# ANNUAL REPORT
# FOR PM0000424 - PM0000426, PM0000479 and PM0000634 and MR0000059 - MR0000061 and MR0000133

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| FDA STN No. | PM0000424 - MR0000059[1]<br>PM0000425 - MR0000060<br>PM0000426 - MR0000061<br>PM0000479 - MR0000133<br>PM0000634 |
| Tobacco Product Name | *Marlboro* Amber *HeatSticks*<br>*Marlboro* Green Menthol *HeatSticks*<br>*Marlboro* Blue Menthol *HeatSticks*<br>*IQOS* System Holder and Charger<br>*IQOS* 3 System Holder and Charger |
| Tobacco Product Category | Cigarette |
| Tobacco Product Sub-category | Non-Combusted |
| Applicant | Philip Morris Products S.A. (PMP S.A.) |
| Date of Report | April 30, 2021 |
| Reporting Period | PM0000424-PM0000426 and PM0000479:<br>March 1, 2020 to February 28, 2021<br>PM0000634: December 7, 2020 to February 28, 2021 |

[1] Exposure Modification Orders for *IQOS* System Holder and Charger with three variants of *Marlboro HeatSticks* require that manufacturing information is submitted together with Annual Report for PMTAs.


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# 1 EXECUTIVE SUMMARY

On April 30, 2019 the U.S. Food and Drug Administration (FDA) determined that issuing a Marketing Order (MO) authorizing the marketing of the *IQOS* System Holder and Charger with three variants[2] of *Marlboro HeatSticks* for the United States (U.S.) market was appropriate for the protection of the public health (APPH). The following year, on December 7, 2020, the FDA granted authorization to market the *IQOS* 3 System Holder and Charger with the issuance of a Marketing Granted Order.[3] Altria Client Services LLC (ALCS)[4] and an ALCS affiliate have been licensed to distribute and sell these products in the U.S. The ALCS affiliate that distributes and sells the product in the U.S. is Philip Morris USA Inc. (PM USA)[5].

The MOs established restrictions and postmarket requirements. In accordance with the MOs, Philip Morris Products S.A. (PMP S.A.)[6] is required to report regularly to FDA certain product and marketing information, including, but not limited to, ongoing and completed studies about the tobacco products, including consumer research studies; advertising; marketing plans; sales data; information on current and new users; manufacturing changes and adverse experiences.

In accordance with Section 910(c)(4) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), FDA may grant a MO when sufficient evidence shows that permitting a product to be marketed would be APPH. Whether a tobacco product is APPH is determined with respect to the risks and benefits to the population as a whole, including users and nonusers of the tobacco product, and taking into account:

(A) the increased or decreased likelihood that existing users of tobacco products will stop using such products; and

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[2] *Marlboro* Amber *HeatSticks* were formerly *Marlboro Heatsticks*
*Marlboro* Green Menthol *HeatSticks* were formerly *Marlboro* Smooth Menthol *Heatsticks*
*Marlboro* Blue Menthol *HeatSticks* were formerly *Marlboro* Fresh Menthol *Heatsticks*

[3] We refer to both the April 30, 2019 Marketing Order and the December 7, 2020 Marketing Granted Order collectively as the Marketing Orders, MOs, or MO.

[4] Altria Client Services LLC (ALCS) is a wholly-owned subsidiary of Altria Group, Inc. ALCS provides certain services to the Altria family of companies.

[5] PMP S.A.'s parent, Philip Morris International Management (PMI), has entered into an agreement with ALCS by which ALCS and its affiliates, including PM USA, are licensed to sell *IQOS* in the United States.

[6] We refer to Philip Morris International ("PMI") in some sections of this annual report. For clarity and ease of review, all of the following entities are included within the term "PMI": (1) Philip Morris International Inc., the general entity; (2) Philip Morris Products S.A. (PMP S.A.), the PMTA MO holder, manufacturer and the legal entity responsible for clinical trials and post marketing studies and surveillance, (3) Philip Morris International Management S.A., the legal entity responsible for market research and management services, (4) Philip Morris International Research Laboratories Pte. Ltd. responsible for pre-clinical in vivo studies, and (5) Philip Morris Manufacturing & Technology Bologna S.p.A. responsible for the manufacture of Tobacco Sticks.

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(B) the increased or decreased likelihood that those who do not use tobacco products will start using such products.

Under section 910(f) of the FD&C Act, the MOs require that PMP S.A. submit to FDA postmarket periodic reports that include a summary of how the marketing of the tobacco products continues to be APPH. The MOs require submission of reports on a quarterly and annual basis.

This is the second Annual Report for the *IQOS* System Holder and Charger with three variants of *Marlboro HeatSticks* covering the time period between March 1, 2020 and February 28, 2021, and the first Annual Report for the *IQOS* 3 System Holder and Charger, which covers the time period between December 7, 2020 and February 28, 2021. The report provides summaries of required information and records for the *IQOS* System Holder and Charger (PM0000479), the *IQOS* 3 System Holder and Charger (PM0000634) and three variants of *Marlboro HeatSticks* (PM0000424 – PM0000426). Detailed discussion concerning respective reporting obligations, as specified in Appendix B and C to the MOs, is provided later in this report (Sections 1 – 18 with corresponding Annexes).

The evidence supplied with this Annual Report confirms that the marketing of the authorized tobacco products continues to be APPH because:

- PMP S.A.-sponsored studies, as well as findings reported in publications by PMP S.A and independent researchers not previously reported to the FDA show that the intented audiences of *IQOS* is indeed adult cigarette smokers. Moreover, studies show that *IQOS* use is low among non-users (never or former) of tobacco products, including youth;
- There were no serious and unexpected adverse experiences (SAEs) reported by consumers in the U.S. during the reporting period. The analysis of all reported adverse experiences (AEs) for the tobacco products confirms that there were no changes to risk information related to the products including the nature of AEs and their frequency;
- The summary of the U.S. sales and distribution of the tobacco products indicates that the market dynamics and the products uptake is generally in-line with the initial estimates within the geographies that the product is available, and the company's policies and procedures regarding restrictions on youth access to the products are effective;
- Changes to the manufacturing process, facilities, and/or controls during the reporting period did not result in any modification of the tobacco products (including a change in design, any component, any part, or any constituent, including a smoke or aerosol constituent, or in the content, delivery, or form of nicotine, or any other additive or ingredient);
- None of the reported manufacturing deviations (including deviations associated with processing, testing, packing, labeling, storage, holding, and distribution) affect the characteristics of the products;

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- Labeling, advertising, marketing and promotional materials and plans comply with marketing restrictions of the MOs. Materials and plans were shared with the FDA in advance of their use on an ongoing basis through the 30 Day Notifications.

Considering the above, PMP S.A. concludes that the grounds for the marketing authorization for the *IQOS* System Holder and Charger (PM0000479), *IQOS* 3 System Holder and Charger (PM0000634) and three variants of *Marlboro HeatSticks* (PM0000424 – PM0000426) have not changed. The risks and benefits to the population as a whole, including users and nonusers of the tobacco products, have not changed after the products were introduced on the U.S. market, and therefore the continued marketing of those products remains APPH.

## 2 SUMMARY OF SCIENTIFIC STUDIES AND PUBLICATIONS

This chapter provides an overview of PMP S.A. scientific studies that are either completed or ongoing as well as significant findings from scientific publications by PMP S.A. and independent researchers. While these studies and publications are listed separately in Annex 1 and Annex 2, we present a summary of these studies here, organized by scientific area using the structure of the seven step scientific assessment program for the Tobacco Heating System (THS[7]) as outlined in section 2.7.4.[8] of the original PMTA[9] ("original PMTA") for this product.

Throughout this chapter, we reference studies and publications that are related to the *IQOS* THS generally. The MOs authorized marketing of particular versions of the *IQOS* System Holder and Charger (device versions 2.4 and 3) and three variants of *Marlboro HeatSticks* (*Marlboro* Amber *HeatSticks*; *Marlboro* Green Menthol *HeatSticks*; and *Marlboro* Blue Menthol *HeatSticks*) (collectively, "Authorized Products"). PMP S.A. sells other versions of the *IQOS* System Holder and Charger and additional variants of *HeatSticks* in markets outside the U.S. The studies and publications in this Scientific Summary may be related to versions of the *IQOS* System Holder and Charger and *HeatSticks* other than the Authorized Products. Nevertheless, PMP S.A. believes it is important to provide this information because those other versions are designed to have the same principles of operation and performance as the Authorized Products, and studies and publications about them are therefore relevant to the Authorized Products.

[7] Tobacco Heating Systems (THS) consists of the Authorized *IQOS* System Holder and Charger and *Marlboro HeatSticks* variants.

[8] PMI's seven step assessment program consists of studies related to 1) Product Design and Control Principles, 2) Aerosol Chemistry and Physics, 3) Standard Toxicology Assessments, 4) Systems Toxicology Assessments, 5) Clinical Studies, 6) Consumer Perception and Behaviour Assessment and 7) Post-Market Studies and Surveillance

[9] Original PMTA refers to PM0000424-426 and PM0000479

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A substantial number of studies that relate directly to the *IQOS* Authorized Products have been completed by independent researchers, PMP S.A., and other manufacturers of tobacco and nicotine-containing products during the reporting period.

In this reporting period we are reporting 12 PMI ongoing studies in the various areas, with completion dates ranging from March 2021 to September 2025. These studies encompass various scientific investigations, *e.g.* research of new PLA based polymers with enhanced biodegradability and lesser environmental impact, as well as *in vitro* toxicological studes, clinical studies on both functional and health outcomes (*e.g.*, exercise capacity, oral health and cardiovascular health) and also studies evaluating tobacco use prevalence and patterns of tobacco product use.

During this period PMP S.A. completed 19 additional scientific studies relevant for the Authorized Products to further strengthen the evidence that the product is APPH. Summaries of these studies are provided in Annex 1.

**Table 1: Overview of the studies provided in Annex 1**

| Study category | Number of ongoing studies | Number of competed studies |
| --- | --- | --- |
| Aerosol Chemistry and Physics | 3 | 7 |
| Standard & System Toxicology | 3 | 6 |
| Clinical | 3 | 1 |
| Behavioral | 1 | 0 |
| Post-market study | 2 | 5 |

A systematic literature search and review of retrieved articles was conducted according to a pre-defined Literature Review Protocol and originally identified 188 publications that reported data related to the Authorized Products published in the time period between March 1, 2020 and February 28, 2021.

104 publications have been excluded from reporting here as they (a) did not represent original research, (b) did not represent a systematic review, (c) were not available in English, or (d) were not relevant to *IQOS*.

Therefore, this summary includes 84 publications, which are listed and summarized in Annex 2. Of those 84 publications, 13 publications report results from studies conducted or sponsored by PMP S.A. or other tobacco and nicotine containing product manufacturers, and 71 publications report data from studies conducted by independent researchers.

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The publications included in our literature summary encompass various scientific fields including:

- Aerosol chemistry and physics, including data on product properties related to non-combustion, emissions of harmful and potentially harmful constituent (HPHCs), indoor air quality and secondhand exposure.
- Standard and systems toxicology, including standard toxicology testing *in vitro*, *in vivo* inhalation studies and animal models of disease.
- Clinical studies on exposure reduction to HPHCs, effect on biomarkers of potential harm (BoPH) and early markers of disease risk.
- Perception and behavioral studies and post-market studies, to assess the impact of the *IQOS* Tobacco Heating System on consumer perception, tobacco use prevalence, patterns of tobacco product use, product acceptability and the impact of marketing approaches.

Our review of the literature, considering varying methodology used across studies and balancing sometimes overstated conclusions considering the underlying study design, further supports our assessment of APPH because:

- The studies presented on aerosol chemistry and physics and related methodologies add further evidence that THS produces significantly lower levels of HPHCs compared with cigarette smoke;
- These studies also provide further evidence that there is no combustion occurring in THS and that, for this reason, not only HPHCs but also other entities emitted in smoke, such as free radicals, are significantly reduced compared to cigarette smoke emissions;
- The studies completed on standard and systems toxicology by PMP S.A. and independent researchers add further evidence that (a) THS aerosol is significantly less toxic than cigarette smoke (b) THS aerosol causes significantly less disease-associated network perturbations *in vitro* and *in vivo* and (c) THS aerosol causes significantly less emphysema and atherosclerotic plaque in animal models of disease compared to cigarette smoke;
    - This is despite the fact that some studies by independent researchers report contradictory results to the studies conducted and published by PMP S.A.These differences have been carefully considered when many could be explained by methodological differences. The conclusions drawn by some authors were considered to be overstated. Overall these studies were not found to challenge the data that is supportive of APPH;
- The clinical studies on THS, including both studies conducted by independent researchers and PMP S.A., add further evidence that switching from cigarette smoking to THS use leads to (a) significantly reduced exposure to HPHCs, approaching the reductions in exposure seen with smoking abstinence, and (b) switching from cigarette

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smoking to THS results in positive changes in certain BoPH that are similar to those seen following smoking cessation;

- The cross-sectional surveys were conducted by PMP S.A. in markets outside the U.S. Additionally, multiple studies by independent researchers on perception, product use behavior, and product use trajectories in markets outside the U.S. add to the available evidence on the population impact of THS. These studies provide further evidence that THS will not adversely impact the overall opportunity for harm reduction in the population by either reversing the decision of smokers who intend to quit smoking or by attracting adult nonsmokers who might be influenced to begin the use of tobacco products.

## 2.1 Ongoing and summary of completed studies

A status report of on-going and completed scientific studies performed by PMP S.A. and not previously submitted to the Agency is provided in Annex 1. This includes completed scientific studies already submitted in previous annual report (or from March 1, 2020) until February 28, 2021.

## 2.2 Significant findings on publications not previously reported

A summary of significant findings on publications by PMP S.A. and independent researchers not previously submitted including full copies of the articles is included in Annex 2.

This section summarises the latest scientific findings from external publications by PMP S.A. and independent researchers that assess Heated Tobacco Products (HTPs), including PMI's commercialised HTP known as *IQOS*. The time period covered by the search is from March 1, 2020 to February 28, 2021.

Publications on medical case studies and scientific data pertaining to the safety profile of THS are not discussed in this scientific overview but listed in Annex 2 and discussed in Annex 3.

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### *2.2.1 PMI's publications*

#### 2.2.1.1 Aerosol Chemistry and Physics

(1) Goujon C, Kleinhans S, Maeder S, et al. Robustness of HPHC Reduction for THS 2.2 Aerosol Compared with 3R4F Reference Cigarette Smoke Under High Intensity Puffing Conditions, Beiträge zur Tabakforschung International/Contributions to Tobacco Research, 2020, 29(2): 66-83.

In the absence of standards specific for testing the reduction robustness of the levels of HPHCs, the aerosol from the THS 2.2, a heated tobacco product, was compared with the mainstream smoke of the 3R4F reference cigarette over a broad range of machine-smoking regimes. The average reduction and the introduced concept of threshold limits of robust reduction were derived from HPHC concentrations, in mass per tobacco-stick normalized per total puff volume, to propose an alternative for the assessment of products where nicotine-adjusted yields would be inappropriate. In addition, this study explores the influence of 3R4F reference cigarette filter ventilation, and discusses the roles of temperature and precursors in the present context of robustness of HPHC reduction. Fifty-four HPHCs were analyzed under multiple regimes in THS 2.2 aerosol and 3R4F cigarette smoke. The average reduction of HPHC concentrations compared across all regimes characterized the robustness. Threshold limits of reduction of individual HPHCs were statistically determined across all regimes. The results observed under Health Canada Intense (HCI) and more intense regimes indicated that on average the reductions in HPHCs levels investigated in THS 2.2 aerosol were more than 90% and that the majority of the 54 HPHCs investigated in THS 2.2 aerosol showed more than 90% reduction. The robustness of THS 2.2 in maintaining the levels of reduction of representative HPHCs, whatever the puffing regime, can be quantified. The mass of HPHC per tobacco-stick normalized per total puff volume is a valuable approach to compare the robustness of the performance of a product over a large range of puffing conditions. The findings complement the assessment for robustness of current and future similar products where classical approaches would present limitations (*e.g.*, e-cigarettes and combustible cigarettes with a lower content of nicotine).

(2) Rodrigo G, Jaccard G, Tafin Djoko D, et al. Cancer potencies and margin of exposure used for comparative risk assessment of heated tobacco products and electronic cigarettes aerosols with cigarette smoke, Archives of Toxicology, 2021, 95(1): 283-298.

Health risk associated with the use of combustible cigarettes is well characterized and numerous epidemiological studies have been published for many years. Since more than a decade, innovative non-combusted tobacco products have emerged like HTP or electronic cigarettes (EC). Long-term effects of these new products on health remain unknown and there is a need to characterize associated potential health risks. The time dedicated to epidemiological data generation (at least 20 to 40 years for cancer endpoint), though, is not compatible with innovative development. Surrogates need, therefore, to be developed. In this work, non-cancer and cancer risks were estimated in a range of HTP and commercial

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combustible cigarettes based upon their harmful and potentially harmful constituent yields in aerosols and smoke, respectively. It appears that mean lifetime cancer risk values were decreased by more than one order of magnitude when comparing HTPs and commercial cigarettes, and significantly higher margin of exposure for non-cancer risk was observed for HTPs when compared to commercial cigarettes. The same approach was applied to two commercial ECs. Similar results were also found for this category of products. Despite uncertainties related to the factors used for the calculations and methodological limitations, this approach is valuable to estimate health risks associated to the use of innovative products. Moreover, it acts as predictive tool in absence of long-term epidemiological data. Furthermore, both cancer and non-cancer risks estimated for HTPs and ECs highlight the potential of reduced risk for non-combusted products when compared to cigarette smoking.

#### 2.2.1.2 Toxicology and Systems Toxicology

(3) Sewer A, Zanetti F, Iskandar AR, et al. A meta-analysis of microRNAs expressed in human aerodigestive epithelial cultures and their role as potential biomarkers of exposure response to nicotine-containing products, Toxicology Reports, 2020, 7: 1282-1295.

The expression of some microRNAs (miRNA) is modulated in response to cigarette smoke (CS), a leading cause of major preventable diseases. However, whether miRNA expression is also modulated by the aerosol/extract from potentially reduced-risk products is not well studied. The present work is a meta-analysis of 12 in vitro studies in human organotypic epithelial cultures of the aerodigestive tract (buccal, gingival, bronchial, nasal, and small airway epithelia). These studies compared the effects of exposure to aerosols from electronic vapor (e-vapor) products and heated tobacco products, and to extracts from Swedish snus products (in the present work, will be referred to as reduced-risk products [RRPs]) on miRNA expression with the effects of exposure to CS or its total particulate matter fraction. This meta-analysis evaluated 12 datasets of a total of 736 detected miRNAs and 2775 exposed culture inserts. The t-distributed stochastic neighbor embedding method was used to find similarities across the diversity of miRNA responses characterized by tissue type, exposure type, and product concentration. The CS-induced changes in miRNA expression in gingival cultures were close to those in buccal cultures; similarly, the alterations in miRNA expression in small airway, bronchial, and nasal tissues resembled each other. A supervised clustering was performed to identify miRNAs exhibiting particular response patterns. The analysis identified a set of miRNAs whose expression was altered in specific tissues upon exposure to CS (*e.g.*, miR-125b-5p, miR-132-3p, miR-99a-5p, and 146a-5p). Finally, we investigated the impact of RRPs on miRNA expression in relation to that of CS by calculating the response ratio r between the RRP- and CS-induced alterations at an individual miRNA level, showing reduced alterations in miRNA expression following RRP exposure relative to CS exposure (94 % relative reduction). No specific miRNA response pattern indicating exposure to aerosols from heated tobacco products and e-vapor products, or extracts from Swedish snus was identifiable.

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(4) Schlage WK, Titz B, Iskandar A, et al. Comparing the preclinical risk profile of inhalable candidate and potential candidate modified risk tobacco products: A bridging use case, Toxicology Reports, 2020, 7: 1187-1206.

Cigarette smoking causes major preventable diseases, morbidity, and mortality worldwide. Smoking cessation and prevention of smoking initiation are the preferred means for reducing these risks. Less harmful tobacco products, termed modified-risk tobacco products (MRTP), are being developed as a potential alternative for current adult smokers who would otherwise continue smoking. According to a regulatory framework issued by the US Food and Drug Administration, a manufacturer must provide comprehensive scientific evidence that the product significantly reduces harm and the risk of tobacco-related diseases, in order to obtain marketing authorization for a new MRTP. For new tobacco products similar to an already approved predicate product, the FDA has foreseen a simplified procedure for assessing "substantial equivalence". In this article, we present a use case that bridges the nonclinical evidence from previous studies demonstrating the relatively reduced harm potential of two heat-not-burn products based on different tobacco heating principles. The nonclinical evidence was collected along a "causal chain of events leading to disease" (CELSD) to systematically follow the consequences of reduced exposure to toxicants (relative to cigarette smoke) through increasing levels of biological complexity up to disease manifestation in animal models of human disease. This approach leverages the principles of systems biology and toxicology as a basis for further extrapolation to human studies. The experimental results demonstrate a similarly reduced impact of both products on apical and molecular endpoints, no novel effects not seen with cigarette smoke exposure, and an effect of switching from cigarettes to either MRTP that is comparable to that of complete smoking cessation. Ideally, a subset of representative assays from the presented sequence along the CELSD could be sufficient for predicting similarity or substantial equivalence in the nonclinical impact of novel products; this would require further validation, for which the present use case could serve as a starting point.

(5) Titz B, Sewer A, Luettich K, et al. Respiratory Effects of Exposure to Aerosol From the Candidate Modified-Risk Tobacco Product THS 2.2 in an 18-Month Systems Toxicology Study With A/J Mice, Toxicological Sciences, 2020, 178(1): 138-158.

