PMI SCIENCE
PHILIP MORRIS INTERNATIONAL

SCIENTIFIC UPDATE FOR SMOKE-FREE PRODUCTS

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Past issues can be found here

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

WHAT'S INSIDE:

INTRODUCTION

It has been an exciting few months since we announced the topline results on the Exposure Response Study (ERS) and interim results on our Smoking Cessation Study. These studies compare the body's response upon switching from cigarettes to one of our Electrically Heated Tobacco System (EHTS) or to smoking cessation, respective-ly. We're sharing the results with regulatory agencies, including the US FDA in support of the on-going scientific review of our Modified Risk Tobacco Product Application (MRTPA) package on EHTS, which is known commercially as *IQOS*. We've presented the results at conferences, including the Tobacco Harm Reduction Summit June 8-9 in Greece, the International Symposium on Atherosclerosis June 9-12 in Toronto, Canada, the Global Forum on Nicotine June 14-16 in Warsaw, Poland, and many other public events. At each of these conferences, we took part in meaningful discussions about the promise of less harmful alternatives to cigarettes, and what these studies mean for our most advanced smoke-free product. This edition of the Scientific Update focuses on the results of our ERS study and provides an update on the progress of our other smoke-free platforms.

We conducted the ERS to measure the biological response in adults who switch from cigarettes to EHTS, and to identify whether eight important clinical risk endpoints improve when someone switches from cigarettes to EHTS compared with those who continue to smoke during the study. These endpoints were selected because they are sensitive to smoking, they are linked to smoking-related diseases, and they are known to start improving within six months after smoking cessation. After six months of study, the results show that all eight clinical risk markers changed favorably in smokers who switched to EHTS, with statistically significant changes for five out of the eight compared to on-going smoking.

Simply put:
We see an improvement in biological functions related to heart disease, lung disease, and cancer for people who switch from cigarettes to EHTS.

These latest clinical results further add to the totality of evidence substantiating EHTS's ability to present less risk of harm compared to continued smoking for those who switch completely. As a reminder, we aim to achieve two objectives: 1) create a product that presents less risk of harm compared to continued smoking for those smokers who switch to it completely, and 2) have as many adult smokers who would otherwise continue to smoke to switch to them as possible. We also consider the likelihood of unintended use by those who don't currently use tobacco products or would otherwise quit, in order to demonstrate that the introduction of our products really makes a positive public health impact.

Smoking related diseases are complex and take a long time to manifest, so absent long term epidemiology data, it is not possible to have data on the actual reduction in morbidity and mortality associated with EHTS use. But the totality of the evidence, which includes independent research on aerosol chemistry, air quality, pre-clinical and clinical data, clearly demonstrates that EHTS presents less risk of harm compared to continuing to smoke. Concerning the second objective, available pre-market data indicates that the vast majority of people who are interested in EHTS are people who currently smoke. And today 5.9 million smokers around the world have already switched to EHTS. To further strengthen this positive trend, adults who continue to smoke cigarettes need to be provided with accurate and non-misleading information about EHTS.

In addition to describing our ERS results, we would like to share our efforts to improve our data sharing platform called INTERVALS.science, and are inviting scientists to contribute their own methods, data, and results to the community. This platform helps us to achieve some of our primary goals, including sharing data transparently, encouraging independent verification of our results, and supporting the scientific community and the advancement of science. We believe that these goals can only be achieved when we work together with the scientific community in this open and collaborative way.

Following the previous issue that summarized the independent literature on EHTS, we have introduced a new section to our update that will keep our readers up to date on some of the independent research on our smoke-free products and the product category in general. We also share an exciting new update on our *MESH* e-cigarette. Finally, we have included summaries on a range of our own recent publications, several of which show advancements in the assessment of our carbon-tipped heated tobacco product.

As always, we know how important it is to share our science with society, and this issue of the Scientific Update is a celebration of that sharing, from collaborative validation of data to our most exciting clinical results yet.

Prof. Manuel C. Peitsch
Chief Scientific Officer

Dr. Frank Luedicke
Chief Medical Officer

ASSESSMENT PROGRESS OF OUR PRODUCT PORTFOLIO

HEATED TOBACCO PRODUCTS

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

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

DESCRIPTION

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

ASSESSMENT PROGRESS

We have conducted 18 non-clinical and 10 clinical studies for this platform with results consistently showing the EHTS presents less risk of harm compared to continuing to smoke. Our 6- plus 6-month Exposure Response Study including nearly 1000 participants was completed at the end of 2017, and the results available for the first 6-month term are described on page 6. The study report and results of the first six months were submitted to the FDA in the second quarter of 2018. The report for the second six-month term of the study should be finalized soon.

PLATFORM 2
CARBON-HEATED TOBACCO PRODUCT (CHTP)

DESCRIPTION

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

ASSESSMENT PROGRESS

The results of our pharmacokinetic study and our five-day reduced exposure study indicate that CHTP could be an acceptable substitute for adults who smoke who seek an alternative to cigarettes. We completed a three-month reduced exposure study in 2017 and the related report was finalized in the second quarter of this year. We will share the conclusions in scientific forums and submit them for inclusion in peer-reviewed journals in 2019.

