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Summary of Evidence on the Pulmonary and Immunosuppressive effects of *IQOS*

Response to the Research Paper entitled

"Assessment of industry data on pulmonary and immunosuppressive effects of *IQOS*"

by Moazed et al., 2018[1]

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TABLE OF CONTENTS

EXECUTIVE SUMMARY

The Department of Medicine, University of California, San Francisco, California, USA recently published a Research Paper in *Tobacco Control* (Moazed 2018) claiming that "*IQOS* is associated with significant pulmonary and immunomodulatory toxicities with no detectable differences between conventional cigarette smokers and those who were switched to *IQOS* in Philip Morris International's studies". The Research Report further states that "Philip Morris International also failed to consider how dual use and secondhand aerosol exposure may further impact, and likely increase, the harms associated with these products."

We have assessed the claims in this Research Paper, based on a careful review of our scientific data submitted to the U.S. Food and Drug Administration (FDA). The interpretation of the data included in PMI's MRTP application for IQOS to the U.S. FDA requires knowledge of the design and conduct of toxicology and clinical studies. In order to reach accurate, science-based conclusions, a careful review and analysis of the procedures and all available data should be done. Such an analysis was not performed by the authors and therefore, the conclusions they have drawn are incorrect and misleading.

We have prepared a detailed 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 toxicological studies and clinical studies performed according to international standards of Good Laboratory and Good Clinical Practice, the Tobacco Heating System (THS, marketed in various countries under the brand name *IQOS*) presents less risk of harm and can reduce the risk of smoking-related diseases compared with continued smoking. This includes a significant reduction in inflammatory response and favorable changes in lung function.

Although *THS* is not risk-free, switching completely to *THS* is a much better choice for adult smokers than continuing to smoke cigarettes.

1 INTRODUCTION

The Department of Medicine, University of California, San Francisco, California, USA recently published a Research Paper in *Tobacco Control* (Moazed 2018) claiming that "*IQOS* is associated with significant pulmonary and immunomodulatory toxicities with no detectable differences between conventional cigarette smokers and those who were switched to *IQOS* in Philip Morris International's studies". The Research Report further states that "Philip Morris International also failed to consider how dual use and secondhand aerosol exposure may further impact, and likely increase, the harms associated with these products."

From their analysis of Philip Morris International's (PMI) non-clinical studies, the authors report on rats exposed to *IQOS* aerosol, mainstream smoke from 3R4F reference cigarettes, or room air (Sham). The authors mention that there is evidence of pulmonary inflammation through increased lung weights (normalized to body weight), increased bronchoalveolar lavage (BAL) cell counts and inflammatory markers, as well as respiratory epithelial hyperplasia and metaplasia. They conclude that "these data suggest that *IQOS* induces significant inflammatory injury, but less severe than that observed with intense cigarette smoke exposure." The authors' further highlight that *IQOS* exposure may be

associated with substantial immunomodulatory effects as evidenced by higher blood neutrophil counts, decreased thymus weight, and higher histologic thymic atrophy severity score.

This report aims to clarify these findings and to provide context by summarizing the scientific data available on THS (marketed in various countries under the brand name *IQOS*) to date with regards to lung inflammation and immunomodulation, which was also reported in PMI's Modified Risk Tobacco Product (MRTP) Application (MRTPA) for *IQOS* and associated relevant scientific literature.

First, the level of inflammation observed in PMI's non-clinical studies after THS exposure is extremely low compared with that observed following 3R4F smoke exposure. Furthermore, the changes observed with regards to inflammatory response are not only reduced but in most cases only occur at the highest THS exposure concentration, which is not representative of human exposure. Unfortunately, the authors fail to discuss the changes reported in relation to:

1) the levels of exposure, which are different in the THS and 3R4F experimental groups, and
2) the specificity of rodent inhalation studies.

The authors therefore consider neither the basic principles of toxicology, such as dose-response, nor the translatability or relevance of certain findings specific to the animal model used for human risk assessment.

It is also important to note that the changes observed are transient and adaptive in nature and therefore cannot be considered adverse effects indicative of substantial THS exposure-related immunomodulatory effects.

Finally, the authors fail to analyze the mechanisms involved in the reported changes by ignoring relevant scientific literature referenced and explained in PMI's study reports and associated peer-reviewed publications.

Data from our clinical studies on systemic inflammation and pulmonary effects clearly demonstrate favorable changes that are in accordance with the reduction in emissions of harmful and potentially harmful constituents (HPHCs) (on average greater than 90%) and significantly reduced toxicity in a laboratory setting. These changes occur even under dual-use conditions (also PMI 2018).

In addition, the studies on secondhand exposure to THS have shown that the measured analytes remain at background levels after THS use, with the exception of nicotine and acetaldehyde, for which measured levels remain significantly below the levels defined in air quality guidelines and are well below what is observed for cigarettes (Mitova, 2016; see PMIs MRTP Application for *IQOS*, section 6.1.1 – Aerosol Chemistry).

PMI is open to and welcomes independent public review of our data. However, a review of scientific results needs to take into consideration the study's design and limitations and bring the results into context of other available evidence in order to draw conclusions. Specifically, when evaluating tobacco harm reduction and assessing the potential benefits of switching from smoking cigarettes to using a candidate MRTP, the results have to be considered in the context of both smoking and smoking cessation, as these represent both the highest and lowest risk of smoking-related disease for smokers.

In summary, the statements made by the authors are selective, incorrect, 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 with continued smoking. This includes a significant reduction in inflammatory response and favorable changes in lung function.

Although THS is not risk-free, switching completely to THS is a much better choice for adult smokers than continuing to smoke cigarettes.

2 SUMMARY OF NON-CLINICAL DATA AND RESULTS

PMI's non-clinical studies are carried out according to accepted toxicological practice, including exposure to the test item that are close to Maximum Tolerated Dose (MTD), in order to discover any possible test item-related change. To interpret any results from PMI's non-clinical studies, it is important to recognize the MTD for exposure to THS is significantly higher compared to the MTD of exposure to cigarettes (see section 2.1) and significantly higher than real-life exposure conditions. Furthermore, for a risk assessment relevant to human exposure, real-life exposure conditions need to be taken into consideration.

