SCIENTIFIC UPDATE

PMI SCIENCE – PHILIP MORRIS INTERNATIONAL

JULY 2020 | ISSUE 10

CONTENTS

INTRODUCTION

We read with interest a study[1] that was published earlier this year describing a scale to measure peoples' information preferences. The authors highlighted decades-old predictions that decision-makers would be eager to take advantage of the wealth of information available today. Instead, study after study finds that people avoid learning information that could be painful in some way: unwanted medical diagnoses, seeing losses in a stock portfolio, or ranking poorly versus peers in intelligence or attractiveness.

"Across contexts, people seem to deliberately and actively avoid information, even when it could be instrumentally useful and lead people to make different decisions," the authors write. Essentially, the truth can hurt. But in our opinion, perhaps the most beautiful thing about science is that eventually, it becomes impossible to ignore. So, let's rip that bandage off, take advantage of the wealth of information science has to offer, and apply that newfound knowledge to public health decisions.

The decision by U.S. Food & Drug Administration (FDA) regarding our Modified Risk Tobacco Product (MRTP) application was a function of the U.S. laws and regulations, and also just one example of a science-based approach to harm reduction. We're glad that the Agency has recently authorized marketing of our IQOS Tobacco Heating System as a Modified Risk Tobacco Product with reduced exposure claims. We'll delve deeper into this decision and what it means in our next issue.

References can be found online at: *www.pmiscience.com/SU10refs*

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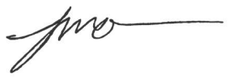
Scientific Writer,
Managing Editor



Dr. Moira Gilchrist
Vice President Strategic
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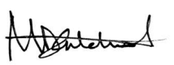

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EVENTS

International Conference on Harm Reduction

Paris, France 2-3 February 2020

The International Conference on Harm Reduction in Non-Communicable Diseases was held in Station F in Paris, described as the biggest start up campus in the world. The meeting was chaired by Professor David Khayat, former President of the French National Cancer Institute, and Doctor Peter Harper, former head of oncology of Guy's, King's and St Thomas Hospital in London. The conference highlighted how harm reduction has been applied to improve health outcomes related to diet, sun exposure and tanning, various causes of cancer including smoking, and others. After the conference, PMIScience hosted a separate event where several speakers including Dr. Gizelle Baker, Director Global Scientific Engagement of PMI, discussed harm reduction in regards to smoking.

Global Forum on Nicotine (GFN)

Online 11-12 June 2020

Dr. Moira Gilchrist, VP Strategic & Scientific Communications, spoke at this year's GFN. She was invited to present on the topic of our corporate transformation. During her presentation, she discussed statistics that have so far marked our transformation progress, emphasized the need for objective, evidence-based conversation around smoke-free products like EHTS. The conference, usually held in Warsaw, Poland, was held online this year with an abbreviated program and without the usual poster session.

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Open Science

Online 15 June 2020

ANGELA VAN DER PLAS, MD, PhD
Manager Scientific and Medical Engagement

We hosted Open Science, an online webinar where our researchers presented their most recent posters. Three sessions were hosted, each with the same content, to enable researchers from multiple time zones to participate. The five scientists pre-recorded themselves presenting their posters, and those videos were played at each session, followed by a live scientific question and answer session. The event was free and open to registered participants.

Dr. Marija Bosilkovska presented on results comparing switching to EHTS to the gold standard of smoking cessation. Dr. Karina Fischer explained how people's perceptions of certain substantiated claims about EHTS can affect their use patterns. Dr. Christelle Haziza and Dr. Loyse Felber Medlin presented posters on the effects of switching to EHTS on weight gain and on smokers' cough, respectively. And Dr. Angela van der Plas presented an analysis of real-world data on EHTS.

With over 1,000 people registered for the online event and some excellent questions during the question and answer sessions, we're looking forward to hosting additional Open Science events in the future.

Learn more about Open Science: www.pmiscience.com/open-science

THE IMPORTANCE OF **SCIENCE-BASED** DECISIONS

Evidence-based decision-making is key when objective facts are used to determine the correct decision to make. I'm writing here about tobacco harm reduction specifically, but any decision worth making is worth making right. And those decisions should always be made in the context of the totality of available evidence.

Dr. Moira Gilchrist,
Vice President Strategic
& Scientific Communications

Humans can be terrible decision makers, especially in the heat of the moment and when tensions are high. Scientists and regulators are only human too, and they have the same weaknesses as anybody else when it comes to decision-making.

This is why philosophers have developed various guidelines for drawing conclusions and making decisions. No two people see the world the same way, which is why it's so important to gather data using methods and tools everyone can agree on. That's also why it's important to debate the data openly and transparently, and to do so while being clear about both implicit and explicit biases. It gives us all common context to work from.

Appropriate and validated methods

Research is – and should be – deliberate. A good scientist defines their hypothesis and selects their experiments, tools, and methods deliberately. They make choices that ensure they are measuring what they intend to measure, so that the data they collect is complete enough to make sound conclusions. Solid data lets other researchers accept those conclusions and use that data as a comparison or a launching pad for their own research.

For example, one can conduct a survey of current e-cigarette users, track the health of this population over time, and determine whether these consumers have an increased or decreased health risk of some kind, relative to other populations. But sufficient data must be collected, and necessary questions must be asked, to ensure the researchers accurately rule out confounding factors. Many e-cigarette users are also either former or current smokers, and that smoking history is well known to carry increased health risks. Using appropriate methods and statistical analysis can help to clarify whether and how each factor might contribute to increased risk, or to risk reduction.

