

The Difference between *IQOS* and Continued Smoking

Response to the article entitled “PMI’s own in vivo clinical data on biomarkers of potential harm in Americans show that *IQOS* is not detectably different from conventional cigarettes,” by Stanton Glantz, 2018¹

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EXECUTIVE SUMMARY

The Department of Medicine, University of California, San Francisco, California, USA has recently published an article in *Tobacco Control* raising concerns that “PMI’s own *in vivo* clinical data on biomarkers of potential harm in Americans show that IQOS is not detectably different from conventional cigarettes” [1]. The main conclusion reported by the author of this article is that “the application [Philip Morris International’s {PMI’s} Modified Risk Tobacco Product Application {MRTPA} for IQOS] includes comparisons of the levels of 24 biomarkers of potential harm in human smokers, including comparisons with people who smoke conventional cigarettes...[...]...and that in people who actually use IQOS, the levels of these biomarkers of potential harm are not detectably different from conventional cigarettes.” This is considered to be “consistent with the data PMI reported on the levels of toxicants in IQOS mainstream aerosol compared with mainstream smoke of 3R4F reference cigarettes. While many toxicants were lower in IQOS aerosol, 56 others were higher in IQOS emissions and 22 were more than twice as high, and 7 were more than an order of magnitude higher.” Furthermore, the author states that “IQOS uses an aerosol of ultrafine particles to deliver the nicotine. These ultrafine particles cause heart and lung disease.”

In short, the statements made by the author are incorrect and misleading, and do not take into consideration good scientific practice. They ignore the overarching assessment approach required for candidate Modified Risk Tobacco Products (MRTP) such as the Tobacco Heating System (THS; marketed in various countries under the brand name IQOS). Furthermore they do not consider the study designs and objectives and ignore the totality of evidence available to date.

PMI’s assessment approach for THS is in line with the MRTP draft guidance from the U.S. Food and Drug Administration (FDA) Center for Tobacco Products (CTP). There is no single endpoint or study that is considered to prove risk reduction of smoking-related diseases on its own when switching from cigarette smoking to THS. The strength of the evidence available to date for THS lies in the coherence of change across the spectrum of multiple studies and endpoints, including clinical risk endpoints (CREs), how they reflect the changes that would be induced by smoking cessation, and to what extent they provide mutual evidentiary support for each other (coherence and consistency). Taken together, all data form a system that facilitates the risk assessment of a candidate MRTP, such as THS. In other words, assessing the risk of diseases that take decades to develop, and to come to sound scientific conclusions on the risk reduction potential of a candidate MRTP, requires the totality of the evidence to be considered, and not just isolated studies or endpoints.

In summary, the level of emissions of harmful and potentially harmful constituents (HPHCs) generated by THS are on average 90% lower than found in cigarette smoke. Furthermore, our untargeted screening of the THS aerosol demonstrated that the THS aerosol is significantly less complex than

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cigarette smoke, and that the exposures to the four compounds of potential toxicological concern elevated in the THS aerosol (compared with cigarette smoke) are actually below the level of toxicological concern. Moreover, and in contrast to cigarette smoke, THS aerosol does not contain carbon-based nanoparticles, which are known to cause cardiovascular and lung disease. Furthermore, our numerous non-clinical studies, which have consistently demonstrated a 90% reduction in toxicity for the THS aerosol compared with cigarette smoke across a wide range of *in vitro* and *in vivo* test systems. More importantly, studies in animal models of smoking-related diseases have clearly demonstrated the potential of THS to reduce the adverse effects of smoking.

To investigate how the reduction in emissions of HPHCs would translate into a reduction in exposure in humans, PMI conducted two 3-Month Reduced Exposure Studies in Japan and in the U.S. These two studies were primarily designed to assess the extent of exposure reduction to HPHCs in smokers who switched to THS in comparison with those who continued to smoke cigarettes. Furthermore, the studies compared the effects of switching to THS with those of smoking abstinence. This allows a comparison of the exposure reduction achievable when switching to THS with the maximum exposure reduction achieved by smoking cessation.

In these studies, we also monitored multiple CREs (or biomarkers of potential harm) to gain early indications as to whether the reduction in exposure leads to favorable changes in risk indicators. To select the CREs to assess, PMI conducted an extensive literature review and applied the following criteria:

1. The CRE must be linked to smoking-related diseases (e.g., through epidemiology).
2. The CRE must be responsive to smoking (smoking causes negative changes).
3. The CRE must reverse upon smoking cessation (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 were included in the study to monitor the respective CRE but were not expected to change over the duration of these studies. This was clearly outlined in the study protocols (see section 7.3.1 [07 REXA07 JP](#) and 7.3.1 [08 REXA08 US](#) of PMI's MRTPA for *IQOS*).

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.

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It is also important to consider that the Reduced Exposure Studies were NOT DESIGNED to serve as the sole pivotal evidence with regards to changes in CREs and to show 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 7.3.1 [08 REXA08 US](#) Appendices 16.1.8 to the clinical study reports).

Therefore, drawing confirmative conclusions on CREs from the Reduced Exposure Studies alone is invalid. However, the results observed for CREs in these studies confirmed that the reduction in exposure to HPHCs and the reduction in toxicity starts to translate into favorable biological and functional changes (i.e., the changes observed upon switching to THS move in the same direction and are of similar magnitude as those observed upon smoking cessation).

Our latest results from the 6-Month Exposure Response Study clearly demonstrate significant favorable changes in CREs in smokers switching to THS, even under conditions of up to 30% concomitant cigarette use. This study also demonstrated that the degree of exposure reduction and favorable changes in CREs is maximized following complete switching (i.e., abandoning cigarettes completely).