The changes in body weight as well as the immunomodulatory effects observed in PMI non-clinical studies are related either to exposure to very high nicotine concentrations (i.e., at or close to the MTD) or to stress because of exposure to high concentrations of nicotine. They are transient and adaptive in nature and therefore are not adverse effects indicative of substantial THS exposure-related immunomodulatory effects. The changes in the pulmonary findings reflect effects that are linked to the residual levels of HPHCs found in the THS aerosol and become visible upon exposure to extreme aerosol concentrations (i.e., at or close to the MTD). However, the changes observed after exposure to THS aerosol are, in general, much lower than the effects measured upon 3R4F smoke exposure.

2.1 Clarification on Exposure Levels

The exposure to nicotine in THS-exposed rats is much higher than in 3R4F smoke-exposed rats in the PMI non-clinical studies because of the differences in MTDs between cigarette smoke and THS aerosol, thus by design. Therefore, effects related to the nicotine exposure levels are expectedly more prominent in THS-exposed rats than in smoke-exposed rats. The THS-exposed rats in the cited study were exposed to up to 50 µg/L nicotine in the test atmospheres. This exposure concentration is near to MTD as required for toxicity studies and by the Organisation for Economic Cooperation and Development (OECD) Test Guidelines 412/413 (OECD 2009). In the same study, the exposure concentration of 3R4F smoke was up to MTD as well and up to 23 µg/L nicotine in the test atmospheres. For 3R4F smoke exposure, the MTD is driven by the carbon monoxide (CO) concentration in the test atmosphere rather than by the nicotine because the levels of CO in smoke are much higher than in THS aerosol. Thus, the nicotine exposure levels in the THS groups were up to twice as high as in the smoke-exposed groups due to the fact that THS aerosol is intrinsically less toxic than cigarette smoke. When exposures are extrapolated from the nicotine concentrations in inhalation studies to human exposure levels using the Alexander formula (Alexander 2008) and the Guidance Document from the FDA (FDA 2005) based on body surface area, THS exposure levels reach the equivalent of more than 100 *HeatSticks* per day, whereas for 3R4F smoke exposure, levels reach half of this. For a detailed calculation, refer to Wong et al. (Wong 2016). In addition, due to the irritation caused by cigarette smoke constituents, the respiratory minute volume of the 3R4F smoke-exposed

rats was decreased by approximately 40%, whereas no reduction was observed upon THS exposure, even at twice the nicotine test atmosphere concentration (see Table 2 in Wong 2016). This results in much higher nicotine exposure levels in THS aerosol-exposed rats than in 3R4F smoke-exposed rats, as evidenced by the quantity of total urinary nicotine metabolites in 24-hour urine (i.e., a measure of nicotine exposure). For example, in the urine of the male rats, the level of total nicotine metabolites was 5146.1 ± 648.86 nmol in the group with the highest THS exposure, whereas it was 1548.4 ± 355.49 nmol (means ± SD) in the 3R4F high dose group. At equal nicotine test atmosphere concentration (i.e., approximately 23 µg/L), the total nicotine metabolites in the THS group was 2619.3 ± 306.20 nmol vs. 1548.4 ± 355.49 nmol in the 3R4F group (see Table 4 in Wong 2016).

Thus, comparing the findings of THS exposure at the highest exposure concentration with those from 3R4F smoke at the highest exposure concentration is not a scientifically sound approach. Comparing biological outcomes at equivalent nicotine exposure levels would be better, although the differences in uptake still remain.

2.2 Changes Related to Nicotine Exposure – Systemic Immune Effects

The systemic immune effects highlight by the authors (Moazed 2018) are non-adverse changes linked to nicotine and stress responses, and not specific to THS exposure. Several rodent responses, including increased blood neutrophil counts, decreased thymus weight with associated thymic atrophy, and increased adrenal gland weights, have been found in studies in which rats have been exposed to nicotine-containing aerosols, including cigarette smoke. This is the case not only for other THS studies (Oviedo 2016) but also when exposing rats to aerosols from another heat-not-burn platform, namely the Carbon-Heated Tobacco Product 1.2 (Phillips 2018), when assessing the effect of nebulized nicotine-containing e-liquid aerosols (Phillips 2017) and when studying the effects of nicotine exposure *per se* (Phillips 2015). There is a clear nicotine concentration exposure-related effect, as shown in **Figure 1**, for the blood neutrophil counts in male rats, for example, as discussed in the Moazed et al. paper. In the studies referenced above, similar effects have been found upon cigarette smoke exposure (when such groups were included in the study designs), and their magnitudes depend on the nicotine exposure levels and dose. All of these effects have been identified previously as stress response phenotypes (Everds et al. 2013) and are linked to the hypothalamic-pituitary-adrenal responses. Notably, complex interactions of nicotine and other sources of stress have been observed (e.g., (Chen, Fu, and Sharp 2008; Cheng et al. 2005; Faraday, O'Donoghue, and Grunberg 1999; Faraday, Blakeman, and Grunberg 2005)), which could have further modulated (induced or suppressed) the stress-related effects in the PMI studies, in which the rats were concurrently exposed to the stress of the nose-only exposure procedure and nicotine-containing aerosols. Furthermore, histopathological analysis of other organs important in immune regulation did not show any indication of additional immunomodulatory sequelae. Finally, it should be noted that all of these effects are transient and adaptive in nature, as they revert after a post-inhalation recovery period of 42 days (Wong 2016; Oviedo 2016).