PRODUCTS WITHOUT TOBACCO

Another approach to reduce the levels of toxicants emitted by novel products is to produce an aerosol without the use of tobacco. We precisely design the composition of the aerosol-producing components, and this provides improved control over the resulting aerosol. These platforms may be best suited for people who smoke but are not necessarily looking for the taste and sensory experience of tobacco or are already using e-vapor products.

PLATFORM 3
E-VAPOR PRODUCT USING NICOTINE SALT

DESCRIPTION

Includes products in which nicotine (a weak base) reacts with a weak organic acid to generate a respirable nicotine salt. We have explored two routes for this platform, one with electronics and one without.

ASSESSMENT PROGRESS

We finished the clinical phase of a nicotine pharmacokinetic study for the version without electronics, and the final study report will be finalized this year. We will also initiate a clinical product use and adaptation study.

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

DESCRIPTION

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

ASSESSMENT PROGRESS

The non-clinical assessment on our e-liquids is well advanced. We have completed the clinical phase of a nicotine pharmacokinetic study and expect to finalize the report this year. The results of this study are expected to inform further developments of Platform 4 products. We will also initiate a clinical reduced exposure study to measure selected biomarkers of exposure to HPHCs and assess changes in clinical risk markers.

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

OTHER DEVELOPMENTS

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

PMI STEP BY STEP ASSESSMENT PROGRAM

To learn more about the steps of our assessment program, please visit pmiscience.com Colored blocks indicate progress completed.

PLATFORM UPDATES: *MESH* AND EHTS

Two of our smoke-free products have received some technological updates this year: EHTS, and *MESH*. Most recently, developments on EHTS include making it more compact, charge 15% faster, and be physically more robust compared to earlier designs. The new holder now magnetically locks into the charger, automatically rotating into place and generating the correct force to initiate charging even with the charger open. We also introduced a new, integrated version of the product that combines the charger and holder into a single unit and supports consecutive uses.

Updates to *MESH* include a host of design changes to make the product more robust, more consistent, and more intuitive to use. All changes to *MESH* are made with fully automated manufacturing in mind, including the German-built *MESH* heater and the durable aluminum housing. The disposable cap that contains the *MESH* heater and e-liquid is now easier to snap onto the battery unit. The cap is also a completely closed system to prevent tampering and protect the quality of the e-liquid, with an improved seal to prevent liquid leakage. We redesigned how the liquid is transported to the heater and increased the power of *MESH* from 6 W to 7.5 W to meet the consumer demand of a larger aerosol mass per puff.

EXCITING RESULTS TO-DATE

The research from our product assessment of *MESH* is advancing swiftly, and we are very encouraged by our latest results and new studies. Aerosol chemistry studies have shown that the *MESH* aerosol delivers consistent levels of nicotine and emits on average 99% lower levels of harmful chemicals compared with cigarette smoke (3R4F[1]), though MESH is not risk-free.[2] We also measured an average reduction of 85% in the levels of harmful chemicals compared to the median reduction measured in a selection of popular e-cigarette systems (open, closed systems, and MODs) currently sold in the UK market. Systems toxicology studies have shown that the main e-liquid ingredients have limited biological effects and no signs of toxicity in the laboratory,[3] and that they have similar effects on human lung cells as nicotine alone.[4]

Clinical studies have also begun, with one focused on the nicotine pharmacokinetic profiles and pharmacodynamic effects of *MESH* to learn how different levels of nicotine in *MESH* affects the blood-nicotine levels in healthy adult experienced users of e-cigarettes in the U.S. compared to the e-cigarettes they already use.[5] The study combines this with information on subjective effects, cravings, and user behaviors to support ongoing development of new technologies, like *MESH*, that can be scientifically shown to be a better choice for adults who smoke.

1 Consumable cap
2 Hand device with temperature control
3 E-liquid tank
4 MESH heater
5 Power button with low liquid indicator
6 Low battery indicator
7 Micro USB charging port

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1 The Standard Reference Cigarette (3R4F) is used throughout the tobacco industry and academic laboratories as a consistent and uniform test item for inhalation toxicology research. It was developed by the University of Kentucky.

2 Average reduction of a broad range of harmful chemicals listed by Health Canada (nicotine excluded) compared to the smoke of a reference cigarette designed for research purposes (3R4F) using Coresta smoking regimen for IQOS MESH and Health Canada Intense Smoking regimen for 3R4F.

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5 Study is posted on clinicaltrials.gov, identifier: NCT03379740

INTERVALS.SCIENCE:
A COMMUNITY PLATFORM FOR TRANSPARENT DATA SHARING

Ensuring that scientific results are reproducible is a challenge that extends beyond industry-driven research. As reported in a publication in the journal Nature in 2012, the reproducibility of publications in cancer research is as low as 11%.[6] This means that peer review is not enough to ensure reproducible results, and that the community needs to see improved study design, documentation of methods and datasets, and increased sharing of data and methods within the community.[7] We agree that all of these improvements are essential for researchers to replicate published results, and we rely in part on these ideas to build our own credibility as part of the research community.

