

PMI SCIENCE
PHILIP MORRIS INTERNATIONAL

REDUCED-RISK PRODUCT SCIENTIFIC UPDATE

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Philip Morris International (PMI) is investing in the development and assessment of Reduced-Risk Products (RRPs)*, a range of non-combustible alternatives to cigarettes with the potential to reduce individual risk and population harm in comparison with cigarette smoking. This Scientific Update explains PMI's approach to product development and assessment, and provides an overview of the latest research, key peer-reviewed publications, and presentations at scientific conferences. More detailed information can be found at www.pmis-science.com.



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*Reduced-Risk Products ("RRPs") is the term we use to refer to products with the potential to reduce individual risk and population harm in comparison to smoking cigarettes. PMI's RRP's are in various stages of development and commercialization, and we are conducting extensive and rigorous scientific studies to determine whether we can support claims for such products of reduced exposure to harmful and potentially harmful constituents in smoke, and ultimately claims of reduced disease risk, when compared to smoking cigarettes. Before making any such claims, we will rigorously evaluate the full set of data from the relevant scientific studies to determine whether they substantiate reduced exposure or risk. Any such claims may also be subject to government review and authorization, as is the case in the U.S. today.



INTRODUCTION

It is our pleasure to introduce the first Reduced-Risk Product (RRP) Scientific Update. The report will be published on a regular basis to provide a summary of the latest research and developments relating to PMI's RRP's.

We recognize that cigarettes are a dangerous product, and it is well known that the best way to avoid the harms of smoking is never to start, or to quit. Nevertheless, based on the World Health Organization's own predictions, there will be more than one billion smokers by the year 2025.¹ Therefore, alternative products that significantly reduced risk of disease compared with cigarette smoking are a fundamental complement to the regulatory efforts aimed at reducing smoking prevalence.

WE HAVE BROUGHT TOGETHER OVER 300 WORLD-CLASS SCIENTISTS FROM 30 FIELDS OF EXPERTISE – INCLUDING TOXICOLOGY, SYSTEMS BIOLOGY AND MEDICINE – TO DEVELOP AND ASSESS PRODUCTS THAT HAVE THE POTENTIAL TO REDUCE INDIVIDUAL RISK AND POPULATION HARM COMPARED WITH SMOKING

For this reason, PMI is investing in the development and rigorous assessment of a portfolio of potentially reduced-risk alternatives to cigarette smoking. In fact, our objective is to replace cigarettes with RRP's as soon as possible. The scientific work we're conducting is at the heart of this transformation. Our approach is based on the acknowledgment that innovative products will benefit public health if they meet two conditions: first, they must significantly reduce risk of disease compared with cigarettes; and, second, they must be acceptable enough to smokers to encourage them to switch to such reduced-risk alternatives.

In order to demonstrate that switching to our RRP's results in a significant reduction in the risk of disease compared with cigarette smoking, we are following a rigorous scientific assessment program. The program utilizes well-recognized

practices of the pharmaceutical industry, as well as an innovative Systems Toxicology-based approach to risk assessment. Our program is in line with the draft guidance from the U.S. Food and Drug Administration for Modified-Risk Tobacco Products (MRTPs).²

Sharing and gathering feedback is an important element of ensuring that our research answers the questions society, scientific experts and regulators ask. This Scientific Update is intended to complement our ongoing efforts to share our methodologies and findings through scientific publications, presentations at scientific conferences, and our R&D website (PMIScience.com). We register all our clinical studies with ClinicalTrials.gov, and since 2011 we have published over 160 book chapters and articles in peer-reviewed scientific journals.

We recognize that our scientific work must also be assessed by independent experts. We welcome such review and are committed to share scientific data for independent verification by qualified third parties. Towards this end we are utilizing a very contemporary platform called sbvIMPROVER.com to foster the verification of both our methods and results by independent scientists. As outlined in this issue, we have recently launched an Investigator Initiated Study program, a first step towards encouraging third parties to conduct studies with our RRP's.

In the following sections you will find summaries of some of our most recent scientific publications along with presentations made at scientific conferences and other events.

If you have any comments or questions about our science, be it about the methods we use or the results we have obtained, let us know. We look forward to hearing from you.



PROF. MANUEL C. PEITSCH
CHIEF SCIENTIFIC OFFICER

BIOGRAPHY

Manuel Peitsch joined PMI in 2008 after 15 years in the pharmaceutical industry. He obtained his Ph.D. in biochemistry from the University of Lausanne (Switzerland) and since 2002 is an Adjunct Professor for Bioinformatics at the University of Basel. Additionally, Manuel co-founded several initiatives, including the Swiss Institute of Bioinformatics where he is Chairman of the Board. He is an active scientific advisor to several academic and commercial entities and served as a member of the Swiss National Research Council between 2004 and 2010. LinkedIn



MICHELE CATTONI
VICE PRESIDENT, TECHNOLOGY & OPERATIONS RRP

BIOGRAPHY

Michele Cattoni obtained an engineering degree in Microtechnology and joined PMI in 1991. In over 25 years he has accumulated a broad set of skills and experiences including engineering, product development, manufacturing scale up and complex industrial production. He has also led highly technical teams of engineers and scientists in R&D as well as large multi-factory operations throughout Europe. Michele recently led the development and implementation of PMI's RRP production capability and product commercialization. He was appointed Vice President, Technology & Operations Reduced-Risk Products, in 2015.