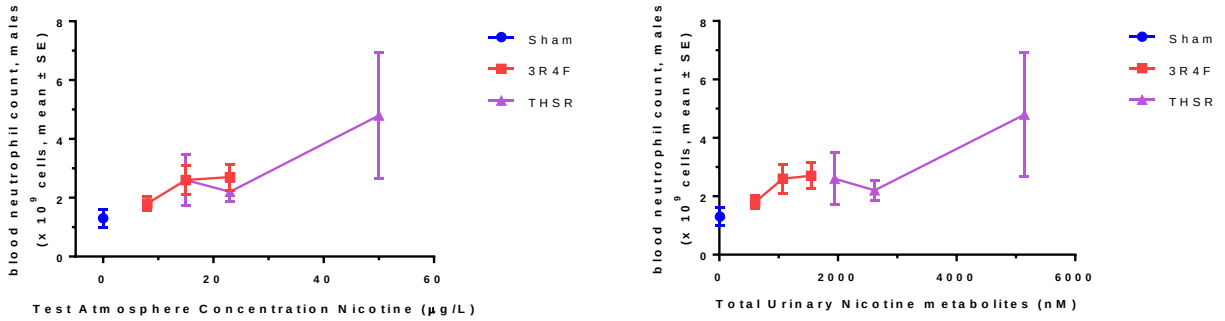

Figure 1. Blood neutrophil counts in male rats in function of the nicotine test atmosphere concentration (left panel), and the total nicotine metabolites measured in 24-hour urine (right panel) after exposure to THS aerosol (THSR) and 3R4F smoke (data from Wong et al., 2016).

Notes: Means are shown ± standard errors. Statistically significant differences are not shown but can be retrieved in the original publications.

2.3 Lung Inflammation

The lung inflammation related to THS exposure in the PMI non-clinical study is very low and in most cases comparable to fresh air exposure (Sham), which is different than the lung inflammatory changes caused by cigarette smoke. For the assessment and evaluation of pulmonary inflammation, it is important to take into account the overall picture of the changes in (all) free lung cells, pro-inflammatory cytokines, and chemokines as well as the lung histopathology. Focusing on a single statistically significant change is not sufficient for a scientific evaluation. Increases in the weights of the lungs with larynx and trachea (normalized to body weight), and not only the lung weights, as mentioned in the research paper, may be indicative for lung inflammation. However, in this study, the changes were not THS exposure concentration-dependent, and therefore, the single statistically significant change found should not be used to claim a biologically relevant effect. In fact, statistical significance is likely driven only by the fact that in the THS high exposure concentration group, the variance on the mean is smaller in other groups.

For the lung inflammation parameters, the totality of evidence presented should be taken into account. Importantly, at the highest exposure concentration for THS in the female rats, the total BAL cell count, as well as the differential counts, such as the macrophage, neutrophil, and lymphocyte counts, were similar to Sham. The increase in total cell count in the medium THS exposure concentration group (**Table 1**; Moazed 2018) was driven by an increase in the macrophage count, with no exposure concentration response and in only one sex. A similar effect was not seen in the male rats. **Figure 2** shows the total BAL and neutrophil cell counts for male and female rats in the study to facilitate the correct evaluation of the data obtained. A markedly lower level of the lung inflammation in THS-exposed rats as compared with 3R4F-exposed rats is obvious. A very low residual level of inflammation in THS-exposed animals cannot be excluded, as also indicated by changes in inflammatory mediators such as Macrophage inflammatory protein-1β (MIP-1β), Monocyte chemoattractant protein 3 (MCP-3), Myeloperoxidase (MPO), and Plasminogen activator inhibitor-1

(PAI-1) in some of the THS groups relative to the Sham. However, all changes were much more pronounced upon 3R4F smoke exposure (**Table 1**). From the histopathological analysis of the left lungs of the study rats, no or a very low level of inflammation is noted in the THS-exposed rats, with one statistically significantly higher severity score (severity scores have a range from 0 to 5) for the finding "macrophages without pigmentation" (severity score 1.5 ± 0.17 vs. Sham: 0.7 ± 0.15) in the THS female rats exposed to 50 µg/L nicotine in the test atmosphere. As a reference, the severity score for the 3R4F female rats exposed at 23 µg/L nicotine was 3.4 ± 0.19 (all values as means ± standard error). Taken together, all data clearly indicate only a very low level of pulmonary inflammation in THS-exposed rats, even at twice the nicotine test atmosphere concentration for THS aerosol as compared with 3R4F smoke.

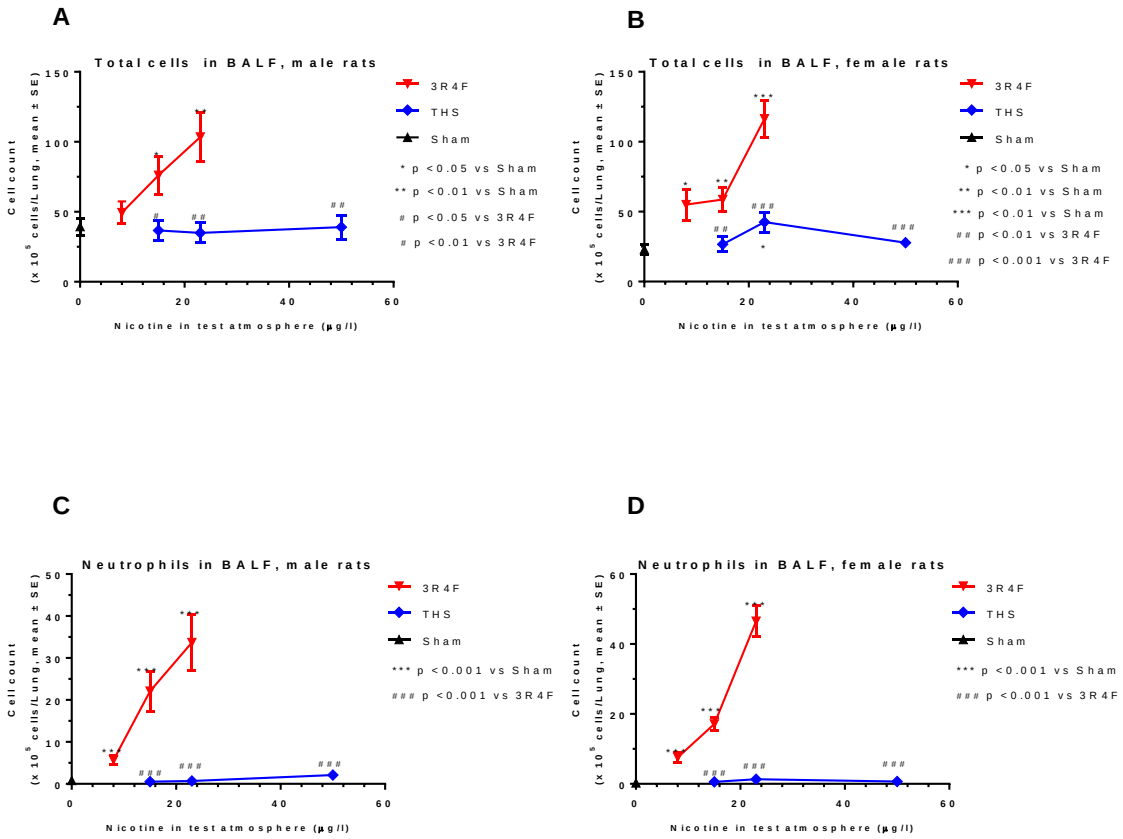

Figure 2. Lung inflammation of THS- and 3R4F-exposed rats.