One deliberate choice that scientists can make is to transparently publish their methods. This is usually done within a research paper, though some researchers take transparency to the next level. Data analysis programs can be published online for others to freely explore. In some cases, scientists can rely on publicly available and validated methods or standard protocols for things like measuring Nicotine-Free Dry Particulate Matter (NFDPM) and using well-known "smoking regimes" for collecting and comparing aerosols in a reproducible way. It's also important to have accepted standards that help contextualize results, such as regional or national guidelines for chemical exposure, or limits on the presence of certain chemicals in the context of indoor air quality.

"Sufficient data must be collected, and necessary questions must be asked, to ensure the researchers accurately rule out confounding factors."

Evidence?

Transparency and scientific discussion

When a company, a scientist, or a regulator acts with transparency, it's a signal that their actions and their intentions match their words. Transparent actions build trust by inviting and withstanding scrutiny, even from the harshest of critics.

But what does it actually mean to act transparently?

There are some great ways to make research more open and transparent. For example, many scientists provide the analysis code and even the raw data behind their study so others can analyze the same data and come to their own conclusions. Indicating whether and why data was excluded, and explaining how the study's sample size was selected are also important for transparent reporting of results.

Our INTERVALS.Science platform enables independent data re-analysis and collaboration by openly sharing protocols, tools, and research data. We also publish our assessment of our products openly in scientific journals, especially because of the peer-review process. In fact, we prefer to publish our work in journals that provide an open access option as often as possible. We also respond openly to comments on our publications.

Transparent actions like these all make it easier for critics to scrutinize our work. That scrutiny is welcome. We are confident that our work and results are built on a strong foundation of evidence – so confident that we're willing to share that foundation. But we also recognize that there may be gaps in our research that others can see more easily.

Addressing bias in research

Everyone has a bias of some kind. When a manufacturer of any product conducts or funds scientific research on it, there is always a potential for bias, whether it is food, pharmaceuticals, or smoke-free products. This is why we require researchers to acknowledge our involvement when they present or publish results of studies we have financially supported.

Independent researchers can have a bias too: in favor of their funding organizations, their research collaborators, or even their own personal opinions. The scientific method calls for a hypothesis in order to design the experiment, and we humans prefer to be right. Confirmation bias is the devil on a person's shoulder, making it difficult to accept the evidence that shows their hypothesis may be wrong or that someone else's hypothesis might be right.

Don't get me wrong: a little healthy competition is actually great for pushing science forward! But antagonistic factions with an "us vs them" mentality have no place in the scientific community. With that in mind, it's even more important for every scientist – industry and independent scientists alike – to use validated methods, to share their research openly, and to invite discussion and feedback. Individual studies, no matter how well they're designed, can only ever tell part of the story.

"Weigh each bit of research by the extent to which it contributes to the current understanding of the topic."

Big decisions require big-picture thinking

Studies that have strong, thorough, and well-validated methods should be weighted more impactfully than those using weak or poorly described methods. Studies where the authors or funders have known biases should face scrutiny, but they should not be excluded on that basis alone. Where several different groups of researchers have presented similar data or come to similar conclusions, that reproducibility gives them a stronger collective voice in the discussion, provided that the data are of high enough quality.

This is why it's so important to consider all the available evidence, to weigh each bit of research by the extent to which it contributes to the current understanding of the topic. Each published study is one tiny window to the world, with its own angle and frame. It takes many such windows and an understanding of their perspective on the world to get a clear picture.

TOBACCO HARM REDUCTION

DR. GIZELLE BAKER EXPLAINS THE BASICS OF HEATED TOBACCO PRODUCTS

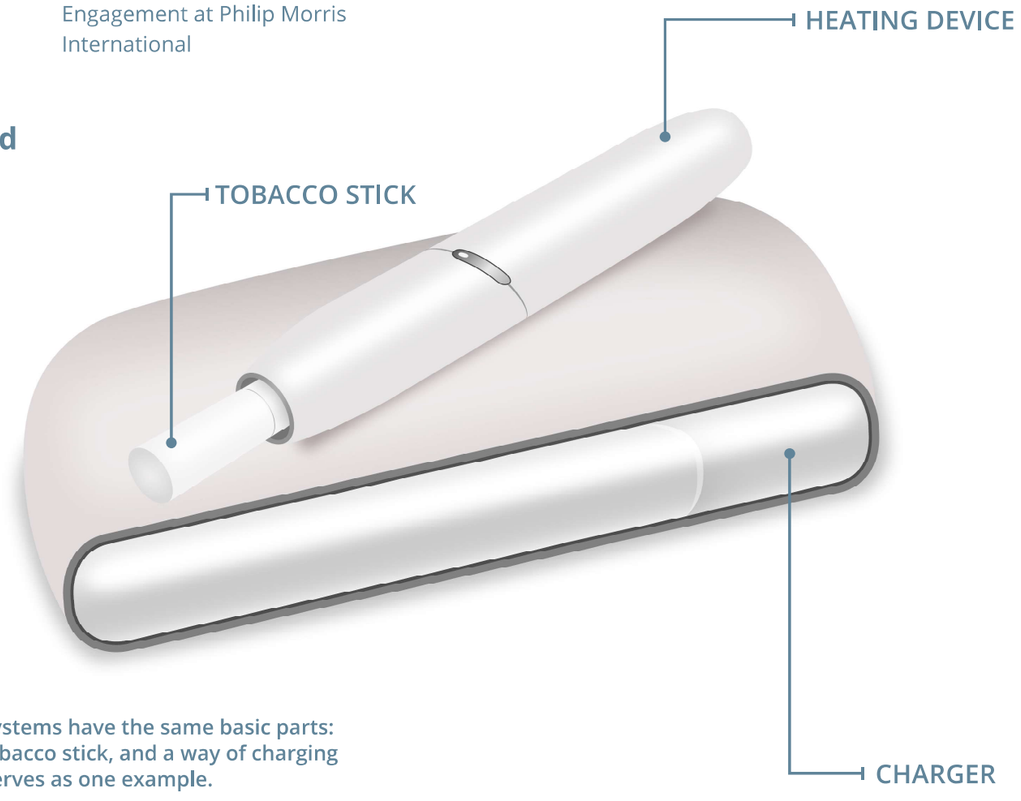
Dr. Gizelle Baker,
Director Global Scientific Engagement at Philip Morris International