In summary, the statements made by the authors are incorrect, selective and misleading. The totality of evidence available on THS clearly demonstrates that THS presents less risk of harm, can reduced the risk of smoking-related diseases compared to continued smoking and is therefore different in risk profile. Although not risk free switching completely to THS is a much better choice for current adult smokers compared to continued smoking.

1 INTRODUCTION

The Department of Medicine, University of California, San Francisco, California, USA has recently published an article in Tobacco Control [reference] raising concerns that *“PMI’s own in vivo clinical data on biomarkers of potential harm in Americans show that IQOS is not detectably different from conventional cigarettes”* [1]. The statements and conclusions made by the author are based on the results reported in the context of Philip Morris International’s (PMI) Modified Risk Tobacco Product (MRTP) Application (MRTPA) for IQOS.

The main conclusion reported by the author is that *“the application [PMI’s MRTPA for IQOS] includes comparisons of the levels of 24 biomarkers of potential harm in human smokers, including comparisons with people who smoke conventional cigarettes...[...]...and that in people who actually use IQOS, the levels of these biomarkers of potential harm are not detectably different from conventional cigarettes.”*

This is considered to be *“consistent with the data PMI reported on the levels of toxicants in IQOS mainstream aerosol compared with mainstream smoke of 3R4F reference cigarettes. While many toxicants were lower in IQOS aerosol, 56 others were higher in IQOS emissions and 22 were more than twice as high, and 7 were more than an order of magnitude higher.”*

Furthermore, the author states that *“IQOS uses an aerosol of ultrafine particles to deliver the nicotine. These ultrafine particles cause heart and lung disease.”*

This report aims to clarify these findings and conclusions and to provide context by summarizing PMI’s scientific approach to the assessment of THS as a candidate MRTP.

2 SUMMARY OF DATA ON AEROSOL CHEMISTRY, TOXOCITY, AND ANIMAL MODELS OF DISEASE

PMI has previously demonstrated that that the level of emissions of harmful and potentially harmful constituents (HPHCs) generated by the Tobacco Heating System (THS; marketed in several countries under the brand name IQOS) are on average 90% lower than found in cigarette smoke. Our full analysis of THS aerosol compared with cigarette smoke showed that only 750 compounds were present in THS aerosol, whereas we identified 4,330 compounds in smoke from the 3R4F reference cigarette developed by the University of Kentucky. This further confirmed the reduced complexity of the THS aerosol. Among these compounds, we identified that 53, 57, and 60 aerosol constituents were higher in concentration in *IQOS Regular*, *IQOS Smooth Menthol*, and *IQOS Fresh Menthol*, respectively, compared with 3R4F smoke. An analysis of this list of compounds, which are essentially tobacco blend- and flavor-related, highlighted only four compounds of potential toxicological concern. 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. This is consistent with the *in vitro* and *in vivo* toxicological investigations of the THS aerosol, which systematically demonstrated an overall decrease in toxicity compared with cigarette smoke. The compounds referred to by the author as being one order of magnitude higher in THS vs. 3R4F are menthol and menthol-related flavors, not toxicants. Therefore, the statement “While many toxicants were lower in THS aerosol, 56 others were higher in THS emissions and 22 were more than twice as high, and 7 were more than an order of magnitude higher,” is incorrect ([Amendment to PMI’s MRTPA for IQOS – published Dec 08th 2017](#)).

Furthermore, the author stated that “*IQOS uses an aerosol of ultrafine particles to deliver the nicotine. These ultrafine particles cause heart and lung disease.*” When looking at the possible impact of ultrafine particles, it is important to consider their origin and chemical composition and not merely their presence and size. THS aerosol consists exclusively of liquid droplets, mainly composed of water and glycerin and contains significantly lower levels of HPHCs compared to cigarette smoke. In contrast, cigarette smoke contains, besides HPHCs, a large number of solid carbon-based nanoparticles (cbNP). These cbNPs are produced during combustion and are well known to be associated with heart and lung disease. While a single cigarette delivers in the order of 0.5×10^{12} cbNPs, THS delivers no cbNPs [2].

3 SUMMARY OF CLINICAL DATA ON CLINICAL RISK ENDPOINTS AND HOW TO CONSIDER THEM IN THE CONTEXT OF THE TOTALITY OF EVIDENCE

The disorders induced by smoking are complex, and the diseases develop over a period of many years. No single endpoint or biomarker can, on its own, be considered as a surrogate measure for all of the adverse health effects associated with smoking.

In the PMI clinical studies, submitted as part of PMI’s MRTPA for *IQOS*, clinical risk endpoints (CREs) (or biomarkers of potential harm) are used to provide collective evidence about the modification of the risk profile of THS in support of the available totality of evidence (non-clinical, clinical, and perception and behavioral studies) demonstrating the potential of THS to reduce the risk of smoking-related diseases.

The CREs included in the PMI clinical studies were assessed against a set of evidentiary prerequisites, namely [3]:

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- 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.

3.1 The 3-Month Reduced Exposure Studies

Two of the eight clinical studies, part of PMI's original MRTPA for IQOS (December 2016), were the 3-month, *ad libitum* use Reduced Exposure Studies in a confined and ambulatory setting (see PMI's MRTPA for IQOS, section 6.1.4.1.2 - Table 3), conducted in Japan (ZRHM-REXA-07-JP) [3] and in the U.S. (ZRHM-REXA-08-US). These two studies were primarily designed to assess the extent of exposure reduction to HPHCs in smokers who switched to THS in comparison with those who continued to smoke cigarettes [4]. The studies furthermore compared the effects of switching to THS with those of smoking abstinence. This provides an estimate of the maximum possible exposure reduction under the study conditions achievable by smoking cessation [4,5]. The Reduced Exposure Studies were not designed to show 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 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.