Notes: Total cell counts recovered from the BAL fluid (BALF) from the right lung (panel A and B, male and female rats, respectively), and BALF neutrophil counts (panel C and D, male and female rats, respectively), means ± standard errors, * indicate statistically significant values relative to Sham, # indicate statistically significant differences between THS and 3R4F at the same nicotine test atmosphere concentration, or from THS at 50 µg/L nicotine relative to 3R4F at 23 µg/L nicotine in the test atmosphere. Data from Wong et al., 2016.

The low level of residual inflammation may be related to the fact that there is a low residual level of HPHCs in the aerosol from THS. However, relative to 3R4F smoke, the level of pulmonary

inflammation upon THS exposure is at least one order of magnitude lower than that elicited by 3R4F smoke.

Finally, an extensive Systems Biology evaluation of the lung tissue has revealed that upon exposure to THS, perturbations of the inflammatory biological networks was minimal and transient (full recovery at the end of the post-inhalation recovery period), whereas for the 3R4F-exposed rats, the perturbation of the inflammatory network was much more pronounced and recovered only partially after the post-inhalation period. This was demonstrated in the lung transcriptome and proteome (Wong et al. 2016; Oviedo et al. 2016; Kogel et al. 2016).

Table 1. Inflammatory mediators in THS aerosol- and 3R4F smoke-exposed rats.

Mediator	Unit	Sex	Group			
			Sham	3R4F 23 µg/L	THS 23 µg/L	THS 50 µg/L
MCP3	pg/ml	male	5.438 ± 2.367	29.130 ± 8.778**	3.364 ± 1.122	6.950 ± 3.308
		female	1.620 ± 0.144	32.000 ± 4.497 ***	4.890 ± 1.681	4.950 ± 1.533**
MIP-1β	pg/ml	male	21.100 ± 3.270	85.700 ± 15.851**	30.500 ± 5.282*	35.700 ± 4.372*
		female	22.600 ± 1.733	108.778 ± 12.265***	26.100 ± 2.706	42.900 ± 6.468**
MPO	ng/ml	male	2.012 ± 0.765	21.600 ± 2.721***	1.663 ± 0.472	2.368 ± 0.626
		female	0.785 ± 0.082	32.222 ± 2.783***	1.974 ± 0.582	2.280 ± 0.517 **
PAI-1	ng/ml	male	0.058 ± 0.009	0.108 ± 0.023*	0.064 ± 0.011	0.063 ± 0.007
		female	0.033 ± 0,002	0.089 ± 0.009***	0.049 ± 0.009	0.056 ± 0.006*

Notes: Data is shown for the only mediators with statistically significantly higher mediator levels in BAL in the THS groups as compared to Sham. Comparisons vs. Sham: *p<0.05, **p<0.01, ***p<0.001. Comparisons between 3R4F and THS at the same nicotine test atmosphere concentrations (23 µg/L), or at a higher concentration (50 µg/L): all THS values are lower than 3R4F, with p values of at least p<0.01, except for PAI-1 males, where there was no difference.

Abbr.: MCP-3 = Monocyte chemoattractant protein 3; MIP-1β = Macrophage inflammatory protein-1β; MPO = Myeloperoxidase; and PAI-1 = Plasminogen activator inhibitor-1

2.4 Respiratory Epithelial Hyperplasia and Metaplasia

The assessment of epithelial changes in the overall respiratory tract of the THS aerosol-exposed rats showed lower levels of hyperplastic and metaplastic changes than in 3R4F-exposed rats. For a number of parameters, THS-related effects were statistically significantly higher than in Sham-exposed rats, as indicated in Wong et al. (Wong 2016). Because it is not clear from the publication which changes the authors are referring to (see Table 1, Moazed 2018), a general overview of the complete respiratory

tract hyperplastic and metaplastic changes is provided, together with an overall interpretation in the context of rodent inhalation studies.

In the evaluation of the histopathological findings in the respiratory tract, expert histopathologists used for the assessment, scored both, the number of animals showing a specific lesion (incidence) and the severity of the changes, according to well and pre-defined criteria. This is done following the recommendations of the Society of Toxicologic Pathology and is reported to be important in the assessment of exposure to xenobiotic agents (Crissman 2004; Morton 2006). Although the reported incidence of a number of changes were similar in the 3R4F- and THS-exposed animals, the severity of the changes observed in THS-exposed rats was systematically lower (more than 20-fold) than in 3R4F-exposed rats. It is well known that certain locations of the respiratory tract are very sensitive to even mild irritants, and changes such as hyperplasia or metaplasia have been reported to occur with inert chemicals. The occurrence of these findings in rodents, especially in the upper respiratory tract, and obvious for the nose at section level 1, is related to the fact that rats are obligate nose-breathers with high volumes of air flow along the respiratory epithelium (Renne 2007). It should, however, be noted that in the PMI studies, hyperplastic and metaplastic changes at nose level 1 reach a maximum severity at low concentrations of 3R4F smoke (8 µg/L nicotine in test atmosphere), while lower severity scores were observed at high exposure concentrations of THS (50 µg/L nicotine in test atmosphere). In the more distal parts of the nose, epithelial changes caused by THS, even at the highest exposure concentration, are very low or absent (see Table 12 in Wong 2016).

