A Response from Philip Morris International to Selected Claims

From Chapter 9.4.6: "Tobacco Industry Science as a Further Threat to Tobacco Control"

In the Report:

"E-cigarettes and Harm Reduction: An Evidence Review"

by Royal College of Physicians (RCP), April 2024

Claim
"Major TTCs have also sought to obfuscate information and create confusion[144] about the harms of their products, including HTPs.[33,47,136–138]"

Response
Regarding Philip Morris International (PMI), this statement is false and represents an unsubstantiated dismissal of our scientific research based purely on a well-used narrative that major TTCs cannot be trusted – it is not supported by fact. More than a decade ago, PMI made a deliberate choice to embrace scientific transparency and openness, ensuring that our scientific studies are published, and data is shared in a proactive manner. This approach empowers individuals to engage directly with the data, enabling them to independently analyze and interpret the findings. By committing to open science and transparent disclosure of our scientific data, PMI fosters an environment where scientific integrity is paramount. PMI's commitment to openness and transparency is evident in several key practices. Clinical studies are registered on widely recognized platforms like clinicaltrials.gov, and data, study designs, and methods are shared in publicly accessible repositories.

Our practices are inspired by the pharmaceutical industry and are aligned to the 2012 draft guidance for modified risk tobacco product (MRTP) application issued by the U.S. Food and Drug Administration's (FDA's) Center for Tobacco Products. On July 7th, 2020, after thoroughly reviewing PMI's scientific data, the FDA granted authorization for the commercialization of *IQOS* in the U.S. as a modified risk tobacco product with reduced exposure claims. This decision highlights how robust the scientific evidence provided to the Agency is, and ultimately, the potential of *IQOS* to reduce harm compared with continued smoking. Although the request for modified risk claims was not accepted, FDA acknowledged the substantial potential for public health benefits and concluded that "*the applicant has demonstrated that the products sold or distributed with the proposed modified risk information meet the standard under section 911(g)(2) of the FD&C Act, including that a measurable and substantial reduction in morbidity or mortality among individual tobacco users is reasonably likely in subsequent studies, and issuance of an order is expected to benefit the health of the population as a whole, taking into account both users of tobacco products and persons who do not currently use tobacco products*" (TPL page 11).

Moreover, the number of independent studies on *IQOS* and other heated tobacco products (HTPs) has significantly increased over the past years, as shown on PMIScience.com. These studies often reinforce key findings from our own research efforts. However, it is important to acknowledge that variations may exist between studies, including differing results, data interpretations, methodological approaches, and conclusions drawn. It is essential to recognize that individual studies, regardless of their quality, only provide a fragment of the overall picture. A comprehensive understanding of the harm reduction potential of our smoke-free products emerges from the accumulation of evidence over time.

Supporting references:

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6. **Lüdicke F, Picavet P, Baker G, et al.** Effects of switching to the tobacco heating system 2.2 Menthol, smoking abstinence, or continued cigarette smoking on biomarkers of exposure: A randomized, controlled, Open-Label, multicenter study in sequential confinement and ambulatory settings (Part 1). *Nicotine & Tobacco Research.* 2017;20(2):161-172. doi:10.1093/ntr/ntw287.
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Claim

"A growing number of studies demonstrate that PMI's claims around the reduced-risk potential of IQOS are not entirely substantiated by its own scientific research.[123,139–143]"

Response

Our claims about *IQOS* are based on a rigorous, multi-step scientific assessment, which includes product design and control principles, aerosol chemistry, physics, and indoor air quality studies, as well as non-clinical and clinical assessment, perception and behaviour research, and post-market studies and surveillance. To accurately assess the risk of diseases that develop over decades and determine the potential for risk reduction with a modified risk tobacco product, it is essential to consider the full body of evidence rather than isolated studies or endpoints. The totality of evidence available on *IQOS* clearly shows that it poses less risk of harm compared with continued smoking and can reduce the risk of smoking-related diseases compared with continued smoking, and therefore has a different risk profile. Although not risk-free, switching completely to *IQOS* is a much better choice for adults who smoke compared with continued smoking. Our research demonstrates that, by eliminating combustion, the levels of harmful and potentially harmful constituents (HPHCs) are reduced on average by 90-95% in *IQOS* aerosol compared with cigarette smoke.

We have further demonstrated that this substantial reduction translates into a reduction in toxicity in laboratory models and multiple clinical studies show reduced exposure to HPHCs approaching levels observed with smoking cessation. In our one-year exposure response study, which involved a 6-month study followed by a six-month extension study, we measured eight biomarkers of potential harm (BoPH) involved in pathomechanistic pathways relevant for diseases associated with smoking. Study results showed that smokers who switched from cigarettes to *IQOS* for 12 months had favorable changes in all eight BoPH, in the same direction as smoking cessation. Moreover, recent findings from a cross-sectional risk marker study further substantiate the benefits of switching to *IQOS* compared with continued smoking by showing favorable differences in nine BoPH after at least 2 years of *IQOS* use while providing real-life data on *IQOS* users who chose to switch to it without intervention (study not yet published).

PMI's scientific assessment extends beyond aerosol chemistry, toxicology, and clinical studies. It also includes systems toxicology, an approach that examines the comparative biological impact of *IQOS* aerosol and cigarette smoke on large networks of molecular and functional changes occurring across multiple levels of biological organization (e.g., molecular, cellular, tissue, organ, whole organism) that, if disrupted, can lead to disease.

