Module 6: Summary

6.3 Summary of Health Risk Investigations

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1. INTRODUCTION

The *IQOS* System, like any other consumer electronics product, continuously evolves to reflect technological advances and adult consumer needs. Indeed, this evolution is critical to maintaining the acceptability of the *IQOS* System used with *HeatSticks* to adult smokers and avoiding relapse to combustible cigarettes (CC). Therefore, in order to (a) maintain the acceptability of the *IQOS* System used with *HeatSticks* as an alternative for adult smokers who would otherwise continue smoking; (b) improve the adult consumer experience; and (c) keep pace with the evolving electronics technology that maintains the device current and user friendly, Philip Morris Products S.A. (PMP S.A.) updated the Authorized *IQOS* System.

During the development of the *IQOS* 3 System, PMP S.A. followed its Development Process and Change Management Process (CMP) as presented in the PMTA for the Authorized *IQOS* System (PM0000479) (Section 2.7).

This section provides a summary of the evidence and data supporting the conclusion that since the *IQOS* 3 System retains all functional elements of the Authorized *IQOS* System, it is therefore comparable to the Authorized *IQOS* System as the three critical principles are preserved in the modified *IQOS* System, i.e. (i) System performance, (ii) System safety and (iii) Consumer behavior.

2. AEROSOL CHEMISTRY AND PHYSICS

2.1 Background

Development of a product that significantly reduces the formation of Harmful and Potentially Harmful Constituents (HPHCs) compared with CC was central to the PMI's approach when developing the Authorized *IQOS* System. Significant reduction of HPHCs levels was also an essential requirement during the development of the *IQOS* 3 System.

In order to demonstrate that the *IQOS* 3 System is comparable to the Authorized *IQOS* System, the aerosol chemistry and physics data were generated and compared for both *IQOS* Systems.

2.2 Aerosol Chemistry: History and Context of Different HPHCs Lists

Reference is made to Section 6.1.1.1 *Aerosol Chemistry* of the PMTA for the Authorized *IQOS* System..

2.3 Aerosol Physics

Reference is made to Section 6.1.1.2 *Aerosol Physics* of the PMTA for the Authorized *IQOS* System.

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2.4 Results

Table 1 below shows an overview of studies conducted in the context of the aerosol chemistry and physics evaluation for the modified version of the Authorized *IQOS* System, the *IQOS* 3 System.

(b) (4) **(b) (4)** studies covering the PMI-58 HPHCs list were conducted for the *IQOS* 3 System with two heating profiles (C28-6 and C28)[1] to demonstrate that under both operating conditions the aerosol produced by the *IQOS* 3 System is comparable to the one generated by the Authorized *IQOS* System. The *IQOS* 3 System's aerosol generated under both heating profiles maintains significant reductions in the levels of HPHCs compared to those contained in the smoke generated by a reference combustible cigarette (3R4F). Studies quantifying the analytes on the PMI-58 list of analytes were conducted with Monitor *HeatSticks* using the Health Canada Intense machine-puffing protocol (ISO 20778:2018) consistent with the CMP described in the PMTA for the Authorized *IQOS* System. For this comparision, 3R4F reference cigarette values were used from a research study conducted in 2018 at Labstat International ULC.

Studies covering the FDA-18 HPHCs list were conducted with the authorized *HeatSticks* commercially available in the U.S. and the *IQOS* 3 System operating with the commercial firmware settings, using the Health Canada Intense machine-puffing protocol (ISO 20778:2018) and the ISO puffing regime (ISO 3308:2012), to demonstrate that, under commercial settings with the Authorized *HeatSticks,* the *IQOS* 3 System's aerosol contains significantly reduced levels of HPHCs compared to those of combustible cigarette (1R6F[2]) smoke as previously demonstrated for the Authorized *IQOS* System.

(b) (4) **(b) (4)** PMI-58 studies were conducted for the *IQOS* 3 System with firmware modified to study two heating profiles, the "standard" heating profile, also referred to as "C28 Heating Profile" and "alternative", referred to as "C28-6 Heating Profile". In **(b) (4)**

[2] Reference cigarettes 1R6F (provided by the University of Kentucky, Kentucky Tobacco Research & Development Center) were used in the FDA-18 and the four additional consituents studies because as of December 31, 2018, the 3R4F reference cigarette was no longer available for purchase. The 3R4F reference cigarette was used in earlier studies because the 1R6F was not available at the time of those studies.

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Four constituents were further measured as they were previously[3] detected at higher levels in the aerosol generated by the Authorized *IQOS* System compared to the 3R4F reference cigarette smoke. These four HPHCs are neither part of the PMI-58 list nor of the FDA-18 list of HPHCs.The studies measuring these four additional constituents (glycidol, furfural, 2-furanmethanol, 3-chloro-1,2-propondiol) were conducted at PMI R&D laboratories in Neuchâtel, Switzerland. The studies used monitor *Heatsticks* (comparable to the ones used in studies submitted as part of the PMTA for the Authorized *IQOS* System) and included the *IQOS* 3 System yields with both heating profiles, the Authorized *IQOS* System yields, and the yields of the 1R6F reference cigarette. The four additional constituents were measured usingthe Health Canada Intense (ISO 20778:2018) regime.

PMI-58 and FDA-18 assays were conducted by Labstat ULC[4], according to their procedures and methods.

The doplet size distribution (DSD) (physics evaluation) was performed by Enthalpy Analytical[5].

All methods (chemistry and physics) were accredited according to ISO 17025.

[3] The December 8, 2017, Amendment and the Response to the FDA's April 23, 2018 Advice/Information Request concerning PMTA for the Authorized *IQOS* System providing Non-Targeted Differential Screening (NTDS) reports identifying chemical constituents present in the THS aerosol that are either unique, or present at higher concentration compared with 3R4F cigarette smoke.

[4] *Labstat International ULC, 262 Manitou Drive, Kitchener, Ontario, N2C 1L3*

[5] *Enthalpy Analytical, 1 Park Plaza, Suite 1000 Irvine, CA 92614*

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Table 1 Aerosol chemistry and physics assessment studies summary. For the FDA-18 and the 4 additional constituents, a reference cigarette (1R6F) was tested in parallel to the *IQOS* 3 System

Assay	*IQOS* System	Tobacco Sticks	Batch number	Study number
PMI-58	*IQOS* 3 System with C28-6 Heating Profile	Monitor *HeatSticks*[6]	Device B-72500 Stick IC2911171	Labstat report NS487-H
	IQOS 3 System with C28 Heating Profile	Monitor *HeatSticks*	Device B-79348 Stick IC2911171	Labstat report NS530-H
	Authorized *IQOS* System	Monitor *HeatSticks*	Device B-72348 Stick IC2911171	Labstat reports NS487-H; NS530-H
	NA	3R4F Reference Cigarette	NA	Labstat report NS407-GLP
FDA-18*	*IQOS* 3 System Commercial Firmware[7]	Marlboro *HeatSticks* (PM0000424)	Device B-81234 Stick B-82173	Labstat report NS531-H
	IQOS 3 System Commercial Firmware	Marlboro Smooth Menthol *HeatSticks* (PM0000425)	Device B-81234 Stick B-82172	Labstat report NS531-H
	IQOS 3 System Commercial Firmware[7]	Marlboro Fresh Menthol *HeatSticks* (PM0000426)	Device B-81234 Stick B-82175	Labstat report NS531-H
	1R6F Reference Cigarette	NA	NA	Labstat report NS531-H

(table continues)

[6] A single batch of Marlboro *HeatSticks* (Regular) with Dorado II blend and Flavor AC Ron used as reference for product assessment, and control for the analytical testing.

[7] Firmware version 1.3.0 and temperature profile C28 corresponding to BOM in present application (see Module 3)

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Assay	*IQOS* System	Tobacco Sticks	Batch number	Study number
4 Additional constituents Glycidol, Furfural, 2-furanmethanol, 3-chloro-1,2-propondiol	*IQOS* 3 System with C28-6 Heating Profile	Monitor *HeatSticks*	Device B-79852 Stick IC2911171	RLS-THR-2020-1; RLS-THR-2020-2
	IQOS 3 System with C-28 Heating Pprofile	Monitor *HeatSticks*	Device B-79858 Stick IC2911171	RLS-THR-2020-1; RLS-THR-2020-2
	Authorized *IQOS* System	Monitor *HeatSticks*	Device B-72348; Stick IC2911171	RLS-THR-2020-1; RLS-THR-2020-2
	NA	1R6F Reference Cigarette	NA	RLS-THR-2020-1; RLS-THR-2020-2
DSD	*IQOS* 3 System with C28-6 Heating Profile	Monitor *HeatSticks*	Device B-79852 Stick IC2911171	Q19494
	IQOS 3 System with C-28 Heating Profile	Monitor *HeatSticks*	Device B-79858 Stick IC2911171	Q19494
	Authorized *IQOS* System	Monitor *HeatSticks*	Device B-79883; Stick IC2911171	Q19494

* No data are provided for the 6 tobacco constituents, as the scope of this supplemental PMTA is exclusive of the System, and tests on emissions were performed with *HeatSticks* already commercially available on the U.S. market with both the Authorized *IQOS* System, currently marketed, and the *IQOS* 3 System, the subject of the present Application.

2.4.1 Aerosol and smoke generation

Reference is made to section 6.1.1.1 of the PMTA for the Authorized *IQOS* System.

In addition to the data previously provided as part of the PMTA for the Authorized *IQOS* System, data for the FDA-18 list of HPHCs, as well as for four additional constituents, *i.e.*, glycidol, furfural, 2-furanmethanol, 3-chloro-1,2-propondiol which were previously reported as present at higher levels in the *IQOS* aerosol in comparison to 3R4F reference cigarette smoke (PMTA for the Authorized *IQOS* System; December 8, 2017 Amendment and PMI's Response to the FDA's April 23, 2018 Advice/Information Request), all measured under the Health Canada Intense machine-smoking protocol (ISO 20778:2018), and ISO Standard machine-smoking protocol for the FDA-18 with the *HeatSticks* variants commercially

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available in the U.S. are presented in this section in accordance with the clarifications provided by the FDA in the written response to the PMP S.A.'s Meeting Request of October 11, 2019.[8]

[8] December 18, 2019, FDA's written response to the Meeting Request for an upgraded modified version of the *IQOS* System Holder and Charger (STN: TC0005319)

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2.4.2 PMI-58, FDA-18, and four additional constituents for the *IQOS* 3 System – Tables and Graphs

Table 2 Summary of PMI-58 results of the *IQOS* 3 System yields with C28-6 Heating Profile, the Authorized *IQOS* System yields, and the yields of the 3R4F[9] reference cigarette. SD – standard deviation; n – sample size.