In an 18-month chronic carcinogenicity/inhalation toxicity study in A/J mice (OECD Test Guideline 453), the aerosol of Tobacco Heating System 2.2 (THS 2.2), was compared with 3R4F cigarette smoke (CS). Standard toxicology endpoints were complemented with in-depth systems toxicology analyses. This publication reports the integrative assessment of the apical and molecular exposure effects on the respiratory tract (nose, larynx, and lungs). Changes were found in inflammatory response following 3R4F CS exposure (e.g., antimicrobial peptide response in the nose), with both shared and distinct oxidative and xenobiotic responses. Compared with 3R4F CS, THS 2.2 aerosol exerted far fewer effects on respiratory tract histology, including adaptive tissue changes in nasal and laryngeal epithelium and inflammation and emphysematous changes in the lungs. Integrative analysis of molecular

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changes confirmed the substantially lower impact of THS 2.2 aerosol than 3R4F CS on toxicologically and disease-relevant molecular processes such as inflammation, oxidative stress responses, and xenobiotic metabolism. The results from this study were shared previously with FDA as part of the MRTPA process.

(6) Wong ET, Luettich K, Krishnan S, et al. Reduced Chronic Toxicity and Carcinogenicity in A/J Mice in Response to Life-Time Exposure to Aerosol From a Heated Tobacco Product Compared With Cigarette Smoke, Toxicological Sciences, 2020, 178(1): 44-70.

The in-life and post-mortem results of the study outlined above in (5) are provided. All exposed mice showed lower thymus and spleen weight, blood lymphocyte counts, and serum lipid concentrations than sham mice, most likely because of stress and/or nicotine effects. Unlike THS 2.2 aerosol-exposed mice, CS-exposed mice showed increased heart weight, changes in red blood cell profiles and serum liver function parameters. Similarly, increased pulmonary inflammation, altered lung function, and emphysematous changes were observed only in CS-exposed mice. Histopathological changes in other respiratory tract organs were significantly lower in the THS 2.2 aerosol-exposed groups than in the CS-exposed group. Chronic exposure to THS 2.2 aerosol also did not increase the incidence or multiplicity of bronchioloalveolar adenomas or carcinomas relative to sham, whereas CS exposure did. Male THS 2.2 aerosol-exposed mice had a lower survival rate than sham mice, related to an increased incidence of urogenital issues that appears to be related to congenital factors rather than test item exposure. The totality of the evidence from this study further supports the risk reduction potential of THS 2.2 for lung diseases in comparison with cigarettes. The results from this study were shared previously with FDA as part of the MRTPA process. The in-life and post-mortem results of the study outlined above in (5) are provided. All exposed mice showed lower thymus and spleen weight, blood lymphocyte counts, and serum lipid concentrations than sham mice, most likely because of stress and/or nicotine effects. Unlike THS 2.2 aerosol-exposed mice, CS-exposed mice showed increased heart weight, changes in red blood cell profiles and serum liver function parameters. Similarly, increased pulmonary inflammation, altered lung function, and emphysematous changes were observed only in CS-exposed mice. Histopathological changes in other respiratory tract organs were significantly lower in the THS 2.2 aerosol-exposed groups than in the CS-exposed group. Chronic exposure to THS 2.2 aerosol also did not increase the incidence or multiplicity of bronchioloalveolar adenomas or carcinomas relative to sham, whereas CS exposure did. Male THS 2.2 aerosol-exposed mice had a lower survival rate than sham mice, related to an increased incidence of urogenital issues that appears to be related to congenital factors rather than test item exposure. The totality of the evidence from this study further supports the risk reduction potential of THS 2.2 for lung diseases in comparison with cigarettes. The results from this study were shared previously with FDA as part of the MRTPA process. The in-life and post-mortem results of the study outlined above in (5) are provided. All exposed mice showed lower thymus and spleen weight, blood lymphocyte counts, and serum lipid concentrations than sham mice, most likely because of stress and/or nicotine effects. Unlike THS 2.2 aerosol-exposed mice, CS-exposed mice showed increased heart weight, changes in red blood cell profiles and serum liver function parameters.

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Similarly, increased pulmonary inflammation, altered lung function, and emphysematous changes were observed only in CS-exposed mice. Histopathological changes in other respiratory tract organs were significantly lower in the THS 2.2 aerosol-exposed groups than in the CS-exposed group. Chronic exposure to THS 2.2 aerosol also did not increase the incidence or multiplicity of bronchioloalveolar adenomas or carcinomas relative to sham, whereas CS exposure did. Male THS 2.2 aerosol-exposed mice had a lower survival rate than sham mice, related to an increased incidence of urogenital issues that appears to be related to congenital factors rather than test item exposure. The totality of the evidence from this study further supports the risk reduction potential of THS 2.2 for lung diseases in comparison with cigarettes. The results from this study were shared previously with FDA as part of the MRTPA process. The in-life and post-mortem results of the study outlined above in (5) are provided. All exposed mice showed lower thymus and spleen weight, blood lymphocyte counts, and serum lipid concentrations than sham mice, most likely because of stress and/or nicotine effects. Unlike THS 2.2 aerosol-exposed mice, CS-exposed mice showed increased heart weight, changes in red blood cell profiles and serum liver function parameters. Similarly, increased pulmonary inflammation, altered lung function, and emphysematous changes were observed only in CS-exposed mice. Histopathological changes in other respiratory tract organs were significantly lower in the THS 2.2 aerosol-exposed groups than in the CS-exposed group. Chronic exposure to THS 2.2 aerosol also did not increase the incidence or multiplicity of bronchioloalveolar adenomas or carcinomas relative to sham, whereas CS exposure did. Male THS 2.2 aerosol-exposed mice had a lower survival rate than sham mice, related to an increased incidence of urogenital issues that appears to be related to congenital factors rather than test item exposure. The totality of the evidence from this study further supports the risk reduction potential of THS 2.2 for lung diseases in comparison with cigarettes. The results from this study were shared previously with FDA as part of the MRTPA process. The in-life and post-mortem results of the study outlined above in (5) are provided. All exposed mice showed lower thymus and spleen weight, blood lymphocyte counts, and serum lipid concentrations than sham mice, most likely because of stress and/or nicotine effects. Unlike THS 2.2 aerosol-exposed mice, CS-exposed mice showed increased heart weight, changes in red blood cell profiles and serum liver function parameters. Similarly, increased pulmonary inflammation, altered lung function, and emphysematous changes were observed only in CS-exposed mice. Histopathological changes in other respiratory tract organs were significantly lower in the THS 2.2 aerosol-exposed groups than in the CS-exposed group. Chronic exposure to THS 2.2 aerosol also did not increase the incidence or multiplicity of bronchioloalveolar adenomas or carcinomas relative to sham, whereas CS exposure did. Male THS 2.2 aerosol-exposed mice had a lower survival rate than sham mice, related to an increased incidence of urogenital issues that appears to be related to congenital factors rather than test item exposure. The totality of the evidence from this study further supports the risk reduction potential of THS 2.2 for lung diseases in comparison with cigarettes. The results from this study were shared previously with FDA as part of the MRTPA process. The in-life and post-mortem results of the study outlined above in (5) are provided. All exposed mice showed lower thymus and spleen weight, blood lymphocyte counts, and serum lipid concentrations than sham mice, most

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likely because of stress and/or nicotine effects. Unlike THS 2.2 aerosol-exposed mice, CS-exposed mice showed increased heart weight, changes in red blood cell profiles and serum liver function parameters. Similarly, increased pulmonary inflammation, altered lung function, and emphysematous changes were observed only in CS-exposed mice. Histopathological changes in other respiratory tract organs were significantly lower in the THS 2.2 aerosol-exposed groups than in the CS-exposed group. Chronic exposure to THS 2.2 aerosol also did not increase the incidence or multiplicity of bronchioloalveolar adenomas or carcinomas relative to sham, whereas CS exposure did. Male THS 2.2 aerosol-exposed mice had a lower survival rate than sham mice, related to an increased incidence of urogenital issues that appears to be related to congenital factors rather than test item exposure. The totality of the evidence from this study further supports the risk reduction potential of THS 2.2 for lung diseases in comparison with cigarettes. The results from this study were shared previously with FDA as part of the MRTPA process. The in-life and post-mortem results of the study outlined above in (5) are provided. All exposed mice showed lower thymus and spleen weight, blood lymphocyte counts, and serum lipid concentrations than sham mice, most likely because of stress and/or nicotine effects. Unlike THS 2.2 aerosol-exposed mice, CS-exposed mice showed increased heart weight, changes in red blood cell profiles and serum liver function parameters. Similarly, increased pulmonary inflammation, altered lung function, and emphysematous changes were observed only in CS-exposed mice. Histopathological changes in other respiratory tract organs were significantly lower in the THS 2.2 aerosol-exposed groups than in the CS-exposed group. Chronic exposure to THS 2.2 aerosol also did not increase the incidence or multiplicity of bronchioloalveolar adenomas or carcinomas relative to sham, whereas CS exposure did. Male THS 2.2 aerosol-exposed mice had a lower survival rate than sham mice, related to an increased incidence of urogenital issues that appears to be related to congenital factors rather than test item exposure. The totality of the evidence from this study further supports the risk reduction potential of THS 2.2 for lung diseases in comparison with cigarettes. The results from this study were shared previously with FDA as part of the MRTPA process. The in-life and post-mortem results of the study outlined above in (5) are provided. All exposed mice showed lower thymus and spleen weight, blood lymphocyte counts, and serum lipid concentrations than sham mice, most likely because of stress and/or nicotine effects. Unlike THS 2.2 aerosol-exposed mice, CS-exposed mice showed increased heart weight, changes in red blood cell profiles and serum liver function parameters. Similarly, increased pulmonary inflammation, altered lung function, and emphysematous changes were observed only in CS-exposed mice. Histopathological changes in other respiratory tract organs were significantly lower in the THS 2.2 aerosol-exposed groups than in the CS-exposed group. Chronic exposure to THS 2.2 aerosol also did not increase the incidence or multiplicity of bronchioloalveolar adenomas or carcinomas relative to sham, whereas CS exposure did. Male THS 2.2 aerosol-exposed mice had a lower survival rate than sham mice, related to an increased incidence of urogenital issues that appears to be related to congenital factors rather than test item exposure. The totality of the evidence from this study further supports the risk reduction potential of THS 2.2 for lung diseases in comparison with cigarettes. The results from this study were shared previously with FDA as part of the MRTPA process. The in-life

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and post-mortem results of the study outlined above in (5) are provided. All exposed mice showed lower thymus and spleen weight, blood lymphocyte counts, and serum lipid concentrations than sham mice, most likely because of stress and/or nicotine effects. Unlike THS 2.2 aerosol-exposed mice, CS-exposed mice showed increased heart weight, changes in red blood cell profiles and serum liver function parameters. Similarly, increased pulmonary inflammation, altered lung function, and emphysematous changes were observed only in CS-exposed mice. Histopathological changes in other respiratory tract organs were significantly lower in the THS 2.2 aerosol-exposed groups than in the CS-exposed group. Chronic exposure to THS 2.2 aerosol also did not increase the incidence or multiplicity of bronchioloalveolar adenomas or carcinomas relative to sham, whereas CS exposure did. Male THS 2.2 aerosol-exposed mice had a lower survival rate than sham mice, related to an increased incidence of urogenital issues that appears to be related to congenital factors rather than test item exposure. The totality of the evidence from this study further supports the risk reduction potential of THS 2.2 for lung diseases in comparison with cigarettes. The results from this study were shared previously with FDA as part of the MRTPA process. The in-life and post-mortem results of the study outlined above in (5) are provided. All exposed mice showed lower thymus and spleen weight, blood lymphocyte counts, and serum lipid concentrations than sham mice, most likely because of stress and/or nicotine effects. Unlike THS 2.2 aerosol-exposed mice, CS-exposed mice showed increased heart weight, changes in red blood cell profiles and serum liver function parameters. Similarly, increased pulmonary inflammation, altered lung function, and emphysematous changes were observed only in CS-exposed mice. Histopathological changes in other respiratory tract organs were significantly lower in the THS 2.2 aerosol-exposed groups than in the CS-exposed group. Chronic exposure to THS 2.2 aerosol also did not increase the incidence or multiplicity of bronchioloalveolar adenomas or carcinomas relative to sham, whereas CS exposure did. Male THS 2.2 aerosol-exposed mice had a lower survival rate than sham mice, related to an increased incidence of urogenital issues that appears to be related to congenital factors rather than test item exposure. The totality of the evidence from this study further supports the risk reduction potential of THS 2.2 for lung diseases in comparison with cigarettes. The results from this study were shared previously with FDA as part of the MRTPA process. The in-life and post-mortem results of the study outlined above in (5) are provided. All exposed mice showed lower thymus and spleen weight, blood lymphocyte counts, and serum lipid concentrations than sham mice, most likely because of stress and/or nicotine effects. Unlike THS 2.2 aerosol-exposed mice, CS-exposed mice showed increased heart weight, changes in red blood cell profiles and serum liver function parameters. Similarly, increased pulmonary inflammation, altered lung function, and emphysematous changes were observed only in CS-exposed mice. Histopathological changes in other respiratory tract organs were significantly lower in the THS 2.2 aerosol-exposed groups than in the CS-exposed group. Chronic exposure to THS 2.2 aerosol also did not increase the incidence or multiplicity of bronchioloalveolar adenomas or carcinomas relative to sham, whereas CS exposure did. Male THS 2.2 aerosol-exposed mice had a lower survival rate than sham mice, related to an increased incidence of urogenital issues that appears to be related to congenital factors rather than test item exposure. The totality of the evidence from this study

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further supports the risk reduction potential of THS 2.2 for lung diseases in comparison with cigarettes. The results from this study were shared previously with FDA as part of the MRTPA process. The in-life and post-mortem results of the study outlined above in (5) are provided. All exposed mice showed lower thymus and spleen weight, blood lymphocyte counts, and serum lipid concentrations than sham mice, most likely because of stress and/or nicotine effects. Unlike THS 2.2 aerosol-exposed mice, CS-exposed mice showed increased heart weight, changes in red blood cell profiles and serum liver function parameters. Similarly, increased pulmonary inflammation, altered lung function, and emphysematous changes were observed only in CS-exposed mice. Histopathological changes in other respiratory tract organs were significantly lower in the THS 2.2 aerosol-exposed groups than in the CS-exposed group. Chronic exposure to THS 2.2 aerosol also did not increase the incidence or multiplicity of bronchioloalveolar adenomas or carcinomas relative to sham, whereas CS exposure did. Male THS 2.2 aerosol-exposed mice had a lower survival rate than sham mice, related to an increased incidence of urogenital issues that appears to be related to congenital factors rather than test item exposure. The totality of the evidence from this study further supports the risk reduction potential of THS 2.2 for lung diseases in comparison with cigarettes. The results from this study were shared previously with FDA as part of the MRTPA process. The in-life and post-mortem results of the study outlined above in (5) are provided. All exposed mice showed lower thymus and spleen weight, blood lymphocyte counts, and serum lipid concentrations than sham mice, most likely because of stress and/or nicotine effects. Unlike THS 2.2 aerosol-exposed mice, CS-exposed mice showed increased heart weight, changes in red blood cell profiles and serum liver function parameters. Similarly, increased pulmonary inflammation, altered lung function, and emphysematous changes were observed only in CS-exposed mice. Histopathological changes in other respiratory tract organs were significantly lower in the THS 2.2 aerosol-exposed groups than in the CS-exposed group. Chronic exposure to THS 2.2 aerosol also did not increase the incidence or multiplicity of bronchioloalveolar adenomas or carcinomas relative to sham, whereas CS exposure did. Male THS 2.2 aerosol-exposed mice had a lower survival rate than sham mice, related to an increased incidence of urogenital issues that appears to be related to congenital factors rather than test item exposure. The totality of the evidence from this study further supports the risk reduction potential of THS 2.2 for lung diseases in comparison with cigarettes. The results from this study were shared previously with FDA as part of the MRTPA process. The in-life and post-mortem results of the study outlined above in (5) are provided. All exposed mice showed lower thymus and spleen weight, blood lymphocyte counts, and serum lipid concentrations than sham mice, most likely because of stress and/or nicotine effects. Unlike THS 2.2 aerosol-exposed mice, CS-exposed mice showed increased heart weight, changes in red blood cell profiles and serum liver function parameters. Similarly, increased pulmonary inflammation, altered lung function, and emphysematous changes were observed only in CS-exposed mice. Histopathological changes in other respiratory tract organs were significantly lower in the THS 2.2 aerosol-exposed groups than in the CS-exposed group. Chronic exposure to THS 2.2 aerosol also did not increase the incidence or multiplicity of bronchioloalveolar adenomas or carcinomas relative to sham, whereas CS exposure did. Male THS 2.2 aerosol-exposed mice had a lower

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survival rate than sham mice, related to an increased incidence of urogenital issues that appears to be related to congenital factors rather than test item exposure. The totality of the evidence from this study further supports the risk reduction potential of THS 2.2 for lung diseases in comparison with cigarettes. The results from this study were shared previously with FDA as part of the MRTPA process. The in-life and post-mortem results of the study outlined above in (5) are provided. All exposed mice showed lower thymus and spleen weight, blood lymphocyte counts, and serum lipid concentrations than sham mice, most likely because of stress and/or nicotine effects. Unlike THS 2.2 aerosol-exposed mice, CS-exposed mice showed increased heart weight, changes in red blood cell profiles and serum liver function parameters. Similarly, increased pulmonary inflammation, altered lung function, and emphysematous changes were observed only in CS-exposed mice. Histopathological changes in other respiratory tract organs were significantly lower in the THS 2.2 aerosol-exposed groups than in the CS-exposed group. Chronic exposure to THS 2.2 aerosol also did not increase the incidence or multiplicity of bronchioloalveolar adenomas or carcinomas relative to sham, whereas CS exposure did. Male THS 2.2 aerosol-exposed mice had a lower survival rate than sham mice, related to an increased incidence of urogenital issues that appears to be related to congenital factors rather than test item exposure. The totality of the evidence from this study further supports the risk reduction potential of THS 2.2 for lung diseases in comparison with cigarettes. The results from this study were shared previously with FDA as part of the MRTPA process. The in-life and post-mortem results of the study outlined above in (5) are provided. All exposed mice showed lower thymus and spleen weight, blood lymphocyte counts, and serum lipid concentrations than sham mice, most likely because of stress and/or nicotine effects. Unlike THS 2.2 aerosol-exposed mice, CS-exposed mice showed increased heart weight, changes in red blood cell profiles and serum liver function parameters. Similarly, increased pulmonary inflammation, altered lung function, and emphysematous changes were observed only in CS-exposed mice. Histopathological changes in other respiratory tract organs were significantly lower in the THS 2.2 aerosol-exposed groups than in the CS-exposed group. Chronic exposure to THS 2.2 aerosol also did not increase the incidence or multiplicity of bronchioloalveolar adenomas or carcinomas relative to sham, whereas CS exposure did. Male THS 2.2 aerosol-exposed mice had a lower survival rate than sham mice, related to an increased incidence of urogenital issues that appears to be related to congenital factors rather than test item exposure. The totality of the evidence from this study further supports the risk reduction potential of THS 2.2 for lung diseases in comparison with cigarettes. The results from this study were shared previously with FDA as part of the MRTPA process. The in-life and post-mortem results of the study outlined above in (5) are provided. All exposed mice showed lower thymus and spleen weight, blood lymphocyte counts, and serum lipid concentrations than sham mice, most likely because of stress and/or nicotine effects. Unlike THS 2.2 aerosol-exposed mice, CS-exposed mice showed increased heart weight, changes in red blood cell profiles and serum liver function parameters. Similarly, increased pulmonary inflammation, altered lung function, and emphysematous changes were observed only in CS-exposed mice. Histopathological changes in other respiratory tract organs were significantly lower in the THS 2.2 aerosol-exposed groups than in the CS-exposed group. Chronic exposure

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to THS 2.2 aerosol also did not increase the incidence or multiplicity of bronchioloalveolar adenomas or carcinomas relative to sham, whereas CS exposure did. Male THS 2.2 aerosol-exposed mice had a lower survival rate than sham mice, related to an increased incidence of urogenital issues that appears to be related to congenital factors rather than test item exposure. The totality of the evidence from this study further supports the risk reduction potential of THS 2.2 for lung diseases in comparison with cigarettes. The results from this study were shared previously with FDA as part of the MRTPA process. The in-life and post-mortem results of the study outlined above in (5) are provided. All exposed mice showed lower thymus and spleen weight, blood lymphocyte counts, and serum lipid concentrations than sham mice, most likely because of stress and/or nicotine effects. Unlike THS 2.2 aerosol-exposed mice, CS-exposed mice showed increased heart weight, changes in red blood cell profiles and serum liver function parameters. Similarly, increased pulmonary inflammation, altered lung function, and emphysematous changes were observed only in CS-exposed mice. Histopathological changes in other respiratory tract organs were significantly lower in the THS 2.2 aerosol-exposed groups than in the CS-exposed group. Chronic exposure to THS 2.2 aerosol also did not increase the incidence or multiplicity of bronchioloalveolar adenomas or carcinomas relative to sham, whereas CS exposure did. Male THS 2.2 aerosol-exposed mice had a lower survival rate than sham mice, related to an increased incidence of urogenital issues that appears to be related to congenital factors rather than test item exposure. The totality of the evidence from this study further supports the risk reduction potential of THS 2.2 for lung diseases in comparison with cigarettes. The results from this study were shared previously with FDA as part of the MRTPA process. The in-life and post-mortem results of the study outlined above in (5) are provided. All exposed mice showed lower thymus and spleen weight, blood lymphocyte counts, and serum lipid concentrations than sham mice, most likely because of stress and/or nicotine effects. Unlike THS 2.2 aerosol-exposed mice, CS-exposed mice showed increased heart weight, changes in red blood cell profiles and serum liver function parameters. Similarly, increased pulmonary inflammation, altered lung function, and emphysematous changes were observed only in CS-exposed mice. Histopathological changes in other respiratory tract organs were significantly lower in the THS 2.2 aerosol-exposed groups than in the CS-exposed group. Chronic exposure to THS 2.2 aerosol also did not increase the incidence or multiplicity of bronchioloalveolar adenomas or carcinomas relative to sham, whereas CS exposure did. Male THS 2.2 aerosol-exposed mice had a lower survival rate than sham mice, related to an increased incidence of urogenital issues that appears to be related to congenital factors rather than test item exposure. The totality of the evidence from this study further supports the risk reduction potential of THS 2.2 for lung diseases in comparison with cigarettes. The results from this study were shared previously with FDA as part of the MRTPA process. The in-life and post-mortem results of the study outlined above in (5) are provided. All exposed mice showed lower thymus and spleen weight, blood lymphocyte counts, and serum lipid concentrations than sham mice, most likely because of stress and/or nicotine effects. Unlike THS 2.2 aerosol-exposed mice, CS-exposed mice showed increased heart weight, changes in red blood cell profiles and serum liver function parameters. Similarly, increased pulmonary inflammation, altered lung function, and emphysematous changes were

