The supplemental modified risk tobacco product application for IQOS 3 does not adequately address new published research and information on emissions of HPHCs and other toxic substances in IQOS aerosol and does not demonstrate benefits to individual or population health, so FDA should not issue an exposure modification MRTP order for IQOS 3

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Docket No. FDA-2021-N-0408
Modified Risk Tobacco Product Application: Application for the IQOS 3 System Holder and Charger Submitted by Philip Morris Products S.A.

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The supplemental modified risk tobacco product application for IQOS 3 (sMRTPA) does not address new research and information on emissions of HPHCs and other toxic substances found in IQOS 2.4 aerosol and published since August 31, 2018, the date when Philip Morris Products S.A. (PMPSA) submitted its "FDA Requested Tabulated Index of [7,733] Scientific References" as an amendment to its IQOS 2.4 MRTPA.[1] These outdated references are cross-referenced and used to support the IQOS 3 sMRTPA. New papers published since August 2018 have found that although IQOS emits lower amounts of some HPHCs compared to conventional cigarettes, IQOS aerosol also exposes users to higher amounts of some toxic or potentially toxic substances than found in conventional cigarettes, and the amounts of carcinogenic TSNAs it emits are significantly higher than from e-cigarettes, a similar type of product on the market. Moreover, IQOS 3 aerosol emits higher amounts of chemicals that are included on FDA's August 2019 proposed list of HPHCs (glycidol, furfural, glycerol, propylene glycol) as well as 2-furanmethanol, 3-chloro-1,2-propondiol. **Glycidol and 3-chloro-1,2-propondiol are of particular concern because they are carcinogens.** PMPSA's application does not demonstrate benefits to individual or population health and fails to meet the statutory requirements for MRTPAs. Therefore, FDA should not issue an MRTP order for IQOS 3.

1. Background

[1] Philip Morris Products S.A. Modified Risk Tobacco Product (MRTP) Applications, IQOS 3 System Holder and Charger, Previously Reviewed Application(s), IQOS Tobacco Heating System, Part 1 to Part 7 (posted December 17, 2018), August 31, 2018 Amendment to IQOS 2.4 MRTPA: Submission of FDA Requested Tabulated Index of Scientific References (.zip – 1.8 MB) (added October 1, 2018). Available at: https://www.fda.gov/tobacco-products/advertising-and-promotion/philip-morris-products-sa-modified-risk-tobacco-product-mrtp-applications

Philip Morris Products S.A. (PMPSA) submitted to FDA a supplemental modified risk tobacco product application (sMRTPA) for its IQOS 3 system holder and charger on March 18, 2021. In its sMRTPA, PMPSA stated that the IQOS 3 is essentially the same as the IQOS 2.4 and therefore PMPSA did not conduct additional studies with the IQOS 3 or provide any new health risk information or data about the IQOS 3. Instead, PMPSA cross-referenced to its previous MRTP and PMTA applications to demonstrate that the IQOS 3 system generates an aerosol that is comparable to that generated by the IQOS 2.4 system, exposes users to similar levels of the HPHCs it analyzed in its IQOS 2.4 applications, and that therefore there is sufficient evidence to support the modified risk claim that this process "significantly reduces the production of harmful and potentially harmful chemicals."[2] However, as we discuss below, ***since these premarket applications were submitted, important new evidence has been published that PMPSA did not report to FDA and that raise questions about whether IQOS is appropriate for the protection of the public health. FDA should therefore revisit its premarket tobacco product marketing orders for IQOS 2.4[3] and IQOS 3[4] and its reduced exposure modified risk order for IQOS 2.4,[5] and these orders should not be relied on to support PMPSA's sMRTPA for IQOS 3.*** [6,7]

On August 31, 2018, PMPSA submitted as an amendment to its MRTPA for IQOS 2.4 the last update to its list of references, which included 7,733 references.[8] Since PMPSA submitted its MRTPA for the IQOS 2.4, more than 100 papers have been published on IQOS (see attached list of IQOS publications 2018-2021). However, PMPSA's Supplemental Premarket Tobacco Product Application (sPMTA) for IQOS 3, which is cross-referenced in and used to support the IQOS 3 sMRTPA, includes references in Module 9[9] for only 14 additional papers, none of which analyze the chemical

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[2] Philip Morris Products S.A. Modified Risk Tobacco Product (MRTP) Applications, IQOS 3 System Holder and Charger Supplemental MRTP Application Executive Summary, Module 2.4 and Summary of Health Risk Investigations, Module 6.1. Available at: https://www.fda.gov/tobacco-products/advertising-and-promotion/philip-morris-products-sa-modified-risk-tobacco-product-mrtp-applications

[3] US Food and Drug Administration, 2019 Premarket Tobacco Product Marketing Orders, Philip Morris Products S.A., IQOS System Holder and Charger, Marlboro Heatsticks, Marlboro Smooth Menthol Heatsticks, Marlboro Fresh Menthol Heatsticks, April 30, 2019. Available: https://www.fda.gov/tobacco-products/premarket-tobacco-product-applications/premarket-tobacco-product-marketing-orders

[4] US Food and Drug Administration, 2020 Premarket Tobacco Product Marketing Orders, Philip Morris Products S.A., IQOS System Holder and Charger, December 7, 2020. Available: https://www.fda.gov/tobacco-products/premarket-tobacco-product-applications/premarket-tobacco-product-marketing-orders

