Programmatic Environmental Assessment for Marketing Orders for New Heated Tobacco Products Manufactured by Philip Morris Products S.A.

Prepared by Center for Tobacco Products U.S. Food and Drug Administration

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1. Introduction

1.1 Background

On December 14, 2020, Philip Morris Products S.A submitted supplemental premarket tobacco product applications (sPMTAs) for heated tobacco products (HTP) broadly termed "IQOS HeatSticks" in this document. In the sPMTAs, the applicant requested the U.S. Food & Drug Administration to issue marketing orders under section 910(b)(1) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) (Public Law 111-31).

The new IQOS HeatSticks differ from the authorized IQOS HeatSticks in slight changes in the formulation of the cast leaf tobacco substrate, and modifications to mouth piece filter, paper adhesives, and flavor profiles (Confidential Appendix 1).

This document reviews the potential environmental impacts from marketing the IQOS HeatSticks in the United States and from the no-action alternative of the Agency not issuing marketing orders for the IQOS HeatSticks.

1.2 Applicant and Manufacturer Information

Applicant Name:	Philip Morris Products S.A.
Applicant Address:	Quai Jeanrenaud 3, 2000 Neuchatel, Switzerland
Manufacturer Name:	Philip Morris Products S.A. Philip Morris Manufacturing & Technology Bologna S.p.A.
Product Manufacturing Location:	Quai Jeanrenaud 3, 2000 Neuchatel, Switzerland Via Piemonte 1540069 Zola PredosaBologna, Italy

1.3 Product Information

New Product Names and Submission Tracking Numbers (STNs)

STN New Product	New Product Name	Authorized Product
PM0004337 – PD1	Marlboro Sienna HeatSticks	Marlboro HeatSticks
PM0004337 – PD2	Marlboro Bronze HeatSticks	Marlboro HeatSticks

Product Identification

Product Category	Heated Tobacco Product (HTP)
Product Subcategory	HTP Consumable
Product Number per Retail Unit	20 HeatSticks per pack
Product Package	The packaging material consists of an inner frame, an inner liner and a hinge lid. The inner liner is made of white paper. The other materials comprise paperboard, inks/varnishes, lacquer, adhesives, and cardboard.

2. The Need and Purpose for the Proposed Actions

Purpose: The applicant wishes to introduce new IQOS HeatSticks in interstate commerce for commercial distribution in the United States and submitted sPMTAS to the Agency to obtain marketing orders. Upon receipt of an sPMTA, FDA considers the submission, using criteria detailed in section 910(b)(1) of the FD&C Act, to make a finding as to whether a marketing order for the product would be appropriate for the protection of public health.

Need: FDA's responsibility to review a PMTA, make a finding as described in the previous paragraph, and subsequently determine whether or not to issue a marketing order for the tobacco product is a statutory requirement under section 910(b)(1) of the FD&C Act.

3. Proposed Actions and Alternatives

The proposed actions, requested by the applicant, are for FDA to issue marketing orders under the provisions of section 910(b)(1) of the FD&C Act for introduction or delivery for introduction of new IQOS HeatSticks into interstate commerce in the United States after finding the new IQOS HeatSticks would be appropriate for the protection of public health.

The no-action alternative is FDA does not issue marketing orders for the new IQOS HeatSticks. The IQOS HeatSticks would not be marketed in the United States and, for the purposes of the analysis in this programmatic environmental assessment, it is assumed that there would be no changes to the current HTP market and no changes to the current or future use of tobacco products.

4. Potential Environmental Impacts of the Proposed Actions and Alternatives – Manufacturing the New Products

The applicant stated that the manufacturing facilities are in compliance with all the applicable environmental regulations in the countries of manufacture. However, because the facilities are located outside the United States, the environmental impacts associated with manufacturing the new IQOS HeatSticks will not be discussed. The projected first- and fifth-year market volumes are available in Confidential Appendix 3.

5. Potential Environmental Impacts of the Proposed Actions and Alternatives – Use of the New Products

Euromonitor reports show that in 2020, the retail value of heated tobacco products in the United states was approximately 21 million dollars accounting for a miniscule proportion of the tobacco product retail market. The retail value of HTPs is forecasted to grow to approximately 6.1 billion dollars by 2025 (Euromonitor International Ltd, 2021). HTP consumption in the United States to date has been modest compared to cigarettes, with consumption increasing from 12.3 million sticks in 2019 to 41.8 million sticks in 2020 (Euromonitor International Ltd, 2021).