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observed only in CS-exposed mice. Histopathological changes in other respiratory tract organs were significantly lower in the THS 2.2 aerosol-exposed groups than in the CS-exposed group. Chronic exposure to THS 2.2 aerosol also did not increase the incidence or multiplicity of bronchioloalveolar adenomas or carcinomas relative to sham, whereas CS exposure did. Male THS 2.2 aerosol-exposed mice had a lower survival rate than sham mice, related to an increased incidence of urogenital issues that appears to be related to congenital factors rather than test item exposure. The totality of the evidence from this study further supports the risk reduction potential of THS 2.2 for lung diseases in comparison with cigarettes. The results from this study were shared previously with FDA as part of the MRTPA process. The in-life and post-mortem results of the study outlined above in (5) are provided. All exposed mice showed lower thymus and spleen weight, blood lymphocyte counts, and serum lipid concentrations than sham mice, most likely because of stress and/or nicotine effects. Unlike THS 2.2 aerosol-exposed mice, CS-exposed mice showed increased heart weight, changes in red blood cell profiles and serum liver function parameters. Similarly, increased pulmonary inflammation, altered lung function, and emphysematous changes were observed only in CS-exposed mice. Histopathological changes in other respiratory tract organs were significantly lower in the THS 2.2 aerosol-exposed groups than in the CS-exposed group. Chronic exposure to THS 2.2 aerosol also did not increase the incidence or multiplicity of bronchioloalveolar adenomas or carcinomas relative to sham, whereas CS exposure did. Male THS 2.2 aerosol-exposed mice had a lower survival rate than sham mice, related to an increased incidence of urogenital issues that appears to be related to congenital factors rather than test item exposure. The totality of the evidence from this study further supports the risk reduction potential of THS 2.2 for lung diseases in comparison with cigarettes. The results from this study were shared previously with FDA as part of the MRTPA process. The in-life and post-mortem results of the study outlined above in (5) are provided. All exposed mice showed lower thymus and spleen weight, blood lymphocyte counts, and serum lipid concentrations than sham mice, most likely because of stress and/or nicotine effects. Unlike THS 2.2 aerosol-exposed mice, CS-exposed mice showed increased heart weight, changes in red blood cell profiles and serum liver function parameters. Similarly, increased pulmonary inflammation, altered lung function, and emphysematous changes were observed only in CS-exposed mice. Histopathological changes in other respiratory tract organs were significantly lower in the THS 2.2 aerosol-exposed groups than in the CS-exposed group. Chronic exposure to THS 2.2 aerosol also did not increase the incidence or multiplicity of bronchioloalveolar adenomas or carcinomas relative to sham, whereas CS exposure did. Male THS 2.2 aerosol-exposed mice had a lower survival rate than sham mice, related to an increased incidence of urogenital issues that appears to be related to congenital factors rather than test item exposure. The totality of the evidence from this study further supports the risk reduction potential of THS 2.2 for lung diseases in comparison with cigarettes. The results from this study were shared previously with FDA as part of the MRTPA process. The in-life and post-mortem results of the study outlined above in (5) are provided. All exposed mice showed lower thymus and spleen weight, blood lymphocyte counts, and serum lipid concentrations than sham mice, most likely because of stress and/or nicotine effects. Unlike THS 2.2 aerosol-exposed mice, CS-exposed mice showed

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spleen weight, blood lymphocyte counts, and serum lipid concentrations than sham mice, most likely because of stress and/or nicotine effects. Unlike THS 2.2 aerosol-exposed mice, CS-exposed mice showed increased heart weight, changes in red blood cell profiles and serum liver function parameters. Similarly, increased pulmonary inflammation, altered lung function, and emphysematous changes were observed only in CS-exposed mice. Histopathological changes in other respiratory tract organs were significantly lower in the THS 2.2 aerosol-exposed groups than in the CS-exposed group. Chronic exposure to THS 2.2 aerosol also did not increase the incidence or multiplicity of bronchioloalveolar adenomas or carcinomas relative to sham, whereas CS exposure did. Male THS 2.2 aerosol-exposed mice had a lower survival rate than sham mice, related to an increased incidence of urogenital issues that appears to be related to congenital factors rather than test item exposure. The totality of the evidence from this study further supports the risk reduction potential of THS 2.2 for lung diseases in comparison with cigarettes. The results from this study were shared previously with FDA as part of the MRTPA process.The in-life and post-mortem results of the study outlined above in (5) are provided. All exposed mice showed lower thymus and spleen weight, blood lymphocyte counts, and serum lipid concentrations than sham mice, most likely because of stress and/or nicotine effects. Unlike THS 2.2 aerosol-exposed mice, CS-exposed mice showed increased heart weight, changes in red blood cell profiles and serum liver function parameters. Similarly, increased pulmonary inflammation, altered lung function, and emphysematous changes were observed only in CS-exposed mice. Histopathological changes in other respiratory tract organs were significantly lower in the THS 2.2 aerosol-exposed groups than in the CS-exposed group. Chronic exposure to THS 2.2 aerosol also did not increase the incidence or multiplicity of bronchioloalveolar adenomas or carcinomas relative to sham, whereas CS exposure did. Male THS 2.2 aerosol-exposed mice had a lower survival rate than sham mice, related to an increased incidence of urogenital issues that appears to be related to congenital factors rather than test item exposure. The totality of the evidence from this study further supports the risk reduction potential of THS 2.2 for lung diseases in comparison with cigarettes. The results from this study were shared previously with FDA as part of the MRTPA process.

(7) Lavrynenko O, Titz B, Dijon S, et al. Ceramide ratios are affected by cigarette smoke but not heat-not-burn or e-vapor aerosols across four independent mouse studies, Life Sciences, 2020, 263: 118753.

Smoking is an important risk factor for the development of chronic obstructive pulmonary disease and cardiovascular diseases. This study aimed to further elucidate the role of ceramides, as a key lipid class dysregulated in disease states. Main methods: developed and validated LC–MS/MS method for ceramides (Cer(d18:1/16:0), Cer(d18:1/18:0), Cer(d18:1/24:0) and Cer(d18:1/24:1(15Z)) for the absolute quantification. This was deployed together with proteomics and transcriptomic analysis to assess the effects of cigarette smoke (CS) from the reference cigarette as well as aerosols from heat-not-burn (HnB) tobacco and e-vapor products in apolipoprotein E-deficient (ApoE−/−) mice over several time points. In the lungs, CS exposure substantially elevated the ratios of Cer(d18:1/24:0) and Cer(d18:1/24:1) to Cer(d18:1/18:0) in two independent ApoE−/− mouse inhalation studies. Data from previous

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studies, in both ApoE−/− and wild-type mice, further confirmed the reproducibility of this finding. Elevation of these ceramide ratios was also observed in plasma/serum, the liver, and—for the Cer(d18:1/24:1(15Z)) to Cer(d18:1/18:0) ratio—the abdominal aorta. Also, the levels of acid ceramidase (Asah1) and glucocerebrosidase (Gba)—lysosomal enzymes involved in the hydrolysis of glucosylceramides—were consistently elevated in the lungs after CS exposure. In contrast, exposure to HnB tobacco product and e-vapor aerosols did not induce significant changes in the ceramide profiles or associated enzymes. This work in mice contributes to the accumulating evidence on the importance of ceramide ratios as biologically relevant markers for respiratory disorders, adding to their already demonstrated role in cardiovascular disease risk assessment in humans.

#### 2.2.1.3 Clinical

(8) de La Bourdonaye G, Costanzo R, Haziza C. Tobacco harm reduction: The potential to reduce the risk from smoking: a six-month exposure response study on switching from cigarettes to tobacco heating system (THS), Medicinska reč, 2020, 1(1): 45-48.

The primary goal of the Exposure Response Study (ERS) was to generate direct evidence that actual use of THS2.2, can reduce smokers' risk of harm compared to continuing to smoke cigarettes. In the study eight biomarkers of potential harm (BoPH) were measured, to provide further evidence on effects of current adult smokers switching to THS. These biomarkers were selected because they are associated with smoking-related diseases, are negatively impacted by smoking and are reversible following smoking cessation. The eight BoPH were included and tested as co-primary endpoints as they cover eight different pathways of disease. In total 984 smokers were randomized to either switch to THS use, or continue to smoke cigarettes. The eight BoPH were assessed over a period of six months in an ambulatory setting. The results showed that when smokers switched to THS, all eight BoPH showed a changes similar to what is reported in the literature following smoking cessation, and five of the eight BoPH were statistically significantly better in smokers who switched to THS than smokers who continued to smoke cigarettes. This led to the conclusion that switching from cigarettes to THS-use likely reduces a smoker's risk of tobacco-related disease and may present less risk of harm compared to continued smoking. The results from this study were shared previously with FDA as part of the MRTPA process.

(9) van der Plas A, Pouly S, Blanc N, et al. Impact of switching to a heat-not-burn tobacco product on CYP1A2 activity, Toxicology Reports, 2020, 7: 1480-1486.

Cigarette smoking induces cytochrome P450 1A2 (CYP1A2) expression and activity, while smoking cessation normalizes the levels of this enzyme. The aim of this publication is to summarize the data on CYP1A2 gene expression and activity in preclinical and clinical studies

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on the THS, currently marketed as *IQOS* with *HEETS*[10], and to summarize the potential effects on CYP1A2 to be expected upon switching to reduced-risk products (RRPs). A summary was prepared of PMI's preclinical and clinical data on the effects of switching from cigarette smoking to THS.

Data from four preclinical mouse and rat studies showed that, upon either cessation of cigarette smoke exposure or switching to THS exposure, the upregulation of CYP1A2 observed with exposure to cigarette smoke reverted close to fresh-air levels. Data from four clinical studies yielded similar results on CYP1A2 activity within a time frame of five days. Furthermore, the effects of switching to THS were similar to those seen after smoking cessation. The authors conclude that because smoking cessation and switching to either electronic cigarettes or THS seem to have similar effects on CYP1A2 activity, the same measures taken for patients treated with narrow therapeutic index drugs that are metabolized by CYP1A2 and who quit smoking should be recommended for those switching to RRPs.

### *2.2.2 PMI sponsored publications and publications from other tobacco companies*

#### 2.2.2.1 Aerosol Chemistry and Physics

(1) Hirn C, Kanemaru Y, Stedeford T, et al. Comparative and cumulative quantitative risk assessments on a novel heated tobacco product versus the 3R4F reference cigarette, Toxicol Rep, 2020, 7: 1502-1513.

The aim of the study was to further investigate the potential reduction in toxicology risk associated with the use of HTP when compared to cigarettes by applying Quantitative Risk Assessment (QRA) principles.

Japan Tobacco Inc. has developed a novel HTP that eliminates combustion through indirectly heating a tobacco blend (commercialized with the name *Ploom* Tech). The product uses a hybrid technology to create a tobacco-enriched aerosol, by heating a non-nicotine containing liquid, which passes through a capsule containing granulated tobacco. In doing so, the tobacco is heated at around 30°C and no combustion occurs throughout the process. Their published research showed that biologically active smoke constituents are substantially reduced in the aerosol generated from the HTP compared to a reference cigarette and that the aerosol displayed reduced genotoxic or cytotoxic response in *in vitro* assays.

The authors used a QRA approach to compare non-cancer and cancer risk estimates for emissions generated by an HTP with smoke from a reference cigarette (3R4F). Fifty-four analytes were evaluated from the HTP aerosol and the 3R4F cigarette smoke. Emissions were generated using the ISO and the Health Canada Intense smoking regimes. The measured values were extrapolated to define a conservative exposure assumption for per day use and lifetime

[10] In countries outside the U.S. *HeatSticks* are sold under the brand name *HEETS*.

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use based on an estimated maximum usage level of 400 puffs per day *i.e.*, approximately 8 HTP tobacco capsules or 40 combustible cigarettes. Non-cancer and cancer risk estimates were calculated using these exposure assumptions for individual and per health outcome domains based on toxicological reference values derived by regulatory and/or public health agencies. The results of this assessment showed a reduction of non-cancer and cancer risk estimates by more than 90 % for the HTP versus the 3R4F cigarette, regardless of the smoking regime.

As stated by the authors "Though the above results are suggestive of a considerable (over 90 %) reduction in non-cancer and cancer risks between the HTP and the 3R4F reference cigarette, these findings are theoretical and not based on empirical data for control and exposed populations. In comparison, the causal link between combustible cigarettes and adverse health outcomes, including cancer is well established through human data. It is unclear how much of a reduction in the levels of HPHCs generated by a non-combustible tobacco product would translate to a reduction in adverse health outcomes, including cancer."

The results presented complement the results from Slob et al 2020[11] and Rodrigo et al 2020[12] providing orthogonal assessments of reduced formation and reduced exposure from HTPs compared with cigarettes leading to the likelihood of reduced morbidity and mortality for smokers that do not quit tobacco/nicotine use completely but switch to using HTPs.

As noted by Warner[13] "Given the multiple types of alternative nicotine delivery products, and those to come, and multiple patterns of use, scientists likely will be unable to develop a precise estimate of risk reduction for decades, if ever."

#### 2.2.2.2 Behavioral

(2) Adamson J, Kanitscheider C, Prasad K, et al. Results from a 2018 cross-sectional survey in Tokyo, Osaka and Sendai to assess tobacco and nicotine product usage after the introduction of heated tobacco products (HTPs) in Japan, Harm Reduct J, 2020, 17(1): 32.

The aim of this pilot study was to examine the current use of combustible tobacco products and HTPs in three cities in Japan and to examine changes in usage over 12 months.

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[11] Slob W, Soeteman-Hernandez LG, et al. A Method for Comparing the Impact on Carcinogenicity of Tobacco Products: A Case Study on Heated Tobacco Versus Cigarettes. Risk Anal, 2020, 40(7): 1355-1366. DOI: 10.1111/risa.13482

[12] Rodrigo G, Jaccard G, et al. Cancer potencies and margin of exposure used for comparative risk assessment of heated tobacco products and electronic cigarettes aerosols with cigarette smoke. Archives of toxicology, 2021, 95(1): 283-298. DOI: 10.1007/s00204-020-02924-x

[13] Warner KE. How to think-not feel- about tobacco harm reduction. Nicotine & Tobacco Research, 2019, 21(10): 1299-1309. DOI: 10.1093/ntr/nty084

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The study was a cross-sectional epidemiological survey administered in Sendai, Tokyo and Osaka, Japan, from May 19th to June 25th, 2018. Participants were selected with a three-stage probability random sampling process that first identified primary sampling units, then households and finally individuals. Eligible participants were aged at least 20 years who were willing to participate after information about the study was provided. People younger than 20 years and those living in institutions were excluded. Questionnaires were paper based and administered door to door.

For combustible tobacco products and HTPs, additional information was requested on duration and frequency of product use, amount consumed, flavor preferences, tar level (cigarettes), quit attempts and use at '12 months before' and at the time of the survey. Current and former tobacco users were asked about awareness of the foremost brands of HTP available in the study areas at that time: *IQOS*, *glo* and *Ploom* Tech.

Results for HTP use from the 779 participants who were current tobacco product users, 81% had heard of *IQOS*, 55% of *glo* and 45% of *Ploom* Tech. Half (51%) had tried HTPs at least once. Of the 254 respondents who identified themselves as HTP users, most were users of *IQOS* (67%), followed by *glo* (18%) and *Ploom* Tech (16%), and most used them daily (*IQOS* 85%; *glo* 72%; *Ploom* Tech 52%). The proportion of current daily *IQOS* users was similar for men and women (69% and 67%, respectively), for *glo* use it was higher for women (86%) than for men (66%) and for *Ploom* Tech use was higher for men (19%) than for women (9%).

Daily *IQOS* users consumed on average 15 sticks per day, glo users 13 sticks per day and *Ploom* Tech users 3 tobacco capsules per day (equivalent to 12 – 18 conventional cigarettes). Amongst all current HTP users, the preferred flavor was menthol (62%), followed by regular (35%) and other flavors (3%). Females showed a slightly higher preference for menthol than males (68% versus 60%).

When asked about reasons of HTP use, most HTP users selected 'reduced harm to people around them and themselves compared with conventional cigarettes'. Only around 10% indicated use to cut back smoking cigarettes or to quit overall smoking.

Assessment of pattern of usage amongst current tobacco users at the time of the survey indicated, sole use of manufactured or roll-your-own cigarettes was reported by 70% and sole use of HTP by 16%. Rates in men and women were similar for sole use of manufactured or roll-your-own cigarettes (68% and 71%, respectively), but more women than men used HTPs (21% versus 15%). Sole use of HTPs was highest in the age groups 25 – 29 years (23%) and 30 – 39 years (28%). Dual (15%). Sole use of HTPs was highest in the age groups 25 – 29 years (23%) and 30 – 39 years (28%). Dual use of manufactured or roll-your-own cigarettes and HTPs was reported by 11% of participants at the time of the survey and was more common in males (12%) than females (8%).

Usage data for tobacco products at the time of the survey and 12 months previously were available for 791 participants. Twelve percent of current combustible tobacco product users 12 months ago reported having started to use HTPs within the previous 12 months. The

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initiation of HTP use was higher for females than males and in the three age groups between 25 and 49 years, than in the 20 – 24-year age groups and ≥ 50-year age groups. The initiation rate per HTP was greatest for *IQOS* (8%), followed by *glo* (3%) and *Ploom* Tech (3%), with some participants using multiple HTPs.

Amongst sole users of combustible tobacco products 12 months before the survey, 5% had switched to exclusive HTP use. A complete switch was observed from more women than men (7% versus 4%). The highest switching rate was observed in the age group 25 – 29 years (8%). Seven percent of sole combustible tobacco users 12 months before the survey had switched to dual use with HTPs. Switching to dual use was slightly more frequent amongst males (7%) than in females (6%) and was most common in the 25 – 49-year age groups. Within the previous 12 months, 5% of sole combustible tobacco product users had quit their use of tobacco products completely. Most (94%) participants using only HTPs 12 months before the survey continued to do so. Four percent had quit tobacco use completely.

Over two-thirds of dual users 12 months before the survey had maintained this behavior at the time of the survey (67%), 14% switched to using only HTPs and 4% quit tobacco use completely. However, 12% of dual users switched back to solely using combustible tobacco products. Stratified by sex, 72% of male dual users were still dual users after 12 months, 7% switched to HTPs alone and 15% switched back to using only combustible tobacco products. For female dual users, the percentages were 50%, 40% and 0%, respectively.

Amongst never users of combustible tobacco products 12 months before the survey, 0.1% had started using HTPs and 0.2% had started using combustible tobacco products by the time of the survey. For former tobacco users 12 months before the survey, 1% re-initiated the use of a tobacco product, but all with HTPs. This rate was higher in females (4%) than in males (0.6%).

Amongst HTP users 12 months ago, 10 users reported having never used any combustible tobacco products. Amongst these, none had switched to sole or dual use of any combustible tobacco product at the time of the survey. In addition, no participants who were former sole combustible tobacco product users but had switched completely to HTPs 12 months before the interview reported reverting to cigarette smoking, alone or as dual use, at the time of the interview.

The authors recognized some weaknesses of the research mainly linked to inherent limitations of this type of survey and also some strengths from the methodology applied. They concluded "*HTPs seem to be accepted as an alternative tobacco product amongst combustible tobacco users. Given complex findings for dual use, improved understanding of the motivations underlying this behavior would be of interest.*"

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### *2.2.3 Independent publications*

#### 2.2.3.1 Aerosol Chemistry and Physics

(1) Ilies BD, Moosakutty SP, Kharbatia NM, et al. Identification of volatile constituents released from *IQOS* heat-not-burn tobacco *HeatSticks* using a direct sampling method. Tobacco Control, 2020, 0: 1-7.

The stated aim of the study was to identify the chemicals released in *IQOS* aerosol and to assess their potential human health toxicity. *IQOS* (v3.0) and *HeatSticks* purchased in Romania using 2 systems, and 3 packs of the 6 different *IQOS HeatSticks* variants available in the market (Amber, Blue, Bronze, Sienna, Turquoise and Yellow).

The in-use thermal temperature profile of the *IQOS* device was captured using a thermographic VarioCam HD head 640G camera. The thermographic camera was used to monitor the temperature of the heating blade with the cover of the *IQOS* holder removed.

The ISO standard puffing regime (35 mL for 2 seconds) was used to generate aerosol from *IQOS*. Each of the 6 variants were tested in triplicate, with a blank before starting the analysis of each set. Compounds found in the aerosol using a direct sampling method were identified by comparing their mass spectra with that found in the U.S. National Institute of Standards and Technology (NIST) #11 mass spectrometry database library. Chemicals with ≥ 70% probability were listed as identifiable.

