Module 3: Product Description

3.2.1.5 Constituents

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Appendix 3.2.1.5-1: TSH 2.2 Comparability Strategy (version 5.1)

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Development of a product that significantly reduces the formation of HPHCs compared with combustible cigarettes (CC) was central to the PMI approach to the Authorized *IQOS* System (*IQOS* 2.4 System). It is therefore essential that the *IQOS* 3 System, being an upgraded modified version of the Authorized *IQOS* System, preserves these critical attributes.

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

During this characterization, three testing were performed and compared with the Authorized *IQOS* System and the reference combustible cigarettes (3R4F or 1R6F):

- Determination of the PMI's list of 58 compounds (PMI-58[1]), which contain 54 Harmful and Potentially Harmful Constituents (HPHCs) and four other aerosol constituents,
- Determination of four additional HPHCs (glycidol, furfural, 2-furanmethanol, 3-chloro-1,2-propondiol), which were identified in the non-targeted differential screening from the Authorized *IQOS* System and
- Determination of the droplet size distribution (DSD).

As the *IQOS* 3 System has been upgraded **(b) (4)** **(b) (4)** *Operation*, chapter 3.2. Heating profiles), PMI-58 studies were conducted for the *IQOS* 3 System with the firmware modified in order to force the both heating profiles ("standard[2]" heating profile (C28 profile) and "alternative[3]" heating profile (C28-6 profile), which is **(b) (4)** **(b) (4)** o demonstrate that under both operating conditions the aerosol produced by the *IQOS* 3 System is comparable to the Authorized *IQOS* System and maintains significant reductions in HPHCs compared to combustible cigarette smoke (3R4F). PMI-58 studies were conducted with monitor *HeatSticks* using the Health Canada Intense machine-smoking protocol consistent with current version of the TSH 2.2 Comparability Strategy (see Appendix

[1] For additional information about of how this list of constituents was selected and justification, please refer to the original submission of PMTA for *IQOS* 2.4 System with three variants of *Marlboro HeatSticks* (STNs: PM0000424-PM0000426 and PM0000479), Module 3, Appendix A3.2.1-12 and Appendix A3.3-2.

[2] Standard heating profile (C28 profile) is also referred in reports as operating conditions with no "warm aerosol" mitigation ("no-WA" operating conditions).

[3] Alternative heating profile (C28-6 profile) is also referred in reports as operating conditions with "warm aerosol" mitigation ("WA" operating conditions).

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3.2.1.5-1). For this comparison, 3R4F reference cigarette values were used from a research study conducted in 2018 at Labstat International ULC.

Four additional constituents (HPHCs) were also measured as these were detected at higher levels in the Authorized *IQOS* System in comparison to the 3R4F reference cigarette in the original PMTA for the Authorized *IQOS* System (PM0000479). The studies for these four HPHCs (glycidol, furfural, 2-furanmethanol, 3-chloro-1,2-propondiol) were conducted at PMI R&D laboratories in Neuchâtel, Switzerland. Method details and validation results are included in corresponding chapters below. These studies also used monitor *HeatSticks* (consistent with the original PMTA) and included the *IQOS* 3 System yields with both firmware operating modes, the Authorized *IQOS* System yields, and the yields of the 1R6F reference cigarette. The testing was performed under the Health Canada Intense regime. Reference cigarettes 1R6F (provided by the University of Kentucky, Kentucky Tobacco Research & Development Center) were used in the four additional HPHC studies because 3R4F was no longer available for purchase as of December 31, 2018.

The physical properties of an aerosol are 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. Also included in this section is a comparison of the Droplet Size Distribution (DSD) measuring MMAD and GSD of the aerosol generated by both the Authorized *IQOS* System and the *IQOS* 3 System (under both modes of operation) using monitor *HeatSticks*.

This section demonstrates that there is comparable aerosol chemistry and physics (DSD) between the Authorized *IQOS* System (*IQOS* 2.4 System) and the *IQOS* 3 System under both modes of operation using monitor *Heatsticks*. This section also demonstrates that, analogous to the Authorized *IQOS* System, the HPHCs in the aerosol of *IQOS* 3 System are significantly reduced compared to smoke from combustible cigarette. For a comparison of the FDA's abbreviated list of 18 HPHCs[4] in the aerosol produced by the Authorized *IQOS* System and the *IQOS* 3 System under commercial operating mode using all three currently commercialized *Heatstick* variants under both the ISO Standard and Health Canada Intense smoking regimes, see section 3.2.4 *Product Testing and Analysis Information*, which also contains a comparison of the *IQOS* aerosols to combusted cigarette smoke (1R6F).

[4] FDA's Draft Guidance for Industry: Reporting Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke Under Section 904(a)(3) of the Federal Food, Drug, and Cosmetic Act, March 2012

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1. PMI-58 TESTING (PROJECT CODES NS530-H AND NS487-H)

Testing of PMI's 58 aerosol constituents was performed by independent laboratory Labstat International Inc. The testing laboratory is accredited by the Standards Council of Canada to comply with ISO/IEC 17025:2017.

Table 1: Testing laboratory details

Laboratory name	Labstat International Inc.
Address	262 Manitou Drive, Kitchener, Ontario N2C 1L3, Canada
Telephone no.	+1 (519) 748-5409
Fax no.	+1 (519) 748-1654
E-mail	labstat@labstat.com

Testing was performed on the US version of the *IQOS* 3 System with modified firmware and on Authorized *IQOS* System using reference *HeatSticks* (also referred as "monitor" *HeatSticks*). (b) (4) (b) (4) (b) (4) Therefore two comparisons were conducted. In the first comparison (study project code NS530-H) *IQOS* 3 System was forced to use "standard" heating profile (C28 profile), while in the second comparison (study project code NS487-H) the device was forced to use "alternative" heating profile (C28-6 profile), (b) (4) ("warm aerosol" mitigation). In addition aerosol constituent levels of reference combustible cigarettes 3R4F from the Labstat's study NS407-GLP, which was conducted in 2018 are provided for reference purposes as well. The sample details are summarized in the table below.

Table 2: Sample information

Sample Type	Sample ID / Batch no.	Manufacturing date
IQOS 3 System (forced C28 profile)	B-79845	December 20, 2019
IQOS 3 System (forced C28-6 profile)	B-72500	June 18, 2019
IQOS 2.4 System	B-72348	June 17, 2019
P1M2 monitor *HeatSticks*	IC2911171	May 23, 2017
3R4F Kentucky reference cigarette*	V346Y61B5	N/A

Note: * Used in the Labstat's study NS407-GLP from 2018.

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Prior to testing, the *HeatSticks* and Kentucky reference cigarettes (from study NS407-GLP) were conditioned under the ambient conditions from ISO 3402 (1999) for minimum of 48 hours and up to 10 days.

Table 3: Ambient conditions according to ISO 3402 (1999)

	Conditioning	Testing
Ambient temperature	22 ± 1°C	22 ± 2°C
Relative humidity	60 ± 3 %	60 ± 5 %

Testing was performed using intense aerosol-generating regime – Health Canada Intense (HCI) regime (Table 4) as this regime is considered as the "worst case scenario". However as the *HeatSticks* do not have any ventilation holes, no vent blocking was applied.

Table 4: Parameters of HCI aerosol-generating regime

	Health Canada Intense
Puff volume (ml)	55
Interval (s)	30
Duration (s)	2
Vents*	"fully blocked"
Note: * Health Canada 100% vent blocking method	

For information regarding the analytical methods used to analyze samples please refer to the TPMF no. MF0000243. Corresponding Letter of Authorization (LoA) is provided in section 1.3 *Letters of Authorization*.

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Table 5:Summary of results of the PMI 58 testing measured under the HCI regime for *IQOS* 3 device with forced "standard" (C28) heating profile and Authorized *IQOS* System and comparison to reference levels in smoke of the 3R4F reference cigarette