Furthermore, it is important to consider that all of the 24 CREs included in the Reduced Exposure Studies were linked to smoking-related disease and responsive to smoking, following the selection criteria outlined above. However, data as reported in the literature for several of the CREs included in these studies was sparse or inconclusive with regards to the effect of smoking cessation. Therefore, several of the CREs included in the study were included for the purpose of monitoring these CREs and were not necessarily 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 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.

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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 favorable 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.

First, the magnitude of change in these CREs in smokers who abstained for the duration of the studies were small, which is expected in a healthy study population, yet their direction of change was consistent with the literature upon smoking cessation. Because these changes occurred upon smoking abstinence, which is known to reduce the risk of smoking-related disease, these changes are clinically 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, all markers changed in the direction of cessation upon switching to THS. The magnitudes of change were also not very different from those observed in the smoking abstinence groups. This is a strong indication that the reduction in HPHC exposure induced by switching to THS leads to positive changes in CREs. This is entirely coherent with the causal chain of events linking smoking to disease [3, 5].

Table 1 provides an overview on the changes observed for THS compared with those observed for continued smoking and smoking abstinence based on the data reported in section 6.1.4.4 of PMI's MRTPA for *IQOS* (see also PMI's MRTPA for *IQOS*, section 7.3.1.7 [07 REXA07 JP](#) and 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) as well as the time frame when we expect changes in CREs to occur as reported in the literature.

3.2 The 6-Month Exposure Response Study

The clinical Exposure Response Study conducted in the U.S. (ZRHR-ERS-09-US) was designed to demonstrate favorable changes in CREs (or biomarkers of potential harm) in healthy smokers who switched from cigarette smoking to THS use in comparison with those who continued to smoke cigarettes. Therefore, the study design was different from the two 3-Month Reduced Exposure studies reported above in several aspects: (1) the duration of the exposure was longer (6 months versus 3 months), (2) it was conducted in a more real-life setting, without a confinement period at the beginning of the study, and (3) the number of study participants was much larger, which allowed a more accurate description of product use patterns in a more diverse study population. This data adds substantial clinical information about the U.S. adult smoker population and THS use.

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Furthermore, the International Conference on Harmonization (ICH) E-9 “Statistical Principles for Clinical Trials” recommends that confirmatory clinical trials have a single primary endpoint with additional supporting endpoints [6]. In order for a single primary endpoint approach to be appropriate in the context of assessing a candidate MRTP, such as THS, the endpoint would need to provide sufficient information to adequately capture the multifaceted disease process and the range of clinically relevant changes required to demonstrate a “modification of the risk” of smoking-related diseases. To date no single marker has been identified which would fulfill such criteria. Therefore to demonstrate the risk reduction potential of a candidate MRTP, the Exposure Response Study considered multiple co-primary endpoints tested individually. However, the interpretation is based on the results across all of them (e.g., at least one endpoint is significant, a subset of the endpoints are significant, or all of the endpoints are significant). The approach PMI has taken for this study, i.e., to test each component and across the eight co-primary endpoints, is consistent with the reality of a range of organ and physiological systems affected by smoking. When assessing a set of co-primary endpoints the probability of finding one or more significant results due to chance alone needs to be considered and can be calculated. Using a Bernoulli process, the probability of finding five significant tests ($p < 0.05$) by chance alone is extremely low (0.006%), which illustrates two important points related to the analysis strategy taken in this study:

1. The more individual tests that are required to simultaneously fall below the set α -level, the lower the probability they are all spurious. [7]
2. Several relatively high p-values (closer to 0.05) can be a stronger indication of a significant result than one relatively low p-value (less than 0.001). [8]

Based on the aforementioned, it is reasonable to assume that if a product is ineffective, the probability of finding favorable changes in most or all of the CREs that are part of the primary objective of this study is small. Therefore, it should not be necessary to require all of the co-primary endpoints to be statistically significant (p -value < 0.05) in order to control the error rate of wrongly approving an ineffective product [9].

Therefore, PMI has defined the success criteria for this study as:

- (1) Having statistically significant improvements in the majority of the co-primary CREs (i.e., five out of eight co-primary CREs) using a one-sided test with adjusted type I error ($\alpha = 1.5625\%$), and
- (2) With all endpoints changing in the direction observed upon smoking cessation in the literature.

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Another important aspect when using co-primary endpoints is to address multiplicity. For this purpose the Hailperin-Rüger method [10, 11] was used for this study which preserves the study-wise α -level by requiring that a subset of endpoints is found to be statistically significant. It tests each of the co-primary endpoints at an adjusted test-wise α -level and success is declared on the overall null hypothesis if a predefined subset of endpoints is found to be statistically significant.

In this study, the Hailperin-Rüger method was used to protect the overall study-wise two-sided α -level of 5% which allows to determine a one-sided testwise type I error level of 1.5625%. This was required for each of the eight tested co-primary CREs with at least five of them required to be statistically significantly modified in the direction expected upon smoking cessation and without the need for prior specification of which ones. Furthermore all co-primary CREs were required to shift in the same direction as reported in the literature for smoking cessation. The scientific justification for the design, sample size and analysis approach was submitted to the US Food and Drug Administration (FDA) on June 8, 2018, as part of the clinical study report together with the results of this study.

