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Response to the article entitled "IQOS: examination of Philip Morris International claim of reduced exposure"

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1 Executive Summary

The Division of Clinical Pharmacology, Department of Medicine, University of California San Francisco, California, USA, has recently published a research paper in *Tobacco Control* (St Helen, 2018) claiming that "*PMI's data […] show significantly higher levels of several substances that are not recognised as HPHCs by the FDA in IQOS emissions compared with combustible cigarette smoke. The impact of these substances on the overall toxicity or harm of IQOS is not known. We examined PMI's MRTP application, specifically sections on aerosol chemistry and human exposure assessment, to assess the validity of PMI's claims of reduced exposure and risk*."

In summary, we have assessed these claims based on a careful review of our scientific data (PMI's Modified Risk Tobacco Product Application (MRTPA) for *IQOS*) submitted to the U.S. Food and Drug Administration (FDA). The scientific data is in the FDA submission and requires knowledge of the design and conduct of aerosol chemistry and clinical studies, together with a careful and detailed review of the resulting data, to reach accurate, science-based conclusions. While we welcome scientific review and discussion of our results, the authors of this paper failed to consider the totality of the available evidence and therefore led to conclusions that are incorrect and misleading.

We have prepared a point-by-point assessment of the claims made by the authors, and this detailed analysis can be found below.

In conclusion, based on an analysis of our aerosol chemistry and human exposure studies performed according to international standards of good practice, the totality of evidence supports the claim of Philip Morris International (PMI) that the Tobacco Heating System (THS) emits significantly lower levels of harmful and potentially harmful constituents (HPHC) that are emitted in cigarette smoke and, consequently, leads to significant reduction in exposure to HPHCs in smokers who completely switch to THS.

Although THS is not risk-free, the totality of evidence available for THS clearly demonstrates that switching completely to THS significantly reduces the exposure to harmful compounds contained in cigarette smoke and presents less risk of harm compared with continuing to smoke.

2 Introduction

The Department of Medicine, University of California San Francisco, California, USA, has recently published a research paper in *Tobacco Control* (St Helen, 2018) raising concerns about high levels of several substances not recognized by the FDA as HPHCs in THS emissions and their potential toxicity and harm.

From their analysis of PMI's aerosol chemistry, the authors reported that "*PMI reported levels for only 40 of 93 harmful and potentially harmful constituents (HPHCs) on FDA's HPHC list in IQOS mainstream aerosol. All substances in PMI's list of 58 constituents (PMI-58) were lower in IQOS emissions compared with mainstream smoke of 3R4F reference cigarette. However, levels of 56 other constituents, which are not included in the PMI-58 list or FDA's list of HPHCs, were higher in IQOS emissions; 22 were >200% higher and seven were >1000% higher than in 3R4F reference cigarette smoke.*"

From their analysis of human exposure studies, the authors highlighted that "*11 of the 17 HPHCs measured are included in a list of 18 HPHCs that FDA recommends to be measured and reported in users of tobacco products. PMI assessed systemic exposure to pyrene, which is not included in FDA's list of HPHCs, as a proxy for exposure to polycyclic aromatic hydrocarbons (PAHs) using 1-hydroxypyrene. PMI did not assess systemic exposure to inorganic compounds, phenols and metals.*"

This report aims to clarify these findings and to provide context by summarizing the scientific data available to date on THS (marketed in a number of countries under the brand name *IQOS*) with regards to aerosol chemistry and reduced exposure, which was also reported in PMI's MRTPA for *IQOS*.

3 Summary of Aerosol Chemistry

PMI has demonstrated that the level of emissions of HPHCs generated by THS are, on average, 90-95% lower than in cigarette smoke. This comparison was based on a list of 58 compounds, known as the PMI-58 list, which includes all prioritized HPHCs listed by regulatory bodies and was part of the original submission of PMI's MRTPA for *IQOS*. Since then, we have extended our assessment to include the full FDA list of 93 HPHCs and have submitted this data to the FDA as an amendment to the MRTPA. PMI also conducted a full non-targeted differential screening (NTDS) of the THS aerosol, which demonstrated that the aerosol of THS contains far fewer compounds and is significantly less complex compared with smoke from a 3R4F reference cigarette (University of Kentucky). The NTDS also showed that there were 85 compounds found to be more abundant in THS aerosol than in 3R4F cigarette smoke. These compounds are related to the tobacco blend and flavors that are naturally found in cured tobacco or added during the manufacturing process, plant metabolites, or from compounds that are the result of sugar (naturally present in tobacco) transformation upon heating. From these 85 compounds, four compounds were of potential toxicological concern, and our evaluation, based upon published inhalation toxicology literature, indicates that the level of exposure to these compounds through the use of THS is below the level of toxicological concern. These results were further corroborated by PMI's extensive *in vitro* and *in vivo* toxicology testing, showing a significantly reduced overall toxicity of THS (more than 90%) compared with 3R4F. All detailed results are available in PMI's MRTPA for *IQOS*.