Prof. Manuel C. Peitsch
Chief Scientific Officer

Michele Cattoni
Vice President, Technology & Operations RRP

REFERENCES

- 1 Bilano V, Gilmour S, Moffiet T, d'Espaignet ET, Stevens GA, Commar A, Tuyl F, Hudson I, Shibuya K. (2015) Global trends and projections for tobacco use, 1990–2025: an analysis of smoking indicators from the WHO Comprehensive Information Systems for Tobacco Control. *Lancet* 385:966-76.
- 2 Food and Drug Administration (2012) Modified Risk Tobacco Product Applications. Vol. 77 FR 20206, Federal Register.



RRP DEVELOPMENT AND ASSESSMENT AT PMI

A RIGOROUS STEP-BY-STEP PRODUCT ASSESSMENT PROGRAM

Our aim at PMI is to develop a range of RRPs as alternatives to cigarettes that are both scientifically demonstrated to reduce the risk of smoking-related diseases compared with cigarette smoking and sufficiently attractive to adult smokers to encourage them to switch completely. To assess our RRPs we are taking a thorough and systematic stepwise approach which is inspired by the assessment methods used by the pharmaceutical industry and aligned with the U.S. Food and Drug Administration draft guidance for MRTP applications.³ We conduct our research in accordance with international standards and practices, such as the internationally accepted Good Laboratory Practices (GLPs) and Good Clinical Practices (GCPs).

The foundation of our assessment program consists of laboratory-based studies. We start by demonstrating that our product designs do not cause combustion [see next section] of the nicotine-containing materials and then verify that the absence of combustion results in the formation of significantly lower levels of harmful and potentially harmful compounds (HPHCs) in the RRP aerosol generated. Using long-established laboratory-based tests, we then assess whether this reduced formation of HPHCs results in a reduced toxicity of the aerosol generated in comparison with cigarette smoke.

Sophisticated laboratory-based models of diseases help in determining whether a reduction in toxicity leads to a reduction in disease-related endpoints as well as a parallel reduction of the impact on key biological mechanisms known to underlie smoking-related diseases. Taken together, the laboratory-based study results permit the evaluation of the risk reduction potential of an RRP in laboratory models.

Clinical studies conducted with adult smokers are a cornerstone of our assessment program. These studies are designed to assess whether



the reduced formation of HPHCs in the aerosol of an RRP also leads to reduced exposure in adult smokers who switch, and whether this reduced exposure leads to the reversal of key clinical risk markers in human subjects. The results of these studies allow us to evaluate to what degree the effects of cessation are matched by switching to an RRP, both in terms of exposure reduction and clinical risk marker reversal.

The totality of the evidence collected in the laboratory and the clinic allows us to evaluate the risk reduction potential of an RRP.

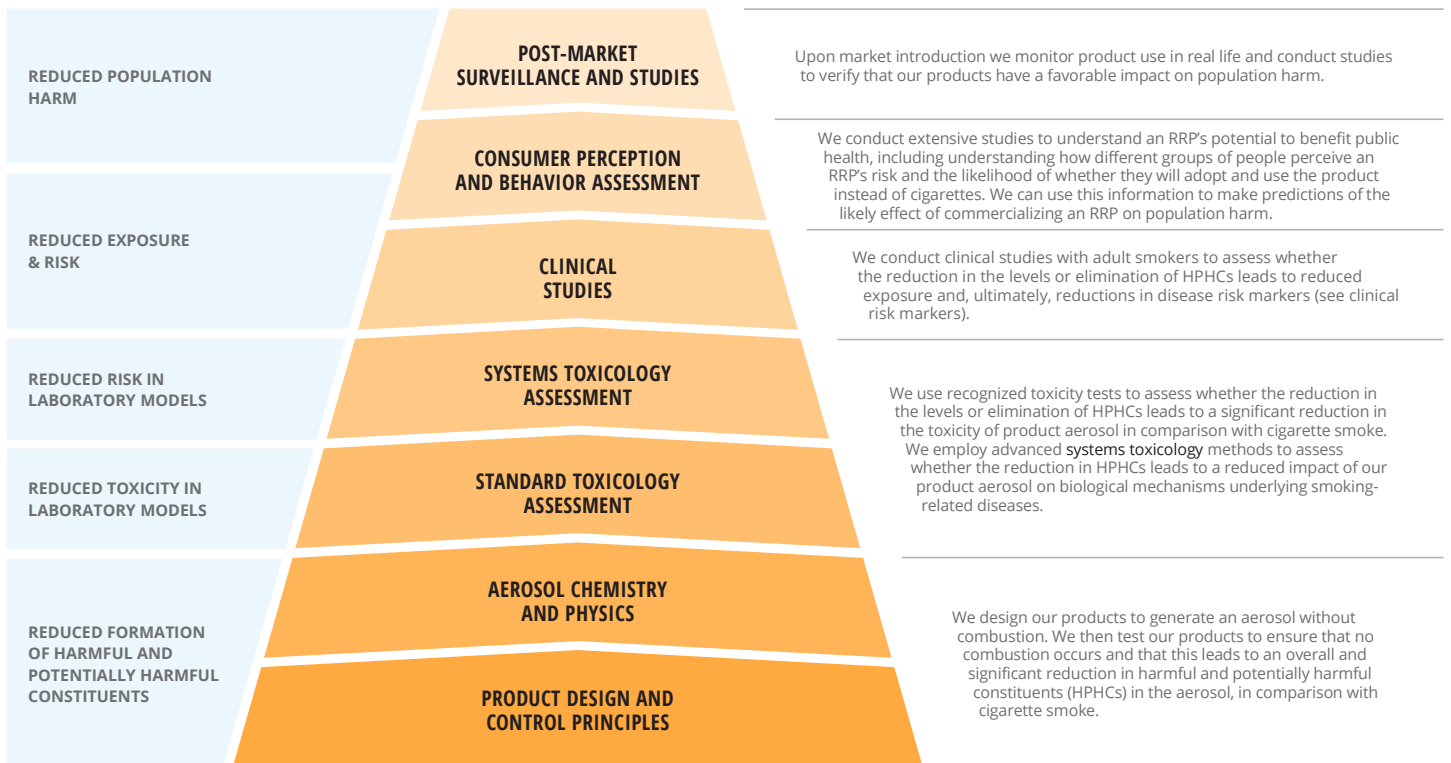
To evaluate the potential of our RRPs to benefit public health, we conduct perception and behavior studies that are designed to assess intention to use among never- and former smokers, as well as assessing whether adult smokers correctly understand potential product communications and have the correct perception of the health risks associated with switching to an RRP in comparison with ongoing smoking and cessation.