ROBUST SCIENCE REQUIRES THAT:

- Experiments are **repeatable and reproduceable**
- Methods and Materials (including cell lines and antibodies) are **validated**
- **Analyses and statistical tests are defined a priori and appropriate**
- Whenever possible, the study is **blinded**
- Most importantly, **all results, including negative and positive controls, are shared**

Evidence regarding smoke-free products has accumulated rapidly in the scientific literature. However, it is essential to share the methods, data, and results of the assessment to enable independent reviewers to fully compare studies. With these thoughts in mind, we built **INTERVALS.science** to become a community platform, to encourage transparent sharing of data in a way that allows for easy review, easy understanding, and to facilitate objective evaluation of all currently available evidence.[8]

The INTERVALS platform is intended to share information about toxicology, clinical, and population-level studies on products that span the interval between continuous cigarette smoking and smoking cessation. The portal allows users to browse the data by study or mechanism (e.g., inflammation, oxidative stress) and download data relevant to study design, methods, and results.

With the help of our fellow scientists, INTERVALS aims to enable the necessary dialogue between industry, independent reviewers, the public health community, the research community, and regulatory agencies that can validate the harm reduction potential of smoke-free products. Scientists are invited to prepare and upload their own data for publishing on the website. Helpful tutorials and guidelines for formatting associated materials are available in the documentation center. An independent editorial board will be assembled to review studies and protocols suitable for publication on INTERVALS, as per COPE guidelines for Editors.

We hope that INTERVALS will foster a much-needed collaboration between scientists in academia, industry working groups, and regulatory bodies.

INTERVALS CORE VALUES

Integrity
Network
Transparency
Education
Reproducibility
Validation
Access
Learning
Science

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RECENT MILESTONES IN PMI'S RESEARCH

FOCUS ON: RESULTS OF LARGEST EXPOSURE RESPONSE STUDY TO-DATE CONFIRMS REDUCED RISK PROFILE

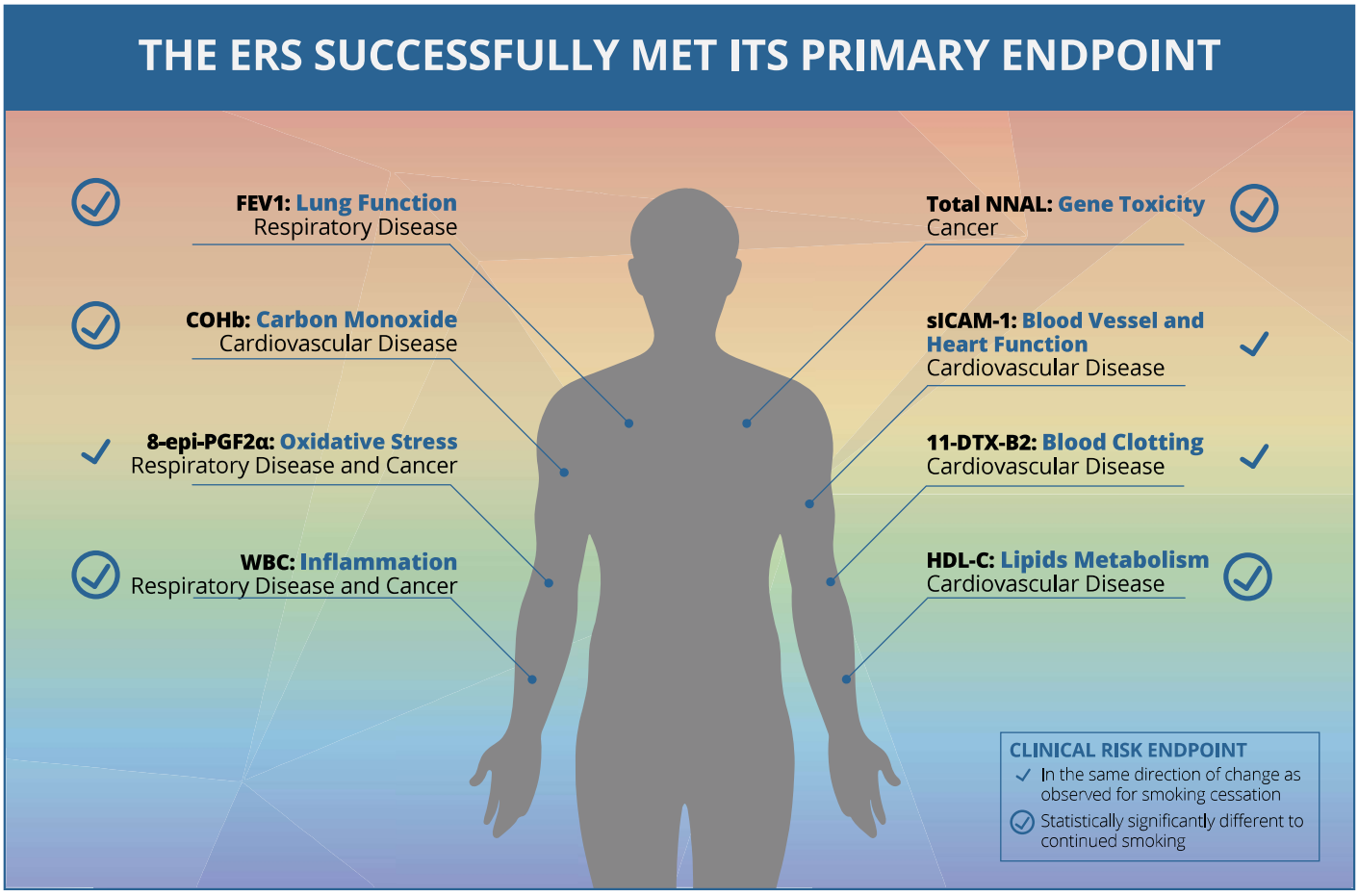
So far, our assessment program has demonstrated that EHTS produces an average of 90-95% lower levels of harmful chemicals compared to cigarettes (3R4F). It also showed reduced toxicity in the laboratory, and in clinical studies reduced exposure to harmful chemicals in those who switched compared to those who continued to smoke. In fact, exposure reductions approached levels measured in those who abstain from smoking for the duration of the studies.