HPHCs	CAS no.	Unit	*IQOS* 3 System (C28) + monitor *HeatStick*			*IQOS* 2.4 System + monitor *HeatStick*			3R4F reference cigarette			Analytical method
			Mean	SD	n	Mean	SD	n	Mean	SD	n	
1,3-Butadiene	106-99-0	µg/cig	0.218	0.0252	9	0.213	0.0196	9	100	6.87	4	TMS-00124
1-Aminonaphthalene	134-32-7	ng/cig	0.0276	NA	9	0.0321	NA	9	29.1	2.56	4	TMS-00128
2-Aminonaphthalene	91-59-8	ng/cig	< 0.012	NA	9	< 0.012	NA	9	18.1	2.32	4	TMS-00128
3-Aminobiphenyl	2243-47-2	ng/cig	0.007	0.0023	9	0.007	0.0019	9	5.44	0.226	4	TMS-00128
4-(Methyl-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK)	64091-91-4	ng/cig	6.43	0.334	9	6.58	0.33	9	295	32.5	4	TMS-00135
4-Aminobiphenyl	92-67-1	ng/cig	0.0082	NA	9	0.009	0.0021	9	3.91	0.293	4	TMS-00128
Acetaldehyde	75-07-0	µg/cig	201	13.6	9	197	15.8	9	1838	105	4	TMS-00104
Acetamide	60-35-5	µg/cig	3.25	0.268	9	3.38	0.0814	9	12.2	1.86	4	TMS-00112
Acetone	67-64-1	µg/cig	35.3	2.86	9	35.4	3.25	9	749	44.4	4	TMS-00104
Acrolein	107-02-8	µg/cig	8.34	0.846	9	8.52	1.11	9	180	12.6	4	TMS-00104
Acrylamide	79-06-1	µg/cig	1.5	0.118	9	1.56	0.0777	9	3.92	0.522	4	TMS-00112
Acrylonitrile	107-13-1	µg/cig	0.127	NA	9	0.116	NA	9	20.5	1.81	4	TMS-00124
Ammonia	7664-41-7	µg/cig	10.2	0.986	9	10.5	0.841	9	34	0.497	4	TMS-00101
Arsenic	7440-38-2	ng/cig	< 1.2	NA	9	< 1.2	NA	9	< 7.49	NA	4	TMS-00109
Benz[a]anthracene	56-55-3	ng/cig	1.65	0.0639	9	1.59	0.0504	9	28.9	1.96	4	TMS-00120
Benzene	71-43-2	µg/cig	0.563	0.0383	9	0.557	0.0278	9	88.8	6.31	4	TMS-00124
Benzo[a]pyrene	50-32-8	ng/cig	0.635	0.0425	9	0.617	0.0332	9	15.1	0.63	4	TMS-00120
Butyraldehyde	123-72-8	µg/cig	20.8	1.49	9	20	1.3	9	93	4.35	4	TMS-00104
Cadmium	7440-43-9	ng/cig	< 0.09	NA	9	< 0.09	NA	9	93.2	7.42	4	TMS-00109
Carbon monoxide (CO)	630-08-0	mg/cig	0.438	0.0533	9	0.42	0	9	30.5	1.81	4	TMS-00115a
Catechol	120-80-9	µg/cig	15	0.904	9	15.7	0.628	9	86.9	5.42	4	TMS-00139
Chromium	7440-47-3	ng/cig	< 11	NA	9	< 3.31	NA	9	< 11.9	NA	4	TMS-00109
Crotonaldehyde	4170-30-3	µg/cig	< 3.29	NA	9	< 3.29	NA	9	59.5	4.41	4	TMS-00104
Dibenz[a,h]anthracene	53-70-3	ng/cig	< 0.124	NA	9	< 0.124	NA	9	1.34	0.0918	4	TMS-00120

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HPHCs	CAS no.	Unit	*IQOS* 3 System (C28) + monitor *HeatStick*			*IQOS* 2.4 System + monitor *HeatStick*			3R4F reference cigarette			Analytical method
			Mean	SD	n	Mean	SD	n	Mean	SD	n	
Ethylene oxide	75-21-8	µg/cig	< 0.119	NA	9	0.119	NA	9	19.2	1.81	4	TMS-00124
Formaldehyde	50-00-0	µg/cig	7.87	1.05	9	7.51	0.66	9	87.1	7.37	4	TMS-00104
Glycerol	56-81-5	mg/cig	4.55	0.287	9	5.07	0.261	9	2.25	0.072	4	TMS-00115a
Hydrogen cyanide	74-90-8	µg/cig	2.77	0.432	9	2.57	0.507	9	390	22.8	4	TMS-00107
Hydroquinone	123-31-9	µg/cig	7.5	0.557	9	8.11	0.424	9	78.1	6.52	4	TMS-00139
Isoprene	78-79-5	µg/cig	1.59	0.17	9	1.6	0.177	9	799	61	4	TMS-00124
Lead	7439-92-1	ng/cig	< 1.62	NA	9	< 0.49	NA	9	< 25.7	NA	4	TMS-00109
m-Cresol	108-39-4	µg/cig	0.025	NA	9	0.029	0.0031	9	2.77	0.194	4	TMS-00139
Mercury	7439-97-6	ng/cig	2.52	0.0759	9	2.35	0.0928	9	4.92	0.0635	4	TMS-00108
Methyl-ethyl-ketone (MEK)	78-93-3	µg/cig	8.6	0.855	9	8.87	0.722	9	199	13.1	4	TMS-00104
Nickel	7440-02-0	ng/cig	< 15.9	NA	9	< 15.9	NA	9	< 12.9	NA	4	TMS-00109
Nicotine	54-11-5	mg/cig	1.19	0.0444	9	1.25	0.0445	9	1.99	0.131	4	TMS-00115a
Nitric oxide (NO)	10102-43-9	µg/cig	11.1	0.79	9	10.4	1.12	9	471	16.5	4	TMS-00110
Nitro benzene	98-95-3	µg/cig	< 0.011	NA	9	< 0.011	NA	9	< 0.027	NA	4	TMS-00112
Nitrogen oxides (NOx)	11104-93-1	µg/cig	12.9	0.903	9	12.1	1.14	9	524	17.2	4	TMS-00110
N-nitrosoanabasine (NAB)	1133-64-8	ng/cig	2.07	0.111	9	2.12	0.162	9	31.8	1.02	4	TMS-00135
N-nitrosoanatabine (NAT)	71267-22-6	ng/cig	13.6	0.458	9	14	0.958	9	334	12.3	4	TMS-00135
N-Nitrosonornicotine (NNN)	16543-55-8	ng/cig	6.31	0.216	9	6.47	0.495	9	336	28.4	4	TMS-00135
o-Cresol	95-48-7	µg/cig	0.058	0.0095	9	0.068	0.0033	9	3.22	0.265	4	TMS-00139
o-Toluidine	95-53-4	ng/cig	0.957	0.0673	9	0.965	0.0526	9	121	1.04	4	TMS-00128
p-Cresol	106-44-5	µg/cig	0.051	0.007	9	0.06	0.0041	9	6.83	0.53	4	TMS-00139
Phenol	108-95-2	µg/cig	1.24	0.165	9	1.44	0.11	9	11.1	0.896	4	TMS-00139
Propionaldehyde	123-38-6	µg/cig	12.5	1.07	9	12.4	1.23	9	135	8.15	4	TMS-00104
Propylene oxide	75-56-9	ng/cig	117	6.51	9	115	5.14	9	1000	78.8	4	TMS-00124
Pyrene	129-00-0	ng/cig	5.62	0.224	9	5.42	0.188	9	91.9	7.5	4	TMS-00120
Pyridine	110-86-1	µg/cig	5.52	0.276	9	5.53	0.321	9	35.2	6.4	4	TMS-00112
Quinoline	91-22-5	µg/cig	< 0.011	NA	9	< 0.011	NA	9	0.315	0.0333	4	TMS-00112
Resorcinol	108-46-3	µg/cig	< 0.055	NA	9	< 0.055	NA	9	< 1.32	NA	4	TMS-00139
Selenium	7782-49-2	ng/cig	< 0.83	NA	9	< 0.83	NA	9	< 4.42	NA	4	TMS-00109
Styrene	100-42-5	µg/cig	0.416	0.0253	9	0.418	0.0313	9	21.7	2.4	4	TMS-00112
Toluene	108-88-3	µg/cig	1.84	0.146	9	1.91	0.0784	9	153	11.5	4	TMS-00124

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HPHCs	CAS no.	Unit	*IQOS* 3 System (C28) + monitor *HeatStick*			*IQOS* 2.4 System + monitor *HeatStick*			3R4F reference cigarette			Analytical method
			Mean	SD	n	Mean	SD	n	Mean	SD	n	
(b) (4)												
Vinyl chloride	75-01-4	ng/cig	< 2.19	NA	9	< 2.19	NA	9	94.6	7.44	4	TMS-00124

Legend: SD – standard deviation; n – sample size; "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.

Table 6:Summary of results of the PMI 58 testing measured under the HCI regime for *IQOS* 3 device with forced "alternative" (C28-6) heating profile and Authorized *IQOS* System and comparison to reference levels in smoke of the 3R4F reference cigarette

HPHCs	CAS no.	Unit	*IQOS* 3 System (C28-6) + monitor *HeatStick*			*IQOS* 2.4 System + monitor *HeatStick*			3R4F reference cigarette			Analytical method
			Mean	SD	n	Mean	SD	n	Mean	SD	n	
1,3-Butadiene	106-99-0	µg/cig	0.115	NA	9	0.169	0.0375	9	100	6.87	4	TMS-00124
1-Aminonaphthalene	134-32-7	ng/cig	0.033	NA	9	0.0351	NA	9	29.1	2.56	4	TMS-00128
2-Aminonaphthalene	91-59-8	ng/cig	0.0161	NA	9	0.019	0.00469	9	18.1	2.32	4	TMS-00128
3-Aminobiphenyl	2243-47-2	ng/cig	0.00651	0.000942	9	0.00679	0.00102	9	5.44	0.226	4	TMS-00128
4-(Methyl-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK)	64091-91-4	ng/cig	7.52	0.365	9	7.6	0.336	9	295	32.5	4	TMS-00135
4-Aminobiphenyl	92-67-1	ng/cig	0.00884	0.00157	9	0.00947	0.00193	9	3.91	0.293	4	TMS-00128
Acetaldehyde	75-07-0	µg/cig	221	5.83	9	218	7.57	9	1838	105	4	TMS-00104
Acetamide	60-35-5	µg/cig	3.55	0.135	9	3.68	0.297	9	12.2	1.86	4	TMS-00112
Acetone	67-64-1	µg/cig	38.3	1.56	9	36.6	2.13	9	749	44.4	4	TMS-00104
Acrolein	107-02-8	µg/cig	8.71	0.461	9	8.75	0.748	9	180	12.6	4	TMS-00104
Acrylamide	79-06-1	µg/cig	1.55	0.0994	9	1.6	0.14	9	3.92	0.522	4	TMS-00112
Acrylonitrile	107-13-1	µg/cig	< 0.107	NA	9	< 0.107	NA	9	20.5	1.81	4	TMS-00124
Ammonia	7664-41-7	µg/cig	9.9	1.05	9	11	0.343	9	34	0.497	4	TMS-00101
Arsenic	7440-38-2	ng/cig	< 1.2	NA	9	< 1.2	NA	9	< 7.49	NA	4	TMS-00109
Benz[a]anthracene	56-55-3	ng/cig	1.94	0.0756	9	1.91	0.108	9	28.9	1.96	4	TMS-00120
Benzene	71-43-2	µg/cig	0.513	0.126	9	0.551	0.147	9	88.8	6.31	4	TMS-00124