3.1 Characterization of THS Aerosol

PMI conducted a comprehensive review of the methodologies available and the scientific literature linking specific compounds to negative health effects. The compounds used to characterize THS aerosol were selected according the following criteria:

1. Priority toxicants in tobacco smoke as listed by regulatory bodies
2. Smoke constituents with established biomarkers of exposure (BoExp) (smoke/aerosol constituents or metabolites), not already included in criterion 1
3. HPHCs that are predominantly formed below 400°C, not already included in criterion 1
4. HPHCs that are predominantly formed above 400°C, not already included in criterion 1
5. Product-specific analytes (such as glycerol and menthol)
6. Availability of well-established testing and analytical methods

Altogether, PMI established a list of 58 compounds, referred to as the PMI-58, which included 54 HPHCs. Importantly, this list includes all of the prioritized HPHCs listed by the FDA (FDA Harmful and Potentially Harmful Constituents), Health Canada, and the World Health Organization (WHO). The quantification of the 58 constituents was performed in compliance with published international standards and practices. All aerosols and smoke samples were generated according to international standards, using the Health Canada Intense smoking regimen. The results show that the levels of these HPHCs are reduced by 90-95%, on average, in THS aerosol compared with the smoke of the 3R4F reference cigarette. For examples, the formation of aldehydes, such as acetaldehyde, formaldehyde, and acrolein, have been assessed for THS, with reductions in the levels of emissions of 86.6%, 90.6%, and 93.8%, respectively. The tobacco-specific nitrosamines (TSNA) N-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) were reduced by more than 95% in THS aerosol compared with 3R4F smoke. Furthermore, the International Agency for Research on Cancer (IARC) group 1 carcinogens (12 constituents) were reduced by 97%, on average. Inorganic compounds, phenols, and metals were also assessed in PMI's aerosol characterization studies, and levels of these compounds were reduced by 92% for phenols and 95% or more for most metals assessed (such as lead, cadmium, chromium, nickel) in THS aerosol compared with 3R4F smoke (Schaller, 2016). Mercury was reduced by more than 64% in THS aerosol compared with 3R4F smoke (**Table 1**). For details, please see PMI's MRTPA for *IQOS*, section 7.1 Product Analyses.

Independent studies on THS aerosol chemistry (Bekki, 2017; Li, 2018), including the assessment of the FDA (Office of Science Center for Tobacco Products Food and Drug Administration), have shown results consistent with PMI studies.

Table 1. Reduction in levels of inorganic compounds, phenols, and heavy metals in THS aerosol compared with 3R4F smoke.

HPHC	% reduction in THS aerosol to 3R4F cigarette smoke *
Inorganic compounds	
Ammonia	63.2%
Hydrogen cyanide	>99.5%
Nitric oxide	97.4%
Nitrogen oxides	97.4%
Phenols	
o-Cresol	98.4%
m-Cresol	99.4%
p-Cresol	99.5%
Catechol	83.3%
Hydroquinone	93.1%
Phenol	90.6%
Resorcinol	>96.8%
Heavy metals	
Arsenic	NA
Cadmium	>99.7%
Chromium	NA
Lead	94.0%
Mercury	64.2%
Nickel	NA
Selenium	NA

*: on stick basis
N/A: THS and 3R4F HPHC levels under the limit of detection
Source: PMI's MRTPA for *IQOS*, section 7.1 Product Analyses

3.2 Aerosol Chemistry on Extended FDA List of 93 HPHCs

Since the initial aerosol chemistry on the PMI-58 list, new testing and analytical methods have been developed and validated. This has allowed PMI to compare the composition of the aerosol generated by THS with the smoke from a 3R4F reference cigarette based on the measurement of the extended FDA list of 93 HPHCs.

The study was performed by an independent laboratory, Labstat International ULC, which is accredited by the Standards Council of Canada to ISO 17025:2005 ("General requirements for the competence of testing and calibration laboratories"). The measurements were conducted on two tobacco stick variants (i.e., Regular and Smooth Menthol) and compared with the measurements from a 3R4F reference cigarette. The total reduction of the levels of HPHCs in THS Regular aerosol and Smooth Menthol aerosol compared with 3R4F reference cigarette smoke was found to be >90.5% and >91.0%, respectively. This reduction is fully in alignment with the one previously calculated using the PMI-58 list. This provides evidence that the PMI-58 list correctly assesses the overall reduction of the levels of HPHCs emitted by THS compared with a 3R4F reference cigarette. In addition, the results observed for both THS Regular and Smooth Menthol were very similar, providing further evidence that the reduction of the levels of HPHCs generated is not impacted by the nature of the flavor system. For details, please see PMI's MRTPA for *IQOS*, amendment Submission of an Amended Study Report as part of "P1 Characterization" and an Updated Clinical Study.

3.3 Non-Targeted Differential Screening (NTDS)

In addition to our standard aerosol chemistry studies, we conducted an in-depth comparative analysis of the composition of THS aerosol and 3R4F smoke using an NTDS approach, combining liquid and gas chromatography coupled to high-resolution mass spectrometry. This non-targeted analysis of THS aerosol was performed in order to identify new or increased levels of compounds compared with 3R4F smoke and evaluate their toxicological profile. The results were submitted to the FDA on December 8, 2017, and presented on January 24-25, 2018, at the FDA's Tobacco Products Scientific Advisory Committee (TPSAC) meeting on *IQOS*. This analysis allowed us to identify approximately 4,330 constituents (≥100 ng/stick) from the 3R4F reference cigarette, while about 750 constituents (≥100 ng/stick) were identified in the aerosol from Regular THS HeatSticks (**Figure 1**). This further confirmed that the absence of combustion leads to a reduced complexity of the THS aerosol.

