infectious agent that was neither a bacterium nor a toxin. It has been central to the study of virology—plant, animal, and particularly human—ever since. Rosalind Franklin, most famous for her work on the structure of DNA, published a structure of TMV in 1955 and the virus is currently used by molecular biologists to deliver genetic material into plant cells. In the 1930s, tobacco breeders defeated TMV by introducing a gene from a resistant *Nicotiana* species, *N. glutinosa*, into the Burley genome through hybridization. These days, many commercial Burley and Virginia tobacco varieties carry this resistance gene.



Genetic tree showing the relationships between 567 different tobacco varieties. The circular format enables the representation of many varieties in one image. The tips of the tree, at the outer rim of the circle, represent the different varieties. The nodes towards the center represent common ancestors, each in a different color signifying the different types. The branches that are closest together are the most related.

Nicotiana as a model plant

N. tabacum plays an important role as a model organism in plant research. It was used in the 19th century to understand plant hybridization, and since the 20th century to study fundamental plant biology. Nevertheless, only fragmented genomic sequences were available until 10 years ago, when we published high-quality draft genomes for the three main tobacco varieties, Burley (TN90), Virginia (K326), and Oriental (BX). In 2024, we published chromosome-level genome assemblies of *N. tabacum* and its progenitors, *N. sylvestris* and *N. tomentosiformis*, which will broaden our understanding of their contributions to tobacco genetics and enable more efficient synteny-based cross-species *Solanaceae* research.

Nicotiana is also used in research to examine the vulnerability of commercially important *Solanaceae* crops to various diseases, including TMV, tobacco vein mottling virus (TVMV), tobacco etch virus (TEV), and potato virus Y (PVY). The Burley tobacco plant has been bred to resist all these infections.

Reducing harmful compounds in tobacco

We routinely monitor harmful and potentially harmful constituents in tobacco. For example, alkaloids in tobacco plants are associated with the generation of harmful tobacco-specific nitrosamines (TSNAs). We have worked extensively to find ways of lowering levels of TSNAs and other harmful compounds in tobacco.

Without doubt the best way to reduce the risk of smoking related disease is never to start, or for those who smoke, to quit tobacco and nicotine altogether. On our end, we are continuously working on ways to further improve our smoke-free products intended for those adult smokers who don't quit. In these efforts, tobacco plant research can play an important part as well.

"We have worked extensively to find ways of lowering levels of TSNAs and other harmful compounds in tobacco."

The future of tobacco

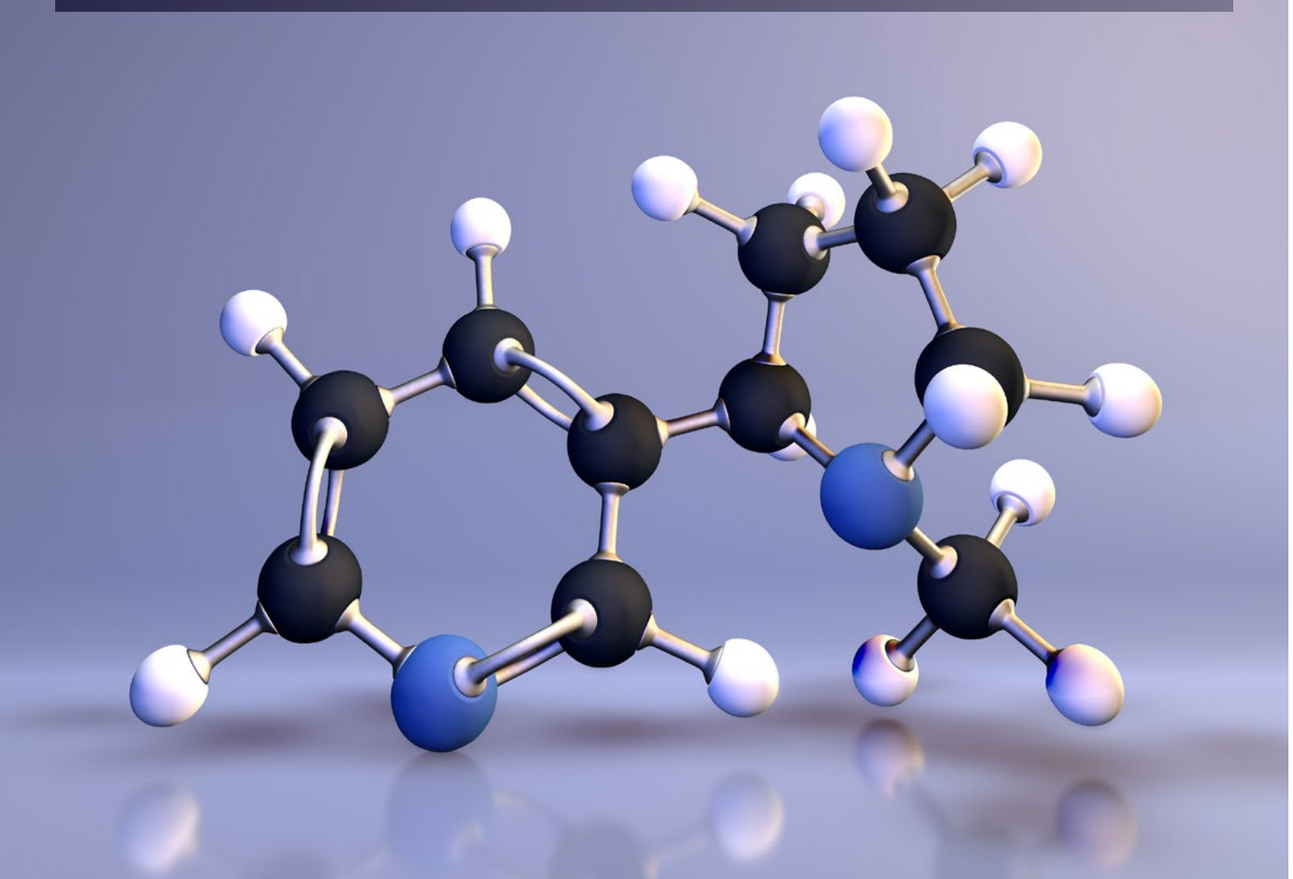
With our focus on driving the obsolescence of combustible tobacco, the future of tobacco is clearly evolving. Research on the genetics of the tobacco plant is helping further our efforts towards tobacco harm reduction as well as creating new opportunities in plant biology. The raw materials used in our products rely on fertile soil, stable climate conditions, and access to water. As a business with an agricultural supply chain, it is paramount that we take needed steps to protect and preserve the ecosystems where we operate.