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HPHCs	CAS no.	Unit	*IQOS* 3 System (C28-6) + monitor *HeatStick*			*IQOS* 2.4 System + monitor *HeatStick*			3R4F reference cigarette			Analytical method
			Mean	SD	n	Mean	SD	n	Mean	SD	n	
Benzo[a]pyrene	50-32-8	ng/cig	0.747	0.0422	9	0.741	0.0659	9	15.1	0.63	4	TMS-00120
Butyraldehyde	123-72-8	µg/cig	20.4	0.569	9	20.2	0.617	9	93	4.35	4	TMS-00104
Cadmium	7440-43-9	ng/cig	< 0.09	NA	9	< 0.09	NA	9	93.2	7.42	4	TMS-00109
Carbon monoxide (CO)	630-08-0	mg/cig	0.345	0.028	9	0.364	0.042	9	30.5	1.81	4	TMS-00115a
Catechol	120-80-9	µg/cig	17.4	0.749	9	18.6	0.736	9	86.9	5.42	4	TMS-00139
Chromium	7440-47-3	ng/cig	< 11	NA	9	< 11	NA	9	< 11.9	NA	4	TMS-00109
Crotonaldehyde	4170-30-3	µg/cig	< 3.29	NA	9	< 3.29	NA	9	59.5	4.41	4	TMS-00104
Dibenz[a,h]anthracene	53-70-3	ng/cig	< 0.124	NA	9	< 0.124	NA	9	1.34	0.0918	4	TMS-00120
Ethylene oxide	75-21-8	µg/cig	0.189	0.00597	9	0.205	0.0218	9	19.2	1.81	4	TMS-00124
Formaldehyde	50-00-0	µg/cig	9.7	0.819	9	9.88	0.645	9	87.1	7.37	4	TMS-00104
Glycerol	56-81-5	mg/cig	4.22	0.311	9	4.56	0.211	9	2.25	0.072	4	TMS-00115a
Hydrogen cyanide	74-90-8	µg/cig	2.61	0.206	9	2.87	0.23	9	390	22.8	4	TMS-00107
Hydroquinone	123-31-9	µg/cig	8.11	0.425	9	9.2	0.429	9	78.1	6.52	4	TMS-00139
Isoprene	78-79-5	µg/cig	1.27	0.271	9	1.5	0.189	9	799	61	4	TMS-00124
Lead	7439-92-1	ng/cig	< 0.49	NA	9	< 1.62	NA	9	< 25.7	NA	4	TMS-00109
m-Cresol	108-39-4	µg/cig	0.0321	0.00297	9	0.0369	0.00577	9	2.77	0.194	4	TMS-00139
Mercury	7439-97-6	ng/cig	2.27	0.102	9	2.17	0.15	9	4.92	0.0635	4	TMS-00108
Methyl-ethyl-ketone (MEK)	78-93-3	µg/cig	7.76	0.389	9	7.55	0.541	9	199	13.1	4	TMS-00104
Nickel	7440-02-0	ng/cig	< 53.1	NA	9	< 15.9	NA	9	< 12.9	NA	4	TMS-00109
Nicotine	54-11-5	mg/cig	1.31	0.0315	9	1.34	0.06	9	1.99	0.131	4	TMS-00115a
Nitric oxide (NO)	10102-43-9	µg/cig	10.8	0.471	9	10.6	0.446	9	471	16.5	4	TMS-00110
Nitro benzene	98-95-3	µg/cig	< 0.011	NA	9	< 0.011	NA	9	< 0.027	NA	4	TMS-00112
Nitrogen oxides (NOx)	11104-93-1	µg/cig	12	0.464	9	11.9	0.491	9	524	17.2	4	TMS-00110
N-nitrosoanabasine (NAB)	1133-64-8	ng/cig	2.2	0.0975	9	2.17	0.126	9	31.8	1.02	4	TMS-00135
N-nitrosoanatabine (NAT)	71267-22-6	ng/cig	16	0.544	9	16.1	0.837	9	334	12.3	4	TMS-00135
N-Nitrosonornicotine (NNN)	16543-55-8	ng/cig	12.6	0.461	9	12.5	0.533	9	336	28.4	4	TMS-00135
o-Cresol	95-48-7	µg/cig	0.0734	0.00828	9	0.0856	0.0106	9	3.22	0.265	4	TMS-00139
o-Toluidine	95-53-4	ng/cig	1.02	0.0728	9	1.13	0.246	9	121	1.04	4	TMS-00128
p-Cresol	106-44-5	µg/cig	0.0665	0.00538	9	0.0786	0.0108	9	6.83	0.53	4	TMS-00139
Phenol	108-95-2	µg/cig	1.48	0.168	9	1.69	0.142	9	11.1	0.896	4	TMS-00139
Propionaldehyde	123-38-6	µg/cig	12.7	0.467	9	12.5	0.704	9	135	8.15	4	TMS-00104

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HPHCs	CAS no.	Unit	*IQOS* 3 System (C28-6) + monitor *HeatStick*			*IQOS* 2.4 System + monitor *HeatStick*			3R4F reference cigarette			Analytical method
			Mean	SD	n	Mean	SD	n	Mean	SD	n	
Propylene oxide	75-56-9	ng/cig	118	10.7	9	130	15	9	1000	78.8	4	TMS-00124
Pyrene	129-00-0	ng/cig	8.19	0.49	9	8.13	0.597	9	91.9	7.5	4	TMS-00120
Pyridine	110-86-1	µg/cig	5.58	0.175	9	5.65	0.356	9	35.2	6.4	4	TMS-00112
Quinoline	91-22-5	µg/cig	< 0.003	NA	9	< 0.003	NA	9	0.315	0.0333	4	TMS-00112
Resorcinol	108-46-3	µg/cig	< 0.016	NA	9	< 0.016	NA	9	< 1.32	NA	4	TMS-00139
Selenium	7782-49-2	ng/cig	< 0.83	NA	9	< 0.83	NA	9	< 4.42	NA	4	TMS-00109
Styrene	100-42-5	µg/cig	0.445	0.0185	9	0.491	0.0575	9	21.7	2.4	4	TMS-00112
Toluene	108-88-3	µg/cig	1.54	0.405	9	1.7	0.428	9	153	11.5	4	TMS-00124
Total Particulate Matter (TPM)	-	mg/cig	51	0.701	9	51.9	1.63	9	47	2.62	4	TMS-00115a
Vinyl chloride	75-01-4	ng/cig	< 2.19	NA	9	< 2.19	NA	9	94.6	7.44	4	TMS-00124

Legend: SD – standard deviation; n – sample size; "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.

For Labstat's study reports with datasets please refer to module 7 *Scientific Studies and Analyses*.

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2. TESTING FOR ADDITIONAL FOUR HPHCS (STUDY NOS. RLS-THR-2020-1 AND RLS-THR-2020-2)

Four additional constituents (HPHCs) were also measured as these were detected at higher levels in the Authorized *IQOS* System in comparison to the 3R4F reference cigarette in the original PMTA for the Authorized *IQOS* System (PM0000479). The studies for the determination of the four additional HPHCs (glycidol, furfural, 2-furanmethanol, 3-chloro-1,2-propondiol) were conducted at PMI R&D laboratories in Neuchatel, Switzerland.

Table 7: Testing laboratory details

Laboratory name	Philip Morris Products S.A., R&D Cube
Address	Quai Jeanrenaud 5, 2000 Neuchatel, Switzerland
Telephone no.	+41 (0) 58 242 21 13
Fax no.	N/A
E-mail of Contact Person:	Antoine.Zuend@pmi.com

The studies used monitor *Heatsticks* (consistent with the original PMTA) and included the *IQOS* 3 System yields with both operating conditions (forced standard C28 profile and forced alternative C28-6 profile), the Authorized *IQOS* System yields, and the yields of the 1R6F reference cigarette. The sample details are summarized in the table below.

Table 8: Sample information

Sample Type	Sample ID / Batch no.	Manufacturing date
IQOS 3 System (forced C28 profile)	B-79858	December 20, 2019
IQOS 3 System (forced C28-6 profile)	B-79852	December 18, 2019
IQOS 2.4 System	B-72348	June 17, 2019
P1M2 monitor *HeatSticks*	IC2911171	May 23, 2017
1R6F Kentucky reference cigarette	2061646[5] and 2064636[6]	N/A

Prior to testing, the *HeatSticks* and Kentucky reference cigarettes were conditioned under the ambient conditions for minimum of 48 hours.