HPHCs	Unit	3R4F			*IQOS* 3 System with C28-6 Heating Profile			Authorized *IQOS* System		
		Mean	SD	n	Mean	SD	n	Mean	SD	n
1,3-Butadiene	µg/cig	100	6.87	4	0.115	NA[10]	9	0.169	0.0375	9
1-Aminonaphthalene	ng/cig	29.1	2.56	4	0.033	NA	9	0.0351	NA	9
2-Aminonaphthalene	ng/cig	18.1	2.32	4	0.0161	NA	9	0.019	0.00469	9
3-Aminobiphenyl	ng/cig	5.44	0.226	4	0.00651	0.000942	9	0.00679	0.00102	9
4-(Methyl-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK)	ng/cig	295	32.5	4	7.52	0.365	9	7.6	0.336	9
4-Aminobiphenyl	ng/cig	3.91	0.293	4	0.00884	0.00157	9	0.00947	0.00193	9
Acetaldehyde	µg/cig	1838	105	4	221	5.83	9	218	7.57	9
Acetamide	µg/cig	12.2	1.86	4	3.55	0.135	9	3.68	0.297	9
Acetone	µg/cig	749	44.4	4	38.3	1.56	9	36.6	2.13	9
Acrolein	µg/cig	180	12.6	4	8.71	0.461	9	8.75	0.748	9

(table continues)

[9] 3R4F reference cigarette values from a research study conducted in 2018 at Labstat International ULC.

[10] « NA » in place of standard deviation indicates the emissions levels for some or all replicates were below the limit of quantification (LOQ) of the analytical method. In these cases instead of the mean, the median is reported for endpoints classified as being generally quantifiable, and the maximum value is reported for endpoints classified as being generally below the limit of quantification.

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HPHCs	Unit	3R4F			*IQOS* 3 System with C28-6 Heating Profile			Authorized *IQOS* System		
		Mean	SD	n	Mean	SD	n	Mean	SD	n
Acrylamide	µg/cig	3.92	0.522	4	1.55	0.0994	9	1.6	0.14	9
Acrylonitrile	µg/cig	20.5	1.81	4	<0.107	NA	9	<0.107	NA	9
Ammonia	µg/cig	34	0.497	4	9.9	1.05	9	11	0.343	9
Arsenic	ng/cig	<7.49	NA	4	<1.2	NA	9	<1.2	NA	9
Benz[a]anthracene	ng/cig	28.9	1.96	4	1.94	0.0756	9	1.91	0.108	9
Benzene	µg/cig	88.8	6.31	4	0.513	0.126	9	0.551	0.147	9
Benzo[a]pyrene	ng/cig	15.1	0.63	4	0.747	0.0422	9	0.741	0.0659	9
Butyraldehyde	µg/cig	93	4.35	4	20.4	0.569	9	20.2	0.617	9
Cadmium	ng/cig	93.2	7.42	4	<0.09	NA	9	<0.09	NA	9
Carbon monoxide (CO)	mg/cig	30.5	1.81	4	0.345	0.028	9	0.364	0.042	9
Catechol	µg/cig	86.9	5.42	4	17.4	0.749	9	18.6	0.736	9
Chromium	ng/cig	<11.9	NA	4	<11	NA	9	<11	NA	9
Crotonaldehyde	µg/cig	59.5	4.41	4	<3.29	NA	9	<3.29	NA	9
Dibenz[a,h]anthracene	ng/cig	1.34	0.0918	4	<0.124	NA	9	<0.124	NA	9
Ethylene oxide	µg/cig	19.2	1.81	4	0.189	0.00597	9	0.205	0.0218	9
Formaldehyde	µg/cig	87.1	7.37	4	9.7	0.819	9	9.88	0.645	9
Glycerol	mg/cig	2.25	0.072	4	4.22	0.311	9	4.56	0.211	9

(table continues)

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HPHCs	Unit	3R4F			*IQOS* 3 System with C28-6 Heating Profile			Authorized *IQOS* System		
		Mean	SD	n	Mean	SD	n	Mean	SD	n
Hydrogen cyanide	µg/cig	390	22.8	4	2.61	0.206	9	2.87	0.23	9
Hydroquinone	µg/cig	78.1	6.52	4	8.11	0.425	9	9.2	0.429	9
Isoprene	µg/cig	799	61	4	1.27	0.271	9	1.5	0.189	9
Lead	ng/cig	<25.7	NA	4	<0.49	NA	9	<1.62	NA	9
m-Cresol	µg/cig	2.77	0.194	4	0.0321	0.00297	9	0.0369	0.00577	9
Mercury	ng/cig	4.92	0.0635	4	2.27	0.102	9	2.17	0.15	9
Methyl-ethyl-ketone (MEK)	µg/cig	199	13.1	4	7.76	0.389	9	7.55	0.541	9
Nickel	ng/cig	<12.9	NA	4	<53.1	NA	9	<15.9	NA	9
Nicotine	mg/cig	1.99	0.131	4	1.31	0.0315	9	1.34	0.06	9
Nitric oxide (NO)	µg/cig	471	16.5	4	10.8	0.471	9	10.6	0.446	9
Nitro benzene	µg/cig	<0.027	NA	4	<0.011	NA	9	<0.011	NA	9
Nitrogen oxides (NOx)	µg/cig	524	17.2	4	12	0.464	9	11.9	0.491	9
N-nitrosoanabasine (NAB)	ng/cig	31.8	1.02	4	2.2	0.0975	9	2.17	0.126	9
N-nitrosoanatabine (NAT)	ng/cig	334	12.3	4	16	0.544	9	16.1	0.837	9
N-Nitrosonornicotine (NNN)	ng/cig	336	28.4	4	12.6	0.461	9	12.5	0.533	9
o-Cresol	µg/cig	3.22	0.265	4	0.0734	0.00828	9	0.0856	0.0106	9
o-Toluidine	ng/cig	121	1.04	4	1.02	0.0728	9	1.13	0.246	9

(table continues)

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HPHCs	Unit	3R4F			*IQOS* 3 System with C28-6 Heating Profile			Authorized *IQOS* System		
		Mean	SD	n	Mean	SD	n	Mean	SD	n
p-Cresol	µg/cig	6.83	0.53	4	0.0665	0.00538	9	0.0786	0.0108	9
Phenol	µg/cig	11.1	0.896	4	1.48	0.168	9	1.69	0.142	9
Propionaldehyde	µg/cig	135	8.15	4	12.7	0.467	9	12.5	0.704	9
Propylene oxide	ng/cig	1000	78.8	4	118	10.7	9	130	15	9
Pyrene	ng/cig	91.9	7.5	4	8.19	0.49	9	8.13	0.597	9
Pyridine	µg/cig	35.2	6.4	4	5.58	0.175	9	5.65	0.356	9
Quinoline	µg/cig	0.315	0.0333	4	<0.003	NA	9	<0.003	NA	9
Resorcinol	µg/cig	<1.32	NA	4	<0.016	NA	9	<0.016	NA	9
Selenium	ng/cig	<4.42	NA	4	<0.83	NA	9	<0.83	NA	9
Styrene	µg/cig	21.7	2.4	4	0.445	0.0185	9	0.491	0.0575	9
Toluene	µg/cig	153	11.5	4	1.54	0.405	9	1.7	0.428	9
Total Particulate Matter (TPM)	mg/cig	47	2.62	4	51	0.701	9	51.9	1.63	9
Vinyl chloride	ng/cig	94.6	7.44	4	<2.19	NA	9	<2.19	NA	9

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Table 3 Summary of PMI-58 results of the *IQOS* 3 System yields with C-28 Heating Profile, the Authorized *IQOS* System yields, and the yields of the 3R4F reference cigarette.

HPHCs	Unit	3R4F			*IQOS* 3 System with C28 Heating Profile			Authorized *IQOS* System		
		Mean	SD	n	Mean	SD	n	Mean	SD	n
1,3-Butadiene	µg/cig	100	6.87	4	0.218	0.0252	9	0.213	0.0196	9
1-Aminonaphthalene	ng/cig	29.1	2.56	4	0.0276	NA	9	0.0321	NA	9
2-Aminonaphthalene	ng/cig	18.1	2.32	4	<0.012	NA	9	<0.012	NA	9
3-Aminobiphenyl	ng/cig	5.44	0.226	4	0.007	0.0023	9	0.007	0.0019	9
4-(Methyl-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK)	ng/cig	295	32.5	4	6.43	0.334	9	6.58	0.33	9
4-Aminobiphenyl	ng/cig	3.91	0.293	4	0.0082	NA	9	0.009	0.0021	9
Acetaldehyde	µg/cig	1838	105	4	201	13.6	9	197	15.8	9
Acetamide	µg/cig	12.2	1.86	4	3.25	0.268	9	3.38	0.0814	9
Acetone	µg/cig	749	44.4	4	35.3	2.86	9	35.4	3.25	9
Acrolein	µg/cig	180	12.6	4	8.34	0.846	9	8.52	1.11	9
Acrylamide	µg/cig	3.92	0.522	4	1.5	0.118	9	1.56	0.0777	9
Acrylonitrile	µg/cig	20.5	1.81	4	0.127	NA	9	0.116	NA	9
Ammonia	µg/cig	34	0.497	4	10.2	0.986	9	10.5	0.841	9
Arsenic	ng/cig	<7.49	NA	4	<1.2	NA	9	<1.2	NA	9
Benz[a]anthracene	ng/cig	28.9	1.96	4	1.65	0.0639	9	1.59	0.0504	9

(table continues)