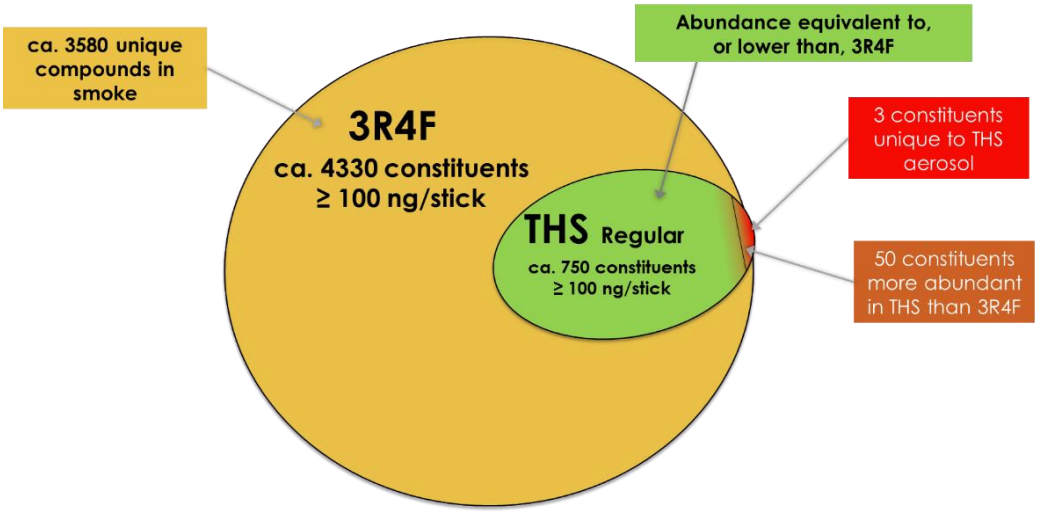

Figure 1. Comparison between THS Regular aerosol and 3R4F smoke composition.

The compounds that were higher in concentration in THS Regular aerosol than in 3R4F cigarette smoke were presented in the Addendum to the briefing document of 24-25th January 2018 TPSAC meeting. These results come from the output of PMI's NTDS analysis. All together, we identified that 53, 57, and 60 aerosol compounds were higher in concentration in THS Regular, THS Smooth Menthol, and THS Fresh Menthol, respectively. This results 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, 2) plant metabolites, or 3) compounds that are the result of sugar (naturally present in tobacco) transformation upon heating. For instance, substances such as Hexadecanoic acid, ethyl ester and Trans-4-hydroxymethyl-2-methyl-1,3-dioxolane were more than 1,000% higher than in 3R4F reference cigarette smoke. Overall, these differences were expected based on blend differences between THS HeatSticks and 3R4F reference cigarettes as well as the fact that some THS variants are mentholated, 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.

To determine whether these 85 constituents could potentially form a new hazard related to THS, we conducted a full toxicological evaluation of these constituents and identified four to be of toxicological

concern, because they are classified as potential carcinogens. These constituents are glycidol (IARC 2A), 2-furanemethanol (IARC 2B), 3-monochloro-1,2-propanediol (IARC 2B), and furfural (IARC 3). Our evaluation, based on the published inhalation toxicity literature, indicates that the levels of exposure to these compounds through THS use are below the level of toxicological concern defined by the Human Equivalent Concentration (HEC) (**Table 2**). The HEC was derived from the lowest observable adverse effect concentration in animal studies following FDA guidance for industry "Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers". For details, please see PMI's MRTPA for *IQOS*, amendment Response to August 4, 2017, FDA Advice and Information Request Letter including Non-targeted Differential Screening, Toxicological Assessment, and Peer Review Reports.

Table 2. "Non-PMI-58" compounds of toxicological concern

Name	IARC classification	THS mean (µg/stick)	Ratio Dose/HEC
Glycidol	2A	5.71	0.026
3-monochloro-1,2-propanediol	2B	9.94	N/A
2-Furanmethanol	2B	39.18	0.33
Furfural	3	31.08	0.0017

N/A: No inhalation toxicity data available, but positive in Ames test
Dose: Assuming 40 THS HeatSticks per day for a 60 kg person
HEC: Human Equivalent Concentration