Our latest completed clinical study, the Exposure Response Study (ERS), was designed to answer important questions about the effects of EHTS as it is actually used by adult smokers who switch to it. The ERS is the first ever clinical study of this magnitude to assess the risk-reduction potential of a smoke-free product in people who switch to it. In this study, we evaluated changes in clinical risk endpoints in healthy adult smokers who either switched to EHTS or continued to smoke their own brand of cigarettes. The results of this study further support the findings of our previous studies, all of which point towards risk reduction.

THE GOLD STANDARD FOR ASSESSING RISK REDUCTION: CESSATION

Both our ERS study and our Smoking Cessation Response study assessed clinical risk endpoints that are associated with smoking-related disease, are negatively impacted by smoking, and are known to reverse upon smoking cessation. Eight of these clinical risk endpoints were tested as part of the primary objective of the ERS. These eight endpoints were also included in the Smoking Cessation Response study, which was designed to establish a "gold standard" of cessation for assessing our smoke-free products. It measured the improvement in clinical risk endpoints when adult smokers quit smoking for one year.

When a person quits smoking, carbon monoxide levels in the blood drop within 12 hours, and oxygen levels begin to increase. Within the first 6 months of quitting, clinical risk endpoints linked to smoking and smoking related disease, such as cardiovascular diseases, lung diseases, and cancer, improve in a clinically meaningful way. And they continue to improve as time goes on. These favorable changes are well described in the scientific literature.



All eight primary clinical risk endpoints improved in smokers who switched to EHTS. Five of these eight endpoints showed statistically significant differences between people who switched to EHTS compared to those who continued smoking.

TWO BIG TAKEAWAYS

The results of our ERS are twofold:

- All eight primary clinical risk endpoints improved in smokers who switch to EHTS by the end of the six month study.
- The majority of these clinical risk endpoints (five of the eight endpoints) showed statistically significant differences between smokers who switched to EHTS compared with those who continued smoking.

To use the pharmaceutical industry's language for describing the outcomes of a clinical study: together, these two findings mean that our ERS successfully met its primary objective.

This was achieved even though some of the EHTS users in the study, who made up part of the primary analysis population, continued to smoke cigarettes in addition to using EHTS (up to 30% cigarette use). In addition to the favorable changes to the eight primary endpoints summarized in point 1 above, numerous additional clinical risk endpoints assessed in the same study also saw favorable changes.

These results contribute to the totality of evidence available on EHTS and were produced as part of PMI's extensive research and assessment program relating to EHTS. This program is inspired by the well-recognized practices of the pharmaceutical industry and the draft guidance of the U.S. FDA for Modified Risk Tobacco Product Applications.

THE ERS WAS DESIGNED TO ADDRESS KEY QUESTIONS RELATED TO THE IMPACT OF SWITCHING TO EHTS AS THE PRODUCT IS ACTUALLY USED.

THIS STUDY SUCCESSFULLY DEMONSTRATES EARLY IMPROVEMENTS IN CERTAIN MEDICAL TESTS WHEN A PERSON SWITCHES FROM CIGARETTES TO EHTS.

KEY DETAILS

The ERS was designed to address key questions related to the impact of switching EHTS as it is actually used. It was a six month, controlled study conducted out of multiple clinical centers in the US. It followed 984 adults who had no intention to quit smoking who were randomly selected to either continue smoking cigarettes (496 people) or to switch to EHTS (488 people) for six months. We asked that participants use their assigned product, but also to record all tobacco products used during the period of study.

By the end of the study, about 60% of the EHTS user group had continued to use the product at least 70% of the time, and this is the group we consider as having switched to EHTS for our primary analysis. People in this group used an average of 16.5 EHTS per day and 2 cigarettes per day. Compared to the cigarette smoking group, the group that switched to EHTS demonstrated favorable changes in all eight co-primary clinical risk endpoints assessed, with statistically significant changes in five of the eight, despite up to 30% cigarette-use.