Our tobacco supply chain, leaf curing, fertilizer use, and mechanization all add to our carbon footprint. We are relentlessly working toward achieving an absolute reduction in carbon emissions in our tobacco supply chain of 35 percent by 2025 and 50 percent by 2030 versus our 2019 baseline. To deliver on these targets, we seek to decarbonize the tobacco curing process while implementing additional reduction initiatives focused on the use of fertilizer and mechanization.

Our understanding of this crop, which people have grown and used for millennia, continues to expand and promises to keep revealing valuable data for many industries. Our publications library provides the details of our research, and we share literature reviews of our own.

THE BENEFITS OF KNOWING THE FACTS ABOUT NICOTINE

Nicotine's role in smoking-related diseases is often misunderstood by many, including physicians. In this article, we hear from Dr. Matthew Holman, Vice President and Chief Scientific and Regulatory Strategy Officer at Philip Morris International (PMI). Here, he shares some of the facts about nicotine and why having and sharing accurate information on nicotine is so important.



Nicotine is addictive and not risk free, but its role in smoking-related diseases is often misunderstood. Here is what the world's hundreds of millions of adult smokers—and their physicians—need to know about nicotine and smoke-free alternatives, so they can make better choices than continuing to smoke.

Nicotine is a plant-based stimulant

Nicotine belongs to a class of organic compounds called alkaloids and occurs naturally in the family of plants commonly known as "nightshades," including—at very low dosages—in tomatoes and potatoes. What's most commonly known is that it is found—at its highest levels—in the tobacco plant. Although the primary purpose of the chemical in plants is not definitively known, studies have shown that at least one of its functions is to protect the plant from insects.

Nicotine's effects in people, however, are different from its role in plants. Since prehistoric times, people have recognized the stimulating effects of the smoke created by burning tobacco, and smoking has become the most common form of nicotine uptake ever since. Nicotine is addictive and it's one of the reasons why people smoke. Nonetheless, other factors also play a role in making smoking addictive—such as ritual, sensory experience, and social setting.

Nicotine's effects in people, however, are different from its role in plants.