[5] US Food and Drug Administration, Modified Risk Orders, Philip Morris Products S.A., IQOS System Holder and Charger, Marlboro Heatsticks, Marlboro Smooth Menthol Heatsticks, Marlboro Fresh Menthol Heatsticks, Modified Risk Granted Orders - Exposure Modification, July 7, 2020. Available: https://www.fda.gov/tobacco-products/advertising-and-promotion/modified-risk-orders

[6] Lempert LK, Glantz S. Analysis of FDA's IQOS marketing authorisation and its policy impacts. Tob Control. 2020 Jun 29:tobaccocontrol-2019-055585. doi: 10.1136/tobaccocontrol-2019-055585. Epub ahead of print. PMID: 32601147; PMCID: PMC7952009.

[7] Lempert LK, Bialous S, Glantz S. FDA's reduced exposure marketing order for IQOS: why it is not a reliable global model. Tob Control. 2021 Apr 2:tobaccocontrol-2020-056316. doi: 10.1136/tobaccocontrol-2020-056316. Epub ahead of print. PMID: 33811155.

[8] Philip Morris Products S.A. Modified Risk Tobacco Product (MRTP) Applications, IQOS 3 System Holder and Charger, Previously Reviewed Application(s), IQOS Tobacco Heating System, Part 1 to Part 7 (posted December 17, 2018), August 31, 2018 Amendment to IQOS 2.4 MRTPA: Submission of FDA Requested Tabulated Index of Scientific References (.zip – 1.8 MB) (added October 1, 2018). Available at: https://www.fda.gov/tobacco-products/advertising-and-promotion/philip-morris-products-sa-modified-risk-tobacco-product-mrtp-applications

[9] Philip Morris Products S.A. IQOS 3 System Holder and Charger Supplemental Premarket Tobacco Product Application (PMTA), Module 9 (m9): References, posted July 1, 2021. Available at:

composition of IQOS emissions. This is especially troublesome because PMPSA is seeking a reduced exposure MRTP marketing order for which the law requires that all applications "**shall** include… all documents (including underlying scientific information) relating to **research findings conducted, supported, or possessed by the tobacco product manufacturer** relating to the effect of the product on tobacco-related diseases and health-related conditions, **including information both favorable and unfavorable to the ability of the product to reduce risk or exposure** and relating to human health…" (emphasis added).[10] PMPSA conducted at least one[11] of the 100 studies (described below) that it did not report, and it is unreasonable to argue that it did not possess information on other published studies that analyzed its IQOS product.

Further, the law[12] requires the applicant to demonstrate, among other things, that issuance of an order is expected to benefit the public health, including both current users and non-users of tobacco products, and that:

> (1) The magnitude of the overall reductions in exposure to the substance or substances which are the subject of the application is substantial, such substance or substances are harmful, and the product as actually used exposes consumers to the specified reduced level of the substance or substances;
> (2) The product as actually used by consumers will not expose them to higher levels of other harmful substances compared to the similar types of tobacco products then on the market unless such increases are minimal and the reasonably likely overall impact of use of the product remains a substantial and measurable reduction in overall morbidity and mortality among individual tobacco users…

To fulfill these requirements, it is essential that the applicant conduct and report chemical and toxicological analyses of its new product, including reporting those conducted by independent researchers who have published their results in the peer-reviewed literature as of the time of the application. PMPSA fails to meet this standard because it failed to address the relevant new research that is now available.

Specifically, to obtain an exposure modification MRTP marketing order, applicants are required to demonstrate that the product, as it is actually used by consumers, will "benefit the health of the populations as a whole taking into account both users of tobacco products and persons who do not currently use tobacco products"[13] and that issuance of an exposure modification order would be "appropriate to promote the public health."[14] To assess the potential effect that marketing the product with the proposed exposure modification claims may have on tobacco-related morbidity and mortality in the population as a whole, FDA recommends that MRTP applicants submit quantitative estimates

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https://digitalmedia.hhs.gov/tobacco/hosted/mrtpa/pmi/Cross-referenced%20PMTA%20Submission%20%28PM0000364%29.zip

[10] Family Smoking Prevention and Tobacco Control Act, section 911(d)(5), Public Law 111-31, June 22, 2009.

[11] Bentley MC, Almstetter M, Arndt D, Knorr A, Martin E, Pospisil P, Maeder S. Comprehensive chemical characterization of the aerosol generated by a heated tobacco product by untargeted screening. Anal Bioanal Chem. 2020 Apr;412(11):2675-2685. doi: 10.1007/s00216-020-02502-1. Epub 2020 Feb 18. PMID: 32072212; PMCID: PMC7136312.

[12] Family Smoking Prevention and Tobacco Control Act, section 911(g)(2)(b), Public Law 111-31, June 22, 2009.

[13] Family Smoking Prevention and Tobacco Control Act, section 911(g)(2)(B)(iv), Public Law 111-31, June 22, 2009.