4 Summary of Toxicology Assessment

The THS pre-clinical assessment strategy includes a systematic evaluation of biological activity of the produced aerosol *in vitro* and *in vivo* in order to assess its toxicity and its potential for reduced toxicity compared with cigarette smoke. First, three standard *in vitro* assays were used to assess the cytotoxicity, genotoxicity, and mutagenicity of the THS aerosol in comparison with the smoke from the 3R4F reference cigarette (Schaller, 2016). The neutral red uptake assay results showed that the *in vitro* cytotoxicity of the THS aerosol was reduced by approximately 90% compared with the smoke of

the 3R4F reference cigarette. The Ames assay for bacterial mutagenicity did not show any activity, and the activity in the mouse lymphoma assay for mammalian cell mutagenicity was significantly decreased for THS compared with 3R4F smoke exposure. These results are consistent with a reduction of mutagenicity of more than 95% for THS aerosol compared with 3R4F smoke. These results are consistent with the average reduction in levels of HPHCs of 90-95% in THS aerosol compared to cigarette smoke. Furthermore, *in vivo* data from 90-day sub-chronic inhalation studies in rats show that exposure to THS aerosol resulted in a significant reduction in pulmonary and systemic inflammation and revealed only adaptive changes when compared with 3R4F smoke (Phillips, 2015; Phillips, 2016; Wong, 2016; PMI science, 2018). In summary, the evidence available for THS to date systematically demonstrated an overall decrease in toxicity compared with cigarette smoke, which is consistent with the reduction in emissions of HPHCs for THS. For details, please see PMI's MRTPA for *IQOS*, section 7.2 Preclinical Studies.

5 Summary of Evidence for Reduced Exposure to HPHCs in PMI Clinical Studies

PMI conducted four clinical Reduced Exposure Studies providing pivotal evidence about the reduction in exposure to HPHCs when switching to THS relative to continuing to smoke cigarettes. Overall, the clinical studies demonstrated a significant, sustained reduction of BoExp levels over three months (ranging from 34% to 94% relative to continuing smoking cigarette), approaching the exposure levels observed upon smoking abstinence. In fact, switching to THS achieved, on average, 95% of the reduced exposure results observed upon smoking abstinence for the duration of the studies.

5.1 Selection of HPHCs / BoExp to Be Assessed in PMI Reduced Exposure Studies

Exposure to 17 HPHCs (including nicotine) was evaluated in PMI clinical studies, either by measuring the parent compound (e.g., 4-aminobiphenyl), by measuring one or several of their metabolites, or by using a surrogate BoExp representative of a chemical class of compounds. For example, 1-hydroxypyrene (1-OHP) can be used as a surrogate marker for polycyclic aromatic hydrocarbons (PAH) (Institute of Medicine, 2012). The criteria applied by PMI that qualified HPHCs and their related BoExp to be assessed were:

1. The HPHC selected are representative of a variety of chemical classes and organ toxicity classes as defined by the FDA (carcinogen, cardiovascular toxicant, respiratory toxicant, reproductive and development toxicant, addiction potential)
2. The HPHC reflects a specific toxic exposure or is a reliable surrogate of exposure to HPHCs
3. The HPHC assessed cover a broad range of formation temperatures
4. The HPHC is specific to smoking with other sources being minor or non-existent
5. The BoExp to an HPHC is reliably detectable using validated, reproducible, precise analytical methods
6. The BoExp to an HPHC has a half-life that is suitable with the schedule of assessments

Out of the 17 HPHCs considered by PMI (**Table 3**), 14, including nicotine, are from compounds listed in the FDA-18 list of HPHCs (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). Four of the HPHCs listed by the FDA (i.e., isoprene, formaldehyde, acetaldehyde, and ammonia) were not included in the set of HPHCs assessed in PMI exposure studies due to the following reasons: 1) lack of reliable measurement methods; 2) lack of meaningful BoExp to assess the difference in exposure between smokers and non-smokers; and 3) presence due to other sources (therefore subject to strong confounding factors). Two HPHCs, which are in the FDA-93 list (FDA Harmful and Potentially Harmful Constituents) (i.e., ethylene oxide, and *o*-toluidine), have also been included in current PMI's clinical assessment studies, because the bioanalytical methods were available to measure them reliably (or one of their metabolites).

Although S-benzylmercapturic acid (S-BMA) has been described as being a valuable BoExp to measure occupational exposure to toluene, this BoExp appeared to be not suitable to measure exposure to toluene when the goal is to discriminate smokers from smokers who switch to THS or remain abstinent for the duration of a study. The results of PMI's clinical Reduced Exposure Studies demonstrated that exposure to toluene could not be discriminated in the three study groups using S-BMA as a BoExp. This was further supported by a study reporting no significant difference in S-BMA excretion between smokers and non-smokers (Pluym, 2015).

PMI used 1-OHP, a metabolite of pyrene, as a BoExp for PAHs in exposure studies. Pyrene is not present on any of the HPHC lists, as it is considered non-carcinogenic. However, due to its abundance

in any mixture of PAHs, its metabolite 1-OHP has often been used to monitor exposure to PAHs, several of which are carcinogenic. Pyrene is one of the PAHs found in cigarette smoke and is often used as an indicator/surrogate of total PAH exposure. Total 1-OHP is generally considered an appropriate BoExp to toxicologically relevant PAHs (Roethig, 2008), such as benzo[a]pyrene, as it is rapidly distributed, metabolized, and eliminated from the body. In addition, 1-OHP in urine represents a constant fraction (~2%) of total pyrene intake. Finally, 1-OHP is listed in the report of the Institute of Medicine "Scientific Standards for Studies on Modified Risk Tobacco Products" as being a "representative exposure biomarker related to tobacco carcinogens and toxicants" (Institute of Medicine, 2012). Furthermore, PMI also included the measurement of 3-hydroxybenzo[a]pyrene (3-OH-B[a]P), a metabolite of benzo[a]pyrene and well-accepted BoExp for PAH. Comparable reductions in both 3-OH-B[a]P and 1-OHP were found among smokers who switched completely to THS.