The results confirmed that the temperature of the heating blade reached 300 °C after approximately 30 seconds. The temperature reached a maximum value of 320 °C after 40s and then plateaued around 285 °C.

A total of 62 volatile compounds were identified across the 6 different *HeatSticks* variants using a real-time gas chromatography–mass spectrometry (GC-MS) set up.

Four compounds were identified that were claimed to present high health risks:

- Furans (including hydroxymethylfurfural) – hypothesized to arise from the "decomposition of the sugar-made cigarette filter" (*i.e.*, polylactic acid [PLA] filter).
- Phthalates such as DEHP (di–ethylhexyl phthalate - a plasticizer)
- Diacetyl
- 2,3-pentanedione

The authors concluded that the temperature profile of the heating blade indicates a non-combustible process is used to generate the *IQOS* aerosol.

62 volatile compounds were identified across the 6 different *HeatSticks* variants, that were considered by the authors to complement the results of the targeted assessment studies

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conducted by PMI (Schaller et al 2016[14]) looking at compounds known to be found in cigarette smoke.

The authors commented that employing highly sensitive mass spectrometers in future studies would "*identify more compounds that may exhibit high toxicity for human health and thereby help to improve the tobacco regulatory system*".

The final statement made by the authors is that "*quantitative measurements of these studies are relevant for determining the toxicity of the IQOS tobacco sticks.*"

Comments on the study

The authors did not make the distinction between a targeted analytical assessment of tobacco product aerosol constituents (*i.e.*, the analytical detection and quantification of compounds identified by regulatory authorities to be harmful and potentially harmful compounds (HPHCs) found in cigarette smoke) from that of a non-targeted analysis. In the latter case an aerosol is screened using a combination of analytical techniques to identify as many compounds as possible in the aerosol chemical space (and subsequently to quantify compounds of potential toxicological concern). The authors did not refer to the non-targeted analysis that was submitted to FDA in support of *IQOS* and published in a peer-reviewed journal by Bentley et al. 2020[15], where a total of 529 chemical constituents were identified (excluding water, glycerin, and nicotine), as present in the mainstream aerosol of *IQOS*. A suite of untargeted methods were used to characterize 99.7% of the total aerosol mass (at ≥ 100 ng/stick). The results demonstrated a 95% reduction in the average levels of HPHCs compared with reference cigarette (3R4F) smoke and 7X fewer chemicals in the aerosol than in cigarette smoke.

Compared to the reference cigarette, 3 unique chemicals were identified in *IQOS* aerosol. Following an assessment of the potential toxicity of these compounds, PMI determined that they were either not of toxicological concern, or that the exposure was below the level of toxicological concern.

26 of the 62 compounds reported in the Ilies (2020) paper, were not identified in PMIs untargeted assessment (Bentley 2020).

These differences may be explained by:

- Ilies et al., analyzed 6 different HeatStick variants, whereas Bentley analyzed a non-mentholated regular variant.

[14] Schaller JP, et al. Evaluation of the Tobacco Heating System 2.2. Part 2: Chemical composition, genotoxicity, cytotoxicity and physical properties of the aerosol. Reg. Pharm.Tox., 2016, 81: S27-S47

[15] Bentley MC, et al. Comprehensive chemical characterization of the aerosol generated by a heated tobacco product by untargeted screening. Analytical and Bioanalytical Chemistry, 2020, 412: 2675-2685. https://doi.org/10.1007/S00216-020-02502-1

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- The methodology used by Ilies et al. was not capable of definitively identifying the 62 compounds listed in the paper. The identities were proposals based upon a comparison of the mass spectra data with a mass spectral database (US National Institute of Standards and Technology (NIST) 11 database), without positive confirmation of the compounds using reference standards. Additionally, the database (version 11) has already been superseded by versions 14, 17 and now 20.
- Differences in the identification methods could lead to discrepancies in the identities of compounds. To truly identify each chromatographic peak, it is necessary to compare the spectral data to a database of compounds to propose a chemical name and determine a semi-quantified concentration, but this needs to be followed by a quantitative assessment using reference compounds to confirm the identity, especially for chemicals of toxicological concern.

*IQOS* aerosol contains some compounds of toxicological concern and is therefore not risk free. However, making definitive statements such as "…compounds present in *IQOS* aerosol are highly toxic" creates a misleading impression of the results of this study, particularly when:

- The compounds are neither definitively identified nor, very importantly, quantified.
- The results are not compared to those found for the appropriate comparator (cigarette smoke).
- A toxicological risk assessment of exposure to the compounds has not been performed for the compounds that are unique or more abundant in *IQOS* aerosol, was not performed by the authors.

In the Discussion, the authors state that glycerol accounts for 50% of the aerosol mass, this is incorrect (see Bentley et al., 2020). Glycidol, a breakdown product of glycerol was detected at very low levels in *IQOS* aerosol and the amounts present have been determined to not be of toxicological concern. These data have been reported to US FDA and other regulators.

Acrolein was also identified by the authors and described as a highly carcinogenic compound, linked to the presence of glycerol. Schaller (2016)[14] data confirm that acrolein is present in *IQOS* aerosol, but at a level approximately 95% lower than that observed in cigarette smoke (3R4F). In the U.S., the Department of Health and Human Services has not classified acrolein as to its carcinogenicity. And the International Agency for Research on Cancer (IARC) has determined that acrolein is not classifiable as to carcinogenicity in humans (Group 3).

In reference to the furans – the authors refer to thermal degradation of the "sugar-made e-cigarette filter" possibly leading to the formation of furans. It is not clear from this statement, what the authors are referring to, as *IQOS* is not an e-cigarette. And although this may be a simple confusion, it is further compounded when the authors state that the "degradation of sugar-made filters is highly influenced by the e-cigarette coil and maximum temperature obtained."

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In summary, whilst the study reported by Ilies et al. (2020) is an important effort to identify additional compounds in *IQOS* aerosol, there are a number of fundamental errors that render the authors conclusions unsupportable, particularly when taking account of other state-of-the-art analytical studies performed by experts in aerosol and tobacco product assessment.

The journal editors for this paper have also published an 'Expression of Concern' in relation to this paper[16]. *"The paper, 'Identification of volatile constituents released from IQOS heat-not-burn tobacco HeatSticks using a direct sampling method' was published in Tobacco Control in May 2020 after undergoing peer review. After a Rapid Response was received calling attention to questionable citations in the Introduction which did not support the statements being made, the authors were invited to respond with corrections. We have posted this Expression of Concern until the authors revise the section and the paper undergoes additional peer review."*

(2) Kim YH, An YJ and Shin JW. Carbonyl Compounds Containing Formaldehyde Produced from the Heated Mouthpiece of Tobacco Sticks for Heated Tobacco Products, Molecules, 2020, 25(23), 5612.

The aim of the study was to identify if harmful compounds are emitted from heated tobacco products when non-tobacco components of such products are heated.

The authors compared emission of carbonyl compounds from 3 different types of HTPs (unidentified, and referred to as HTP-1; HTP-2 and HTP-3) when the consumable was inserted into the heating device under different conditions:

A – Tobacco heatstick without tobacco

B – Tobacco consumable without tobacco + parts of the mouthpiece

C – Tobacco consumable

Only condition C replicates the intended use of the tobacco heatstick. In condition B, the remaining parts of the heatstick were pushed down into the heating device so that parts of the filter system were heated directly by the device heater. In condition A, the tobacco heatstick, with the tobacco component removed, was positioned as intended in the device with no tobacco surrounding the heating element. So, in this latter condition, the filter elements would also be exposed to temperatures that do not replicate the intended product use. The authors concluded that "*Although the method for the generation of the mouthpiece aerosols is not the conventional one and may have led to a different energy absorption during heating, these results show that more formaldehyde can be generated by heating the filter than by heating the tobacco. Similar to formaldehyde, acrolein was also generated by the partial heating of HTP stick filters. In*

[16] Tob Control, 2020, 0:1. DOI: 10.1136/tobaccocontrol-2019-055521

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*addition, acetaldehyde and proprionaldehyde were detected in the HTP aerosol generated by the partial heating of HTP stick filters*."

When the carbonyl results for the aerosol generated under condition C were compared by the authors with results published in the literature, the carbonyl levels generated by Kim et al. were lower than the published results (partially because the aerosol collection was done for 6 puffs whereas the literature results were from a collection of typically 12 puffs). All values were substantially lower than the carbonyl levels present in cigarette smoke.

It is important to note that during product development at PMI all parts of the EHTP are tested separately for release of volatile materials that could be of toxicological concern at temperatures that are representative of 'in use' conditions.

(3) Bitzer ZT, et al. Free Radical Production and Characterization of Heat-Not-Burn Cigarettes in Comparison to Conventional and Electronic Cigarettes. Chem. Res. Toxicol., 2020, 33(7): 1882-1887.

The aim of the study was to measure and partially characterize the production of free radicals in HTP aerosols from *IQOS* and *Glo*, the hybrid product *Ploom* and 3 e-cigarettes (*JUUL*, a modifiable Wismec Reuleaux RX200S e-cigarette (used in constant temperature mode) and the U.S. National Institute on Drug Abuse standardized research e-cigarette (SERC)) and compared to the 1R6F reference cigarette. The puff profile chosen was based on the CORESTA method with modifications (increased volume and shortened puff duration) made in order to achieve an adequate flow rate to activate all devices tested.[17] The number of puffs in a puffing sessions for HTPs were determined when the device turned off based on the manufacturer's parameters which resulted in 7 puffs for the Glo and 12 puffs for the *IQOS*. In the case of the *Ploom*, *JUUL*, SREC, and the Mod e-cig, 10 puffs were chosen to represent a session. A session for the 1R6F was determined to be 1 cigarette or roughly 11 puffs.

Aerosol particulate phase radicals were captured using a Cambridge Filter Pad (CFP) and analyzed using electromagnetic paramagnetic resonance (EPR) spectroscopy. Gas phase radicals that passed through the CFP were captured in an impinger containing a nitrone spin trap and measured using EPR spectroscopy.

The results demonstrated that the1R6F cigarette produced the most gas-phase radicals, 12-fold more than any of the other products tested. Results for the HTPs were similar to each other (less than for the two e-cigarettes tested but greater than *JUUL*).

The authors concluded that these new alternative nicotine delivery devices greatly reduce a user's exposure to highly reactive free radicals (compared to cigarettes), though exposure levels are still much higher than those obtained from other environmental sources. Particulate-

[17] CORESTA. Routine Analytical Machine for E-Cigarette Aerosol Generation and Collection -Definitions and Standard Conditions. 2015; https://www.coresta.org/routine-analyticalmachinee-cigarette-aerosol-generation-and-collection-definitions-and-standard.

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phase radicals were detected only for conventional cigarettes. Gas-phase free radicals were detected in smoke/aerosol from all products with levels for HTP being similar to e-cigs and hybrid devices but 50-fold lower than conventional cigarettes (1R6F reference cigarette). Gas phase radicals differed in polarity with HTP products and conventional cigarettes producing more polar radicals compared to those produced from e-cigs.

(4) Slob W, Soeteman-Hernandez LG, Bil W, et al. A Method for Comparing the Impact on Carcinogenicity of Tobacco Products: A Case Study on Heated Tobacco Versus Cigarettes, Risk Anal, 2020, 40(7): 1355-1366.

The aim of the study was to compare the harmful health effects related to two different tobacco products using a method that considers the change in cumulative exposure (CCE) of the compounds emitted by the two products (as opposed to applying common risk assessment methods to each individual compound).

Scientists from the Dutch RIVM (National Institute for Public Health and the Environment) illustrated how the method could work in a practical analysis, by applying the method to *IQOS* using the data on 8 carcinogens that are common to both *IQOS* aerosol and cigarette smoke, and for which emission and cancer dose-response data were available for both.

The CCE was estimated to be 10- to 25-fold lower when using HTPs instead of cigarettes. Such a change indicates a substantially smaller reduction in expected life span, based on available dose-response information in smokers. However, this is a preliminary conclusion, as only eight carcinogens were considered so far. Furthermore, an unfavourable health impact related to HTPs remains as compared to complete abstinence. The authors commented "*Our analysis is based on only eight carcinogenic smoke components, while many more carcinogens are present in smoke. However, if it were assumed that these eight compounds are a representative sample of all carcinogens occurring in smoke, then increasing the number of compounds in the analysis will make the estimate of the CCE more reliable, but most likely not dramatically different. Nonetheless, it would be better to include more carcinogens in the analysis when the data are available*."

PMI recently published an approach (Rodrigo et al., 2020[18]) combining margin of exposure (MOE) and cancer potency values with the goal of quantifying cancer and non-cancer risks associated with exposure to HPHCs from a range of commercial HTPs and electronic cigarettes (ECs). These were compared with those from reference and commercial cigarettes on the basis of available compound specific toxicological threshold references from official regulatory agencies. The PMI authors concluded "*that mean lifetime cancer risk values were decreased by more than one order of magnitude when comparing HTPs and commercial cigarettes, and significantly higher margin of exposure for non-cancer risk was observed for HTPs when*

[18] Rodrigo G, et al. Cancer potencies and margin of exposure used for comparative risk assessment of heated tobacco products and electronic cigarettes aerosols with cigarette smoke. Arch. Toxicol., 2020, 95: 283-298. https://doi.org/10.1007/s00204-020-02924-x

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*compared to commercial cigarettes. The same approach was applied to two commercial ECs. Similar results were also found for this category of products.*"

(5) Protano C, Manigrasso M, Cammalleri V, et al. Impact of Electronic Alternatives to Tobacco Cigarettes on Indoor Air Particular Matter Levels. Int J Environ Res Public Health, 2020,17(8): 2947.

The study reported by Protano et al., was designed to evaluate the levels of different fractions of particulate matter ($PM_1$, $PM_{2.5}$, $PM_4$, and $PM_{10}$) emitted into indoor air during the use of the different variants of *IQOS*, *JUUL* and *Glo* when compared to cigarettes.

This was an open label study where the order of product use was randomized based on a 2 block set of 15 sessions (30 sessions total). Each session consisted of 3 consecutive experiments of the same product combination, with each of the 3 volunteers participating in the sessions, meaning in total there were 6 tests for each combination (3 tests/session of the 2 block set). The products used included the variants of *IQOS* Heatsticks (Amber; Blue; Bronze; Sienna; Turquoise and Yellow label), *JUUL* and *Glo* that were available on the Italian market and *Marlboro* Gold was included as the comparator cigarette.

Particulate matter concentrations for $PM_{10}$, $PM_4$, $PM_{2.5}$, and $PM_1$ were measured from 5 minutes before until 1 hour after each session, with a 3-second time resolution, using a laser-operated aerosol mass analyzer placed 1.5 m above the floor level and 1.5 m from the volunteer.

Each session used a fixed product use regimen of 12 puffs over about 5.5 minutes (1 puff/30 seconds) to mimic the typical smoking of a cigarette (defined as 10-12 puffs over 5-6 minutes).

The study was conducted in a test room (52.7 $m^3$) with controlled temperature (20-23 °C) and relative humidity (36-40%). The air exchange rate (measured using $CO_2$ tracer gas technique) was 0.69 changes/hour (this is comparable to the residential airflows used in the PMI studies ranging from 0.5 to 1.2 changes/hour). The window and door to the room were closed during the experiments but opened after each experiment to reset the room conditions to the initial levels of particulate matter.

Statistical analysis was performed on the concentrations of $PM_1$ as this fraction represented >95% of the total particulate matter emitted. The particulate matter data was skewed as the monitoring device detected peaks and troughs as the aerosols (smoke for cigarettes) were exhaled, therefore, the median rather than arithmetic mean was used for the comparisons. The mean and standard deviations were reported, but only to show the high variability of the data within and between products and product combinations.

The results indicated that during product use sessions, the concentration of $PM_1$ increased compared to before the session. This increase was statistically significant for all experiments. Cigarettes produced the highest concentrations of $PM_1$ (median = 3430.0 $\mu g/m^3$). There was

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high variability of particle emissions between different products and within the same product with the different variants of sticks/pods.

- 6 variants of *IQOS* range: 11.0 (Bronze) - 337.5 (Sienna) $\mu g/m^3$
- 4 variants of *Glo* range: 13.0 (Beryl) - 66.0 (Aegean) $\mu g/m^3$
- 4 variants of *JUUL* range: 11.0 (Mango) - 110.0 (Golden Tobacco) $\mu g/m^3$

The authors stated that particulate matter concentrations were up to 100X higher for electronic devices and > 1000X higher for cigarettes than WHO guideline for the daily exposure of general population to outdoor air ($PM_{10}$ = 50 $\mu g/m^3$ and $PM_{2.5}$ = 25 $\mu g/m^3$).

The authors concluded that although cigarettes had the greatest impact on indoor air quality, all the alternative products impacted the indoor air quality with transient increases in $PM_1$ as puffs are taken and exhaled. The authors call for legislative measures to regulate the use of these devices in public indoor environments. They also propose educational interventions to increase the perception of risks of indoor use for active and passive smokers.

Discussion:

This study demonstrates that the aerosol from smoke-free products is fundamentally different from cigarette smoke in concentrations and persistence of the particulate matter. As noted by the authors *"- for a complete evaluation of the environmental risk related to electronic alternatives to tobacco cigarettes (EATC) emissions, the chemical and size distribution aerosol characteristics, together with the relevant aerosol respiratory dosimetry of the passively exposed subjects will have to be carried out."* Therefore, the conclusions drawn by the authors need to be considered bearing in mind the need for further evaluation.

Cigarette smoke is comprised of a mixture of solid particles and liquid droplets that contains many HPHCs. The HTP and e-cigarette aerosols, are fundamentally different than cigarette smoke because these products do not burn the tobacco, and therefore substantially reduce the levels of emitted HPHCs while eliminating the solid particles generated by combustion

The analyzer used in this study to measure particulate matter was placed approximately 1.5 m from the person, this resulted in concentrations peaks that were detectable on exhalation but that dissipated very quickly, returning to background between puffs.

In the absence of indoor air quality guidelines the authors compared the results of the transient levels of particulate matter with guideline of unspecified particulate matter outdoors. Although, this may be a good starting point, it is not specific and does not consider the differences in the composition of the particulate matter that drove the guidelines. Other peer reviewed studies have tested and confirmed that unlike cigarette smoke, *IQOS* aerosol dissipates quickly in the atmosphere and does not linger in the air.

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The data reported by Protano et al., are not consistent with the published results from Ruprecht et al., 2017[19] where they reported a mean indoor $PM_1$ concentration of 1.4 µg/m$^3$ for *IQOS* use compared to 151 µg/m$^3$ for cigarettes.

In our own laboratories Mitova et al., 2019[20], studied the impact of *IQOS* use on indoor air quality was assessed under controlled experimental conditions using ventilation representative of residential buildings (0.5 changes/hour). Smoking of cigarettes (*Marlboro* Gold) under the same conditions was used as positive control. When *IQOS* was used indoors (2 panelists, 120 minute session, 12 sticks, 3 replicates), of the 24 constituents measured, only nicotine, acetaldehyde and glycerin were found to be above the level of background. The concentrations of these constituents were significantly below the levels defined as harmful in the air quality guidelines.

For particulate matter, measured with a laser-operated aerosol mass analyzer positioned at 1.2 m from the 2 panelists (we have not assessed the influence of the distance to the emission source). During the *IQOS* session, a flat line trace during the session with the mean for $PM_1$ and $PM_{2.5}$ below the limit of quantification (11 µg/m$^3$) was observed. In contrast, during the cigarette session, we observed a progressively increasing saw-tooth like trace during the session, with the mean $PM_1$ = 687 µg/m$^3$ and $PM_{2.5}$ = 688 µg/m$^3$.

The difference in results for particulate matter between various studies conducted under comparable conditions raises a question of the calibration of the aerosol analyzer used in the Protano study. The need for careful calibration and a methodology (applied in Philip Morris laboratories) to achieve this have been described by Susz et al., 2020[21].

(6) Peruzzi M, Cavarretta E, Frati G, et al. Comparative Indoor Pollution from Glo, Iqos, and Juul, Using Traditional Combustion Cigarettes as Benchmark: Evidence from the Randomized SUR-VAPES AIR Trial, Int J Environ Res Public Health, 2020, 17(17): 6029.

A later paper by Peruzzi et al., (2020) from the same group as Protano et al., extended the reporting of the same study with an additional 7 volunteers (compared to the results from 3 volunteers report previously). The authors stated "*We hereby aim at providing a more poignant comparison of aggregate MRP, as well as different flavors of each MRP type, in order to*

[19] Ruprecht AA, et al. Environmental pollution and emission factors of electronic cigarettes, heat-not-burn tobacco products and conventional cigarettes. Aerosol Science and Technology, 2017, 51: 674-684. DOI: 10.1080/02786826.2017.1300231

[20] Mitova MI, et al. Air quality assessment of the Tobacco Heating System 2.2 under simulated residential conditions. Air Quality, Atmosphere & Health, 2019, 12: 807-823. https://link.springer.com/article/10.1007/s11869-019-00697-6

[21] Susz A, et al. Real-time monitoring of suspended particulate matter in indoor air: 2 validation and application of a light-scattering sensor. Aerosol and Air Quality Research, 2020, 20(11): 2384-2395 DOI: 10.4209/aaqr.2019.11.0604

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*expand and confirm prior findings, while capitalizing on modern state-of-the-art statistical modeling tools*."