Nicotine activates the reward system

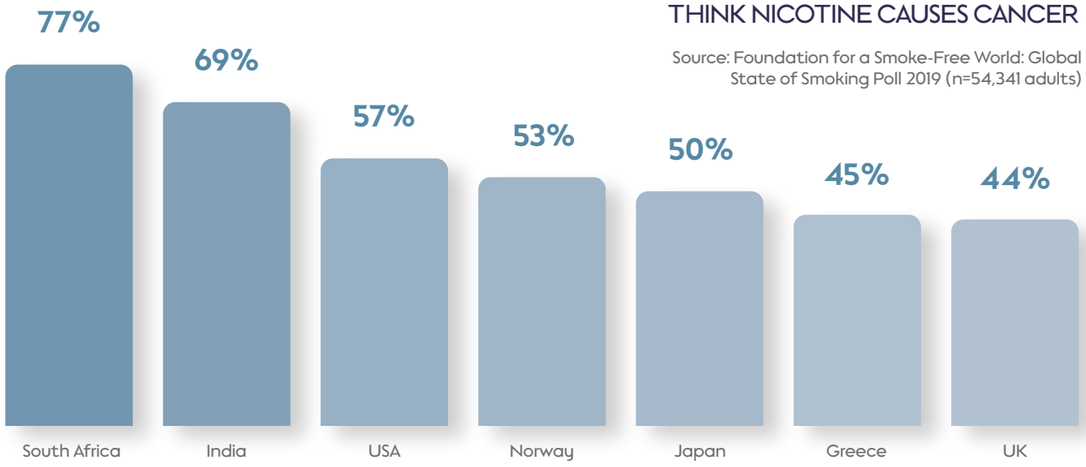
It's recognized that the addictive properties of smoking are caused by a complex interaction of factors—not just nicotine. These factors substantially enhance the action that would be caused by nicotine alone. Exposure to nicotine and the extent of its effects can also be influenced by individual differences in smoking behavior, metabolism, body mass index, and genetics.

Nicotine can be absorbed in a variety of ways, like through the lungs, the mouth, or the skin—such as via cigarettes, chewing tobacco, or nicotine patches, for example. The dosage and how it's absorbed can also determine the speed and intensity of its delivery. Once absorbed, it enters the bloodstream and is distributed, at various concentrations, to all tissues and organs, including the brain. Nicotine modulates the brain's "reward system" by binding to specific receptors distributed in certain regions. When it does, it triggers 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—although it is possible, and millions of smokers quit every year.

PERCENTAGE OF ADULTS WHO WRONGLY THINK NICOTINE CAUSES CANCER

Source: Foundation for a Smoke-Free World: Global State of Smoking Poll 2019 (n=54,341 adults)

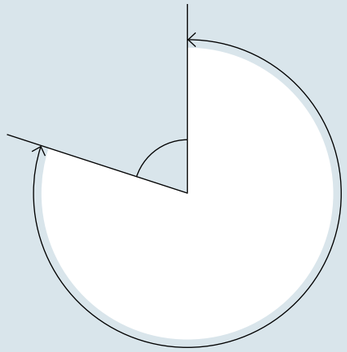


But nicotine is not what makes cigarettes so harmful

Nicotine is addictive, and it is not risk free. Minors, pregnant women, nursing mothers, and people with conditions such as heart disease, high blood pressure, or diabetes should not use tobacco or nicotine-containing products. But, nicotine is not the primary cause of smoking-related diseases. The highest risk of harm comes from burning tobacco to produce smoke. Tobacco smoke contains more than 6,000 chemicals, of which around 100 harmful and potentially harmful constituents (HPHCs) have been classified by public health agencies as contributing to smoking-related disease.

Eliminating combustion—and consequently, dramatically reducing the levels of harmful chemicals—is the cornerstone of smoke-free product development. These products are not risk free and contain nicotine, which is addictive, but can offer taste, ritual, sensation, and nicotine levels comparable to cigarettes to help ensure that adults, who would otherwise continue to smoke, can fully switch.

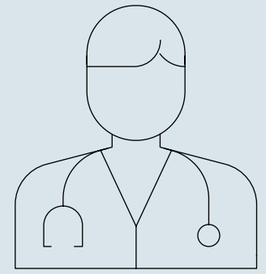
Unfortunately, people often conflate the effects of nicotine with the more harmful effects of cigarette smoke, preventing adult smokers from understanding that different nicotine-containing products have different risks associated with them. Such misunderstandings aren't limited to consumers—some professionals also wrongly attribute the harmful effects of cigarette smoke to nicotine.



