PMI SCIENCE
PHILIP MORRIS INTERNATIONAL

SCIENTIFIC UPDATE FOR SMOKE-FREE PRODUCTS

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This Scientific Update explains **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 activities to share** our methodologies and results.

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

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RECENT MILESTONES IN PMI'S RESEARCH

FOCUS ON: PMI'S DIRECTOR MEDICAL AFFAIRS DISCUSSES OUR PRACTICE OF CONDUCTING HIGH-QUALITY CLINICAL RESEARCH

WHAT'S INSIDE?

INTRODUCTION

At PMI, our company's objective is clear: our future is in products that have been scientifically demonstrated to be less harmful than cigarettes. If our science is not credible, millions of smokers who might otherwise benefit from the alternatives we are developing might not do so.

Our assessment program is built on best practices and guidelines in their respective fields. Not only do we adhere to the internationally recognized Good Clinical Practices (GCP), which you'll read about in the focus section of this issue, but we also follow Good Laboratory Practices (GLP), Good Epidemiological Practices, and Good Manufacturing Practices. You can see more about PMI's quality management system in the appendix on page 10. In order to explain our efforts to safeguard the validity of our research and the safety of our study participants, this issue features an interview with our Director Medical Affairs, Dr. Patrick Picavet, discussing how we apply best practices in support of our clinical program. He explains how we hold our scientists to strict standards to ensure that the data they collect is accurate, that every action is well documented, and that the participants in our studies are treated with care.

We are also actively sharing our methods and data, making them available to the public for those who wish to verify our approaches and results. In addition to presenting our results at conferences, sharing our evidence with health experts and scientists, and encouraging peer review of our work, we also post our clinical study protocols and subsequent results on ClinicalTrials.gov. We invite scientists from around the globe to verify our systems biology methods through a crowd-sourcing platform called sbvIMPROVER.com.[1]

And we are now going a step further by gradually making the data and results from our non-clinical and clinical program around our flagship smoke-free product, *IQOS*, available to the public by early 2018, in part through a program called INTERVALS (see page 6).

Beyond simply conducting the research, it is also important that smokers have access to accurate, non-misleading information about the range of smoke-free products they may benefit from. As it turns out, we are seeing that many who currently smoke do not believe that better alternatives currently exist. For example, in the UK, a report by the public health charity Action on Smoking and Health (ASH) earlier this year illustrated the concerning correlation between the growing belief amongst smokers that e-cigarettes are no less harmful than cigarettes, and the plateauing of e-cigarette usage among smokers.[2]

Sharing information reflective of current research could help reverse that trend. This requires the participation of stakeholders across society. So that, through science, not just PMI can transition to a future without smoke, but millions more smokers can too.

Prof. Manuel C. Peitsch
Chief Scientific Officer

REFERENCES

1 https://www.sbvimprover.com/
2 ASH, Use of e-cigarettes among adults in Great Britain 2017 (May 2017), http://ash.org.uk/download/use-of-e-cigarettes-among-adults-in-great-britain-2017/.

ASSESSMENT PROGRESS OF OUR PRODUCT PORTFOLIO

HEATED TOBACCO PRODUCTS

One approach to significantly reduce the levels of toxicants generated and inhaled is to heat tobacco to temperatures below 400°C, below which combustion does not occur. From a smoker acceptance standpoint, these products have the advantage of more closely approximating the taste, sensory satisfaction and ritual they expect from cigarettes.

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 unit to temperatures below 350°C. The experience lasts six minutes or 14 puffs, similar to that of a cigarette.

ASSESSMENT PROGRESS
Our studies on EHTP, which include a large number of non-clinical and clinical studies, are very advanced and point in the direction of risk reduction and potential to improve public health. An exposure response study designed to measure clinical risk markers when adult smokers switch to EHTP over a 12-month period is currently underway, results pertaining to the first six-month period will be available by year-end. Our post-market program has been launched, with encouraging results from the initial phases of two observational studies underway in Japan.