[14] Family Smoking Prevention and Tobacco Control Act, section 911(g)(2)(A)(i), Public Law 111-31, June 22, 2009.

that "integrate *all of the information* regarding the marketing of the product and its potential effects on health, tobacco use behavior and tobacco use initiation."[15]

Moreover, to help FDA determine whether continued marketing of IQOS is appropriate for the protection of public health or if there are grounds for FDA to withdraw marketing authorization, the marketing orders for IQOS 2.4[16] and for IQOS 3[17] each require (under the authority of the Family Smoking Prevention and Tobacco Control Act section 910(f)) PMPSA to submit to FDA on an annual basis:

> **A summary of significant findings in publications not previously reported and full copies of the article. This must include any new scientific data (published or otherwise)** on the likelihood of product use by current users of tobacco products within the same tobacco product category, current users of tobacco products in other tobacco product categories, former users of any tobacco product, and youth and young adults.

We do not know whether PMPSA met this requirement as FDA has not made these submissions public.

2. IQOS emissions expose users to higher levels of several toxic substances that are not on FDA's current list of HPHCs, but likely impact the product's overall toxicity or harm

In November 2017 we submitted a public comment regarding the IQOS 2.4 MRTPA (Docket Number: FDA-2017-D-3001) in which we discussed our concerns about the emissions of toxic chemicals from IQOS. In that public comment, we concluded that ***PMPSA had failed to demonstrate that IQOS, as actually used, exposes consumers to reduced levels of many significantly harmful substances and will expose consumers to higher levels of other harmful substances compared to similar types of tobacco products currently on the market, and failed to prove that IQOS will significantly reduce harm and the risk of tobacco-related disease to individuals and failed to prove that IQOS would benefit the health of the population as a whole as required by section 911(g).***

Some IQOS constituents – Furfural, Glycerol, Glycidol, Propylene Glycol – are on FDA's list of additional chemicals identified by FDA as harmful and potentially harmful constituents[18] (HPHCs) and are found in higher levels in IQOS than in conventional cigarettes. At its meeting of the Tobacco Products Scientific Advisory Committee (TPSAC) considering the IQOS MRTPA in January 2018, the FDA's Center for Tobacco Products provided an exhaustive list of substances in IQOS aerosol, with

[15] FDA, Guidance for Industry: Modified Risk Tobacco Product Applications, Draft Guidance, March 2012. Available: https://www.fda.gov/regulatory-information/search-fda-guidance-documents/modified-risk-tobacco-product-applications
[16] FDA, Marketing Order IQOS System Holder and Charger, Marlboro Heatsticks, Marlboro Smooth Menthol Heatsticks, and Marlboro Fresh Menthol Heatsticks, April 30, 2019, FDA Submission Tracking Numbers (STNs): PM0000424-PM0000426, PM0000479,Available: https://www.fda.gov/media/124248/download
[17] FDA, Marketing Granted Order IQOS System Holder and Charger, December 07, 2020, FDA Submission Tracking Number (STN): PM0000634. Available: https://www.fda.gov/media/144700/download
[18] Harmful and Potentially Harmful Constituents in Tobacco Products; Established List; Proposed Additions; Request for Comments. 84 FR 38032, August 5, 2019. Available: https://www.federalregister.gov/documents/2019/08/05/2019-16658/harmful-and-potentially-harmful-constituents-in-tobacco-products-established-list-proposed-additions

concentrations compared to those in mainstream smoke of a reference cigarette.[19] For example, TPSAC's list reports that the carcinogen Glycidol is increased over a reference cigarette by 224%, and three constituents included in FDA's list of additional HPHCs because they were identified by the National Institute for Occupational Safety and Health (NIOSH) as having adverse respiratory effects – Propylene Glycol, Glycerol, and Furfural – are increased over a reference cigarette by 638%, 141% and 20% respectively. (See FDA addendum to TPSAC briefing materials, highlighted to indicate compounds with increased levels of HPHCS, attached and incorporated by reference.) In October 2019 we submitted to FDA a public comment (attached and incorporated by reference) on its proposed list of additional HPHCs in which we supported FDA's proposed additions of these chemicals for several reasons including their carcinogenic, immunotoxic, pulmonary, and other potential harms.

In November 2018 we published a peer-reviewed paper[20] (attached and incorporated by reference) based on our earlier comment that found that PMPSA reported levels for only 40 of the 93 chemicals on FDA's established HPHC list that are found in IQOS mainstream aerosol. All substances in PMPSA's list of 58 constituents (the "PMI-58") were lower in IQOS emissions compared with mainstream smoke of 3R4F reference cigarettes. However, levels of 56 other constituents (which are not included in the PMI-58 or FDA's established list of 93 HPHCs) were higher in IQOS emissions; 22 were >200% higher and seven were >1000% higher than in 3R4F reference cigarette smoke. PMPSA's studies also show significantly lower systemic exposure to some HPHCs from use of IQOS compared with smoking combustible cigarettes. Our paper concluded that although PMPSA's data appear to support their claim that IQOS reduces exposure to HPHCs, these data also show significantly higher levels of several substances in IQOS emissions compared with combustible cigarette smoke that were then not recognized as HPHCs by the FDA. The impact of these substances on the overall toxicity or harm of IQOS is not known. (However, as discussed above, since this paper was published in 2018, four of the toxicants are included in FDA's proposed list of additions to the established list of HPHCs.)

PMPSA's sMRTPA does not cite this paper or address any of these issues.