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HPHCs	Unit	3R4F			*IQOS* 3 System with C28 Heating Profile			Authorized *IQOS* System		
		Mean	SD	n	Mean	SD	n	Mean	SD	n
Benzene	µg/cig	88.8	6.31	4	0.563	0.0383	9	0.557	0.0278	9
Benzo[a]pyrene	ng/cig	15.1	0.63	4	0.635	0.0425	9	0.617	0.0332	9
Butyraldehyde	µg/cig	93	4.35	4	20.8	1.49	9	20	1.3	9
Cadmium	ng/cig	93.2	7.42	4	<0.09	NA	9	<0.09	NA	9
Carbon monoxide (CO)	mg/cig	30.5	1.81	4	0.438	0.0533	9	0.42	0	9
Catechol	µg/cig	86.9	5.42	4	15	0.904	9	15.7	0.628	9
Chromium	ng/cig	<11.9	NA	4	<11	NA	9	<3.31	NA	9
Crotonaldehyde	µg/cig	59.5	4.41	4	<3.29	NA	9	<3.29	NA	9
Dibenz[a,h]anthracene	ng/cig	1.34	0.0918	4	<0.124	NA	9	<0.124	NA	9
Ethylene oxide	µg/cig	19.2	1.81	4	<0.119	NA	9	0.119	NA	9
Formaldehyde	µg/cig	87.1	7.37	4	7.87	1.05	9	7.51	0.66	9
Glycerol	mg/cig	2.25	0.072	4	4.55	0.287	9	5.07	0.261	9
Hydrogen cyanide	µg/cig	390	22.8	4	2.77	0.432	9	2.57	0.507	9
Hydroquinone	µg/cig	78.1	6.52	4	7.5	0.557	9	8.11	0.424	9
Isoprene	µg/cig	799	61	4	1.59	0.17	9	1.6	0.177	9
Lead	ng/cig	<25.7	NA	4	<1.62	NA	9	<0.49	NA	9
m-Cresol	µg/cig	2.77	0.194	4	0.025	NA	9	0.029	0.0031	9

(table continues)

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HPHCs	Unit	3R4F			*IQOS* 3 System with C28 Heating Profile			Authorized *IQOS* System		
		Mean	SD	n	Mean	SD	n	Mean	SD	n
Mercury	ng/cig	4.92	0.0635	4	2.52	0.0759	9	2.35	0.0928	9
Methyl-ethyl-ketone (MEK)	µg/cig	199	13.1	4	8.6	0.855	9	8.87	0.722	9
Nickel	ng/cig	<12.9	NA	4	<15.9	NA	9	<15.9	NA	9
Nicotine	mg/cig	1.99	0.131	4	1.19	0.0444	9	1.25	0.0445	9
Nitric oxide (NO)	µg/cig	471	16.5	4	11.1	0.79	9	10.4	1.12	9
Nitro benzene	µg/cig	<0.027	NA	4	<0.011	NA	9	<0.011	NA	9
Nitrogen oxides (NOx)	µg/cig	524	17.2	4	12.9	0.903	9	12.1	1.14	9
N-nitrosoanabasine (NAB)	ng/cig	31.8	1.02	4	2.07	0.111	9	2.12	0.162	9
N-nitrosoanatabine (NAT)	ng/cig	334	12.3	4	13.6	0.458	9	14	0.958	9
N-Nitrosonornicotine (NNN)	ng/cig	336	28.4	4	6.31	0.216	9	6.47	0.495	9
o-Cresol	µg/cig	3.22	0.265	4	0.058	0.0095	9	0.068	0.0033	9
o-Toluidine	ng/cig	121	1.04	4	0.957	0.0673	9	0.965	0.0526	9
p-Cresol	µg/cig	6.83	0.53	4	0.051	0.007	9	0.06	0.0041	9
Phenol	µg/cig	11.1	0.896	4	1.24	0.165	9	1.44	0.11	9
Propionaldehyde	µg/cig	135	8.15	4	12.5	1.07	9	12.4	1.23	9
Propylene oxide	ng/cig	1000	78.8	4	117	6.51	9	115	5.14	9
Pyrene	ng/cig	91.9	7.5	4	5.62	0.224	9	5.42	0.188	9

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HPHCs	Unit	3R4F			*IQOS* 3 System with C28 Heating Profile			Authorized *IQOS* System		
		Mean	SD	n	Mean	SD	n	Mean	SD	n
Pyridine	µg/cig	35.2	6.4	4	5.52	0.276	9	5.53	0.321	9
Quinoline	µg/cig	0.315	0.0333	4	<0.011	NA	9	<0.011	NA	9
Resorcinol	µg/cig	<1.32	NA	4	<0.055	NA	9	<0.055	NA	9
Selenium	ng/cig	<4.42	NA	4	<0.83	NA	9	<0.83	NA	9
Styrene	µg/cig	21.7	2.4	4	0.416	0.0253	9	0.418	0.0313	9
Toluene	µg/cig	153	11.5	4	1.84	0.146	9	1.91	0.0784	9
Total Particulate Matter (TPM)	mg/cig	47	2.62	4	51.5	1.09	9	52.6	1.13	9
Vinyl chloride	ng/cig	94.6	7.44	4	<2.19	NA	9	<2.19	NA	9

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Table 4 Percent reductions in yields of the *IQOS* 3 System with both heating profiles (C28-6 and C28) and the Authorized *IQOS* System yields in comparison to the yields of the 3R4F reference cigarette. When the HPHCs yields for both *IQOS* Systems and the reference 3R4F reference cigarette are below LOD or LOQ, % reductions are not calculated and ND (Not defined) are reported. For HPHCs below LOD or LOQ in the *IQOS* Systems, but not in the 3R4F reference cigarette, the % reductions are calculated using the LOD or LOQ values.

HPHCs	*IQOS* 3 System with C28-6 Heating Profile	*IQOS* 3 System with C28 Heating Profile	Authorized *IQOS* System with C28-6 Heating Profile	Authorized *IQOS* System with C28 Heating Profile
1,3-Butadiene	>99.9%	99.8%	99.8%	99.8%
1-Aminonaphthalene	>99.9%	>99.9%	>99.9%	>99.9%
2-Aminonaphthalene	>99.9%	>99.9%	99.9%	>99.9%
3-Aminobiphenyl	99.9%	99.9%	99.9%	99.9%
4-(Methyl-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK)	97.5%	97.8%	97.4%	97.8%
4-Aminobiphenyl	99.8%	>99.8%	99.8%	99.8%
Acetaldehyde	88.0%	89.1%	88.1%	89.3%
Acetamide	70.9%	73.4%	69.8%	72.3%
Acetone	94.9%	95.3%	95.1%	95.3%
Acrolein	95.2%	95.4%	95.1%	95.3%
Acrylamide	60.5%	61.7%	59.2%	60.2%
Acrylonitrile	>99.5%	>99.4%	>99.5%	>99.4%
Ammonia	70.9%	70.0%	67.6%	69.1%

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HPHCs	*IQOS* 3 System with C28-6 Heating Profile	*IQOS* 3 System with C28 Heating Profile	Authorized *IQOS* System with C28-6 Heating Profile	Authorized *IQOS* System with C28 Heating Profile
Arsenic	ND	ND	ND	ND
Benz[a]anthracene	93.3%	94.3%	93.4%	94.5%
Benzene	99.4%	99.4%	99.4%	99.4%
Benzo[a]pyrene	95.1%	95.8%	95.1%	95.9%
Butyraldehyde	78.1%	77.6%	78.3%	78.5%
Cadmium	>99.9%	>99.9%	>99.9%	>99.9%
Carbon monoxide (CO)	98.9%	98.6%	98.8%	>98.6%
Catechol	80.0%	82.7%	78.6%	81.9%
Chromium	ND	ND	ND	ND
Crotonaldehyde	>94.5%	>94.5%	>94.5%	>94.5%
Dibenz[a,h]anthracene	>90.7%	>90.7%	>90.7%	>90.7%
Ethylene oxide	99.0%	>99.4%	98.9%	>99.4%
Formaldehyde	88.9%	91.0%	88.7%	91.4%
Hydrogen cyanide	99.3%	99.3%	99.3%	99.3%
Hydroquinone	89.6%	90.4%	88.2%	89.6%
Isoprene	99.8%	99.8%	99.8%	99.8%
Lead	ND	ND	ND	ND
m-Cresol	98.8%	>99.1%	98.7%	99.0%

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HPHCs	*IQOS* 3 System with C28-6 Heating Profile	*IQOS* 3 System with C28 Heating Profile	Authorized *IQOS* System with C28-6 Heating Profile	Authorized *IQOS* System with C28 Heating Profile
Mercury	53.9%	48.8%	55.9%	52.2%
Methyl-ethyl-ketone (MEK)	96.1%	95.7%	96.2%	95.5%
Nickel	ND	ND	ND	ND
Nitric oxide (NO)	97.7%	97.6%	97.7%	97.8%
Nitro benzene	ND	ND	ND	ND
Nitrogen oxides (NOx)	97.7%	97.5%	97.7%	97.7%
N-nitrosoanabasine (NAB)	93.1%	93.5%	93.2%	93.3%
N-nitrosoanatabine (NAT)	95.2%	95.9%	95.2%	95.8%
N-Nitrosonornicotine (NNN)	96.2%	98.1%	96.3%	98.1%
o-Cresol	97.7%	98.2%	97.3%	97.9%
o-Toluidine	99.2%	99.2%	99.1%	99.2%
p-Cresol	99.0%	99.3%	98.8%	99.1%
Phenol	86.7%	88.8%	84.8%	87.0%
Propionaldehyde	90.6%	90.7%	90.7%	90.8%
Propylene oxide	88.2%	88.3%	87.0%	88.5%
Pyrene	91.1%	93.9%	91.2%	94.1%
Pyridine	84.1%	84.3%	83.9%	84.3%
Quinoline	>99%	>96.5%	>99%	>96.5%