[5] Designation of the sample used in analytical procedure for determination of 2-Furanmethanol, Furfural and Glycidol

[6] Designation of the sample used in analytical procedure for determination of 3-Chloro-1,2-propanediol

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Table 9: Ambient conditions

	Conditioning	Testing
Ambient temperature	22 ± 1°C	22 ± 2°C
Relative humidity	60 ± 3 %	60 ± 5 %

Testing was performed using intense aerosol-generating regime – Health Canada Intense (HCI) regime (described in the Table 10) as this regime is considered as the "worst case scenario". However as the *HeatSticks* do not have any ventilation holes, no vent blocking was applied.

Table 10: Parameters of HCI aerosol-generating regime

	Health Canada Intense
Puff volume (ml)	55
Interval (s)	30
Duration (s)	2
Vents*	"fully blocked"
Note: * Health Canada 100% vent blocking method	

Samples were analyzed using two in-house developed the analytical methods (see chapters 2.1 and 2.3)

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Table 11: Results of 4 additional HPHCs testing measured under the HCI regime for both forced operating conditions of *IQOS* 3 System and Authorized *IQOS* System using same monitor *HeatSticks* and comparison to 1R6F reference cigarette

HPHCs	CAS no.	Unit	*IQOS* 3 System (C28) + monitor *HeatStick*			*IQOS* 3 System (C28-6) + monitor *HeatStick*			*IQOS* 2.4 System + monitor *HeatStick*			1R6F reference cigarette		
			Mean	SD	n	Mean	SD	n	Mean	SD	n	Mean	SD	n
2-Furanmethanol	98-00-0	µg/stick	31.2	2.1	4	35.7	3.08	4	31.5	1.66	4	4.57	0.351	4
3-Chloro-1,2-propanediol	96-24-2	µg/stick	13.67	1.65	4	10.95	0.79	4	12.38	1.27	4	4.40	0.20	4
Furfural	98-01-1	µg/stick	31.7	1.74	4	33.9	2.13	4	32.1	3.77	4	26.1	3.65	4
Glycidol	556-52-5	µg/stick	5.44	0.268	4	6.07	0.307	4	5.69	0.333	4	2.41	0.278	4

Legend: SD – standard deviation; n – sample size

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2.1. Analytical method for determination of 3-Chloro-1,2-propandiol (3-MCPD) compound in aerosol generated by HCI regime

Note: Results are expressed as µg/stick for *IQOS* System and µg/cigarette for 3R4F.

Aerosol from a smoking machine is collected using a Cambridge Filter Pad (CFP) and two serially connected impingers, each containing 10 mL of extraction solution (dichloromethane/methanol 80:20 vol/vol) with the stable isotope-labeled internal standard (ISTD) isophorone-d_8 and retention index marker (RIM) compounds (Methyl hexanoate, Methyl decanoate-d_{19} and Methyl tetradecanoate-d_{27}). Impingers are cooled at approximatively -78°C. After the aerosol collection, the pad was extracted with the 20 mL from the two micro-impingers. An aliquot is transferred into a fresh pyrex tube and sodium sulfate added. Dried extract samples are analyzed by gas chromatography with high resolution mass spectrometry detection (GC-HRAM-TOFMS).

Samples are conditioned at least 48h at target conditions of 22 ± 1 °C and a relative humidity of 60 ± 3%, before being used for aerosol generation.

Four replicates were performed by accumulating five sticks per replicate.

The equipment and conditions are described in chapters 2.1.2.1, 2.1.2.2 and 2.1.2.3.

Preceding the analysis of each batch, calibration is performed according to the details provided in chapter 2.1.3. Each analytical sequence consists of a reference run, followed by a number of sample runs, and is terminated by three standard solutions with a low, medium and high concentration to validate the results and verify the calibration (requirement: deviation of not more than ± 20% from the theoretical value).

2.1.1. *Preparation of Solutions*

2.1.1.1. Calibration Solutions

Ten standard (STD) solutions containing different concentrations of the target compound and fixed concentrations of internal standards are prepared in extraction solution (dichloromethane/methanol 80:20 vol/vol) containing the stable isotope-labeled internal standard (ISTD) isophorone-d_8 and retention index marker (RIM) compounds (Methyl hexanoate, Methyl decanoate-d_{19} and Methyl tetradecanoate-d_{27}). The ranges of concentrations cover the ranges relevant for analysis and are provided in Table 12.

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Table 12: Calibration Standard Ranges

	Compound	Calibration Standard Range
Target Compound	3-MCPD	0.056 – 44.461 µg/mL
Internal Standards	Isophorone-d_8	2.22 µg/mL
RIM_Methyl hexanoate	Methyl hexanoate	2.21 µg/mL
RIM_Methyl decanoate-d_{19}	Methyl decanoate-d_{19}	2.15 µg/mL
RIM_Methyl tetradecanoate-d_{27}	Methyl tetradecanoate-d_{27}	2.09 µg/mL

2.1.2. *Experimental Conditions*

2.1.2.1. Equipment

Gas chromatograph: A suitable GC with high resolution mass spectrometry detection HRAM-TOFMS and data acquisition software

Capillary column: Agilent DB-FFAP, 30m × 0.25mm × 0.25µm film thickness or equivalent

Pre-Column: Agilent DB-FFAP, 1m × 0.25mm × 0.25µm film thickness or equivalent

2.1.2.2. Chromatographic Conditions

Injector: Cool-on column, track-oven mode

Injection: On-column

Injection volume: 0.1 µL

Carrier gas: Helium, constant flow (1.0 mL/min)

Temperature program: 40°C, hold 2 min
Heating to 250°C, 15°C/min, hold 5 min

2.1.2.3. Mass Spectrometer Settings

Acquisition delay: 240 s

Mass range: 35-300 u

Mass resolution: 25.000

Data acquisition rate: 10 spectra/s

Detector voltage: 1450 – 2000 V

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Detector offset: 150 V

Extraction frequency: 2 kHz

Electron energy: -70 V

Emission current: 1.0 mA

Ion source temperature: 230°C

2.1.3. *Calibration*

Calibration is performed with internal standard solutions for each target compound and the concentration of internal standards listed in Table 12. A ratio of compound to the internal standard is determined and a quadratic regression model is applied using 1/x weighing factor.

$$\frac{A_a}{A_{iStd}} = q \times C_a^2 + p \times C_a + b$$

where

A_a area of target analyte

A_{istd} area of internal standard

C_a concentration of target analyte

Calibration is considered valid if a coefficient of determination of $r^2 > 0.99$ is obtained and the individual data points do not deviate by more than ± 15% from their theoretical value (20% for the lowest concentration).

2.1.4. *Retention Index*

Typical retention index for the compound, internal standards and retention index markers are provided in Table 13.

Table 13: Typical Retention Index

Retention Index	
3-MCPD	1458.0
Isophorone-d_8	1030.0
Methyl hexanoate	600.0
Methyl decanoate-d_{19}	1000.0
Methyl tetra decanoate-d_{27}	1400.0

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2.2. Partial validation of the analytical method for determination of 3-Chloro-1,2-propandiol (3-MCPD) compound in aerosol generated by HCI regime

The performance of this method has only been tested for selectivity, recovery, intermediate precision and robustness. This method has been developed for research specific topics and has not been fully validated.

2.2.1. *Recovery*

Recovery experiments have been performed by adding defined amounts of the analyte at 3 levels (low, medium, high) to sample extracts of 3R4F cigarette smoke and *IQOS* aerosol. Results are provided in Table 14.

Table 14: Summary of Recovery experiments

Test Item	Concentration unfortified	Added concentration (µg/item)	Mean Recovery (%)	Range (%)
3R4F	5.93 (µg/cigarette)	1.32	113.0	104.9 – 118.7
		12.10	116.2	110.0 – 123.4
		51.88	113.8	108.9 – 117.7
THSR*	9.94 (µg/stick)	5.19	110.6	103.3 – 117.2
		10.38	111.9	104.5 – 117.6
		51.88	112.5	109.0 – 117.0

Note: * Tobacco Heating System (*IQOS* System) with regular tobacco sticks

2.2.2. *Calibration Curve*

The sample series for the recovery experiments have been split into 2 measure sequences, each sequence was quantified with 2 calibration curves (start of series and end of series). For both calibration series no linear curve FIT could be obtained, indicative for significant interactions between analyte and analytical system (e. g due to strong adsorptive effects), see Figure 1 and Figure 2.

