SCIENTIFIC UPDATE

PMI SCIENCE – PHILIP MORRIS INTERNATIONAL

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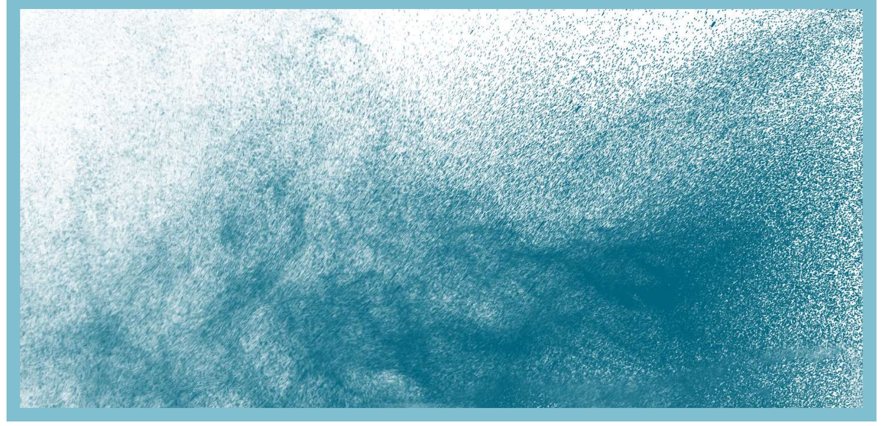

INTRODUCTION

According to a series of surveys analyzed in 2016, many people did not have even a basic understanding of how harmful chemicals end up in cigarette smoke.[1] Unfortunately, it seems that's still true today.

People in general do not recognize that most of the toxicants in cigarette smoke come from the burning and high-temperature pyrolysis of tobacco. While they probably know that nicotine is present in cigarette smoke, they likely fail to realize that it is not the primary cause of smoking-related diseases. It's the other toxicants in cigarette smoke, some more well-known than others, that pose the greater risk to health.

This is why the ninth issue of the Scientific Update explores the concept of combustion. Ultimately, we need to have a sensible conversation about tobacco harm reduction. Adult smokers have a right to be part of that conversation, supported by accurate and non-misleading information about the products they use.

References can be found online at: *www.pmiscience.com/SU9refs*

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WHY WE DON'T NEED **COMBUSTION**

First: what is combustion?

Combustion is the process of burning something, and it requires three elements: a fuel source, like tobacco; oxygen, found in air; and enough heat to kickstart the self-sustaining, heat-generating reaction. During combustion, in ideal conditions, hydrocarbons and oxygen react to form carbon dioxide and water. In more realistic settings, for example in combusted cigarettes, there is not enough oxygen available for complete combustion to occur. Incomplete combustion leads to the production of carbon monoxide and numerous other molecules, of which many have been recognized by health authorities to be harmful or potentially harmful. Some of the toxicants emitted during combustion form liquid and solid particles that, together with the rest of the emissions, result in smoke that can be harmful to health if inhaled.

The best choice: stop smoking completely

Smoking a cigarette involves combustion and the generation of smoke. Millions of smokers every year decide that they don't need cigarettes in their lives and quit completely. They make the single best possible choice a smoker can make for their health: they quit tobacco and nicotine completely.

Still, there are many men and women who decide that while they don't want to smoke, they do want to continue using nicotine and tobacco products. They are looking for similar taste, rituals, and nicotine uptake as those of cigarettes, but without the smoke. Thanks to technological advancements in smoke-free products, those experiences can be delivered without combustion.

Where is the line between heating and burning tobacco?

Roughly 400 °C

EVAPORATION
< 100–300°C (heating)
Turning liquid into vapor.

TORREFACTION
200–300°C (heating)
A kind of mild decomposition that does not require oxygen.

PYROLYSIS
300–600°C (heating)
A kind of decomposition that does not require oxygen.

COMBUSTION
400°C and higher (burning)
Requires oxygen. Smoldering at lower temperatures and flames at higher temperatures.

We need heat – not combustion – to release nicotine

Nicotine in cigarette smoke is transferred from the tobacco at temperatures up to its boiling point around 247°C. That's far below the temperature at which tobacco begins to burn, around 400°C.[2] That means it's possible to heat tobacco enough to release nicotine without burning it and producing smoke. Heated tobacco products do exactly this, for example. Alternately, e-vapor products heat an e-liquid to release nicotine and flavors, while also avoiding combustion and smoke.