As new smoke-free products reach more people, it's more important than ever to provide people accurate and non-misleading information about these products. Dr. Gizelle Baker walks us through the current scientific understanding of heated tobacco products.

What are heated tobacco products?

Heated tobacco products (HTPs) are a range of relatively new products that were developed and assessed to reduce the harms associated with smoking for adult smokers who would otherwise continue to smoke cigarettes. Unlike cigarettes, HTPs heat the tobacco without burning it. This creates an aerosol that contains nicotine, as well as much lower levels of harmful chemicals than cigarette smoke. Both of these points should be confirmed for each product via scientific assessment. Even so, the best choice is to quit nicotine and tobacco products altogether.

In this category, you have products that vary in tobacco heating temperature (though all below the ignition point of tobacco), heating sources, tobacco processing, flavors, and designs, with new technologies still in development. So, although HTPs are a class of products, each specific product really needs to be assessed separately.



Most heated tobacco systems have the same basic parts: a heating device, the tobacco stick, and a way of charging the heater. Our EHTS serves as one example.

How do they work?

HTPs heat tobacco, sometimes by means of e-vapor passing through the tobacco portion at temperatures well below combustion (burning). How the heating source works depends on the product, but in all cases the heat aerosolizes nicotine directly from the tobacco. The user draws on the mouthpiece to inhale the nicotine-containing aerosol.

Because the tobacco is heated and not burned, the aerosol that's inhaled is fundamentally different in composition from cigarette smoke. HTPs contain tobacco, which is why they can provide a taste and nicotine delivery similar to cigarettes. At the same time, the number and levels of other toxic chemicals in the aerosol may vary from product to product, but should be reduced compared to cigarette smoke.

Are HTPs the same as electronic cigarettes?

No, they're not the same. HTPs heat tobacco to generate a nicotine-containing aerosol directly from specially processed tobacco, while e-cigarettes vaporize an e-liquid containing nicotine and flavors. Both are types of smoke-free products that can deliver a nicotine-containing aerosol and—when scientifically substantiated and regulated—can be a better alternative to cigarettes for adults who would otherwise continue smoking. Since both product types generally deliver nicotine, they are addictive. Neither product type is risk-free. The best choice for any smoker is still to quit tobacco and nicotine altogether.

95%

AVERAGE REDUCTION IN LEVELS OF HPHCs IN EHTS AEROSOL COMPARED TO CIGARETTE SMOKE

Are HTPs safer than cigarettes?

HTPs are not risk-free. They have the potential to contribute to better health outcomes for adult smokers who switch to them completely, since they can significantly reduce exposure to the toxicants in cigarette smoke that are known to cause smoking-related diseases.

Quitting tobacco and nicotine use altogether completely eliminates the exposure to these toxicants and is certainly the best way for a smoker to reduce the risk of smoking-related diseases. But many smokers do not quit. HTPs are for those men and women who would otherwise continue to smoke. They should be encouraged to switch completely.

Do HTPs expose users to new chemicals?

HTPs are a class of products, which means the aerosol from each product must be individually assessed. For our Electrically Heated Tobacco System (EHTS),* it is estimated that 99.7% of the emitted aerosol is of known composition. The results demonstrated a 95% reduction in the average levels of Harmful and Potentially Harmful Constituents (HPHCs) compared with reference cigarette (3R4F) smoke and fewer chemicals in the aerosol than in cigarette smoke.[2]

Three chemicals were identified in the aerosol of EHTS that were not in the smoke from the reference cigarette, but all of these chemicals have previously been reported in the smoke of marketed cigarettes. This means that there are no unique chemicals in the HTP aerosol. While some chemicals are found at higher levels in the aerosol of EHTS compared to cigarette smoke, U.S. Food and Drug Administration (FDA), in their review of our data, has concluded that, *"these chemicals are present in very low levels and potential effects are outweighed by the substantial decrease in the number and levels of HPHCs (harmful and potentially harmful constituents) found in combusted cigarettes".*[3]

References can be found online at: *www.pmiscience.com/SU10refs*

* EHTS is marketed under the brand name *IQOS.*

"Not all tobacco products are the same. They exist along a continuum of risk."

Is there second-hand exposure from HTPs?

Indoor air quality studies are an important part of assessing the overall reduced-risk profile of HTPs. Studies on the use of HTPs indoors focus mostly on EHTS, showing that the levels of HPHCs in the air can be dramatically reduced compared to cigarettes, but not entirely eliminated. Most of the chemicals analyzed were detected at levels indistinguishable from background with the exception of nicotine, acetaldehyde, and glycerin. The levels of nicotine and acetaldehyde were well below the levels measured when cigarettes were used, and all were well below the thresholds defined in air quality guidelines. Based on these results, EHTS causes no negative impact on indoor air quality.