PLATFORM 2
CARBON-HEATED TOBACCO PRODUCT (CHTP)

DESCRIPTION
A carbon tip heat source precisely heats tobacco to a similar temperature to EHTP. The heat source is fully separated from the tobacco by a proprietary design.

ASSESSMENT PROGRESS
Our non-clinical studies and short-term clinical studies are progressing well and show comparable results to EHTP, including a five-day human reduced exposure study. The clinical phase of a three-month reduced exposure study has been completed, with results expected by year-end.

PRODUCTS WITHOUT TOBACCO

Another approach is to produce an aerosol without the use of tobacco. The ability to precisely design the composition of the originating substance leads to better control of 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 are already using e-vapor products.

PLATFORM 3
E-VAPOR PRODUCT USING NICOTINE SALT

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

ASSESSMENT PROGRESS
Our non-clinical studies for the electronic version are progressing well, and we have completed a clinical study showing a comparable nicotine profile to cigarettes. The results on this are described on page 6. We have initiated a new nicotine pharmacokinetic study.

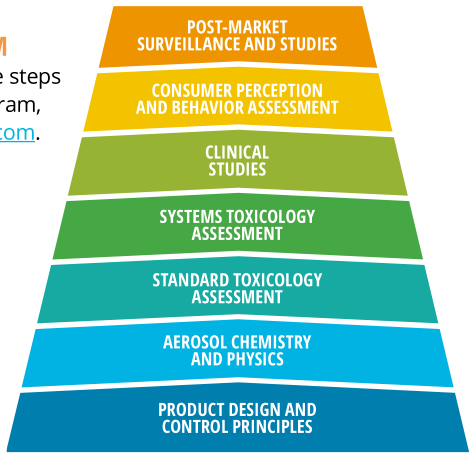
PLATFORM 4
E-VAPOR PRODUCTS (COMMERCIALIZED UNDER VARIOUS TRADEMARKS)

DESCRIPTION
Battery-powered devices that vaporize a liquid nicotine solution (also known as e-cigarettes). Includes our new technology, *MESH*, designed to improve aspects such as product quality and consistency.

ASSESSMENT PROGRESS
The non-clinical assessment on our e-liquids is well advanced. For our *MESH* device, we expect the final report from a pharmacokinetic clinical study early next year. The results of this study are expected to contribute to further developments of Platform 4 products. An indoor air quality study on our e-vapor products demonstrates no negative impact on air quality.

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.



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 continued smoking. Our Idea Submission Portal offers innovators an opportunity to provide technical solutions that can enhance our product portfolio.

RECENT MILESTONES IN PMI'S RESEARCH

PATRICK PICAVET
DIRECTOR MEDICAL AFFAIRS AT PMI

Dr. Patrick Picavet, a physician by training, joined PMI over seven years ago after working in the University Hospital in Mannheim and afterwards in the pharmaceutical industry. Since then, Patrick has held several roles in PMI, including Director, Clinical Assessment, in which he was responsible for the planning and execution of clinical studies on our smoke-free products. Since early 2017, as Director, Medical Affairs, Patrick is helping to establish the next steps in the strategy for PMI's assessment program and supports PMI's efforts to inform the scientific and medical communities about our science.

Focus on: PMI's Director Medical Affairs discusses our practice of conducting high-quality clinical research

COULD YOU DESCRIBE EXACTLY WHAT IT IS THAT A MEDICAL DOCTOR IS DOING AT PMI?

There's plenty of work for the many medical doctors we have at PMI. For example, we have Medical or Clinical Scientists who oversee our studies in people from a medical and scientific point of view. There are also Medical Safety Officers, who are responsible for overseeing the well-being and safety of participants involved in our clinical studies, as is the case in any other company conducting clinical studies. So it's not unusual that someone like myself would be working here.

WHAT GUIDELINES DOES PMI HOLD ITSELF TO IN ITS CLINICAL RESEARCH PROGRAM?