Finally, we conduct post-market studies to understand how RRPs are adopted and used once they are introduced in the market. These monitoring studies are supplemented with long-term clinical studies aimed at verifying that an RRP is indeed reduced-risk compared with smoking.

REFERENCES

- 3 Institute of Medicine, 2012. Scientific standards for studies on modified risk tobacco products. The National Academies Press, Washington, DC.

FIGURE 1. THE RRP ASSESSMENT PROGRAM



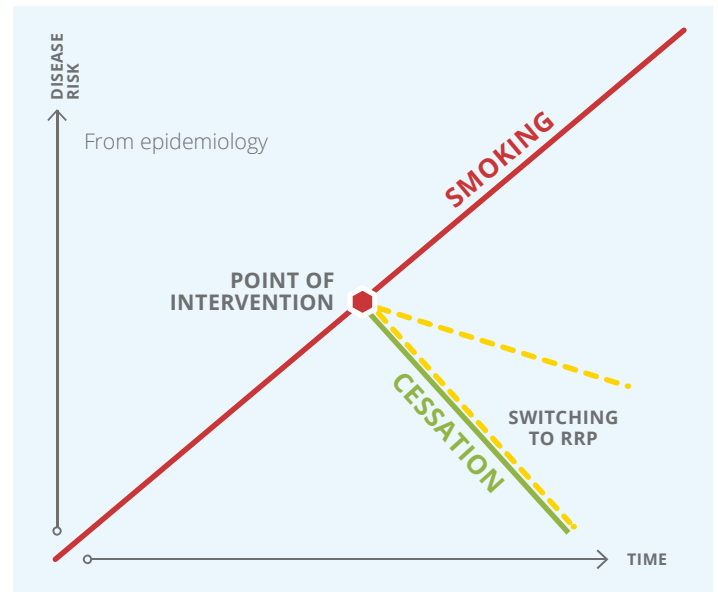
A RISK FRAMEWORK FOR RRP ASSESSMENT

PMI's multi-tiered scientific program takes into account the wealth of epidemiological data, or population-level research, demonstrating that continued exposure to cigarette smoke leads to increases in the risk of developing smoking-related diseases, such as cardiovascular disease (CVD), chronic obstructive pulmonary disease (COPD), and lung cancer. **Epidemiology also demonstrates that this increasing health risk can be reduced gradually by smoking cessation.** This is conceptually depicted in Figure 2 by the red and green lines.

The United States Institute of Medicine states that cessation is the "gold standard" for the assessment of an RRP, providing "an aspirational goal for risk and exposure."³ This sets the fundamental objective of an RRP: "switching to an [RRP] must reduce the risk of developing smoking-related diseases with a risk profile approaching that of cessation," and is depicted in Figure 2 by the orange lines.

Using this framework, we are assessing the extent to which switching to our RRP results in a reduction of exposure to HPHCs and risk of smoking-related diseases by evaluating how different they are from continued smoking and how similar they are to smoking cessation.

FIGURE 2. RISK FRAMEWORK FOR RRP ASSESSMENT



NOTE THAT THE STRAIGHT LINES USED IN THIS FIGURE ARE FOR ILLUSTRATION PURPOSES ONLY, AS THE ACCUMULATION OF DISEASE RISK AND THE REDUCTION UPON CESSATION AND SWITCHING TO AN RRP FOLLOW DIFFERENT TRAJECTORIES FOR SPECIFIC DISEASES.

REFERENCES

- 3 Institute of Medicine, 2012. Scientific standards for studies on modified risk tobacco products. The National Academies Press, Washington, DC.





OUR PRODUCT PORTFOLIO

Developing products without combustion

Our product development is based on technologies which produce a nicotine-containing aerosol without combustion, while continuing to deliver smokers a satisfying experience. Experts agree that nicotine, while addictive, is not the primary cause of smoking-related diseases. It is instead the harmful and potentially harmful constituents (HPHCs) found in cigarette smoke, most of which are associated with combustion.

The lit end of a cigarette can reach temperatures of up to 900 °C. This high temperature causes a large number of chemical reactions to take place which breaks down the tobacco into the thousands of chemicals that appear in cigarette smoke. Many of these chemicals are HPHCs.

If the tobacco is instead heated to temperatures of around 300 °C or lower, an aerosol is produced that is not the product of combustion. At these lower temperatures, many of the chemical reactions associated



with combustion don't take place. As a result, the tobacco aerosol contains significantly lower amounts of HPHCs than cigarette smoke.

We are currently developing four product platforms – two with tobacco and two without tobacco – which produce aerosol that significantly reduces or eliminates the formation of HPHCs when compared with cigarette smoke, while preserving as much as possible the taste, satisfaction and ritual characteristics of cigarettes.