**Table 2: Levels of particulate matter ($PM_1$), expressed as µg/m3, comparing the results from Protano (2020) with those of Peruzzi (2020) for two different flavors of *IQOS***

| Device | Timing* | Protano (2020) $PM_1$ Median values $\mu g/m^3$ | Peruzzi (2020) $PM_1$ Median values $\mu g/m^3$ |
| --- | --- | --- | --- |
| Cigarette | Before | 4.0 | 8 |
| | During | 3430.0 | 1245 |
| | After | - | 1390 |
| *IQOS* + Sienna | Before | 7.0 | 12 |
| | During | 337.5 | 79 |
| | After | - | 22 |
| *IQOS* + Turquoise | Before | 22.0 | 19 |
| | During | 32.0 | 37 |
| | After | - | 42 |

Note: *Timing refers to particulate material measurements made 5 minutes before, during and 5 minutes after the product use session; – indicates that the 'after' value was not reported by Protano et al.

The authors speculated on the potential causes for differences in particulate material generated by different device combinations without data to underpin the speculative causes. The large variability in the results from replicates and a small number of volunteers in the study, means that it is not possible to draw firm conclusions and the differences observed may be due to chance. The authors make one incorrect assertion in the discussion that "*Particulate material produced by heat-not-burn cigarettes consists of largely solid material*" (without any basis and ignoring the studies confirming the absence of solid particles in the aerosol from *IQOS*).

Overall the authors state "*In conclusion, leading modified risk products (MRP) have significantly less intense and persistent effects on indoor pollution in comparison to traditional combustion cigarettes (TCC). Yet, when focusing solely on MRP, between-product and between-flavor differences appear, with quantitative estimates suggesting lower polluting effects with IQOS. These results, if confirmed externally, could be used to individualize product and flavor choice to minimize the untoward effects of electronic vaping cigarettes (EVC) and HNBC on indoor pollution.*"

Therefore, whilst the results from Protano (2020) and extended by Peruzzi (2020) indicate a possible increase in particulate material using the Sienna variant when compared to other flavor

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variants, the difference is small and the overall impact is substantially less than for cigarette use.

(7) Hirano T, Shobayashi T, Takei T, et al. Exposure Assessment of Environmental Tobacco Aerosol from Heated Tobacco Products: Nicotine and PM Exposures under Two Limited Conditions, Int J Environ Res Public Health, 2020, 17, 8536.

Hirano et al sought to validate the results obtained by PMI on the impact on indoor air quality from *IQOS* use (Mitova et al., 2016)[22] using an independent study to more appropriately evaluate the effect of HTP use in Japanese restaurant and bar environments and to compare the results three different HTPs sold in Japan, *IQOS*, *Glo* and *Ploom* Tech, compared with a bestselling cigarette in Japan (Mevius One), under the same conditions.

Measurements were made of the concentration of nicotine and particulate matter ($PM_{2.5}$) in the air following 50 puffs of each HTP or cigarette in a small shower cubicle.

They then measured these concentrations in comparison with the use equivalent of smoking 5.4 cigarettes per hour in a 25 $m^2$ room[23], as a typical indoor environment test condition.

In the shower cubicle test (volume 1.43$m^3$), nicotine concentrations in indoor air using the three types of HTP were 25.9–257 µg/$m^3$ and $PM_{2.5}$ concentration of about 300 to 500 µg/$m^3$ using *IQOS* or *Glo*.

In the 25 $m^2$ room test, in contrast, nicotine concentrations in indoor air with the three types of HTP did not exceed 3 µg/$m^3$ (a tolerable level of nicotine exposure calculated by the authors from rodent toxicology studies). The authors stated that $PM_{2.5}$ concentrations were below the standard value of 15 µg/$m^3$ per year for *IQOS* and *Ploom* Tech (applying air quality standards from the U.S. and Japan), but were slightly high for *Glo*, with some measurements exceeding 100 µg/$m^3$.

As stated by the authors "*In our present study, nicotine concentrations did not differ significantly from those in the PMI study of IQOS, although there were some differences in condition settings, such as the presence/absence of ventilation*."

(8) Hirano T and Takei T. Estimating the Carcinogenic Potency of Second-Hand Smoke and Aerosol from Cigarettes and Heated Tobacco Products, Int J Environ Res Public Health, 2020, 17, 8319.

Hirano et al used the nicotine concentration results obtained in the previous study (above), and compared the unit risk and average concentration of International Agency for Research on

[22] Mitova MI, et al. Comparison of the impact of the Tobacco Heating System 2.2 and a cigarette on indoor air quality. Regul. Toxicol. Pharmacol. 2016, 80: 91-101.

[23] There was some confusion in the paper about the volume of the test room, the floor area was approximately 25 $m^2$ and the volume was 63.9 $m^3$.

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Cancer (IARC) type 1 and 2 carcinogens measured in tobacco smoke and HTP aerosols and calculated the consumption risk using data from Stephens (2018)[24]. The estimated risk ratio for HTP mainstream aerosol to tobacco smoke was 0.024.

The authors recognized some limitations of the study: "*First, a detailed study is required to determine if there are significant differences in the composition of carcinogens in mainstream and environmental smoke, even though Mevius One was used as the number one selling cigarette product in this brand in Japan. Second, extrapolation of cancer risk based on nicotine concentrations from mainstream aerosol has a potential large caveat. Environmental secondhand aerosol may differ in composition from mainstream aerosol. Third, although the approach was based on the chemical composition of mainstream aerosol, it would be preferable to calculate excess cancer risk based on the concentration of chemicals in environmental secondhand aerosol. However, there is also the issue of measurable limits for each substance in HTP secondhand aerosol. Since only nicotine and acetaldehydes have been detected in secondhand IQOS aerosol, the result obtained in the present study may be an overestimate*.

*Last, the estimated risk ratio for HTP mainstream aerosol compared with tobacco smoke, regarded as 0.024 in the present study, may vary by brand and type of HTP. Since existing studies show that mainstream HTP aerosols and cigarette smoke contain similar amounts of nicotine, the approach used in the present study is likely the most plausible at this time.*"

They concluded that "*Exposure to aerosol from HTPs in a designated smoking room under usual conditions is estimated to be tolerable since the lifetime cancer risk is expected to be below a virtually safe dose (VSD) of $10^{-5}$ (1/100,000), which is three orders of magnitude lower than that for cigarettes smoked under the same conditions.*"

(9) Cammalleri V, Marotta D, et al. How Do Combustion and Non-Combustion Products Used Outdoors Affect Outdoor and Indoor Particulate Matter Levels? A Field Evaluation Near the Entrance of an Italian University Library. Int J Environ Res Public Health, 2020, 17(14): 5200.

The aims of the study were to assess outdoor and indoor particulate matter (PM) concentrations due to use of combustion and/or non-combustion products outdoors and to compare the PM levels emitted by different products. PM with an aerodynamic diameter ≤ 10, 4, 2.5 and 1 µm ($PM_{10}$, $PM_4$, $PM_{2.5}$, $PM_1$) was simultaneously measured in two areas, respectively, indoors (with smoking ban) and outdoors (where people commonly smoke) forming part of a university library during the morning and the afternoon of two weekdays. The indoor aerosol was sampled directly through the entry of the laser-operated aerosol mass analyzer instrument, positioned at about 1 meter above the floor level, without using any tube, thus simulating the breathing zone

[24] Stephens WE. Comparing the cancer potencies of emissions from vapourised nicotine products including e-cigarettes with those of tobacco smoke. Tob. Control, 2018, 27: 10-17.

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of a passive, exposed, sitting subject. The outdoor aerosol was sampled through a tube placed approximately 1.5 m above floor level, connected to the second instrument, for simulating the breathing zone of a standing subject. The combustion products used were either commercial cigarettes or hand rolled cigarettes. Non-combustion products were an e-cigarette, *IQOS*, *glo* and *JUUL*. As the $PM_1$ fraction was greater than 95% of the aerosols generated during use sessions, this fraction was the only one considered in detail.

The authors reported a relevant worsening of outdoor air quality, with the highest $PM_1$ levels achieved when a single traditional cigarette (9920 $\mu g/m^3$), a single e-cigarette (9810 $\mu g/m^3$) and three simultaneous traditional cigarettes (8700 $\mu g/m^3$) were smoked. $PM_1$ level increases reached statistical significance (p-value < 0.05) for all the monitored devices except for IQOS. The authors concluded "*firstly, smoking/vaping outdoors causes a relevant increase in $PM_1$ levels in the proximity of the smoker/s determining the possibility of environmental tobacco smoke exposure for those who are near the smoker/s, also outdoors. Secondly, smoking/vaping outdoor, but in the proximity of an entrance of a building, causes an increase in indoor $PM_1$ levels, too; this finding means that indoor environments with smoking bans are not entirely free from smoking coming from outside*."

The authors recognized an important limitation to the study "*in our study we measured only the levels of PM and we did not evaluate other pollutants emitted during smoking or vaping. It would, therefore, be desirable to carry out additional experiments under controlled conditions, characterizing the chemical composition of PM and evaluating other substances of the released aerosol that can contaminate indoor and outdoor air*."

(10) Khalaf HNB, et al. Particulate matter variation for different types of cigarettes in indoor air. AIP Conference Proceedings 2313, 080016 (2020)

The study aimed to characterize PM emissions from 3 different types of product (cigarette, e-cigarette and *IQOS*).

The experiments were carried out in a $65m^3$ laboratory room measuring $PM_1$, $PM_{2.5}$ and $PM_{10}$ concentrations before, during and after use of the three product types using a diffusion aerosol spectrometer (DAS). The DAS was placed 3 meters from the aerosol generation source - a volunteer that smoked the cigarette, or e-cigarette, or *IQOS* for approximately 10 minutes each.

E-cigarettes were found to generate the highest mass concentration for all PM sizes measured followed by cigarettes and *IQOS*. The quality of the descriptions in the paper make it challenging to draw further conclusions though the authors concluded "Because tobacco in *IQOS* is heated and not burned as tobacco cigarettes, the levels of inhaled PM and harmful chemicals are significantly reduced."

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(11) Savdie J, Canha N, Buitrago N, et al. Passive Exposure to Pollutants from a New Generation of Cigarettes in Real Life Scenarios, Int J Environ Res Public Health, 2020, 17(10): 3455.

This indoor air quality study measured the particulate matter ($PM_{0.01-1.00}$, $PM_1$, $PM_{2.5}$ and $PM_{10}$), black carbon, carbon monoxide (CO) and carbon dioxide ($CO_2$) in two real life scenarios, in the home and in the car.Three different types of nicotine delivery systems (NDS) were used in this work, all used by volunteer smokers: cigarettes; two types of e-cigarette (*JUUL* with 5% nicotine pods and an iStick using a nicotine-free liquid) and the heated tobacco product *IQOS*.

Home measurements were performed in a 73 $m^3$ sitting room of an occupied flat in Lisbon (Portugal). During experiments, the room was occupied by two people. The air quality monitoring equipment was placed 1.5 m away from the smoker with probes and absorption tubes pointed upwards approximately 1.0 m from the floor.

Car measurements were performed inside a medium volume car travelling on a low traffic intensity route of 4.95 km at a mean speed of 34 km/h. The monitoring equipment was secured in the back seat of the car with probes and absorption tubes in positions corresponding to the breathing zone of a child. The study was performed with two occupants: a driver (the smoker) and a non-smoking passenger seated in the front passenger seat.

In the home, an initial non-smoking scenario was recorded for 2 hours and used as a control. Afterwards, each each NDS use was continuously measured for 2 hours divided into eight 15-minute intervals. Each interval consisted of NDS being smoked with 10 “puffs” for 5 minutes leaving a 10-minute decay period between smokes.

In the car, the measurement for each NDS was made by completing three repetitions composed of three different individual laps. Lap A consisted of a “cleaning lap” where all windows were open and there was no product use; Lap B was a “blank/control lap” where all windows were closed except for the driver’s, which was opened halfway, with no product use; and Lap C consisted of a “smoking lap”, which replicated the conditions of the blank/control lap (all windows closed except for the driver’s) with use of each NDS. During Lap C, measurements were registered separately for the complete lap (measurements C1), which included the pollutants’ decay, and only during the smoking period within the lap, beginning when the cigarette was lit until it was turned off (measurements C2). Each lap lasted between 8 and 10 minutes in which 10 “puffs” were taken per NDS, for an average use time of 3 minutes and with a 7-minute decay period. To maintain the external conditions, the study test drives took place outside of the traffic peak period.

The results from the home study showed that there was a significant difference between the contributions of the three particle size ranges to the $PM_{10}$ in the non-smoking and NDS trials. $PM_1$ was the dominant size fraction for cigarettes (98.6%), e-cigarettes (91.1%) and *IQOS* (92.1%) followed by $PM_{2.5–10}$ (cigarettes: 1.2%, e-cigarettes: 6.5% and *IQOS*: 6.8%), whereas in the control, the contribution of the coarsest particles to the $PM_{10}$ mass increased to 43.9%.

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The use of cigarettes led to the highest increase in $PM_1$ (3470-1570 µg/m³), $PM_{2.5}$ (3480-1570 µg/m$^3$) and $PM_{10}$ (3480-1570 µg/m$^3$) concentrations, followed by the e-cigarettes ($PM_1$: 1350-1510 µg/m$^3$; $PM_{2.5}$: 1370-1520 µg/m$^3$; $PM_{10}$: 1380-1520 µg/m$^3$) and *IQOS* ($PM_1$: 80.6-51.3 µg/m$^3$; $PM_{2.5}$:81.6-51.3 µg/m$^3$; $PM_{10}$: 87.8-51.7 µg/m$^3$).

For ultrafine particles (UFP) the number concentrations were significantly higher during all the product use sessions than during the background, but the levels for cigarettes (110,000-36,000 particles/cm$^3$) stood out compared with those for e-cigarettes (37,800-19,000 particles/cm$^3$) and *IQOS* (35,700-11,500 particles/cm$^3$). The levels for cigarettes, e-cigarettes and *IQOS* were 23.4, 8.1 and 7.6 times higher than background, respectively.

The real-time UFP number concentration showed an initial cumulative behavior in cigarettes that reached a plateau at around 150,000 particles per cm$^3$. The UFP temporal pattern for e-cigarettes and *IQOS* shows a behavior characterized by non-accumulation and rapid decay.

The authors stated that for Black Carbon (BC) particles resulting from the incomplete combustion of carbon-containing materials, the highest BC levels were detected when cigarettes were being used, with much lower levels for e-cigarettes and a further reduction for *IQOS*.

Carbon monoxide results showed that both e-cigarettes and *IQOS* had a steady, non-cumulative behavior, unlike cigarettes, which had a cumulative and incremental behavior without reaching a plateau.

All the NDS as well as the control scenario (also with two occupants) exceeded the recommended WHO $CO_2$ maximum concentration (1800 mg/m$^3$) and were thought by the authors to arise from the altered breathing pattern of the room occupants rather than from the NDS.

A qualitatively similar picture was seen for the in-car studies. However, the e-cigarette vape showed the highest mean levels of $PM_{2.5}$ and $PM_{10}$, even when comparing with cigarettes though cigarette values take a longer time to return to background compared with e-cigarettes and *IQOS*.

The authors concluded that "*the results showed that although the levels of pollutants emitted by e-cigarettes and IQOS are substantially lower compared to those from cigarettes, the new smoking devices are still a source of indoor air pollutants. All smoking options are avoidable sources of indoor pollutants, and to protect the health of smokers and non-smokers, they should not be used in homes and cars.*"

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#### 2.2.3.2 Standard and Systems Toxicology

(12) Wang L, et al. Harmful chemicals of heat not burn product and its induced oxidative stress of macrophages at air-liquid interface: Comparison with ultra-light cigarette. Toxicology Letters, 2020, 331: 200-207.

The aim of the study was to compare HPHC emissions of *IQOS* (described as full flavour *HeatSticks*) with an ultra-light cigarette and the 3R4F reference cigarette and measure their induced oxidative stress on macrophages cultured at air-liquid interface (ALI). The emissions from the reference cigarette 3R4F were not assessed concurrently but results from Roemer et al., 2012[25] were used.

The ISO puffing regime (35 ml puff volume, drawn over 2 seconds, once every minute with ventilation holes unblocked) was used to generate the aerosol from the *IQOS* and smoke from the two test cigarettes. While it is recognized that no puffing regime fully captures the range of puffing parameters used by smokers, it is agreed that the Health Canada Intense (HCI) regime (55 ml puff volume, drawn over 2 second every 30 seconds with ventilation holes blocked) is more representative than the ISO regime. Therefore, the rationale used by the authors for choosing the ISO regime is unclear when they state "*Under HCI smoking regime, some ultra-light cigarettes even delivered much more HPHCs than high-tar cigarette. If adopting HCI smoking regime, it is not necessary to compare aerosol emissions of HTP product with ultra-light cigarette. Thus, it's better to adopt ISO smoking regime (excluded HCI) to compare HPHCs and biological effect of HTP product with ultra-light cigarette*."

It was demonstrated that all HPHCs from *IQOS* were less than that from the 3R4F cigarette and most were lower than ultra-light cigarette, except for some small increases in carbonyl compounds in *IQOS* aerosol compared to the ultra-light cigarette smoke. Mouse mononuclear macrophages were exposed in an ALI cell culture exposure system, reduced glutathione and reactive oxygen species were determined when the cells were exposed to *IQOS* aerosol, the ultra-light cigarette smoke or 3R4F cigarette smoke. At the same exposure dose and time, the order of cell viability induced by aerosol was HnB > ultra-light > 3R4F, the order of content of intracellular reduced glutathione induced by aerosol was HnB > ultra-light > 3R4F. It was confirmed that *IQOS* induced oxidative stress in macrophages, although less than that of the ultra-light cigarette and 3R4F.

[25] Roemer E, et al. Mainstream smoke chemistry and in vitro and in vivo toxicity of the reference cigarettes 3R4F and 2R4F. Beiträge zur Tabakforschung International, 2012, 25(1): 316-335.

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(13) Dusautoir R, et al. Comparison of the chemical composition of aerosols from heated tobacco products, electronic cigarettes and tobacco cigarettes and their toxic impacts on the human bronchial epithelial BEAS-2B cells. Journal of Hazardous Materials, 2021, 401: 123417

The aim of this study was to compare the chemical composition and the toxicological effects of aerosols from *IQOS*, conventional cigarette smoke (3R4F) and aerosol from one nicotine-containing e-liquid vaporized by different e-cig models. The study compared emissions from *IQOS* (Amber *HeatSticks*) with two models of e-cigarettes from a French manufacturer (*NHOSS* brand) and with the University of Kentucky 3R4F reference cigarette. The first e-cigarette is described as the second generation "Lounge" model, equipped with a 2.8 Ω nichrome coil and 4.6 W power supply. The coil heating was triggered by air suction. The second one was a third generation "ModBox" model, used with the "Air Tank" clearomiser equipped with a 0.5 Ω kanthal coil and with a partially closed air flow. The ModBox model was tested at two power settings, 18 W and 30 W. These settings correspond to the lower and upper range power supplies recommended by the manufacturer for the coils used. One e-liquid was used, "blond tobacco" flavoured (NHOSS® brand) and with the following formulation: propylene glycol < 65 %; glycerol < 35 %; food flavourings; nicotine 16 mg/ml.

The authors also compared the impact of the aerosols from *IQOS* and e-cigarettes with the smoke from a cigarette on human bronchial epithelial BEAS-2B cells. They concluded that the emission of polycyclic aromatic hydrocarbon HPHCs and carbonyl compounds were reduced in *IQOS* compared to cigarettes but further reduced in the e-cigarette aerosols. Likewise, for the cytotoxicity effects of *IQOS* aerosol exposure on BEAS-2B cells, were reduced compared to cigarette smoke but further reduced in the case of e-cigarette aerosols. The authors concluded "*This study provides important data necessary for risk assessment by demonstrating that HTP might be less harmful than tobacco cigarette but considerably more harmful than e-cig*."

There are some important limitations of this study to be considered, firstly with the measurement of carbonyl compounds in the test samples that differ from those previously reported by PMI and other authors (Farsalinos et al., 2018)[26]. This appears to be due to the way that the aerosols were collected using sorbent cartridges. To avoid the problem with saturation and breakthrough of the cartridges for e-cigarettes, HTP and 3R4F analyses, 20, 4 and 1 puff(s) were respectively found to be the best compromise with satisfying efficiency without saturation of the cartridge. Concerning the e-cigarettes, they measured carbonyl emissions in the twenty last puffs of one-hour-exposure session (100 – 120 puffs). To compare the different aerosol samples, the levels of the carbonyls were then expressed in mass of each compound by puff. Collecting one puff from a cigarette and comparing with 4 puffs from the HTP and 20

[26] Farsalinos KE, et al. Carbonyl emissions from a novel heated tobacco product (IQOS): comparison with an e-cigarette and a tobacco cigarette. Addiction, 2018, 113: 2099-2106. DOI: 10.1111/add.1436

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(last) puffs for e-cigarettes will generate uncertain results when compared with the standard methods where all puffs are collected and analysed using an impinger collection system (see for example the puff by puff results for a reference cigarette reported by Wagner et al., (2005)[27].

Exposure of BEAS-2B cells to aerosol/smoke at the air-liquid interface was performed without dilution and the immortalized cell line lacks certain metabolic enzymes (Hiemstra et al., 2018)[28] and is therefore not realistic for human exposure but does provide an important hazard identification analysis. The challenge when comparing an HTP to an e-cigarette is that the results will apply to the particular e-cigarette/e-liquid combination (as shown by the results of this study) and cannot be generalized to a comparison of HTPs with e-cigarettes in general.

PMI has performed similar studies using an *in vitro* human small airway epithelium model (*e.g.*, Iskandar et al., 2017[29]). The three dimensional (3D) organotypic culture system, grown at an air–liquid interface where they can be directly exposed to inhalable gases and aerosol. Functional and systems toxicology endpoints following *IQOS* aerosol or 3R4F cigarette smoke (matched for nicotine levels) were compared. The results showed that *IQOS* aerosol exposure at the tested doses elicited lower cytotoxicity levels and lower changes in the secreted pro-inflammatory mediators than 3R4F smoke. Although THS 2.2 exposure elicited alterations in the gene expression, a higher transcriptome-induced biological impact was observed following 3R4F smoke: The effects of THS 2.2 aerosol exposure, if observed, were mostly transient and diminished more rapidly after exposure than those of 3R4F smoke.