For EHTS, this led U.S. FDA to conclude that *"reduced HPHC (harmful and potentially harmful constituent) exposure also is beneficial for those who would be secondarily exposed to the aerosol [of EHTS] as compared to environmental tobacco smoke".*[3]

Is HTP use common among non-smokers and youth?

Although there are a limited number of studies that have researched HTP uptake by never smokers, former smokers, and youth, there are some data available, mostly from countries where EHTS is sold. Generally, the data show that the population most likely to use EHTS are current smokers, with low uptake by youth and non-smokers, and a slightly higher, but still low likelihood of uptake in former smokers. Data from studies conducted in Japan,[4] Germany,[5] and Switzerland[6] by local health ministries and organizations find that HTP use among youth are in the low single-digits while cigarette use tends to be higher among the same age groups.

Studies may show conflicting results, but it's important to remember that "trying" a product is not the same as "established use" of a product. The 2010 Global Youth Tobacco Survey Italian data showed 60.3% (CI 52.7–67.3) of participants aged 15 replied yes to the question *"Have you ever tried or experimented with cigarette smoking, even one or two puffs?"* Compared to that value, 12.7% (CI 9.1–17.5) of the study participants reported smoking cigarettes daily.[7]

Any additional thoughts?

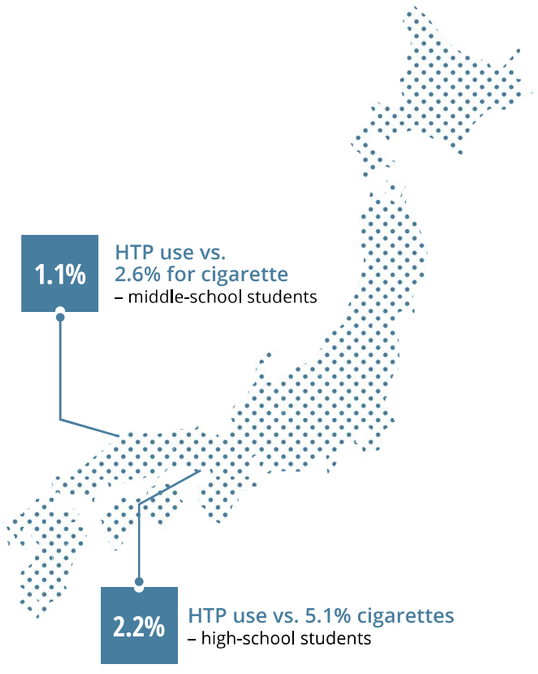
Not all tobacco products are the same. They exist along a continuum of risk between combusted tobacco at the most harmful to complete cessation of nicotine and tobacco products altogether. Risk-proportionate regulations could help encourage adult smokers who do not quit to switch to better alternatives.

Scientists – both in the tobacco industry and outside of it – as well as regulators and public health authorities continue to build the evidence on HTPs. Together, we have the responsibility to promote research and assess the evidence on HTPs as it evolves in order to fully understand the benefits and risks of these products. This includes monitoring product use behavior to ensure that HTPs are marketed in a way that encourages adult smokers to switch while minimizing uptake by non-smokers and youth.

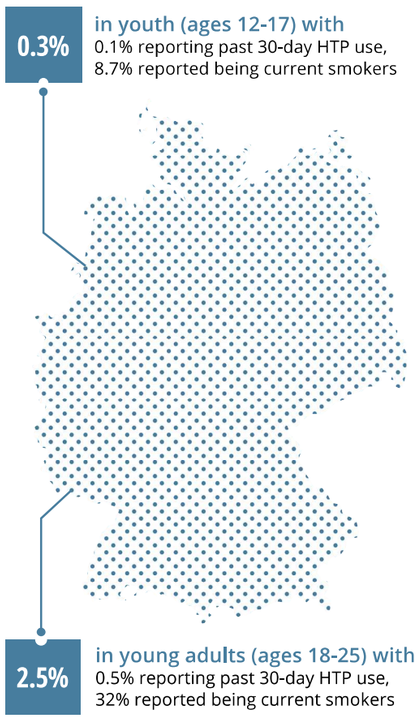
References can be found online at: *www.pmiscience.com/SU10refs*

Statistics on youth use of heated tobacco products

JAPAN



GERMANY



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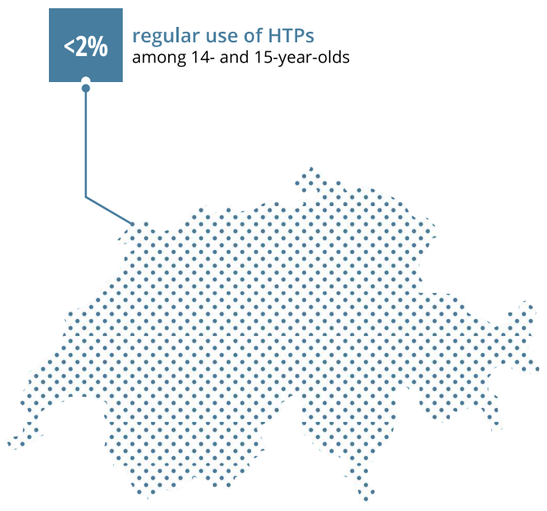

