PMI SCIENCE
PHILIP MORRIS INTERNATIONAL

SCIENTIFIC UPDATE FOR SMOKE-FREE PRODUCTS

JUNE 2018 • ISSUE 05
Past issues can be found here

This Scientific Update provides an overview of the **most recent developments of the science 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, as well as our initiatives to share** our methodologies and results.

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

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WHAT'S INSIDE?

INTRODUCTION

Innovation and technology can improve lives. This applies just as much to our industry as it does to others. It is the burning of tobacco that generates smoke and the vast majority of harmful toxicants generally associated with smoking-related diseases. Smoke-free products, backed by science, offer a promising way to reduce the risk of harm for those who would otherwise continue to smoke.

PMI's smoke-free product development is based on this fundamental principle, coupled with high-quality manufacturing to ensure every product meets those standards. We see very encouraging results at every step of our assessment program, which is in line with international standards for pharmaceutical research and US Food and Drug Administration (FDA) draft guidance for Modified Risk Tobacco Product Applications (2012).

As a leading cigarette manufacturer, we know that our science draws heightened scrutiny - that scrutiny is important. This is why we make our methods and study results available for public review, including the data from our non-clinical and clinical studies on smoke-free products. We believe consumers deserve our commitment to transparently engaging in scientific debate, and accurately explaining the benefits of switching to smoke-free products.

But skepticism is difficult to overcome. As recently flagged by the UK's Public Health England, an executive agency of the UK's Department of Health and Social Care, the reporting of some academic studies has been misleading.[1] Sound, controlled science is of paramount importance to avoid unsupported headlines that could mislead policy makers and the millions who could benefit from smoke-free alternatives.

That's why we are focusing this issue on the latest government reports and peer-reviewed research on our most advanced smoke-free product, our electronically heated tobacco product or EHTP[2]. Every month there are publications that enrich the discussion about the potential role of EHTP in public health. For example, several high-profile government reports and other publications confirm our results on the drastically reduced levels of harmful chemicals in EHTP aerosol compared to cigarette smoke.

This independent research from around the world helps demonstrate to governments, public health experts, the scientific community and civil society not only that PMI's research is robust, but that smoke-free products have the potential to play a pivotal role in changing the lives of millions and make a positive impact on public health.

As our own research continues to evolve, we will share updates in the coming months. We look forward to communicating the results from our Exposure Response and Smoking Cessation studies, looking at the clinical risk endpoints in smokers who switch to EHTP and in those who quit smoking. We will also share the results of our non-clinical carcinogenicity studies that look at the risk of lung cancer in laboratory models.

If you have any questions about our science, we look forward to hearing from you.

Prof. Manuel C. Peitsch
Chief Scientific Officer

Prof. Frank Luedicke
Chief Medical Officer

REFERENCES

1 McNeill, A. et al., Evidence review of e-cigarettes and heated tobacco products 2018. Report commissioned by Public Health England (PHE). February 2018. p 19
https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/684963/Evidence_review_of_e-cigarettes_and_heated_tobacco_products_2018.pdf

2 The EHTP is not authorized for commercialization use in the US. Outside the US the EHTP is commercialized under the *IQOS* brand.

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 smokers looking to switch to an alternative product.

PLATFORM 1
ELECTRICALLY HEATED TOBACCO PRODUCT (EHTP, 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, which ever comes first, similar to that of a cigarette.

ASSESSMENT PROGRESS
We have conducted many non-clinical and clinical studies for this platform with all results consistently pointing in the direction of risk reduction. Our large 6- plus 6-month Exposure Response Study was completed at the end of 2017, and the study report and scientific publications of the results of the first six months are in preparation and will be submitted to the FDA in the second quarter of 2018. We expect to receive the results of the six-month extension of the study (12-month study) in the second quarter of this year.

PLATFORM 2
CARBON-HEATED TOBACCO PRODUCT (CHTP)

DESCRIPTION
A carbon heat source precisely heats the tobacco to a similar temperature as the EHTP. 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 adult smokers who seek an alternative to cigarettes. We completed a three-month reduced exposure study in 2017 and expect to finalize the report in the second quarter of this year. We will share the conclusions in scientific forums and submit them for inclusion in peer-reviewed publications.

PRODUCTS WITHOUT TOBACCO

Another approach to reduce the levels of toxicants generated and inhaled 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 smokers who are not necessarily looking for the taste and sensory experience of tobacco or already use 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 initiated a new nicotine pharmacokinetic study for the version without electronics for analysis in the second quarter of 2018.

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”.

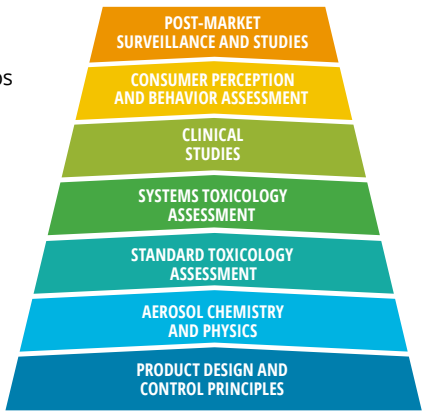
ASSESSMENT PROGRESS
The non-clinical assessment on our e-liquids is well advanced. We have initiated a nicotine pharmacokinetic study for which we expect to receive the study results in the second quarter of this year. The results of this study are expected to contribute to further developments of Platform 4 products.

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.



RECENT MILESTONES

Focus on: Independent Verification of PMI's Research

PMI has published over 35 peer-reviewed articles on the EHTP covering the different steps of our assessment program. For individual risk, these include aerosol chemistry, toxicology and clinical studies, all in line with applicable Good Laboratory and Good Clinical Practices. These studies demonstrate that the EHTP aerosol contains significantly reduced levels of toxicants compared with cigarette smoke and that this leads to a significantly reduced exposure to toxicants in smokers who switched to EHTP use. Furthermore, all studies conducted in laboratory models demonstrate that reduced toxicant emission significantly reduces the toxicity and the disease risk of the EHTP aerosol compared with cigarette smoke.

A crucial step toward the acceptance of PMI's research on EHTP is the corroboration and verification from independent researchers and experts. Now that the product is in the market, we are starting to see an increasing number of independent peer-reviewed publications on EHTP and government reports that review this evidence or even present research of their own. Studies focused on topics ranging from aerosol chemistry to the potential health impact on users. Encouragingly, the body of literature on EHTP, including conclusions from both peer-reviewed publications and government reports, is generally in line with our own results.

The summary below presents the government reports on EHTP, as well as the peer-reviewed research that was published by independent experts in the past six months. The Appendix on page 12 provides a list of these publications, including those published earlier.

GOVERNMENT REPORTS REVIEWING EHTP:

US: Food and Drug Administration
In December 2016, PMI submitted applications to the FDA for authorization to market the EHTP as a Modified Risk Tobacco Product in the United States – the authorization required to communicate information about the reduction in risk or exposure to consumers in relation to a tobacco product. As a part of this process, research on EHTP, including PMI's data, was discussed at a meeting with the Tobacco Products Scientific Advisory Committee (TPSAC) on January 24-25, 2018.

TPSAC makes non-binding recommendations that the FDA will take into consideration together with the public comments and findings from the FDA's scientific review. More information on this meeting is provided on page 9, and related documents can be found on the FDA's website[3]

UK: Public Health England
On February 6, 2018, Public Health England (PHE), an executive agency of the UK's Department of Health and Social Care, released a new report on the evidence behind cigarette alternatives, the fourth such review on e-cigarettes and the first time it included heated tobacco products.[4] An earlier statement made by the UK Committee on Toxicity[5] helped to provide perspective on the toxicological risks of heated tobacco products.[6] PHE's analysis of independent evidence on heated tobacco products, which was heavily focused on EHTP, considered eight independent studies in its review.