Given the ambulatory nature and duration of the study, it was assumed that some subjects randomized to THS would concomitantly use THS and cigarettes. This assumption was based on: (1) that this study was a clinical study with forced switching to a new product with different characteristics than the study subject's own brand of cigarettes; (2) that communication on potential benefits of the product, which may encourage switching, is not possible in a clinical study setting; and (3) that the data on the earlier heated tobacco product prototype "electrically heated cigarette smoking system" showed that concomitant cigarette use was reported in 30% of the users [12]. This is also in line with our experience regarding product use patterns in markets where THS is commercialized, where we observed that 70%–90% of THS users actually use THS more than 70% of the time, with 5%–15% of initial THS users switching back to cigarettes [13]. Therefore, the primary analysis in this study focuses on THS "as actually used," allowing up to 30% of concomitant cigarette use in the primary analysis population. This is another important difference compared with the 3-Month Reduced Exposure Studies, where the primary analysis population used THS for more than 95% of all product use experiences and not more than two cigarettes per study day. Product use assessment in the Exposure Response Study was based on self-reported tobacco product use by study participants, as recorded in their diaries over the 6-month post-randomization period.

Of the 984 randomized participants, 488 were randomized to THS, and 496 were randomized to continued cigarette (CC) smoking. In the THS group, 245 study participants (51.4%) were categorized as THS users, 142 study participants (29.8%) were categorized as dual-users, 3 study participants (0.6%) were categorized as CC users (analyzed together with subjects randomized to CC), and 24 study participants (4.9%) were categorized as users of other tobacco or nicotine-containing products. In the

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CC group, 425 study participants (85.6%) were categorized as CC smokers, and 18 study participants (4.2 %) were categorized as users of other tobacco or nicotine-containing products. One hundred and twenty seven (127) study participants (74 study participants in the THS group and 53 study participants in the CC group) were excluded from the study³. In total, 803 randomized subjects completed the 6-month study.

The baseline smoking intensity (prior to the run-in period) across the study population was, on average, about 19 cigarettes per day (CPD), with an average smoking history of about 26 years (~24 pack years). Post-randomization, the 428 participants in the CC use category smoked, on average, 16.8±6.8 CPD. In the dual use category, the average daily consumption was 7.6±5.2 *HeatSticks*/day and 10.0±5.9 CPD, while in the THS use category, the average daily consumption was 16.5±8.9 *HeatSticks*/day and 2.0±2.4 CPD.

In short, the results observed in this larger and longer-term Exposure Response Study confirmed the initial trends of favorable changes in CREs observed in the 3-Month Reduced Exposure Studies.

First, the primary statistical objective of the 6-Month Exposure Response Study was met and demonstrated favorable changes in the eight co-primary CREs in smokers who switched from cigarette smoking to THS use. The eight co-primary CREs assessed as part of the primary objective were selected *a priori* based on the same criteria as described above. By using a one-sided test with the Hailperin-Rüger-adjusted α -level for multiple testing (1.5625%), five out of the eight predefined endpoints for the hypothesis test showed a statistically significant change. At a nominal testwise α -level of 5%, seven out of eight endpoints would have been significant.

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

Furthermore, multiple CREs assessed as secondary endpoints showed favorable change in the direction observed upon smoking cessation. The CREs assessed in this study as part of the secondary objectives included all CREs also assessed in the Reduced Exposure Studies.

[Error! Reference source not found.](#) provides an overview on the endpoints assessed in this study as well as the timeframe when we expected changes in CREs to occur as reported in the literature. The results of this study were reported on June 8, 2018, as an amendment to PMI's MRTPA for *IQOS* to the U.S. FDA.

³ Reasons for exclusion from the study: no valid baseline value, no post randomization data for at least one primary endpoint, absence of at least one post-randomization product use record, or subjects excluded due to site termination.

PMI is currently finalizing a smoking cessation study (NCT02432729) that will provide further perspective to the results obtained in the Exposure Response Study.

4 DISCUSSION

As there is no single endpoint or study that is sufficient, on its own, to demonstrate the risk reduction potential of a candidate MRTP, such as THS, PMI's approach to the assessment of THS is based on the totality of evidence generated through a very broad range of studies [5]. The strength of the evidence available for THS lies in the consistent changes of a broad spectrum of endpoints, including CREs, across multiple studies and test systems, how these changes reflect those that would be induced by smoking cessation, and the extent that these changes provide mutual evidentiary support (coherence). Taken together, all data form a coherent system that facilitates the risk assessment of a candidate MRTP, such as THS.

Smoking-related cardiovascular diseases (CVD) develop because of chronic exposure to HPHCs, which cause oxidative stress and inflammation. These mechanisms, in turn, cause perturbations of biological networks linked to endothelial dysfunction, lipid metabolism, and platelet activation. These changes lead to atherosclerotic plaque formation and increased cardiovascular risk.

In PMI's MRTPA for *IQOS*, we have presented multiple lines of evidence that switching from cigarette smoking to THS use would be accompanied by a lower risk of CVD (summarized in see PMI's MRTPA for *IQOS*, section 2.7.6).

First, the level of emissions of HPHCs generated by THS are on average more than 90% lower than found in 3R4F cigarette smoke (see PMI's MRTPA for *IQOS*, section 6.1.1) [14-17]. The Reduced Exposure Studies have demonstrated that the reduced emission of HPHCs results in a significant reduction in exposure to HPHCs, including cardiovascular toxicants [4, 18-19]. Furthermore, the results of the 6-Month Exposure Response Study confirm these observations and show that these favorable changes are achieved even under conditions of concomitant cigarette use (up to 30% concomitant cigarette use in the THS group).