NEARLY

80%

of doctors worldwide believe nicotine causes lung cancer



OVER

80%

of U.S. physicians believe nicotine causes cardiovascular disease—including cardiologists

MORE THAN

60%

of U.S. physicians believe all tobacco and nicotine products have equal risk

MORE THAN

80%

of U.S. physicians in the country believe nicotine causes chronic obstructive pulmonary disease (COPD) —including pulmonologists

22%

of U.S. physicians recommend smoke-free alternatives to smoking patients as a better option to continued smoking

Even physicians often misunderstand the risk of nicotine

The U.S. Food and Drug Administration (FDA) Commissioner and the Center for Tobacco Products (CTP) Director stated in 2017, *"Nicotine, though not benign, is not directly responsible for the tobacco-caused cancer, lung disease, and heart disease that kill hundreds of thousands of Americans each year. The FDA's approach to reducing the devastating toll of tobacco use must be rooted in this foundational understanding: other chemical compounds in tobacco, and in the smoke created by combustion, are primarily to blame for such health harms."*

Yet, astoundingly, a 2022 survey demonstrated that nearly 80% of doctors worldwide believe nicotine causes lung cancer. What's more, over 80% of U.S. physicians believe nicotine causes cardiovascular disease—including cardiologists. And more than 80% of U.S. physicians in the country believe nicotine causes chronic obstructive pulmonary disease (COPD) —including pulmonologists. Another survey from 2022 revealed that more than 60% of U.S. physicians believe all tobacco and nicotine products have equal risk. And 22% of U.S. physicians recommend smoke-free alternatives to smoking patients as a better option to continued smoking.

The best choice for anyone is to quit or, better yet, never begin using tobacco and nicotine products. Still, many continue to smoke. For the hundreds of millions of adult smokers who don't stop smoking, proper understanding of the role of nicotine and of the smoke-free category is critical. Accurate and non-misleading communication, increased awareness and better options for adults who would otherwise continue to smoke will help accelerating the end of cigarettes.

PMI PUBLICATIONS

Plasma protein binding and tissue retention kinetics influence the rate and extent of nicotine delivery to the brain

In this study, we used a physiologically based pharmacokinetic model to understand how retention of nicotine in the body's tissues and plasma protein binding can reduce the amount of nicotine that is delivered to an adult smoker's brain as a result of smoking cigarettes. It is known that some of the nicotine gets taken up by lysosomes in cells, and it can bind to proteins in blood plasma. The results of this model showed that increasing the number of lysosomes in the body's tissues to 3 times the base value or increasing the number of these proteins in the plasma to 1.5 times the base value, reduced the amount of nicotine reaching the brain by 20.8% and 39.4%, respectively. This study shows how these two factors can influence the amount of nicotine that reaches the brain, and as a result might influence smokers' nicotine consumption habits.

Tobacco alkaloid assessment in a DSS-induced colitis mouse model with a fully humanized immune system

PMI researchers and co-authors have investigated potentially anti-inflammatory activities of the tobacco alkaloids nicotine and anatabine in a mouse model of ulcerative colitis (UC) with a fully humanized immune system, and identified a possible mechanism for this effect. There is some preclinical, clinical, and epidemiological evidence to suggest potentially anti-inflammatory activities of naturally occurring alkaloids in UC and Crohn's disease. In the study, administration of nicotine in drinking water reduced colitis clinical symptoms in nicotine-treated versus non-treated mice, and improved colitis-specific endpoints, including colon inflammation and tissue damage. The tobacco alkaloid anatabine showed similar effectiveness trends, although they were generally weaker or not significant. The study enables further investigation of possible molecular mechanisms by which tobacco alkaloids might attenuate UC symptoms.

Suppression of pyrrolidine ring biosynthesis and its effects on gene expression and subsequent accumulation of anatabine in leaves of tobacco (*N. tabacum L.*)

The aim of this study was to better understand the biosynthesis of alkaloids in *N. tabacum*. PMI researchers confirmed that nicotine accumulation depends on functional methyl putrescine oxidase (MPO) activity. Alkaloid production is increased in tobacco when the plant is stressed by topping, i.e., removal of the flowers. The researchers stressed MPO-supressed plants where the alkaloid production is redirected from nicotine towards anatabine. By doing so they were able to pinpoint where anatabine is produced and accumulated in the plant. Looking at the pattern of gene expression that took place during this redirection, the researchers have increased our understanding of the genetics of the overall alkaloid synthesis and transport.

Chromosome-level genome assemblies of *Nicotiana tabacum, Nicotiana sylvestris, and Nicotiana tomentosiformis*

In this study, PMI researchers updated previous *N. tabacum* genome publications to provide more precise tools for tobacco researchers. The previously published genome assemblies for *N. tabacum, N. sylvestris,* and *N. tomentosiformis* relied primarily on short DNA-sequence reads, and only partially represented the genomes. Here, the researchers generated annotated *de novo* chromosome-level genomes. They focused on genome construction and annotation, reducing the fragmentation of the previously available data. The new data will broaden understanding of the contributions of both *N. tabacum* progenitors (*N. tomentosiformis* and *N. sylvestris*) to the makeup of tobacco and enable more efficient comparisons with other species of the *Solanaceae* genus, for example conservation of the nature and organization of genes within a chromosome region.

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.