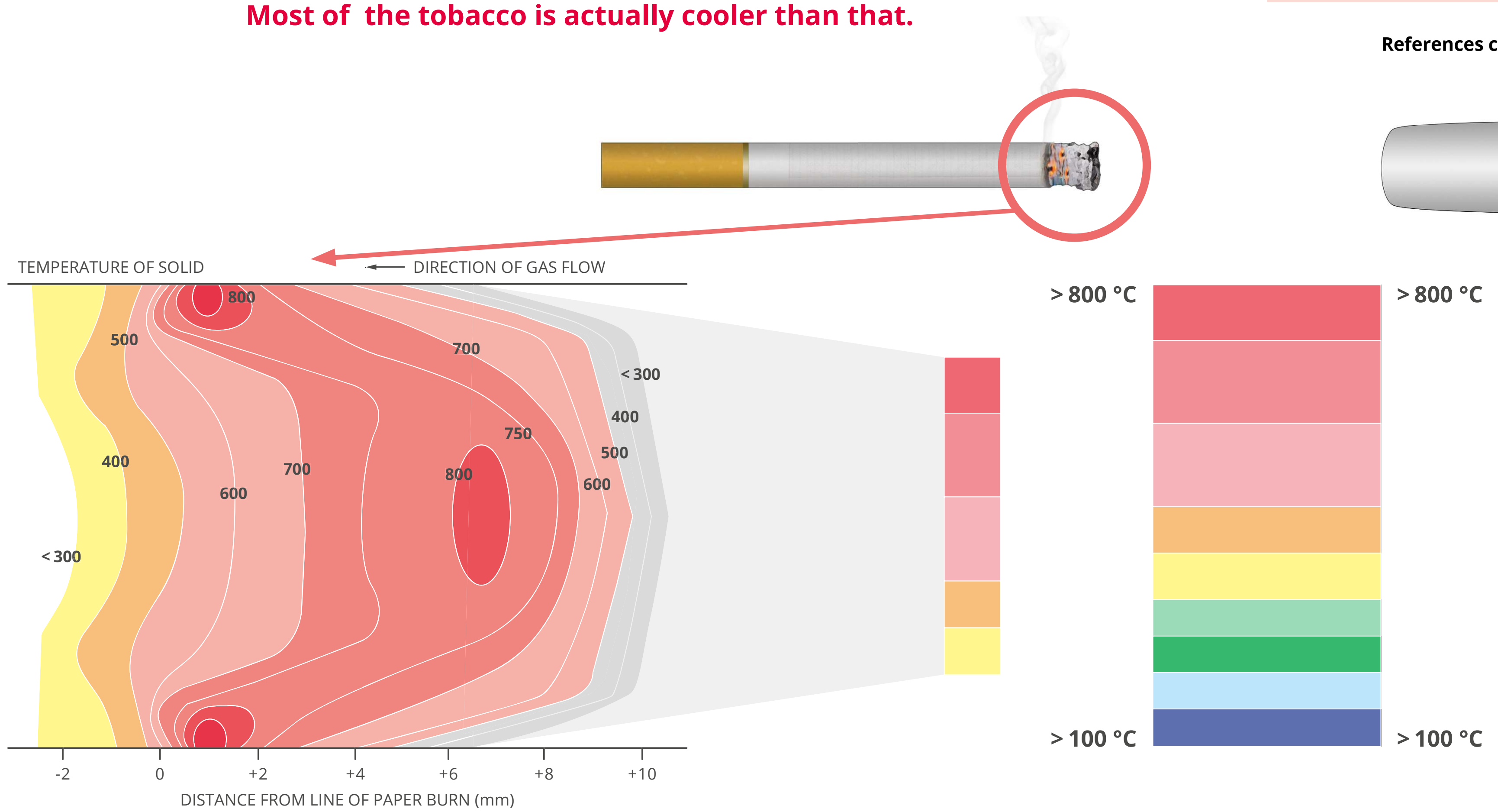
Tobacco – like many materials – loses mass into the air as it is heated through a range of temperatures.[2] First, the drying process: it loses moisture between 30-150°C. From around 100-300°C, various chemicals besides water are evaporated from the tobacco as a result of the heat alone, and some of the tobacco components are broken down. Nicotine is also released from the tobacco at these temperatures.