The Agency considered potential impacts to resources in the environment that could be affected by use of the new IQOS HeatSticks and found no significant impacts based on Agency-gathered information and the applicant's submitted information. Included in the information the Agency considered were - (1) potential impacts of the proposed action and no action, from product use discussed in the environmental assessment for the authorized IQOS HeatSticks (Marlboro Amber HeatStick; PM0000424); (2) the changes in the new IQOS HeatSticks in comparison to the authorized IQOS HeatSticks (Confidential Appendix 1); (3) comparison of mainstream aerosol data from the new and the authorized IQOS HeatSticks (Confidential Appendix 2); and (4) the projected market volumes (Confidential Appendix 3) for the first- and fifth year of marketing of the new IQOS HeatSticks.

5.1. Affected Environment

The affected environment includes human and natural environments in the United States because the marketing orders would allow for the new HeatSticks to be sold to consumers in the United States.

5.2. Air Quality

The Agency does not anticipate the release of new chemicals into the environment as a result of use of the new IQOS HeatSticks, relative to chemicals released into the environment due to use of other heated tobacco products already on the market because (1) the new IQOS HeatSticks consists of minor modifications to the authorized IQOS HeatSticks (Confidential Appendix 1); (2) the new IQOS HeatSticks are similar to the authorized IQOS HeatSticks in terms of their chemical composition and constituents in mainstream aerosol emissions (Confidential Appendix 2); (3) the new IQOS HeatSticks are intended to compete with other currently marketed HTPs.

The impacts from use of heated tobacco products include second and thirdhand aerosol exposure. Secondhand aerosol is created when a HTP user exhales mainstream aerosol into the environment (Hirano & Takei, 2020). Thirdhand aerosol is created when a HTP aerosol is inhaled and the chemicals in the vapor, exhaled by the user, deposit on surrounding surfaces. Available evidence indicate that HTP aerosols exposed users and bystanders to toxicants and affected indoor air quality, with potential health implications (Cancelada et al., 2019; Hirano & Takei, 2020; Ruprecht et al., 2017; Simonavicius et al., 2019). However, more research is needed to determine the health implications that secondhand and thirdhand exposure from HTP aerosol has on public and environmental health (Hirano & Takei, 2020, 2020; Ruprecht et al., 2017).

Studies on aerosols of Marlboro HeatSticks showed that *IQOS* aerosols are free from metal emissions, in contrast to combustible cigarettes (Ruprecht et al., 2017). When using the non-mentholated HeatSticks, no systematic increase in the total volatile organic compounds above background concentrations was

observed. Further, airborne compounds measured, other than nicotine, acetaldehyde and glycerin, remained below the reporting limits or at background levels (Mitova et al., 2016).

The applicant submitted a comparison of the aerosol emissions in the new and authorized IQOS HeatSticks (Confidential Appendix 2). Negligible amounts of constituents change in the aerosols generated in the new IQOS HeatSticks compared with the authorized IQOS HeatSticks. Additionally, although there is a reduction in mainstream aerosol harmful and potentially harmful constituents (HPHCs), certain constituents, such as propylene glycol, butyrolactone, pyranone, and 2-furanmethanol, not listed on FDA's HPHC list, had higher levels in IQOS HeatSticks when compared with a reference cigarette (St.Helen et al., 2018).

5.3. Environmental Justice

There are few available studies describing HTP use among Environmental Justice (EJ) populations. National Youth Tobacco Survey data for 2019 and 2020 indicate that HTP product awareness and ever use did not differ by the race/ethnicity of middle school and high school students (Dai, 2020); however, current HTP-use prevalence was higher among Hispanic school students compared to non-Hispanic Whites (Dai, 2020; Gentzke et al., 2020). Among adults, 2019 Tobacco Use Supplement to the Current Population Survey data indicates that HTP product awareness and ever use did not differ based on race/ethnicity, income levels or education attainment (Azagba & Shan, 2021). Overall, these findings do not indicate disproportionately high HTP use prevalence among minorities and low-income groups. Therefore, the agency does not anticipate potential disproportionate environmental impacts on EJ populations from using the new IQOS HeatSticks.

5.4. Impacts from the No-Action Alternative

The environmental impacts of the no-action alternative would not change the existing condition of use of HTP because the authorized IQOS HeatSticks and many similar tobacco products would continue to be used in the United States.