Guidelines for Good Clinical Practices (GCP) as issued by the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use are a set of internationally recognized principles that regulatory bodies around the world expect researchers to follow when conducting clinical studies. These guidelines are far reaching, covering topics such as ethical research conduct, protecting the rights, safety and well-being of study subjects, as well as the proper documentation of all study records. Like other organizations, PMI abides by these principles for our clinical research, as well as following the recommendations in the FDA's 2012 Draft Guidance on Modified Risk Tobacco Products.[3]

PMI's quality management processes are based on these standards, requiring that PMI researchers perform their work ethically, using scientifically sound methods and describe the aim of the research upfront in a clear and detailed study protocol. All information related to the research must be recorded in accurate records properly stored and protected from tampering. The records serve as indispensable documentation of the conduct of the research, provide evidence that the collected data is traceable and credible, and that the rights of all study participants are protected.

For each clinical study, we establish a PMI study team that focuses on both designing individual studies and overseeing the conduct of the study as the sponsor is required by GCP. Per common practice, we outsource study-related activities to qualified Contract Research Organizations (CROs), including the actual conduct of the study, during which the PMI study team works closely with their CRO counterparts.

HOW DOES PMI ENSURE THE SAFETY OF ITS RESEARCH PARTICIPANTS?

One of the key principles in GCP and related guidelines is that the safety of study participants must be ensured. These guidelines form the basis for the processes we apply in our studies to ensure the rights and well-being of study subjects are protected. One essential part is that our clinical studies are all conducted under continuous medical oversight under the responsibility of a trained and board-registered physician in the role of the Principal Investigator (PI).

The PI is responsible for managing and documenting potential adverse events (expected or unexpected medical effects during the cause of the study) which may or may not be associated with the product being tested. In this context, as a sponsor of the research, we are responsible for what happens during a study, and so we may provide opinions or suggestions, but ultimately we must defer to the PI's medical judgement. The sponsor can never overwrite the PI's evaluation of a study subject's medical condition.

One such situation illustrating this relationship between PMI and the PI occurred in a 2013 clinical study. During the study, a few participants produced an excessive quantity of urine in a 24-hour period, which is quite uncommon. The subjects confirmed drinking increased amounts of water during each of the study days, all medical tests came back normal and the study subjects did not show any signs of medical concern.

Therefore the PI considered these events initially not to be adverse events. As the recorded urine volumes were unusual, PMI as the sponsor and following GCP initiated an investigation to understand the underlying cause of these cases.

The PMI study team discussed these cases with the CRO and the study site and decided that a study audit should be performed by PMI's quality assurance team. The audit concluded that the study site had correctly followed all processes as required by the study protocol and GCP, and the PI and staff had properly documented the cases and their response to the issues.

After discussing with the medical monitors of the study as well as PMI, the PI also decided to mark these incidents as adverse events and to monitor consumption of water for the remaining participants.

OUR RESEARCH MEETS RIGOROUS STANDARDS

TRANSPARENCY
We are committed to publishing all of our methods and data, and presenting research publicly

BEST PRACTICES
Our studies meet a wide range of internationally accepted research and ethical standards

TRACEABILITY
Samples and measurements are documented at every step to ensure their validity

SUBJECT SAFETY
Our primary responsibility is to ensure the safety and well-being of our study subjects

HOW CAN THE PUBLIC KNOW THAT YOUR DATA ARE NOT TAMPERED WITH?

GCP also provides clear guidance on how to document clinical research. The guidelines require significant documentation at every point of the research process to provide a reliable record of events – also called "essential documents". Documentation on clinical studies should furthermore follow the ALCOA principles (Attributable, Legible, Contemporaneous, Original and Accurate). This is to ensure data integrity and traceability and, in consequence, the validity of the research.