Above this range, the presence of oxygen begins to become important as the tobacco draws closer to the ignition temperature. Below about 400°C, there's not too much of a difference between the processes that occur in tobacco that's heated in air with oxygen versus tobacco that's heated without oxygen. But above 400°C, there's a big difference: in oxygen, it burns.

In our Electrically Heated Tobacco System (EHTS), there's no combustion.[3] The temperature of the tobacco is carefully controlled. It simply never reaches a high enough temperature, and the composition of the aerosol further verifies this. EHTS operation does involve heating, evaporation, torrefaction (think: roasting coffee beans), and some low-temperature pyrolysis, but no combustion. Further, the processes that occur in the EHTS do not create smoke, which is why we call it a smoke-free product.

Temperature of tobacco material in EHTS compared to cigarettes

The temperatures of burning tobacco in a cigarette range from 600°C to over 800°C in the hottest regions, while the tobacco touching the heating blade in EHTS doesn't rise above 350°C. Most of the tobacco is actually cooler than that.



Chemicals in tobacco smoke

Thousands of components have been identified in tobacco plants, and it's estimated that thousands more are waiting to be discovered, according to Rodgman and Perfetti.[4] Like any plant, tobacco takes simple elements and converts them into macromolecules for growth and self-maintenance. That process is further compounded by the burning of its cured and dried leaves to create the complex mixture of more than 6000 chemicals that constitute tobacco smoke. Here are a few components of that smoke as described by Rodgman and Perfetti, 2013.

Cigarette smoke contains certain metals because tobacco plants require essential minerals for growth, and because the metals are also found in soil. Almost every metal found in tobacco can transfer in small amounts into cigarette smoke when the tobacco is combusted. Among these, arsenic, beryllium, chromium, nickel, and cadmium are listed as human carcinogens by the International Agency for Research on Cancer (IARC) as of 1985.

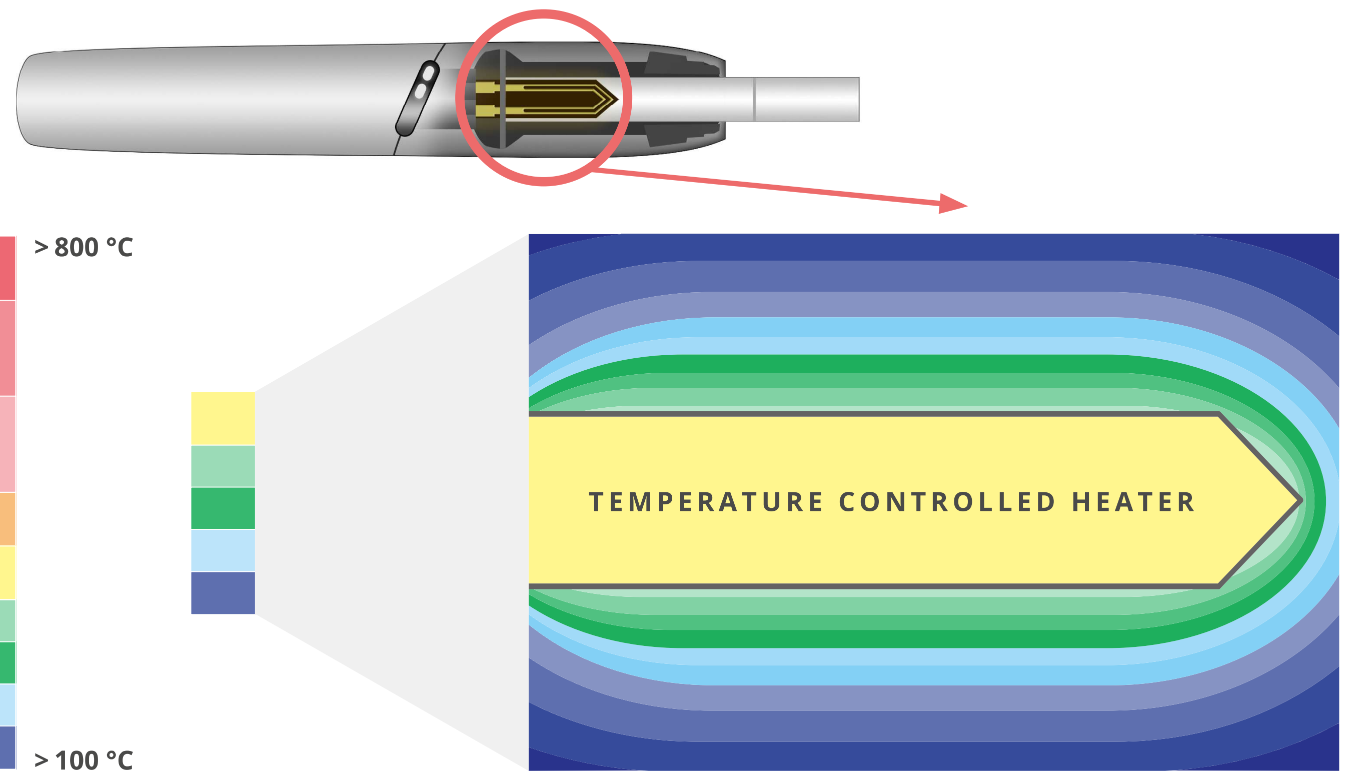
N-Nitrosamines are organic compounds recognized as carcinogenic, they're formed during tobacco processing and during the burning of a cigarette. N-Nitrosamines may be categorized as tobacco-specific N-nitrosamines (TSNAs), as volatile or non-volatile N-nitrosamines (VNAs or NVNAs). The transfer of these constituents to smoke varies per N-nitrosamine. For example 6.9-11 percent of the TSNA N-nitrosonornicotine (NNN) is reported to be transferred from tobacco plant to smoke, and so is ~40 percent of the TSNA nicotine-derived nitrosamine ketone (NNK).