6. Potential Environmental Impacts of the Proposed Actions and Alternatives – Disposal of the New Products

The Agency considered potential impacts to resources in the environment that could be affected by the disposal of the new IQOS HeatSticks and found no significant impacts based on Agency-gathered information and the applicant's submitted information. Included in the information the Agency considered were - (1) potential impacts of the proposed action and no action, from product disposal discussed in the environmental assessment for the authorized IQOS HeatSticks (Marlboro HeatStick; PM0000424); (2) the changes in the new IQOS HeatSticks in comparison to the authorized IQOS HeatSticks (Confidential Appendix 1); (3) comparison of heavy metals measured in the cast leaf of the new and authorized IQOS HeatSticks (Confidential Appendix 4); (4) the projected market volumes for the first- and fifth year of marketing of the new IQOS HeatSticks (Confidential Appendix 3); and (5) results of screening-level assessment of the cumulative acute toxicity risks to aquatic organisms from nicotine and heavy metals of concern in the new and authorized IQOS HeatSticks (Confidential Appendix 5).

6.1. Affected Environment

The affected environment includes human and natural environments in the United States because the marketing orders would allow for the new IQOS HeatSticks to be sold to consumers nationwide who

would dispose of the used products and packaging as municipal solid waste (MSW), recycled material, or litter.

6.2. Air Quality

The Agency does not anticipate disposal of the new IQOS HeatSticks or the packaging material would lead to the release of new or increased chemicals into the air.

Studies describing air quality impacts from disposal of used heatsicks are currently not available. However, similar to cigarette butts, discarded heatstick may emit toxic chemicals such as nicotine into the air (Gong et al., 2017, 2020; Poppendieck et al., 2020). Airborne emissions from cigarette butts after disposal depend on the environmental conditions and the chemicals in the butts (Poppendieck et al., 2020) as well as other factors, such as the cigarette brand, cigarette length, filter material, filler, ingredients in the cigarette, number of puffs, and the mass transfer behavior of combustion products along the cigarette (Gong et al., 2017).

The Agency does not anticipate disposal of the new IQOS HeatSticks or the packaging material would lead to the release of new or increased chemicals into the air. No changes in air quality from disposal of the packaging materials in the new IQOS HeatSticks would be expected because (1) the paper and plastic components of the packages are more likely to be recycled or at least a portion of the packaging waste is likely to be recycled, (2) the packaging materials are commonly used in the United States, and (3) the waste generated due to disposal of the packaging is a minuscule portion of the MSW based on the projected market volume of the new IQOS HeatSticks.

6.3. Biological Resources

The proposed actions are not expected to change the continued existence of any endangered species or result in the destruction or adverse modification of the habitat of any such species, as prohibited under the U.S. Endangered Species Act. Proper disposal of the used new IQOS HeatSticks and packaging into MSW would not affect biological resources. If improper disposal as litter occurs, the new IQOS HeatSticks are not expected to result in new or additional compounds emitted to the environment. Unlike combusted tobacco products, smoldering of used products is not a major concern with disposal of the new IQOS HeatSticks. Therefore, the risk of fires from smoldering tobacco products and associated impacts to natural environments from littering are negligible. The Agency does not anticipate disposal of the new IQOS HeatSticks or the packaging material would lead to significant impacts on biological resources.

6.4. Water Resources and Water Quality

Proper disposal of the used new IQOS HeatSticks and packaging into MSW would not affect water resources and water quality. If improper disposal as litter occurs, the leaching of metals and nicotine poses a concern for potential impacts on aquatic organisms and water resources (Baran et al., 2019; Beutel et al., 2021; Koutela et al., 2020). Toxic compounds in littered HeatSticks can leach out into water, potentially threatening human health and the environment, especially marine ecosystems. Recent literature shows a range of chemical constituents including metals such as chromium and lead leach from used HeatSticks and exhibit high toxicity to certain aquatic organisms (Baran et al., 2019; Koutela et al., 2020).

The Agency conducted a screening-level assessment of the cumulative acute toxicity risks to aquatic organisms from nicotine and heavy metals of concern in the new and authorized IQOS HeatSticks. The agency calculated Risk Quotients (RQ) from estimated aquatic expected environmental concentrations (EEC) of the chemicals of concern and their lowest acute toxicity endpoint values (Confidential Appendix 5). The RQ values are several orders of magnitude lower than the Level of Concern for acute risks (high, restricted use or endangered species) to aquatic animals (US EPA, 2015) (Confidential Appendix 5). Based on the screening-level risk assessment, nicotine and heavy metals in the HeatSticks do not pose risks to aquatic animals. Therefore, no significant impacts on water resources and water quality from the disposal of new IQOS HeatSticks are expected.