HEATED TOBACCO PRODUCTS

PLATFORM

1

ELECTRICALLY HEATED TOBACCO PRODUCT (EHTP) OR TOBACCO HEATING SYSTEM (THS)



DESCRIPTION

Uses an electrically controlled heating mechanism to precisely heat a specially designed tobacco stick, at operating temperatures well below combustion, generating a nicotine-containing aerosol.

ASSESSMENT PROGRESS

Laboratory-based studies have been completed. Clinical studies are well advanced. Perception and behavioral studies nearing completion. Indoor air quality studies completed. Post market surveillance and studies ongoing.

PLATFORM

2

CARBON-HEATED TOBACCO PRODUCT (CHTP)



DESCRIPTION

Uses a carbon tip heat-source to precisely heat tobacco at temperatures well below combustion. A proprietary design separates the tobacco from the carbon heat source and provides an effective and controlled temperature transfer to generate a nicotine-containing aerosol similar to EHTP.

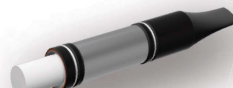
ASSESSMENT PROGRESS

Laboratory-based and clinical studies are ongoing with the current version.

PLATFORM

3

NICOTINE DELIVERY SYSTEM



DESCRIPTION

Based on technology we acquired from Professor Jed Rose of Duke University – co-inventor of the nicotine patch – and other co-inventors in May 2011. This product creates an aerosol of nicotine salt formed by the chemical reaction of nicotine with a weak organic acid and replicates the feel and ritual of smoking.

ASSESSMENT PROGRESS

Laboratory-based and clinical studies are ongoing.

PLATFORM

4

E-VAPOR PRODUCTS



DESCRIPTION

Battery-powered devices that contain no tobacco and instead produce an aerosol by vaporizing a liquid nicotine solution. Also known as e-cigarettes. Besides current generation technology, we are also developing next-generation technologies to address the challenges presented by products currently on the market, such as manufacturing processes and product performance consistency.

ASSESSMENT PROGRESS

Laboratory-based studies are under way. Indoor air quality pilot study completed.

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.



RECENT MILESTONES IN PMI'S RESEARCH

Focus on: Reduced exposure studies with the Electrically Heated Tobacco Product (EHTP)

We recently completed two three-month reduced-exposure clinical studies in Japan⁴ and the U.S.⁵, which represent a core element of our clinical evidence program. They serve as important additions to two shorter term five-day reduced exposure studies,⁶ as they were designed to test the sustainability of exposure reduction in ambulatory mode. We have previously completed pharmacokinetic and pharmacodynamic clinical studies⁷ demonstrating nicotine uptake and suppression of the urge to smoke similar to cigarettes.

Reduced exposure studies are designed to help us understand the extent to which adult smokers who switch from cigarettes to our Electrically Heated Tobacco Product (EHTP) reduce their exposure to measured HPHCs. We compared these levels of exposure to those measured in smokers who continued to use cigarettes and those who quit smoking for the duration of the study, the "gold standard" for risk reduction.⁸

These studies were carried out over three months, and each involved 160 healthy adult smokers who were split into three groups: one group of 40 who continued smoking; another group of 40 who were asked to stop smoking for the duration of the study; and a final group

of 80 smokers who switched to EHTP. The first five days of the study were spent in the clinic, and thereafter participants went home and were followed up at day 30, 60 and 90. We measured biomarkers of exposure to HPHCs, the substances the body generates when exposed to chemicals found in cigarette smoke.

As is customary in clinical trials, PMI outsourced the studies to contract research organizations, which also conduct studies on behalf of organizations like pharmaceutical companies. The Japan study, for example, was conducted by Osaki Hospital Tokyo Heart Center from August 2013 to July 2014, and the U.S. study was conducted from December 2013 to October 2014 in Daytona Beach, Florida, and Dallas, Texas, by Covance. These studies, like our entire clinical program, were conducted according to internationally recognized Good Clinical Practices.

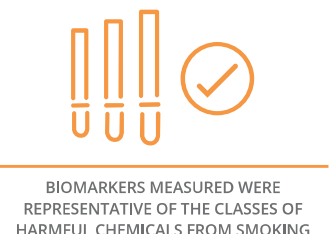
Biomarkers of exposure were selected based on well-established criteria, such as covering a broad range of chemical classes, their presence in cigarette smoke and their relationship to EHTP aerosol. Importantly, participants were allowed to smoke cigarettes or use EHTP without limitation.



RESULTS SHOW REDUCTIONS IN EXPOSURE TO HPHCS APPROACH LEVELS OBSERVED IN SMOKERS WHO QUIT

REFERENCES

- Information about the Japan study can be found on [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/NCT01970995?term=nct01970995&rank=1) under the identifier NCT01970995, <https://clinicaltrials.gov/ct2/show/NCT01970995?term=nct01970995&rank=1>.
- Information about the United States study can be found on [ClinicalTrials.gov](https://clinicaltrials.gov/ct2/show/record/NCT01989156?term=ZRHM-REXA&rank=1) under the identifier NCT01989156, <https://clinicaltrials.gov/ct2/show/record/NCT01989156?term=ZRHM-REXA&rank=1>.
- Reduced exposure five-day studies: <http://www.clinicaltrials.gov/show/NCT01959932>, <http://www.clinicaltrials.gov/show/NCT01970982>.
- Pharmacokinetic and pharmacodynamic clinical studies: <http://ClinicalTrials.gov/show/NCT01967706>, <http://ClinicalTrials.gov/show/NCT01959607>, <http://ClinicalTrials.gov/show/NCT01967719>, <http://ClinicalTrials.gov/show/NCT01967732>.
- U.S. Institute of Medicine, Scientific Standards for Studies on Modified Risk Tobacco Products (2012).