There are over 1200 hydrocarbons in tobacco smoke, including alkanes, alkenes, alkynes, alicyclic hydrocarbons, monocyclic aromatic hydrocarbons, and polycyclic aromatic hydrocarbons (PAHs). Over 500 tobacco smoke PAHs are known, many of which have been extensively studied because of their link to potential health concerns. This has led to the classification of PAHs as toxicants.

Knowledge about tobacco smoke constituents grew vastly in the 1950s, and as a result a list of specific aldehydes (such as formaldehyde, acetaldehyde, acrolein) and ketones (such as 3-pentanone; 4-heptanone; and 2,3-butanedione) were identified, which were reported to play a role in tumor formation and in ciliastasis – stopping the beating of mucous membrane cilia.

These are just a few of the thousands of chemicals and constituents that comprise tobacco smoke, many of which have been identified as harmful and potentially harmful constituents (HPHCs). Research has shown that a majority of HPHCs in cigarette smoke are caused by combustion. By eliminating combustion, we can reduce the level of HPHCs produced. Our studies have also shown an average reduction in EHTS aerosol HPHCs of 95 percent, compared to cigarette smoke.

References can be found online at: ***www.pmiscience.com/SU9refs***



Based on 2D simulations

CLEANER AEROSOL, CLEANER AIR

How we assess indoor air quality

How would you know whether the quality of the air you're breathing is poor? To some, the first indication might be visual; for example, smog or black smoke. But the presence of something visible doesn't reveal how harmful the compounds in the air can be. The best way is to analyze those individual airborne compounds regardless of their smell or color.

Assessing air quality is an important factor of the science behind our smoke-free products – in this case EHTS – as it provides a strong indication of the potential impact that a product's use may have on bystanders. So how exactly do we measure air quality? By analyzing the effect of EHTS and cigarettes, compared to background air.[5] We explored this influence over three settings: home, office, and restaurant. Then we simulated each of these in a lab by varying the number of people occupying the space, and the amount of air being circulated – based on the European ventilation performance standard.[6]

The office setting involved three people and a ventilation rate (the amount of air being pumped into/out of the room) of 156 m^3/hour. The restaurant environment involved five people in total, paired with a ventilation rate of 555 m^3/hour. The scenario for home tests used the same number of participants, but with an 87 m^3/hour ventilation rate. Additionally, another study we carried out later focused exclusively on the home setting, involving three people at 37 m^3/hour.[7]

To ensure accurate measurements and no cross-contamination, we air-washed the room overnight with a ventilation rate of 750 m^3/hour of clean filtered air, and the furniture was cleaned with a water-ethanol mixture. To establish a background baseline, the air quality was also determined before any EHTS or cigarette use.

The order of events for each test was: air wash, background measurement, another air wash, then EHTS or cigarette use. We evaluated 18 different compounds for all three settings, and 24 compounds in the additional home environment study (all listed in the 'Compounds tested' sidebar), for both EHTS and cigarette use. Across the settings, EHTS use showed no significant difference compared to background air for 16 of 18 measured compounds, and the two that were higher – nicotine and acetaldehyde – were still far lower than the existing guideline levels.[8] Comparatively, cigarette use showed a significant difference in all 18 compounds versus background levels, and at higher levels than EHTS. This led us to conclude that the use of EHTS in an indoor environment does not adversely affect the overall indoor air quality.

