Review of the article entitled "Heat-Not-Burn Tobacco Cigarettes: Smoke by Any Other Name"[1]

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Philip Morris International (PMI) supports scientific data transparency, data sharing and actively encourages the conduct of independent studies on *IQOS* that are aimed at advancing scientific and medical knowledge or verifying the results we obtained through our assessment program described by Smith *et al.*[2] To date we have published over 30 peer-reviewed articles describing studies specifically conducted with *IQOS*.[3] We have also submitted a Modified Risk Tobacco Product (MRTP) application with the U.S. FDA.[4] It is important that independent studies are conducted with a high degree of scientific rigor, the same degree of rigor that is expected from our company. Key standards for scientific research are:

1. Studies should be conducted using fit-for-purpose and validated methods
2. Study results should be interpreted in an appropriate and non-misleading manner
3. Resulting publications should be subject to appropriate peer review

As independent scientists from different backgrounds are starting to analyze our products, it is perhaps not surprising that different methodologies are applied. We note, for example, that the methods described by Auer *et al.* published by *JAMA Internal Medicine* on May 22, 2017, reporting on a chemical analysis of the *IQOS* aerosol, were based on a "*smoking device designed and tested in [their] facility*".[1] Without further description of the system they used, it is hard to compare their analysis to those which we have reported previously, using standard and validated smoking machine systems and procedures. While some of the reported results seem consistent with those that we have previously published, significant points of difference in the described methodologies may account for the disagreements in results obtained by Auer *et al*. in comparison to our peer-reviewed and published data.

Methodology:

1. Methodologies for smoke and aerosol generation have been amply described in the literature. We are therefore surprised that the authors did not use a recognized smoking regime, but rather used a hybrid between the ISO and the Health Canada Intense (HCI) regime,[5] and then used this data to compare their results with those published using the HCI regime.[6] Fundamental principles of science generally recommend to compare the comparable and use of appropriate controls. All commercial accredited laboratories systematically use a reference cigarette (e.g. 3R4F) to verify their analytical procedures. The reference cigarette data is always

[1] Auer R, Concha-Lozano N, Jacot-Sadowski I, Cornuz J and Berthet A (2017) Heat-Not-Burn Tobacco Cigarettes: Smoke by Any Other Name. JAMA Intern Med. E-pub ahead of print. doi: 10.1001/jamainternmed.2017.1419.
[2] Smith M, Clark B, Luedicke F, Schaller J-P, Vanscheeuwijck P, Hoeng J and Peitsch MC (2016) Evaluation of the Tobacco Heating System 2.2. Part 1: Description of the System and the Scientific Assessment Program. Regulatory Toxicology and Pharmacology, 81 Suppl 2:S17-S26. doi: 10.1016/j.yrtph.2016.07.006.
[3] Smith M, Haziza C, Hoeng J, Lüdicke F, Maeder S, Vanscheeuwijck P and Peitsch MC (2017) The Science behind the Tobacco Heating System: a summary of published scientific articles. Available at: https://www.pmiscience.com/library/pmi-science-ths-executive-summary.
[4] U.S. Food and Drug Administration (FDA). Philip Morris Products S.A. Modified Risk Tobacco Product (MRTP) Applications. May 24, 2017. Available from: https://www.fda.gov/TobaccoProducts/Labeling/MarketingandAdvertising/ucm546281.htm.
[5] Health Canada (2000). Health Canada - Tobacco Products Information Regulations SOR/2000-273, Schedule 2. http://laws-lois.justice.gc.ca/PDF/SOR-2000-273.pdf.
[6] Vu AT, Taylor KM, Holman MR, Ding YS, Hearn B and Watson CH (2015) Polycyclic Aromatic Hydrocarbons in the Mainstream Smoke of Popular U.S. Cigarettes. Chem. Res. Toxicol. 28:1616-1626. doi: 10.1021/acs.chemrestox.5b00190.

provided along with the results of the tested product. Should the reference cigarette data be out of the expected range, all associated results have to be discarded. It is also the practice we apply in our laboratories.

2. We were surprised by the measurement results Auer *et al.* obtained for the volatile organic compounds. For instance, it is perplexing that they report yields of approximately 1 µg acrolein per stick for both *IQOS* and the cigarette they used in their study. However, on closer analysis it appears that the acrolein values reported by Auer *et al.* for Lucky Strike Blue are 50 times lower than those published for similar cigarettes by Health Canada.[7] Similarly Auer *et al.* find 10 times lower levels of formaldehyde in cigarettes than Health Canada. Furthermore, the yields of acetone, crotonaldehyde and propionaldehyde are underestimated by 69%, 24% and 39% respectively.
3. It is generally established that the HCI regime is more relevant to human smoking topography than the ISO regime. Under HCI we find that the combustible reference cigarette 3R4F yields 154±20 µg acrolein per stick,[8] which is similar to the 142±17 µg/stick reported by Health Canada.[7] We have also reported that *IQOS* yields 11±2.36 µg acrolein per stick under HCI.[8] Furthermore, under the ISO, *IQOS* yields 4.89±0.74 µg acrolein per stick.
4. We noted that the values reported in the table (footnote c) from Vu *et al.*[6] for the ISO smoking regimen and for a mean of the 35 top-selling US cigarette brands are in fact the values reported for the HCI smoking regimen for the 50 cigarettes tested by Vu *et al*.[6]
5. Regarding the polycyclic aromatic hydrocarbons, Auer *et al*. reported a level of acenaphthene for *IQOS* that is three fold higher than for cigarettes. Acenaphthene is not part of the list of 58 substances we routinely quantify,[9] nor is it part of any regulatory lists (including the most extensive list, the FDA 93). It is, however, a compound we have measured in the smoke of 3R4F, but could not detect in the *IQOS* aerosol. This is most likely due to the fact that our method is based on mass spectrometry, which is a specific detector, as opposed to the non-specific detection system used by the authors. Their reported level for *IQOS* may therefore come from an artefact, not linked specifically to acenaphthene. As for the organic volatile compounds, the authors did not seem to validate their methods using a reference cigarette and compare these validation results with publicly available data such as Vu *et al.*[6]
6. Unfortunately, the results for carbon monoxide (CO) measurements are reported in ppm (parts per million). We would recommend that they should have been converted to mg/stick. Reporting in the way the authors do precludes a comparison of the measured levels with a standard reference cigarette. In addition, the level of CO for the combustible cigarette was above the measurement range of the used instrument, which precludes a comparison between the *IQOS* and cigarette yields. In fact, CO is reduced by >98% when measured with adequate and validated methods.[3,4] This is further corroborated by a reduction in blood COHb in smokers who switch completely to *IQOS* that equals that of those who abstain from smoking in four clinical studies.[3,4]
7. The nicotine level reported for the Lucky Strike Blue is 0.36 mg per cigarette, for a 0.5 mg cigarette (printed figures on the pack). The difference between the measured level and the printed figures exceeds the accepted tolerance described in ISO 8243, which indicates that the author's nicotine analysis method may be inadequate.
8. It is also surprising that for many analytes, the reported standard deviations are close to, or even larger than the mean values.
9. Taken together, these issues lead us to question the analytical methods that were used. For future studies we recommend that the authors should validate their methods with a reference cigarette (e.g. 3R4F) and compare their results with those published by a recognized regulatory agency.