Amongst the report's findings on heated tobacco products are a likely reduction in user's exposure to harmful chemicals compared to cigarettes, and that:

"The available evidence suggests that heated tobacco products may be considerably less harmful than tobacco cigarettes and moreharmful than [e-cigarettes]."

The report also stressed the need for more research that is independent of commercial interests.

Germany: Federal Institute for Risk Assessment
On May 5, 2018, the German Federal Institute for Risk Assessment (BfR) published an article on EHTP in Archives of Toxicology.[7] Their research analyzed the mainstream EHTP aerosol using the Health Canada Intense Smoking Regimen, finding significant reductions in selected toxicants (80-99%), which was in line with PMI's own research.

The significant reductions in selected toxicants measured by the Institute "*are likely to reduce toxicant exposure*." The study states that while further studies are required to address the magnitude of exposure reduction, the measured reductions "*lead to the relevant questions of putatively reduced health risks.*"

BfR noted that its findings are also largely consistent with other recent studies, including Li et al.,[8] Farsalinos, et al.,[9] Bekki et al.,[10] the US FDA's Tobacco Laboratory.[11]

REFERENCES
3 2018 TPSAC Meeting Materials and Information, FDA website. January 24-25, 2018. https://www.fda.gov/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/ucm583080.htm
4 Public Health England, Evidence review of e-cigarettes and heated tobacco products 2018, https://www.gov.uk/government/publications/e-cigarettes-and-heated-tobacco-products-evidence-review
5 With support from the Committees on Carcinogenicity and Mutagenicity of Chemicals in Food, Consumer Products, and the Environment.
6 Committee on Toxicity, "Statement on the toxicological evaluation of novel heat-not-burn tobacco products" https://cot.food.gov.uk/sites/default/files/heat_not_burn_tobacco_statement.pdf

Netherlands: National Institute for Public Health and the Environment

On May 15, the Dutch National Institute for Public Health and the Environment (RIVM) published a "Factsheet on novel tobacco products that are heated."[12] RIVM concluded that *"The use of heatsticks with the iQOS is harmful to health, but probably less harmful than smoking tobacco cigarettes,"* based on their aerosol chemistry measurements, which are *"of the same order of magnitude as in the data of Philip Morris."*

PEER-REVIEWED INDEPENDENT RESEARCH ON EHTP FROM THE LAST SIX MONTHS:

PMI is encouraged by the growing number of independent assessments of EHTP, conducted in countries around the world. We have included an overview of the independent, peer reviewed studies on EHTP over the past six months. The general trend amongst these studies is that, irrespective of methodology, EHTP aerosol shows favorable differences when compared with cigarette smoke.

Aerosol chemistry

The China National Tobacco Quality Supervision and Test Centre, a member of the WHO Tobacco Laboratory Network, compared the levels of harmful chemicals in EHTP aerosol against cigarette smoke.[8] The authors found that EHTP "*delivered fewer harmful constituents than the conventional cigarette 3R4F. Simulated pyrolysis results showed that the lower temperature instead of specially designed ingredients contributed to the distinct shift*."

A team in the US at the University of California, Riverside, focused on specific components in EHTP aerosol as a result of user maintenance and use of the device.[13] The study found that EHTP *"appears to be well manufactured, and performance data were consistent between heatsticks."* The authors also reported results of testing the biopolymer filter, which is made from vegetable starch, reporting that it "*readily melts during use and releases formaldehyde cyanohydrin, a dangerous toxicant."* PMI scientists performed similar measurements as the author and found that this chemical was not present in the aerosol. Our findings are consistent with the fact that the toxicant the authors reported is not used in any step of the manufacturing process. The methods and results of PMI's own analysis have been shared with the publication's editor and are available on PMIScience.com.

A research team from the University of Cassino and Southern Lazio in Italy analyzed the number and size of particles in the aerosol of EHTP aerosol.[14] They found that the number of particles are *"lower than those characteristics in traditional cigarettes and electronic cigarettes,"* though "*the non-volatile amount of particle surface area was… up to 4-fold larger than that received by electronic cigarette vapers.*" They concluded that *"future researches should be performed to fill the gap about the chemical characterization of the [EHTP]-emitted particles."*

Toxicology

Researchers at the British American Tobacco R&D Centre conducted a toxicological assessment of both their own heated tobacco product and EHTP on a human airway cell culture.[15] The researchers found that a high-concentration exposure of the cell culture to aerosol from their own product or EHTP produced less of a stress response, a lower pro-inflammatory effect, and *"have a reduced impact on gene expression compared to 3R4F."*

Public perception and use statistics

Researchers from Italy interviewed approximately 3,000 people about their interest in and trial of EHTP and their cigarette smoking status.[16] The results showed that, *"Overall, 1.0% of never smokers, 0.8% of ex-smokers and 3.1% of current cigarette smokers have tried [EHTP]."* The authors concluded that *"the absolute number of never smokers who have already tried [EHTP] in Italy is comparable to that of current smokers,"* however, our own studies have not supported this conclusion.

In Japan, our most developed market for EHTP, nearly all tobacco users initiated with cigarettes rather than another tobacco product like EHTP. One reason for the difference in results might be that it is in general difficult to draw the conclusions that were made based on the Italian sample, which measured intention to try in a small sub-population of non-smokers in the study and then extrapolated the findings to a population level of established use. PMI is currently conducting studies in several other countries on the effect of EHTP on tobacco prevalence, including Italy, and the results for each will be made available.

REFERENCES

7 Mallock, N. et al ., "Levels of selected analytes in the emissions of 'heat not burn' tobacco products that are relevant to assess human health risks." *Arch Toxicol.* 2018. doi: 10.1007/s00204-018-2215-y

8 Li, X. et al., "Chemical Analysis and Simulated Pyrolysis of Tobacco Heating System 2.2 Compared to Conventional Cigarettes." *Nicotine Tob. Res.* Accepted Manuscript. 2018. doi: 10.1093/ntr/nty005

9 Farsalinos, C. et al., "Toxicant Exposure: Heated tobacco products vs. e-cigarettes," (June 16, 2018) (presentation at the Global Forum on Nicotine 2017), https://gfn.net.co/downloads/Presentations_2017_/Dr%20Konstantinos%20Farsalinos.pdf

10 Bekki, K. et al., "Comparison of Chemicals in Mainstream Smoke in Heat-not-burn Tobacco and Combustion Cigarettes." *J. UOEH.* 39 (3) 2017. pp 201-207. doi: 10.7888/juoeh.39.201

11 Office of Science Center for Tobacco Products Food and Drug Administration. *FDA Briefing Document.* January, 2018 Meeting of the Tobacco Products Scientific Advisory Committee (TP SAC), https://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/UCM593109.pdf

12 RIVM *Factsheet on novel tobacco products that are heated.* May 2018. http://www.rivm.nl/dsresource?objectid=e1ce3c72-1436-444f-a4d0-e9f93dc30da6&type=pdf&disposition=inline and English-language summary of results: https://www.rivm.nl/en/Documents_and_publications/Common_and_Present/Newsmessages/2018/Addictive_nicotine_and_harmful_substances_also_present_in_heated_tobacco

13 Davis, B; et al., "iQOS: evidence of pyrolysis and release of a toxicant from plastic." *Tob. Control.* 2018 doi:10.1136/tobaccocontrol-2017-054104.

