PHILIP MORRIS
PRODUCTS S.A.

TABLE OF CONTENTS

PHILIP MORRIS
PRODUCTS S.A.

THS AEROSOL OVERVIEW

As part of the comprehensive Scientific Assessment Program for THS, PMI has conducted numerous scientific studies to assess the chemistry and physics of the aerosol. The scientific assessment has focused on the THS aerosol in the context of what a THS user is exposed to during use as well as studies to determine the level of environmental emissions and potential exposure of bystanders when THS is used indoors. It should be noted that although there is no side-stream aerosol from the THS device, THS users do exhale levels of some aerosol constituents that can be measured under indoor air conditions. This document summarizes previously submitted data and new findings from recently concluded studies, in order to provide a complete overview of the THS aerosol characterization.

1. MAINSTREAM AEROSOL

1.1 Summary of data submitted to date

PMI previously provided an Aerosol Chemistry and Physics assessment in the MRTP application for THS (November 18th, 2016 Chapter 6.1.1 Aerosol chemistry, 2.7 Executive Summary), in which PMI had presented the following findings: (1) a consistent and substantially reduced formation (or emission) of HPHCs, (2) confirmation that the aerosol particle size is respirable, and (3) confirmation of the absence of solid particles in the aerosol of THS.

In addition, (4) PMI submitted on December 8th an amendment to the MRTPA on the evaluation of potential new hazards of THS compared to 3R4F cigarette smoke through an untargeted differential screening analysis (NTDS).

Specifically and in more detail:

> *(1) THS aerosol studies consistently demonstrate substantial reductions in the levels of Harmful and Potentially Harmful Constituents (HPHCs) compared to cigarette smoke (MRTPA Section 6.1.1)*

PMI has conducted a thorough chemical analysis of the aerosol for the regular and a mentholated *HeatSticks* variants. This analysis consisted of the quantification of 54 HPHCs, in comparison with the levels determined for the reference cigarette, 3R4F. The list of HPHCs measured by PMI includes all of the prioritized HPHCs listed by the US FDA, Health Canada and WHO.

Data from this analysis demonstrated that all quantified HPHCs were reduced in THS aerosol compared to 3R4F. For the regular *HeatSticks*, there was an average reduction of >92 % on a per stick basis, and >89 % normalized for nicotine delivery. The mentholated *HeatStick* showed a very similar average reduction of >93 % on a stick basis and >88 % on a nicotine basis. PMI also determined that the average reduction of HPHCs prioritized by FDA (FDA, Reporting Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke Under Section 904(a)(3) of the Federal Food, Drug, and Cosmetic Act, March 2012) was similar when

comparing THS to the median values determined for 31 combustible cigarette brands from Philip Morris USA. These brands used were selected to be representative of the US market. These data also demonstrated that the presence of menthol had no impact on the levels of measured HPHCs.

(2) THS Aerosol is Respirable (MRTPA Section 6.1.1)

PMI has conducted a physical characterization assessment of THS aerosol (droplet size distribution) to determine whether the aerosol is respirable. As discussed in the MRTP application, nicotine delivery is an attribute that is considered important by adult smokers when they are exposed to alternative, lower-risk tobacco products. In order to meet this adult smoker's expectation, THS aerosol, which contains nicotine, must be respirable. As discussed in the MRTPA section referenced above, studies have shown that the droplet particle size distribution for both THS aerosol and cigarette smoke fall within the respirable range. This finding is also confirmed by the PK/PD studies (MRTPA Section 6.2) which confirm that nicotine delivery is similar to that of a conventional cigarette.

(3) Absence of Carbon Based Particles (MRTPA Section 6.1.1)

A thermodenuder (a heated tube at 300 °C) was used to strip the smoke/aerosol of its volatile content and the remaining fraction was collected on an impactor, and the impactor was scanned with an electron microscope to identify the potential remaining content. This study (Pratte et al., 2017) revealed that cigarettes smoke contains carbon based particles in the sub-micron range. The solid carbon-based nanoparticles in cigarette smoke are a hallmark of combustion and have been shown to trigger inflammation and demonstrated to cause lung and cardiovascular disease. The electron microscopy images demonstrate that the smoke from a burning cigarette contains many solid particles, while the THS aerosol is exempt of such particles, confirming that heating tobacco only produces an aerosol composed of liquid droplets.

(4) THS Aerosol does not present any new hazards compared to 3R4F cigarette smoke (MRTPA Amendment Dec. 08th, 2017)

The purpose of the Non Targeted Differential Screening (NTDS) study was to identify potential new hazards contained in THS aerosol, beyond the known and listed HPHCs, by analyzing and comparing the whole chemical content of the THS aerosol vs. the smoke of the 3R4F, and focusing only on compounds either unique or higher in THS compared to the smoke from 3R4F reference cigarette, followed by a toxicological evaluation of such compounds.