6.5. Solid Waste and Hazardous Materials

Like cigarette butts, littered HeatSticks may present environmental effects from heated or unheated tobacco, filter and other polymer components. Used HeatSticks consist of heated tobacco, polymer, paper, and filters containing low-density cellulose acetate similar to conventional cigarettes (Schaller et al., 2016; Smith et al., 2016).

Concentrations of metals leaching out of HeatSticks are similar between unheated and heated tobacco, and less than unused combustible cigarettes (Koutela et al., 2020). Particularly, chromium, arsenic cadmium, mercury, selenium, and lead, listed as hazardous constituents per the Resource Conservation and Recovery Act (40 C.F.R. § 261. Identification and Listing of Hazardous Waste, 2020) are found in the IQOS HeatStick and in negligible concentrations in the leachate from used HeatSticks (Koutela et al., 2020). The Agency anticipates that the potential exposure of heavy metals from the disposal of the new tobacco products would be comparable to the authorized IQOS HeatSticks (Confidential Appendix 4). Additionally, the Agency does not anticipate that new chemicals would be released into the environment as a result of disposal of the new IQOS HeatSticks because (1) the new IQOS HeatSticks consists of minor modifications to the authorized IQOS HeatSticks; (2) the IQOS HeatSticks are intended to compete with other marketed HTPs.

The Agency does not foresee that the introduction of the new IQOS HeatSticks into the U.S. market would notably affect the nationwide waste generated from the use of HTP. The distribution of waste generated due to disposal of the new IQOS HeatSticks and packaging is anticipated to correspond to the pattern of the products use in the United States. Therefore, no significant environmental impacts due to solid waste and hazardous materials introduced from the disposal of new IQOS HeatSticks are expected.

6.6. Socioeconomics and Environmental Justice

The Agency does not anticipate changes in impacts on socioeconomic conditions or environmental justice from disposal of the new IQOS HeatSticks. The waste generated due to disposal of the new IQOS HeatSticks would be handled in the same manner as the waste generated from disposal of other HTP products in the United States. No new emissions or effluents are expected due to disposal of the new IQOS HeatSticks; therefore, there would be no disproportionate impacts on EJ populations.

6.7. Impacts from the No-Action Alternative

The environmental impacts of the no-action alternative would not change the existing condition of disposal of HTP products and their packaging, as the authorized IQOS HeatSticks and many other similar HTP products would continue to be disposed of in the United States.

7. List of Preparers

The following individuals were primarily responsible for preparing and reviewing this programmatic environmental assessment:

Preparer:

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Education: M.S. in Ecology and Ph.D. in Entomology
Experience: Eighteen years in various scientific activities
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Reviewer:

Susana Addo Ntim, Ph.D., Center for Tobacco Products
Education: Ph.D. in Environmental Science
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Expertise: NEPA analysis; fate, transport, and ecotoxicology of new and emerging contaminants; applications and environmental implications of nanotechnology

8. A Listing of Agencies and Persons Consulted

Not applicable.

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CONFIDENTIAL APPENDIX 1: Product Modifications

Component	Authorized HeatSticks	Sienna HeatSticks PM0004337-PD1	Bronze HeatSticks PM0004337-PD2
Total Weight	790 mg/stick	777 mg/stick	777 mg/stick
Tobacco Blend	(b) (4)		
Flavor System *Flavor Name* *Weight Impact*	(b) (4)		
Cast Leaf Tobacco Substrate Formulation *Tobacco* (b) (4) (b) (4) (b) (4)	(b) (4)		
Enhanced Mouth Piece Filter *Plasticizer %* *Weight (Acetate Tow)* *Weight Impact (Plasticizer)*	(b) (4)		
Plug Wrap Paper *Mouth Piece Filter Grammage* *Mouth Piece Filter Thickness* *Mouth Piece Filter Weight* *Poly Lactic Acid Grammage* *Poly Lactic Acid Thickness* *Poly Lactic Acid Weight*	(b) (4)		

CONFIDENTIAL APPENDIX 2: Comparability Aerosol Data

The applicant submitted a comparison of mainstream aerosols generated by the user in the new and authorized IQOS HeatSticks presented in the tables below.