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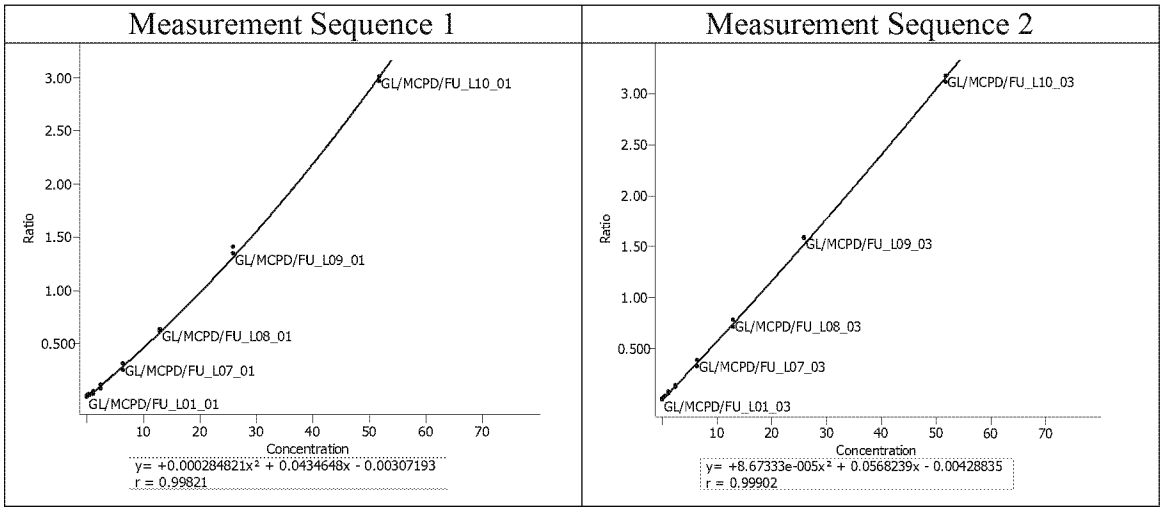


Figure 1: Calibration curves for 3-MCPD obtained for the recovery measurement experiment

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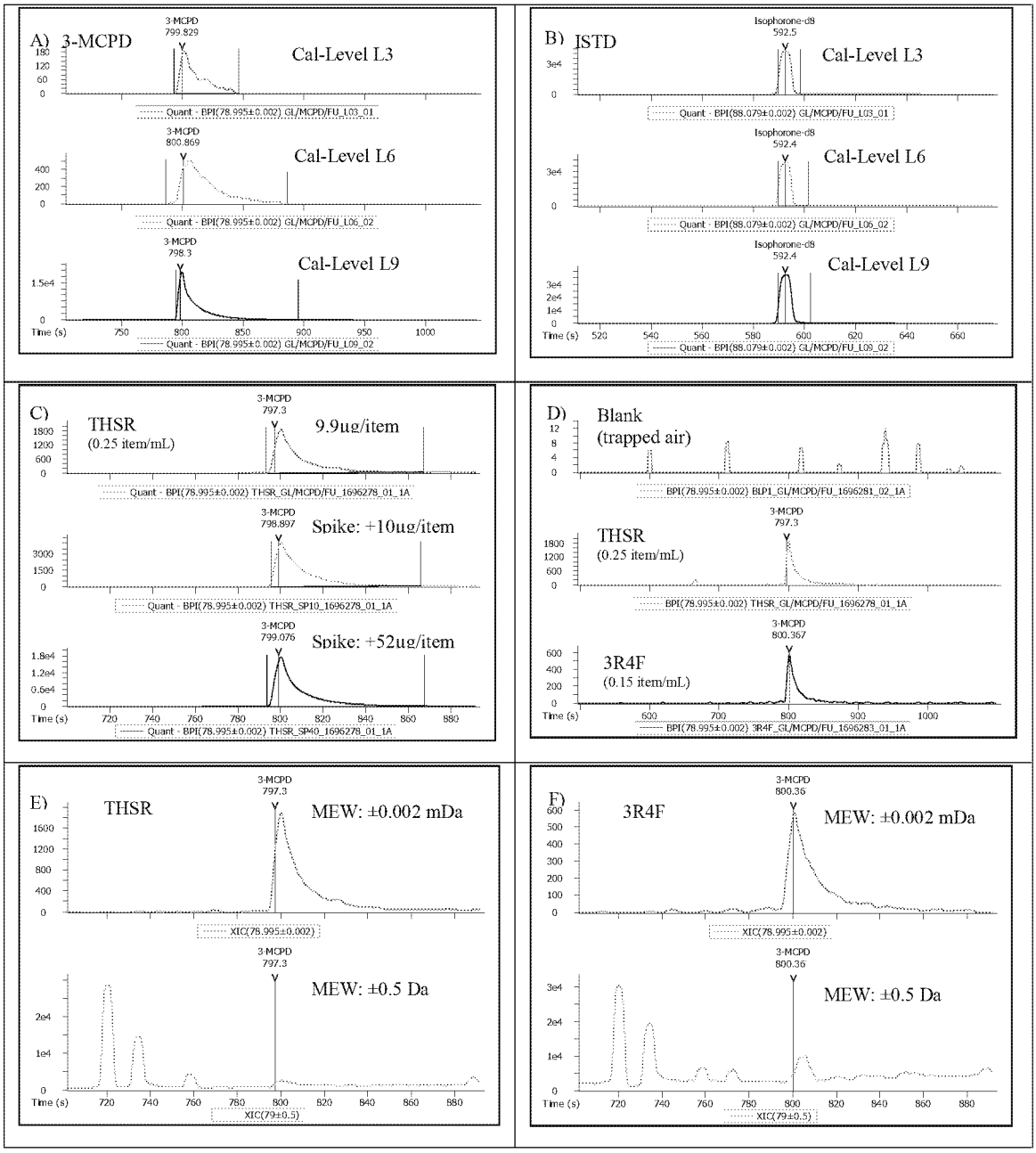


Figure 2: Examples of extracted ion chromatograms, A) 3-MCPD in calibration solutions level 3, 6 and 9, B) internal standard isophorone-d8 in same calibration solutions, C) recovery experiment for THSR, D) samples: air trapped blank, THSR and 3R4F, E) quantitation ion extracted with mass extraction window (MEW) ±0.002mDa compared with ±0.5Da (unit mass resolution) for THSR, F) for 3R4F

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2.2.3. *Quality Control Samples*

Several QC samples have been measured for the recovery experiment for which all passed, see Table 15.

Table 15: Quality Control Samples (QCs) for recovery experiment measurement series

QCs	Theor. Conc. [µg/mL]	Exp. Conc. [µg/mL]	Accuracy [%]	AVG Accuracy [%]	SE [%]	Passed Y/N
QC1_01	0.324	0.30	92.6	106.0	9.9	Y
QC1_02	0.324	0.32	98.8			Y
QC1_03	0.324	0.34	104.9			Y
QC1_04	0.324	0.34	104.9			Y
QC1_05	0.324	0.38	117.3			Y
QC1_06	0.324	0.38	117.3			Y
QC2_01	2.594	2.59	99.8	104.2	9.1	Y
QC2_02	2.594	2.74	105.6			Y
QC2_03	2.594	2.29	88.3			Y
QC2_04	2.594	2.79	107.6			Y
QC2_05	2.594	2.94	113.3			Y
QC2_06	2.594	2.87	110.6			Y
QC3_01	25.938	24.37	94.0	100.8	4.6	Y
QC3_02	25.938	27.10	104.5			Y
QC3_03	25.938	25.72	99.2			Y
QC3_04	25.938	25.48	98.2			Y
QC3_05	25.938	26.45	102.0			Y
QC3_06	25.938	27.70	106.8			Y

2.2.4. *Accuracy and Precision*

2.2.4.1. Intermediate precision

Intermediate precision was estimated by four independent smoke/aerosol generation under Health Canada Intense (HCI) smoking conditions. Results are provided in Table 16.

Table 16: Intermediate precision

3R4F			THS		
Mean (µg/cigarette)	IP (%)	IR (%)	Mean (µg/stick)	IP (%)	IR (%)
5.93	6.2	6.7	9.94	13.3	7.2

Legend: IP - intermediate precision; IR - injection reproducibility

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2.3. Analytical method for determination of Glycidol, Furfural and 2-Furanmethanol compounds in aerosol generated by HCI regime

Notes: - The method also quantitates other compounds such as carbon disulfide, acetol, diacetyl, caprolactam, furan, 2,3-pentanedione and 5-(hydroxymethyl)furfural.

- Results are expressed as µg/stick for *IQOS* System.

Aerosol from a smoking machine is collected using a Cambridge Filter Pad (CFP) and two serially connected impingers, each containing 10 mL of extraction solution (ethyl acetate/methanol 95/5% vol/vol), keeping the first impinger at 0°C and the second at -75°C ± 5°C. After the aerosol collection, the pad was extracted with the 20 mL from the two micro impingers. An aliquot of 250 µL of the solution is transferred to a vial, diluted with further 750 µL of the extraction solution (ethyl acetate/methanol 95/5% vol/vol) and then spiked with 100 µL of the internal standards solution (Benzene-D6, Styrene-D8 and Phenol-D6). Samples are analyzed gas chromatography - mass spectrometry (GC-MS) operating under Selective Ion Monitoring (SIM).

The samples are conditioned at least 48h at target conditions of 22 ± 1 °C and a relative humidity of 60 ± 3%, before being used for aerosol generation.

Four replicates were performed by accumulating five sticks per replicate.

The equipment and conditions are described in chapters 2.3.2.1, 2.3.2.2 and 2.3.2.3.

Preceding the analysis of each batch, calibration is performed according to the details given in chapter 2.1.3. Typically, four sequences of measurement are performed per batch. Each sequence consists of a reference run, followed by a number of sample runs, and is terminated by a standard solution with a medium concentration to validate the results and verify the calibration (requirement: deviation of not more than ± 15% from the theoretical value).