Since publication of our paper, at least 12 additional peer-reviewed papers[21] have published that analyze the chemical composition and toxicology of IQOS and/or emissions of HPHCs and other

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[19] Center for Tobacco Products, Food and Drug Administration, Addendum to FDA Briefing Document: January 24-25, 2018, Meeting of the Tobacco Products Scientific Advisory Committee (TPSAC). Available: https://www.fda.gov/media/110668/download

[20] St Helen G, Jacob Iii P, Nardone N, Benowitz NL. IQOS: examination of Philip Morris International's claim of reduced exposure. Tob Control. 2018 Nov;27(Suppl 1):s30-s36. doi: 10.1136/tobaccocontrol-2018-054321. Epub 2018 Aug 29. PMID: 30158205; PMCID: PMC6252487.

[21] St Helen G, Jacob Iii P, Nardone N, Benowitz NL. IQOS: examination of Philip Morris International's claim of reduced exposure. *Tob Control*. 2018;27(Suppl 1):s30-s36. doi:10.1136/tobaccocontrol-2018-054321; Bitzer ZT, Goel R, Trushin N, Muscat J, Richie JP Jr. Free Radical Production and Characterization of Heat-Not-Burn Cigarettes in Comparison to Conventional and Electronic Cigarettes. *Chem Res Toxicol*. 2020;33(7):1882-1887. doi:10.1021/acs.chemrestox.0c00088; Kopa PN, Pawliczak R. IQOS - a heat-not-burn (HnB) tobacco product - chemical composition and possible impact on oxidative stress and inflammatory response. A systematic review. *Toxicol Mech Methods*. 2020;30(2):81-87. doi:10.1080/15376516.2019.1669245; Farsalinos KE, Yannovits N, Sarri T, Voudris V, Poulas K, Leischow SJ. Carbonyl emissions from a novel heated tobacco product (IQOS): comparison with an e-cigarette and a tobacco cigarette. *Addiction*. 2018;113(11):2099-2106. doi:10.1111/add.14365; Li X, Luo Y, Jiang X, et al. Chemical Analysis and Simulated Pyrolysis of Tobacco Heating System 2.2 Compared to Conventional Cigarettes. *Nicotine Tob Res*. 2019;21(1):111-118. doi:10.1093/ntr/nty005; Bentley MC, Almstetter M, Arndt D, et al. Comprehensive chemical characterization of the aerosol generated by a heated tobacco product by untargeted screening. *Anal Bioanal Chem*. 2020;412(11):2675-2685. doi:10.1007/s00216-020-02502-1; El-Hage R, El-Hellani A, Salman R, Talih S, Shihadeh A, Saliba NA. Vaped

toxic substances from IQOS aerosol. One paper reported formation of highly toxic formaldehyde cyanohydrin during IQOS aerosol generation, likely arising from plastic in the heating unit.[22] Others demonstrated that although IQOS aerosol contains lower concentrations of tobacco-specific nitrosamines (TSNAs) and toxic carbonyl compounds than mainstream smoke of combusted cigarettes, the corresponding amounts in e-cigarette aerosols are much lower than IQOS.[23, 24] Since IQOS exposes consumers to higher levels of harmful substances compared to e-cigarettes (which are more similar to IQOS than conventional cigarettes; indeed, Philip Morris has cobranded its e-cigarette product as "IQOS VEEV" and markets IQOS VEEV as part of its "smoke-free" line of products[25] along with its IQOS heated tobacco product), PMPSA's application failed to demonstrate the statutorily required finding that "the product as actually used by consumers will not expose them to higher levels of other harmful substances compared to the similar types of tobacco products then on the market."[26]

Although compared to combusted cigarettes, the aerosol generation process in IQOS (heat as opposed to combustion) reduces the delivery of some toxic substances (such as polycyclic aromatic hydrocarbons (PAHs) that are pyrolysis products formed during combustion) or relatively non-volatile substances (such as TSNAs that largely remain in the used heatstick), some toxic substances of concern are delivered in higher amounts. This is likely due to the applied heat being sufficient to produce toxic substances from the heated tobacco, in particular some reactive chemicals that in combusted cigarettes do not survive the combustion process (largely or in part) and are transformed into non-toxic or less toxic substances. Examples include the four additional HPHCs furfural, glycidol, 2-furanemethanol, 3-chloro-1,2-propanediol. Of these, 3-chloro-1,2-propanediol is of greatest concern as it is recognized to be fatal or acutely toxic if inhaled and it presents several grave dangers including carcinogenicity, reproductive toxicity, organ toxicity, and other likely health hazards.[27] Glycidol is

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Humectants in E-Cigarettes Are a Source of Phenols. *Chem Res Toxicol*. 2020;33(9):2374-2380. doi:10.1021/acs.chemrestox.0c00132; Davis B, Williams M, Talbot P. iQOS: evidence of pyrolysis and release of a toxicant from plastic. *Tob Control*. 2019;28(1):34-41. doi:10.1136/tobaccocontrol-2017-054104; Gómez Lueso M, Mitova MI, Mottier N, Schaller M, Rotach M, Goujon-Ginglinger CG. Development and validation of a method for quantification of two tobacco-specific nitrosamines in indoor air. *J Chromatogr A*. 2018;1580:90-99. doi:10.1016/j.chroma.2018.10.037; Leigh NJ, Palumbo MN, Marino AM, O'Connor RJ, Goniewicz ML. Tobacco-specific nitrosamines (TSNA) in heated tobacco product IQOS. *Tob Control*. 2018;27(Suppl 1):s37-s38. doi:10.1136/tobaccocontrol-2018-054318; Ilies BD, Moosakutty SP, Kharbatia NM, Sarathy SM. Identification of volatile constituents released from IQOS heat-not-burn tobacco HeatSticks using a direct sampling method [published online ahead of print, 2020 May 26]. *Tob Control*. 2020;tobaccocontrol-2019-055521. doi:10.1136/tobaccocontrol-2019-055521; Sawa M, Ushiyama A, Inaba Y, et al. A newly developed aerosol exposure apparatus for heated tobacco products for in vivo experiments can deliver both particles and gas phase with high recovery and depicts the time-dependent variation in nicotine metabolites in mouse urine [published online ahead of print, 2021 Jun 10]. *Nicotine Tob Res*. 2021;ntab123. doi:10.1093/ntr/ntab123