(14) Aspera-Werz RH, Ehnert S, et al. Assessment of tobacco heating system 2.4 on osteogenic differentiation of mesenchymal stem cells and primary human osteoblasts compared to conventional cigarettes. World J Stem Cells, 2020, 12(8): 841-856.

The aim of the study was to examine the effects of *IQOS* on osteoprogenitor cell viability and function compared to conventional cigarette smoke.

Human immortalized mesenchymal stem cells and primary human pre-osteoblasts isolated from cancellous bone samples were osteogenically differentiated with aqueous extracts generated from either the *IQOS* (THS 2.2 and three commercially available variants; Bronze, Amber and Yellow were provided by Philip Morris (Germany), or conventional "*Marlboro*" cigarettes for up to 21 d. Cell viability was analyzed using resazurin conversion assay

[27] Wagner KA, et al. Puff-by-Puff Analysis of Selected Mainstream Smoke Constituents in The Kentucky Reference 2R4F Cigarette. Beiträge zur Tabakforschung International, 2005, 21(5): 273-279. DOI: 10.2478/cttr-2013-0793

[28] Hiemstra PK, et al. Human lung epithelial cell cultures for analysis of inhaled toxicants: Lessons learned and future directions. Toxicology in Vitro, 2018, 47: 137-146

[29] Iskandar AR, et al. Comparative effects of a candidate modified-risk tobacco product Aerosol and cigarette smoke on human organotypic small airway cultures: a systems toxicology approach. Toxicol. Res., 2017, 6(6): 930-946. DOI: 10.1039/c7tx00152e

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(mitochondrial activity) and calcein-AM staining (esterase activity). Osteogenic differentiation and bone cell function were evaluated using alkaline phosphatase (AP) activity, while matrix formation was analyzed through alizarin red staining. Primary cilia structure was examined by acetylated α-tubulin immunofluorescent staining. Free radical production was evaluated with 2',7'-dichlorofluorescein-diacetate assay.

The aqueous extracts of *IQOS* aerosol and cigarette smoke were generated using the Health Canada Intense puffing regime and bubbling the aerosol/smoke through cell culture media (prepared fresh for each use and sterile filtered prior to use).

*IQOS* aerosol was shown to be significantly less toxic to bone cells than cigarette smoke when analyzed by mitochondrial and esterase activity ($P < 0.001$). No significant differences in cytotoxicity between the diverse flavors of THS were observed. Harmful effects from THS on bone cell function were observed only at non-physiological concentrations. In contrast, cigarettes significantly reduced the AP activity (by two-fold) and matrix mineralization (four-fold) at low concentrations. Moreover, morphologic analysis of primary cilia revealed no significant changes in the length of the organelle involved in osteogenesis of osteoprogenitor cells, nor in the number of ciliated cells following THS treatment. Assessment of free radical production demonstrated that THS induced significantly less oxidative stress than conventional CS in osteoprogenitor cells.

The authors concluded that *"the present study demonstrate reductions in the harmful effects on bone-forming cells and bone progenitor cells treated with THS compared to conventional cigarettes. THS could be a potential alternative for smokers to maintain appropriate bone homeostasis and delay development of secondary osteoporosis, which consequently would reduce health system costs."*

The authors recognized certain limitations *"this study focused on the effect of IQOS aqueous extract only in human bone marrow mesenchymal stem cells and human osteoblasts (obtained from 5 donors 1 male and 4 females with an average aged of approximately 73 years). As several cell types are involved in bone homeostasis, THS could potentially influence the function of other cells, such as immune cells, osteoclasts, or osteocytes. Co-culture systems may provide a better alternative for screening the effects of ENDS on bone metabolism and predicting cytotoxicity in bone tissue."*

Furthermore, exposure of cells to aqueous extracts of aerosol or smoke are not representative of how these cells would be exposed to compounds in the aerosol or smoke in real life. However, within the limitations of the study, the reduction in harmful effects on the bone forming cells and bone progenitor cells when exposed to *IQOS* aerosol, is consistent with the reduced formation of harmful and potentially harmful compounds in *IQOS* aerosol compared with cigarette smoke.

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(15) Ito Y, Oshinden K, et al. Heat-Not-Burn cigarette induces oxidative stress response in primary rat alveolar epithelial cells. PLoS One, 2020, 15(11): e0242789.

In this study, primary rat Alveolar Epithelial Cells (AECs) were isolated, cultured and stimulated by *IQOS* aerosol extract and compared with cigarette smoke extract from a commercial cigarette.

As explained by the authors "*AECs play critical roles in the pathogenesis of cigarette smoke-related respiratory diseases. The alveolar epithelium consists of two cell types, type I alveolar epithelial (ATI) cells and type II alveolar epithelial (ATII) cells. ATI cells are responsible for gas exchange, and liquid homeostasis in the alveoli, but are highly susceptible to injury and incapable of self-renewal. In contrast, ATII cells are highly resistant to insults, able to self-renew, and repopulate ATI cells*."

ATII cells isolated from rat lung were transdifferentiated into ATI-like cells, and maintained in a differentiated state prior to use.

The aerosol/smoke were generated from one *IQOS* 3 device (with an unspecified variant of *HeatSticks*) or one *Marlboro* Red cigarette using the Health Canada Intense smoking regime and then individually bubbled at a constant rate through a 25 mL tissue culture flask containing 12.5 mL serum-free culture media. The freshly prepared culture media was sterile filtered and immediately applied to the cell cultures.

The authors stated that the data indicate that rat AECs exposed to *IQOS* CSE induced oxidative stress response genes. The expressions of these genes were higher in ATII cells than ATI-like cells in response to *IQOS* and a commercial cigarette, but there was no significant difference in their expression levels between *IQOS* and the cigarette.

The authors recognized some limitations of their study "*First, we observed only acute response to IQOS CSE generated from one IQOS stick. Second, we used an in vitro system with cells from rats, not humans. Thus, long term, repeated exposure experiments and in vivo studies with animals and/or IQOS users must be conducted to verify our in vitro cell-based results*."

(16) Scharf P, Da Rocha GHO, et al. Immunotoxic mechanisms of cigarette smoke and heat-not-burn tobacco vapor on Jurkat T cell functions. Environ Pollut, 2021, 268(Pt B): 115863.

This study compared the potential immunotoxic effects of *IQOS* aerosol with cigarette smoke on Jurkat T cells (an immortalized line of human T lymphocyte cells). Cells were exposed to air, cigarette smoke or *IQOS* aerosol for 30 minutes and were stimulated or not with phorbol myristate acetate (PMA). Cell viability, proliferation, reactive oxygen species (ROS) production, 8-OHdG, MAP-kinases and nuclear factor κB (NFκB) activation and metallothionein expression (MTs) were assessed by flow cytometry; nitric oxide (NO) and cytokine levels were measured by Griess reaction and ELISA, respectively.

Additional studies were also carried out using male C57Bl/6 mice (8-weeks old) whole body exposed to air, cigarette smoke or *IQOS* aerosol generated using the Health Canada Intense

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(HCI) puffing regime. Mice were exposed for 1 hour, twice a day, for 5 days to simulate the cigarette smoke consumption of heavy smokers. The number of cigarettes and heatsticks used was matched by the amount of nicotine for each hour of exposure. A total of 12 conventional cigarettes and 24 heatsticks were used. The mice were euthanized 16 hours after the last exposure for liver and lung removal. Tissues were then assessed for metallothionein I and II using immunohistochemical staining.

Results from the Jurkat T cell studies indicated that cigarette smoke and *IQOS* aerosol caused cell death mainly by necrosis. The effects caused by cigarette smoke were more intense than those evoked by *IQOS* aerosol. Cigarette smoke exposure induced 8-OHdG formation in Jurkat cells, independent of PMA stimuli. Formation of 8-OHdG in cells exposed to *IQOS* vapor was equivalent to that detected in cells exposed to air only.

Investigation of the delivery of metals into the Jurkat cell exposure chamber showed lower amounts of iron, copper, chromium, aluminum, arsenic and nickel in *IQOS* aerosol than in cigarette smoke samples, and no detectable levels of cadmium and manganese in *IQOS* samples.

Jurkat cells also showed higher expression of MTs on exposure to cigarette smoke than in counterpart cells exposed to air or *IQOS* aerosol. The quantification of levels of pro-inflammatory cytokines TNF-α, IFN-γ and IL-8 showed that cigarette smoke exposure increased their secretions by Jurkat cells; moreover, the secretion of TNF-α evoked by PMA was markedly increased in cigarette smoke exposed cells. PMA stimulation caused IL-2 secretion by Jurkat cells exposed to air, which was abrogated in cells exposed to *IQOS* aerosol or cigarette smoke.

Monitoring cell proliferation for 72 hours, it was observed that cells exposed to cigarette smoke and *IQOS* aerosol showed an impaired proliferation capacity, even upon PMA stimulation. As expected, the decrease of IL-2 secretion observed 24 hours after cigarette smoke or *IQOS* aerosol exposures, impacted the proliferation rate of Jurkat T cells. It is important to highlight that *IQOS* aerosol-exposed cells displayed an accentuated proliferation impairment with or without PMA stimulation, when compared to the cigarette smoke-exposed group.

Knowing that nicotine plays a suppressive role in IL-2 secretion and cell proliferation, Jurkat T cell were treated with the same concentration of nicotine released by cigarette smoke and *IQOS* aerosol for 30 minutes. Nicotine concentrations used here did not have a significant cytotoxic effect on Jurkat T cells; nevertheless, nicotine decreased IL-2 secretion even upon PMA stimulation and, in accordance with the effects seen for cigarette smoke and *IQOS* aerosol exposure, nicotine suppressed the proliferation of Jurkat T cells.

In the lung and liver tissues from the exposed mice, expression of MT was markedly enhanced in liver and lung tissues collected from mice exposed to cigarette smoke in comparison to tissues obtained from mice exposed to air or *IQOS* aerosol. The authors noted that in these tissues MT were not expressed by T lymphocytes, as mice were not subjected to local or systemic inflammation that could elicit influx of lymphocytes into tissues. The

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immunostaining showed that cigarette smoke exposure induces expression of MT by cells other than lymphocytes. MT are expressed by resident lung cells, such as lung epithelial cells, hepatocytes, mast and Kupffer cells, as well as macrophages.

The authors concluded "*Cigarette smoke exposure activates either damaging or protective pathways in T cells, resulting in a clear activation of oxidative and inflammatory pathways, which are related to the development of autoimmune diseases and cancer. As these end points were reduced in IQOS aerosol exposed cells, we confirm IQOS tobacco products are toxic, aggressively affecting T lymphocytes, even if IQOS products possess lower levels of combustible products. Our data highlight the severe downregulation of IL-2 and the disruption of T cell proliferation caused by both cigarette smoke and IQOS aerosol exposures, which might implicate in impaired protection exerted by the immune system against self-aggressions and cancer development. The latter effects are associated with nicotine delivery by both cigarette smoke and IQOS aerosol. Considering nicotine is also toxic to systems other than the immune system, the toxicity of IQOS delivery products must be further investigated in in vitro and in vivo models.*"

(17) Bhat TA, Kalathil SG, et al. Acute effects of heated tobacco product (*IQOS*) aerosol-inhalation on lung tissue damage and inflammatory changes in the lungs. Nicotine & tobacco research, 2020, ntaa267.

The study examined the effects of short-term inhalation of aerosols emitted from HTP *IQOS* compared to cigarette smoke and control air, on lung damage and immune-cell recruitment to the lungs in mice. Eight week old C57BL/6NCr mice with 5 males and 5 females per treatment group (*IQOS* aerosol exposure [*IQOS* devices (model 2.0) and *HEETS* Red Label inserts], 3R4F Kentucky reference cigarette smoke exposure and control group exposed to filtered air). Mice were exposed for 5 hours/day for 2 weeks to emissions from 20 *IQOS* Heatsticks or 20 cigarettes/day. The 10 animals per treatment group were held in 15-liter exposure chambers with two sections separated with a 0.5 cm steel wire mesh with 5 males or females either side of the mesh.

Aerosols were generated according to the Health Canada Intense (HCI) puffing regime, the puff duration of 2 seconds for cigarettes complied with HCI requirements, though for some unexplained reason, the puff duration for *IQOS* aerosol generation was increased to 5 seconds. Twenty cigarettes or 20 *IQOS* Heatsticks were used each day. For each cigarette 8 puffs were taken from each cigarette over a period of 4 minutes with a rest period (exposure to filtered air) for 11 minutes. For *IQOS*, 12 puffs were taken from each Heatstick over a period of 6 minutes with a rest period (exposed to filtered air) for 9 minutes.

Numerous markers of lung damage and inflammation including albumin and lung immune-cell infiltrates, proinflammatory cytokines and chemokines were quantified in lungs and bronchoalveolar (BAL) fluid from *IQOS* aerosol, cigarette smoke or air-exposed (negative control) mice.

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From the results obtained the authors concluded "Our study demonstrates that short-term inhalation of aerosols from *IQOS* generates damage and proinflammatory changes in the lung that are substantially similar to that elicited by cigarette smoke exposure."

The human relevance of the findings from this study are not clear as the exposure regime is extreme, the airborne nicotine concentration in the exposure chamber for *IQOS* was approximately 2.5 times greater than the levels measured in the cigarette smoked exposure chamber. The authors also recognized some further limitations of the study in that it was a one-time point investigation following a 2-week exposure period and there was no histopathological evaluation of lung tissue. In addition, for laboratory animal studies the results of daily clinical observations should be reported to assess if there were signs of stress/acute reactions to the exposure regime.

(18) Yoshida S, Ichinose T, et al. Effects of Fetal Exposure to Heat-Not-Burn Tobacco on Testicular Function in Male Offspring. Biol Pharm Bull, 2020, 43(11): 1687-1692.

The aim of the study was to investigate the effects on testicular function of male offspring from pregnant CD-1 female mice exposed to either *IQOS* aerosol (*HeatSticks* Regular), 3R4F cigarette smoke or filtered air (control group). Pregnant female mice at day 5 post coitum were housed in groups of 5 up to day 16 and then housed individually. The pregnant mice were whole-body exposed to their respective treatments on day 7 and day 14 of gestation. *IQOS* aerosol and 3R4F cigarette smoke were generated in 10 puffs according to the Health Canada Intense puffing regime from 4 *IQOS* heatsticks/3R4F cigarettes a day with a 20 minute aerosol/smoke exposure on days 7 and 14 of gestation. Exposure began after implantation and initial organ development had taken place. Control mice received filtered air according to the same procedure.

24 dams (8 mice per treatment group) were selected. Each dam and her delivered offspring were housed for 24-26 days after birth in nesting boxes, then male pups were removed from their mother's cage. All male offspring were anaesthetized for examination at 5 weeks or 15 weeks with 8 animals per group at each time point. Spermatogenesis, sperm characteristics, serum testosterone, and seminiferous tubule morphology were evaluated.

The authors concluded that prenatal *IQOS* aerosol exposure increased abnormal seminiferous tubule morphology and decreased sperm production at 5 weeks, but 3R4F exposure did not. Prenatal exposure to *IQOS* aerosol delays sexual maturation of male offspring or adversely affects the male testicular function of the offspring more than smoke from a combustion cigarette.

Exposure of the treatment groups were not matched for nicotine and uptake of nicotine into the mice was not measured for the treated animals. Nicotine is known to affect sperm production in male offspring when the mother has been exposed to nicotine (Vigueras-Villasenor et al

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2020[30]). It is possible that a difference in uptake of nicotine from *IQOS* aerosol may contribute to this effect.

#### 2.2.3.3 Clinical

Clinical evidence on THS from studies conducted by independent researchers is still limited. However, some pertinent clinical studies were published during the reporting period, which are summarized below.

A longitudinal cohort observational study by Sharman et al. (Sharman et al., 2020), which was financially supported by a grant from PMP S.A., followed two large cohorts of cigarette smokers (N = 801) and *IQOS* users (N = 400) for one year in Kazakhstan. The study investigated the health effects of switching from cigarettes to *IQOS*. All participants had a smoking history of over 10 pack-years. The measured outcomes were standard lung function parameters (using spirometry measurements), respiratory symptoms (using the COPD assessment test [CAT]), and functional incapacity (six-minute walk test). Although some results were mixed, the authors reported that they observed significantly better outcomes for *IQOS* users compared to smokers after one year compared to baseline. These included an improvement of 40% in the total CAT score, longer total distance walked over 6 minutes (change from baseline: 17.92m for *IQOS* users and 9m for smokers), and a slight overall improvement in spirometry outcomes pre- or post-bronchodilator. In contrast, smokers generally had a faster decline in health status, particularly for changes in CAT scores, and their $FEV_1$ over FVC ratios worsened at a higher pace compared to *IQOS* users. Overall, the authors concluded that *IQOS* users had better health outcomes.

In this independent study by Pataka et al. (Pataka et al., 2021), the authors evaluated the acute effects of *IQOS* on the pulmonary function of non-smokers (N = 25) and current smokers (N = 25) who were asked to use *IQOS*. The study measured a variety of pulmonary functions and exhaled CO before and after *IQOS* use. A single use of *IQOS* had a small acute effect by decreasing various pulmonary parameters such as saturation in oxygen ($SaO_2$%), forced expiratory flow at 25% and 50% of vital capacity (FEF25% and FEF50%, respectively), peak expiratory flow and diffusion lung capacity, while exhaled CO and airway resistance were slightly increased. No notable differences were observed between non-smokers and smokers. Regarding exhaled CO, the authors noted that levels increased from baseline after *IQOS* use, but they acknowledged that the levels of exhaled CO were within the expected range for non-smokers. The absence of a control group where participants would have been asked to smoke a cigarette in comparison to a single *IQOS* use, in addition to the relatively low sample size acknowledged by the authors, was a study limitation. The authors concluded that the changes

[30] Vigueras-Villasenor RM, et al. Fetal and Postnatal Nicotine Exposure Modifies Maturation of Gonocytes to Spermatogonia in Mice. Anal Cell Pathol (Amst), 2020, 8892217.

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were not considered to be of major clinical importance and stated that further studies are needed to understand the chronic effect on *IQOS* on pulmonary functions.

Quitting smoking is suggested to reverse the impairment of the mucociliary clearance structure caused by smoking. In a cross-sectional study by Polosa et al. (Polosa et al., 2021), measurement of saccharin transit time to assess mucociliary clearance (MCC), suggested by the authors as a biomarker of physiological effect for the detection of early respiratory health changes, was conducted to investigate if alternative products to cigarettes have beneficial impact on MCC across five groups (N = 159): (i) current smokers; (ii) former smokers; (iii) never smokers; (iv) exclusive e-cigarette users (ex-smokers); and (v) exclusive heated tobacco product (HTP) users. The median saccharin transit time was almost twice as long in cigarette smokers (13.15 min.) as in never (7.24 min.) and former smokers (7.26 min.). Subjects in the e-cigarette group (7.00 min) and the HTP study group (8.00 min) had a saccharin transit time similar to former and never smokers. The authors concluded that these results suggested a beneficial impact of switching from cigarettes to e-cigarette or HTP on mucociliary clearance that could be considered an early respiratory health change.

Two studies, Franzen et al. and Ioakemidis et al., (Franzen et al., 2020; Ioakemidis et al., 2020) investigated whether Heat-not Burn (HNB) products have an effect on arterial stiffness as an indicator of vascular functions and hemodynamics.

In the crossover study design by Franzen et al., 20 healthy smokers were asked to use a single cigarette or HTP (*IQOS*), or to use e-cigarette (with or without nicotine), with a minimum of 10 puffs at a pre-specified regimen. The use of cigarettes, *IQOS*, and e-cigarettes led to a transient increase in systolic blood pressure and heart rate, returning to baseline values after 60 minutes, while such an effect was not observed for e-cigarettes without nicotine. In addition, the use of cigarettes, HTP, and electronic cigarettes containing nicotine resulted in a temporary increase in both augmented index (Aix) and pulse wave velocity (PWV), two indicators of arterial stiffness. These transient effects were considered by the authors to be attributed to the combined presence of nicotine and residual harmful compounds in HTP and electronic cigarettes containing nicotine. It was stated by the authors that further studies are needed to evaluate the long-term chronic effect of these products on arterial stiffness and hemodynamics beyond the acute effects.

Ioakeimidis et al. studied twenty-two young smokers in a crossover, randomized trial after randomly using *IQOS*, cigarettes, or a sham cigarette, for five minutes on three separate occasions. When compared to the sham cigarette, systolic blood pressure, heart rate, Aix corrected for heart rate, and both carotid-femoral and brachial-ankle PWV increased transiently, immediately after cigarette smoking or *IQOS* use. However, the authors reported that the acute effect of *IQOS* was lower than cigarettes. Systolic blood pressure increased immediately after smoking a tobacco cigarette and increased to a slightly lesser extent after consuming an *IQOS* heat stick. These effects of nicotine are expected as reported in the literature.