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[7] Hammond D and O'Connor RJ (2008) Constituents in Tobacco and Smoke Emissions from Canadian Cigarettes. Tob. Control, 17 Suppl I:i24–i31. doi:10.1136/tc.2008.024778.

[8] Schaller J-P, Keller D, Poget L, Pratte P, Kaelin E, McHugh D, Cudazzo G, Smart D, Tricker AR, Gautier L, Yerly M, Pires RR, Le Bouhellec S, Ghosh D, Hofer I, Garcia E, Vanscheeuwijck P and Maeder S (2016) Evaluation of the Tobacco Heating System 2.2. Part 2: Chemical composition, genotoxicity, cytotoxicity, and physical properties of the aerosol. Regulatory Toxicology and Pharmacology, 81 Suppl 2:S27-S47. doi: 10.1016/j.yrtph.2016.10.001.

[9] The PMI list of 58 analytes captures priority toxicants in tobacco smoke listed by regulatory bodies such as FDA and Health Canada.

Interpretation:

1. Contrary to the authors' suggestions, "*Heat-not-burn*" is not an advertising slogan but a shorthand for a product description. We have clearly demonstrated the absence of combustion in *IQOS* through robust scientific substantiation, which we summarized on pmiscience.com[3] and in our MRTP application to the U.S. FDA.[4] This has been corroborated by several combustion experts. Furthermore, we have never claimed that *IQOS* is devoid of pyrolytic processes, which are well known to increase with increasing temperature, and are responsible for much of the remaining HPHCs found in the *IQOS* aerosol. However, combustion does not occur in *IQOS*. One of several lines of evidence in support of this assertion is that *IQOS* yields the same levels of HPHCs when operated in a 100% nitrogen atmosphere than in air (oxygen is of course needed for combustion)[3,4].
2. The authors suggest that we are "*dancing around the definition of smoke to avoid indoor-smoking bans*". Unfortunately, the authors did not present any data regarding the impact of *IQOS* on indoor use. As there are fundamental differences in how *IQOS* functions and is used, its impact on air quality cannot be linearly extrapolated from mainstream aerosol chemistry data (even if these were correct). Towards that end, proper indoor air quality studies, using validated methods are needed. One such example can be found in Mitova *et al.*[10]

Peer review:

While we recognize that there is a need to scrutinize the scientific work performed and/or funded by the tobacco industry, it would seem equally important to adequately scrutinize the work emanating from academia in this field. Indeed, the issue of *reproducibility in science* is of growing concern and journals are paying special attention to upholding the value of the peer review system. We are therefore puzzled that the peer review system did not identify some of the methodological and interpretational findings outlined above.

Concluding remarks:

1. PMI has consistently communicated that *IQOS* aerosol is not devoid of HPHCs, and has transparently published the relative yields of HPHCs in comparison with cigarette smoke.[8] Chemical analysis of the *IQOS* aerosol shows that it contains on average >90% reduction in the levels of HPHCs when compared with the smoke of the 3R4F reference cigarette. This was furthermore corroborated by a concomitant reduction in cytotoxicity and genotoxicity.[8]
2. Since we understand the skepticism around tobacco industry-generated data, we also commissioned an independent, recognized and accredited laboratory in Canada to quantify the 58 analytes we routinely measure in our aerosol chemistry studies.[11] The data was submitted as part of our MRTP application to the U.S. FDA.[4]
3. The totality of the evidence collected to date, across a broad range on toxicology, systems toxicology and clinical studies, indicates that *IQOS* has the potential to present less risk of harm compared to continued smoking for adult smokers who switch to it completely.[3,4]

[10] Mitova MI, Campelos PB, Goujon-Ginglinger CG, Maeder S, Mottier N, Rouget EG, Tharin M and Tricker AR (2016) Comparison of the impact of the Tobacco Heating System 2.2 and a cigarette on indoor air quality. Regulatory Toxicology and Pharmacology, 80:91-101. doi: 10.1016/j.yrtph.2016.06.005.

[11] Available at: https://www.pmiscience.com/platform-development/platform-development/aerosol-chemistry-physics/hphcs/levels-hphcs-measured