Assessment of systemic exposure to any inorganic compounds, phenols, and metals in PMI clinical studies was not possible due to the absence of fit-for-purpose and reliable BoExp and, for metals, due to the longevity in the body, which would not allow an adequate identification of the source.

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Table 3 – List of PMI's Selected HPHCs with their corresponding biomarkers of exposure

HPHCs	WHO-9	FDA-18	Biomarkers of exposure
Acrolein	●	●	3-hydroxypropylmercapturic acid (3-HPMA)
Acrylonitrile		●	2-cyanoethylmercapturic acid (CEMA)
4-Aminobiphenyl		●	4-aminobiphenyl (4-ABP)
Benzene	●	●	S-phenylmercapturic acid (S-PMA)
Benzo[a]pyrene	●	●	3-hydroxybenzo[a]pyrene (3-OH-B[a]P)
1,3-Butadiene	●	●	monohydroxybutenylmercapturic acid (MHBMA)
Carbon monoxide (CO)	●	●	blood carboxyhemoglobin (COHb) and exhaled CO (COex)
Crotonaldehyde		●	3-hydroxy-1-methylpropyl-mercapturic acid (3- HMPMA)
Ethylene oxide			2-hydroxyethylmercapturic acid (HEMA)
1-Aminonaphthalene		●	1-aminonaphthalene (1-NA)
2-Aminonaphthalene		●	2-aminonaphthalene (2-NA)
Nicotine		●	nicotine equivalents (NEQ) Plasma Nicotine and cotinine
NNK	●	●	total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (total NNAL)
NNN	●	●	total N-nitrosonornicotine (total NNN)
o-Toluidine			o-toluidine
Pyrene			total 1-hydroxypyrene (1-OHP)
Toluene		●	S-benzylmercapturic acid (S-BMA)

5.2 Clinical Reduced Exposure Studies Design and Results

The clinical Reduced Exposure Studies were conducted with adult smokers randomized into three groups: i) continued cigarette smoking, ii) smoking abstinence for the duration of the study, or iii) switching to the THS. Studies conducted in complete clinical confinement for five days of exposure were used to quantify the maximum possible reduction in HPHC exposure when switching to THS compared with continued smoking and smoking abstinence (Haziza, 2016a; Haziza, 2016b). This type of study was then complemented with studies conducted in an ambulatory setting to assess whether the reductions in HPHC exposure observed in short-term confinement can be sustained for a longer period in a near-to-real-world setting (Ludicke, 2018). Overall, in the per-protocol populations, the clinical Reduced Exposure Studies demonstrated a significant and sustained reduction in BoExp (ranging from 34% to 94%) after three months of switching to THS use relative to cigarette smoking, approaching the exposure levels observed upon smoking abstinence (**Figure 2** and **Table 4**). In fact, switching to THS achieved, on average, 95% of the results observed upon smoking abstinence for the duration of the studies. For details please see PMI's MRTPA for *IQOS*, section 7.3.1 03 REXC03, 7.3.1 04 REXC04, 7.3.1 07 REXA07 JP and 7.3.1 08 REXA08 US.