Second, this reduction in exposure to HPHCs has been shown across multiple *in vitro* and *in vivo* studies to result in a significantly reduced biological impact compared with cigarette smoke. This reduced impact is evidenced by the reduced perturbations of biological networks associated with the causation of CVD (e.g., oxidative stress, inflammation, monocyte-endothelial cell interaction) and the reduced monocyte adhesion to endothelial cells *in vitro* [20]. The results of the clinical Reduced Exposure Studies conducted in Japan (ZRHM-REXA-07-JP) [3] and the U.S. (ZRHM-REXA-08-US) showed that switching from cigarette smoking to THS use leads to a trend of favorable changes in the CREs of

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oxidative stress, inflammation, endothelial function, lipid metabolism, and platelet activation, similar to those seen following smoking abstinence.

Third, the ApoE^{-/-} mouse switching study demonstrated that animals that were initially exposed to cigarette smoke and subsequently switched to either THS aerosol or fresh air exposure showed very similar reductions in atherosclerotic plaque growth rates [21].

Fourth, the results of the 6-Month Exposure Response Study confirmed the previous clinical observation that the CREs associated with CVD all change in the direction of smoking cessation after switching from cigarette smoking to THS use, and this finding was maintained even under conditions of concomitant cigarette smoking (up to 30% of all product uses in the THS group) (Error! Reference source not found.).

Overall, the scientific data is remarkably consistent across all biological systems that were studied. Compared with cigarette smoke, THS aerosol had significantly reduced effects on mechanisms causally linked to atherosclerotic plaque formation in human-derived *in vitro* systems. Switching from cigarette smoke to THS aerosol exposure caused positive changes in CREs associated with cardiovascular risk and reduced atherosclerotic plaque growth in an animal model of disease. THS aerosol exposure performs in a manner similar to smoking cessation/abstinence when examined in both animal and human switching studies. Furthermore, the magnitude of the biological effects across all systems are coherent with a, on average, more than 90% reduction of HPHC emission by THS compared with cigarettes. The congruence of scientific findings (i.e., the totality of the evidence) indicates that smokers who switch to THS would have a lower risk of CVD development and progression compared with continued smoking

Chronic obstructive pulmonary disease (COPD) in smokers is triggered by exposure to cigarette smoke constituents, resulting in oxidative stress and inflammation. Oxidative stress and chronic inflammation, in turn, cause perturbations of biological networks and changes in alveolar and airway tissues. These changes in alveolar/airway cell functioning have an adverse impact on overall pulmonary function, leading to COPD.

In PMI's MRTPA, we have presented multiple lines of evidence that switching from cigarette smoking to THS use would be accompanied by a lower risk of COPD (summarized in PMI's MRTPA for IQOS, section 2.7.6).

First, THS significantly reduces the emission of HPHCs compared with cigarettes. Reduced Exposure clinical studies have demonstrated that this reduced HPHC emission results in a reduced exposure to HPHCs, including respiratory toxicants.

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Second, this reduced exposure to HPHCs has been shown across multiple *in vitro* [22] and *in vivo* studies to result in a significantly reduced biological impact compared with cigarette smoke [21, 23-24]. This reduction in impact is evidenced by the reduced perturbations of biological networks associated with the causation of COPD (including inflammation, oxidative stress, apoptosis), less severe adaptive histopathological changes, the lack of alveolar destruction (emphysema), and reduced pulmonary dysfunction in animal models of emphysema [21] (summarized in PMI's MRTPA for IQOS, section 2.7.6). The results of the clinical Reduced Exposure Studies conducted in Japan (ZRHM-REXA-07-JP) [3] and the U.S. (ZRHM-REXA-08-US) showed that switching from cigarette smoking to THS use leads to a trend of positive changes in CREs of oxidative stress and inflammation, similar to those seen following smoking abstinence. Furthermore, measurements of forced expiratory volume in one second (FEV₁), although only studied over 3 months, indicated that lung function in smokers who switched to THS improved in the same manner as was seen in smokers who abstained for the duration of the study.

Third, the ApoE^{-/-} mouse switching study demonstrated that animals that were initially exposed to cigarette smoke and subsequently switched to either THS aerosol or fresh air exposure showed very similar reductions in pulmonary inflammation and a stabilization of emphysema progression [21].

Fourth, the results of the 6-Month Exposure Response Study confirmed the previous clinical observation that the WBC count and FEV₁, the CREs associated with inflammation and COPD, changed in the direction of smoking cessation upon switching from cigarette smoking to THS use, even under conditions of concomitant cigarette use (up to 30%) (Error! Reference source not found.).

Overall, the scientific data are remarkably consistent across all biological systems that were studied. Compared with cigarette smoke, THS aerosol had significantly reduced effects on mechanisms causally linked to lung inflammation and COPD in human-derived *in vitro* systems. Switching from smoke to THS aerosol exposure caused positive changes in markers associated with COPD and reduced emphysema progression as well as lung function loss in an animal model of disease. This is now further corroborated by the results of the 6-Month Exposure Response Study, where switching from cigarette smoking to THS use, even under conditions of concomitant cigarette use (up to 30% of all product use in the THS group), led to a reduced decline in FEV₁, which is the expected direction of change upon smoking cessation. THS aerosol exposure thus performs in a manner similar to smoking cessation/abstinence when examined in both animal and human switching studies. Furthermore, the magnitude of the biological effects across all systems are coherent with an, on average, more than 90% reduction of HPHC emission by THS compared with cigarettes. The congruence of scientific findings (i.e., the totality of the evidence) indicates that smokers who switch to THS would have a lower risk of COPD development and progression compared with continued smoking.