14 Paciotto, A. et al., "Characterization of airborne particles emitted by an electrically heated tobacco smoking system." *Environ. Pollut.* 240, 2018. pp 248-254.

Health impact

A research paper from the University of St. Andrews, Scotland,[17] concluded that EHTP fits into the spectrum of risk with a similar conclusion to that of PHE noted earlier. The study states that, *"Samples of a prototype heat-not-burn device have lower cancer potencies than tobacco smoke by at least one order of magnitude, but higher potencies than most e-cigarettes."*

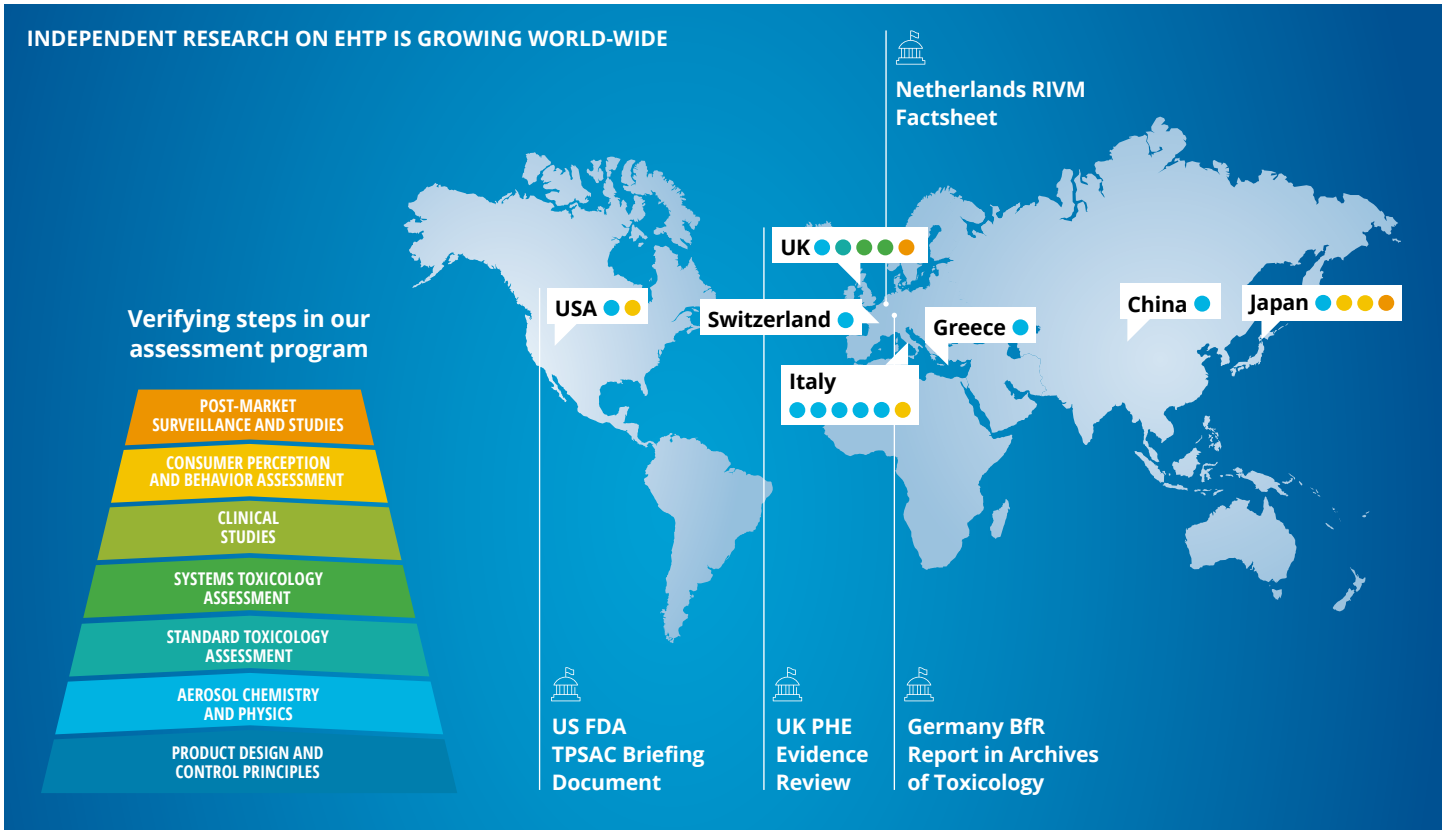
CONCLUSIONS

Both the FDA and PHE made clear in their publications the importance of robustness in drawing conclusions adequately supported by the data. For example, the FDA concluded about one study:

"The data published is not considered adequate for comparing the levels of HPHCs between the IQOS products and combusted cigarettes. There are significant analytical issues in the [authors'] study, such as lack of testing reference samples, low number of replicates, lack of selectivity on some analytical methods."

PHE also highlighted in their report that adult smokers are poorly informed about relative risks of different products, stating that *"the way the results of some studies with particular limitations have been designed and reported, and then subsequently presented in the media, may have caused serious concerns about [electronic cigarettes],"* and that such *"inaccurate or inadequate reporting"* is very likely playing a key role in the persistent misperceptions. The agency added that *"while such inaccurate reporting is not confined to the tobacco harm reduction field," "smoking is uniquely dangerous,"* and *"there are few other scientific areas where the gains and losses to public health are so high."*

We believe that these statements apply equally across the growing body of research on all smoke-free products that have the potential to positively impact public health. The trend amongst the available independent studies on aerosol chemistry support our conclusions about the reduced levels of harmful chemicals, and several other studies are showing encouraging results toward other parts of our assessment program. All of these studies contribute to the much-needed scientific and regulatory discussions on smoke-free products.



Whether positive, negative, or neutral, the body of independently published research on EHTP continues to grow. The map above shows government reports and independent peer-reviewed research from around the globe and what portions of our assessment program their work addresses. The studies indicated here represent the available literature we could identify at this time. The list of publications for this graphic can be found on page 12.

REFERENCES
15 Haswell, L. E et al. "In viro RNA-seq-based toxicogenomics assessment shows reduced biological effect of tobacco heating products when compared to cigarette smoke." *Sci. Rep.* 8, 2018. p. 1145.
16 Liu, X. et al. "Heat-not-burn tobacco products: concerns from the Italian experience." *Tob. Control.* 2018. doi: 10.1136/tobaccocontrol-2017-054054.
17 Stephens, W. E. "Comparing the cancer potencies of emissions from vapourised nicotine products including e-cigarettes with those of tobacco smoke." *Tob. Control.* 27, 2018. pp 10-17.

PEER-REVIEWED PUBLICATION HIGHLIGHTS

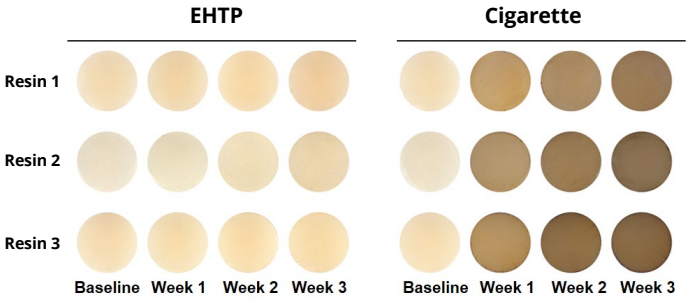


Image adapted from Zhao et al. 2017.