A. Comparison of *Marlboro* Sienna HeatSticks and Amber Authorized HeatSticks

HPHCs/Analytes	***Unit***	***Marlboro Sienna HeatSticks***			***Marlboro Amber HeatSticks ("Authorized HeatSticks")***			***% HPHCs Difference Marlboro Sienna Vs. Marlboro Amber HeatSticks" ("Authorized HeatSticks")***
		Mean	***SD***	***n***	***Mean***	***SD***	***n***	
1,3-Butadiene	µg/cig	0.199	0.0321	9	0.207	0.016	3	-3.86
1-Aminonaphthalene	ng/cig	0.0356	0.007	9	0.0427	0.00513	3	-16.63
2-Aminonaphthalene	ng/cig	<0.012	NA*	9	0.0223	0.00321	3	-46.19
3-Aminobiphenyl	ng/cig	0.00871	0.00176	9	0.007	0.003	3	24.43
4-(Methyl-nitrosamino)-1-(3-pyridyl)-1-	ng/cig	7.09	0.808	9	7.8	0.423	3	-9.10
4-Aminobiphenyl	ng/cig	0.00901	0.00178	9	0.0087	0.0012	3	3.56
Acetaldehyde	µg/cig	214	9.79	9	192	11.6	3	11.46
Acetamide	µg/cig	3.66	0.144	9	2.96	0.134	3	23.65
Acetone	µg/cig	37.7	1.94	9	30.7	1.86	3	22.80
Acrolein	µg/cig	9.62	0.892	9	8.32	0.755	3	15.63
Acrylamide	µg/cig	1.73	0.104	9	1.58	0.0543	3	9.49
Acrylonitrile	µg/cig	0.138	0.0111	9	0.145	0.0112	3	-4.83
Ammonia	µg/cig	12.5	1.04	9	12.2	0.973	3	2.46
Arsenic	ng/cig	<1.2	NA	9	<0.36 (LOD)	NA	3	233.33
Benz[a]anthracene	ng/cig	1.67	0.187	9	2.65	0.0647	3	-36.98
Benzene	µg/cig	0.527	0.012	9	0.452	0.0395	3	16.59

Benzo[a]pyrene	ng/cig	0.656	0.0683	9	0.736	0.0973	3	-10.87
Butyraldehyde	µg/cig	20.6	0.806	9	20.7	1.52	3	-0.48
Cadmium	ng/cig	<0.09	NA	9	<0.28 (LOQ)	NA	3	-67.86
Carbon monoxide (CO)	mg/cig	0.37	0.0438	9	0.347	0.0462	3	6.63
Catechol	µg/cig	16.5	1.4	9	14	0.522	3	17.86
Chromium	ng/cig	<3.31	NA	9	<11.0 (LOQ)	NA	3	-69.91
Crotonaldehyde	µg/cig	<3.29	NA	9	<3.29 (LOQ)	NA	3	0.00
Dibenz[a,h]anthracene	ng/cig	<0.413	NA	9	<0.124 (LOD)	NA	3	233.06
Ethylene oxide	µg/cig	0.134	NA	9	<0.119 (LOQ)	NA	3	12.61
Formaldehyde	µg/cig	7.75	0.722	9	14.1	0.43	3	-45.04
Glycerol	mg/cig	4.47	0.434	9	5.02	0.101	3	-10.96
Hydrogen cyanide	µg/cig	3.16	0.43	9	<1.75 (LOQ)	NA	3	80.57
Hydroquinone	µg/cig	7.43	0.678	9	6.55	0.461	3	13.44
Isoprene	µg/cig	2.04	0.181	9	1.51	0.129	3	35.10
Lead	ng/cig	<0.49	NA	9	2.23	0.351	3	-78.03
m-Cresol	µg/cig	0.027	0.00565	9	0.0424	0.0045	3	-36.32
Mercury	ng/cig	2.26	0.207	9	1.38	0.163	3	63.77
Methyl-ethyl-ketone (MEK)	µg/cig	7.57	0.549	9	10.1	0.759	3	-25.05
Nickel	ng/cig	<15.9	NA	9	<15.9 (LOD)	NA	3	0.00
Nicotine	mg/cig	1.31	0.0798	9	1.29	0.047	3	1.55
Nitric oxide (NO)	µg/cig	11.2	0.847	9	12.6	0.418	3	-11.11
Nitro benzene	µg/cig	<0.011	NA	9	<0.011 (LOD)	NA	3	0.00
Nitrogen oxides (NOx)	µg/cig	12.4	0.896	9	14.2	0.413	3	-12.68
N-nitrosoanabasine (NAB)	ng/cig	2.86	0.342	9	2.35	0.0589	3	21.70
N-nitrosoanatabine (NAT)	ng/cig	19.1	2.28	9	14.7	1.25	3	29.93
N-Nitrosonornicotine (NNN)	ng/cig	13.4	0.811	9	10.1	0.205	3	32.67