SHARING OUR RESULTS

We shared these results publicly at several conferences this year. They were presented at multiple conferences at the beginning of June, coinciding with our submission of these results to the US FDA. They have been shared with other regulatory agencies as well. Dr. Christelle Haziza, PMI's Director of Health Science and Biostatistics, presented at the Global Forum on Nicotine on June 14-16, followed by Dr. Manuel Peitsch's presentation of the results at a press conference in Korea on June 18. The full results will be submitted for publication in a peer-reviewed journal shortly.

CONCLUSIONS

Our Exposure Response Study results form part of the totality of evidence[9] to-date, showing that switching completely to EHTS, although not risk free, presents less risk of harm than continuing to smoke.

This information was submitted to the relevant authorities in the US, Canada, and Australia to lend additional support to the totality of evidence on EHTS. Taken together with that context, this data further supports our research demonstrating that EHTS can play a positive role in public health. Right now, EHTS is not for sale in the US, and the US FDA is still reviewing the evidence in support of our Premarket Tobacco Product Application as well as our Modified Risk Tobacco Product Application. We look forward to this and other independent expert reviews of this data, and we are confident that they will come to similar conclusions.

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9 Based on reductions in toxic emissions, exposure, molecular changes, biological mechanism, cell and tissue changes, and disease are in comparison to the mainstream smoke from a 3R4F reference cigarette and commercially available cigarettes.

PMI'S PEER-REVIEWED PUBLICATION HIGHLIGHTS

Candidate modified-risk tobacco product causes lower carcinogenicity than cigarettes

Cigarette smoking is the leading cause of preventable lung cancer, and this study suggests that switching from cigarettes to EHTS may reduce that risk. It is the carcinogens in cigarette smoke that are responsible for the changes that take place in cells that make them become cancerous. Because EHTS produces significantly lower levels of these carcinogens than cigarettes, it is expected that its aerosol would be less likely to cause cancer. The results of this study support that hypothesis.

In this *in vitro* study, human bronchial cells were exposed for 12 weeks to the particulate matter from either cigarette smoke (dose of 7.5 µg/mL) or EHTS aerosol (doses of 7.5 µg/mL, 37.5 µg/mL, and 150 µg/mL). The specific line of bronchial cells used in this study has been shown in the scientific literature to be a good model for cancer risk assessment. Exposing these cells to cigarette smoke changed the cells' gene expression and caused the cultures to alter key cell-cell binding and communication activities that enable cancerous cells to invade and colonize other parts of the body. Some response was seen for EHTS, but a much higher dose was needed to achieve any response – about 20 times the exposure compared to cigarette smoke. Therefore, EHTS aerosol has a lower biological impact than cigarette smoke when it comes to carcinogenicity.

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Carbon-heated tobacco product aerosol (CHTP) has lower impact on human airway cell cultures compared to cigarette smoke

This study, one of two recently published in Food and Chemical Toxicology, represents the first *in vitro* assessment of the CHTP using organotypic human cells from the airway nose. Both these cell cultures were also used previously in assessment of EHTS,[10,11] because they provide information on cell-to-cell interactions and functions – information that is more representative of how these cells would be in the body, as compared to normal cell cultures. These cells are cultured by mimicking the human airway using an air-liquid interface, and this method allows for direct exposure of gases and aerosols. The cultures were exposed to either cigarette smoke or EHTS aerosol at nicotine-equivalent levels (0.14 – 0.16 mg nicotine/L aerosol) for 28 minutes. Following this, the cultures were tested to determine how many cells had survived or changed shape, whether the cells showed an increased inflammation response, and whether there were changes to key biological processes inside the cells. As expected, the cigarette smoke exposure caused pronounced changes to cell shape and resulted in cell toxicity, as well as significant changes to biological processes. CHTP, on the other hand, caused only subtle changes to certain cell processes and immune response, with no observed changes to cell shape even at higher exposure levels. Overall, CHTP aerosol had a much lower impact on the cell biology compared to cigarette smoke.

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Carbon-heated tobacco product aerosol (CHTP) has lower impact on human cheek and gum cell cultures compared to cigarette smoke

This second publication in the same issue of Food and Chemical Toxicology studied organotypic human skin cell cultures from the mouth – from inside the cheeks, and the gums – to compare the effects of CHTP aerosol against cigarette smoke on tissues in the human mouth. These cells were exposed either one time or repeatedly over three days for 28 minutes to equivalent nicotine concentrations of cigarette smoke or CHTP aerosol. Following this, the cultures were subjected to a range of tests determining cell survival or shape change, changes to inflammation response, and changes to key biological processes inside the cells. The results of this study demonstrated that CHTP aerosol had an overall reduced impact compared to the reference cigarette smoke cell cultures from the mouth. CHTP had significantly reduced effects compared to cigarettes on inflammation and stress responses of the cells, and the way the cells organize themselves into a physical structure.