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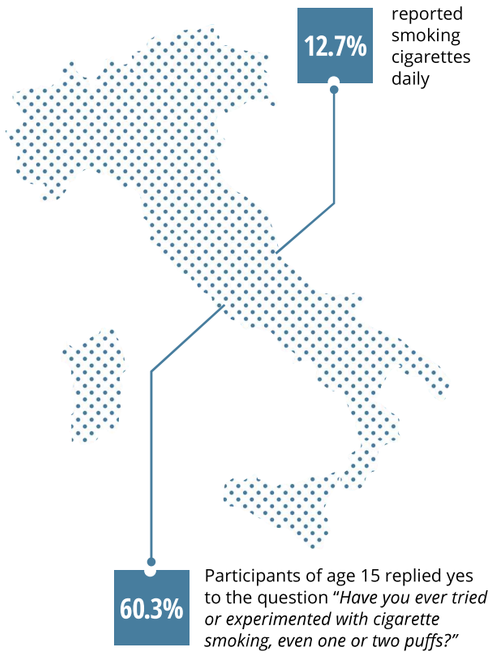
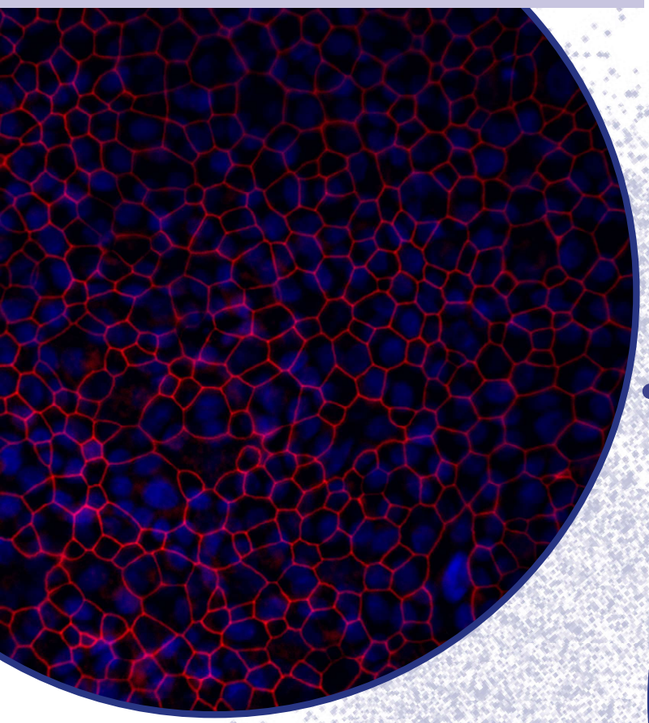


Through all the research we produce, there's an aspect that's always there but is rarely the center of focus: the visuals.

In the nine prior issues of the Scientific Update we've covered a range of topics, from regulatory applications regarding harm reduction to nicotine. Research can sometimes be difficult to decipher thanks to scientific jargon. But the beauty of science can be seen in many ways. It's not often we get to take a step back and share a peek behind the curtain at the stains, slides, and scans that bring out the beauty behind the data.

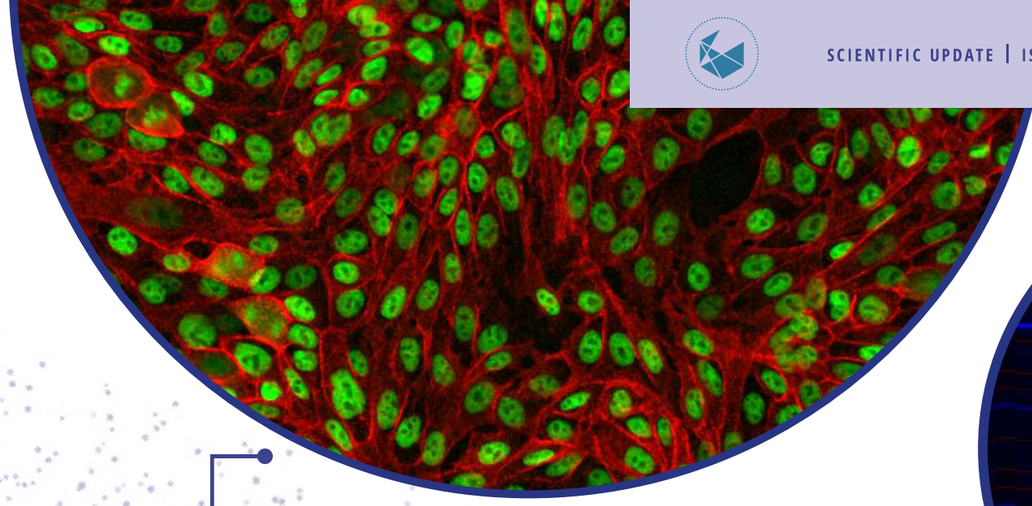
We've collated a few samples of the images captured daily by our scientists to show the beauty that science has to offer.

From humble cell staining to growing cultures made from tens of thousands of cells, there's always an element of optical beauty in often unexpected places in the lab. Whether you're a researcher, physician, or someone with a passing interest in science, we hope you can appreciate a beautiful image and take an interest in the research behind their creation.