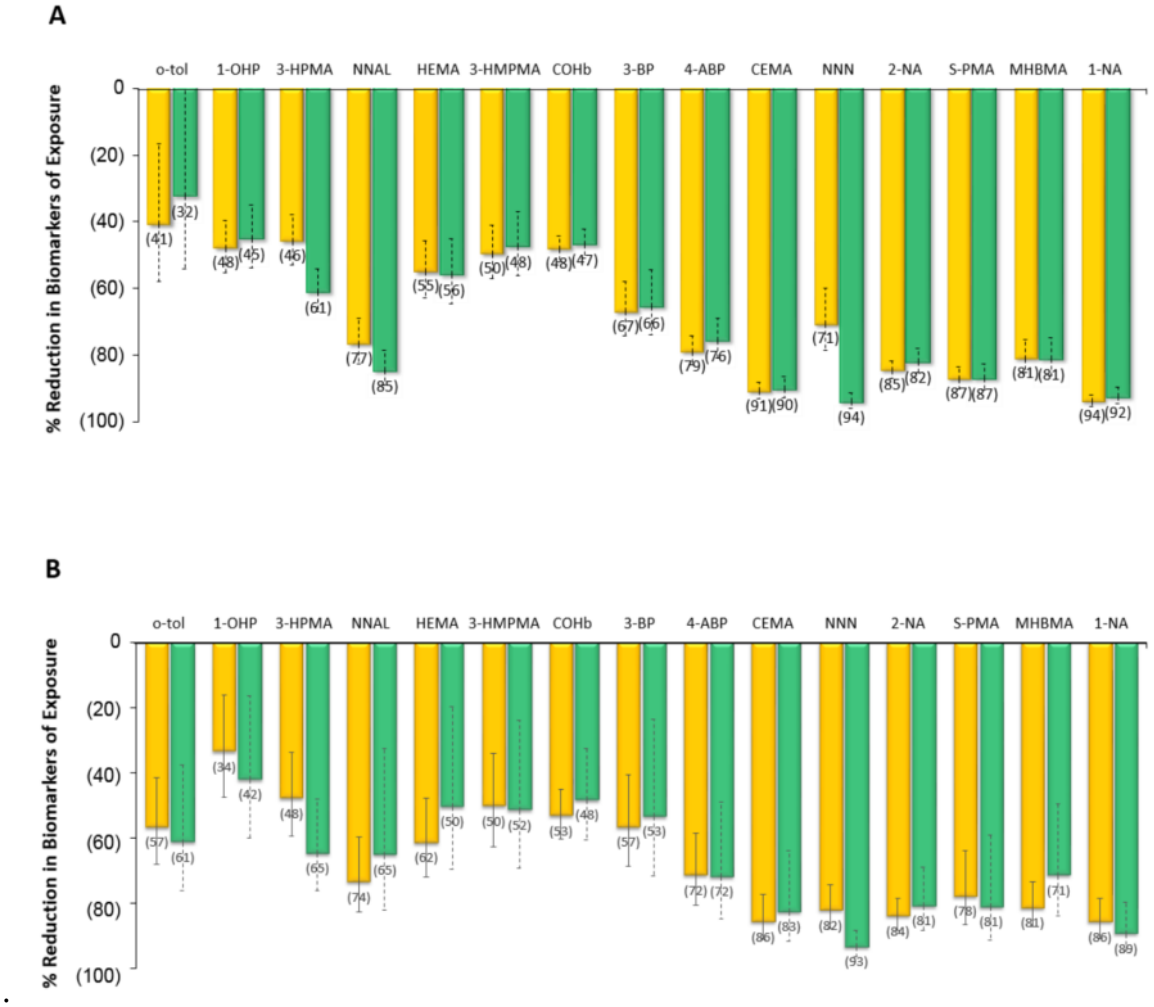

Figure 2. Percent reduction in BoExp relative to continuing smoking cigarettes after switching to THS (yellow bars) and smoking abstinence (green bars) after three months. A: study conducted in Japan (REXA07 JP), B: study conducted in the U.S. (REXA08 US).

Note: BoExp for nicotine not included in the figure, as no exposure reduction was expected. BoExp for toluene not included in the figure, as values for all three study groups remained comparable throughout the studies.

Abbreviations: o-tol=o-toluidine; 1-OHP=total 1-hydroxypyrene; 3-HPMA=3-hydroxypropylmercapturic acid; NNAL=total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol; HEMA=2-hydroxyethyl-mercapturic acid; 3-HMPMA=3-hydroxy-1-methylpropyl-mercapturic acid; COHb=carboxyhemoglobin; 3-BP=3-hydroxybenzopyrene; 4-ABP=4-aminobiphenyl; CEMA=2-cyanoethylmercaturic acid; NNN=total N-nitrosonornicotine; 2-NA=2-aminonaphthalene; S-PMA=S-phenylmercapturic acid; MHBMA=monohydroxybutenyl mercapturic acid; 1-NA=1-aminonaphthalene

Table 4. Reduction in BoExp relative to continuing cigarette smoking (CC) after switching to THS and smoking abstinence (SA) after three months in the studies conducted in Japan (REXA07 JP) and the US (REXA08 US).

HPHC	Biomarker of Exposure	Japan Study		US Study	
		% Reduction THS vs CC (CI)[a]	% Reduction SA vs CC (CI)	% Reduction THS vs CC (CI)	% Reduction SA vs CC (CI)
1,3-butadiene	Monohydroxybutenyl-mercapturic acid (MHBMA)	−81% (−85; −75)	−81% (−86; −75)	−81% (−87; −73)	−71% (−84; −49)
1-aminonaphthalene	1-Aminonaphthalene (1-NA)	−94% (−95; −92)	−92% (−94; −90)	−86% (−91; −78)	−89% (−95; −80)
2-aminonaphthalene	2-Aminonaphthalene (2-NA)	−85% (−87; −82)	−82% (−85.2; −77.9)	−84% (−88; −78)	−81% (−88; −69)
4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)	Total 4-(methylnitrosamino)- 1-(3-pyridyl)-1-butanol (Total NNAL)	−77% (−83; −67)	−85% (−89; −79)	−74% (−83; −60)	−65% (−82; −33)
4-aminobiphenyl	4-Aminobiphenyl (4-ABP)	−79% (−83; −74)	−76% (−81; −69)	−72% (−81; −58)	−72% (−85; −49)
Acrolein	3-Hydroxypropyl- mercapturic acid (3-HPMA)	−46% (−53; −38)	−61% (−66.8; −54.0)	−49% (−59; −34)	−65% (−76; −48)
Acrylonitrile	2-Cyanoethylmercaturic acid (CEMA)	−91% (−93; −88)	−90% (−93; −86)	−86% (−91; −77)	−83% (−92; −64)
Benzene	S-Phenyl-mercapturic acid (S-PMA)	−87% (−90; −83)	−87% (−90; −83)	−78% (−87; −64)	−81% (−91; −59)
Benzo[a]pyrene	Total 3-Hydroxybenzopyrene (3-OH-B[a]P)	−67% (−74; −58)	−66% (−74; −55)	−57% (−69; −40)	−53% (−72; −24)
Carbon monoxide	Carboxyhemoglobin (COHb)	−48% (−52; −44)	−47% (−51; −42)	−53% (−60; −45)	−48% (−60; −33)
Crotonaldehyde	3-Hydroxy-1-methylpropyl-mercapturic acid (3-HMPMA)	−50% (−57; −41)	−48% (-56; −37)	−52% (−69; −24)	−52% (−69; −24)
Ethylene oxide	2-Hydroxyethyl-mercapturic acid (HEMA)	−55% (−63; −46)	−56% (−65; −45)	−62% (−72; −48)	−51% (−70; −20)
N-nitrosonornicotine (NNN)	Total N-nitrosonornicotine (total NNN)	−71% (−79; −60)	−94.0% (−96; −91)	−82% (−88; −74)	−93% (−96; −88)
o-toluidine	o-Toluidine (o-tol)	−41% (−58; −17)	−32% (−54; 0)	−57% (−68; −47)	-61% (−76; −38)
Pyrene	Total 1-hydroxypyrene (1-OHP)	−48% (−55; −40)	−45% (−54; −35)	−34% (−47; −16)	−42% (−60; −17)