As an example, GCP helped safeguard against what could have been a break in the chain of sample custody that arose in one of our clinical studies in the U.S. in 2015. A PMI-contracted laboratory received a shipment of samples from one of our clinical study sites and found that the shipment contained fewer samples than expected, where the samples' labels did not match the shipping manifest provided by the clinical site. PMI requested a detailed investigation. Under the guidance of our CRO and oversight by PMI, the laboratory and the clinical study site developed a reconciliation plan, which was thoroughly documented and then executed to discover and resolve the discrepancies.

Toward this end, the CRO-assigned team flew to the laboratory and the respective study site, spending multiple days at both locations reviewing every single sample collected from the time of collection to time of analysis. As a result, the discrepancies were resolved, and the integrity and traceability of the data collected from these samples were confirmed.

GCP requirements make the research sponsor accountable for the study independent of the level of its involvement. This means that it is our responsibility as a research sponsor to ensure the safety and well-being of our study subjects, and the integrity of the research. As I mentioned before, the sponsor's role during the execution of study is oversight. In other words, the sponsor does not create records linked to study participants, so it goes without saying that this also excludes the possibility of a sponsor altering such records undetectably.

WHAT CORRECTIVE ACTIONS DOES PMI TAKE IF NECESSARY PROCEDURES ARE NOT FOLLOWED?

If essential elements of GCP are not followed by the study site, corrective actions are required. PMI has taken action in such cases, up to closing a specific research site.

In such cases, PMI follows a strict and structured process as defined in our quality management system, which is based on GCP. This begins with a For-Cause audit: an on-site investigation by PMI's quality assurance group or an external party. If such an audit detects non-conformance with GCP that would impact the safety of study participants or the ethical conduct or validity of the research, then closing a study site might be the outcome.

These types of situations are not unique to the tobacco industry; they also happen in clinical studies conducted by the pharmaceutical and other industries. And it's part of the reason why GCP principles are so important. They guide study teams on a daily basis and ensure that decisions are properly made and documented.

One such case occurred very early in the conduct of a 2013 study in Japan – even before posting the study on ClinicalTrials.gov. During a routine site-monitoring visit, the CRO overseeing the study noticed discrepancies to the requirements of the study protocol and to GCP. These discrepancies triggered a For-Cause audit by the CRO's and PMI's quality assurance groups.

The audit confirmed the identified discrepancies to the requirements of the study protocol and to GCP. As a consequence, these issues prompted PMI to immediately close this study site. However, we were able to successfully complete the respective study by instead recruiting the entire number of subjects required by the protocol at the remaining study site.

HOW COMMON ARE SITE CLOSURES, EXACTLY?

The standards and controls we have in place are designed to help avoid incidents such as a site closure. But they do happen, not just for us but in any industry conducting clinical studies, such as the pharmaceutical industry. Examples can be found online. Companies conducting clinical studies, including PMI, have multiple proactive controls in place to ensure study integrity and adherence to GCP. Like with international pharmaceutical companies, these controls are also designed to detect non-adherence to GCP and trigger appropriate remediation actions where issues are found.

HOW DO YOU ENSURE THAT THE STUDY SITES AND PERSONNEL ARE QUALIFIED, AND HOW DO YOU TRAIN THE SITES PARTICULARLY IF THEY DON'T SPEAK ENGLISH?

GCP requires that all study personnel involved in clinical research are qualified to ensure appropriate study conduct. Therefore before starting a study, a so-called qualification visit for each potential study site is performed by our CROs. These visits are performed as face-to-face visits, where they review and assess the qualifications, experience, and capabilities of the site personnel, and the suitability of the facility to conduct the study. This is then documented in a Qualification Visit Report, which PMI receives prior to approving a site to participate in the study. Last but not least, each study and the PI for each study site are reviewed and approved by an Institutional Review Board (IRB) prior to conducting the study.

To ensure proper understanding by personnel involved in our studies who do not speak English, the protocol, investigator's brochure (a summary of all relevant information on the product studied) and other study documentation are translated to the local language (e.g., Japanese) as appropriate and required. These are provided to the PI and the IRB.