[22] Davis B, Williams M, Talbot P. iQOS: evidence of pyrolysis and release of a toxicant from plastic. Tob Control. 2019 Jan;28(1):34-41. doi: 10.1136/tobaccocontrol-2017-054104. Epub 2018 Mar 13. PMID: 29535257.

[23] Farsalinos KE, Yannovits N, Sarri T, Voudris V, Poulas K, Leischow SJ. Carbonyl emissions from a novel heated tobacco product (IQOS): comparison with an e-cigarette and a tobacco cigarette. Addiction. 2018 Nov;113(11):2099-2106. doi: 10.1111/add.14365. Epub 2018 Jul 10. PMID: 29920842.

[24] Leigh NJ, Palumbo MN, Marino AM, O'Connor RJ, Goniewicz ML. Tobacco-specific nitrosamines (TSNA) in heated tobacco product IQOS. Tob Control. 2018 Nov;27(Suppl 1):s37-s38. doi: 10.1136/tobaccocontrol-2018-054318. Epub 2018 Sep 21. PMID: 30242043; PMCID: PMC6252482.

[25] Philip Morris International, Our Smoke-Free Products. https://www.pmi.com/smoke-free-products (Accessed August 25, 2021).

[26] Family Smoking Prevention and Tobacco Control Act, section 911(g)(2)(B)(ii), Public Law 111-31, June 22, 2009.

[27] National Center for Biotechnology Information (2021). PubChem Compound LCSS for CID 7290, 3-Chloro-1,2-propanediol. Retrieved August 25, 2021 from https://pubchem.ncbi.nlm.nih.gov/compound/3-Chloro-1_2-propanediol#datasheet=LCSS.

included in the International Agency for Research on Cancer Group 2A's list of probable carcinogens[28] and in the National Toxicology Program's 14th Report on Carcinogens as "*reasonably anticipated to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in experimental animals. [emphasis in original]"[29]

In February 2020 scientists from Philip Morris International Research and Development at PMPSA (Bentley et al.) published an untargeted analysis of the chemicals in IQOS aerosol.[30] They found 529 chemical constituents (excluding water, glycerin, and nicotine) in IQOS mainstream aerosol, generated using the Health Canada intense smoking regimen at concentrations ≥ 100 ng/item. The majority were present in the particulate phase (n = 402), representing more than 80% of the total mass determined by untargeted screening; a proportion were present in both particulate and gas-vapor phases (39 compounds).

Table 1 in the Bentley et al. paper lists the top 100 most abundant chemical constituents present in IQOS aerosol. Seventeen of these compounds are present in higher concentrations in IQOS aerosol than in conventional cigarette smoke:

1. 1-Hydroxy-2-propanone/1,2-propenediol (this is one chemical, but 2 forms exist in equilibrium)
2. Propylene glycol
3. Pyranone
4. Furfural
5. 2-Monoacetin
6. 2-Furanmethanol
7. 3-Chloro-1,2-propanediol
8. 3-Methylpentanoic acid
9. 5-Methylfurfural
10. 1-Acetyloxy-2-propanone
11. Heptacosane
12. 12 a-Cembratriene-diol
13. 2-Cyclopentene-1,4-dione
14. 14 2H-Pyran-2-one, tetrahydro-5-hydroxy
15. 15.Hexadecanoic acid, ethyl ester
16. 2(5H)-Furanone
17. Butyrolactone

This table indicates that the level of furfural is 123% higher in IQOS aerosol than in conventional cigarette smoke, the level of 2-furanemethanol is 393% higher, and the level of 3-chloro-1,2-propanediol

[28] World Health Organization, International Agency for Research on Cancer, IARC Monographs on the Identification of Carcinogenic Hazards to Humans. Agents Classified by the IARC Monographs, Volumes 1–129. Available at: https://monographs.iarc.who.int/list-of-classifications

[29] US Department of Health and Human Services, National Toxicology Program, Report on Carcinogens,14th Edition (2016). Available: https://ntp.niehs.nih.gov/go/roc14

[30] Bentley MC, Almstetter M, Arndt D, Knorr A, Martin E, Pospisil P, Maeder S. Comprehensive chemical characterization of the aerosol generated by a heated tobacco product by untargeted screening. Anal Bioanal Chem. 2020 Apr;412(11):2675-2685. doi: 10.1007/s00216-020-02502-1. Epub 2020 Feb 18. PMID: 32072212; PMCID: PMC7136312.