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The latency of smoking-related lung cancer appearance does not allow for clinical demonstrations of reduced risk with candidate MRTPs. However, there are multiple factors that make it likely that switching to THS aerosol from cigarette smoke would be accompanied by a lower risk of lung cancer than continued smoking. The rationale for this claim is based on the Adverse Outcome Pathway (AOP), which outlines the sequence of causally linked events leading from smoke/HPHC exposure to disease [5]. In the case of lung cancer, chronic exposure to high levels of carcinogenic HPHCs and cbNPs causes the perturbations in biological networks (genetic damage, inflammation, and oxidative stress), cellular dysfunction/death, tissue injury, and finally, disease. Cessation is known to reduce the risk of tobacco-related disease. This corresponds to removing the first causative step in the AOP (i.e., eliminating the exposure to HPHCs and cbNPs from cigarette smoke). This leads to a reduced perturbation of biological networks, reduced cell death and dysfunction, reduced tissue injury, and reduced organ damage. It is therefore expected that a candidate MRTP capable of reducing the exposure to carcinogenic HPHCs and cbNPs in a way similar to cessation will also show a biological outcome similar to cessation (i.e., a reduced risk of lung cancer).

One of the most recognized and highly carcinogenic compounds in cigarette smoke are the tobacco-specific nitrosamines (TSNA). TSNA's unique source is tobacco, with no other source known to date. Studies such as the Shanghai Cohort Study [25] reported a significant relationship between the TSNA 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) and its biomarker of exposure, Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (Total NNAL), and lung cancer, and N-nitrosornicotine (NNN) and its biomarker of exposure Total N-nitrosornicotine (Total NNN) and esophageal cancer [25]. Hecht and colleagues reported odds ratios (OR) of 1.89 to 2.6 for lung cancer depending on the levels of Total NNAL (biomarker of exposure to NNK) as well as ORs of 3.99 to 17 for esophageal cancer, again, depending on the levels of NNN. In the PMI Reduced Exposure clinical studies conducted in an Asian population, the absolute levels of Total NNAL and NNN observed after switching to THS (22.48 pg/mg creatinine [95% CI: 18.82, 26.84] for Total NNAL; 0.90 pg/mg creatinine [95% CI: 0.70, 1.14] for NNN) are comparable with the levels reported by Hecht and colleagues in the control group (<29.29 for Total NNAL and <5.17 pg/mg creatinine for NNN). This provides clinical relevance to the observed levels of reduction.

The PMI studies reported in the PMI's MRTPA for *IQOS* have provided several demonstrations that switching from cigarette smoke to THS aerosol would significantly reduce the risk of lung cancer.

First, THS aerosol contains significantly reduced levels of carcinogenic HPHCs compared with cigarette smoke (on average by more than 93%) and no cbNPs.

Second, switching from cigarette smoking to THS use reduced the exposure to carcinogenic HPHCs to a level approaching the reductions induced by smoking cessation (all clinical Reduced Exposure

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Studies). In fact, switching to THS achieved more than 95% of the effects of cessation in the 90-day clinical Reduced Exposure ambulatory studies.

Third, THS aerosol is significantly less genotoxic than cigarette smoke. Furthermore, THS aerosol induces significantly less DNA damage than cigarette smoke in multiple non-clinical studies conducted both *in vitro* and *in vivo* (summarized in PMI's MRTPA for IQOS, section 2.7.6). Moreover, advanced systems toxicology studies conducted in multiple *in vitro* and *in vivo* models have demonstrated that THS aerosol is significantly less toxic and induces significantly fewer perturbations of all studied biological networks (including inflammation, DNA damage-response, xenobiotic metabolism response, and oxidative stress response) than cigarette smoke.

Fourth, the results of the 6-Month Exposure Response Study and post-hoc analyses confirmed the previous clinical observation that exposure to carcinogens, including NNN and NNK, is significantly reduced upon switching from cigarette smoking to THS use (Total NNAL Relative Reduction = 43.5% [96.875% CI: 33.7, 51.9]; $p < 0.001$), even under conditions of concomitant cigarette use (up to 30% of all product use in the THS group) ([Error! Reference source not found.](#)).

Taken together, these demonstrations offer evidence that smokers who switch from cigarette smoking to THS use would experience a significant reduction in exposure, biological impact, and ultimately, risk of lung cancer compared with continued smoking.

5 CONCLUSIONS

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

- THS reduces the emissions of HPHCs by 90%–95% compared to cigarette smoke.
- Our untargeted screening of the THS aerosol demonstrated that the THS aerosol is significantly less complex compared with cigarette smoke.
- The level of exposure to four compounds that were elevated in THS aerosol and of potential toxicological concern are below the level of toxicological concern through the use of THS.
- In contrast to cigarette smoke, THS aerosol does not contain cbNPs, which are known to cause CVD and lung disease.
- Our non-clinical studies have demonstrated a 90% reduction in toxicity for THS compared with cigarette smoking.
- Animal models of smoking-related diseases have clearly demonstrated the potential of THS to reduce the adverse effects of smoking.

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- In PMI clinical studies, CREs are used to provide collective evidence about the modification of the risk profile of THS in support of the totality of evidence available (non-clinical, clinical, and perception and behavioral studies) demonstrating the potential of THS to reduce the risk of smoking-related diseases.
- The primary objective of the 3-Month Reduced Exposure Studies was to demonstrate reduced exposure to HPHCs and not to serve as the sole pivotal evidence with regards to changes in CREs. Hence, the study was powered to assess changes in levels of biomarkers of exposure in a confirmatory manner and not CREs. Therefore, drawing confirmative conclusions on CREs from this study alone is invalid.
- CREs were included in these 3-Month Reduced Exposure Studies to investigate if a reduction in exposure to HPHCs starts to translate into favorable biological and functional changes (i.e., the changes observed upon switching to THS move in the same direction and are of similar magnitude as smoking cessation). The results of these studies confirmed these initial favorable changes, which were in line with what was observed upon smoking abstinence.
- Our latest results from the 6-Month Exposure Response Study have clearly demonstrated significant favorable changes in CREs achieved by smokers when they switch to THS, even under up to 30% concomitant use of cigarettes.
- The 6-Month Exposure Response Study also demonstrated that the degree of exposure reduction and favorable changes in CREs is maximized with complete switching (i.e., abandoning cigarettes completely).