Effects of cigarette smoking on color stability of dental resin composites

Cigarette smoke has been recognized as one of the factors causing stain and discoloration of dental resin composites since the early years of the resin's development. Reducing or eliminating the deposits derived from combustion of tobacco has the potential to minimize the impact of smoking on the color of composite resin restorations. A collaboration between PMI and researchers at the University of Rochester Eastman Institute for Oral Health in the US found that the aerosol of EHTP was significantly less likely to stain dental resins than cigarette smoke from a 3R4F reference cigarette.

In this study of three different commercial composite resins, 20 discs of each type of resin were measured for surface roughness, color, and gloss before the study. Then, 10 disks of each resin were exposed to the equivalent of 20 cigarettes per day for four days, afterwards brushed with toothpaste and measured again. At night, the disks were incubated in artificial saliva to mimic their environment in the mouth. The same was done for 10 disks of each resin exposed to EHTP aerosol. After three weeks of continuing with this treatment, the resins exposed to EHTP aerosol were stained six- to ten-fold less than those treated with cigarette smoke. Also, cigarette smoke stained each of the resins by different amounts, while EHTP consistently caused only very minor staining, similar for all resins measured.

Zhao, Xiaoyi; Zanetti, Filippo; Majeed, Shoaib; Pan, Jie; Malmstrom, Hans; Peitsch, Manuel C; Hoeng, Julia; Ren, Yanfang. "Effects of cigarette smoking on color stability of dental resin composites." American Journal of Dentistry, 2017; 30 (6):316-322.

In the research literature, EHTP is referred to as Tobacco Heating System (THS or THS 2.2)

Determination of eight carbonyl compounds in aerosols trapped in phosphate buffer saline solutions to support *in vitro* assessment studies

When investigating the toxic impact of aerosols in cell cultures and other *in vitro* systems, it is important to have a clear way to measure the chemicals that the cells are exposed to. Carbonyl compounds like formaldehyde and acetone are an important category of chemicals to be able to measure because they can indicate exposure to certain toxic substances, including cigarette smoke, but there is no standard method to measure them in liquids suitable for cell culture measurements. When *in vitro* studies are performed to study the effects of cigarette smoke on cells, for example, these compounds must be measured in the liquid that will be added to the cell culture to learn exactly what concentration of these chemicals the cells will be exposed to. PMI scientists developed a new method of measurement for eight carbonyls in a saline solution, and the method was compared with other methods of measuring cigarette smoke (outside of a cell culture liquid) for the eight carbonyl compounds. The new method, using a combination of mass spectroscopy and chromatography techniques, is highly specific for the chemicals of interest and was shown to be accurate over a wide range of concentrations. This is important because these compounds are found at significantly lower concentrations in EHTP aerosol compared to cigarette smoke.

Buratto, Roberto; Correia, Daniela; Parel, Monique; Crenna, Maude; Bilger, Mickaël; Debrick, Audrey. "Determination of eight carbonyl compounds in aerosols trapped in phosphate buffer saline solutions to support *in vitro* assessment studies."Talanta, 2018; 184:42-49.

Comparative systems toxicology analysis of cigarette smoke and aerosol from a candidate modified risk tobacco product in organotypic human gingival epithelial cultures: A three-day repeated exposure study

Using a systems toxicology approach, the effects of cigarette smoke and EHTP aerosol on skin cells from human gums were tested as a step toward understanding the potential for EHTP use to minimize risk of periodontal disease compared to cigarette smoke. Human gum cells were cultured to form organotypic structures, which are similar to their arrangement in the human mouth. They were exposed for 28 minutes at nicotine-equivalent concentrations of EHTP aerosol or cigarette smoke from a 3R4F reference cigarette at two different levels of nicotine (low: 4.94 µg and high: 8.46 µg), and this procedure was repeated once per day for three days. During experiments, the cell cultures were wetted with a saline solution to mimic the environment in the mouth.

The results in this study show that EHTP had a reduced impact on human gum epithelia compared with cigarette smoke. No cytotoxicity, a reduced inflammation response, and fewer of the processes associated with periodontal disease were observed in the tissues repeatedly exposed to EHTP compared with cigarette smoke. The results of this study indicate that exposure to EHTP aerosol had no obvious acute toxicity and had lower impact on the mechanisms that cause disease in human gums than cigarette smoke. Cigarette smoke, on the other hand, showed some toxicity at four hours after exposure, with increased toxicity 24 hours after exposure, and a higher impact on the processes involved in periodontal disease.

Zanetti, Filippo; Titz, Bjoern; Sewer, Alain; Lo Sasso, Giuseppe; Scotti, Elena; Schlage, Walter; Mathis, Carole; Leroy, Patrice; Majeed, Shoaib; Torres, Laura Ortega; Keppler, Brian R.; Elamin, Ashraf; Trivedi, Keyur; Guedj, Emmanuel; Martin, Florian; Frentzel, Stefan; Ivanov, Nikolai V.; Peitsch, Manuel C.; Hoeng, Julia. "Comparative systems toxicology analysis of cigarette smoke and aerosol from a candidate modified risk tobacco product in organotypic human gingival epithelial cultures: A 3-day repeated exposure study." Food and Chemical Toxicology, 2017; 101:15-35.

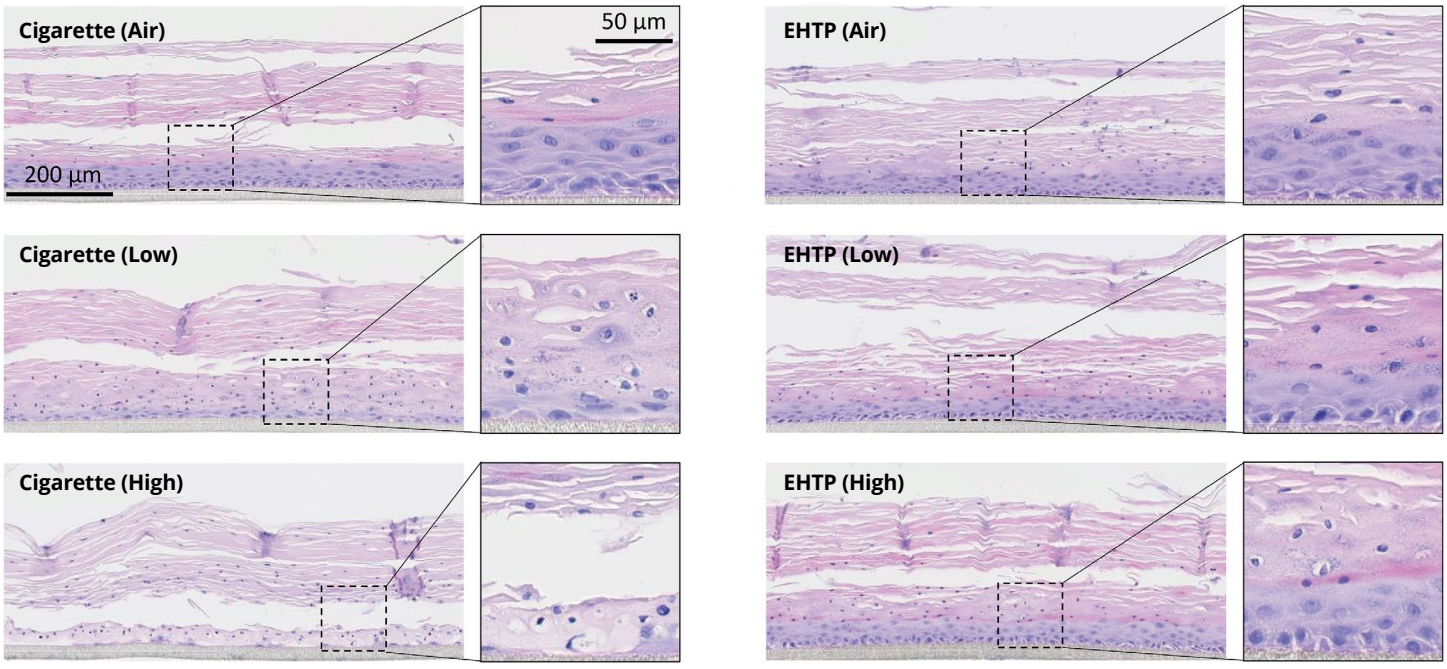


Image adapted from Zanetti et al. 2017.