The area of the rat larynx that is the most sensitive to squamous metaplasia is the ventral floor of the anterior larynx at the base of the epiglottis. It is not surprising that at this location, the incidences of lesions are similar in THS and 3R4F-smoke exposed rats. However, these findings should also be examined with regards to the severity of the changes.

In the PMI studies, at the lowest exposure concentration of 3R4F smoke, at a test atmosphere nicotine concentration of 8 µg/L, the severity of the squamous metaplasia was maximal (i.e., score 5 on a scale from 0 to 5). In comparison, the severity of the same lesion for THS-exposed rats was scored 3 to 4 at the highest test atmosphere nicotine concentration of 50 µg nicotine/L. An example of these comparative changes is shown for the squamous metaplasia, at the mid-base of the epiglottis (larynx), for female and male rats in the THS exposure group in **Figure 3**. It should, however, be noted that at these specific sites in the larynx, maximum effects are already reached with cigarette smoke at nicotine test atmosphere concentrations below 3 µg/L (Terpstra 2003).

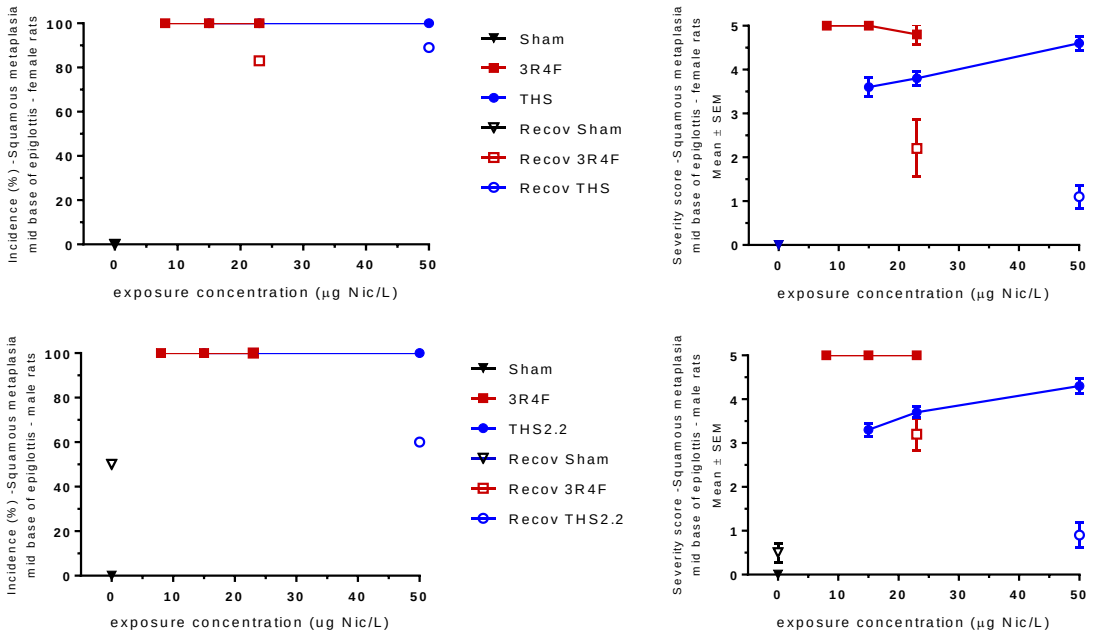

Figure 3. Squamous metaplasia at the mid-base of the epiglottis. Incidence of findings (left panels) and severity of the findings (right panels). Data is shown for female (upper panels) and male (lower panels) rats.

Hyperplasia and metaplasia may represent pre-neoplastic changes but can also represent transient adaptive changes in tissue. There are a number of histopathologic findings, such as inflammation, necrosis, ulceration, atypia, dysplasia, keratinization, dose-response, and reversibility of the lesion, that are important determinants as to the likelihood of whether such changes may proceed to cancer or are transient and reversible (Burger 1989). In our studies, cigarette smoke-exposed rats display keratinization (100% incidence, severity score of 5 at the low exposure concentration), whereas THS-exposed rats have lower dose-matched incidence, or a high incidence but with a maximum severity score of 2.2 at the base of the epiglottis. There were no signs of inflammation, atypia, or dysplasia in any of the rats at this sensitive location. Partial recovery, more specifically in the severity scores, was found to be more frequent in THS-exposed rats. All of these factors together support the conclusion that changes are most likely adaptive in nature rather than prone to evolving into neoplasia.

This has been further demonstrated in an 18-month combined chronic toxicity and carcinogenicity study on A/J mice (unpublished results, full study report submitted to the FDA on August 30, 2018) (see also section 2.4).

All histopathological changes in the respiratory tract organs from rodent inhalation studies should be evaluated in the light of a continuum, as many similar epithelial structures are observed throughout the respiratory tract. Changes at one location in a specific epithelium should be seen in another location, perhaps with a different severity but consistent with the exposure levels, and a certain number of findings may evolve into other changes over time. For example, a degenerated or atrophied epithelium can evolve into an adapted squamous epithelium, or a squamous epithelium may undergo keratinization upon continued exposure to strong irritants. Some of the epithelial transition areas in the

nose and larynx are extremely sensitive to inhaled substances, even to non-toxic ones and changes at these locations are often rodent-specific and not really representative of the human situation. Highlighting isolated changes at such locations, without considering the magnitude (severity) of the changes, the continuum of the alterations, and the translatability to the human situation, is therefore not always appropriate (Renne 2007).

Finally, PMI is using 90-day inhalation exposure studies with the main focus of comparing overall systemic toxicity and histopathology of the respiratory tract of cigarette smoke with that of our novel products, such as *IQOS*, rather than performing a classical risk assessment. The effects of cigarette smoke in such a model are well characterized and reproducible. In addition, PMI is performing systems toxicology evaluation in the relevant organs to reinforce the quality of the assessment through addition of mechanistic information.

2.5 Results of the 18-month combined chronic toxicity and carcinogenicity study on A/J mice

Remark: *The information provided in this section may not have been accessible to the authors of the research paper discussed in this document. This data was submitted by PMI to the U.S. FDA on August 30th 2018 and was not yet published by the FDA under PMI's MRTP for IQOS on the respective website at the time of the writing of the research paper.*

In addition to the already available results from the 10-month interim dissection time point, the full study report of our 18-month combined chronic toxicity and carcinogenicity study on A/J mice were submitted to the FDA on August 30th, 2018 and published on the FDA website for PMIs MRTPA on November 9th 2018. The following results were presented publically by PMI on August 9th, 2018 in Seoul, South Korea.