in IQOS aerosol is 195% than in conventional cigarettes. These three chemicals are among the four additional HPHCs (Furfural, Glycidol, 2-furanemethanol, and 3-chloro-1,2-propanediol (which is abbreviated as "3-MCPD") discussed in a report from PMPSA's IQOS 3 sPMTA that is a cross-referenced submission included in PMPSA's sMRTPA.[31] In this cross-referenced submission, the four additional HPHCs were reported to be delivered at higher levels in IQOS 3 aerosol compared to conventional cigarettes, and three of these HPHCs (Furfural, Glycidol, 2-furanemethanol) were also reported to be delivered at higher levels in IQOS 3 aerosol as compared to IQOS 2.4 aerosol. This is especially problematic because the IQOS 3 sMRTPA relies almost entirely on FDA's determination that the IQOS 2.4 PMTA and MRTPA demonstrated *reduced* exposure to harmful or potentially constituents. In contrast, ***PMPSA's own report reveals that IQOS 3 in fact exposes consumers to increased levels of at least four HPHCs as compared to conventional cigarettes and e-cigarettes.***

As discussed above, 3-chloro-1,2-propanediol is of great concern because it is a known carcinogen and has other acute toxicities,[32] and glycidol is a probable carcinogen and included on FDA's list of additional HPHCs.[33,34,35] Furfural has known adverse respiratory effects and is also included on FDA's list of additional HPHCs. According to the harmonized classification and labeling (ATP01) approved by the European Union, 2-furanemethanol is toxic if inhaled, harmful if swallowed, harmful in contact with skin, causes serious eye irritation, is suspected of causing cancer, may cause damage to organs through prolonged or repeated exposure, and may cause respiratory irritation.[36]

Four of the 17 chemicals are carbonyl compounds (1-hydroxy-2-propanone/1,2-propenediol, 5-methylfurfural, 1-acetyloxy-2-propanone, and 2-cyclopentene-1,4-dione) and two are furans (2-furanmethanol and 5-methylfurfural). Concerns about the toxicity of carbonyl compounds and furans in IQOS aerosol were discussed in the previously described 2018 paper by St. Helen et al.[37] The chemical class α,β-unsaturated carbonyl compounds, such as 2-cyclopentene-1,4-dione, are known to have significant toxicity and are of particular concern especially when they interact with other

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[31] PMI Confidential Information, Experimental Report: IQOS 3.0 System 4 Additional Harmful or Potentially Harmful Constituents (HPHCs), Reference document: PMI-RRP-WKI-120438, Module 7, Section 7.1: Aerosol Characterization, posted July 20, 2021. Available: https://www.fda.gov/tobacco-products/advertising-and-promotion/philip-morris-products-sa-modified-risk-tobacco-product-mrtp-applications

[32] National Center for Biotechnology Information (2021). PubChem Compound LCSS for CID 7290, 3-Chloro-1,2-propanediol. Retrieved August 25, 2021 from https://pubchem.ncbi.nlm.nih.gov/compound/3-Chloro-1_2-propanediol#datasheet=LCSS.

[33] World Health Organization, International Agency for Research on Cancer, IARC Monographs on the Identification of Carcinogenic Hazards to Humans. Agents Classified by the IARC Monographs, Volumes 1–129. Available at: https://monographs.iarc.who.int/list-of-classifications

[34] US Department of Health and Human Services, National Toxicology Program, Report on Carcinogens,14th Edition (2016). Available: https://ntp.niehs.nih.gov/go/roc14

[35] Harmful and Potentially Harmful Constituents in Tobacco Products; Established List; Proposed Additions; Request for Comments. 84 FR 38032, August 5, 2019. Available: https://www.federalregister.gov/documents/2019/08/05/2019-16658/harmful-and-potentially-harmful-constituents-in-tobacco-products-established-list-proposed-additions

[36] IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Some chemicals that cause tumours of the urinary tract in rodents. Lyon (FR): International Agency for Research on Cancer; 2019. (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, No. 119.) 1, Exposure Data. Available from: https://www.ncbi.nlm.nih.gov/books/NBK546917/

[37] St Helen G, Jacob Iii P, Nardone N, Benowitz NL. IQOS: examination of Philip Morris International's claim of reduced exposure. Tob Control. 2018 Nov;27(Suppl 1):s30-s36. doi: 10.1136/tobaccocontrol-2018-054321. Epub 2018 Aug 29. PMID: 30158205; PMCID: PMC6252487

substances resulting in a wide range of adverse effects, including general toxicity, allergenic reactions, mutagenicity, and carcinogenicity.[38] Furans can be genotoxic and have other toxicities.[39,40,41,42]

Bentley et al. argue that concentrations are low and counterbalanced by reductions in other HPHCs, but the fact is that the concentrations of all four of these HPHCs are higher in IQOS aerosol than a 3RF4 reference cigarette. Specifically, these PMPSA scientists are arguing: (1) Since the 529 compounds were also found in the reference cigarette smoke, there are no significant differences in the types of chemical reactions that occur during IQOS aerosol formation compared to cigarette smoking. In other words, their nontargeted analyses did not identify chemicals unique to IQOS and using the same list of toxic substances for both types of products is justified. (2) Because relatively few of the 529 chemicals are present in higher amounts in IQOS, and because those that are toxic are present in small amounts (the "four additional" HPHCs), their contributions are outweighed by the larger reduction of other HPHCs. While point (1) above is reasonable, point (2) is not because ***it implies that IQOS is safe, or much safer than combusted cigarettes.***

It will take many years to conduct and complete epidemiology studies to determine whether and how much IQOS reduces or increases risk. For example, Bentley et al quote FDA as saying, "FDA summarized their review of these toxicological findings with the statement that 'Although some of the chemicals are genotoxic or cytotoxic, these chemicals are present in very low levels and potential effects are outweighed by the substantial decrease in the number and levels of HPHCs found in combusted cigarettes' [30]."