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In a study, conducted by Nga et al. (Nga et al., 2020), smokers (N = 45) were recruited in Kuala Lumpur from an Asiatic population (the majority [51.1%] were of Chinese ethnicity) to measure end tidal carbon monoxide (eCO) levels as a marker of combustion after use of non-combustible products versus cigarettes. Eligible subjects were smoking at least 10 cigarettes per day with a baseline exhaled CO of ≥ 10 ppm. Subjects chose one of three tobacco products based on individual preference: (i) their own preferred brand of cigarettes; (ii) electronic cigarettes (ENDS) with a propylene glycol/vegetable glycerin ratio of 70/30 and 10 ng/ml nicotine; or (iii) heated tobacco (HTP) with *IQOS Marlboro HeatSticks*. After a period of at least 12 hours of abstinence post-baseline visit, subjects were asked to use a single stick of their self-selected product according to specific instructions (number of puffs and interval between puffs). The authors observed minimal changes in eCO levels after HTP and ENDS use that progressively decreased thereafter. The maximum peak of 8.8 ppm ± 1.56 at 15 minutes for ENDS was even lower for HTP with 6.0 ppm ± 1.36 at 10 minutes. For cigarettes, the maximum peak was of 20.2 ppm ± 0.86 at 30 minutes. The authors suggested that additional studies are needed to investigate further the impact of the observed minimal increase from baseline with ENDS and HTP on health. In conclusion, Nga et al. found that HTPs generated much lower levels of exhaled CO as no combustion takes place.

In a case report Makurina et al. mentioned a patient complaining of a rash in the form of rough skin on the lower lip that was accompanied by itching and burning pain occurring after 4-5 months of daily *IQOS* use. As the patient refused the biopsy with further histological examination as well as the surgical treatment, the following diagnosis was made: verrucous leukoplakia of the red border (lower lip), plaque type. A topical therapy was prescribed with a combination of glucocorticosteroid, antibacterial, and antimycotic components for one month, which reduced the affected area and its infiltration. As the patient continued smoking and refused other treatments, the clinical improvement was mitigated. However, patient was planned to continue the therapy with 1 % pimecrolimus cream together with further long-term clinical and dermatoscopic follow-up to examine the skin state.

A case reported by Yumoto et al. described a 59 years old patient with a history of depression who intentionally ingested 8 heat sticks (*Marlboro* Menthol *HeatSticks*) in addition to several benzodiazepine pills. On hospital arrival, he was oriented but appeared lethargic. He denied any symptoms of nausea, headache, abdominal pain, or vomiting. As the estimated nicotine ingested was 100 mg, gastric lavage was conducted about an hour after ingestion. Carefully observed for 24 hours, the patient complained of temporary nausea and vomiting that relieved after several hours. The patient was discharged the following day and referred to the psychiatric hospital, where he had been treated for depression.

(19) Fried ND, et al. Heat-Not-Burn Tobacco Products: an Emerging Threat to Cardiovascular Health. Am J Physiol Heart Circ Physiol, 2020, 319(6): H1234-H1239.

Fried et al prepared a selective review of the literature and described HTPs as an emerging threat to cardiovascular health in the title of their paper. They explain that the HTP commercialized as *IQOS* by Philip Morris was available for purchase in the United States as

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of October 2019. The authors did not mention that the availability of *IQOS* on the U.S. market was only possible "*Following a rigorous science-based review through the premarket tobacco product application (PMTA) pathway, the agency (FDA) determined that authorizing these products for the U.S. market is appropriate for the protection of the public health because, among several key considerations, the products produce fewer or lower levels of some toxins than combustible cigarettes.*"[31]

Furthermore, they failed to mention that "the carbon monoxide exposure from *IQOS* aerosol is comparable to environmental exposure" that resulted in "Removal of the warning: "SURGEON GENERAL'S WARNING: Cigarette Smoke Contains Carbon Monoxide." from the required warnings to be displayed on the product package labels and advertisements under FCLAA (Federal Cigarette Labelling and Advertising Act)."[32]

A number of the studies reviewed by the authors have been included above in this review and provide further important context to the authors' comments. The mini-review is not a balanced critical review of the available evidence and concentrates on the published literature that may support the title of the paper, rather than considering the potential for risk reduction when adult smokers switch to using *IQOS* based on all available evidence.

The authors make a statement that "a comprehensive study performed by Philip Morris using two-dimensional gas chromatography with time-of flight mass spectrometry and liquid chromatography with high-resolution accurate mass spectrometry revealed 529 different compounds in the aerosol of HNB tobacco products. These 529 compounds are also found in the mainstream smoke of combustible cigarettes, hinting at a similar toxicological profile (Bentley et al., 2020)[33]."

This statement confirms a misunderstanding of the basis of the PMI study to characterize the *IQOS* aerosol using a non-targeted screen for constituents that are not detected by the targeted analysis of the aerosol.

The authors concluded that "*The body of literature on HNB tobacco products is small but expanding. Current evidence suggests that HNB tobacco products (and electronic cigarettes) are less dangerous than combustible cigarettes, but not without health risk.*"

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[31] FDA News Release "*FDA permits sale of IQOS Tobacco Heating System through premarket tobacco product application pathway"* April 30, 2019, available at: https://www.fda.gov/news-events/press-announcements/fda-permits-sale-iqos-tobacco-heating-system-through-premarket-tobacco-product-application-pathway

[32] The PMTA Technical Project Lead (TPL) Review (page 90), available at: https://www.fda.gov/media/124247/download

[33] Bentley MC, et al. Comprehensive chemical characterization of the aerosol generated by a heated tobacco product by untargeted screening. Analytical and Bioanalytical Chemistry, 2020, 412: 2675-2685. https://doi.org/10.1007/s00216-020-02502-1

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#### 2.2.3.4 Behavioral

We have identified a series of studies conducted by independent researchers on perception and product use behavior. These studies mainly investigated the observed or the likely effect of THS on several sections of the population and the perceptions associated to THS. In the subsequent paragraphs, we are providing a summary of some of them grouped according to themes.

During the review period, five publications reported results on **use patterns in Japan**. Three of those publications (Hori, 2020, Matsuyama, 2021, Sugiyama, 2020) used data from the Japan 'Society and New Tobacco' Internet Survey (JASTIS) survey and two publications (Sutanto, 2020, Thompson, 2020) used data from the International Tobacco Control (ITC) Japan Survey.

Given that several publications are based on the JASTIS survey, we believe it is important to provide some background information regarding this study. The JASTIS study is a longitudinal internet cohort study which investigates perception, attitude, and use of heat-not-burn tobacco, electronic cigarettes (e-cigarettes), and conventional tobacco products in Japan. The survey also includes demographic, health-related, and socioeconomic factors. Participants were randomly selected and invited from internet panelists. The baseline survey was closed when the target number of respondents who had answered the questionnaire was met. The study includes three cohorts (1–3) from the 2015 baseline survey and a cohort (4) from the 2017 baseline survey: cohorts 1 and 4 were recruited based on sex and age: men and women aged 15–69 years (n = 8,240 for cohort 1 and n = 5,897 for cohort 4); cohorts 2 and 3 were created using status-based recruiting: e-cigarette and/or heat-not-burn tobacco ever users (n = 2,188; cohort 2) and combustible cigarette smokers without e-cigarette = heat-not-burn tobacco experience (n = 724; cohort 3)[34].

The JASTIS study provides reliable estimate of tobacco or nicotine-containing product prevalence of use over time (see below) in Japan as cohorts 1 and 4 represent the Japanese population aged 15–69 years. Cohorts 2 (e-cigarette and/or heat-not-burn tobacco ever users) and 3 (combustible cigarette smokers without e-cigarette=heat-not-burn tobacco experience) as stated by Tabuchi aimed to monitor tobacco product use status among users and to observe behavior changes such as smoking cessation, relapse and gateway effect. This means that, for instance, Cohort 2 and 3 data is suitable to provide evidence regarding transition of product use status across time. However, the study design and the quota sampling mode of recruitment of ever users for Cohort 2 and 3 is not suitable to provide reliable estimates on exclusive/single (1 product), dual/concurrent (2 products), or poly (>2 products) tobacco product use as the target quotas are set for each of the specific subgroups without taking into consideration the

[34] Tabuchi T, Shinozaki T, Kunugita N, et al. Study Profile: The Japan "Society and New Tobacco" Internet Survey (JASTIS): A Longitudinal Internet Cohort Study of Heat-Not-Burn Tobacco Products, Electronic Cigarettes, and Conventional Tobacco Products in Japan. J Epidemiol, 2019, 29(11): 444-450. https://doi.org/10.2188/jea.JE20180116

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actual size of the respective product categories at national level. The longitudinal study design and the mode of recruitment of JASTIS Study might explain the discrepancy regarding use patterns between data from the JASTIS Study and data from the Japan National Health and Nutrition Cross-Sectional Survey (2019), which provides data among the adult Japanese population, and which show that more than 75% of all Heated Tobacco Products users in Japan are using those products exclusively.

Sugiyama analyzed data of 10,114 responders from the 2017 JASTIS study. The data show that among Japanese adults, 21.6% were current tobacco/nicotine product users; 20.1% currently used cigarettes; 18.4% currently used a single product; 17.0% currently used cigarettes only; 1.1% currently used HTPs only; and 0.2% currently used e-cigarettes only. In terms of multiple tobacco products use, 3.2% currently used multiple tobacco products; 2.6% currently used dual products; 2.5% currently used dual products including cigarettes; 1.6% currently used both cigarettes and HTPs; 0.6% currently used both cigarettes and e-cigarettes; and 0.6% currently used more than two products. Among current product users (100%), cigarettes were the most popular product in single (78.8%) and multiple (14.2%) tobacco products use, while HTPs were the second most popular product in single (5.2%) and multiple (10.6%) tobacco products use. The authors concluded that this study provides baseline information on multiple tobacco products use (use of more than one product) in Japan, which will enable the examination of trends in the future.

Using ongoing retrospective JASTIS data, Hori, 2020 calculated the prevalence of HTP use from 2015 to 2019. The results show that HTP use in Japan increased from 0.2% in 2015 to 11.3% in 2019, as estimated among participants aged 15–69 years. In 2019, HTP use prevalence was over 30% among current smokers with or without intention to quit (30.8% and 43.2 %, respectively). HTP use prevalence was more than 10% higher among men, participants in their 20s and 30s than other categories. According to product type, the most recent 2019 HTP use prevalence (95% CI) in Japan was estimated as follows: 5.8% (4.4%–7.6%) for *IQOS*, 6.1% (4.7%–7.8%) for *Ploom* Tech and 3.6% (2.6%–5.0%) for *glo*. The authors also stated that the use of HTPs had rapidly extended to current smokers, regardless of their intention to quit and that the widespread availability of HTPs in Japan may encourage smokers of cigarettes to replace them with HTPs. The authors concluded that the study highlights the rapid spread of HTPs in Japan, especially among smokers, men and the younger [adult] population.

Matsuyama analyzed two waves of data from the JASTIS study. Among the 7766 never/former combustible cigarette smokers who answered the baseline survey in 2019, 5947 (follow-up rate: 76.6%) responded to the follow-up survey in 2020 (age range 18–73 years old; 50.5% men). Of the respondents, 308 (5.2%) used HTPs at baseline. 51.0%, 9.2% and 1.0% of recently quit smokers, long-term-quit smokers and never smokers used HTPs, respectively. One year later, 97 (1.7%) non-HTP users and 39 (12.7%) HTP users were smoking combustible cigarettes. Among former smokers who had quit for 1 year or more and among never smokers, HTP use was significantly associated with combustible cigarette smoking 1 year later (OR = 2.80, 95% CI 1.42 to 5.52 and OR = 9.95, 95% CI 3.39 to 29.16, respectively), while the association was not significant among former smokers who recently quit. The authors

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concluded that HTP use was associated with relapse/initiation of combustible cigarette smoking after 1 year.

The below publications are based on Wave 1 (2018) International Tobacco Control (ITC) Japan Survey. The ITC Japan Survey included many established measures used in ITC surveys in 28 other countries to examine the level of effectiveness of each of the WHO Framework Convention for Tobacco Control (FCTC) policy domains over time, and in comparison to other ITC countries.

Thompson described the methods of the Wave 1 (2018) International Tobacco Control (ITC) Japan Survey. The ITC Japan Survey was designed to collect survey data from Japanese cigarette smokers, heated tobacco product (HTP) users, dual cigarette-HTP users and non-users regarding their knowledge, attitudes, beliefs, perceptions, behaviors, and use patterns associated with cigarette smoking and HTP use. The respondents were adults aged 20 years and older in one of four user groups: (1) cigarette-only smokers who smoked at least monthly and used heated tobacco products (HTPs) not at all or less than weekly, (2) HTP-only users who used HTPs at least weekly and smoked cigarettes not at all or less than monthly, (3) cigarette-HTP dual users who smoked at least monthly and used HTPs at least weekly, and (4) non-users who had never smoked or who smoked less than monthly and used HTPs less than weekly. Eligible respondents were recruited by a commercial survey firm from its online panel. Respondents were allocated proportionally to sample strata based on demographic, geographic, and user type specifications benchmarked to a national reference. Survey weights, accounting for smoking/HTP use status, sex, age, education, and geography, were calibrated to benchmarks from a nationally representative survey in Japan. Response rate was 45.1% and cooperation rate was 96.3%. The total sample size was 4615 (3288 cigarette smokers, 164 exclusive HTP users, 549 cigarette-HTP dual users, and 614 non-users). The authors concluded that the 2018 ITC Japan Survey sampling design and survey data collection methods will allow analyses to examine prospectively the use of cigarettes and HTPs in Japan and factors associated with the use of both products and of transitions between them.

Sutanto analyzed data from Wave 1 of the ITC Japan Survey, a nationally representative web survey conducted from February to March 2018. The data show that concurrent cigarette-HTP users only constituted around one-tenth of current smokers (8.8% [8.0 – 9.7%]), they constituted a majority of current HTP users (63.2% [58.3 – 67.9]) in Japan in 2018. Compared to exclusive smokers, a greater proportion of concurrent cigarette-HTP users were male, younger, have higher household income, and higher education. Compared to concurrent cigarette-HTP users, a greater proportion of exclusive HTP users belongs to age group of 40–59. However, there were no difference in the frequency of smoking, number of cigarettes per day (CPD 15.0 [10.0 – 20.0] *vs.* 15.0 [10.0 – 20.0]), and smoking cessation behaviors between exclusive smokers and concurrent cigarette-HTP users, suggesting that HTPs reinforce nicotine dependence. Frequency of HTP use and the number of tobacco-containing inserts per day were significantly different between concurrent cigarette-HTP users and exclusive HTP users, with concurrent cigarette-HTP users reporting a higher frequency of non-daily HTP use and a lower number of tobacco-containing inserts per day (5.0 [1.4 – 12.0] *vs.* 10.0

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[5.0 – 20.0]). Almost all concurrent cigarette-HTP users were daily smokers (93.9% [91.2 – 95.9%]). The largest subgroups of concurrent cigarette-HTP users were dual daily users (48.4% [43.5 – 53.3%], n = 396), followed by predominant smokers (45.5% [40.5 – 50.7%, n = 213]), concurrent non-daily users (5.6% [3.7 – 8.3%], n = 31), and predominant HTP users (0.5% [0.2 – 1.3%]), n = 4). The authors concluded that concurrent user subgroups differed from each other on age, tobacco use behaviors, and quit intention and that alongside heterogeneity between concurrent and exclusive product users, differences across concurrent use subgroups highlight the importance of considering frequency of use in characterizing poly-tobacco users.

The ITC Japan survey, like the JASTIS study, is a cohort study on tobacco use. So similarly, to the JASTIS study, the study design and the quota sampling mode of recruitment of the ITC survey is not suitable to provide reliable estimates on exclusive/single, dual/concurrent, or poly tobacco product use. Moreover, as stated by Thompson, the survey weights to estimates of the user group sizes have been calibrated using the JASTIS study. The study design, the mode of recruitment and the weight calibration using the JASTIS study might explain why those studies found similar results regarding exclusive/single and dual/concurrent tobacco product use, and results quite different from the Japan National Health and Nutrition Cross-Sectional Survey (2019).

During the review period, some publications reported results on **risk perception of HTPs and communication**. Four of them from the ITC surveys conducted in Europe (Lotrean, 2020), in Canada (Sutanto, 2020), and in Japan (Gravely, 2020; Xu, 2020) and one from an online study conducted in 2018 in US.

Analyzing data from the ITC surveys conducted in six European countries (ITC 6E Survey; Germany, Greece, Hungary, Poland, Romania and Spain) in 2016 (Wave 1) and 2018 (Wave 2), Lotrean, 2020 found that factors associated with heated tobacco products (HTPs) use among those who had ever heard about these products at Wave 1 were country of residence, being a daily cigarette smoker and ever use of electronic cigarettes. At Wave 2, ever use of HTPs was significantly higher among those who had tried to quit smoking combustible cigarettes in the last 12 months, had tried electronic cigarettes during lifetime and perceived HTPs as less dangerous than combustible cigarettes.

Sutanto, 2020, based on ITC data collected in Canada in 2018, reported that over half of respondents perceived *IQOS* as equally or more harmful than e-cigarettes (53.7%), while almost a quarter either reported *IQOS* as less harmful than e-cigarettes or were uncertain (22.7% and 23.5%, respectively). Two-thirds of respondents (65.7%) perceived e-cigarettes as less harmful than cigarettes, yet only half (48.1%) perceived *IQOS* as less harmful than cigarettes. Both exclusive and dual e-cigarette users, but not exclusive smokers, had higher odds of perceiving *IQOS* as more harmful than e-cigarettes and less harmful than cigarettes compared to non-users. The authors concluded that most nicotine users and non-users perceive differential health risk across *IQOS*, e-cigarettes, and cigarettes. Although e-cigarettes are generally viewed as less harmful than cigarettes, the perceived harm of *IQOS* was unclear.

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Findings from the 2018 ITC Japan Survey were reported on perceptions of harmfulness of HTPs compared to cigarettes (Gravely, 2020) among exclusive smokers and smokers who use HTPs (concurrent users). Among all smokers, 47.5% perceive that HTPs are less harmful than cigarettes, 24.6% perceive HTPs to be equally as harmful, 1.8% perceive HTPs as more harmful, and 26.1% did not know. Concurrent users are more likely than exclusive smokers to believe that HTPs are less harmful (62.1% versus 43.8%, $p < 0.0001$). Frequent HTP users are more likely than infrequent users to believe that HTPs are less harmful (71.7% *vs*. 57.1%, $p </= 0.001$). In general, HTP users were significantly more likely than non-HTP users to believe that HTPs are less harmful than cigarettes, with this belief being more prominent among frequent users. Smokers who have been exposed to HTP advertising were more likely to perceive HTPs as less harmful than cigarettes.

Xu, 2020 also analyzed data from the 2018 ITC Japan Survey looking at the reasons why current and former smokers are using HTPs. Xu found that the most common reasons for regularly using HTPs were: beliefs that HTP are less harmful than cigarettes to themselves (90.6%) or to others (86.7%), enjoyment (76.5%), and social acceptability (74.4%). About half of current smokers (55.1%) reported using HTPs because these products might help them quit smoking. However, a near-equal percentage (52.0%) of current smokers reported using HTPs to replace some of the cigarettes they smoked so that they did not have to give up smoking altogether.

Lastly, Phan, 2020 reported the results of an online study conducted in US, in 2018 among a sample of 346 young adults (aged between 18 and 30 years). Phan found that cigarette smokers, e-cigarette and dual users had greater curiosity, interest, and likelihood of use than non-tobacco users. Also, that greater perceived risks of *IQOS* were negatively associated with curiosity, interest, and likelihood of use.

Overall, these studies indicate that perceiving the risk of HTPs as reduced compared to combustible cigarettes is associated with interest, likelihood of use and one of the key reason for regularly using HTPs and for using HTPs more frequently. In addition, the studies seem to suggest that where HTP is an established category and it is communicated (Japan), the perceived harm is clearer compared to where the HTP category has still a low prevalence and communication is highly restricted (Canada).

During the review period, several publications reported results about **heated tobacco products use prevalence and use patterns in South Korea**. Some of those publications (e.g. Hwang, 2020) measured use prevalence and use patterns among Youth while other publications (e.g. Kim, 2020) measured use prevalence and use patterns among the adult population (≥19 years old). The studies conducted among youth show that the prevalence of HTPs use among Youth is low, while as stated by Kim et al., HTP use has increased rapidly in Korea since its introduction in 2017.

For instance, Kim et al, 2020 investigated the prevalence and correlates of the current use of HTPs among a nationally representative sample of Korean adults. A total of 6182 participants aged ≥19 years took part in the 2018 Korea National Health and Nutrition Examination Survey

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conducted one year after the introduction of HTPs in Korea. The data show that the prevalence of current HTP use (defined as past 30-day use) among Korean adults was 4.4% (7.8% for males and 0.9% for females) in 2018. The data also show that the prevalence of current HTP use (defined as past 30-day use) among Korean adults was 6.8% among those aged 19–34 years, 7.9% among those aged 35–49 years, and 0.6% among those aged ≥50 years. Moreover, data show that among current HTP users, approximately 90% were dual users with combustible cigarettes (CCs) or electronic cigarettes (ECs), or triple users with CCs and ECs. In multivariable logistic regression analysis, males, younger [adult] participants, and current CC and/or EC users showed greater odds of being current users of HTPs compared with females, older participants, and non-users of CCs and ECs. Moreover, Kim found that compared with current CC-only use, using HTPs with CCs concurrently was not associated with attempts to quit smoking during the past year or with intentions to quit CC smoking. The author concluded that the popularity of HTP use and the pattern of its poly use with CCs and ECs is a new challenge for Korean tobacco control policy.