With regards to the training when a language barrier exists, we can for example conduct a study training meeting in English for the CROs and all supporting study vendors (known as the pre-investigator meeting), who are required to have English-speaking personnel. The CRO then performs the training for each study site including the investigators in local language (i.e., the investigator's meeting / site initiation visit). These include training on Good Clinical Practice, the study protocol and procedures, and the electronic systems used in the study. All trainings and training records are documented in the Study Master File and are available for inspection by regulators at any time.

DO YOU HAVE ANY CLOSING THOUGHTS ABOUT PMI'S CLINICAL PROGRAM?

Clinical studies are a complex undertaking, and as in every complex process, we have to expect that irregularities can and will happen. This is why standards such as GCP exist: to provide clear guidance on each step to minimize the number of issues that can occur and to provide guidance on how to address them when they do.

This is, in fact, why PMI is committed to strictly following these standards. The guidelines are not only integral to maintaining the validity of the data, but also to its transparency, participant safety and overall ethical conduct. Our hope is that our adherence to these principles will allow others to see our research for what we believe it is: a significant contribution to evolving today's scientific knowledge on better alternatives to cigarettes for the millions who smoke around the world.

REFERENCES
3 https://www.fda.gov/downloads/TobaccoProducts/GuidanceComplianceRegulatoryInformation/UCM297751.pdf.

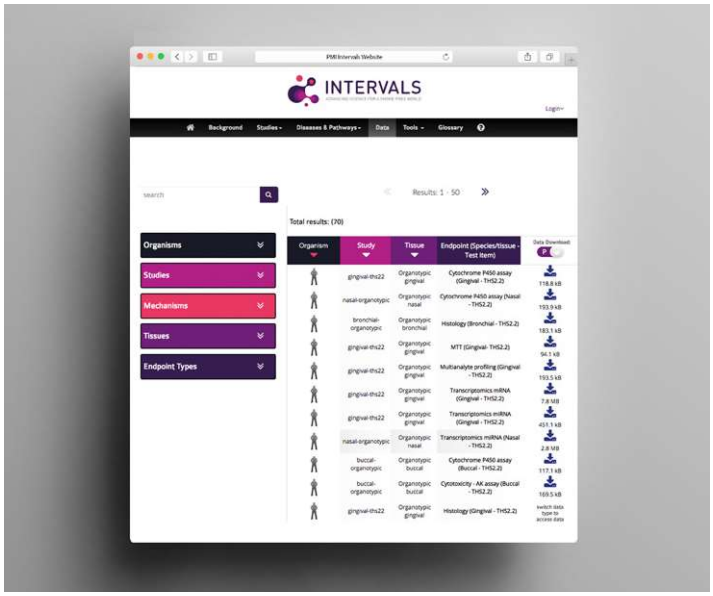
PUBLICATIONS

Supporting evidence-based analysis for modified risk tobacco products through a toxicology data-sharing infrastructure

Evidence and results should be openly shared, as has been proposed by the European Food Safety Authority.[4] This can encourage replication of studies and increase confidence in study findings. Indeed, peer-reviewed scientific literature can be difficult to reproduce for reasons such as inadequate documentation or insufficient sharing of methods and datasets with the community. Processes that encourage transparent sharing of data in a way that allows easy review and understanding will facilitate objective evaluation of the evidence. For this reason, PMI developed a database and associated web portal called INTERVALS to collect relevant information on studies assessing products with the potential to reduce risk.[5]

INTERVALS allows users to browse the data by study or by mechanism (e.g., inflammation, or oxidative stress) and obtain information relevant to study design, methods, and the most important results. Our reported data management method employs the latest standards of data sharing and reproducible research. The data and methods are curated and prepared using ISA-Tab (an open-source, tab-delimited format) fit for review by scientists, and the data are stored in a database that can be accessed via a search portal on the website. Given the successful development of the initial infrastructure, our goal is to grow this initiative. We aim to establish a public repository for PMI's 21st-century systems toxicology assessment data and results that support open data principles.