The NTDS approach utilize complementary analytical methods, based on liquid and 2-dimensional gas chromatography, that were developed to cover the broadest possible chemical space, from low to highly volatile, and from polar to non-polar compounds. Because these methods are semi-quantitative, the concentration of compounds were estimated by comparison with a restricted number of standards as it is impractical to calibrate for all compounds. The identification was based on mass spectra and retention index matching, compared with various databases and, whenever available, by using purchased reference standards.

PHILIP MORRIS
PRODUCTS S.A.

The overall results confirm that heating rather than burning tobacco results in a significant reduction in the number of compounds (approximately 4330 peaks with a semi-quantified abundance ≥100 ng/stick for 3R4F vs. 750 for THS). This is explained because many processes that take place in a combustible cigarette do not occur when the tobacco is heated. Within those compounds, we found that 53, 57 and 60 aerosol constituents were higher in concentration in THS Regular, THS Smooth Menthol and THS Fresh Menthol respectively, when compared to the reference cigarette smoke, resulting in a total of 85 individual compounds for all THS variants (some compounds are common to all three variants).

An evaluation for the likely origins of these 85 constituents demonstrated that the majority are either: 1) flavors that are naturally found in cured tobacco or added to the tobacco, or 2) plant metabolites or 3) compounds that are the result of sugar (naturally present in tobacco) transformation upon heating. These results were expected based on blend differences between THS *HeatSticks* and 3R4F reference cigarettes as well as the fact that THS variants are flavored, unlike 3R4F cigarettes. These two factors explain the differences observed, particularly for those menthol derived or related flavors that are not present in 3R4F cigarettes.

PMI identified 4 compounds of potential toxicological concern within this list of 85 constituents, that were found either in the range of, or in higher quantities than, cigarette smoke. Our evaluation, based upon published inhalation toxicology literature, indicates that the level of exposure to these compounds through the use of THS are below the level of toxicological concern. This is consistent with the *in vitro* and *in vivo* toxicological investigations of THS aerosol, which demonstrated systematically an overall decrease of toxicity compared to cigarette smoke.

1.2. Summary of new data in this amendment

- *THS aerosol studies consistently demonstrate substantial reductions in the levels of HPHCs from the FDA full list compared to cigarette smoke.*

PMI has recently completed a study to quantify and compare the levels of all HPHCs found in THS aerosol with those found in 3R4F smoke from the FDA "Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke; Established List" (77 FR 20034). The study was conducted by Labstat International ULC and the study report is included with this MRTP amendment. Similar to the all previous studies, THS aerosol contained significantly lower levels of all HPHCs compared with the levels found in cigarette smoke. Based on the levels measured in THS and 3R4F, PMI demonstrated an average reduction of HPHCs of more than 91.9% and 87.8% on a stick basis or nicotine basis respectively for THS Regular and greater than 92.6% and 88.8% on a stick basis or nicotine basis respectively for the THS Smooth Menthol.

- *PMI performed a comprehensive in-depth chemical characterization of THS aerosol*

The "P1 characterization study" is based on non-targeted screening (NTS) using the same methodological approaches as for NTDS, except for the use of different data processing and the aerosol trapping.

For the trapping, PMI used a "cold trap" to collect the whole smoke/aerosol for the liquid chromatographic assessment in the NTDS study. For the "P1 characterization study", PMI used a combination of Cambridge pad followed by impingers for all methods. This method allowed PMI to distinguish what is in the particulate phase (pad) and what compounds were found within the gas vapor phase (impinger). However, the overall content trapped is the same between the 2 collections systems.

For data processing, all compounds identified in the THS aerosol with a concentration above 100 ng per stick were considered, whereas for the NTDS study the focus was exclusively on compounds unique or increased in THS compared to 3R4F. Therefore, compared to the NTDS study, the bulk of the data processing effort was the identification of all compounds, matching their mass spectra and retention indices with commercial or in-house libraries and, in the majority of cases, using purchased reference standards. It is important to note that, with the exception of the compounds identified by NTDS, all compounds identified in this study were also present in either equivalent or higher concentrations in the smoke of 3R4F.