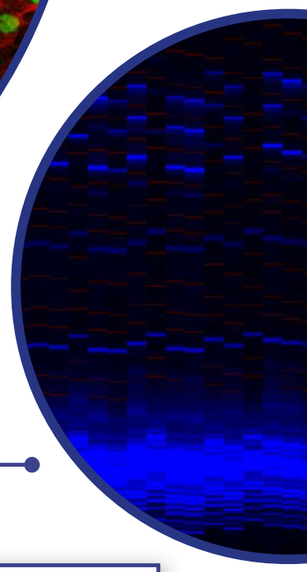
PROTEIN JUNCTIONS

This 3D human organotypic bronchial cell culture is stained to display nuclei (blue) and ZO-1 (red), a protein expressed in tight junctions. This image was captured during development of the staining method and demonstrates just how tightly cells pack together to form epithelia. If any toxicants had caused tissue damage, no ZO-1 staining would be visible.



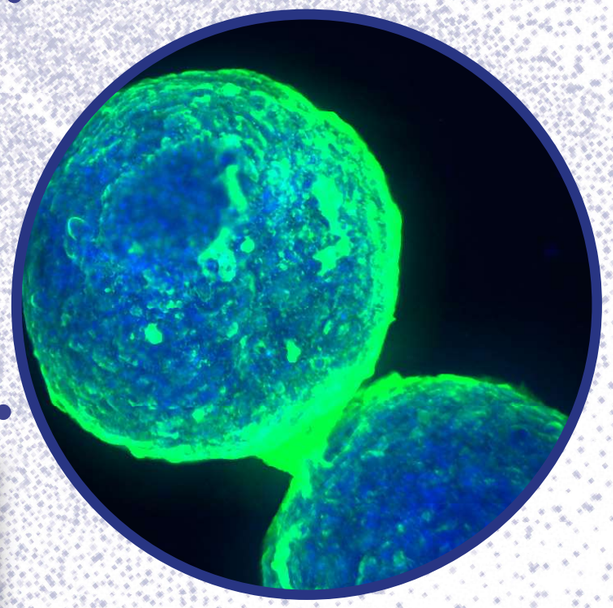
BRONCHIAL BLOOM

The proteins P63 (green) and CD151 (red) of primary human bronchial cells (from the windpipe) have been stained as part of our research to better understand lung tissue physiology. These proteins are basal cell-specific markers that help us demonstrate that basal cell populations aren't just composed of single cells, and that they differentiate into goblet cells (which produce mucus) or ciliated cells (covered in hair-like structures).



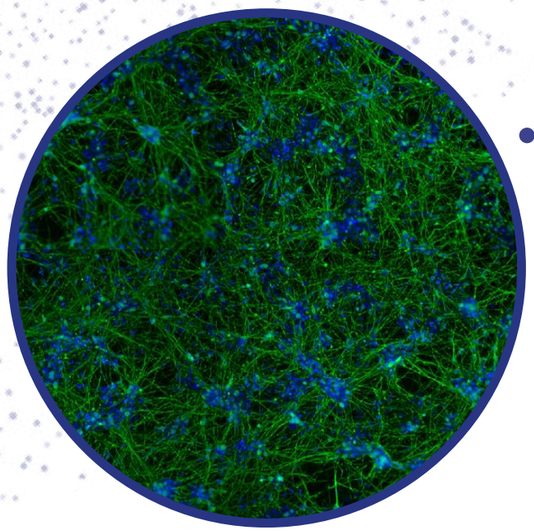
ELECTRIC BLUE

Capillary electrophoresis is ever-present in genetics – separating DNA molecules by size to compare and contrast against other samples. Here we used a blue fluorescent dye-labelled primer to amplify microsatellite marker DNA and reveal the diversity of tobacco plant varieties.



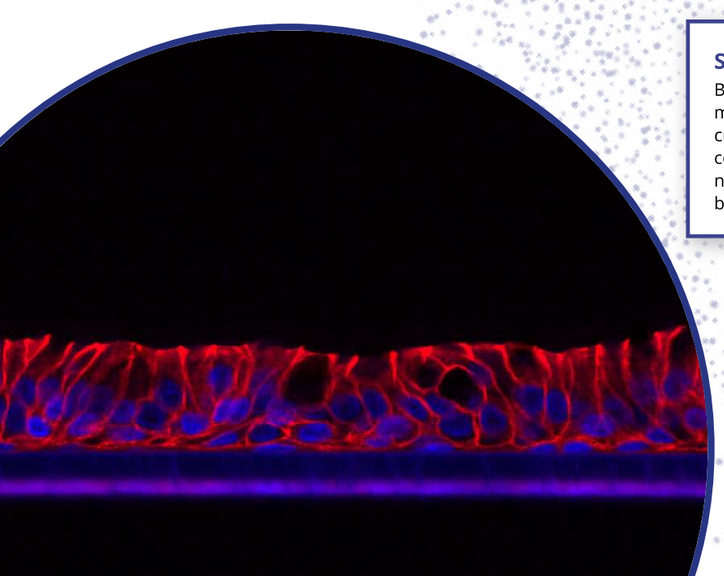
LUMINOUS SPHERES

Around 12,500 human liver cells make up each one of these human liver spheroids. Staining the albumin of the cells gives the green fluorescent glow you see. Similar to 'Tricolore', these liver cells have been cultivated for pre-clinical use, but unlike the prior image these spheroids have been paired with lung tissue to use in organs-on-a-chip technology for toxicity studies.[8] The more tissues we can emulate within a system, the greater the scope of pre-clinical studies we can carry out.