In summary, the statements made by the authors are incorrect, selective and misleading. The totality of evidence available on THS clearly demonstrates that THS presents less risk of harm, can reduce the risk of smoking-related diseases compared to continued smoking and is therefore different in risk profile. Although not risk free, switching completely to THS is a much better choice for current adult smokers compared to continued smoking.

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7 ABBREVIATIONS

3R4F	Reference cigarette from the University of Kentucky, USA
AOP	Adverse Outcome Pathway
cbNP	Carbon-Based-Nanoparticle
CC	Cigarette(s)
COPD	Chronic Obstructive Pulmonary Disease
CPD	Cigarettes Per Day
CRE	Clinical Risk Endpoint
CTP	Center of Tobacco Products
CVD	Cardiovascular Disease
DNA	Deoxyribonucleic Acid
FDA	U.S. Food and Drug Administration
FEV ₁	Forced Expiratory Volume in One Second
HPHC	Harmful and Potentially Harmful Constituent
M RTP	Modified Risk Tobacco Product
M RTPA	Modified Risk Tobacco Product Application
Total NNAL	Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol
(Total) NNN	(Total) N-nitrosornicotine
NNK	4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone
OR	Odds Ratio
PMI, R&D	Philip Morris International, Research and Development
THS	Tobacco Heating System
TSNA	Tobacco Specific Nitrosamines
WBC	White Blood Cell Count

8 APPENDIX 1 – RESULTS OF CLINICAL RISK ENDPOINTS ASSESSED IN THE 3-MONTH REDUCED EXPOSURE STUDIES

Table 1 - Summary of Philip Morris Studies of Changes in CREs in IQOS users compared to Conventional Cigarette Smokers (95% confidence intervals in parenthesis) after 3 months

	3 months Study in Japan		3 months Study in the US		Timeframe of change upon Smoking Cessation
	THS (n=71) vs. CC (n=41)	THS (n=71) vs. SA (n=37)	THS (n=47) vs. CC (n=32)	THS (n=47) vs. SA (n=9)	
Inflammation (6.1.4.4.2*)					
White Blood Cell Count (WBC)	-0.57 GI/L (-1.04, -0.10)	-0.16 GI/L (-0.65, 0.33)	0.17 GI/L (-0.47, 0.81)	1.11 GI/L (0.07, 2.15)	6–12 months [1-4]
C reactive protein (CRP)	6.41% ↓ (-40.75, 37.77)	10.74%↑ (-27.33, 68.76)	16.23% ↓ (-21.69, 42.33)	2.61% ↓ (-46.17, 76.19)	> 12 months [5-7]
Soluble ICAM (sICAM-1)	8.72% ↓ (2.05, 14.94)	2.41%↑ (-4.76, 10.12)	10.59% ↓ (4.03, 16.71)	0.76% ↓ (-11.35, 11.09)	3 months [8-12]
Fibrinogen	5.42% ↓ (-1.80, 12.13)	0.61%↓ (-8.02, 7.40)	1.63% ↓ (-6.42, 9.08)	3.48% ↓ (-14.82, 9.38)	Hours – weeks [13-17]
Oxidative stress (6.1.4.4.3)					
Prostaglandin F2 alpha (8-epi-PGF2α)	12.71% ↓ (2.55, 21.81)	7.22%↓ (-17.2, 3.96)	13.46% ↓ (-1.95, 23.61)	5.41% ↓ (-22.26, 15.10)	2-4 weeks [19-22]
11-dehydro-thromboxane B2 (11-DTX-B2)	8.98% ↓ (-19.52, 2.94)	12.89%↑ (-0.53, 28.12)	3.56% ↓ (-23.31, 24.57)	3.88%↑ (-29.58, 53.23)	3 days [23, 24]

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Cholesterol and Triglycerides (6.1.4.4.4)					
High density lipoprotein-cholesterol (HDL-C)	4.53 mg/dL (1.17, 7.88)	-1.83 mg/dL (-5.28, 1.61)	1.4 mg/dL (-2.3, 5.0)	1.3 mg/dL (-4.4, 7.1)	3 months [25-28]
Low density lipoprotein-cholesterol (LDL-C)	0.87 mg/dL (-6.55, 8.30)	-4.74 mg/dL (-12.46, 2.99)	-3.3 mg/dL (-12.0, 5.4)	-5.1 mg/dL (-18.9, 8.6)	3 months [27-29]
Total cholesterol	2.00 mg/dL (-6.68, 10.67)	-8.30 mg/dL (-17.35, 0.75)	-4.0 mg/dL (-13.3, 5.2)	-1.4 mg/dL (-16.1, 13.2)	2-6 weeks [30][28]
Triglycerides	-6.25 mg/dL (-21.20, 8.69)	-18.69 mg/dL (-34.39, -2.99)	0.9 mg/dL (-12.8, 14.6)	11.6 mg/dL (-13.3, 5.2)	2-8 weeks [31-36][28]
Apolipoprotein A1 (Apo 1)	N/A	N/A	3.1 mg/dL (-4.6, 10.7)	3.7 mg/dL (-8.3, 15.7)	2-6 weeks [30, 37-39]
Apolipoprotein B (Apo B)	N/A	N/A	-1.6 mg/dL (-7.24, 4.03)	-3.17 mg/dL (-12.14, 5.79)	
Physiological measures					
Systolic blood pressure	-0.59 mmHg (-3.80, 2.62)	-0.76 mmHg (-4.16, 2.65)	-0.7 mmHg (-4.5, 3.1)	1.7 mmHg (-4.3, 7.7)	Long-term
Diastolic blood pressure	-0.68 mmHg (-3.04, 1.69)	-1.68 mmHg (-4.16, 0.79)	0.2 mmHg (-3.7, 4.0)	2.4 mmHg (-3.7, 8.4)	Long-term

THE DIFFERENCE BETWEEN IQOS AND CONTINUED SMOKING.