These are two of many studies we've carried out on the indoor air quality effects of EHTS. Our research has also covered the effects of EHTS on the air quality of day-to-day activities, entertainment environments, stores, and other real-world settings which resulted in the same conclusion; no negative impact on the overall indoor air quality. These are outlined in our report of EHTS's lack of environmental tobacco smoke,[9] which also provides an overview of independent studies researching our product's impact on indoor air quality.

Note: studies such as these are part of our product scientific assessment program, not part of regulatory efforts to affect public smoking bans.

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Compounds tested

These 18 were selected as a representation of standard air quality markers[8], and markers non-specific and specific to EHTS aerosol or cigarette smoke:

- RSP
- UVPM
- FPM
- Solanesol
- 3-Ethenylpyridine
- Nicotine
- Acetaldehyde
- Acrolein
- Crotonaldehyde
- Formaldehyde
- Acrylonitrile
- Benzene
- 1,3-Butadiene
- Isoprene
- Toluene
- CO
- NO
- NO_x

The additional study also measured:

- Glycerin
- Propylene glycol
- NNK
- NNN
- PM_1/$PM_{2.5}$
- TVOCs

Ventilation rates of different settings

Restaurant: 555 m^3/hour = 7.68 air changes
Office: 156 m^3/hour = 2.16 air changes
Home: 87 m^3/hour = 1.2 air changes, and 37 m^3/hour = 0.5 air changes.

INDEPENDENT RESEARCH

Study re-confirms cigarette use increases risk of lung disease

According to the first three waves of the Population Assessment of Tobacco and Health, the authors reported an association between e-cigarette use and incidence of chronic respiratory disease.[10] The widespread reporting on this study suggests that the e-cigarettes somehow caused the respiratory disease, which is unlikely. The study is simply not designed to assess and understand the impact of e-cigs on lung disease for several reasons. The study is only 3 years long, too short to observe any serious lung disease developing as a result of e-cigarette use. The vast majority of the e-cigarette users in the study are also current smokers (i.e. dual users), and the study ignores smoking history which is a strong predictor of lung disease development. The authors also showed that smokers might switch to e-cigarettes because they already have symptoms of asthma or pulmonary disorder, though unfortunately this point went mostly unreported.

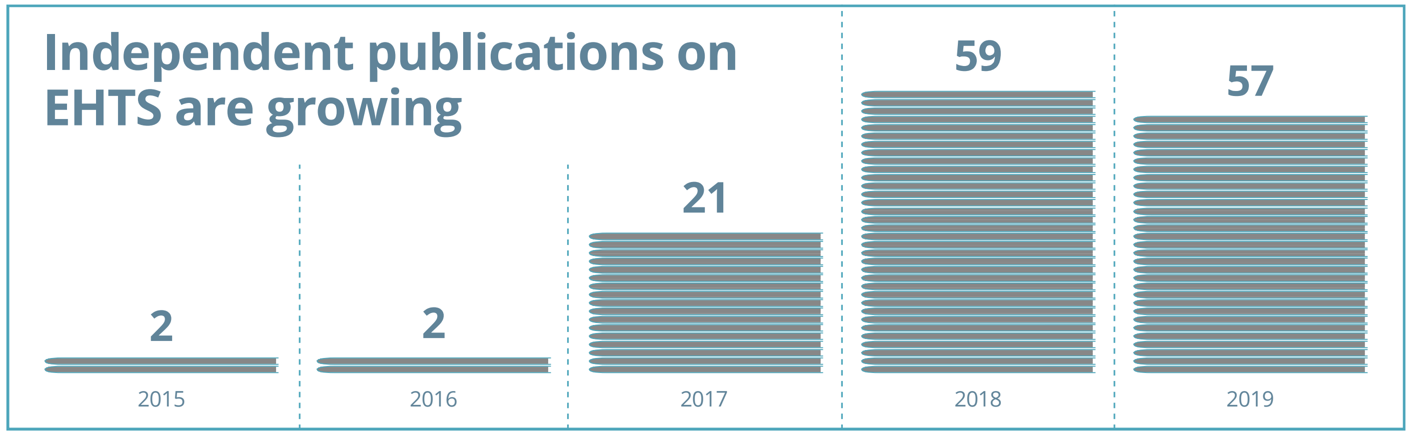
Factors that influence switching to EHTS