2.3.1. *Preparation of Solutions*

2.3.1.1. Calibration Solutions

Standard (STD) solutions containing different concentrations of each target compound and fixed concentrations of internal standards are prepared in extraction solution (ethyl acetate/methanol 95/5% vol/vol). The ranges of concentrations cover the ranges relevant for analysis and are provided in Table 17.

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Table 17: Calibration Standard Ranges

	Compound	Calibration Standard Range
Target Compounds	Glycidol	0.200 µg/mL – 18.280 µg/mL
	Furfural	0.020 µg/mL – 9.758 µg/mL
	2-Furanmethanol	0.020 µg/mL – 9.757 µg/mL
Internal Standard	Phenol-D6	5.0 µg/mL

2.3.2. *Experimental Conditions*

2.3.2.1. Equipment

Gas chromatograph: A suitable GC with a MS detector and data acquisition software

Capillary column: Agilent DB-FFAP, 30m × 0.25mm × 0.25µm film thickness or equivalent

2.3.2.2. Chromatographic Conditions

Injection temperature: 250°C

Injection volume: 1.0 µL

Carrier gas: Helium, split injection (1:20)

Temperature program: 35°C, hold 2.0 min
Heating to 200°C, 10°C/min, hold 2 min
Heating to 250°C, 30°C/min, hold 7 min

2.3.2.3. Mass Spectrometer Settings

MS Quad temperature: 150°C

Ion source temperature: 230°C

Acquisition type: EI

2.3.3. *Calibration*

Calibration is performed with STD solutions for each target compound and the concentration of internal standards listed in Table 17. A ratio of each compound to the internal standard is determined and a linear regression model is applied using 1/x weighing factor:

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$$\frac{A_a}{A_{ISTD}} = b + pC_a$$

where

A_a area of target analyte

A_{ISTD} area of corresponding internal standard

C_a concentration of target analyte

b intercept

p slope

Calibration is considered valid if a coefficient of determination of $r^2 > 0.995$ is obtained and the individual data points do not deviate by more than ± 10% from their theoretical value (15% for the lowest concentration).

2.3.4. *Example Chromatogram*

An example chromatogram of the highest standard is provided in Figure 3.

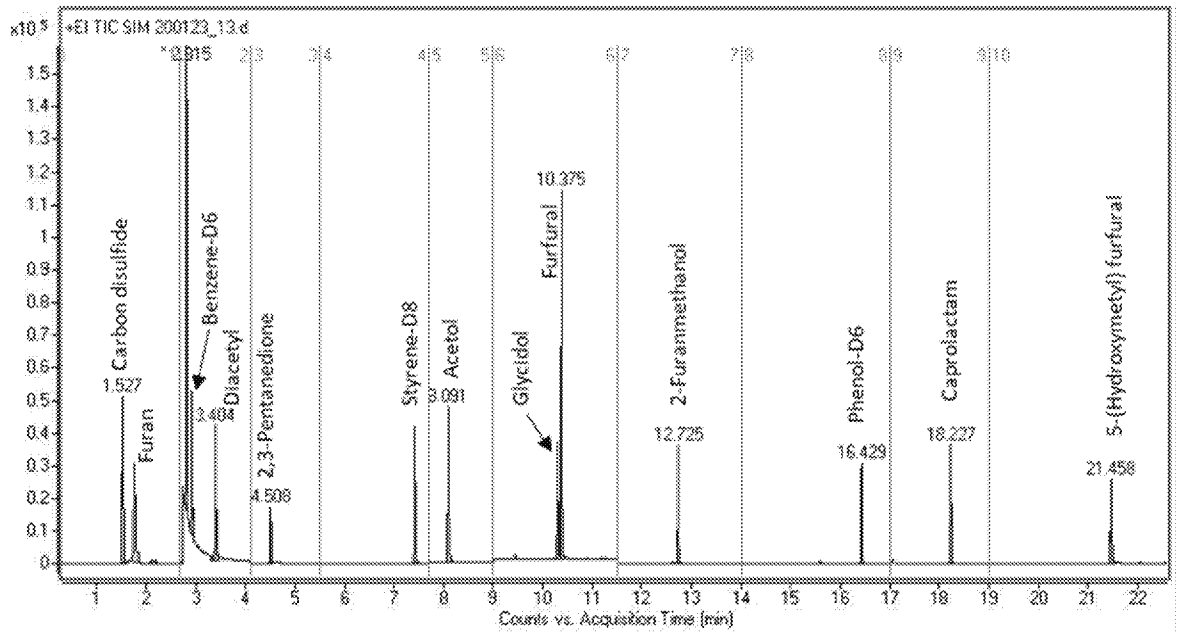


Figure 3: Example Chromatogram

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2.3.5. *Retention Times*

Typical retention times for the compounds and internal standards are provided in Table 18.

Table 18: Typical Retention Times for Compounds and Internal Standards (Minutes)

Compounds		Internal Standard	
Glycidol	10.2 min	Phenol-D6	16.3 min
Furfural	10.3 min		
2-Furanmethanol	12.6 min		

2.3.6. *System Suitability*

The lowest standard is used to assess the instrumental sensitivity (peak response), peak resolution (full peak width at half maximum (FWHM)) and peak tailing (peak symmetry). The acceptance criteria are provided in Table 19.

Table 19: System Suitability Acceptance Criteria

Parameter	Acetol	Furfural
Min area (µv*min)	10	83
FWHM (min)	$0.022 \leq x \leq 0.035$	N/A
Symmetry	$0.6 \leq x \leq 2.6$	$0.7 \leq x \leq 1.8$

Legend: N/A - Not Applicable

2.4. Validation of the analytical method for determination of Glycidol, Furfural and 2-Furanmethanol compounds in aerosol generated by HCI regime

2.4.1. *Specificity (Selectivity)*

The selectivity of the present method was determined by the combination of the following elements during development:

- Chromatographic separation: the target compound peaks in unknown samples must have the same retention times as the corresponding compounds in calibration standards.
- Mass spectrometric detection: the use of Single Ion Monitoring (SIM) mode requires that the detector signal of the target compound is associated with an ion m/z corresponding to a specific fragment.

These two conditions combined provide sufficient evidence to positively assign a target compound, thereby ensuring adequate method selectivity.

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The selectivity of the Internal Standard (ISTD) Phenol-D6 was evaluated in the solvent by comparing blank without ISTD to blank with ISTD, in the smoked blank by comparing smoked blank without ISTD to smoked blank with ISTD and in the matrix by comparing matrix without ISTD to matrix with ISTD. Area response for Internal Standard in blank, smoked blank and matrix without ISTD was shown to be lower than 5% when compared to blank, smoked blank and matrix with ISTD.

The selectivity of the analytes (glycidol, furfural and 2-furanmethanol) was evaluated in the solvent and in the smoked blank by comparing solvent and smoked blank with ISTD to the lowest calibration level of the analyte with ISTD. The concentration of target compounds in the solvent was shown to be lower than 20% when compared to first calibration level concentration and lower than 20% for glycidol and furfural in the smoked blank. A higher selectivity was observed for 2-furanmethanol with a value of 42% instead of 20%. By using the same quality of solvent (same batch) for standards and samples, the higher selectivity for 2-furanmethanol was compensated since a contribution of 2-furanmethanol in the extraction solution was noticed. For this reason, the higher value of 42% for 2-furanmethanol was considered as non-critical and no impact on the accuracy for 2-furanmethanol

The selectivity of target compounds in matrix extracts was evaluated by adding four different amounts of spiking solution to the matrix extract. The addition of different amounts of spiking solution to the matrix extract resulted in an increase of the area response at specific retention time and corresponding transition for glycidol, furfural and 2-furanmethanol.

The selectivity of target compounds in the matrix was evaluated by comparing the response ratio for the qualifier to quantifier ion in the matrix with the response ratio obtained in standards. The response ratio for the qualifier to quantifier ion in the matrix for all compounds was within ± 25% of the response ratio in standards.

2.4.2. *Linearity*

The linearity of the response functions was demonstrated for the range of concentrations spanned by the calibration solutions (Table 20). The deviation between the determined concentrations and the back calculated concentrations (residuals) was within ±15% for the lowest calibration level and within ± 10% for all other calibration levels, for at least nine out of ten standard levels for glycidol and eleven for furfural and 2-furanmethanol. As no curvature was observed, a linear regression model with a weighting factor 1/x was selected for glycidol furfural and 2-furanmethanol. Coefficients of determination R^2 were found higher than 0.995 for all compounds and calibration curves.