Overall, the findings from every line of evidence converge on a single conclusion: switching to *IQOS* has the potential to reduce the risk of smoking-related diseases compared with continued smoking.

PMI has shared its scientific data on *IQOS* publicly through PMIScience.com, scientific conferences as well as in peer-reviewed journals. In particular, a number of public health agencies have reviewed the available evidence. For example, FDA concluded, through its scientific evaluation of PMI's applications, peer-reviewed published literature, and other sources, that the aerosol produced by the *IQOS* Tobacco Heating System contains fewer toxic chemicals than cigarette smoke, and many of the toxins identified are present at lower levels than in cigarette smoke. Public Health England noted in 2018 that the available evidence suggests that heated tobacco products may be considerably less harmful than tobacco cigarettes and more harmful than e-cigarettes. The German Federal Institute for Risk Assessment (BfR) confirmed that levels of major carcinogens are markedly reduced in the emissions of the analysed HNB product in relation to conventional tobacco cigarettes and that monitoring these emissions using standardized machine smoking procedures generates reliable and reproducible data which provide a useful basis to assess exposure and human health risks.

In conclusion, PMI has provided extensive evidence of the potential reduced risk of *IQOS* compared with continued smoking. While *IQOS* is not risk free, the evidence supports our claims, and we welcome further independent review on our smoke-free products.

Supporting references:

1. **A 26-week extension of the ZRHR-ERS-09-US study evaluating biological and functional changes in healthy smokers after switching to THS 2.2.** ClinicalTrials.gov. https://clinicaltrials.gov/study/NCT02649556. Accessed August 29, 2024.
2. **Ansari SM, Hession PS, David M, et al**. Impact of switching from cigarette smoking to tobacco heating system use on biomarkers of potential harm in a randomized trial. Biomarkers. 2024;29:298-314. doi:10.1080/1354750X.2024.2358318.

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Claim

"Recent research that critically appraised interventional clinical trials on HTPs also found that industry-affiliated studies were of poor quality and limited to investigating the impacts of their short-term use.[33]"

Response

The critique in the referenced study focuses on selective endpoints without considering the totality of evidence or the broader context. It fails to acknowledge that not all HPHCs in cigarette smoke have corresponding biomarkers of exposure. Our reduced exposure and exposure response studies have selected biomarkers based on rigorous criteria, including established links to smoking-related diseases and sensitivity to smoking status. The FDA has recognized that although biomarkers of exposure for every HPHC are not available, comparative aerosol data show significant reductions in many HPHCs compared with cigarette smoke. Additionally, our clinical studies follow FDA's guidelines for testing modified risk tobacco products and include short-term reduced exposure studies and 12-month exposure response studies. The integrity of FDA's review process ensures that all submitted studies are thoroughly evaluated. Additionally, recent findings from a cross-sectional risk marker study, conducted on adult participants who have transitioned from cigarettes to *IQOS* over the past 2 years and recruited across 37 healthcare institutions in Asia and Europe, strengthens the findings from previous reduced exposure and exposure response studies and provides real-life data on *IQOS* users who chose to switch without intervention (study not yet published).

Supporting references:

1. **Ansari SM, Hession PS, David M, et al.** Impact of Switching from Cigarette Smoking to Tobacco Heating System Use on Biomarkers of Potential Harm in a Randomized Trial. *Biomarkers*. 2024;29(5):298-314. doi:10.1080/1354750x.2024.2358318
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Claim

"PMI has also misrepresented the science on smoke and aerosol, claiming that IQOS is smoke-free, safer than conventional cigarettes, and even less harmful than e-cigarettes.[47,145]"

Response

This statement is inaccurate and misleading. PMI's claims about *IQOS* are based on scientific evidence demonstrating that it operates without combustion. This is supported by temperature measurements, the absence of exothermic reactions, the absence of solid-based particles arising from combustion, and no involvement of oxygen (required for combustion to start) during the heating process. This is further confirmed by aerosol chemistry studies indicating that HPHCs in *IQOS* aerosol are on average 90-95% lower than in cigarette smoke. Untargeted screenings reveal that *IQOS* aerosol is less complex than cigarette smoke, containing only four elevated compounds, all of which are below toxicological concern thresholds. The FDA's 2020 MRTP decision supports the claim that *IQOS* heats tobacco without burning it, acknowledging the absence of combustion and *IQOS*'s reduced emissions compared with combusted cigarettes. The FDA also noted that *IQOS* is unlikely to generate significant interest among never smokers, youth, or former smokers. *IQOS* is not risk free and we do not claim that *IQOS* is "safe" but assert it is less harmful than continuing to smoke combustible cigarettes. Moreover, we aim to provide clear, accurate information to adult consumers without making direct comparisons between different smoke-free products.

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Claim
"Simultaneously, TTCs have promoted the 'benefits' of nicotine while downplaying its addictiveness and health harms.[138]"

Response
Our position is clear: nicotine is addictive and not risk free. However there is a scientific consensus that nicotine is not the primary cause of smoking-related diseases; instead it is the high levels of HPHCs generated by tobacco combustion. Our smoke-free products contain nicotine, which is one of the reasons why people continue to smoke along with ritual, taste, social and sensorial experience. These factors also play an important role in making smoke-free products acceptable for adults who would otherwise continue to smoke. Our communication is consistent and clear that nicotine is addictive and carries its own risks.

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