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Lung Function (6.1.4.4.5)					
Forced expiratory volume in 1 second (FEV1)	1.91 %Pred (-0.14, 3.97)	-0.2%Pred (-2.15, 2.11)	0.53 % Pred (-2.09, 3.00) 0.05 L (-0.06, 0.15)	-1.46 % Pred (-6.63, 3.71) 0.02 L (-0.14, 0.15)	6-12 months [40-44]
FEV1/FVC (FVC=forced vital capacity)	N/A	N/A	0.00 (-0.02, 0.02)	-0.01 (-0.04, 0.02)	> 6 months
Mid expiratory flow (MEF 25-75) (L/s)	N/A	N/A	-0.67 (-6.33, 4.99)	1.23 (-7.62, 10.07)	> 6 months
Diffusion capacity for lung CO (DLCO) (mL/min/mmHg)	N/A	N/A	0.31 (-1.09, 1.72)	1.95 (-0.33, 4.22)	1 week [45, 46]
Rate constant of CO (KCO) (mmol/min/kPa/L)	N/A	N/A	0.05 (-0.02, 0.12)	0.04 (-0.09, 0.16)	1 – 2 weeks
Total lung capacity (TLC) (L)	N/A	N/A	0.09 (-0.25, 0.43)	0.39 (-0.13, 0.92)	> 6 months
Functional residual volume	N/A	N/A	-0.09 (-0.31, 0.13)	-0.42 (-0.76, -0.07)	> 6 months

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(FRV) (L)					
Inspiratory capacity (IC) (L)	N/A	N/A	0.21 (-0.08, 0.51)	0.88 (0.43, 1.33)	> 6 months
Vital capacity (VC) (L)	N/A	N/A	0.10 (0.00, 0.21)	0.05 (-0.10, 0.21)	> 6 months

9 APPENDIX 2 – RESULTS OF CO-PRIMARY CLINICAL RISK ENDPOINTS ASSESSED IN THE 6-MONTH EXPOSURE RESPONSE STUDIES

Table 2 - Summary of Philip Morris Studies of Changes in CREs in IQOS users compared to Conventional Cigarette Smokers (96.875% Confidence Intervals in parenthesis) after 6 months			
Clinical Risk Endpoint	THS (n=245) vs. CC (n=428)	1-sided p-value (0.0156)	Expected Time to Change
Inflammation			
White Blood Cell Count (WBC)	-0.420 GI/L (-0.717, -0.123)*	0.001	6–12 months
Soluble ICAM (sICAM-1)	2.86% ↓ (-0.426, 6.04)+	0.030	3 months
Oxidative stress			
Prostaglandin F2 alpha (8-epi-PGF2α)	6.80% ↓ (-0.216, 13.3)+	0.018	2-4 weeks
11-dehydro-thromboxane B2 (11-DTX-B2)	4.74% ↓ (-7.50, 15.6)]+	0.193	3 months
Cholesterol and Triglycerides			
High density lipoprotein-cholesterol (HDL-C)	3.09 mg/dL (1.10, 5.09)*	<0.001	3 months
Lung Function			
Forced expiratory volume in 1 second (FEV1)	1.28 % Pred. (0.145, 2.42)*	0.008	6-12 months
Oxygen Transport			
Carboxyhemoglobin (COHb)	32.2% ↓ (24.5, 39.0)+	<0.001	Hours
Genotoxicity			

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Table 2 - Summary of Philip Morris Studies of Changes in CREs in IQOS users compared to Conventional Cigarette Smokers (96.875% Confidence Intervals in parenthesis) after 6 months

Clinical Risk Endpoint	THS (n=245) vs. CC (n=428)	1-sided p-value (0.0156)	Expected Time to Change
Total 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol Total NNAL	43.5% ↓ (33.7, 51.9) +	<0.001	Steady state after 3 months

NOTE: +: %↓ = Observed change presented as % relative reduction (relative to CC), *: Observed change presented as LS Mean Difference

Results of CREs assessed as part of the secondary endpoints, namely C reactive protein (CRP), Albumin in Urine, Homocysteine, Fibrinogen, Myeloperoxidase (MPO), Platelet Count, Low density lipoprotein-cholesterol (LDL-C), Total cholesterol, Triglycerides, Apolipoprotein A1 (Apo A1), Apolipoprotein B (Apo B), Apo B / Apo A1 ratio, HbA1C, Systolic blood pressure, Diastolic blood pressure, FEV1/FVC (FVC=forced vital capacity), Forced expiratory flow (FEF 25-75) (L/s), Total lung capacity (TLC) (%pred), Functional residual capacity (FRC) (%pred), Inspiratory capacity (IC) (%pred), Vital capacity (VC) (%pred), will be published upon release of the results of this study by the FDA in the context of PMIs MRTPA for THS (submitted June 08th 2018).