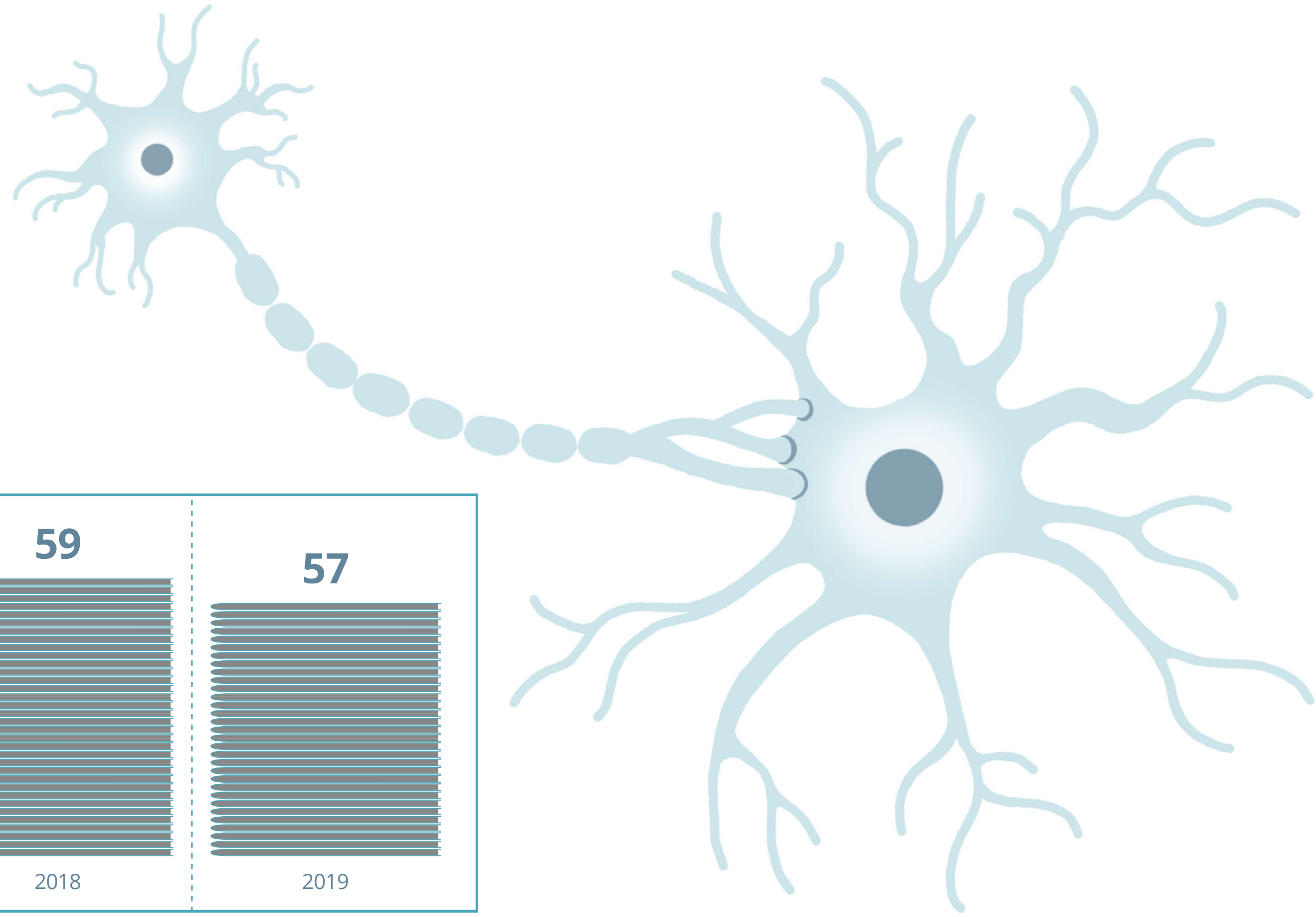
The authors conducted a small-scale qualitative study with EHTS users and ex-users in London, aiming to understand why the people interviewed chose to switch from cigarettes to EHTS.[11] Among 22 current and 8 ex-EHTS users, participants commonly said that they tried the product in order to cut down on cigarette smoking or to replace it entirely. Participant perception of the product is that it is less harmful compared to cigarettes, but they also recognized that it isn't risk-free. Participants who reported changes to their physical health generally reinforced their reduced perceived risk compared to cigarettes, though start-up costs and mixed media messages caused some people to go back to smoking cigarettes. The results of the study have implications for further research on smoke-free products.