The 18-month A/J mouse inhalation study was a study to evaluate the changes in tumor incidence and multiplicity[3] caused by 3R4F smoke and THS aerosol. This model was previously established by PMI and shows that cigarette smoke causes a dose-dependent increase in lung adenocarcinomas (Stinn 2013a, Stinn 2013b). Briefly, female A/J mice were exposed 6 h/day, 5 days/week for 18 months to fresh air (sham), 3R4F smoke at 13.4 µg/L nicotine, and THS aerosol at three concentrations of nicotine: 6.7 µg/L, 14.3 µg/L and 26.8 µg/L[4]. The medium concentration of THS aerosol was set to match that of 3R4F smoke. Furthermore, male mice were exposed to either fresh air (sham) or THS aerosol at 26.8 µg/L nicotine.

The study results show that at the end of the life-long exposure period, a larger number (incidence) of A/J mice exposed to 3R4F smoke had lung carcinomas than mice exposed to fresh air (**Figure 4 – Panel A**). In contrast, mice exposed to THS aerosol did not show an increase in tumor incidence compared to those exposed to fresh air. Furthermore, mice exposed to 3R4F smoke had more lesions

[3] Tumor *incidence* refers to the number of animals with tumors, while tumor *multiplicity* refers to number of tumors per animal having at least one tumor.
[4] The human equivalent exposure to the high concentration corresponds to 56 cig/day for a 60 kg human (based on FDA 2005 guidance).

and tumors per mouse than those exposed to fresh air (multiplicity) (**Figure 4 – Panel B**)[5]. In contrast, mice exposed to THS aerosol did not show an increase in tumor multiplicity compared to those exposed to fresh air.

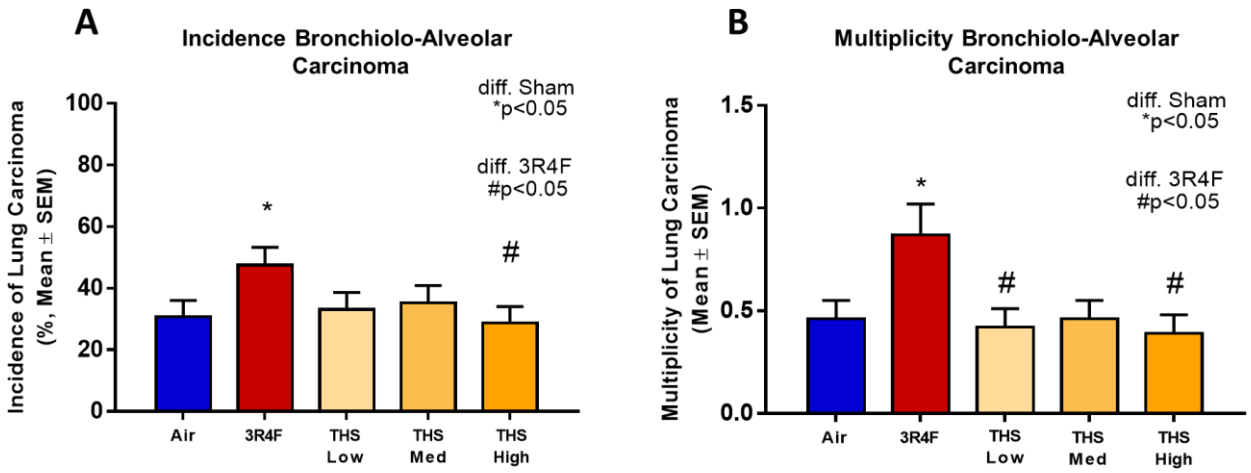

Figure 4. Incidence (Panel A) and Multiplicity (Panel B) of Bronchio-Alveolar Carcinoma in the Lung after 18 months Exposure to Air, 3R4F and THS.

Therefore, the results from this 18-month study in AJ mice provide strong evidence that the hyperplasia and metaplasia observed at the 10-month interim dissection time point do not represent pre-neoplastic changes but are transient adaptive changes in the respiratory tract tissue.

3 SUMMARY OF CLINICAL DATA AND RESULTS

3.1 Three-Month Reduced Exposure Studies

PMI conducted two 3-month Reduced Exposure Studies, one in Japan and the other in the US. These two studies were primarily designed to assess the extent of exposure reduction to HPHCs in smokers who switched to THS compared with those who continued to smoke cigarettes. Furthermore, the studies compared the effects of switching to THS with those of smoking abstinence. This provides an estimate of the maximum possible exposure reduction under controlled and ambulatory study conditions achievable by smoking cessation as well as switching to THS (Luedicke 2018, Part 1).

In these studies, we also monitored changes in multiple clinical risk endpoints (CRE) (i.e., Biomarkers of Potential Harm), including clinical risk endpoints for inflammation and lung function.

[5] The A/J mouse strain is very tumor-sensitive in contrast to most other mouse strains, and therefore has a high background incidence. Tumor multiplicity, which provides the better dynamic range, is reproducible between assays (Witschi 2005).

It is important to consider, that the Reduced Exposure Studies were not designed and powered to detect statistically significant changes in the CREs (i.e., in terms of sample size - see PMI's MRTPA for *IQOS*, section 7.3.1 07 REXA07 JP and section 7.3.1 08 REXA08 US, appendices 16.1.8 to the clinical study reports). A longer and larger study would be needed for this purpose.

However, this approach allowed an initial assessment of the effect of THS on CREs linked to smoking-related diseases and made it possible to gain early indications as to whether the reduction in exposure to HPHCs would lead to changes in CREs and if the changes observed upon switching to THS would move in the same direction and would be of similar magnitude as those observed upon smoking cessation.