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

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90-day toxicology study demonstrates reduced exposure effects on rats exposed to aerosol from CHTP compared with cigarette smoke

These two publications on an *in vivo* rodent study demonstrate that CHTP has a reduced effect on a range of biological functions, even at higher nicotine concentrations, compared to cigarette smoke. Laboratory rats (Sprague-Dawley rats, 96 male and 136 female) were exposed to fresh air, CHTP aerosol, or cigarette smoke at an equivalent nicotine concentration of 23 µg/L for 6 hours per day, 5 days a week for 13 weeks. Additional groups were also exposed to lower (15 µg/L) and higher (50 µg/L) equivalent nicotine concentrations of CHTP. After exposure, they were examined to compare the respiratory and systemic effects between the two products, using both classical (Part 1) and molecular (Part 2) approaches. Rats exposed to CHTP aerosol showed 93% reduced exposure to harmful chemicals compared to rats exposed to cigarette smoke based on urinary chemistry measurements. They also experienced less inflammation of the lungs and a lower level of negative changes in the respiratory tract, as well as smaller changes in gene expression, protein abundance, organ weight, and lipid abundance compared to those exposed to cigarette smoke. The nasal tissue showed particular sensitivity to cigarette smoke, resulting in inflammation and tissue changes, while this effect was much weaker for CHTP even at the highest concentration. Altogether, the systems toxicology analysis complements and confirms the results of the classical toxicological assessment, suggesting potentially reduced respiratory health risks of CHTP compared to cigarettes.

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INDEPENDENT RESEARCH ON SMOKE-FREE PRODUCTS

LEADER IN FIELD OF TOBACCO HARM REDUCTION: LATEST RESULTS ON EHTS IN LINE WITH PMI'S

The latest study by Dr. Konstantinos Farsalinos, MD, MPH, a cardiologist and leader in the field of tobacco harm reduction, analyses the aerosol chemistry of EHTS in comparison with a brand of commercially available cigarettes and an e-cigarette, with results in line with our own. The authors concluded that EHTS *"emits substantially lower levels of carbonyls than a commercial tobacco cigarette* [brand name omitted], *but higher levels than a* [brand name omitted] *e-cigarette."* Carbonyls are among the most toxic compounds in tobacco smoke, and include chemicals like formaldehyde, acetaldehyde, and acrolein. The authors also further explained, *"It should be noted that the absolute difference in carbonyl emissions between* [EHTS] *and the e-cigarette is low when compared to the difference between these products and tobacco cigarette smoke."* This study is another welcome addition to the more than 25 independent studies and government reports on EHTS.

Farsalinos, K. E.; Yannovits, N.; Sarri, T.; Voudris, V.; Poulas, K.; Leischow, S.;. Carbonyl emissions from a novel heated tobacco product (IQOS): comparison with an e-cigarette and a tobacco cigarette. *Addiction*.**2018**;Accepted Article. doi: 10.1111/add.14365.

KOREAN MINISTRY OF FOOD AND DRUG SAFETY DATA CONFIRMS LOWER LEVELS OF HARMFUL CHEMICALS

The Korean Ministry of Food and Drug Safety (KFDA) tested 3 heated tobacco products, including EHTS, and products from BAT and KT&G, finding over 90% average reduction in the levels of nine harmful chemicals[12] in the aerosol of these products compared to levels found in the smoke of the top five cigarette brands in Korea. However, instead of focusing on the significant reductions in harmful chemicals compared to cigarette smoke that the agency's own results show, KFDA points to "tar" measurements to judge the relative risk of tobacco products. But major public health organizations, including the World health Organization, agree that "tar" is not an appropriate measure to compare the harmfulness of different tobacco products. They also agree that when comparing tobacco products, whether they are cigarettes or heated tobacco products, it is much more important to analyze the levels of individual toxicants in the smoke or aerosol. In fact, the WHO said in 2015 that, *"Tar need not be measured, as it is not a sound basis for regulation, and the levels can be misleading."*[13]

To learn more about the analysis of the KFDA's results and why "tar" is a deceptive method to compare products, visit: https://www.pmiscience.com/discover/news/pmi-assessment-of-the-kfda-statement.

UCSF RESEARCHERS REVIEWING PMI DATA IGNORE KEY CONTEXT

Researchers at the University of California, San Francisco have published a series of publications that reviewed various studies we included in our modified risk tobacco product applications to the FDA. One such study claimed that EHTS exposure could be associated with liver toxicity, which the evidence and available information does not support. In fact, we monitor liver function in our clinical studies, and we found no cause for concern to-date. These data are publicly available. The authors have selectively reported individual laboratory parameters at single time points from different studies; they have not accurately reported the results in the full scientific context. These and other authors from this university have since published other reviews with incorrect and misleading conclusions.