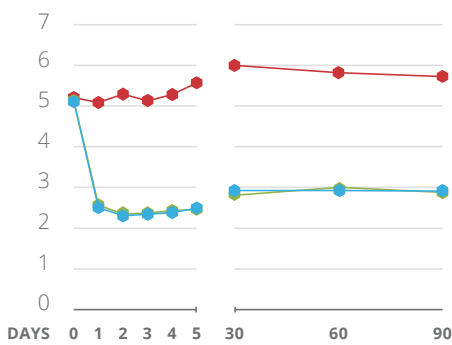


**RESULTS FROM THE JAPAN STUDY FOR FOUR KEY BIOMARKERS OF EXPOSURE**

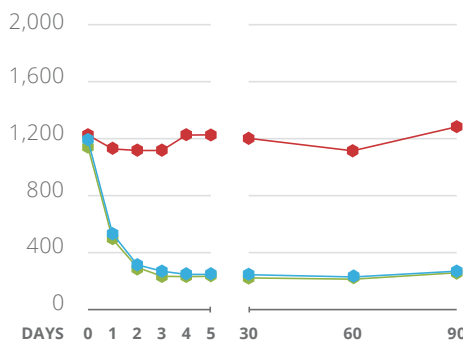
Adult smokers randomized to cigarettes or EHTP were free to use the product as often as they wished, in the clinic (5 days) and then ambulatory (85 days).

● Continued smoking
● Smoking cessation
● EHTP

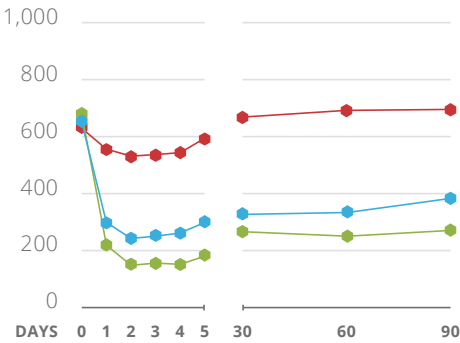
CARBON MONOXIDE - COHB (%)



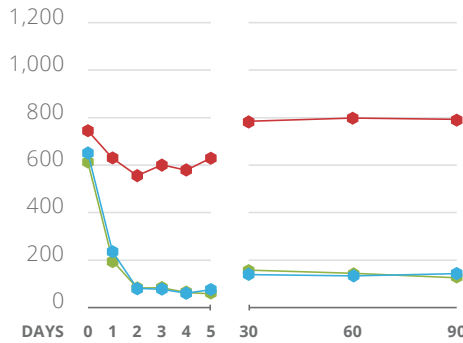
BENZENE - S-PMA (PG/MG CREATININE)



ACROLEIN - 3-HPMA (NG/MG CREATININE)



1,3-BUTADIENE - MHBMA (PG/MG CREATININE)



The results of these studies allow us to conclude that adult smokers who switched to EHTP reduced their exposure to a range of HPHCs to levels that approach those observed in adult smokers who stopped smoking for the duration of the study. Both switching and quitting resulted in substantial exposure reductions compared with adult smokers who continued smoking during the study.

In addition to the biomarkers of exposure, we also measured six clinical risk markers closely associated with smoking-related diseases, all of which were chosen based on extensive literature reviews. The majority of the beneficial effects of cessation were also observed in smokers who switched to EHTP within three months. We plan to submit this study for peer-reviewed publication in a scientific journal this year.

Our next step is to finalize a larger and more long-term exposure response study that is currently ongoing. This study is aimed at measuring the biological changes in smokers who switch to EHTP.

**RESULTS TO DATE FOR EHTP**

Our studies on EHTP are progressing rapidly. We have completed laboratory studies and are well advanced in both clinical studies and in our perception and behavior assessment program. We have already determined that EHTP:

- Does not generate combustion through normal operation
- Generates an aerosol with, on average, 90-95% lower levels of HPHCs compared with **reference cigarette** smoke
- Does not negatively impact indoor air quality
- Is 90-95% less toxic in laboratory-based tests compared with reference cigarette smoke
- Reduces the risk of smoking-related diseases in sophisticated laboratory-based models
- In two three-month clinical studies recently carried out in Japan and the U.S., the average reduction in 15 biomarkers of exposure to corresponding HPHCs measured in smokers who switched to EHTP approached those observed in smokers who quit smoking for the duration of the study
- When presented with potential product messages, non-intended audiences expressed negligible intention to use

WHILE CONCLUSIONS ON THE RISK-REDUCTION PROFILE OF EHTP WILL BE BASED ON THE TOTALITY OF THE EVIDENCE COLLECTED BY OUR ASSESSMENT PROGRAM, RESULTS TO DATE GIVE US CONFIDENCE THAT WE ARE ON COURSE WITH OUR PLANS TO DEMONSTRATE THAT EHTP IS NOT ONLY A REDUCED-EXPOSURE PRODUCT BUT ALSO A LESS HARMFUL ALTERNATIVE FOR SMOKERS WHO SWITCH COMPLETELY

LATEST PUBLICATION HIGHLIGHTS

COMPARISON OF THE IMPACT OF EHTPS AND CIGARETTES ON INDOOR AIR QUALITY

PUBLISHED IN *REGULATORY TOXICOLOGY AND PHARMACOLOGY*⁹

PMI used a purpose-built room to perform studies on EHTP's impact on indoor air quality according to European ventilation standards for office, residential and hospitality environments.¹⁰ Using ISO-accredited methods,¹¹ the levels of 18 chemicals typically found in environmental tobacco smoke were compared.¹² Over the course of four hours, adult smokers smoked cigarettes, used EHTP or did not use any product. The 18 chemicals were measured before any product was used to capture initial background levels, then monitored throughout and at completion.