CI = confidence interval
Note: BoExp for nicotine not included in the table.

6 Discussion

To interpret the results from non-clinical and clinical studies and draw scientifically relevant conclusions, the entire set of results has to be considered, and the study objectives and designs need to be taken into account. Stating the objectives of the reported studies as well as ensuring that results are comparable based on the study design are an important part of a sound scientific evaluation.

Cigarette smoke is a complex mixture in which more than 6,000 compounds have been identified, representing nearly all known organic chemical classes. Within this complex mixture, several HPHCs have been associated with the causation of disease in smokers, such as aromatic amines, gas-phase constituents, oxygen-free radicals, PAHs, and TSNAs. As it is not possible to quantify all constituents present in cigarette smoke, various priority lists of smoke toxicants present in mainstream cigarette smoke have been proposed for the evaluation of commercial market cigarettes, based mainly on risk assessments. The FDA has established a list of 93 HPHCs (FDA Harmful and Potentially Harmful Constituents) in tobacco products and tobacco smoke and issued draft guidance on the reporting of an abbreviated list of 18 HPHCs in mainstream cigarette smoke and nine HPHCs in smokeless tobacco products for which analytical protocols are well established and widely available (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). Finally, the FDA has encouraged tobacco product manufacturers to include HPHC data in new product applications.

In PMI's MRTPA for *IQOS*, aerosol chemistry studies focused on 58 compounds (PMI-58 list) and showed that the emissions of HPHCs generated by THS aerosol are, on average, 90-95% lower than levels in cigarette smoke. At the time of paper submission, the measurement of the full FDA list of 93 HPHCs had not been performed. This was explained by the lack of valid and well-established analytical protocols to measure these HPHCs available at the time, leading to the FDA recommendation of the abbreviated list of 18 HPHCs. We find it regrettable that the authors did not mention this important methodology limitation, as it would have avoided an inaccurate interpretation of the results. Furthermore, validated analytical protocols have since been developed, which allowed PMI to test for all HPHCs listed in the extended FDA list. The total reduction of the levels of HPHCs was found to be on average by 90% in THS aerosol compared to smoke of a reference cigarette, which is fully in alignment with the previous measurement made using the PMI-58 list. Finally, the evidence

available for THS to date systematically demonstrated an overall decrease in toxicity compared with cigarette smoke, which is consistent with the reduction in emissions of HPHCs with THS.

In addition to our standard aerosol chemistry studies, PMI also conducted an in-depth comparative analysis of the composition of THS aerosol and 3R4F smoke using NTDS. This non-targeted analysis of THS aerosol was performed in order to identify new or increased levels of compounds in THS aerosol compared with 3R4F smoke and evaluate their toxicological profile. THS aerosol demonstrated a significantly reduced complexity compared with 3R4F smoke (750 vs. 4,330 compounds, respectively). From these 750 compounds, 85 were found at higher concentrations in THS aerosol compared with 3R4F smoke; these compounds for Regular THS were listed in Table 1 of the research paper. These differences were expected based on blend differences between THS HeatSticks and 3R4F reference cigarettes as well as the fact that some THS variants are mentholated, 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. Within this list of 85 constituents, we identified four compounds of potential toxicological concern. However, none were above the level of toxicological concern according to HECs. The authors accurately reported the fact that "non-PMI-58" compounds were at higher concentration than in cigarette smoke but failed to demonstrate their significance regarding human toxicology. Furthermore, the authors seemed to ignore the conduct of a non-targeted analysis of THS aerosol and incorrectly concluded that "PMI's MRTP application fails to address the important question of whether the aerosol generation process for *IQOS* produces toxic substances not found in the smoke of combustible cigarettes, which could have been answered through non-targeted chemical analysis."