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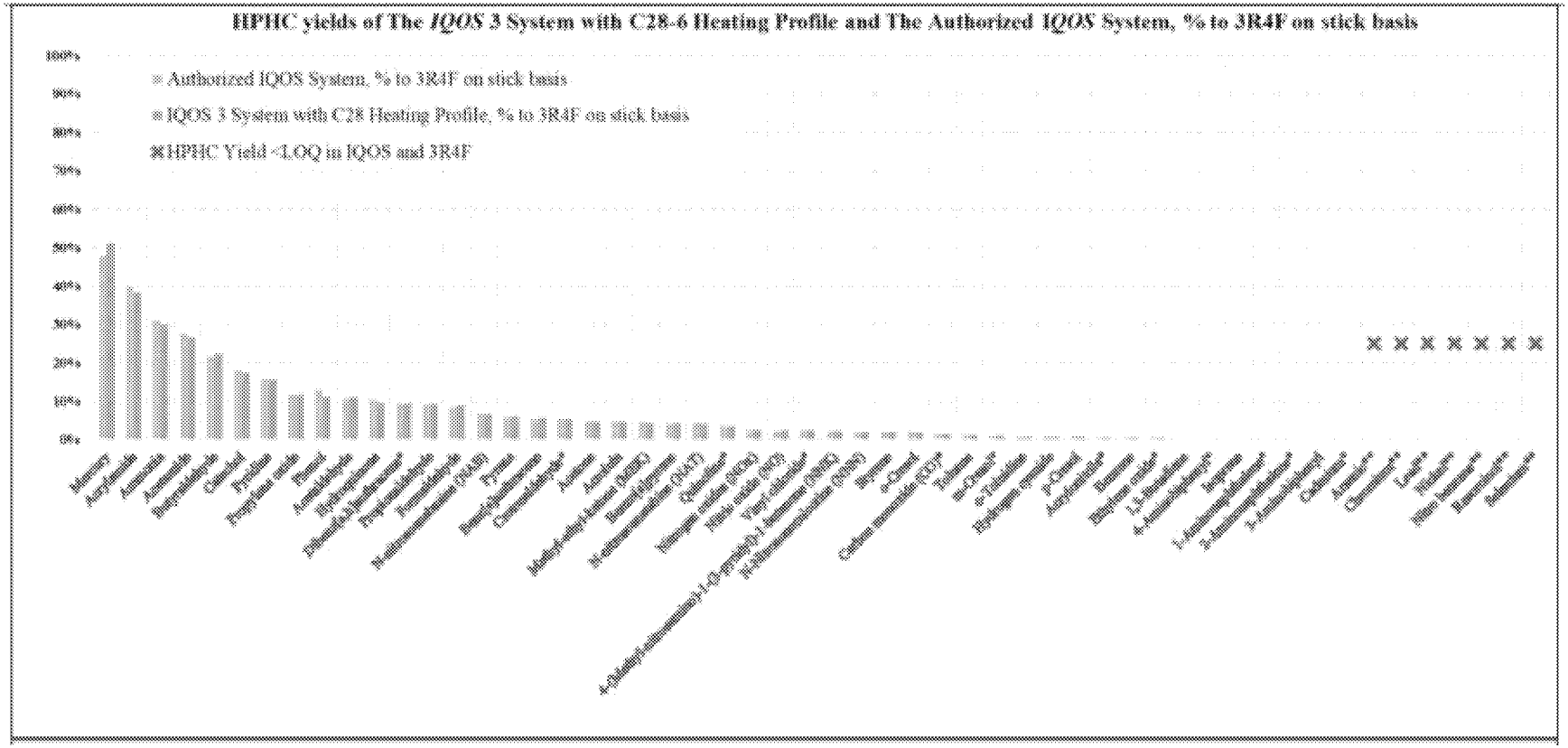
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HPHCs	*IQOS* 3 System with C28-6 Heating Profile	*IQOS* 3 System with C28 Heating Profile	Authorized *IQOS* System with C28-6 Heating Profile	Authorized *IQOS* System with C28 Heating Profile
Resorcinol	ND	ND	ND	ND
Selenium	ND	ND	ND	ND
Styrene	97.9%	98.1%	97.7%	98.1%
Toluene	99.0%	98.8%	98.9%	98.8%
Vinyl chloride	>97.7%	>97.7%	>97.7%	>97.7%

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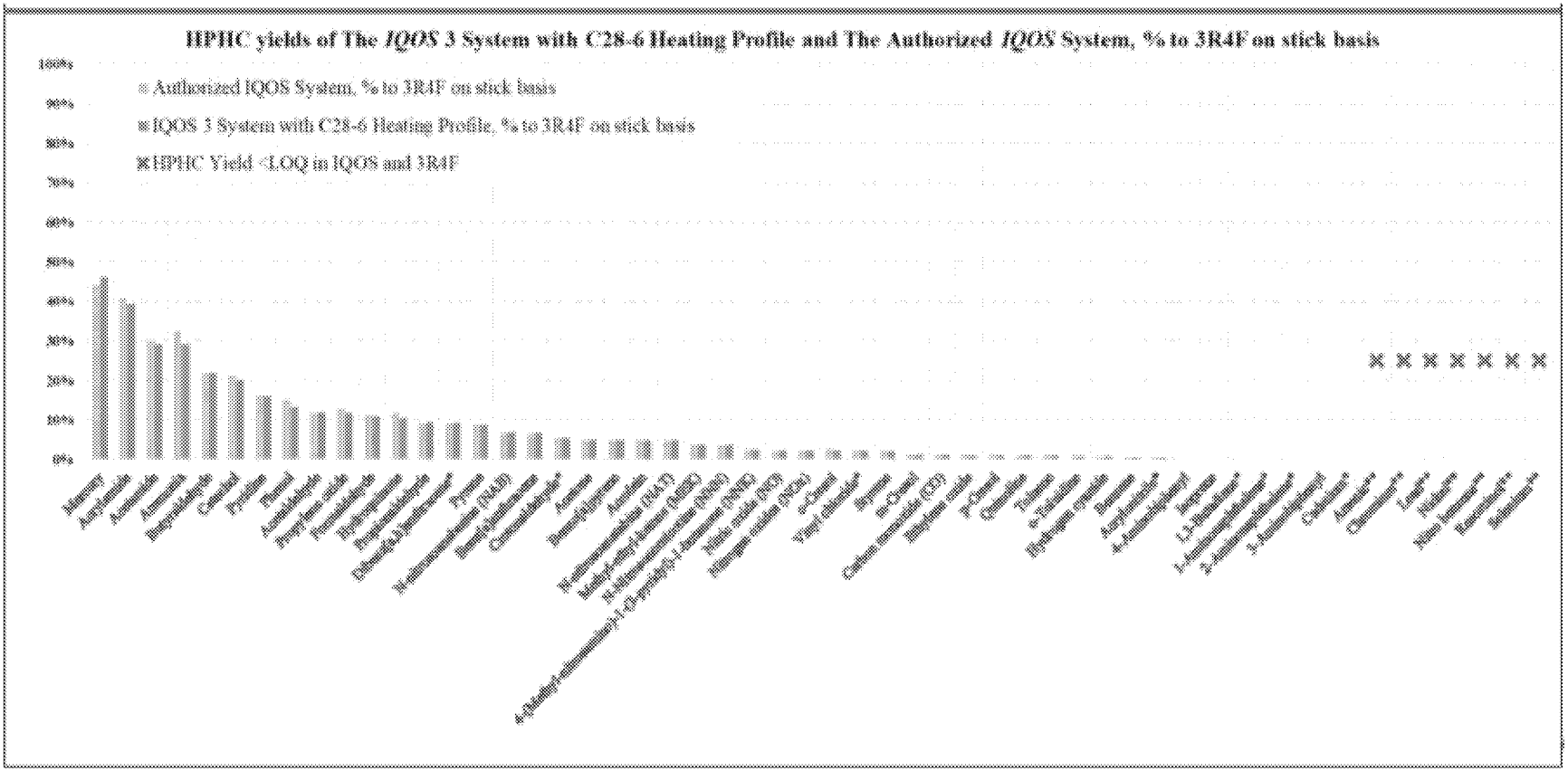
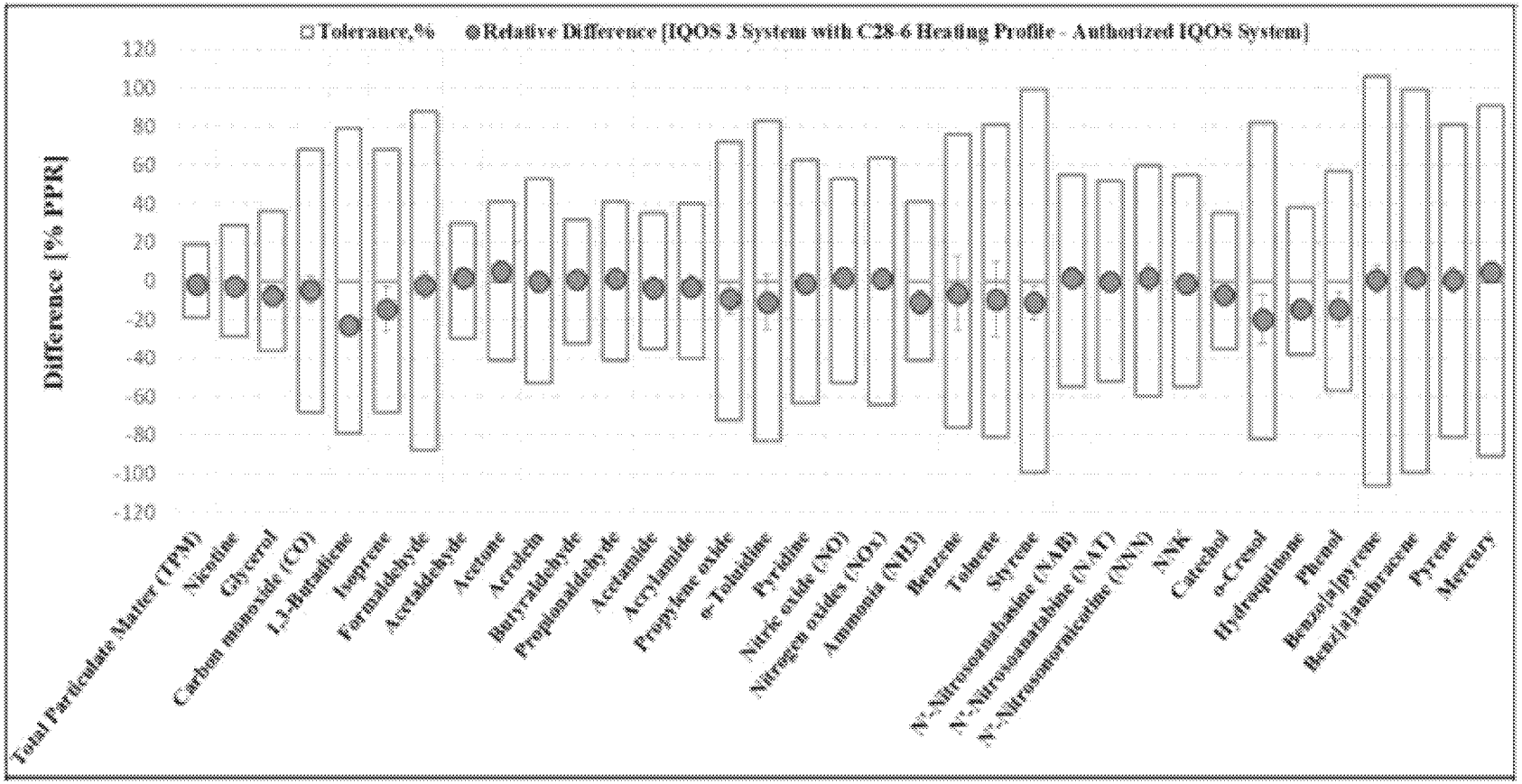


Figure 1 HPHCs of the *IQOS* 3 System with both heating profiles (C28-6 (bottom panel) and C28 (top panel)) and the Authorized *IQOS* System vs. reference cigarette 3R4F, percentage on stick basis in decreasing order.