The CREs included in all PMI clinical studies were assessed against a set of evidentiary prerequisites, namely (Luedicke 2018, Part 2):

- Epidemiological evidence suggesting a robust relationship between each CRE and at least one smoking-related disease
- Clinical evidence linking cigarette smoking to the CRE consistent with the epidemiological evidence (smoking causes negative changes)
- Clinical evidence linking smoking cessation to the CRE, and evidence indicating that the CRE is reversible following smoking cessation consistent with the epidemiological evidence (smoking cessation causes positive changes).

We focused on CREs that cover several smoking-related disease areas and mechanisms known to underlie the development of these diseases, such as cardiovascular and respiratory disease, inflammation, and oxidative stress.

All of the CREs included in the Reduced Exposure Studies were linked to smoking-related disease and responsive to smoking. However, data for several CREs were sparse or inconclusive with regards to the effect of smoking cessation as reported in the literature. Furthermore, several of the CREs included in the study were included as standard monitoring risk endpoints and were not expected to change over the duration of these studies. This was clearly outlined in the study protocols (see PMI's MRTPA for *IQOS*, section 7.3.1 07 REXA07 JP and section 7.3.1 08 REXA08 US).

The CREs we have focused our reporting on were the CREs that have *a priori* fulfilled all three criteria stated above and were reported in the literature to change upon smoking cessation and within the time frame of the study.

First, the magnitude of the changes in these CREs in smokers who abstained for the duration of the studies were small, which is expected in a healthy study population, yet the direction of the changes were consistent with the literature on smoking cessation. Because these changes also occurred upon smoking abstinence, which is known to reduce the risk of smoking-related disease, these changes are relevant. They are indicative of the positive effects of cessation across a broad range of mechanisms, such as inflammation and oxidative stress, which are linked to multiple smoking-related diseases.

Second, apart from the white blood cell (WBC) count in the U.S. study 3 month Reduced Exposure study, all markers changed in the direction of cessation upon switching to THS, and the magnitude of the changes was comparable to that observed in the smoking abstinence groups. This is a strong

indication that the reduction in HPHC exposure induced by switching to *IQOS* leads to positive changes in CREs, indicative of favorable impact on mechanistic pathways involved in the development of smoking-related diseases (Luedicke 2018, Part 2). This is entirely coherent with the causal chain of events linking smoking to disease (Smith 2016).

Detailed results for all CREs included in this study have been published previously (PMI 2018) and as part of PMI's MRTPA for *IQOS* under section 7.3.1.7 07 REXA07 JP and section 7.3.1.8 08 REXA08 US - csr-app-15_2-tables, Table 15.2.4.25.1, Table 15.2.4.25.1.2, and Table 15.2.4.71.

3.2 Six-Month Exposure Response Study

We recently completed and reported the results of our six-month clinical Exposure Response Study (ZRHR-ERS-09-US). This study was designed and powered to demonstrate changes in CREs in healthy smokers who switched from cigarette smoking to THS use in comparison with those who continued to smoke cigarettes (Ansari 2018). The eight co-primary CREs assessed as part of the primary objective were selected *a priori* based on the same criteria described above. Various additional CREs were also assessed in this study as part of the secondary objectives.

The results observed in this larger and longer Exposure Response Study confirmed the initial trends of favorable changes in CREs that were previously observed in the three-month Reduced Exposure Studies.

First, the primary statistical objective of the ZRHR-ERS-09-US study was met and demonstrated biological and functional improvements in smokers who switched from smoking cigarettes to using THS as compared with those who continued to smoke. This was determined with five out of the eight predefined CREs showing a statistically significant favorable change using a one-sided test with the Hailperin-Rüger-adjusted α-level for multiple testing (1.5625%). At a nominal test wise α-level of 5%, at least five out of the eight endpoints would be significant.

Second, all co-primary endpoints shifted in the same direction as in smokers who quit, as reported in the literature.

The eight co-primary endpoints included measures of lung function (forced expiratory volume in one second) and inflammation (WBC count), which directly address the concerns raised by the author. Both of these endpoints showed statistically significant favorable changes in smokers who switched for 6 months to THS compared with those who continued to smoke cigarettes.

Furthermore, these results were achieved despite the fact that a proportion of participants in the THS group used cigarettes concomitantly (up to 30% of all product use), answering the question of whether a beneficial effect by switching to THS can be achieved even under concomitant or dual-use conditions.

Table 2 provides an overview on the changes in the eight co-primary CREs observed for the THS group compared with continued smoking group based on the data reported on June 8, 2018, as an amendment to PMI's MRTPA for *IQOS* to the US FDA.

Table 2. Primary analysis of the selected eight co-primary endpoints between THS-use and CC-use categories at Month 6.

CRE	Mechanism	Change from CC-use	LS Mean Difference/Relative Reduction	96.875% CI	1-sided *p*-value
HDL-C	Lipid metabolism	Difference	3.09 mg/dL	1.10, 5.09	<0.001*
WBC Count	Inflammation	Difference	-0.420 GI/L	-0.717, -0.123	0.001*
sICAM-1	Endothelial dysfunction	% Reduction	2.86 %	-0.426, 6.04	0.030
11-DTX-B_2	Platelet activation	% Reduction	4.74 %	-7.50, 15.6	0.193
8-epi-$PGF_{2\alpha}$	Oxidative stress	% Reduction	6.80 %	-0.216, 13.3	0.018
COHb	Oxygen transport	% Reduction	32.2 %	24.5, 39.0	<0.001*
FEV_1 %pred	Lung function	Difference	1.28 %pred	0.145, 2.42	0.008*
Total NNAL	Carcinogen exposure	% Reduction	43.5%	33.7, 51.9	<0.001*

* Denotes significant p-value at the 1.5625% level, following test multiplicity adjustment using the Hailperin-Rüger approach.

Abbr.: 8-epi-PGF2α = 8-epi-prostaglandin F2α, 11-DTX-B2 = 11-Dehydrothromboxane B2, COHb = carboxyhemoglobin, CRE = clinical risk endpoint, FEV1 = forced expiratory volume in one second, HDL-C = high-density lipoprotein cholesterol, sICAM-1 = soluble intercellular adhesion molecule-1, NNAL = 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol, WBC = white blood cells.