LATEST EVENTS & OTHER MILESTONES

PMI PRESENTS ON MODIFIED RISK TOBACCO PRODUCT APPLICATION FOR EHTP BEFORE THE US FOOD AND DRUG ADMINISTRATION'S TOBACCO PRODUCTS SCIENTIFIC ADVISORY COMMITTEE

SILVER SPRING, MD, US, 24-25 JANUARY, 2018

PMI's Moira Gilchrist, VP Scientific and Public Communications; Manuel Peitsch, Chief Scientific Officer; and Antonio Ramazzotti, VP Human Insights and Behavioral Research, presented on our Modified Risk Tobacco Products (MRTP) Applications for EHTP before the Tobacco Products Scientific Advisory Committee (TPSAC) in January 2018 as another step in the FDA's review process. Gizelle Baker, Director Scientific Engagement, and Dr. Maurice Smith, PMI Scientific Fellow, were also available to answer questions during the presentation. The presentation covered EHTP, its heating technology and the results of our assessment program to date. In addition, a representative from Altria, which will sell EHTP in the United States if authorized by FDA, shared an overview of the company's plans for the introduction of the product, including controls to minimize unintended use, as well as plans for post-market surveillance. We summarized our application in our November 2017 Issue.

The FDA then presented its own assessment and results on EHTP to date, and members of the public had an opportunity to present statements to the committee. At the end of the meeting, the members of the committee discussed and voted on specific questions for which the FDA requested the committee's views. The committee's votes and the discussion from the meeting will be taken into consideration by the FDA, together with all other inputs from their review.

PHILIP MORRIS INTERNATIONAL PRESENTS TO US FDA'S TOBACCO PRODUCT ADVISORY COMMITTEE (TPSAC)

The committee, which is established under US law, advises FDA on issues of tobacco regulation, including the review of Modified Risk Tobacco Product Applications. The committee consists of nine voting members from the scientific and public health communities and additional non-voting members, including industry representatives. The committee raised questions and probed the likelihood and magnitude of potential benefits as well as unintended use. Although it did not agree with some of the specific language of proposed risk and harm consumer communications, it confirmed that evidence supported the statement that switching completely to EHTP significantly reduces exposure to harmful chemicals as well as the low likelihood of users who quit smoking reinitiating nicotine use with EHTP.

Find out more about PMI's presentations here: https://www.pmiscience.com/discover/news/pmi-presents-on-our-modified-risk-tobacco-product-application-for-Platform-1-before-the-tobacco-products-scientific-advisory-committee-(tpsac)

PMI SCIENCE LAUNCHES NEWLY UPDATED WEBSITE: WWW.PMISCIENCE.COM

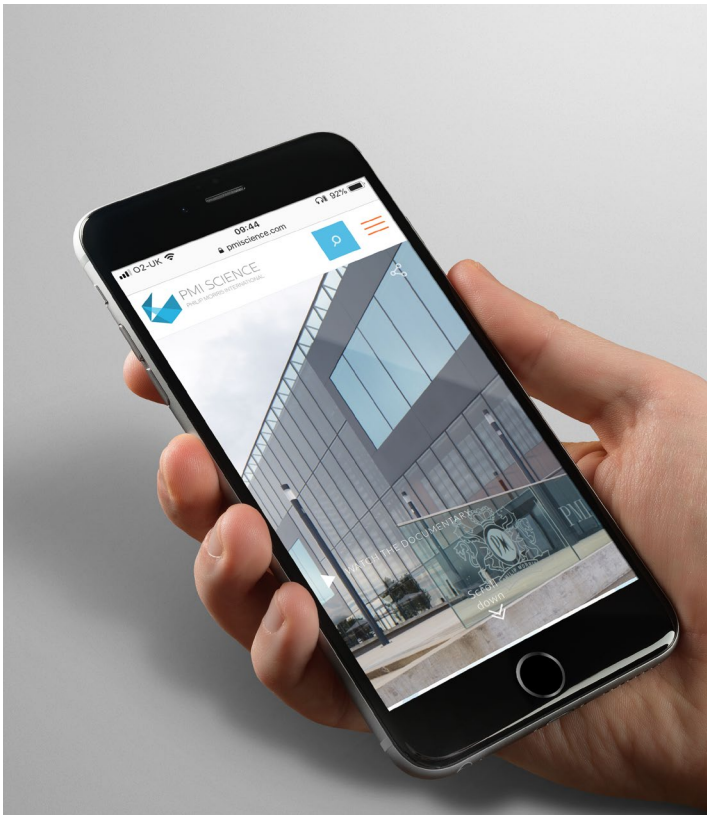
NEUCHATEL, SWITZERLAND

7 MARCH, 2018

We have updated our PMI Science website to enhance sharing of the science, technology, and innovation behind our smoke-free products with interested stakeholders. The newly revamped website explains our smoke-free approach and includes new videos and infographics that explain key concepts. Initially launched in English, the site will be available in additional languages in the coming months.

The new PMI Science website showcases a range of introductory videos explaining why better alternatives to cigarettes have a role to play in public health, as well as explaining the various steps of our robust assessment program. Visitors can also explore our four smoke-free platforms by viewing interactive infographics, showing in detail how each of the products works, and quickly scan an up-to-date overview of scientific results to date on each. The website also includes an overview of our scientific assessment program and our over 250 peer-reviewed publications, as well as presentations and posters presented at scientific conferences.

To check out the updated website, go to: www.pmiscience.com.



SOCIETY FOR RESEARCH ON NICOTINE AND TOBACCO (SRNT) 2018

BALTIMORE, US

21-24 FEBRUARY, 2018

This annual meeting includes an education-packed scientific program that allows more than 1,100 international attendees to stay current with the latest breaking research on nicotine and tobacco. PMI presented posters on topics that included the biological changes after six months of smoking abstinence (resulting from our one-year smoking cessation study), the relationship between intended use and perceived risks of heated tobacco products, and the reduced effect of EHTP use on dental resins and tooth enamel and dentin discoloration compared with cigarette smoke. This last poster by Filippo Zanetti et al. expands on the publication by Xiaoyi Zhao described on page 7.