Boué, S., T. Exner, S. Ghosh, V. Belcastro, J. Dokler, D. Page, A. Boda, F. Bonjour, B. Hardy, P. Vanscheeuwijck, J. Hoeng, M. Peitsch (2017). Supporting evidence-based analysis for modified risk tobacco products through a toxicology data-sharing infrastructure. F1000Research, 6:12 - doi: 10.12688/f1000research.10493.2



PMI developed a database and associated web portal called INTERVALS to collect relevant information on studies assessing products with the potential to reduce risk. Data related to EHTP assessment is being made available on the site

Depiction of our Platform 3 product, described in more detail on page 03

Evaluation of nicotine pharmacokinetics and subjective effects following use of a novel nicotine delivery system

Nicotine plays an important role in encouraging current cigarette smokers to switch to better products, which is why it is part of our harm-reduction strategy. The nicotine delivery capability of platform 3 (P3, see page 3) was tested in 16 healthy smokers at three different nicotine delivery levels in a study conducted by the CRO Christchurch Clinical Studies Trust. P3 was compared against a nicotine inhalator, and blood nicotine levels as well as subjects' perceptions of the product were measured.

Written with input from New Zealand's leading public health specialist for tobacco issues, Murray Laugesen, our publication reports that P3 shows potential over existing nicotine delivery systems by delivering nicotine at a rate and intensity similar to cigarettes. Participants also found the product a more satisfactory alternative than the inhalator and in comparison reported less intention toward smoking cigarettes; no relevant side effects were reported. Altogether, the nicotine delivery, subjects' perception of P3 and safety profile obtained in this study suggest the device will be acceptable to adult smokers as an alternative to cigarettes.

Teichert, A., P. Brossard, L. Felber Medlin, L. Sandalic, M. Franzon, C. Wynne, M. Laugesen and F. Lüdicke (2017). Evaluation of nicotine pharmacokinetics and subjective effects following use of a novel nicotine delivery system. Nicotine Tob Res, in press. - doi:10.1093/ntr/ntx093

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

REFERENCES
4 Rabesandratana T: REGULATORY SCIENCE. Europe's food watchdog embraces transparency. Science. 2015; 350(6259): 368.
5 http://intervals.science.

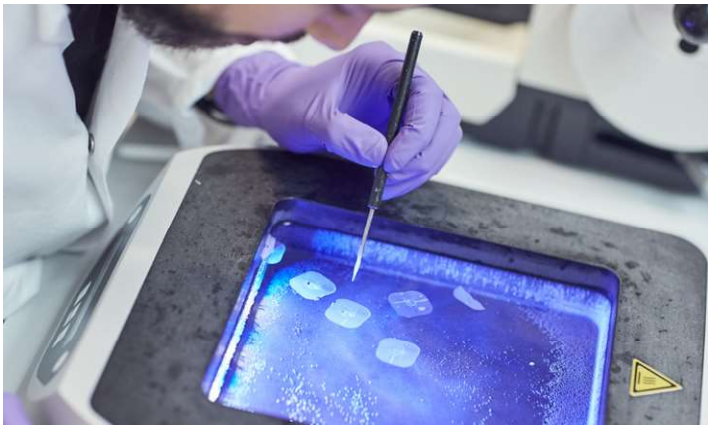
Comparative assessment of HPHC yields in the Tobacco Heating System THS2.2 and commercial cigarettes

The development of products like EHTP (referred to as THS2.2 in this research paper), which has the potential to present less risk compared with continued smoking, requires that clear comparisons be made between those developed products and the cigarettes that current smokers are using. Publications that compare such products with cigarettes generally rely on the reference cigarette 3R4F, the widely used cigarette distributed by the University of Kentucky as a standard for research purposes.