In the PMI's MRTPA for *IQOS*, human Reduced Exposure Studies focused on BoExp selected according to the FDA list. Overall, the clinical studies demonstrated significant and sustained reduction of BoExp levels over three months when switching to THS use compared with continued cigarette smoking. The authors incorrectly reported that BoExp for only 11 compounds of the FDA-18 list were included. In fact, 14 compounds were included, and the other four were not measurable due to the lack of valid measurement methods. Furthermore, in addition to measuring levels of Benzo[a]pyrene, a direct measure of PAH exposure, and to have an additional assessment of PAH, PMI included 1-OHP, a surrogate for the overall exposure to PAHs. Despite the fact that the authors criticized the non-selectiveness of this marker for PAH, it is important to mention that this marker is already well

accepted and was acknowledged by the Institute of Medicine "Scientific Standards for Studies on Modified Risk Tobacco Products" as being a "representative exposure biomarker related to tobacco carcinogens and toxicants" (Institute of Medicine, 2012). The authors highlighted the fact that PMI did not assess inorganic compounds, phenols, and metals and hypothesized that it was "possibly due to the fact that there are no valid biomarkers for some substances or that the time course of the biomarkers may not be optimal for studies of the duration used by PMI." We agree with this last point but think that the fact that most of these compounds were reduced by more than 95% in THS aerosol is a strong indicator of likely reduced systemic exposure.

PMI demonstrated that THS emits significantly reduced levels of HPHCs compared with cigarettes, which leads to a significantly reduced exposure in clinical studies. This reduced exposure has been shown to translate into a significant reduction in the biological impact compared with cigarette smoke across multiple studies. In particular, PMI conducted an A/J mouse chronic inhalation study showing that a lifelong exposure of A/J mice to THS aerosol, even at a multiple of the test atmosphere nicotine concentration used for the 3R4F cigarette-exposed mice, resulted in mild systemic toxicity, no lung inflammation or emphysema, and no increase in lung tumorigenicity. In contrast, 3R4F cigarette exposure resulted in moderate to severe chronic toxicity, lung inflammation, emphysema, and increased tumorigenicity compared with air exposure. For details, please see PMI's MRTPA for *IQOS*, amendment Submission of Finalized *in vivo* Study. Further, PMI conducted a six-month clinical Exposure Response Study in 984 adult smokers randomized to either continued smoking or switching to THS for six months. The results demonstrated that switching to THS leads to favorable changes observed in the evaluated clinical risk endpoints and their related biological or functional pathways (inflammation, lipid metabolism, oxidative stress, lung function) (PMI science, 2018). This demonstrates that switching completely from cigarettes to THS can reduce the risk of smoking-related diseases and presents less risk of harm than continuing to smoke cigarettes. For details, please see PMI's MRTPA for *IQOS*, amendment Additional Information and Data from a Recently Completed Clinical Study.

7 Conclusion

Considering the available evidence to date on THS use compared with continued smoking, we can conclude that:

1. THS reduces the emissions of HPHCs by more than 90%, on average, compared with cigarette smoke.
2. Our NTDS of the THS aerosol demonstrated that the THS aerosol is significantly less complex compared with 3R4F cigarette smoke.
3. For the compounds found at higher concentration in THS aerosol compared with 3R4F smoke, these differences were expected based on blend differences between THS HeatSticks and 3R4F reference cigarettes as well as the fact that some THS variants are mentholated, 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.
4. The levels of exposure to four compounds of potential toxicological concern that were elevated in THS aerosol were confirmed to be below the level of toxicological concern through the use of THS.
5. *In vivo* and *in vitro* toxicological studies have clearly demonstrated the reduced toxicity of the THS aerosol and the potential of THS to reduce the harm of smoking.
6. The clinical Reduced Exposure Studies demonstrate a significant reduction in exposure when switching to THS compared with continuing to smoke cigarettes.

In summary, the statement made by the authors that the impact of THS emissions on the overall toxicity or harm is unknown is inaccurate and misleading. The totality of evidence available on THS clearly demonstrates that THS presents less risk of harm and can reduce the risk of smoking-related diseases compared to continued smoking; THS is therefore different in risk profile. Although not risk-free, switching completely to THS is a much better choice for current adult smokers compared with continued smoking.

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9 Abbreviations

1-OHP	:	1-hydroxypyrene
3-OH-B[a]P	:	3-hydroxybenzo[a]pyrene
3R4F	:	Research Cigarette of the University of Kentucky
BoExp	:	Biomarker of Exposure
FDA	:	Food and Drug Administration
HEC	:	Human Equivalent Concentration
HPHC	:	Harmful Potentially Harmful Constituents
IARC	:	International Agency for Research on Cancer
ISO	:	International Organization for Standardization
MRTPA	:	Modified Risk Tobacco Product Application
NTDS	:	Non-Targeted Differential Screening
PMI	:	Philip Morris International
PAH	:	Polycyclic Aromatic Hydrocarbons
THS	:	Tobacco Heating System (marketed as IQOS)
TPSAC	:	Tobacco Products Scientific Advisory Committee
TSNA	:	Tobacco-Specific Nitrosamines
WHO	:	World Health Organization