A full data evaluation identified a total of 529 chemical constituents (excluding nicotine, water and glycerin, which constitute 90 % of the THS aerosol mass). This number is smaller than the previous estimate of 750 (presented at the TPSAC meeting and based on the NTDS reports) because the full data analysis showed that many compounds were detected by more than one method, and accounting for these overlaps reduced the overall number of unique compounds vs. the numbers of identified chromatographic peaks. Over 80 % of all identified compounds were confirmed by reference standards. The compounds are distributed between the particulate phase (69 %) and the gas vapor phase (24 %), while some are present in both (7 %). When looking exclusively at the particulate phase, i.e. the fraction present on the Cambridge pad used to trap the aerosol, the total weight of the trapped aerosol (obtained by weighing the pad before and after collection) can be compared with the sum of masses for all identified compounds in the aerosol by chromatography. This comparison shows that 99.7 % of the collected mass of the aerosol is of known composition.

To the best of our knowledge, this is the first time that such a comprehensive in-depth chemical characterization of any tobacco product has been reported. It represents several years of effort of systematic development of analytical method and advanced structural identification techniques, which have been applied to the aerosol of THS.

PHILIP MORRIS
PRODUCTS S.A.

2. ENVIRONMENTAL EMISSIONS: INDOOR AIR QUALITY (IAQ)

2.1. Summary of data submitted to date

- *Use of THS indoors does not negatively impact air quality (MRTPA, section 2.7 Executive Summary, Chapter 6.1.1 Aerosol chemistry, section 5.1.2.2)*

PMI conducted several studies to assess the effects of THS on indoor air quality (IAQ) when used indoor. Unlike the lit-end of a cigarette which produces side stream smoke, a significant source of environmental tobacco smoke (ETS), also called second-hand smoke, the THS does not produce side stream aerosol. As a consequence, the main impact on indoor air quality occurs when small amounts of THS aerosol are exhaled from the THS user. The studies were conducted under well-controlled and representative conditions based on accepted building standards and were benchmarked against national and international standards for exposure to environmental pollutants. The study compared the indoor air chemistry during THS use versus the background air chemistry, meaning people were present in the room, but not using any product.

Out of 18 indoor air constituents measured during THS use, the concentrations of 16 constituents did not exceed the background level. Only acetaldehyde and nicotine concentrations were above background, but at levels far below the minimal risk level for chronic exposure, as defined in environmental guidance described in the corresponding MRTPA section mentioned above.

Based on that it can be concluded that using THS indoors does not negatively impact air quality.

- *Use of THS indoors does not negatively impact air quality as demonstrated with additional analytes and under stringent conditions s (Response to March 2nd, 2018 information request)*

On March 29th, as part of a response to the March 2nd information request from the FDA, PMI submitted 2 additional studies in the context of indoor air quality:

Study 1: The first study was performed in the PMI controlled room and is similar to the previous studies, but with additional analytes and a more stringent condition, i.e. the ventilation of the room was decreased to 0.5 air change per hour, which is representative for residential buildings with natural ventilation, and sticks usage was left ad-libitum to the panelists.

The additional analytes were 2 nitrosamines (NNK and NNN), glycerin and propylene glycol as well as the Total Volatiles Organic Compounds, a GC-MS method that screens compounds between C6 (hexane) and C16 (hexadecane) and reports either the total mass (expressed in toluene equivalent) or as chromatographic traces where all peaks can be compared between different conditions. The TVOC method is similar to an untargeted approach as described above for the main stream aerosol, but limited to one method.

Similarly to the previous studies, this study shows that only acetaldehyde, nicotine and glycerin concentrations were increased in the air by the use of the THS, at concentrations much lower than existing air quality guidelines/guidance, therefore not negatively impacting air quality.

PHILIP MORRIS
PRODUCTS S.A.

Study 2: The second study was performed to evaluate the impact on indoor air quality of human presence, as well as the impact of daily living activities such as drinking wine, sport, use of cosmetic and preparation of food. It was demonstrated that human presence and some of the tested activities may have major impact on some compounds concentrations, highlighting the importance of background measurements when performing studies on THS, to eliminate confounding factors.

2.2. Summary of new data in this amendment

- *THS does not negatively affect by-standers exposure to nicotine and TNSAs when passively exposed to THS in a real-life restaurant setting (Final report will be provided July 2018)*

As announced in our last response to the FDA information request dated March 29, 2018, PMI performed a Passive Exposure in a real-life restaurant setting in Japan (P1-PES-JP-01). In this study, the effect of passive exposure to THS aerosol on Non-Smokers in a real-life restaurant during dinner events was investigated. Levels of urinary biomarkers of exposure (BoExp) to selected HPHCs representative of ETS and other exposure markers in Non-Smokers were compared to exposure levels in Non-Smokers without exposure to THS aerosol. Furthermore, the impact of passive exposure to THS aerosol on THS Users and Cigarette Smokers who did not use any nicotine or tobacco-containing nicotine products during the event was also investigated. This allowed us to assess whether individuals with varying levels of background exposure to HPHCs in their personal lives, would be exposed to increased levels of HPHCs from passive exposure to THS aerosol. The study also evaluated IAQ overall through the assessment of concentrations of selected HPHCs representative of IAQ in the air during the dinner events.