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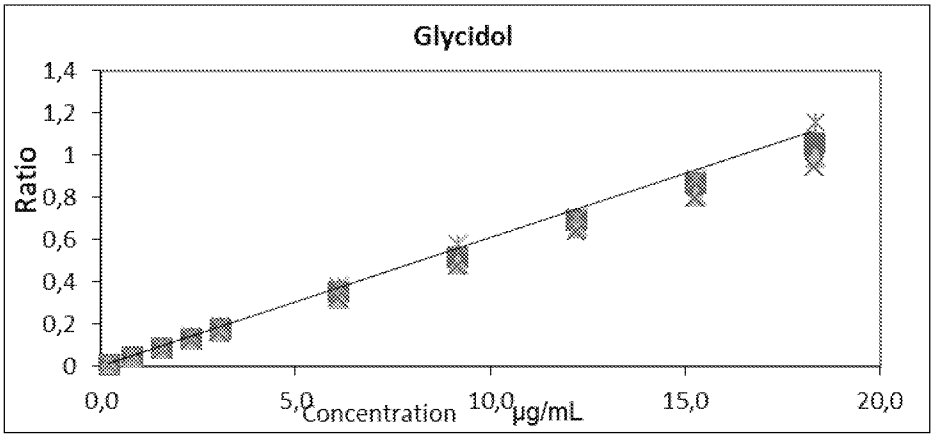


Figure 4: Calibration Curve for Glycidol, Linear using 1/x Weighting Factor

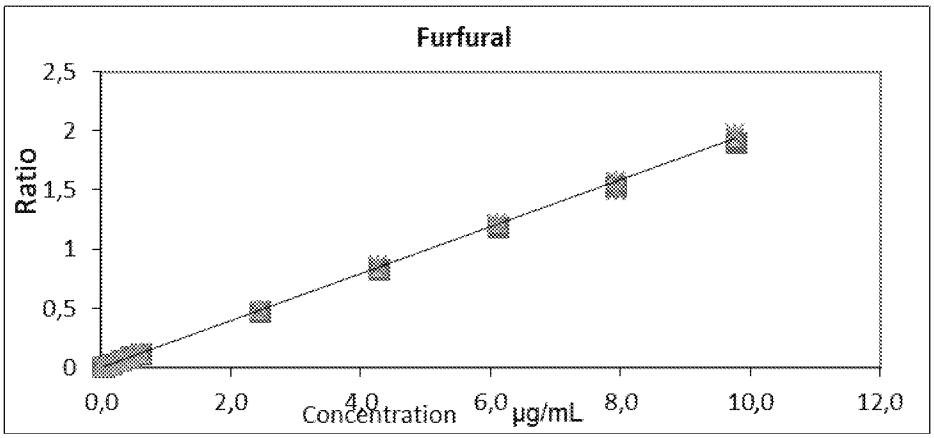


Figure 5: Calibration Curve for Furfural, Linear using 1/x Weighting Factor

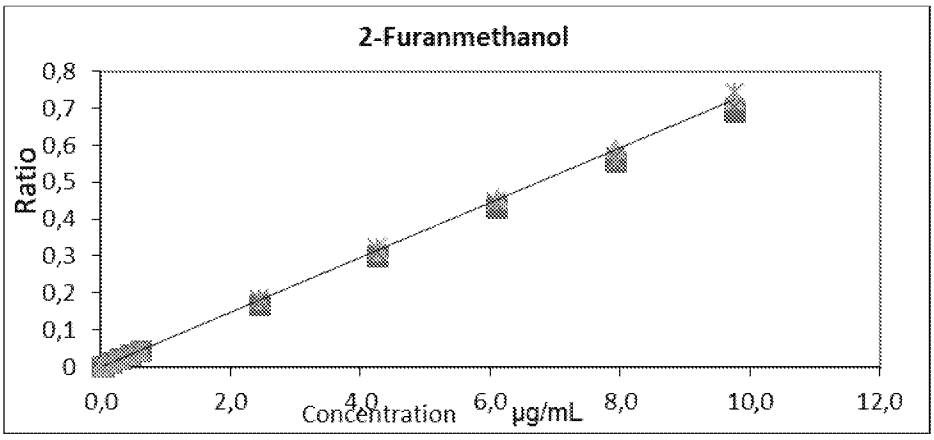


Figure 6: Calibration Curve for 2-Furanmethanol, Linear Using 1/x Weighting Factor

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2.4.2.1. Calibration Curve Parameters

Calibration curve parameters using the selected regression model (linear regression with 1/concentration weighing) were evaluated. The slope, intercept, coefficient of variation and residual sum of square for each compound are provided in Table 20. The acceptance criteria were met for all compounds.

Table 20: Regression parameters under intermediate precision conditions (n = 10×5 = 50 for glycidol and n = 11×5 = 55 for fufural and 2-furanmethanol)

Glycidol						
Series	Tested Range	Regression model, Weighting factor	Intercept	Slope	R^2	SS
1	0.2 - 18.3 µg/mL	Linear, 1/x weighting	6.00E-04	5.44E-02	0.9999	0.1674
2			1.00E-04	5.74E-02	0.9999	0.1867
3			-8.00E-04	5.33E-02	0.9999	0.1611
4			7.00E-04	5.23E-02	0.9999	0.1545
5			1.35E-05	6.08E-02	0.9982	0.2101
Furfural						
Series	Tested Range	Regression model, Weighting factor	Intercept	Slope	R^2	SS
1	0.02 – 9.76 µg/mL	Linear, 1/x weighting	1.46E-05	1.95E-01	0.9999	1.1660
2			1.00E-04	1.94E-01	1.0000	1.1585
3			-3.00E-04	2.01E-01	1.0000	1.2375
4			1.00E-04	1.99E-01	1.0000	1.2178
5			-1.00E-04	1.98E-01	0.9989	1.2102
2-Furanmethanol						
Series	Tested Range	Regression model, Weighting factor	Intercept	Slope	R^2	SS
1	0.02 – 9.76 µg/mL	Linear, 1/x weighting	2.00E-04	7.09E-02	1.0000	0.1545
2			3.00E-04	7.05E-02	0.9999	0.1527
3			4.00E-04	7.40E-02	0.9999	0.1686
4			2.39E-05	7.22E-02	1.0000	0.1604
5			2.00E-04	7.41E-02	0.9989	0.1688

Legend: r^2 - coefficient of determination

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2.4.3. *Range*

The working range is the interval between the upper and lower levels that have been demonstrated to be determined using the accuracy profiles methodology (see Figure 7 for an example).

The accuracy profile is based on a total of 16 replicates per level (4 analytical days × 4 replicates). Two concentration levels lower than the nominal content (dilution) and four concentration levels higher than the nominal content (spiked) were prepared every analytical day from the homogenized aerosol extract.

The intersection point of the beta-expectation tolerance intervals with the acceptance intervals corresponds to the smallest quantity measurable with the desired accuracy. The corresponding concentration of the intersection point represents the lower working range limit (LWRL) in the matrix.

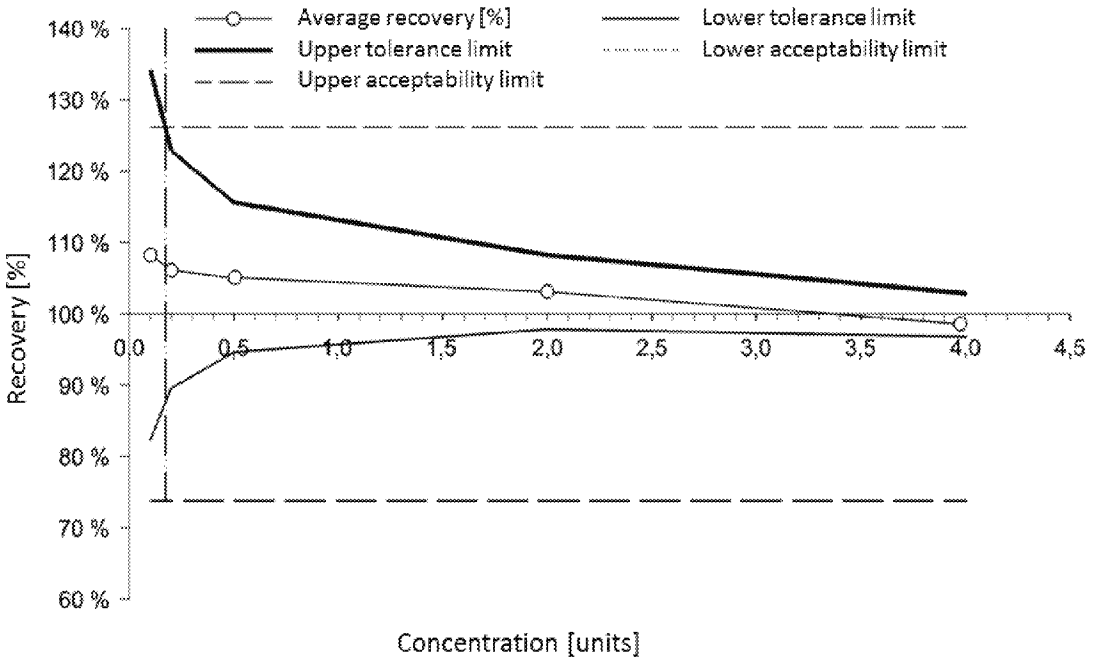


Figure 7: Example of an accuracy profile

Beta-tolerance was set at 80 % and the acceptance intervals limits were set at 75-125 % for all the compounds.

The working ranges for *IQOS* System for the individual compounds are provided in Table 21.

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Table 21: Working Range

Compound	Working Range - *IQOS* (µg/stick)
Glycidol	(b) (4)
Furfural	
2-Furanmethanol	

2.4.4. *Accuracy and Precision*

2.4.4.1. Repeatability

Results for instrumental repeatability limits for GC-MS Lab ID 14630 obtained from six injections of the same aerosol extract are provided in Table 22. The same sequence was injected on the same day under the same operating conditions.