HPHCs marked with a "*" were reported below LOD or LOQ in IQOS and relative % is based on the LOD/LOQ value. HPHCs marked with a "" were found below LOD or LOQ in both reference and THS2.2 and no relative % can be calculated (marked as ND in Table 4).**

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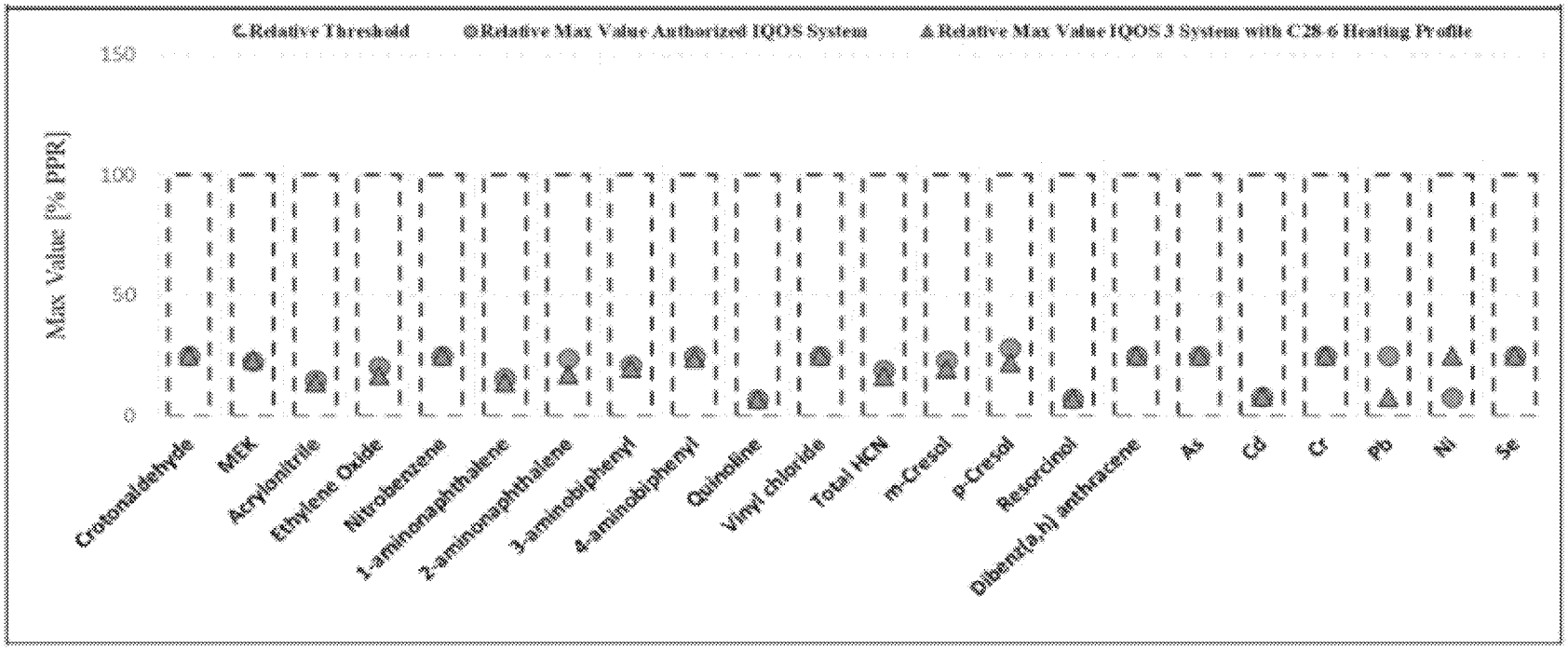
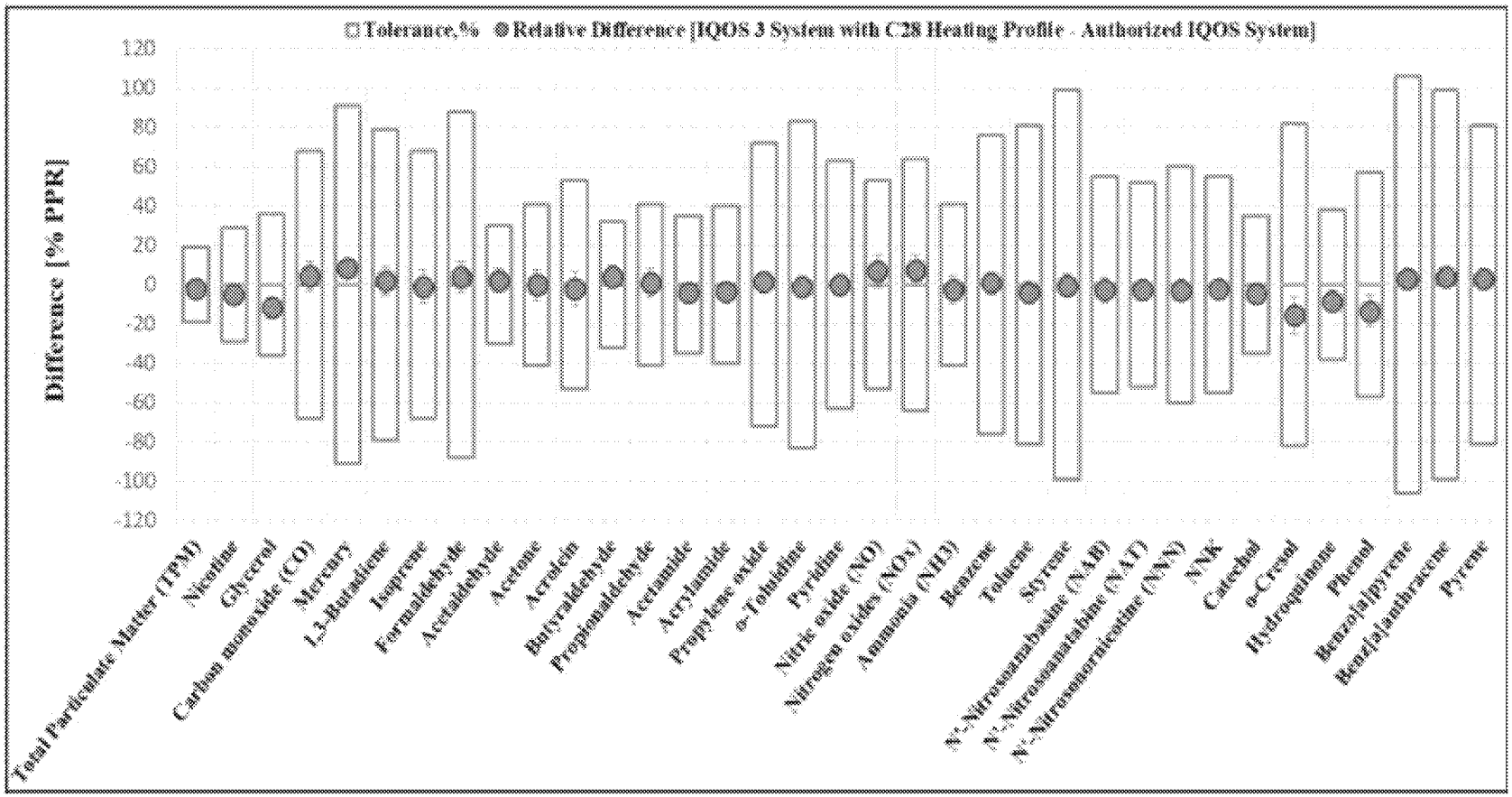


Figure 2 **Levels of HPHCs of *IQOS* 3 System aerosol (with C28-6 Heating Profile) versus their levels in the Authorized *IQOS* System aerosol. Top panel shows constituents classified to be generally quantifiable (above the limit of quantification (LOQ)), and the bottom panel shows constituents classified to be generally non quantifiable (below LOQ or the the limit of detection (LOD). The results are represented relative to the product performance ranges (PPR) of the head-to-head comparability model (Appendix A3.2.1-13). Relative tolerances (Solid bars), relative mean differences (solid circles), 90% relative confidence intervals of the mean differences (vertical solid lines), relative maximum values of the Authorized *IQOS* System (green solid circles), relative maximum values of the *IQOS* 3 System (solid triangles), and relative threshold (dashed bars). The HPHCs levels in *IQOS* 3 System are comparable to the HPHCs levels in the Authorized *IQOS* System - all nominal differences that are within the range of the inherent variability of the methods.**