The use of the EHTP resulted in similar levels of substances in the air to the levels measured when no product was used, well below all measurements for cigarettes. Only acetaldehyde and nicotine levels were increased above background concentrations, at a level 40 and 270 times lower respectively, than regulatory limits for indoor exposure in the EU.¹³ This study therefore concludes **that use of PMI's EHTP indoors has no negative impact on overall indoor air quality.**

A REPRESENTATION OF THE PURPOSE-BUILT ROOM TO TEST INDOOR AIR QUALITY



More information: <https://www.pmisceince.com/library/comparison-impact-tobacco-heating-system-22-and-cigarette-indoor-air-quality>

REFERENCES

- 9 See Bibliography, number 1.
- 10 CEN European Standard EN 15251. Indoor Environmental Input Parameters for Design and Assessment of Energy Performance of Buildings Addressing Indoor Air Quality, Thermal Environment, Lighting and Acoustics. 2006.
- 11 All methods were accredited in 2014 (Accreditation number STS 0045) according to ISO 17025 (International Organization for Standardization, 2005) by the Swiss Accreditation Service (SAS, Bern, Switzerland).
- 12 The 18 substances selected for measurements are typical markers of Environmental Tobacco Smoke (ETS) as defined by ISO standards (ISO 15593, ISO 18144, and ISO 18145).
- 13 For Acetaldehyde, the relevant regulation is the EU Indoor Air Quality guideline; for Nicotine, EU's eight-hour indicative occupational exposure limit.

SYSTEMS TOXICOLOGY-BASED ASSESSMENT OF THE CANDIDATE MODIFIED-RISK TOBACCO PRODUCT THS2.2 (THE COMMERCIALIZED VERSION OF THE EHTP) FOR THE ADHESION OF MONOCYTIC CELLS TO HUMAN CORONARY ARTERIAL ENDOTHELIAL CELLS

PUBLISHED IN *TOXICOLOGY*¹⁴

Smoking is known to accelerate the formation of atherosclerosis – a disease in which plaque builds up inside arteries – which over time can lead to severe cardiovascular disease. An RRP must therefore be significantly less effective than cigarette smoke in triggering key mechanisms leading to development of atherosclerotic plaque. One of the first steps leading to plaque formation is the adhesion (fusing) of monocytes – a type of white blood cell – to the cells lining the inner wall of blood vessels – known as endothelial cells. In this publication, PMI reports on the relative impact of EHTP aerosol and cigarette smoke on this key mechanism of atherosclerotic plaque formation. **The study results show that for these endpoints 10 to 20 times more EHTP aerosol is required to cause effects that are similar to those caused by cigarette smoke.**

EVALUATION OF BIOMARKERS OF EXPOSURE IN SMOKERS SWITCHING TO A CARBON-HEATED TOBACCO PRODUCT (CHTP): A CONTROLLED, RANDOMIZED, OPEN-LABEL 5-DAY EXPOSURE STUDY

PUBLISHED IN *NICOTINE AND TOBACCO RESEARCH*¹⁵

Similar to the reduced exposure clinical studies above in the Recent Milestones in PMI's Research section, exposure to HPHCs were observed for smokers switching to a prototype of the carbon heated tobacco product (CHTP) over five days in a clinic. Healthy adult smokers were split into three groups (112 in total): continued smoking, smoking abstinence and switching to the CHTP prototype. They remained in the controlled clinical environment for the five-day study and were allowed to use the products freely. The nine selected biomarkers of exposure were measured once daily. Switching to the prototype CHTP resulted in marked decreases from pre-switching to Day 5 in all biomarkers of exposure measured; **reductions following switching approached the reductions experienced following smoking cessation for the duration of the study.**

See more: <https://www.pmisceince.com/library/evaluation-biomarkers-exposure-smokers-switching-carbon-heated-tobacco-product-controlled>

¹⁴ See Bibliography, number 2.

¹⁵ See Bibliography, number 3.

¹⁶ See Bibliography, number 4.

¹⁷ See Bibliography, number 5.

IN VITRO SYSTEMS TOXICOLOGY ASSESSMENT OF A CANDIDATE MODIFIED-RISK TOBACCO PRODUCT SHOWS REDUCED TOXICITY COMPARED TO A CONVENTIONAL CIGARETTE

PUBLISHED IN *CHEMICAL RESEARCH IN TOXICOLOGY*¹⁶

The biological impact of EHTP aerosol in comparison with cigarette smoke on human cells derived from the inner lining of the bronchus – the airway in the respiratory tract conducting air into the lungs – was investigated. Towards this end a platform that enables the analysis of multiple cellular toxicity endpoints was used, as well as a systems toxicology-based approach to gain deeper insights into the molecular mechanisms underlying these endpoints. Cells exposed to cigarette smoke showed significant dose-dependent responses in most toxicity endpoints, as well as their underlying biological mechanisms. In contrast, when cells were exposed to EHTP at the same doses as cigarette smoke, no toxic effects were observed. The impact on the biological mechanisms was also significantly reduced following EHTP exposure compared to cigarette smoke exposure at equivalent doses. **Taken together, the data suggest that EHTP aerosol is significantly less toxic than cigarette smoke.**