Measurements that compare EHTP to 3R4F do accurately represent the comparison between EHTP and a wide range of cigarettes. These brands were representative of the commercial landscape available between 2008 and 2016 in a number of leading cigarette markets. They were tested using the Health Canada intense smoking regime[6] to generate the aerosol. On average, a reduction of about 90% of harmful and potentially harmful constituents (HPHCs) was measured in the aerosol of EHTP compared against the levels of HPHCs in smoke of commercially available cigarettes. This mean reduction closely matches the reduction observed against 3R4F smoke constituents in previous studies.

Jaccard, G., D. Tafin Djoko, O. Moennikes, C. Jeannet, A. Kondylis and M. Belushkin (2017). Comparative assessment of HPHC yields in the Tobacco Heating System THS2.2 and commercial cigarettes. Regul Tox Pharmacol 90: 1-8. - doi:10.1016/j.yrtph.2017.08.006

PMI's electronically heated tobacco product (EHTP, referred to as Tobacco Heating System (THS) or THS2.2 in the literature)



Systems toxicology, which integrates standard toxicology with advanced experimental and computational methods, is an important part of PMI's assessment program

3-D nasal cultures: Systems toxicological assessment of a candidate modified risk tobacco product

Standard toxicology studies the adverse effects of exposure to a substance on living organisms, including the prevention of harm. Systems toxicology incorporates standard toxicology along with advanced experimental and computational methods to gain a more detailed understanding of how those adverse effects arise. (See systems toxicology in glossary.) In this study, PMI used EHTP to explore the relevance of a human three-dimensional (3-D) nasal culture model in assessments of the toxicological impact of exposure to chemicals via inhalation. This new culture model is a commercially available 3-D structure developed using different kinds of nasal cells to model a human airway.

The 3-D nasal structure was exposed multiple times to a range of concentrations of aerosol from EHTP, smoke from 3R4F, and fresh air to obtain reproducible measurements. The cellular and molecular changes that occur in the tissue following exposure were observed. In agreement with previous results, EHTP's effect on the 3-D nasal culture was much closer to that of the fresh air sample than to the effect of 3R4F. These results were measured in terms of cell toxicity, changes in the tissue structure, causing inflammation responses, and others.

Iskandar, A. R., C. Mathis, F. Martin, P. Leroy, A. Sewer, S. Majeed, D. Kuehn, K. Trivedi, D. Grandolfo, M. Cabanski, E. Guedj, C. Merg, S. Frentzel, N. V. Ivanov, M. C. Peitsch and J. Hoeng (2017). 3-D nasal cultures: systems toxicological assessment of a candidate modified-risk tobacco product. Altex 34: 23-48. - doi:10.14573/altex

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6 Health Canada (Ed.), Official Method-T115. Determination of Tar, Nicotine and Carbon Monoxide in Mainstream Tobacco Smoke. Tobacco Control Programme, Modified: 2007-11-28 (1999) Ottawa, Canada.

LATEST EVENTS

AMERICAN COLLEGE OF TOXICOLOGY (ACT) 2017

PALM SPRINGS, U.S., 5-8 NOVEMBER 2017

At the ACT's 38th Annual Meeting, PMI scientist Dr. Stephanie Boué presented information about our INTERVALS and sbvIMPROVER platforms.

Her presentation explained the need for a platform like INTERVALS to provide detailed study results and direct links to research data, as well as enable and support in-depth peer review. More information on INTERVALS can be found on page 6.

Boué's presentation transitioned from discussing transparency to verification of PMI's research program by describing the sbvIMPROVER program. Conference-goers learned about the significant achievements made using the platform since its initiation seven years ago, with the aim of verifying methods and data in systems biology and systems toxicology using double blind performance assessment. Furthermore, details on recent challenges and competitions supported by sbvIMPROVER were also available for discussion.

Find out more about PMI's presentations at the event here: https://www.pmiscience.com/events/american-college-toxicology-act-2017

Booth at ACT where PMI presented its sbvIMPROVER platform, pictured with PMI's Stephanie Boué (left) and Laure Cannesson (right). Boué also gave an oral presentation at the conference.