Significantly, through Bentley et al, PMPSA is using the FDA quote to argue that the fact that IQOS exposes users to increased levels of some toxins is not important because the ***health risks*** are balanced by lower levels of other toxins. ***This is a reduced risk claim, not a reduced exposure claim, and the FDA explicitly prohibits Philip Morris from making reduced risk claims for IQOS.***

The bottom line is that PMPSA's own research as published in Bentley et al shows *increased concentrations* of several HPHCs and other toxins, including carcinogens, than a reference cigarette. It is broadly accepted that there is no safe level of carcinogen exposure, and IQOS exposes its users to higher amounts of some carcinogens. This finding is inconsistent with a *reduced exposure claim.* Indeed, as noted above, this is a reduced risk claim, something the FDA has specifically forbidden Philip Morris from claiming about IQOS.

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[38] Koleva YK, Madden JC, Cronin MT. Formation of categories from structure-activity relationships to allow read-across for risk assessment: toxicity of alpha,beta unsaturated carbonyl compounds. Chem Res Toxicol 2008;21:2300–12

[39] Bakhiya N, Appel KE. Toxicity and carcinogenicity of furan in human diet. Arch Toxicol 2010;84:563–78

[40] National Center for Biotechnology Information. Pubchem compound database; CID=10341. 2005 https:// pubchem. ncbi. nlm. nih. gov/ compound/ 10341

[41] Yamashita N, Murata M, Inoue S, et al. Superoxide formation and DNA damage induced by a fragrant furanone in the presence of copper(II). Mutation Research/ Fundamental and Molecular Mechanisms of Mutagenesis 1998;397:191–201

[42] National Center for Biotechnology Information, 2005. Pubchem compound database; CID=7361 https:// pubchem. ncbi. nlm. nih. gov/ compound/ 7361

Also significantly, even though Bentley et al was published February 18, 2020, more than one year before March 18, 2021[43] when PMPSA submitted its sMRTPA, it is not cited or discussed in the application. (See attached Bentley et al paper and supplementary data.)

These new papers and materials from PMPSA reinforce our earlier comment concluding that PMPSA did not report the full range of HPHCs in IQOS aerosol. ***However, PMPSA's sMRTPA for IQOS 3 does not respond to the issues previously raised or fully reflect these new papers. Because PMPSA apparently failed to report this recent literature in any of its PMTA and MRTP applications for IQOS 2.4 and IQOS 3, FDA should not have granted marketing authorizations for IQOS 2.4 and IQOS 3, should not have issued a reduced exposure MRTP order for IQOS 2.4, and should not rely on the cross-referenced submissions because they leave out several important papers that show increased levels of several dangerous chemicals in IQOS aerosol as compared with conventional cigarettes and in some cases e-cigarettes.***

3. PMPSA's new analyses of the chemical composition and HPHCs in IQOS 3 aerosol reveal that IQOS 3 delivers significantly higher concentrations of the 4 additional HPHCs furfural, glycidol, 2-furanemethanol, and 3-chloro-1,2-propanediol than a reference combusted cigarette.

Module 7 of PMPSA's Supplemental Premarket Tobacco Product Application[44] (sPMTA) for IQOS 3, which is cross-referenced in and used to support the IQOS 3 sMRTPA, includes analyses of IQOS 3 aerosol including performing droplet size distribution analysis with forced warm aerosol and forced no-warm aerosol, studying four additional HPHCs (furfural, glycidol, 2-furanmethanol, 3-chloro-1,2-propondiol), and deriving the recommended FDA-18 list of constituents.

The experimental results of PMPSA's analysis of the HPHC levels for these four constituents are found in Tables 2 and 3 in section 4.3 of the "Experimental Report: IQOS 3 System 4 Additional Harmful or Potentially Harmful Constituents (HPHCs)" included in Module 7. (See 4.3 Experimental Results, Tables 2 and 3, copied from the report and pasted below.)

These data, which are very similar to the data presented in FDA's report to the January 2018 TPSAC meeting discussed above, show that depending on the analytical method used, the level of furfural is between 18% and 30% higher in IQOS 3 than in the 1R6F reference cigarette, glycidol is between 126% and 152% higher, 2-furanmethanol is between 583% and 682% higher, and 3-chloro-1,2-propandiol (called "3-MCPD" in the table) is between 149% and 211% higher. Although the tables do not indicate which method was used, the levels of these four additional HPHCs were also significantly higher in the IQOS 2.4 product (called "The Authorized IQOS System" in the tables) for which FDA issued a reduced exposure MRTP order, with the level of furfural 23% higher in IQOS 2.4

[43] Philip Morris Products S.A., Cover letter re MRTPA for the IQOS 3 System Holder and Charger (PM0000634) to Dr. Matthew Homan, Director, Office of Science, Center for Tobacco Products, Food and Drug Administration, March 18, 2021. Available: https://www.fda.gov/media/148606/download

[44] Philip Morris Products S.A. IQOS 3 System Holder and Charger Supplemental Premarket Tobacco Product Application (PMTA), Module 7, Section 7.1: Aerosol Characterization. Posted July 20, 2021. Available at: https://digitalmedia.hhs.gov/tobacco/hosted/mrtpa/pmi/m7-1-aerosol-char.zip

than in the 1R6F reference cigarette, glycidol 136% higher, 2-furanmethanol 589% higher, and 3-chloro-1,2-propondiol ("3-MCPD") 181% higher.