Preliminary results pertaining to nicotine and tobacco specific nitrosamines (TSNAs) exposure as well as related IAQ parameters (nicotine and TSNAs in air as well as concentration of particulate matter [PM_1 and $PM_{2.5}$] in air) are now available. These preliminary results showed that: (1) Non-Smokers passively exposed to THS aerosol in a real-life setting do not have an increase in exposure to nicotine; (2) Non-smokers passively exposed to the THS aerosol in a real-life setting do not have an increase in exposure to TSNAs; and (3) the use of THS did not generate Environmental Tobacco Smoke (ETS) and did not negatively impact indoor air quality

PHILIP MORRIS
PRODUCTS S.A.

as measured by nicotine, TSNAs and respirable suspended particulate matter (PM_1 and $PM_{2.5}$) in air[1].

In summary, the results available to date indicate that THS does not negatively affect by-standers' exposure to nicotine and TSNAs when passively exposed to THS aerosol. The data analysis of the remaining endpoints and the preparation of the final study report are on-going and will be submitted to the FDA in July.

3. CONCLUSION

Over the past few years, PMI has conducted a number of studies related to the aerosol of THS, linked to the impact on the users as well as bystanders.

PMI has demonstrated that all HPHCs listed by different health authorities (FDA, Health Canada, WHO) are reduced compared to the reference cigarette 3R4F, and that the average reduction is around 90 %, whatever list is considered.

Furthermore, PMI has demonstrated that THS does not emit solid particles, a typical byproduct of combustion processes, which are known to trigger inflammation and demonstrated to cause lung and cardiovascular disease. The THS aerosol is exclusively composed of liquid droplets, which size distribution falls into the respiratory region.

In addition to the targeted approach (on HPHCs), PMI has conducted a full chemical screening of the THS aerosol, using a range of complementary chromatographic methods, which concluded that. THS Aerosol does not present any new hazards compared to 3R4F cigarette smoke. Furthermore, using the same approach PMI was able to characterize the THS aerosol to an estimated level of 99.7 %, an unprecedented level of identification of a tobacco product.

Regarding indoor air quality, PMI has conducted a number of studies using targeted quantitative methods measuring air pollutants in a controlled room, as well as an untargeted method referred to as TVOC (Total Volatile Organic Compounds). The studies covered different simulated scenario, such as office, restaurants or private residence. All studied conditions showed that using THS only increases levels of nicotine, acetaldehyde and glycerin, but at levels significantly below all existing indoor air quality guidelines, demonstrating that using THS indoor does not negatively impact the air quality.

[1] Based on Indoor Air Quality Guidelines issued by the Ministry of Health, Labour and Welfare (MHLW), the Ministry of Land, Infrastructure, Transport and Tourism (MLIT) of Japan, the US Office of Environmental Health Hazard Assessment (OEHHA) and the US Office of Occupational Safety and Health Administration (OSHA).

PHILIP MORRIS
PRODUCTS S.A.

The observation that THS does not negatively impact the air quality was then confirmed with clinical data, in a study performed in a real-life restaurant setting in Japan.

Overall, the finding from all aerosol chemistry analyses are consistent with the findings from all of *in vitro* and *in vivo* studies that demonstrated a significant reduction in adverse biological impact of THS aerosol compared with 3R4F smoke. The aerosol chemistry analysis is further substantiated by the reduced exposure studies in animals and humans, confirming that THS aerosol delivers a significantly reduced level of HPHCs and chemicals compared with cigarette smoke. In considering the totality of evidence, the aerosol chemistry provides a strong confirmation for the assertion that adult smokers who switch to THS aerosol will be exposed to significantly lower levels of HPHCs that will, in turn, reduce harm and the risk of tobacco-related diseases compared to continued smoking.

S. M. L

Serge Maeder, PhD
Director Product Research
Philip Morris Products S.A.

26. Apr. 2018

Date

4. REFERENCES

Pratte P, Cosandey S, Goujon Ginglinger C. Investigation of solid particles in the mainstream aerosol of the Tobacco Heating System THS2.2 and mainstream smoke of a 3R4F reference cigarette. Human & Experimental Toxicology. 2017; 36(11): 1115-1120.

U.S. Department of Health and Human Services, FDA (Food and Drug Administration). [Docket No. FDA-2012-N-0143]: harmful and potentially harmful constituents in tobacco products and tobacco smoke; established list. Federal Register 2012; 77: 20034-7