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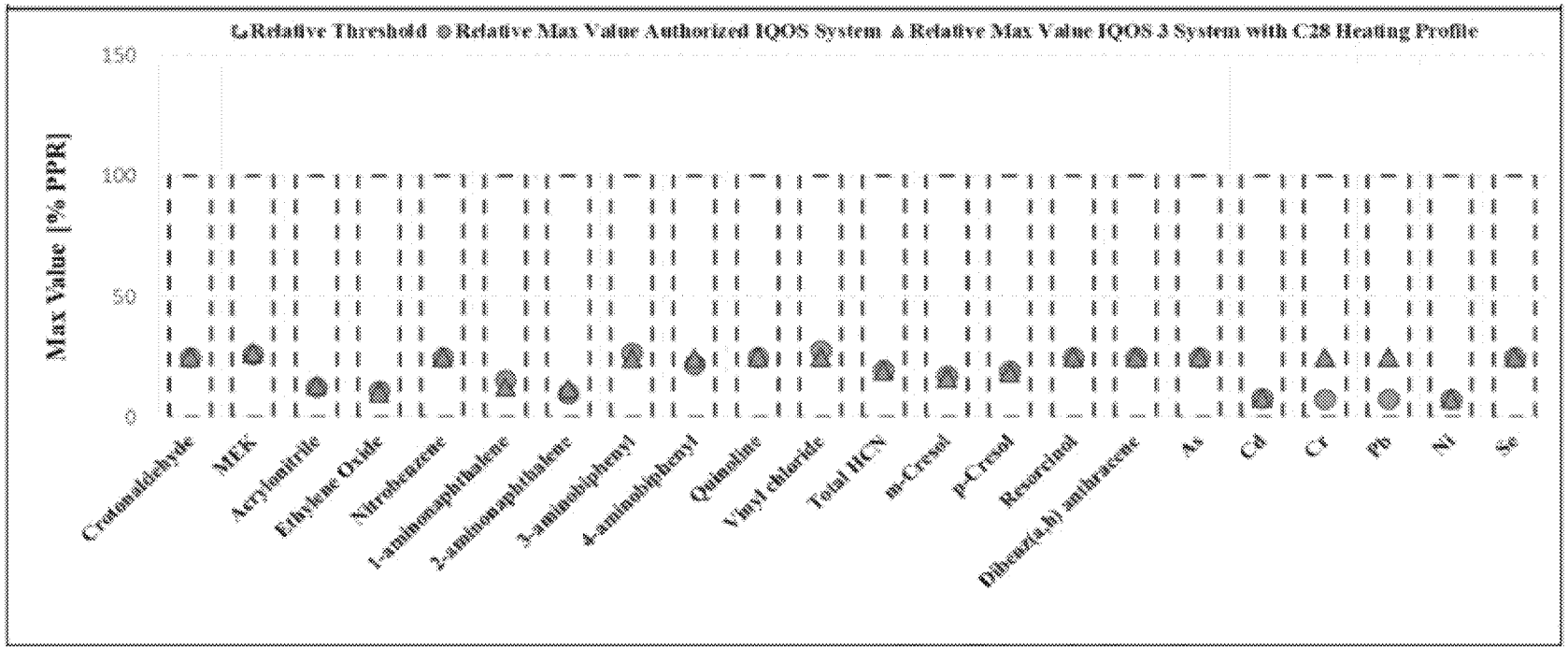


Figure 3 **Levels of HPHCs of the *IQOS* 3 System aerosol (with C28 Heating Profile) versus their levels in the Authorized *IQOS* System aerosol. Top panel shows constituents classified to be generally quantifiable (above the limit of quantification (LOQ)), and the bottom panel shows constituents classified to be generally non quantifiable (below LOQ or the the limit of detection (LOD). The results are represented relative to the product performance ranges (PPR) of the head-to-head comparability model (Appendix A3.2.1-13). Relative tolerances (Solid bars), relative mean differences (solid circles), 90% relative confidence intervals of the mean differences (vertical solid lines), relative maximum values of the Authorized *IQOS* System (green solid circles), relative maximum values of the *IQOS* 3 System (solid triangles), and relative threshold (dashed bars). The HPHCs levels in *IQOS* 3 System aerosol are comparable to the HPHCs levels in the Authorized *IQOS* System aerosol - all nominal differences that are within the range of the inherent variability of the methods.**

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Table 5 Summary of results of the FDA-18 HPHCs measured under the Health Canada Intense regime in the *IQOS* 3 System aerosol with the commercial firmware and each of the three *HeatStick* variants currently commercially available in the U.S., in comparison to their levels in the smoke of the 1R6F reference cigarette. SD – standard deviation; n – sample size.

HPHCs	Unit	1R6F			*IQOS* 3 System Commercial Firmware								
					Marlboro *HeatSticks*			Marlboro Smooth Menthol *HeatSticks*			Marlboro Fresh Menthol *HeatSticks*		
		Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n
1,3-butadiene	µg/cig	104	11	7	0.236	0.037	7	0.264	0.035	7	0.258	0.038	7
1-aminonaphthalene	ng/cig	21.4	0.8	7	0.034	0.001	7	0.042	0.004	7	0.051	0.011	7
2-aminonaphthalene	ng/cig	13.5	0.9	7	< 0.012	NA	7	< 0.012	NA	7	< 0.012	NA	7
4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK)	ng/cig	193	11	7	9.73	1.07	7	8.21	0.65	7	9.38	0.90	7
4-aminobiphenyl	ng/cig	2.96	0.13	7	0.0093	NA	7	0.012	0.003	7	0.010	0.002	7
Acetaldehyde	µg/cig	1539	122	7	190	12	7	216	28	7	192	8	7
Acrolein	µg/cig	172	14	7	9.16	0.88	7	10.1	1.8	7	8.64	0.99	7
Acrylonitrile	µg/cig	22.4	1.7	7	0.141	0.012	7	0.143	0.012	7	0.150	0.012	7
Ammonia	µg/cig	28.7	1.7	7	11.4	1.0	7	12.3	0.4	7	11.7	0.3	7
Benzene	µg/cig	78.3	6.3	7	0.538	0.053	7	0.575	0.060	7	0.586	0.046	7
Benzo(a)pyrene	ng/cig	15.9	0.5	7	0.491	0.038	7	0.718	0.016	7	0.573	0.019	7
Carbon monoxide (CO)	mg/cig	28.7	1.5	20	0.423	0.063	20	0.420	0.071	20	0.429	0.056	20

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HPHCs	**Unit**	**1R6F**			***IQOS* 3 System Commercial Firmware**								
					Marlboro *HeatSticks*			**Marlboro Smooth Menthol *HeatSticks***			**Marlboro Fresh Menthol *HeatSticks***		
		Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n
Crotonaldehyde	µg/cig	46.7	3.9	7	3.378	NA	7	< 3.29	NA	7	< 3.29	NA	7
Formaldehyde	µg/cig	92.8	13.4	7	7.8	0.5	7	8.4	0.6	7	7.5	0.4	7
Isoprene	µg/cig	835	70	7	1.68	0.22	7	1.80	0.20	7	1.73	0.10	7
Nicotine	mg/cig	2.02	0.10	20	1.31	0.07	20	1.25	0.07	20	1.28	0.05	20
Nitrosonornicotine (NNN)	ng/cig	215	10	7	13.9	1.0	7	9.36	1.30	7	9.64	0.72	7
Toluene	µg/cig	115	9	7	1.67	0.16	7	1.64	0.18	7	1.69	0.17	7

Table 6 **Summary of results of the FDA-18 HPHCs measured under the Standard ISO regime in the *IQOS* 3 System aerosol with the commercial firmware and each of the three *HeatStick* variants currently commercially available in the U.S., in comparison to their levels in the smoke of the 1R6F reference cigarette. SD – standard deviation; n – sample size.**

HPHCs	**Unit**	**1R6F**			***IQOS* 3 System Commercial Firmware[5]**								
					Marlboro *HeatSticks*			**Marlboro Smooth Menthol *HeatSticks***			**Marlboro Fresh Menthol *HeatSticks***		
		Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n
1,3-butadiene	µg/cig	34	3	7	< 0.095	NA	7	< 0.095	NA	7	< 0.095	NA	7
1-aminonaphthalene	ng/cig	12.7	0.7	7	< 0.027	NA	7	< 0.027	NA	7	< 0.027	NA	7

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HPHCs	Unit	1R6F			*IQOS* 3 System Commercial Firmware[5]								
					Marlboro *HeatSticks*			Marlboro Smooth Menthol *HeatSticks*			Marlboro Fresh Menthol *HeatSticks*		
		Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n
2-aminonaphthalene	ng/cig	8.7	1.0	7	< 0.012	NA	7	< 0.012	NA	7	< 0.012	NA	7
4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone (NNK)	ng/cig	78	7	7	4.24	0.29	7	4.16	0.47	7	4.53	0.45	7
4-aminobiphenyl	ng/cig	1.47	0.06	7	0.006	NA	7	0.007	NA	7	0.005	NA	7
Acetaldehyde	µg/cig	520	37	7	132	7	7	152	6	7	133	14	7
Acrolein	µg/cig	51	5	7	3.98	0.39	7	4.7	0.5	7	3.81	0.61	7
Acrylonitrile	µg/cig	4.8	0.9	7	< 0.107	NA	7	< 0.107	NA	7	< 0.107	NA	7
Ammonia	µg/cig	8.1	0.6	7	1.8	0.2	7	2.0	0.1	7	2.2	0.3	7
Benzene	µg/cig	25.1	4.1	7	0.248	0.018	7	0.283	0.022	7	0.284	0.021	7
Benzo(a)pyrene	ng/cig	6.8	0.2	7	< 0.354	NA	7	0.407	0.075	7	< 0.354	NA	7
Carbon monoxide (CO)	mg/cig	9.8	0.8	20	0.232	NA	20	0.240	NA	20	0.270	NA	20
Crotonaldehyde	µg/cig	9.3	1.2	7	< 3.29	NA	7	< 3.29	NA	7	< 3.29	NA	7
Formaldehyde	µg/cig	28.7	2.7	7	4.5	0.3	7	4.9	0.2	7	4.6	0.4	7
Isoprene	µg/cig	261	24	7	0.83	0.06	7	0.96	0.08	7	0.97	0.06	7
Nicotine	mg/cig	0.68	0.04	20	0.47	0.04	20	0.52	0.05	20	0.53	0.04	20
Nitrosonornicotine (NNN)	ng/cig	82	5	7	6.4	0.4	7	4.69	0.46	7	5.33	0.69	7
Toluene	µg/cig	31	6	7	0.72	0.07	7	0.77	0.08	7	0.78	0.06	7

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Table 7 Summary of results of the *IQOS* 3 System yields with both heating profiles (C28-6 and C28), the Authorized *IQOS* System yields, and the yields of the 1R6F reference cigarette, for the four additional constituents.