WHO director emphasizes regulation over product bans

"What did Prohibition teach us about banning hazardous products like alcohol, tobacco, or e-cigarettes?" asked Dr. Lawrence O. Gostin, the director of the O'Neill Institute for National & Global Health Law, a WHO Collaborating Center. He cites the failed experiment of prohibition in the U.S. as an example not to follow with respect to nicotine-containing products.

Gostin's editorial in Science Magazine points to regulation as the primary cause of today's lowered smoking rates.[12] Those regulations include taxation, age restrictions for purchasing and marketing tobacco products, graphic health warnings, and efforts to reduce public smoking. Beyond regulation, Gostin also encourages harm reduction efforts. *"Prohibiting vaping would cause a public backlash and extinguish any benefit from harm reduction,"* wrote the director, and that instead, a suite of regulations would serve as a more nuanced approach. *"Government's greatest responsibility is to safeguard the public's health. It can do that through a well-regulated society—that is, with evidence-based interventions to 'nudge' the public to adopt healthier and safer behaviors."*





Study linking e-cigarette use to heart attack retracted

The Journal of the American Heart Association (JAHA) has retracted a study by Drs. Dharma N. Bhatta and Stanton A. Glantz which indicated a link between e-cigarette use and heart attack.[13] The study was widely reported on as indicating that e-cigarettes caused heart attacks. There was concern regarding the timing of heart attacks – the study did not provide information about whether smokers had switched to e-cigarettes before or after their heart attack. The authors had been asked to revise their analysis based on when survey respondents started using e-cigarettes, but they were unable to comply because the authors' access to the Population Assessment of Tobacco and Health (PATH) study's restricted-use data set, necessary to conduct the re-analysis, had been revoked. Ultimately, the editors did not agree with the authors' methodology. The retraction note concludes, *"Given these issues, the editors are concerned that the study conclusion is unreliable."*

References can be found online at:
www.pmiscience.com/SU9refs

PMI PUBLICATIONS

Characterizing alkaloids with receptors

Nicotinic acetylcholine receptors (nAChRs) are crucial receptors involved in most neuron communications in the brain, they're also found outside of the nervous system. In this study we used automated electrophysiology (electrical activity of neurons) to define the effects of 71 tobacco alkaloids (nitrogen-containing organic compounds found in plants) on two types of human nAChRs; α4β2 and α7.[14] We identified that the alkaloids had positive and negative effects on nAChRs. Four alkaloids – nicotine, nornicotine, anabasine, and R-anatabine – potently activated α4β2 and weakly activated α7. We also demonstrated that human α4β2 is the most relevant nAChR for sensing the most abundant alkaloids in tobacco plants.

The effect of non-flavored e-liquids

Using *in vitro* micronucleus assays, we evaluated six non-flavored e-liquids to define the baseline effect they'd have on animal cells.[15] Even though the e-liquids we tested varied in their content of propylene glycol (PG), vegetable glycerin (VG), and nicotine, they all displayed toxic effects on the cells and DNA. Additionally, PG content was linked to DNA damage, but our data suggest that the damage could be potentially misleading and of negligible biological relevance. Future e-liquid DNA toxicity studies may be able to use our reference data to indicate possible genotoxic hazards.

Modeling human airways to understand aerosol deposition

The aerosol studies we carry out deal with composition, toxicology, and deposition. In this study we look to further understand aerosol deposition in human lungs from toxicological and pharmacological viewpoints.[16] We presented a novel protocol and software framework to produce airway models based on anatomical information from a person's inhalation/exhalation measurements, spirometry, and physiological data. What can this be used for? Person-specific simulations of lung physiology, inhalation, and aerosol deposition.

References can be found online at:
www.pmiscience.com/SU9refs

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Important information

This Scientific Update provides an overview of the most recent scientific developments behind PMI's approach to achieving a smoke-free future through a range of alternatives to cigarettes that do not burn tobacco. The following pages include our product development and assessment efforts, our initiatives to share our methodologies and results, as well as independent research and government reports. More detailed information can be found at www.pmiscience.com.