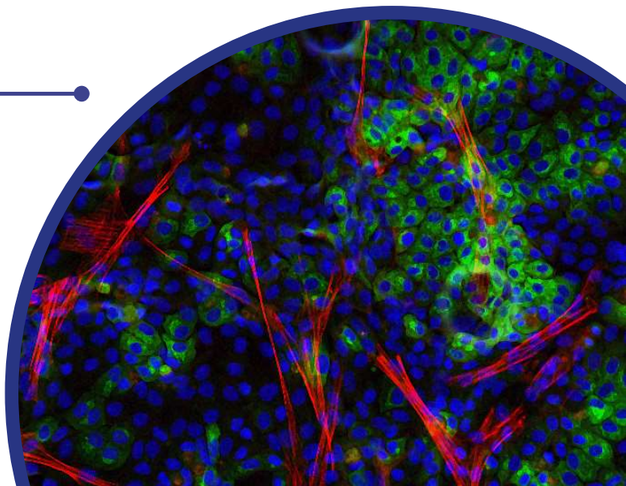
EMERALD NEURONS

In addition to their work leading toward a smoke-free future, our Cellular Systems Biology team has also been investigating neuronal models for another goal. This sprawling network of green and blue is an interconnected system of dopaminergic neuronal cells – which are central nervous system cells that produce dopamine. These have been stained green to display the tubulin beta III, used as a neuronal marker. This culture was established to create a model of Parkinson's Disease. So far, we've presented preliminary findings at the conference AD/PD 2019.[9]



STICKY CELLS

Blue-stained nuclei contrast red-stained E-cadherin molecules in this 3D organotypic human nasal cell culture. Derived from differentiated human primary cells, this culture structurally and functionally resembles native nasal tissue, mimicking the functionality of the body better than 2D counterparts and animal models.



TRICOLORE

Developing cell-based systems that resemble human physiology is an important step towards advancing pre-clinical testing – to get results closer to clinical studies, and to reduce the need for animal testing. Here, liver cells are cultured to develop a more human liver system. The triple-colored image shows a co-culture of human liver cells and human hepatic stellate cells stained to show the nuclei (blue), alpha smooth muscle actin (red), and albumin (green).

References can be found online at:
www.pmiscience.com/SU10refs

INDEPENDENT RESEARCH

Indoor air particulate matter levels

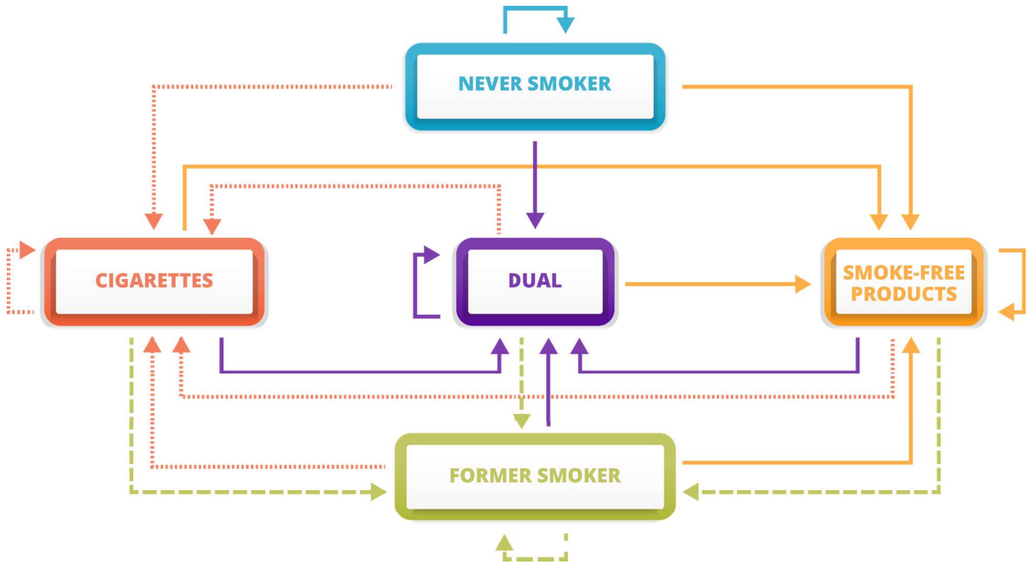
Researchers from Italy reported[10] on their measurements of the aerosol from two HTPs and an e-cigarette. The authors studied the levels of different size fractions of particulate matter emitted into indoor air during the use of one of these three products or cigarette smoke. They reported that *"All studied EATCs* [electronic alternatives to tobacco cigarettes] *caused lower indoor* PM_1 [particles smaller than 1 micron in diameter] *concentrations than conventional tobacco cigarettes,"* but that the HTPs produced higher concentrations of particles compared to outdoor concentrations.

It's important to note that the composition of the particulate matter matters. Based on this study, the tested products, including EHTS, produced fewer particles overall compared to cigarette smoke. However, the analysis did not measure the composition of the particles, nor could it tell the difference between liquid droplets caused by vaporization and solid particles created by combustion.

Declining cigarette sales in Japan

An article published by researchers at the Medical University of South Carolina and at the University of Ottawa explored[12] the relationship between a decline in cigarette sales in Japan between 2011 and 2019, and the introduction of HTPs in late 2015. Data for this study came from the Tobacco Institute of Japan and from PMI. Like an earlier article published by researchers working for the American Cancer Society,[13] this study found that the acceleration in decline in cigarette sales in Japan since 2016 does in fact correspond to the 2015 introduction and growth of sales of HTPs in the country. The authors noted that their work did not address whether cigarette smokers were completely substituting one product for another, just that the data indicate that HTPs have accelerated the decline in cigarette sales.