HPHCs	Unit	1R6F			*IQOS* 3 System with C28-6 Heating Profile			*IQOS* 3 System with C28 Heating Profile			Authorized *IQOS* System		
		Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n
2-furanmethanol	µg/stick	4.57	0.351	4	35.7	3.08	4	31.2	2.1	4	31.5	1.66	4
3-chloro-1,2-Propanediol	µg/stick	4.40	0.20	4	10.95	0.79	4	13.67	1.65	4	12.38	1.27	4
Furfural	µg/stick	26.1	3.65	4	33.9	2.13	4	31.7	1.74	4	32.1	3.77	4
Glycidol	µg/stick	2.41	0.278	4	6.07	0.307	4	5.44	0.268	4	5.69	0.333	4

2.4.3 Droplet Size Distribution

The physical property of an aerosol is characterized by two main parameters. These are the Mass Median Aerodynamic Diameter (MMAD), and the Geometric Standard Deviation (GSD), which describes the distribution of the mass around the MMAD.

The aerosol generated from heating tobacco is composed of liquid droplets, the size (and size distribution) of which determines whether they are respirable, as well as their behavior during inhalation.

Evidence presented in the PMTA for the Authorized *IQOS* System demonstrated that the Authorized *IQOS* System generates an aerosol with particles that fall within the respirable range. This is also the case for the *IQOS* 3 System, as demonstrated by results of the aerosol characterization studies discussed below.

Table 8 shows the MMAD and GSD measured in the *IQOS* 3 System aerosol (with C28-6 Heating Profile and C28 Heating Profile) in comparison to their respective values in the aerosol of the Authorized *IQOS* System with the same batch of Monitor *HeatSticks*.

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Table 8: MMAD and GSD values for the *IQOS* 3 System aerosol, and the Authorized *IQOS* System aerosol with the same batch of Monitor *HeatSticks*.

Replicate	*IQOS* 3 System with C28-6 Heating Profile		*IQOS* 3 System with C28 Heating Profile		Authorized *IQOS* System	
	MMAD [µm]	GSD [-]	MMAD [µm]	GSD [-]	MMAD [µm]	GSD [-]
1	0.821	1.44	0.644	1.55	0.859	2.12
2	0.71	1.38	0.756	1.36	0.84	1.74
3	0.775	1.81	0.667	1.5	0.971	1.87
4	0.771	1.34	0.795	1.37	0.662	1.79
5	0.811	1.5	0.795	1.68	0.599	1.78
6	0.704	1.44	0.71	1.46	0.789	1.58
7	0.756	1.41	0.731	1.43	0.719	1.48
8	0.766	1.52	0.773	1.63	0.662	1.52
9	0.742	1.38	0.663	1.52	0.671	1.51
Mean±SD	0.762±0.0397	1.47±0.139	0.726±0.0581	1.5±0.107	0.752±0.12	1.71±0.209

Figure 4 shows a plot of the same data, where MMAD are plotted as a function of the GSD. The *IQOS* 3 Systems assessed with the two extremes firmware settings show similar Droplet Size Distribution as the Authorized *IQOS* System.

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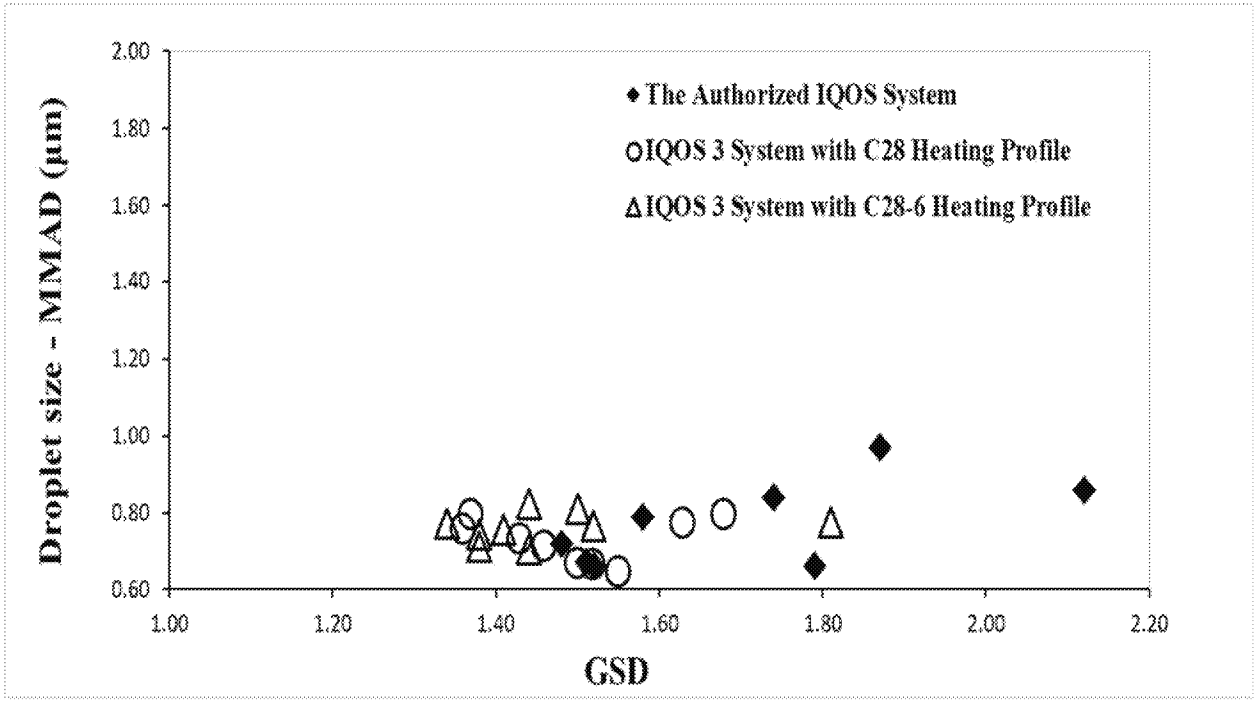


Figure 4 **MMAD plotted as a function of GSD values of the *IQOS* 3 System aerosol with C28-6 and C28 heating profiles , and the Authorized *IQOS* System aerosol. FDA-18 HPHCs List versus market map USA (Altria Client Services) – Tables and Graphs. HCI regimen**

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2.4.4 Discussion on Reduced Emissions Based on the Results

The aerosol chemistry data presented in this section demonstrate that the *IQOS* 3 System generates aerosol which is comparable to the aerosol generated with the Authorized *IQOS* System (relevant data provided in Appendix A3.2.1-16 of the PMTA for the Authorized *IQOS* System). The HPHCs levels in aerosols generated with either System using monitor *HeatSticks* and the Authorized *HeatSticks* are comparable and significantly reduced vs. their levels in smoke from the reference cigarettes. The nominal differences in levels of reductions of HPHCs between the *IQOS* 3 System aerosol and the Authorized *IQOS* System aerosol fall within the range of inherent method variability. This means that the levels of HPHCs in the *IQOS* 3 System aerosol are comparable to those of the aerosol generated by the Authorized *IQOS* System.

In addition, our scientific assessment confirmed that similarly to the Authorized *IQOS* System, the *IQOS* 3 System generates a respirable aerosol, i.e., liquid droplets of the aerosol fall within the respirable range.

The evidence presented in the PMTA for the Authorized *IQOS* System demonstrated that the Authorized *IQOS* System generates aerosol with significantly reduced levels of HPHCs compared with 3R4F cigarette smoke and the aerosol particles fall within the respirable range. Overall, results of the aerosol characterization studies conducted with the *IQOS* 3 System demonstrate that these critical attributes have been preserved in the modified version of the Authorized *IQOS* System – the *IQOS* 3 System.

Therefore, reference is made to section 6.1.1.3.4 of the PMTA for the Authorized *IQOS* System.

Table 9 below provides information on the average reductions in the levels of HPHCs, from the PMI-58 HPHCs list, compared to the 3R4F reference cigarette smoke. Average reductions have been calculated for the Authorized *IQOS* System and the *IQOS* 3 System (tested with the two heating profiles, *i.e.* C28-6 and C28).

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Table 9 Average reduction in the levels of HPHCs (from the PMI-58 HPHCs list) in the *IQOS* 3 System aerosol and the Authorized *IQOS* System aerosol in comparison to their levels in 3R4F reference cigarette smoke (stick basis). Aerosol and smoke generated under Health Canada Intense Regime.

Test	Average reduction [%]
Authorized *IQOS* System (as presented in the PMTA)	>92%
IQOS 3 System with C28-6 Heating Profile, Monitor *HeatSticks*	>92%
IQOS 3 System with C28 Heating Profile, Monitor *HeatSticks*	>92%
Authorized *IQOS* System, Monitor *HeatSticks*	>92%

Table 10 below provides information on the average reductions in the levels of HPHCs, from the FDA-18 HPHCs list, compared to the 3R4F reference cigarette smoke. Average reductions have been calculated for the Authorized *IQOS* System and the *IQOS* 3 System (tested with the two heating profiles, *i.e.* C28-6 and C28).

Table 10 Average reduction in the levels of HPHCs (from the FDA-18) in the *IQOS* 3 System aerosol and the Authorized *IQOS* System aerosol in comparison to their levels in 3R4F or 1R6F reference cigarette smoke (stick basis). Aerosol and smoke generated under Health Canada Intense Regime.

Test	Average reduction [%]
Authorized *IQOS* System vs. 3R4F Reference Cigarette (as presented in the PMTA)	>94%
IQOS 3 System with C28-6 Heating Profile, Monitor *HeatSticks vs.* 3R4F Reference Cigarette	>95%
IQOS 3 System with C28 Heating Profile, Monitor *HeatSticks vs.* 3R4F Reference Cigarette	>95%

(table continues)

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Authorized *IQOS* System, Monitor *HeatSticks* vs. 3R4F Reference Cigarette	>95%
IQOS 3 System Commercial Firmware, Marlboro *HeatSticks vs.* 1R6F Reference Cigarette	>94%
IQOS 3 System Commercial Firmware, Marlboro Smooth Menthol *HeatSticks vs.* 1R6F Reference Cigarette	>94%
IQOS 3 System Commercial Firmware, Marlboro Fresh Menthol *HeatSticks vs.* 1R6F Reference Cigarette	>94%

On a nicotine basis, the results presented in the PMTA for the Authorized *IQOS* System remain equally valid, because the results show that the levels of nicotine generated by the *IQOS* 3 Systems are comparable to the levels of nicotine generated by the Authorized *IQOS* System.

Therefore reference is made to the discussion presented in section 6.1.1.4 of the PMTA for the Authorized *IQOS* System.