Independent researchers also presented their latest studies on EHTP, including results on aerosol chemistry,[18] toxicity,[19] clinical research,[20] and product awareness.[21, 22]

Find out more about PMI's presentations at the event, including the posters and slide decks, here: https://www.pmiscience.com/science/conferences/conference/society-for-research-on-nicotine-and-tobacco-(srnt-2018)

COMPLETION OF INVESTIGATOR-INITIATED STUDIES PILOT PROGRAM

NEUCHATEL, SWITZERLAND

PMI's investigator-initiated studies program was a pilot program to encourage investigator-initiated research on our smoke-free products. As more adult smokers switch to smoke-free products, we are pleased to see an increased number of independent scientific studies on our smoke-free products. As a result, there is less need to support investigator-initiated studies. Established in June 2016, the program has been used to support researchers who design, implement, and oversee their own research on PMI's commercialized smoke-free products. PMI's ongoing role to provide financial, technical or material support to these researchers as they expand the scientific and medical knowledge on our commercialized smoke-free products. Although the program stopped accepting new applications after January 1, 2018, the final committee meeting was held in February to evaluate the last of the proposals. Three studies are currently underway, and two further studies are pending implementation.

Find out more about the program and the research being supported here: https://www.pmiscience.com/iis/supported-investigator-initiated studies

REFERENCES

18 Talih, S. et al. SRNT poster POS5-118 "Is IQOS designed to convert combustible cigarette users? Investigation of free-base and total nicotine, and reactive species in IQOS." American University of Beirut, Lebanon.

19 Leigh, N. et al. SRNT poster PA23-3 "Cytotoxic effects of a tobacco heat-not-burn system on human epithelial cells." Roswell Park Cancer Institute, NY, USA.

20 Gale, N. et al. SRNT poster POS5-188 "Changes in biomarkers of exposure on switching froma conventional cigarette to tobacco heating products: a randomized, controlled study in healthy Japanese subjects." British American Tobacco Ltd. United Kingdom.

21 Diemert, L. et al. SRNT poster POS5-50 "Awareness, perceived risk, and policy perceptions of heat-not-burn products." University of Toronto, ON, Canada.

22 Hammond, D. et al. SRNT poster POS4-108 "Awareness and interest in heat-not-burn IQOS among youth in three countries: Canada, USA, and England." University of Waterloo, ON, Canada.

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 MARKERS

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 conducted with adult smokers.

MODIFIED RISK TOBACCO PRODUCT (MRTP)

The term used to classify a potentially less harmful product by the US Family Smoking Prevention and Tobacco Control Act (2009), which granted to the FDA authority to regulate tobacco products and to authorize claims of reduced risk or exposure. MRTP is defined as "any tobacco product that is sold or distributed for use to reduce harm or risk of tobacco-related diseases 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 adult smokers 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.

SYSTEMS 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.

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 interpretbut also more relevant to effects on the human body compared to standard toxicology methods.

TOBACCO PRODUCTS SCIENTIFIC ADVISORY COMMITTEE (TPSAC)

As part of the FDA review process for MRTP applications, TPSAC reviews the evidence associated with MRTP applications and provides the FDA with recommendations on specific key questions the FDA poses to the committee. TPSAC's recommendation is non-binding, and the FDA considers the recommendations of TPSAC along with other relevant information, including public comments, to make a final decision regarding an MRTP application.

INDEPENDENT PUBLICATIONS AND THEIR RESULTS ON EHTP

Government reviews and independent, peer-reviewed publications on EHTP

GOVERNMENT REVIEWS ON OR INCLUDING EHTP:

UK

1. McNeill, A. et al. "Evidence review of e-cigarettes and heated tobacco products 2018." Report commissioned by Public Health England (PHE). February 2018. https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/684963/Evidence_review_of_e-cigarettes_and_heated_tobacco_products_2018.pdf.

   "The available evidence suggests that heated tobacco products may be considerably less harmful than tobacco cigarettes and more harmful than e-cigarettes."

UNITED STATES:

2. Office of Science Center for Tobacco Products Food and Drug Administration. "FDA Briefing Document." January, 2018 Meeting of the Tobacco Products Scientific Advisory Committee (TPSAC). https://www.fda.gov/downloads/AdvisoryCommitteesCommitteesMeetingMaterials/TobaccoProductsScientificAdvisoryCommittee/UCM593109.pdf.

GERMANY:

3. Federal Institute for Risk Assessment (BfR). "Levels of selected analytes in the emissions of 'heat not burn' tobacco products that are relevant to assess human health risks." Arch Toxicology. 2018. doi: 10.1007/s00204-018-2215-y.

   "...our data confirm absolute values for selected toxicants in the emissions of the analyzed HNB that are in agreement with data published by the manufacturer."

NETHERLANDS:

4. National Institute for Public Health and the Environment (RIVM). "Factsheet on novel tobacco products that are heated." May, 2018 http://www.rivm.nl/dsresource?objectid=e1ce3c72-1436-444f-a4d0-e9f93dc30da6&type=pdf&disposition=inline.

   "The number of substances present in the air that is inhaled when using tobacco sticks with the [EHTP] is lower than in cigarette smoke, but that does not mean that the health risk of HTPs is equally lower."

INDEPENDENT RESEARCH ON EHTP:

CHINA:

5. Li, X. et al. "Chemical Analysis and Simulated Pyrolysis of Tobacco Heating System 2.2 Compared to Conventional Cigarettes." *Nicotine Tob. Res*. Accepted Manuscript. 2018. doi: 10.1093/ntr/nty005.

   "[EHTP] delivered fewer harmful constituents than the conventional cigarette 3R4F. Simulated pyrolysis results showed that the lower temperature, instead of specially designed ingredients contributed to the distinct shift."

GREECE:

6. Farsalinos, K. E. et al. "Nicotine Delivery to the Aerosol of a Heat-Not-Burn Tobacco Product: Comparison With a Tobacco Cigarette and E-Cigarettes." *Nicotine Tob. Res.* 2017. doi: 10.1093/ntr/ntx138.

   "The HnB [heat-not-burn] product delivers nicotine to the aerosol at levels higher than ECs [e-cigarettes] but lower than a tobacco cigarette when tested using Health Canada Intense puffing regime. No change in HnB nicotine delivery was observed at prolonged puff duration with the same puff volume, unlike ECs which deliver more nicotine with longer puff duration."

ITALY:

7. Liu, X. et al "Heat-not-burn tobacco products: concerns from the Italian experience." *Tob. Control.* 2018. doi: 10.1136/tobaccocontrol-2017-054054.

   "We found that the absolute number of never smokers who have already tried [EHTP] in Italy is comparable to that of current smokers."

8. Pacitto, A. et al. "Characterization of airborne particles emitted by an electrically heated tobacco smoking system." *Environ. Pollut.* 240, 2018. pp 248-254. doi: 10.1016/j.envpol.2018.04.137.

   "The dose received by smokers in terms of non-volatile amount of particle surface area was equal to 1–2 mm^2 per puff, i.e. up to 4-fold larger than that received by electronic cigarette vapers."

9. Protano, C. et al. "Second-hand smoke exposure generated by new electronic devices (IQOS and e-cigs) and traditional cigarettes: submicron particle behavior in human respiratory system." *Ann. Ig*. 28 (2) 2016. pp 109-112. doi: 10.7416/ai.2016.2089.

   "During smoking, SMPs [submicronic particles] released by traditional cigarettes resulted four times higher than those released by electronic and heat-not-burn devices and remained high for at least one hour, while SMPs values returned immediately similar to background for electronic and heat-not-burn devices."

10. Protano, C. et al. "Second-hand smoke generated by combustion and electronic smoking devices used in real scenarios: Ultrafine particle pollution and age-related dose assessment." *Environ. Int.* 107, 2017. pp 190-195. doi: 10.1016/j.envint.2017.07.014.

    "The doses due to second-hand smoke from electronic devices [including EHTP] were significantly lower, below 1.60×108particles/kg bw [body weight], than those due to combustion devices. Dosimetry estimates were 50% to 110% higher for [EHTP] than for e-cigarettes."