A FRAMEWORK FOR IN VITRO SYSTEMS TOXICOLOGY ASSESSMENT OF E-LIQUIDS

PUBLISHED IN *TOXICOLOGY MECHANISMS AND METHODS*¹⁷

To enable a more rigorous and consistent assessment of e-cigarettes, PMI has recently proposed a framework for the *in vitro* systems toxicology assessment of e-liquids and their aerosols. **This framework is intended to complement the analytical chemistry investigations of the e-liquid and aerosol compositions and the battery of assays used in standard toxicity assessments.** The framework comprises three main layers: (1) high-throughput toxicity screening of e-liquids using primary human cell culture systems; (2) toxicity-related mechanistic analysis of e-liquids, and (3) toxicity-related mechanistic analysis of aerosols using human airway tissue cultures grown at the air-liquid interface. A systems toxicology-based approach is used for the in-depth analyses of the toxicity-related mechanisms of both e-liquids and their aerosols. The publication presents cases to demonstrate the suitability of the framework for a robust *in vitro* assessment of e-liquids and their aerosols. PMI is now applying this framework to the assessment of our Nicotine Delivery System and E-Vapour products.



LATEST EVENTS, INDEPENDENT REVIEWS AND STUDIES



Patrick Picavet, Director Clinical Assessment and Gizelle Baker, Director Epidemiology and Biostatistics at the Society for Research on Nicotine and Tobacco Annual Meeting

SOCIETY FOR RESEARCH ON NICOTINE AND TOBACCO ANNUAL MEETING

📍 CHICAGO, ILLINOIS, U.S.

📅 2-5 MARCH 2016

The Society for Research on Nicotine and Tobacco (SRNT) is the leading association focused on tobacco-specific research. PMI presented 11 posters, including an analysis of pre-market data from five countries on how consumers use the EHTP, as well as results from our latest systems toxicology studies. SRNT was founded in 1994 to coordinate and advance research on a broad array of topics ranging from the pharmacology of nicotine to the societal influences on use of tobacco. It has over 1,100 members from more than 40 countries around the world.

Find out more about PMI's presence at the event here: <https://www.pmscience.com/events/society-research-nicotine-and-tobacco-srnt-2016-annual-meeting>

GLOBAL FORUM ON NICOTINE

📍 WARSAW, POLAND.

📅 17-18 JUNE 2016

At the Global Forum on Nicotine, one of the most well-known events on policy, science and innovation in the field of nicotine products, PMI presented its findings to date for EHTP. Over 300 policy analysts, regulators, academics, public health professionals, consumer advocates and alternative nicotine product enterprises attended the event this year. The theme of the conference was *"Evidence, Accountability and Transparency."*

PMI's Director of Scientific Engagement, Dr. Moira Gilchrist, presented the latest results on EHTP and focused on our latest research on cardiovascular disease risk assessment (as described in the Recent Milestones in PMI's Research section covering clinical risk markers). PMI also presented five scientific posters to encourage discussions.

Learn more about PMI's presence at the event here: <https://www.pmscience.com/events/global-forum-nicotine-2016>

SOCIETY OF TOXICOLOGY ANNUAL MEETING

📍 NEW ORLEANS, LOUISIANA, U.S.

📅 13-17 MARCH 2016

At the Society of Toxicology Annual Meeting, the largest global gathering of toxicologists – attended by more than 6,500 toxicologists from over 50 countries – PMI showcased three presentations and six posters, which included our latest results from our standard and systems toxicology programs.

Learn more about PMI's presence at the event here: <https://www.pmscience.com/events/sot-2016-annual-meeting-and-toxexpo>

INDEPENDENT REVIEWS: EXPERT OPINIONS CONFIRMING LACK OF COMBUSTION IN THE ELECTRICALLY HEATED TOBACCO PRODUCT

PMI's RRP's are designed to generate an aerosol without combustion, widely recognized as the main origin of harmful chemicals in cigarette smoke. EHTP heats tobacco to around 300°C, well below the 900°C in the lit end of a combustible cigarette. PMI scientists have developed a series of tests that have consistently demonstrated that no combustion occurs during use of the EHTP.

In order to obtain independent verification of our conclusion that no combustion takes place in EHTP, we commissioned a variety of individual scientists and institutions – whose expertise lies in combustion and the properties of heated substances – to review our methods and measurements. These include Prof. Osamu Fujita, Vice President of the Combustion Society of Japan and committee member of the International Combustion Institute, as well as other experts from the U.S., Italy and Poland. All of these experts concluded that **no combustion occurs during the use of PMI's EHTP.**

See more: <https://www.pmscience.com/news/absence-combustion-pmi%E2%80%99s-heated-tobacco-product-platform-1>

INVESTIGATOR-INITIATED STUDIES

Independent reviews of methodologies and findings is very important for the progress of scientific research. This is why we have created an Investigator-Initiated Studies Program (IIS), to promote and support investigator-initiated studies that independently advance scientific/medical knowledge of PMI's RRP's.

Currently in its pilot phase, this global program is open to researchers and institutions with the relevant expertise and scientific credentials to conduct the proposed study, including compliance with local regulations, and who are interested in receiving support to conduct their own research.

Learn more: <https://www.pmscience.com/our-goals/investigator-initiated-studies-program>



GLOSSARY

AEROSOL

A gaseous suspension of fine solid or liquid particles. Cigarette smoke is the result of combustion and contains carbon-based solid particles, whereas PMI's RRP's produce an aerosol either by heating or other technologies which do not involve combustion and do not contain solid particles. Both cigarette smoke and noncombustible RRP emissions are aerosols, but with very different profiles. Given the lack of a term for a liquid-only aerosol to distinguish an RRP emission from smoke, we refer to the emissions of our RRP's as aerosol.