Table 22: Within-Instrument Repeatability (Same Day, n = 6)

	IQOS (µg/stick)			
	Mean	SD	CV	r
Glycidol	8.03	0.640	8.0 %	1.808
Furfural	28.0	0.669	2.4 %	1.888
2-Furanmethanol	29.3	0.357	1.2 %	1.008

Legend: SD - standard deviation; CV - Coefficient of variation; r - correlation coefficient

The repeatability measures the intra-assay precision under the same operating conditions during a short time period. Repeatability was assessed by evaluation of the intra-assay precision of the method including the aerosol collection under the same operating conditions on four different days (four replicates per days). The results are given in Table 23.

Table 23: Repeatability Limit in the Aerosol Matrices (n = 16)

	IQOS (µg/stick)			
	Mean	SD	CV	r
Glycidol	6.12	0.627	10.2 %	1.77
Furfural	34.8	1.24	3.6 %	3.50
2-Furanmethanol	34.7	3.07	8.8 %	8.68

Legend: SD - standard deviation; CV - Coefficient of variation; r - correlation coefficient

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2.4.4.2. Intermediate Precision Limit

The intermediate precision limit was evaluated by injecting the aerosol from each smoking replicate. The individual aerosol replicates were collected on different days. The intermediate precision limits are provided in Table 24.

Table 24: Intermediate Precision Limit (n = 16)

	IQOS (µg/stick)			
	Mean	SD	CV	IP
Glycidol	6.12	0.627	10.2 %	1.77
Furfural	34.8	1.52	4.4 %	4.29
2-Furanmethanol	34.7	3.07	8.8 %	8.68

Legend: SD - standard deviation; CV - Coefficient of variation; IP - intermediate precision

2.4.4.3. Reproducibility

No other laboratory is currently using this method.

2.4.4.4. Combined Uncertainty

The uncertainties (either calculated or estimated) of each identified source of uncertainty in the analytical process were combined through addition of variances to one single global uncertainty (Table 25).

Table 25: Expanded Combined Uncertainty (k=2, 95%)

Compound	Combined Uncertainty
Glycidol	20.8-22.3%
Furfural	8.9-11.6%
2-Furanmethanol	17.8-20.2%

2.4.5. *Limit of Detection (LOD)/Limit of Quantitation (LOQ)*

The limit of detection (LOD) and lower limit of quantitation (LLOQ) are calculated in terms of the standard deviation of the lowest calibration level as determined during validation,

$$LOD = 3 \cdot std_{level1}$$

$$LOQ = 10 \cdot std_{level1}$$

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They were found to be lower than the concentration of the lowest calibration level for all compounds. Detailed results are provided in Table 26.

Table 26: Limits of Detection and Quantitation

	IQOS (µg/stick)		
	LOD	LLOQ	ULOQ
Glycidol	0.218	0.728	293
Furfural	0.0229	0.0763	156
2-Furanmethanol	0.0554	0.185	156

Legend: ULOQ - upper limit of quantitation (highest standard level)

2.4.6. *Robustness*

2.4.6.1. Trapping efficiency

The robustness of the method with respect to trapping efficiency was evaluated by collecting the aerosol with three impingers connected behind the Cambridge filter pad. The first impinger was cooled down at 0°C whereas the second and third impingers were cooled down at -75°C. extracting for 15, 30 and 45 minutes where 30 minutes was considered the reference time. The trapping efficiency was found higher than 95 % with the two impingers behind the Cambridge filter pad at 0°C and -75°C respectively. For this reason, two impingers are found to be sufficient.

2.4.6.2. GC leak simulation

Leak simulation on the GC-MS by decreasing the carrier gas flow rate was assessed. A slight decrease of the flow rate of 0.1 mL/min lower than the reference parameter does not impact the quantification.

2.4.7. *Stability*

2.4.7.1. Stability of internal standard stock solution in freezer (-20 °C)

The internal standard stock solution is stable 57 days when kept in the freezer.

2.4.7.2. Stability of intermediate internal standard solution (mix) in freezer (-20 °C)

The intermediate internal standard solution is stable 57 days when kept in the freezer.

2.4.7.3. Stability of individual standard stock solutions in freezer (-20 °C)

The individual standard stock solutions are stable 57 days when kept in the freezer.

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2.4.7.4. Stability of intermediate standard stock solution A and B in freezer (-20 °C)

The intermediate standard stock solution A and B are stable 49 days when kept in the freezer.

2.4.7.5. Stability of calibration standard solutions in freezer (-20 °C)

The calibration standard solutions (level 1 to 11) are stable 7 days when kept in the freezer.

2.4.7.6. Stability of aerosol collection replicates after aerosol collection, before further sample treatment

The aerosol sample after the aerosol collection is stable 4 hours at room temperature before further sample treatment.

2.4.7.7. Stability of aerosol extracts in freezer (-20 °C)

The aerosol extracts is stable 28 days when kept refrigerated in the freezer.

2.4.7.8. Stability of standard solutions and samples in pierced vials on the auto-sampler

Standard solutions and samples are not stable in pierced vials on the autosampler at room temperature.

2.4.7.9. Stability of standard solutions and samples in unpierced vials on the auto-sampler

Standard solutions and samples are stable up to 70 hours in unpierced vials on the autosampler at room temperature.

2.4.7.10. Stability of extraction solution in the fridge

No stability study was performed for the extraction solution. The stability was evaluated indirectly with the stability of working standards (same solution kept in the fridge). The extraction solutions is stable 7 days when kept in the fridge.

3. DSD TESTING (PROJECT CODE 1219-552 (Q19494R1))

Droplet size distribution testing was performed by independent laboratory Enthalpy Analytical, LLC. The testing laboratory is accredited by A2LA to comply with ISO/IEC 17025:2017.

Table 27: Testing laboratory details

Laboratory name	Enthalpy Analytical, LLC
Address	800-1 Capitola Drive, Durham, NC 27713-4385, USA
Telephone no.	(b) (6)
Fax no.	+1 (919) 850-9012
E-mail of Contact Person:	(b) (6)

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Testing was performed on the U.S. commercial version of the *IQOS* 3 System with modified firmware and on Authorized *IQOS* System using reference *HeatSticks* (also referred as "monitor" *HeatSticks*). Same as for PMI-58 testing, the firmware on the *IQOS* 3 System was modified to prevent the System of selecting between two heating profiles based on the detected moisture content in the *HeatSticks*. Therefore two comparisons were conducted. In the first comparison *IQOS* 3 System was forced to use "standard" heating profile (C28 profile), while in the second comparison the device was forced to use "alternative" heating profile (C28-6 profile), **(b) (4)** **(b) (4)** The sample details are summarized in the table below.

Table 28: Sample information

Sample Type	Sample ID / Batch no.	Manufacturing date
IQOS 3 System (forced C28 profile)	B-79858	December 20, 2019
IQOS 3 System (forced C28-6 profile)	B-79852	December 18, 2019
IQOS 2.4 System	B-79883	January 22, 2020
P1M2 monitor *HeatSticks*	IC2911171	May 23, 2017

Prior to testing, the *HeatSticks* were kept under the ambient conditions.

Testing was performed using intense aerosol-generating regime – Health Canada Intense (HCI) regime (Table 29) as this regime is considered as the "worst case scenario". However as the *HeatSticks* do not have any ventilation holes, no vent blocking was applied.

Table 29: Parameters of HCI aerosol-generating regime

	Health Canada Intense
Puff volume (ml)	55
Interval (s)	30
Duration (s)	2
Vents*	"fully blocked"
Note: * Health Canada 100% vent blocking method	

Samples from three devices and 9 replicates were analyzed on cascade impactor using validated analytical method (ENT520, version 5.0). For additional information regarding the analytical method please refer to the TPMF no. MF0000276. Corresponding Letter of Authorization (LoA) is provided in section 1.3 *Letters of Authorization*.

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Table 30: DSD testing results measured under the HCI regime for both heating profiles of *IQOS* 3 System and Authorized *IQOS* System using same monitor *HeatSticks*

Replicate	*IQOS* 3 System (C28) + monitor *HeatStick*		*IQOS* 3 System (C28-6) + monitor *HeatStick*		*IQOS* 2.4 System + monitor *HeatStick*	
	MMAD [µm]	GSD [-]	MMAD [µm]	GSD [-]	MMAD [µm]	GSD [-]
1	0.644	1.55	0.821	1.44	0.859	2.12
2	0.756	1.36	0.71	1.38	0.84	1.74
3	0.667	1.50	0.775	1.81	0.971	1.87
4	0.795	1.37	0.771	1.34	0.662	1.79
5	0.795	1.68	0.811	1.50	0.599	1.78
6	0.71	1.46	0.704	1.44	0.789	1.58
7	0.731	1.43	0.756	1.41	0.719	1.48
8	0.773	1.63	0.766	1.52	0.662	1.52
9	0.663	1.52	0.742	1.38	0.671	1.51
Mean±SD	0.726±0.0581	1.5±0.107	0.762±0.0397	1.47±0.139	0.752±0.12	1.71±0.209

For Enthalpy's study report with datasets please refer to module 7 *Scientific Studies and Analyses*.

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