11. Ruprecht, A. A. et al. "Environmental pollution and emission factors of electronic cigarettes, heat-not-burn tobacco products, and conventional cigarettes." *Aerosol Sci. Technol*. 51 (6) 2017. pp 674-684. doi: 10.1080/02786826.2017.1300231.

    "Overall, our results indicate that [EHTP] devices, while having substantially lower emissions of most toxic compounds compared to CC [combustible cigarettes], are still not risk-free."

12. Veronese, C. et al. "Cigarette smoke, e-cig vapor and 'heat-not-burn': a comparison between the emissions of toxic compound." *Tabaccologia.* 1, 2017. pp 17-23. ISSN: 1970-1195. (in Italian)

    "The results of our studies show that the [EHTP] devices, while having lower emissions of the majority of the toxic components compared to traditional tobacco products, still cannot be defined as harmless or free of risk factors."

JAPAN:

13. Bekki, K. et al. "Comparison of Chemicals in Mainstream Smoke in Heat-not-burn Tobacco and Combustion Cigarettes." *J. UOEH.* 39 (3) 2017. pp 201-207. doi: 10.7888/juoeh.39.201.

"The concentrations of nicotine in tobacco fillers and the mainstream smoke of [EHTP] were almost the same as those of conventional combustion cigarettes, while the concentration of TSNAs was one fifth and CO was one hundredth of those of conventional combustion cigarettes."

14. Kamada, T. et al. "Acute eosinophilic pneumonia following heat-not-burn cigarette smoking." *Respirol. Case Rep.* 4 (6) 2016. e00190. doi: 10.1002/rcr2.190.

"In the same way as a conventional cigarette, HC [heat-not-burn cigarettes] should be recognized as a potential cause of AEP [acute eosinophilic pneumonia]."

15. Tabuchi, T. et al. "Awareness and use of electronic cigarettes and heat-not-burn tobacco products in Japan." *Addiction.* 111 (4) 2016. pp 706-713. doi: 10.1111/add.13231.

"Approximately half the respondents in a Japanese internet survey were aware of e-cigarettes and heat-not-burn tobacco products, 6.6% had ever used."

16. Tabuchi, T. et al. "Heat-not-burn tobacco product use in Japan: its prevalence, predictors and perceived symptoms from exposure to secondhand heat-not-urn tobacco aerosol." *Tob. Control.* 2017. doi: 10.1136/tobaccocontrol-2017-053947.

"Tobacco control organisations and governments should continue to monitor HNB tobacco and consider how to regulate it, given its impending, likely rapid global diffusion."

SWITZERLAND:

17. Auer, R. et al. "Heat-Not-Burn Tobacco Cigarettes: Smoke by Any Other Name." *JAMA Intern. Med.* 177 (7). 2017. pp 1050-1052. doi: 10.1001/jamainternmed.2017.1419.

"Volatile organic compounds, polycyclic aromatic hydrocarbons, and carbon monoxide were present in [EHTP] smoke. The temperature of the [EHTP] was lower (330 °C) than the conventional cigarette (684 °C). The [EHTP] smoke had 84% of the nicotine found in conventional cigarette smoke."

Our public comment on this article's methods in JAMA Internal Medicine can be found at: https://jamanetwork.com/journals/jamainternalmedicine/article-abstract/2660130.

UNITED KINGDOM:

18. Forster, M. et al. (British American Tobacco) "Assessment of novel tobacco heating product THP1.0 Part 3: Comprehensive chemical characterization of harmful and potentially harmful aerosol emissions." *Reg. Toxicol.* Pharmacol. 93, 2018. pp 14-33. *doi:* 10.1016/j.yrtph.2017.10.006.

"For purposes of quality assurance, the concentrations of the same measurands observed in emissions from a commercial tobacco heating product, THS [EHTP], were assessed and the observed results (Table 5) compared with values previously reported by Schaller et al., (2016)."

19. Haswell, L. E. et al. (British American Tobacco) "In vitro RNA-seq-based toxicogenomics assessment shows reduced biological effect of tobacco heating products when compared to cigarette smoke." *Sci. Rep.* 8, 2018. p 1145. doi: 10.1038/s41598-018-19627-0.

"In conclusion, THPs have a reduced impact on gene expression compared to 3R4F."

20. Stephens, W. E. "Comparing the cancer potencies of emissions from vapourised nicotine products including e-cigarettes with those of tobacco smoke." *Tob. Control.* 27, 2018. pp 10-17. doi: 10.1093/ntr/nty005.

"Mean lifetime risks decline in the sequence: combustible cigarettes >> heat-not-burn >> e-cigarettes (normal power) ≥ nicotine inhaler."

21. Taylor, M. et al. (British American Tobacco) "Assessment of novel tobacco heating product THP1.0 Part 6: A comparative in vitro study using contemporary screening approaches." *Reg. Toxicol. Pharmacol*. 93, 2018. pp 62-70. doi: 10.1016/j.yrtph.2017.08.016.

"TPM [total particulate matter] from 3R4F tobacco products stimulated responses in the ARE RGA and multiple cellular acute response endpoints that could be assessed with an HCS [high content screening] approach and could show relatively little or no activity with two THP TPMs at comparable doses."

22. Thorne, D. et al. (British American Tobacco) "Assessment of novel tobacco heating product THP1.0 Part 7: Comparative in vitro toxicological evaluation." *Reg. Toxicol. Pharmacol*. 93, 2018. pp 71-83. doi: 10.1016/j.yrtph.2017.08.017.

"All the in vitro techniques employed produced a clear positive response [indicating cytotoxicity] *with cigarette smoke and in contrast, a negative response [no or minimal cytotoxicity] to THPs at doses equivalent to or higher than a cigarette smoke test matrix."*

UNITED STATES:

23. Caputi T. L. et al. "They're heating up: Internet search query trends reveal significant public interest in heat-not-burn tobacco products." *PLOS One.* 12 (10) 2017. pp 1-7. doi: 10.1371/journal.pone.0185735.

"Our findings suggest that tobacco control leaders should prepare for substantial demand for these products when they are introduced to new markets and/or expanded in existing markets."

24. Davis, B. et al. "iQOS: evidence of pyrolysis and release of a toxicant from plastic." *Tob. Control*. 2018 doi: 10.1136/tobaccocontrol-2017-054104.

"This study found that the tobacco plug does char and that charring increases when the device is not cleaned between heatsticks. Release of formaldehyde cyanohydrin is a concern as it is highly toxic at very low concentrations."

Our response which has been shared with the author and the publication can be found at: https://www.pmiscience.com/library/publication/analysis-of-polylactic-acid-filters-of-marlboro-heatsticks-response-to-the-article-entitled-iqos-evidence-of-pyrolysis-and-release-of-a-toxicant-from-plastic-by-davis-b-et-al-2018.

PMI'S PEER-REVIEWED PUBLICATIONS ON SMOKE-FREE PRODUCTS: 2018 YEAR-TO-DATE

1. Malinska, D., J. Szymanski, P. Patalas-Krawczyk, B. Michalska, A. Wojtala, M. Prill, M. Partyka, K. Drabik, J. Walczak, A. Sewer, S. Johne, K. Luettich, M. C. Peitsch, J. Hoeng, J. Duszynski, J. Szczepanowska, M. van der Toorn and M. R. Wieckowski. Assessment of mitochondrial function following short- and long-term exposure of human bronchial epithelial cells to total particulate matter from a candidate modified-risk tobacco product and reference cigarettes. Food. *Chem. Toxicol.*, 2018; 115:1-12. (@PMI Science) (PMID: 29448087) doi: 10.1016/j.fct.2018.02.013.