To learn more about our response to this study, visit: https://www.pmiscience.com/discover/news/summary-of-evidence-on-the-absence-of-hepatotoxicity-of-iqos-response

US RESEARCHERS FIND EHTS AEROSOL CAUSES LESS TOXICITY IN HUMAN BRONCHIAL CELLS COMPARED TO CIGARETTE SMOKE

Researchers from the Roswell Park Cancer Institute in New York presented data at SRNT 2018 comparing the cytotoxic effects of cigarette smoke, EHTS aerosol, and e-cigarette aerosol, finding that both the e-cigarette and EHTS showed minimal cytotoxic effects, "not significantly different from the air control." Cigarettes, on the other hand, were cytotoxic both for cell survival and for cell metabolism. The study used a smoking machine to generate nicotine-equivalent aerosols that were allowed to flow across human bronchial cells that were positioned at an air-liquid interface for experimentation. The authors concluded that *"While more comprehensive testing is needed to determine long term effects of inhaling aerosol from HnB products, this new product may be a potential harm reduction tool for smokers unwilling to quit smoking or smokers not interested in switching to e-cigarettes."*

Society for Research on Nicotine and Tobacco (SRNT) Conference 2018. PA23-3: "Cytotoxic effects of a tobacco heat-not-burn system on human bronchial epithelial cells." Noel Leigh, Phillip Tran, Richard O'Connor, Maciej Goniewicz, Roswell Park Cancer Institute, NY, USA https://cdn.ymaws.com/www.srnt.org/resource/resmgr/conferences/2018_Annual_Meeting/65388_SRNT_2018_Abstract_fin.pdf

GOVERNMENT-COMMISSIONED STUDIES IN RUSSIA WITH FINDINGS IN LINE WITH PMI RESULTS

The Russian government commissioned multiple studies on EHTS, including aerosol chemistry, laboratory toxicity studies, and clinical studies studying exposure to harmful chemicals, all with similar conclusions to ours. These results are not yet published but have been announced recently through two scientific institutions that conducted some of the work, the All-Russian Scientific Research Institute of Tobacco, Mahorki, and Tobacco Products[14] and the Kazan Federal Institute.[15] The aerosol chemistry study determined the nicotine content and the nine substances on the WHO priority list, showing that nicotine content in EHTS is similar to cigarettes while containing substantially lower levels of the nine measured toxicants. EHTS aerosol was also found to have substantially lower cytotoxicity, mutagenicity, and genotoxicity effects compared to cigarette smoke. Clinical studies were also reported, showing lower exposure to harmful chemicals in participants who switched to EHTS, with the levels of these chemicals approaching those in participants who stopped smoking for the duration of the study.

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13 WHO, Report on the Scientific Basis for Tobacco Product Regulation: Fifth Report of a WHO Study Group (2015). http://apps.who.int/iris/bitstream/handle/10665/161512/9789241209892.pdf;jsessionid=5393578BE0AE189FC39B1F37FA746C68?sequence=1

14 Federal State Budget Research Institution All-Russian Scientific Research Institute of Tobacco, Mahorki and Tobacco Products (FGBNU VNIITTI), Research of electric heating system of tobacco. (in Russian) http://www.vniitti.ru/research/

15 Kazan Federal Institute. "In KFU evaluated the impact of the electrical heating system of tobacco on the human body." (in Russian) https://7p-medicine.kpfu.ru/v-kfu-otsenili-vozdejstvie-elektricheskoj-sistemy-nagrevaniya-tabaka-na-organizm-cheloveka/

LATEST EVENTS & OTHER MILESTONES

PMI PRESENTS IN GLOBAL FORUM ON NICOTINE

The results of our ERS and Smoking Cessation Response study were presented at the Global Forum on Nicotine in June by Dr. Christelle Haziza, Director of Health Science and Biostatistics, with more focused posters on the ERS results by Dr. Michael Ansari and on the Smoking Cessation Study by Dr. Cam Tuan Tran. Additional posters on a range of topics were also presented, including a cross-sectional survey on product experience in Japan by Dr. Peter Langer, a study on potential predictors of intended use of EHTS by Dr. Felix Beacher, and a model of the population health impact in Japan of EHTS by Dr. Smilja Djurdjevic. Dr. Christelle Chrea also presented a poster describing PMI's new ABOUT Toolbox (**A**ssessment of **B**ehavioral **OU**tcomes related to **T**obacco and nicotine products), providing fit-for-purpose self-report instruments to assess consumer perceptions and behaviors towards smoke-free products compared to other tobacco and nicotine products.

To learn more about PMI's presence at GFN, visit our website at: https://www.pmiscience.com/science/conferences/global-forum-on-nicotine-(gfn)-2018

RESULTS AFTER 1 YEAR: CROSS-SECTIONAL POST-MARKET STUDY IN JAPAN

Of the 2,000 adult EHTS users (from our company database of users) polled in this study, three quarters of them reported to have begun using EHTS within just the past year. Also, the vast majority (98%) of EHTS users surveyed reported to have initiated tobacco use with another tobacco product. Further, the cigarette volume – representing the total tobacco industry volume – was already decreasing steadily 2-3.3% each year until 2016, when EHTS became available nationally. At that point overall tobacco industry volume continued to drop at the same average rate while EHTS cannibalized the cigarette volume, which dropped 5.7% in 2016, and then 18.4% in 2017. And some of the people who probably would have continued to smoke according to the historical trend are switching to a better alternative. These results were achieved with our Good Conversion Practices (GCP) in place. We take seriously our responsibility to commercialize all of our smoke-free products responsibly and have implemented these GCPs to guide our actions.[16]