3.3 Assessment of Indoor Air Quality

Lastly, the impact of using THS on indoor air quality was also experimentally assessed. Different scenarios, based on different air renewal and room occupancy, were experimentally assessed in a furnished control room using validated methods to quantify relevant air quality markers (selected carbonyls and volatile organic compounds, carbon and nitrogen oxides, and environmental tobacco smoke markers). This study (Mitova, 2016) showed that most measured analytes remained at background levels after the use of THS, with the exception of nicotine and acetaldehyde, for which measured levels remain significantly below defined levels in air quality guidelines (see PMI's MRTPA for *IQOS*, section 6.1.1 – Aerosol Chemistry).

4 DISCUSSION

To interpret the results from non-clinical and clinical studies and draw scientifically relevant conclusions, the entire set of results has to be assessed, and the study objectives and designs need to

be accounted for. 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.

In the non-clinical studies, changes indicated as systemic immunomodulatory effects due to the exposure to THS are, in fact, changes related to exposure to stress and nicotine *per se*, which become visible after extended exposure to high concentration of nicotine. These changes are further linked to the applied nose-only exposure mode, which has the advantage of ensuring controlled inhalation exposure, but on the other hand, poses a certain stress to the test animals. These study design-specific effects must be taken into consideration when evaluating the outcome of such 90-day inhalation studies rather than pointing toward a product-specific effect.

First, the inflammation parameters that are statistically significantly higher upon exposure to THS aerosol as compared to Sham are extremely low compared with 3R4F smoke exposure. They may be indicative for a low level of pulmonary inflammation, and it cannot be excluded that this is linked to a low residual level of HPHCs found in the THS aerosol. However, these changes are small and, in most cases, only occur at the highest exposure concentration. The observed THS-induced epithelial changes are only found at specific, highly sensitive areas of the respiratory tract and do not show any progression (e.g., epithelial keratinization).

In addition, for the interpretation of the effects reported in our non-clinical studies, the following points need to be considered:

1) The exposure concentrations used for THS in the reported non-clinical studies were at the maximum tolerable level for rats (50 µg/L nicotine in test atmosphere). They therefore correspond to approximately more than 100 *HeatSticks* per day, extrapolated to human exposure.
2) In contrast, the 3R4F-exposed rats were exposed to a lower test atmosphere nicotine concentration (i.e., 23 µg/L nicotine), which corresponds to about 50 cigarettes per day.

To conclude, the changes observed in PMI's non-clinical studies with regards to inflammatory response are small and, in most cases, only occur at the highest THS exposure concentration, which is not representative of human exposure.

Most importantly, the level of inflammation is extremely low compared with the levels observed following 3R4F smoke exposure. These changes are transient and adaptive in nature and therefore are not adverse effects indicative of substantial THS exposure-related immunomodulatory effects.

Furthermore, the results from the 18-month combined chronic toxicity and carcinogenicity study on A/J mice showed that exposure to THS aerosol did not increase the incidence and multiplicity of lung carcinomas compared to air exposure even at twice the THS aerosol concentration compared to 3R4F smoke. Therefore this study provided strong evidence that the hyperplasia and metaplasia observed at the 10-month interim dissection time point do not represent pre-neoplastic changes but represent transient adaptive changes in respiratory tract tissue.

Data from our clinical studies on inflammation and pulmonary effects clearly demonstrate favorable changes that are in accordance with the reduction in emissions of HPHCs (greater than 90%, on average) and significantly reduced toxicity. These changes occur even under dual-use conditions.

Furthermore, studies on secondhand exposure to THS have shown that measured analytes remained at background levels after THS use, with the exception of nicotine and acetaldehyde, for which measured levels remained significantly below levels defined in air quality guidelines and well below what could be measured for cigarettes.

PMI is open to and welcomes independent public review of our data. However, any review of scientific results needs to take into consideration the study's design and limitations and bring the results into context of other available evidence in order to draw conclusions. Specifically, when evaluating tobacco harm reduction and assessing the potential benefits of switching from smoking cigarettes to using a candidate MRTP, the results have to be considered in the context of both smoking and smoking cessation, as these represent both the highest and lowest risk of smoking-related disease for a current adult smoker.

In summary, the statements made by the authors are selective, incorrect, 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 with continued smoking. This includes a significant reduction in inflammatory response and favorable changes in lung function.

Although not risk-free, switching completely to THS is a much better choice for current adult smokers than continuing to smoke cigarettes.

5 CONCLUSION

Following sounds scientific principles and:

1) Considering study designs and objectives to enable accurate comparison of results between different study groups at equal nicotine exposure concentrations
2) Putting transient, adaptive changes into context and differentiating them from structural, non-reversible histological changes
3) Considering the evidence from PMI's clinical Reduced Exposure Study and Exposure Response Studies as well as the data available from our assessment of the impact of using THS on Indoor Air Quality,

the science-based conclusion that can be reached is that 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 with continued smoking. This includes a significant reduction in inflammatory response and favorable changes in lung function.

Although not risk-free, switching completely to THS is a much better choice for current adult smokers than continuing to smoke cigarettes.

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7 ABBREVIATIONS

8-epi-PGF2α	8-epi-prostaglandin F2α
11-DTX-B2	11-Dehydrothromboxane B2
BAL	Bronchoalveolar lavage
BALF	Bronchoalveolar lavage fluid
CO	Carbon monoxide
COHb	Carboxyhemoglobin
CPD	Cigarettes per day
CRE	Clinical risk endpoint
FDA	U.S. Food and Drug Administration
FEV1	Forced expiratory volume in one second
HDL-C	High-density lipoprotein cholesterol
HPHC	Harmful and potentially harmful constituent
Total NNAL	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
MCP3	Monocyte chemoattractant protein 3
MIP-1β	Macrophage inflammatory protein
MPO	Myeloperoxidase
MRTP	Modified Risk Tobacco Product
MRTPA	Modified Risk Tobacco Product Application
MTD	Maximum tolerated dose
OECD	Organisation for Economic Co-operation and Development
PAI-1	Plasminogen activator inhibitor-1
PMI	Philip Morris International

sICAM-1	Soluble intercellular adhesion molecule-1
THS	Tobacco Heating System (commercialized as *IQOS*)
WBC	White blood cell