2. Van der Toorn, M, A. Sewer, D. Marescotti, S. Johne, K. Baumer, D. Bornand, R. Dulize, C. Merg, M. Corciulo, E. Scotti, C. Pak, P. Leroy, E. Guedj, N. Ivanov, F. Martin, M. Peitsch, J. Hoeng, K. Luettich. The biological effects of long-term exposure of human bronchial epithelial cells to total particulate matter from a candidate modified-risk tobacco product. *Toxicol. in vitro*, 2018; 50:95-108. (@PMI Science) (PMID: 29524472) doi: 10.1016/j.tiv.2018.02.019.

3. Lüdicke, F., P. Picavet, G. Baker, C. Haziza, V. Poux, N. Lama and R. Weitkunat. Effects of switching to the Tobacco Heating System 2.2 menthol, smoking abstinence, or continued cigarette smoking on biomarkers of exposure: a randomized, controlled, open-label, multicenter study in sequential confinement and ambulatory settings (Part 1). *Nicotine Tob. Res.*, 2018; 20 (2):161-172. (@PMI Science) (PMID: 28177489) doi: 10.1093/ntr/ntw287.

4. Lüdicke, F., P. Picavet, G. Baker, C. Haziza, V. Poux, N. Lama and R. Weitkunat. Effects of switching to the menthol Tobacco Heating System 2.2, smoking abstinence, or continued cigarette smoking on clinically relevant risk markers: a randomized, controlled, open-label, multicenter study in sequential confinement and ambulatory settings (Part 2). *Nicotine Tob. Res*., 2018; 20 (2):173-182. (@PMI Science) (PMID: 28177498) doi: 10.1093/ntr/ntx028.

5. Martin, F., G. Vuillaume, G. Baker, Z. Sponsiello-Wang, P. F. Ricci, F. Lüdicke and R. Weitkunat. Quantifying the risk-reduction potential of new Modified Risk Tobacco Products. *Regul Toxicol Pharmacol*., 2018; 92:358-369. (@PMI Science) (PMID: 29258927) doi: 10.1016/j.yrtph.2017.12.011.

6. Peck, M. J., E. B. Sanders, G. Scherer, F. Ludicke and R. Weitkunat. Review of biomarkers to assess the effects of switching from cigarettes to modified risk tobacco products. *Biomarkers,* 2018; in press. (@PMI Science) (PMID: 29297706) doi: 10.1080/1354750X.2017.1419284.

7. Iskandar, A., F. Martin, P. Leroy, W. Schlage, C. Mathis, B. Titz, A. Kondylis, T. Schneider, G. Vuillaume, A. Sewer, E. Guedj, K. Trivedi, A. Elamin, S. Frentzel, N. Ivanov, M. Peitsch, J. Hoeng. Comparative biological impacts of an aerosol from carbon-heated tobacco and smoke from cigarettes on human respiratory epithelial cultures: A systems toxicology assessment. *Food Chem. Toxicol.*, 2018; 115:109-126. (@PMI Science) (PMID: 29501877) doi: 10.1016/j.fct.2018.02.063.

8. Zanetti, F., A. Sewer, E. Scotti, B. Titz, W. Schlage, P. Leroy, A. Kondylis, G. Vuillaume, A. Iskandar, E. Guedj, K. Trivedi, T. Schneider, A. Elamin, F. Martin, N. Ivanov, S. Frentzel, M. Peitsch, J. Hoeng. Assessment of the impact of aerosol from a potential modified risk tobacco product compared with cigarette smoke on human organotypic oral epithelial cultures under different exposure regimens. *Food Chem. Toxicol*., 2018; 115:148-169. (@PMI Science) (PMID: 29505817) doi: 10.1016/j.fct.2018.02.062.

9. Phillips B, Schlage WK, Titz B, Kogel U, Sciuscio D, Martin F, Leroy P, Vuillaume G, Krishnan S, Lee T, Veljkovic E, Elamin A, Merg C, Ivanov NV, Peitsch MC, Hoeng J and Vanscheeuwijck P. A 90-day OECD TG 413 rat inhalation study with systems toxicology endpoints demonstrates reduced exposure effects of the aerosol from the carbon heated tobacco product version 1.2 (CHTP1.2) compared with cigarette smoke. I. Inhalation exposure, clinical pathology and histopathology. *Food Chem. Toxicol*., 2018; e-pub ahead of print. (@PMI Science) (PMID: 29654848)

10. Phillips B, Schlage WK, Titz B, Kogel U, Sciuscio D, Martin F, Leroy P, Vuillaume G, Krishnan S, Lee T, Veljkovic E, Elamin A, Merg C, Ivanov NV, Peitsch MC, Vanscheeuwijck P and Hoeng J. A 90-day OECD TG 413 rat inhalation study with systems toxicology endpoints demonstrates reduced exposure effects of the aerosol from the carbon heated tobacco product version 1.2 (CHTP1.2) compared with cigarette smoke. II. Systems toxicology assessment. *Food Chem. Toxicol*., 2018; 115:284-301. (@PMI Science) (PMID: 29545142).

11. Frederix, E. M. A., A. K. Kuczaj, M. Nordlund, M. Bělka, F. Lizal, J. Jedelský, J. Elcner, M. Jícha and B. J. Geurts. Simulation of size-dependent aerosol deposition in a realistic model of the upper human airways. *J. Aerosol Sci.,* 2018; 115:29-45. (@PMI Science) doi: 10.1016/j.jaerosci.2017.10.007.

12. Winkelmann, C., A. K. Kuczaj, M. Nordlund and B. J. Geurts. Simulation of aerosol formation due to rapid cooling of multispecies vapors. *J Eng Math*, 2018; 108:171-196. (@PMI Science) doi: 10.1007/s10665-017-9918-6.

13. Pratte P, Cosandey S and Goujon Ginglinger C. Innovative methodology based on thermo-denuder principle for the detection of combustion-related solid particles or high boiling point droplets: Applications to cigarette and the Tobacco Heating System THS 2.2. *J. Aerosol Sci.*, 2018; 120:52-61. (@PMI Science) doi: 10.1016/j.jaerosci.2017.12.011.

14. Buratto, R., D. Correia, M. Parel, M. Crenna, M. Bilger and A. Debrick. Determination of eight carbonyl compounds in aerosols trapped in phosphate buffer saline solutions to support in vitro assessment studies. *Talanta*, 184, 2018. pp 42-49. (@PMI Science) doi: 10.1016/j.talanta.2018.02.048.

15. Chen, K., F. D. de Borne, N. Sierro, N. V. Ivanov, M. Alouia, S. Koechler and L. Otten. Organization of the TC and TE cT-DNA regions in Nicotiana otophora and functional analysis of three diverged TE-6b genes. *Plant J.*, 2018. in press. (@PMI Science) (PMID: 29396989) doi: 10.1111/tpj.13853.

16. Veljkovic E, Xia W, Phillips B, Wong ET, Ho J, Oviedo A, Hoeng J and Peitsch MC (2018) Nicotine and other tobacco compounds in neurodegenerative and psychiatric diseases. Preamble by Yohannes D. Publisher: Academic Press. ISBN 978-012-81-2922-7. (@PMI Science)

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PHILIP MORRIS INTERNATIONAL

YOU CAN CONTACT US HERE

FOR PRESS INQUIRIES

MEDIA@PMI.COM

+41 (0)58 242 4500

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