Transitions in product use behaviors



Modeling impact on carcinogenicity: EHTS as an example

Researchers at the National Institute for Public Health and the Environment (RIVM) and the University of St. Andrews highlight[11] that it is problematic to compare the harmful health effects of two different tobacco products by applying typical risk assessment methods to individual compounds. This study presents one of the most advanced approaches to estimate the risk (to the individual) of new tobacco products relative to cigarettes. Two strengths of this work are that the approach also provides the uncertainty in the model results, and that the method is not limited to cancer-related outcomes and can be adapted to other effects and diseases.

In a case study using EHTS, the authors applied their method to eight carcinogens that are present both in cigarette smoke and EHTS aerosol. The authors reported a 10- to 25-fold lower exposure when using EHTS as compared to cigarettes under these conditions, indicating less of a reduction in expected life span. The authors also noted that the results are preliminary because only 8 carcinogens were considered so far, and that HTPs have an unfavorable health impact compared to complete abstinence.

Comparing approaches to model the population health impact of an MRTP

A recently published review article[14] has been written in collaboration between scientists from PMI, Altria, British American Tobacco, Reynolds, as well as several leaders in tobacco harm reduction research. Together, we reviewed approaches that scientists have used to estimate population health impact of introducing a Modified Risk Tobacco Product (MRTP), a product described by U.S. FDA as being *"sold or distributed for use to reduce harm or the risk of tobacco-related disease associated with commercially marketed tobacco products."*[15] As of June 2020, EHTS was not considered an MRTP. The models discuss hypothetical product introduction scenarios for the purpose of understanding the potential population health impact. The study includes 13 health impact models such as PMI's own population health impact model, those of other tobacco companies, and other researchers. Most were cohort-based models, taking the same population with known smoking habits and updating their smoking habits under the two scenarios tested: with and without the introduction of an MRTP.

The strengths and weaknesses of each model were summarized. Despite methodological differences between the models, most of the models' creators assumed that the risk associated with MRTP use was low compared to the risk from cigarette smoking, meaning that the MRTP introduction is likely to have a beneficial impact. Overall, new models being developed should enable more precise prediction of what to expect when an MRTP is introduced, especially if they're supplemented with preliminary results of well-designed epidemiological studies.

Using lasers to trap and study e-vapor aerosol composition

In another collaboration, this time with scientists from the Swiss Federal Institute of Technology (ETH) in Zurich, we studied[16] the composition of droplets found in e-cigarette aerosol using laser-trapping and Raman scattering. Two lasers of the same wavelength and intensity were focused on a single point, making it possible to catch and hold steady single droplets of e-vapor. To measure the composition of the droplet, the researchers recorded the intensity and wavelengths of light scattered by the droplet, known as its Raman spectrum, and compared that against the Raman spectrum of a sample of e-liquid.

This approach made it possible to study the composition of droplets specifically, excluding contributions of the gas phase of the e-liquid, without having to extract a sample from the vapor. The study found that the composition of the droplet was initially very close to that of the e-liquid. Once it was diluted with air, the composition changes over the course of a few seconds, mostly because of propylene glycol evaporation. The nicotine content depends on the pH of the e-liquid – it evaporates from the droplets under basic conditions, but it remains in e-liquid that is more acidic.

References can be found online at: *www.pmiscience.com/SU10refs*

PMI PUBLICATIONS

Developing organs-on-a-chip systems for aerosol exposure studies

This work was a collaboration between PMI and TissUse GmbH,[17] a biotechnology company in Berlin, Germany, that specializes in organ-on-a-chip technology to make pre-clinical studies more predictive of outcomes in people than studies relying on animal models. Together, we created a multi-organ-on-a-chip system including organotypic cell cultures that mimic the human lung and liver. These cell cultures were co-cultured in the same medium, which could flow between the different cell compartments.

The two cell cultures were able to influence each other, or "crosstalk" via the medium. By introducing into the medium aflatoxin B1, a known hepatotoxin and carcinogen, we were able to demonstrate this organ crosstalk. The toxic effect of this chemical on the lung cell cultures alone was reduced when the liver spheroids were present because they acted to detoxify the growth medium. These results reproduced the findings from our earlier study using a different lung cell culture and chip design.[18]

In future work, exposing the lung tissue to an aerosol would provide a more realistic exposure scenario, enabling assessment of not only the toxicity but also the level of inhaled substances in circulation in the body. This kind of test could become an important tool in drug discovery and personalized medicine.

Reduced exposure to harmful chemicals in 3-month study on CHTP vs cigarettes

According to this 3-month clinical study,[19] switching to our carbon-heated tobacco product (CHTP) resulted in favorable changes in certain measured biomarkers compared to continued cigarette smoking. This clinical study randomized current adult smokers to either switch to CHTP (80 people) or to continue using cigarettes (40 people) for 5 days in confinement and for the following 85 days in an ambulatory setting. Biomarkers that indicate exposure to harmful and potentially harmful constituents (HPHCs) were measured, as well as biomarkers for exposure to nicotine, urinary excretion of mutagenic constituents, CYP1A2 activity, and other endpoints.

Among those who switched to CHTP, biomarkers of exposure were 40% - 95% lower compared to people who continued to smoke after 5 days of product use. Those average reductions continued through day 90 (36% - 93% lower). Switching was also associated with observed improvements in some of the measured biomarkers of effect representative of mechanism pathways related to the development of smoking-related disease.

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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.