3. NON-CLINICAL ASSESSMENT

The data presented in this application demonstrates that the aerosol generated with the *IQOS* 3 System is comparable tothe aerosol generated with the Authorized *IQOS* System. Therefore, any user of the *IQOS* 3 System will be exposed to a comparable aerosol than any user of the Authorized *IQOS* System.

Evidence provided with the PMTA for the Authorized *IQOS* System validated the hypothesis that reduced exposure, as seen with switching from exposure to cigarette smoke to exposure to THS aerosol, leads to reduced toxicity. All classical and systems toxicology endpoints, across all non-clinical studies conducted by PMI, have produced a coherent demonstration that reduced formation of HPHCs leads to reduced exposure to HPHCs, which in turn results in reduced toxicity across multiple levels of biological systems (molecular, cellular, tissue and organ-level changes).

Comparable reductions in levels of HPHCs in the aerosol of the *IQOS* 3 System compared to the Authorized *IQOS* System, clearly imply comparable effects observed in preclinical models, and guide the conclusion that bridging to the non-clinical evidence provided with the PMTA for the Authorized *IQOS* System, instead of conducting new studies, is appropriate.

Based on the above justification, evidence from the non-clinical assessment provided within the PMTA for the Authorized *IQOS* System remains equally valid and applicable to the *IQOS* 3 System. Therefore, this part of the PMTA for the Authorized *IQOS* System is cross-referenced in this supplemental PMTA. Thus Section 6.1.2 *Pre-clinical Safety Toxicology* and

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Section 7.2 Executive Summary – Pre-clinical Studies provided with PMTA for the Authorized *IQOS* system are cross-referenced in this application.

4. CLINICAL ASSESSMENT

The data presented in this application demonstrates that the aerosol generated with the *IQOS* 3 System is comparable to the aerosol generated with the Authorized *IQOS* System. When using the *IQOS* 3 System, the user will be inhaling an aerosol with significantly reduced levels of HPHCs, similarly to when the Authorized *IQOS* System is used. Overall, the user of the *IQOS* 3 System will be exposed to a comparable levels of HPHCs as the user of the Authorized *IQOS* System.Therefore, and when considering the comparable exposure to HPHCs, similar cinical effects as with the Authorized *IQOS* System are expected with the *IQOS* 3 System.

Results of the clinical studies submitted with the PMTA for the Authorized *IQOS* System demonstrated a consistent reduction in Biomarkers of Exposure (BoExp) in smokers who switched to the Authorized *IQOS* System and smoking abstinence. These changes were evident as early as 5 days following the switch and were preserved throughout the 90-day duration of the REXA studies. The reductions seen in the Authorized *IQOS* System group were similar in both magnitude and direction to those seen with smoking abstinence. This is plausible, given that the Authorized *IQOS* System aerosol contains levels of HPHCs that are on average reduced > 90% compared with combustible cigarette smoke. Comparable reductions in levels of HPHCs in the aerosol of the *IQOS* 3 System imply comparable effects to those observed in a clinical settings, and guide the conclusion that bridging to the clinical evidence provided with the PMTA for the Authorized *IQOS* System, instead of conducting new studies, is appropriate.

Based on the above justification, evidence from the clinical assessment provided within the PMTA for the Authorized *IQOS* System remain equally valid and applicable to *IQOS* 3 System. Therefore this part of the PMTA for the Authorized *IQOS* System is cross-referenced in this supplemental PMTA. Thus, the following Sections of the PMTA for the Authorized *IQOS* System are cross-referenced in this application:

6.1.3.1 Justification of Selection of Biomarkers of Exposure

6.1.3.2 Summary of Biomarkers of Exposure Assessments

6.1.3.3 Bioanalytical Methods

6.1.3.4 Reduced Exposure - Overview of Studies

6.1.4 Clinical Risk Endpoints

6.2.1.1 Summary of Clinical Pharmacology Studies

6.2.1.2 PK/PD Overview of Studies

7.3.1 Executive Summary – Clinical Studies

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5. THE AUTHORIZED IQOS SYSTEM AND THE IQOS 3 SYSTEM POSTMARKET SAFETY DATA

Outside of the U.S., the *IQOS* System[11], which corresponds to the Authorized *IQOS* System, was commercialized for the first time in November 2014, while the *IQOS* 3 System was introduced only in beginning of November 2018, four years later. Up to the end of November 2019, the Authorized *IQOS* System has been commercialized in 52 countries and the *IQOS* 3 System in 50 countries. With the exception of Mexico and the U.S., the *IQOS* 3 System has been commercialized in the same countries as the Authorized *IQOS* System.

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(b) (4)

[12] In countries outside the U.S. *HeatSticks* are sold under the brand name *HEETS*.

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Authorized *IQOS* System has been commercialized for a longer period of time. Consequently, the number of consumers using the Authorized *IQOS* System is assumed to be higher than with the *IQOS* 3 System.

The assessment of reported adverse experiences (AEs) indicates that the most frequently reported MedRA System Organ Class (SOCs) are the same for both versions of the *IQOS* System and have similar proportions of AEs (*i.e.* count of adverse experiences for a given SOC/count of adverse experiences for all SOCs for each version of the *IQOS* System). Similarly, for both versions of the *IQOS* System, the most frequently reported MedDRA Preferred Terms (PTs) are also the same in term of proportions for serious and for non-serious adverse experiences. This shows that the Authorized *IQOS* System and the *IQOS* 3 System have similar safety profile.

The review of postmarket safety data indicates that there are no safety signals suggesting new or increased risks for smokers switching to the *IQOS* 3 System, as compared to smokers switching to the Authorized *IQOS* System.

A detailed summary of adverse experiences potentially associated with the Authorized *IQOS* System and the *IQOS* 3 System use, derived from the PMI's global safety database is provided in Module 8 *Postmarket Information*.

Overall, the analysis of the available data shows that the Authorized *IQOS* System and *IQOS* 3 System have similar safety profile. Therefore, introduction on the market of the *IQOS* 3 System is not expected to affect user's safety.

6. IQOS 3 SYSTEM USER EXPERIENCE DATA

6.1. Tobacco Use Behavior Among Current IQOS Owners

(b) (4)

[13] Source: PMI's 2019 Third-Quarter Results October 17, 2019, available at: https://philipmorrisinternational.gcs-web.com/static-files/a5f2050f-4fda-4713-9278-d9e39b4b38f7

[14] Source: PMI Financials or estimates

[15] *IQOS* 2.4P superseded *IQOS* 2.4 in international markets

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[16] Outside U.S. and Japan the Tobacco Sticks have been commercialized under the brand name "*HEETS*"

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[17] *IQOS* 3 Multi or *IQOS* 3M is another version of the System which allows several uses before re-charging. The system has been commercialized in countries outside the U.S.

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[19] Technical Project Lead Review (TPL), page 74, available at: https://www.fda.gov/media/124247/download

[20] *Id.*

[21] Technical Project Lead Review (TPL), page 88-89, available at: https://www.fda.gov/media/124247/download

[22] Technical Project Lead Review (TPL), page 74, available at: https://www.fda.gov/media/124247/download

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Conclusions

In view of the above, we believe that irrespective of the *IQOS* System version, current adult cigarette smokers will represent the segment of the population that is most likely to use *IQOS*. PMI pre-market data gathered in the U.S., international PMI post-market data from different countries, and independent studies from non-U.S. countries show low likelihood of starting using *IQOS* among non-smokers, including former and never smokers, regardless of the *IQOS* System version. Therefore, an increased risk of unintended consequences, e.g. high tobacco use initiation and re-initiation with the *IQOS* 3 System, is not to be expected in the U.S. if the *IQOS* 3 System will be authorized for commercialization by the Agency. The marketing and advertising restrictions included in the Marketing Order for the Authorized *IQOS* System will also apply to the *IQOS* 3 System and hence ensure that *IQOS* is only sold to current adult smokers who would otherwise continue smoking and are at least 21 years old.

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7. OVERALL CONCLUSIONS

The *IQOS* 3 System has the same operating principles as the Authorized *IQOS* System. Therefore, the product performance has not changed and the principles of aerosol generation remain the same in the *IQOS* 3 System resulting in a comparable aerosol generated by the *IQOS* 3 System to the one of the Authorized *IQOS* System. The upgraded modified *IQOS* 3 System generates aerosol with nicotine levels comparable with those measured in the aerosol from the Authorized *IQOS* System. The nicotine levels of both aerosols do pose an addiction risk for non-tobacco users who initiate use of the *IQOS* Systems. However, this risk is the same with any version of the *IQOS* Systemand is not higher than for other, currently available, tobacco products. In addition, initiation with the *IQOS* 3 System is expected to be low generally. Similarly to the aerosol of the Authorized *IQOS* System, the aerosol generated by the *IQOS* 3 System contains certain genotoxic or cytotoxic chemicals. They are present in very low levels and their potential negative effects are outweighed by the substantial decrease in the number and levels of harmful and potentially harmful constituents (HPHCs) present in the *IQOS* 3 System aerosol compared to those found in combustible cigarettes smoke. This allows to conclude that the potential for a relative benefit compared to combustible cigarettes for smokers who switch completely to the *IQOS* 3 System is equal to the Authorized *IQOS* System.

The *IQOS* 3 System delivers an aerosol with substantial reductions in the number and levels of HPHCs compared to those of combustible cigarettes smoke and comparable to those of the Authorized *IQOS* System aerosol. *IQOS* 3 System is expected to trigger patterns of use (e.g. 100% *IQOS* use, average daily *HeatSticks* and combustible cigarettes consumption) similar to the ones of the Authorized *IQOS* System. Furthermore, as evidenced by the data from *IQOS* Owner Panels in Germany, Japan, Italy, South Korea, and Switzerland where the *IQOS* 3 System is sold, gender and age profiles of *IQOS* 3 System users are similar to the ones of the Authorized *IQOS* System users (Section 2.1. Tobacco Use Behavior Among Current *IQOS* Owners).

Finally, the design of the *IQOS* 3 System does not contain any features that are anticipated to alter the low level of interest in trial and use among adult never smokers and former smokers that was found with the Authorized *IQOS* System.

The evidence provided with this application guides the conclusion that the authorization of the marketing of the *IQOS* 3 System, would be equally appropriate for the protection of the public health as one for the Authorized *IQOS* System.

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