FROM SINGLE- TO MULTIOMICS: APPLICATIONS AND CHALLENGES IN DATA INTEGRATION

HEIDELBERG, GERMANY

12-14 NOVEMBER 2017

This combined symposium, supported by the European Molecular Biology Organization and the European Molecular Biology Laboratory, allowed computational scientists to learn about different "omics" fields. Here, PMI scientist Dr. Alain Sewer presented a poster, inviting conference participants to learn about the workflow used to more thoroughly analyze complicated toxicology data sets for EHTP assessment compared to cigarette smoke. This method examines the collected data through the lens of different omics modalities, focusing on smoke's effect on organ function, DNA transcription or protein function, for example. As Sewer's poster explains, this integrative approach identifies mechanisms of harm common to multiple modalities, allowing for a more holistic interpretation of results.

Find out more about PMI's presence at the event here: https://www.pmiscience.com/events/single-multiomics-applications-and-challenges-data-integration

12TH INTERNATIONAL CONFERENCE & 5TH ASIAN CONGRESS ON ENVIRONMENTAL MUTAGENS

INCHEON, SOUTH KOREA

12-16 NOVEMBER 2017

PMI scientists presented at the 12th International Conference and 5th Asian Congress on Environmental Mutagens (ICEM-ACEM 2017), hosted by the Korean Environmental Mutagen Society in South Korea. One oral presentation by Dr. James Battey discussed two case studies: one focused on the comparison of the effects of smoke-free products versus cigarette smoke on an *in vivo* model for COPD, and the other summarized a clinical study for EHTP menthol compared to menthol cigarettes or smoking abstention.

In his poster presentation, Dr. Damian McHugh described the series of laboratory tests that showed that the mutagenic and cytotoxic potencies in the mainstream aerosol from EHTP were at least 85-95% reduced compared to the mainstream smoke from 3R4F.

Find out more about PMI's presence at the event here: https://www.pmiscience.com/events/icem-acem-2017

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 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.

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.

MODIFIED RISK TOBACCO PRODUCT (MRTP)

The term used to classify a potentially less harmful product by the U.S. 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.

STANDARD TOXICOLOGY

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

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

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

SYSTEMS TOXICOLOGY

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

RISK-BASED QUALITY MANAGEMENT SYSTEM

OUR RISK-BASED QUALITY MANAGEMENT SYSTEM

At each step of assessing our smoke-free products, we apply rigorous scientific standards during data generation. A risk-based Quality Management System (QMS) has been developed to coordinate and guide activities with the aim of ensuring quality and integrity of data and product during its complete lifecycle, from conception through commercialization. This QMS comprises the following elements:

POST-MARKET SURVEILLANCE AND STUDIES	IEA GEP;[7] Applicable National Regulations s
CONSUMER PERCEPTION AND BEHAVIOR ASSESSMENT	GEP-DGEpi;[8] FDA Guidance on PRO;[9] ISPOR PGP for the TCA;[10] Applicable National Regulations
CLINICAL STUDIES	WMA Declaration of Helsinki;[11] ICH GCP E6 (R1);[12] Applicable National Regulations
SYSTEMS TOXICOLOGY ASSESSMENT	The systems toxicology studies are conducted under a GLP-like quality system
STANDARD TOXICOLOGY ASSESSMENT	OECD GLP,[13] INVITTOX 3A/ERGATT/FRAME; OECD[14] Test Guidelines 412, 413, 471, 487, 451, 453, 490
AEROSOL CHEMISTRY AND PHYSICS	**Aerosol Chemistry** OECD GLP; ISO[15] 17025; ICH Q2 (R1);[16] ISO 3308, *3402, 4387, *8454, 10315:2013, 10362-1, *13110, 19290; CORESTA CRM81[17]
	Indoor Air Quality ISO 17025; EN 15251;[18] ISO 15593, 18144, 18144, 16814, 16000-6, 11454
PRODUCT DESIGN AND CONTROL PRINCIPLES	Quality by Design (QbD)[19]

*With slight modifications needed to adapt to smoke-free products.

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