Overall, many publications from South Korea show high dual and poly tobacco use among Youth and adult HTP users. Among Youth, HTP use is generally based on ever use rather than current use which is likely to reflect experimentation of HTP rather than reflect an established use pattern of HTP. For instance, the Hwang et al, 2020 study was conducted only one year after the launch of *IQOS* in South Korea. Therefore, it appears likely that the use pattern of HTP reflect trial and experimentation rather than established HTP use. Moreover, this study was conducted in only one province of South Korea, which limited the generalizability of the study results. Among adults, the Kim et al, 2020, study measured the current prevalence of use of cigarettes, e-cigarettes and HTP in three different ways. Current CC users were defined as those who had a smoking history of ≥ 100 cigarettes and answered ‘every day’ or ‘some days’ to the question: ‘Do you smoke cigarettes?’. Current EC users included those who answered ‘yes’ to the question: ‘Have you used ECs during the past 30 days?’. Ever HTP users included those who checked ‘heated tobacco’ to the question: ‘Check all the products you have ever used: 1 = snus, 2 = waterpipes, 3 = cigars, 4 = heated tobacco (*IQOS*, *Glo*, etc.), 5 = other, and 6 = none’. Current HTP users included those who checked ‘heated tobacco’ to the question: ‘Check all the tobacco products you have used during the past 30 days’. The absence of consistency of the questions used raise questions about the reliability and the comparability of those measures. For instance, the lifetime criteria applied to cigarette smoking (≥ 100 cigarettes in lifetime) was not applied to e-cigarette and/or HTP use. Lastly, and even though the study also measured use prevalence of cigarettes and e-cigarettes, the publication does not provide any data about those two product categories.

During the review period, we found some publications concerning **HTPs in US**. These independent publications were mostly about awareness, use, and risk perception of HTPs.

Dai, 2020, analyzed the 2019 National Youth Tobacco Survey (NYTS) to assess self-reported awareness and use of HTPs among U.S. students in 2019. The study calculated weighted estimates of the prevalence of self-reported awareness, ever use, and current use (past 30-day) of HTPs. Dai reported that in 2019, 12.8% (a population estimate of 3,438,000), 2.4%

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(632,000), and 1.6 % (425,000) of U.S. students reported awareness, ever use, and current use of HTPs, respectively. Additionally, when examining factors associated with HTPs awareness and use, the authors found that current cigarette smoking, e-cigarette use, and other tobacco use are associated with higher odds of HTPs ever and current use than non-users. The degree of awareness and use of HTPs among youth in early 2019 reported by Dai, 2020, correspond to time period before *IQOS* was authorized and available for sale in the U.S. and when other HTPs were also in very limited distribution in the US. These results suggest possible misreporting of HTP, a relatively new product category.

Zhu, 2021, examined the results of an online study among a national probability sample of 20 449 U.S. adults with respect of awareness, use and risk perceptions of HTPs in the USA following FDA authorization of *IQOS*. Zhu, 2021 reported that 8.1% of respondents had heard of HTP, only 0.55% had tried and 0.10% were current users. Moreover, concerning the relative perceived harm of HTPs compared to e-cigarettes, the majority of respondents considered HTPs either less harmful than (11.6%), or equally harmful as e-cigarettes (42.7%). Another 37.2% chose 'I don't know,' with only 8.5% viewing HTP as more harmful than e-cigarettes. The majority of surveyed adults perceived HTPs and e-cigarettes as equally harmful and more than one-third did not have an opinion, suggesting limited awareness and therefore limited knowledge of the category.

Also Morgan, 2021, examined the harm perceptions and beliefs about potential modified risk tobacco products (MRTPs): e-cigarettes, snus, and HTPs. In this study, 864 adult current and former smokers read a paragraph describing the potential for the FDA to authorize MRTPs and a brief description of MRTPs. The three most endorsed beliefs about using HTPs were that it contains nicotine, that it is risky, and that it causes lung damage. Participants were least likely to endorse the beliefs that HTPs would help smokers quit, that it was not addictive, and that it was cool. The beliefs that HTPs would taste good and would be a good quit aid were associated with increased odds of intentions to try them. With respect to the perceived harm, study participants perceived HTPs as less harmful than snus, but not significantly different from e-cigarettes.

Consistent with Zhu, 2021, Azagba 2021, found low awareness of HTPs and very low ever use. This study used data (n = 42,477) from the 2019 Tobacco Use Supplement to the Current Population Survey and found that approximately 8.6% of U.S. adults were aware of HTPs. Awareness was higher among participants who were younger, male, cigarette smokers, e-cigarette users, and other tobacco product users. Ever use of HTPs was uncommon among U.S. adults (0.51%) but more prevalent among e-cigarette users and cigarette smokers.

The last study is Pokhrel, 2021. This study collected data from 2229 young adults (18-25 years old at the time of recruitment) in Hawaii, at 2 time-points 6 months apart. The study found that current (past 30-day) HTPs use was 1% at both time points. This proportion corresponds to approximately 22 subjects, leading to large confidence intervals on findings related to predictors of HTPs use. With the caution dictated by this limitation, the authors found that

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current cigarette-only use was the strongest concurrent predictor of HTPs product use, followed by dual use, and e-cigarette only use.

Overall, these studies show that HTPs are still a new category in the US and that some of the found awareness and use might be overestimated. In addition, the limited knowledge of the category is reflected in the levels of relative uncertainty about the perceived harm of HTPscompared to more established categories such as e-cigarettes.

In the review period, we found three papers that were investigating **use of HTPs in youth outside US**.

Gottschlich, 2020, conducted a cross-sectional survey on HTP awareness, susceptibility and use among 2870 students between the ages of 13 and 17 in private schools in Guatemala City, Guatemala. Of all students (n = 2870), about half were aware of HTPs (52.4%) and susceptible to future or continued use (52.4%). Whereas 8.4% of students had tried HTPs in the lifetime (but not in the last month), only 2.9% used HTPs in the past month. The authors concluded that the prevalence of HTP use was low but susceptibility to future use was high.

Kuwabara, 2020, analyzed data from a 2017 survey among 22,275 students in grades 7 - 9 (age 12 - 15) and 42,142 in grades 10 - 12 (age 15 - 18) nationwide in Japan. Overall, Kuwabara found that 1.8% were current users of any products: cigarettes, e-cigarettes, HTPs. Among all users, exclusive new product (e-cigarettes and HTPs) users were more likely to participate in club activities and intend to continue to higher education; any conventional cigarette users (including those who also used alternative products) were more likely to be exposed to secondhand smoke at home and to drink alcohol.

Hwang, 2020 analyzed nationally representative data (the 2019 Korea Youth Risk Behavior Web-based Survey) from a sample of 57,303 Korean students from grades 7 - 12. The study shows that total of 2.6% of respondents were current HTP users (at least one puff in the past 30 days), 3.2% were current users of e-cigarettes containing nicotine (days in which e-cigarettes were used in the past 30 days) and 6.8% were current cigarette smokers (days in which cigarettes were smoked in the past 30 days).

The authors also found that, among dual users, the dual use with cigarettes was the most common behavior for both HTPs and e-cigarettes users.

In general, these studies show that the prevalence of HTPs use among youth is low irrespective of the considered country. However, continuous monitoring is needed.

Finally, in this overview we are also including a paper, Gallus et al., 2021, which investigated their public health consequences on conventional cigarette smoking, taking advantage of a series of cross-sectional studies annually conducted between 2001 and 2019 in Italy. Every year, the sample, including around 3000 individuals, was representative of the general Italian population aged 15 years. In Italy, smoking prevalence steadily declined from 29.1% in 2001 to 20.6% in 2013, then increased to 22.0% in 2019. In 2017 – 2019, current electronic cigarette

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users were 2.1% and in 2019 current HTP users were 1.1%. Among 498 ever electronic cigarette users, 23.2% started or re-started smoking and 15.7% quit smoking after electronic cigarette use; of 49 ever HTP users, 19.1% started or re-started smoking combusted cigarettes and 14.6% quit smoking after HTP use. The authors stated that the availability of novel products in Italy resulted in a halt of the decreasing trend in smoking prevalence and that for the first time, they observed an increase of Italians inhaling nicotine, concurrently with the spread of novel (tobacco) products. Additionally, they stated that the use of novel products appears to increase rather than decrease the likelihood of smoking conventional cigarettes. Finally, the authors concluded that, based on this evidence, they see no argument to justify the huge fiscal and regulatory benefits these products continue to have, at least in Italy.

The data on prevalence shown by Gallus et al, 2020, contradicted the data reported by the Italian Ministry of Health[35] based on the Italian National Institute of Statistics survey data[36] showing a declining smoking prevalence overtime to reach 18.4% in 2019. The data on prevalence shown by Gallus et al, 2020, also contradicted with the Eurobarometer survey[37] for Italy which is also showing a declining use smoking prevalence overtime to reach 23% in 2020.

With regards to analysis by Gallus et al, 2020 among ever electronic cigarette users and ever HTP users (n = 49) in particular, the authors recognized that the sample size of each annual survey is relatively limited and may be inadequate to observe annual differences for relatively uncommon habits as current electronic cigarette and HTP use. We would also highlight the fact that such analysis was carried out among ever electronic cigarette users and ever HTP users, while it would be more meaningful to consider current electronic cigarette users and current HTP users to assess the impact on starting or re-starting smoking as well as on quitting smoking as ever use includes trial and experimentation, while current use better reflects established use.

# 3 ADVERSE EXPERIENCES (AES) REPORTED TO PMP S.A.

A summary of global AEs reported to PMP S.A. is presented in the Safety Update Report (SUR) and provided as Annex 3 to this report. The SUR, which has the same format and data collection procedure as previous SURs submitted to FDA, provides a comprehensive and critical analysis of the safety profile of all *IQOS* THS device versions and *HeatSticks* variants sold worldwide. The data presented in the SUR cover the period from January 1, 2020 to December 31, 2020, as well as the period from the first market launch worldwide (November

[35] http://www.salute.gov.it/imgs/C_17_pubblicazioni_2916_allegato.pdf

[36] https://www.istat.it/storage/ASI/AnnuarioStatistico_2020/Asi_2020.pdf

[37] https://ec.europa.eu/commfrontoffice/publicopinion/index.cfm/survey/getsurveydetail/instruments/special/surveyky/2240

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4, 2014) through December 31, 2020. The SUR also includes an appendix that is specific to reported AEs in the U.S.

In the U.S., a total of 25 non-serious AEs potentially associated with the Authorized Products' use[38] were received from unsolicited sources during the reporting period.

The most frequently reported (>5%) non-serious clinical AEs in the U.S. were Thermal burn (8.00%), Cough (8.00%), and Headache (8.00%). The events of Cough and Headache are known class effect AEs associated with the use of nicotine-containing products. The event of Thermal burn is recognized as an Important Potential risk associated with use of the Authorized Products and is monitored by PMP S.A.

There were no serious AEs (SAEs) reported by U.S. consumers during the reporting period.

In total, there were 61 non-serious AEs received from unsolicited sources in the U.S. since distribution of the Authorized Products began. No SAEs were received from the U.S during this period.

Overall, the analysis of the data from the U.S. market did not reveal any unexpected AEs nor new or increased risks in consumers who switched to the Authorized Products. The AEs reported by U.S. consumers are consistent with those reported outside the U.S.

The majority of the spontaneous reports received by PMP S.A. were not medically confirmed, as they were received from consumers and not healthcare professionals. For most of the reports received, information regarding the AEs and their circumstances was limited. PMP S.A. performs information follow-up attempts if the reporter has provided consent to be contacted back, and only in countries where specific local laws governing the collection of personal data permit such activities.

The evaluation of new information and the cumulative analysis did not demonstrate any changes in the safety profile of the THS. PMP S.A. will continue to meticulously collect and evaluate all new safety information in order to maintain adequate supervision of the safety of THS products and their impact on public health.

## 4 SALES AND DISTRIBUTION

Sales and distribution of the Authorized Product was addressed in periodic quarterly reports dated July 30, 2020[39]; October 30, 2020; January 29, 2021 and an Amendment dated December 9, 2020.

[38] The majority of the spontaneous reports received by PMI are not medically confirmed, i.e. they were reported directly by the consumers and not by the health care professionals.

[39] On December 9, 2020 ALCS has submitted an Ammendment to the periodic quarterly reports dated April 30, 2020 and July 30, 2020 to correct the dolar sales provided in those reports.

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In addition, concurrent with the submission of this annual report, a periodic quarterly report dated April 30, 2021 has been submitted with sales and distribution data. Annex 4 contains the previously submitted quarterly reports.

## 5 DATA ON PRODUCT PURCHASERS

Data on product purchasers, based on sales data and post-marketing analysis, was addressed in periodic quarterly reports dated July 30, 2020; October 30, 2020; and January 29, 2021.

In addition, concurrent with the submission of this annual report, a periodic report dated April 30, 2021 has been submitted with data regarding product purchasers. Annex 5 contains the previously submitted quarterly reports.

## 6 SUMMARY OF THE IMPLEMENTED POLICIES AND PROCEDURES REGARDING VERIFICATION OF THE AGE AND IDENTITY OF PURCHASERS DURING THE REPORTING PERIOD

A summary of the implemented policies and procedures regarding verification of the age and identity of purchasers during the reporting period is provided in Annex 6 to this report.

PM USA's policies and controls require that all *IQOS* devices and Marlboro *HeatSticks* transactions are age and identity verified to confirm purchasers are 21 years of age or older. Current policies and controls are working as expected and PM USA is not aware of any sales of the Authorized Products to consumers under the age of 21 through any of PM USA's owned channels or through third-party retail sales channels.

## 7 SUMMARY OF THE IMPLEMENTED POLICIES AND PROCEDURES REGARDING RESTRICTIONS ON YOUTH ACCESS TO THE PRODUCTS

A summary of the implemented policies and procedures regarding restrictions on youth access to the products during the reporting period is provided in Annex 7 to this report.

PM USA's policies and procedures regarding the age and identity of purchasers also restrict youth access to the Authorized Products. These policies and procedures require all purchasers to be 21 years of age or older. Current policies and controls are working as expected and PM USA is not aware of any sales of the Authorized Products to any consumers under the age of 21 through any of PM USA's owned channels or through third-party retail sales channels.

## 8 CHANGES TO THE MANUFACTURING, FACILITIES OR CONTROLS

A summary of changes made to the manufacturing, facilities or controls during the reporting period is provided in Annex 8-1 to this report.

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The summary contains a description of each change together with:

a. a comparison of each change to what was described in the PMTAs/MRTPAs;
b. the rationale for making each change.

As described in the original PMTAs/MRTPA, PMP S.A. uses a Change Management Process (CMP) to ensure that all proposed changes are assessed for their potential impact on product performance, safety, and quality before implementation.

The CMP is a robust safeguard ensuring that commercialized *HeatSticks* and *IQOS* System Holder and Charger are comparable to the earlier versions of these products on which PMP S.A. has performed initial testing. This is a critical requirement for assuring that the scientific assessment and data from studies conducted on the investigational tobacco products are representative and equally applicable to commercialized products.

As required by Marketing Orders and Exposure Modification Orders, this annual report contains a list of changes to the manufacturing process, facilities and/or controls. These changes did not result in any modification (including a change in design, any component, any part, or any constituent, including a smoke or aerosol constituent, or in the content, delivery, or form of nicotine, or any other additive or ingredient) of the Authorized Products.

A certification that the reported changes did not result in any modification of the tobacco product together with the basis for concluding that these changes did not result in any modification to the final product is provided in Annex 8-2.

This annual report contains information collected in the time period from March 1, 2020 to February 28, 2021[40]. These changes were managed according to the PMP S.A's processes for change management as part of a continuous improvement plan to address product quality and none of these changes were deemed to impact product performance. In addition, no significant environmental impacts or risks associated with the postmarket changes were identified and they do not alter the overall conclusions of the previous EIAs and no additional environmental protection measures, mitigation measures, or alternative actions are necessary to address environmental impacts.

## 9 MANUFACTURING DEVIATIONS

A summary of all manufacturing deviations, investigations, and corrective and preventive actions, including, but not limited to, those associated with processing, testing, packing, labeling, storage, holding and distribution during the reporting period March 1, 2020 through

[40] For *IQOS*® 3 System Holder and Charger, this Annual Report covers the reporting period since the issuance of Marketing Order on December 7, 2020 until the February 28, 2021.

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February 28, 2021[40], is provided in Annex 9 to this report as required by Marketing Orders and Exposure Modification Orders.

Only manufacturing deviations for the Authorized Products that were released for sale are reported.

As part of the PMP S.A's quality systems, a risk assessment is performed for products manufactured with any deviation. Those products identified as being manufactured with a deviation potentially affecting product characteristics were not released to the market and therefore have not been included in this report.

For the purpose of this risk assessment, PMP S.A. defined product characteristics broadly as:

- Bill of Materials (BoM) including software (product composition),
- Packaging materials, if they can impact the products performance,
- Product configuration, describing how the components are assembled,
- Product's specifications (release, stability and performance specifications),
- Aerosol Crititical Quality Attributes (CQAs).

None of the reported manufacturing deviations was considered to affect the characteristics of the final product.

## 10 SUMMARY OF STABILITY MONITORING AND TESTING

A summary of stability monitoring and testing of *HeatSticks*, protocols and tests concluded during the reporting period March 1, 2020 through February 28, 2021 are provided in Annex 10 to this report. The report contains the results of the three 24 month follow up stability studies concluded on: Marlboro Amber *HeatSticks*, Marlboro Green Menthol *HeatSticks* and Marlboro Blue Menthol *HeatSticks* ("Authorized *HeatSticks*").

The results of the follow up stability studies did not change the previously submitted product shelf life and demonstrated that the Authorized *HeatSticks* are chemically and microbiologically stable longer than proposed product storage period. No changes were observed that could affect the product's potential health risks.

## 11 LABELING CHANGES

A description of all labeling changes within the reporting period March 1, 2020 to February 28, 2021[40], is provided in Annex 11. The description includes the date the labeling was first disseminated and the date when the labeling was discontinued, with cross-reference to the full color final printed labeling previously submitted in a 30-Day Notifications. The Annex includes the labeling changes that occurred due to the name change of the three authorized *HeatSticks* variants and the dissemination of the *IQOS* 3 Device Kit, along with other small changes. One minor change, the addition of a Julian Date Code sticker is provided in this report

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but was not submitted in a 30-Day Notification. This change was for internal purposes only, on the back of the *IQOS* 2.4 Device Mobility Kit, to identify the date of manufacture.

## 12 ADVERTISING NOT PREVIOUSLY SUBMITTED

Final full-color copies of all advertising for the Authorized Products that have not been previously submitted are provided in Annex 12.

PM USA submitted twenty-nine 30-Day Notifications during the Reporting Period with labeling, advertising, marketing, and promotional materials. Those materials previously submitted are not included in this Annex, but nineteen assets that were not previously submitted are included. These assets represent updated versions of previously submitted assets. Information regarding the original date the advertisements were first disseminated and the date the advertisements were discontinued, as well as a description of changes to the materials is also provided in this Annex.

## 13 CONSUMER RESEARCH STUDIES CONDUCTED IN THE FORMATION OF NEW LABELING, ADVERTISING, MARKETING, AND/OR PROMOTIONAL MATERIALS

PM USA conducted consumer research studies during this reporting period that were not classified as formative or evaluative when conducted. Most of the studies have elements that could be reasonably viewed as formative and evaluative based on the definitions provided in the MO. Therefore, rather than attempt to categorize summaries of the research studies by placement into a particular annex, we have provided a summary of all consumer research studies in Annex 14.

## 14 CONSUMER EVALUATION RESEARCH STUDIES CONDUCTED TO DETERMINE THE EFFECTIVENESS OF LABELING, ADVERTISING, MARKETING AND/OR PROMOTIONAL MATERIALS

A total of eight adult consumer research studies were completed during the Reporting Period.

These studies provided learning and insights on the adult smokers 21 years of age or older (AS 21+) journey towards full conversion to *IQOS* and the effectiveness of marketing communications in advancing AS 21+ to successful conversion to *IQOS*. The studies were meant to guide enhancements to the *IQOS* commercialization plan and its goal of maximizing conversion from combustible cigarettes to *IQOS*. The studies provided learnings on:

- openness to non-combustible tobacco alternatives to conventional cigarette adult smokers;
- awareness levels of *IQOS*; and

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- effectiveness and enhancement opportunities of marketing communications and programs.

We have provided detailed summaries of these consumer research studies in Annex 14.

## 15 CREATION AND DISSEMINATION OF THE PRODUCTS' LABELING, ADVERTISING, AND/OR PROMOTIONAL MATERIALS

A summary of the creation and dissemination of the products' labeling, advertising, marketing, and/or promotional materials, including a list and description of all entities involved and their involvement, are provided in Annex 15 to this report.

During the period covered by this report, PM USA engaged with adult smokers 21+ through owned retail, email, direct mail, print advertisements, digital paid media, owned websites, branded social media pages, brochures and point of sale at third-party retailers. PM USA worked with nine entities to create and disseminate marketing materials.

## 16 DESCRIPTION OF THE IMPLEMENTATION OF ALL ADVERTISING AND MARKETING PLANS

A description of the implementation of all advertising and marketing plans, including strategic creative briefs and paid media plans, is provided in Annex 16 to this report.

During the period covered by this report, PM USA engaged with adult smokers 21+ through owned retail, email, direct mail, print advertisements, digital paid media, owned websites, branded social media pages, brochures and point of sale at third-party retailers. Advertising and marketing plans focused on creating awareness and converting adult smokers 21+ to *IQOS*.

## 17 ANALYSIS OF THE ACTUAL DELIVERY OF ADVERTISING IMPRESSIONS

An analysis of the actual delivery of advertising impressions, by channel, by product, and by audience demographics was referenced in periodic quarterly reports submitted on July 30, 2020; October 30, 2020; and January 29, 2021.

In addition, concurrent with the submission of this annual report, a periodic report dated April 30, 2021 has been submitted that contains the requested analysis. The periodic quarterly reports containing an analysis of the actual delivery of advertising impressions are referenced in Annex 17 to this report.

## 18 SUMMARY OF MEDIA TRACKING AND OPTIMIZATION

A summary of media tracking and optimization, by channel, by product, and by audience demographics referenced in periodic quarterly reports submitted on July 30, 2020; October 30,

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2020; and January 29, 2021. In addition, concurrent with the submission of this annual report, a periodic report dated April 30, 2021 has been submitted that contains summary information. The periodic quarterly reports containing a summary of media tracking and optimization are referenced in Annex 18 to this report.


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