Based on this data provided by PMPSA in its application, FDA cannot grant a MRTP for IQOS 3, and issuing a reduced exposure order for IQOS 2.4 is questionable. The scientific evidence does not support the issuance of a because the product contains significantly increased levels of four dangerous HPHCs.

4.3 Experimental results

The results of analysis of HPHCs levels for the 4 constituents are provided in the Table 2 (furfural, glycidol, 2-furanemethanol) and Table 3 (3-MCPD).

Table 2: Summary of *IQOS* 3.0 System furfural, glycidol, 2-furanemethanol deliveries yields with forced wet profile firmware setting, *IQOS* 3.0 System yields with standard C28 profile, The Authorized *IQOS* System yields, and the yields of 1R6F reference cigarette. SD – standard deviation; n – sample size

Aerosol deliveries	Unit	1R6F			IQOS 3.0 System Forced WA			IQOS 3.0 System Forced no-WA			The Authorized IQOS System		
		Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n
Furfural	µg/stick	26.09	3.65	4	33.93	2.13	4	31.68	1.74	4	32.09	3.77	4
Glycidol	µg/stick	2.41	0.28	4	6.07	0.31	4	5.44	0.27	4	5.69	0.33	4
2-furanemethanol	µg/stick	4.57	0.35	4	35.73	3.08	4	31.20	2.10	4	31.47	1.66	4

Table 3: Summary of *IQOS* 3.0 System 3-chlor-1,2-propanediol deliveries yields with force wet profile firmware setting, *IQOS* 3.0 System yields with standard C28 profile, The Authorized *IQOS* System yields, and the yields of 1R6F reference cigarette. RSD – residual standard deviation (%); n – sample size

Aerosol deliveries	Unit	1R6F			IQOS 3.0 System Forced WA			IQOS 3.0 System Forced no-WA			The Authorized IQOS System		
		Mean	RSD	n	Mean	RSD	n	Mean	RSD	n	Mean	RSD	n
3-MCPD	µg/stick	4.40	4.46	4	10.95	7.24	4	13.67	12.08	4	12.38	10.23	4

4. The scientific evidence does not support the proposed reduced exposure claim requested by PMPSA

In its sMRTPA for IQOS 3, PMPSA seeks to make the same reduce exposure claim that FDA issued for its IQOS 2.4 system.[45] PMPSA seeks to use the following language:

[45] Philip Morris Products S.A. Modified Risk Tobacco Product (MRTP) Applications, IQOS 3 System Holder and Charger Supplemental MRTP Application Executive Summary, Module 2.4. Available: https://www.fda.gov/media/148610/download

AVAILABLE EVIDENCE TO DATE:

- *The IQOS system heats tobacco but does not burn it.*
- *This significantly reduces the production of harmful and potentially harmful chemicals.*
- *Scientific studies have shown that switching completely from conventional cigarettes to the IQOS system significantly reduces your body's exposure to harmful or potentially harmful chemicals.*

However, as we demonstrated above, the "available evidence to date" shows otherwise. As we described above, PMPSA's own analyses included in Module 7 of its application, analyses conducted in published literature that PMPSA failed to discuss, and analyses presented by FDA to the January 2018 TPSAC meeting reveal that although IQOS may reduce exposure to some chemicals, IQOS 3 and IQOS 2.4 in fact expose users to significantly increased levels of several dangerous HPHCs and other toxins including carcinogens.

The Bentley et al paper seems to argue that the fact that IQOS exposes users to increased levels of some toxins is not important because the ***health risks*** are balanced by lower levels of other toxins. ***This is a reduced risk claim, not a reduced exposure claim, and FDA's reduced exposure MRTP order for IQOS 2.4 upon which PMPSA relies explicitly prohibits Philip Morris from making reduced risk claims for IQOS.***

5. Conclusion

PMPSA has not demonstrated that IQOS 3.0, as actually used, exposes consumers to reduced levels of many harmful substances, but in fact the product will expose consumers to higher levels of other harmful substances compared to cigarettes as well as e-cigarettes currently on the market. Further, PMPSA failed to prove that marketing IQOS with reduced exposure MRTP claims will significantly reduce harm and the risk of tobacco-related disease to individuals and failed to prove that IQOS would benefit the health of the population as a whole as required by section 911(g). Importantly, section 911(g)(4) unambiguously states that this showing is required for reduced exposure as well as reduced risk MRTPAs.

Because PMPSA has not presented or made publicly available evidence refuting these points and failed to otherwise demonstrate that IQOS 3 would benefit the health of individuals and of the population as a whole, FDA should deny PMI's Supplemental MRTP application for IQOS 3.