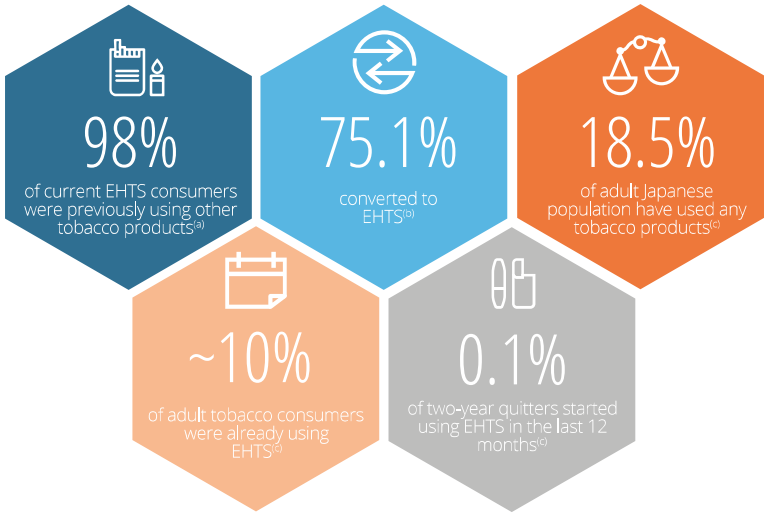
PMI SCIENTISTS CO-AUTHOR PUBLICATION ON NON-ANIMAL APPROACHES TO RISK ASSESSMENT RESEARCH

PMI and 24 other international companies, academic institutions, health authorities, and international organizations collaborated on a publication titled "Pathway-based predictive approaches for non-animal assessment of acute inhalation toxicity" published in *Toxicology in Vitro* in June of this year.[17] In this publication, our coauthors and we explain how it can be difficult to translate results from animal testing to the effect of a product on human health. For this reason, other kinds of tests that involve human cells can provide a more direct understanding of the effect of substances on humans. As the scientific understanding of the human body grows, we also have stronger computer-based predictive tools that can minimize the number of laboratory experiments that need to be completed, giving us faster access to results relevant to human health.

This collaborative project developed a decision tree to help researchers in deciding the optimal inhalation toxicity testing strategy for their products, using *in vitro* and computer-based experiments while avoiding animal testing. This approach recognizes that the best approach depends on the product and substances being tested and currently available approaches. As our work shows: development, implementation, and global acceptance of non-animal testing for inhalation toxicity is a goal that we can achieve as long as we work together.

More information about this publication can be found on PMIScience at: https://www.pmiscience.com/library/publication/pathway-based-predictive-approaches-for-non-animal-assessment-of-acute-inhalation-toxicity

FIRST YEAR RESULTS FROM JAPAN



(a) EHTS user sample
(b) EHTS is >95% of all tobacco use
(c) General population sample – adults only
Source: PMI Research & Development. Study report on cross-sectional survey (P1-PMX-01-JP: Year 1 Results)

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16 Link to our 2017 Sustainability Report for more information on our GCPs: https://www.pmi.com/sustainability/sustainability-report

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GLOSSARY

AEROSOL
An aerosol is a suspension of fine solid particles and/or liquid droplets in a gas (usually air). Cigarettes generate a smoke aerosol that is the result of the combustion (burning) of tobacco and contains carbon-based solid particles. While smoke is an aerosol, not all aerosols are smoke.

PMI's smoke-free products do not produce smoke because they do not burn tobacco. Instead, they generate a nicotine-containing aerosol, either by heating tobacco or through other technologies that do not involve combustion.

Consumers typically use the term "vapor" to refer to the aerosol generated from heated tobacco products or other nicotine-containing products.

BIOMARKERS
Biomarkers can be classified into *biomarkers of exposure* and *clinical risk markers.*

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

CLINICAL RISK MARKERS OR ENDPOINTS
See Biomarkers.

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

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

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

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

REDUCED-RISK PRODUCT (RRP)
The term PMI uses to refer to products that present, are likely to present, or have the potential to present less risk of harm to smokers who switch to these products versus continued smoking. We have a range of RRPs in various stages of development, scientific assessment and commercialization. Because our RRPs do not burn tobacco, they produce far lower quantities of harmful and potentially harmful compounds than found in cigarette smoke.

REFERENCE CIGARETTE (3R4F)
A standard cigarette for laboratory testing provided by the University of Kentucky. The current version is known as 3R4F and is used for non-clinical investigations by tobacco manufacturers, contract and government laboratories, and academic institutions.

STANDARD TOXICOLOGY
To compare whether the reduction in the levels of harmful and potentially harmful chemicals generated by our smoke-free products reduces the toxicity of their aerosol, we perform a range of standard toxicological assays. For example, we have conducted a number of widely used *in vitro* assays comparing the toxicity of our smoke-free products' aerosol to cigarette smoke. These include, but are not limited to:

- The Neutral Red Uptake cytotoxicity assay (measuring mammalian cell toxicity)
- The Ames bacterial mutagenicity assay (measuring bacteria cell mutations)
- The Mouse Lymphoma mammalian mutagenicity assay (measuring mutations in mammalian cells)

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

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

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

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