BIOLOGICAL MECHANISM

A causal chain of biological events – occurring at the molecular or cellular level – that produce one or more effects, e.g., the various causal chains (mechanisms) involved in the onset of smoking-related diseases. If the mechanisms of a smoking-related disease are identified, and the necessary causal links in all these mechanisms' chains are missing, then the disease will not manifest. Many biological mechanisms involved in the onset of smoking-related diseases have been represented by biological network models and include inflammation, cell stress and cell proliferation.

BIOMARKERS

A biomarker is used as a measure of how well the body responds to a treatment for a disease or condition. Biomarkers can be classified into biomarkers of exposure and clinical risk markers.

- Biomarkers of exposure: indicates 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 and that can provide a measure of internal dose (i.e., the amount of the constituent taken up into the body);
- Clinical risk markers: a measurable biochemical, physiological, behavioral, or other alteration within an organism that, depending upon the magnitude, can be recognized as associated with an established or possible health impairment or disease.

CLINICALTRIALS.GOV

Registration of clinical trials and disclosure of results is deemed an ethical obligation. One of the most widely used registries for clinical trials is the U.S. government's ClinicalTrials.gov, a website maintained by the U.S. National Institutes of Health (NIH). PMI is registering its clinical studies on ClinicalTrials.gov. The website provides information on publicly and privately supported clinical studies on a wide range of diseases and conditions conducted in 185 countries.

CLINICAL RISK MARKERS

See Biomarkers.

CLINICAL STUDIES

Clinical research is research that involves humans (or material of human origin). PMI is conducting clinical research following well-designed protocols, focusing on exposure to harmful and potentially harmful constituents (HPHCs) and biomarkers that are relevant to assessing the risk of smoking-related disease. Evidence from both short- and long-term studies will be the key evidence used to support claims that switching from cigarettes to our RRP products reduces the risk of smoking-related diseases and approaches the risk profile of cessation.

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 harmful or potentially harmful constituents (HPHCs) found in cigarette smoke.

EXPOSURE RESPONSE STUDY

Designed to assess whether switching to an RRP leads to favorable changes in clinical risk markers that are benchmarked to smoking cessation. This is a longer-term study conducted with adult smokers.

FDA'S DRAFT GUIDANCE FOR INDUSTRY ON MODIFIED-RISK TOBACCO PRODUCT (MRTP) APPLICATIONS

Issued in March 2012, the Draft Guidance provides details to manufacturers on the process and content for application to market a modified risk tobacco product. The Draft Guidance includes details on "how to organize and submit an MRTP application, what scientific studies and analyses should be submitted, and what information should be collected through post-market surveillance and studies." Although the document is a draft, the details provide direction as to the FDA's views.

GOOD CLINICAL PRACTICES (GCPs)

GCPs are used in clinical trials throughout the globe with the aim of protecting people participating in research and ensuring quality data. The International Conference on Harmonization (ICH) is an international body that defines standards for designing, conducting, recording and reporting clinical trials involving human subjects. Many countries have adopted GCP principles as laws and/or regulations. PMI's clinical studies are designed and conducted in line with the requirements of the ICH GCPs.

GOOD LABORATORY PRACTICES (GLPs)

GLPs embody a set of principles that provide a framework within which nonclinical studies are planned, performed, monitored, recorded, reported and archived. GLPs help assure regulatory authorities that the data submitted are a true reflection of the results obtained during the study and can therefore be relied upon when making risk/safety assessments. Our nonclinical assessment facilities in Switzerland and Singapore are certified by the relevant authorities as GLP compliant.

HARMFUL AND POTENTIALLY HARMFUL CONSTITUENTS (HPHCs)

The constituents in tobacco products and tobacco product emissions that cause or have the potential to cause harm. Organizations such as the FDA have identified lists of harmful and potentially harmful constituents (HPHCs) in tobacco and cigarette smoke. These include acrolein, benzene, carbon monoxide, tobacco specific nitrosamines, cadmium and arsenic. Many (but not all) of the HPHCs are associated with combustion.

MODIFIED-RISK TOBACCO PRODUCTS (MRTPs)

The term used to classify reduced-risk products in the U.S. Tobacco Control Act, which granted to the FDA authority to regulate tobacco products and to authorize claims of reduced risk. The statute defines modified-risk tobacco products 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."

PEER REVIEW

Articles reviewed by independent experts in the appropriate field before the article is published in order to ensure the article's credibility and quality of science.

REDUCED-RISK PRODUCTS (RRPs)

Reduced-Risk Products (RRPs) is the term PMI uses to refer to products with the potential to reduce individual risk and population harm in comparison to smoking cigarettes. PMI's RRP's are in various stages of development and commercialization, and PMI is conducting extensive and rigorous scientific studies to determine whether we can support claims for such products of reduced exposure to harmful and potentially harmful constituents (HPHCs) in smoke and, ultimately, claims of reduced disease risk, when compared with smoking cigarettes. Before making any such claims, we will rigorously evaluate the full set of data from the relevant scientific studies to determine whether they substantiate reduced exposure or risk. Any such claims may also be subject to government review and authorization, as is the case in the U.S. today.

REFERENCE CIGARETTE

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 HPHCs reduces the toxicity of the aerosol generated by our RRP's, 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 RRP's 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

To further refine our understanding of the biological impact of our products, PMI uses an approach known as systems toxicology,¹⁸ which 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.

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