o-Cresol	µg/cig	0.0499	0.00613	9	0.0779	0.0093	3	-35.94
o-Toluidine	ng/cig	0.828	0.0396	9	1.1	0.0243	3	-24.73
p-Cresol	µg/cig	0.0613	0.00889	9	0.0706	0.00816	3	-13.17
Phenol	µg/cig	0.948	0.106	9	1.47	0.206	3	-35.51
Propionaldehyde	µg/cig	13.3	0.907	9	10.8	0.675	3	23.15
Propylene oxide	ng/cig	137	14	9	142.3	6.67	3	-3.72
Pyrene	ng/cig	6.71	0.625	9	8.2	0.152	3	-18.17
Pyridine	µg/cig	7.34	0.422	9	6.58	0.185	3	11.55
Quinoline	µg/cig	<0.011	NA	9	<0.011	NA	3	0.00
Resorcinol	µg/cig	<0.055	NA	9	<0.055	NA	3	0.00
Selenium	ng/cig	<0.83	NA	9	1.27	0.0577	3	-34.65
Styrene	µg/cig	0.442	0.0302	9	0.577	0.0916	3	-23.40
Toluene	µg/cig	1.63	0.038	9	1.42	0.162	3	14.79
Total Particulate Matter (TPM)	mg/cig	52.5	1.35	9	50.9	2.9	3	3.14
Vinyl chloride	ng/cig	<2.19	NA	9	<0.657 (LOD)	NA	3	233.33

Note 1: When the HPHCs yields for both IQOS System and the reference 3R4F reference cigarette are below LOD or LOQ, percent reductions are not calculated and NA (Not Applicable) are reported. For HPHCs below LOD or LOQ in the IQOS Systems, but not in the 3R4F reference cigarette, the percent reductions are calculated using the LOD or LOQ values, respectively. SD – standard deviation; n – sample size.

Note 2: * "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.

Note 3: ** 3R4F reference cigarette values from a research study (NS407) conducted in 2018 at Labstat International ULC

B. Comparison of *Marlboro* Bronze HeatSticks and Amber Authorized HeatSticks

HPHCs/ Analytes	***Unit***	***Marlboro Bronze HeatSticks***			***Marlboro Amber HeatSticks" ("Authorized HeatSticks")***			***% HPHCs Difference Marlboro Bronze Vs. Marlboro Amber HeatSticks" ("Authorized HeatSticks")***
		Mean	***SD***	***n***	***Mean***	***SD***	***n***	
1,3-Butadiene	µg/cig	0.178	0.024	9	0.207	0.016	3	-14.01
1-Aminonaphthalene	ng/cig	0.0327	NA*	9	0.0427	0.00513	3	-23.42
2-Aminonaphthalene	ng/cig	<0.012	NA	9	0.0223	0.00321	3	-46.19
3-Aminobiphenyl	ng/cig	0.0074	0.00171	9	0.007	0.003	3	5.71
4-(Methyl-nitrosamino)-1-(3-pyridyl)-1-	ng/cig	4.63	0.312	9	7.8	0.423	3	-40.64
4-Aminobiphenyl	ng/cig	0.0094	0.00166	9	0.0087	0.0012	3	8.05
Acetaldehyde	µg/cig	210	9.98	9	192	11.6	3	9.38
Acetamide	µg/cig	3.32	0.106	9	2.96	0.134	3	12.16
Acetone	µg/cig	36.8	2.25	9	30.7	1.86	3	19.87
Acrolein	µg/cig	9.22	0.88	9	8.32	0.755	3	10.82
Acrylamide	µg/cig	1.62	0.056	9	1.58	0.0543	3	2.53
Acrylonitrile	µg/cig	0.119	NA	9	0.145	0.0112	3	-17.93
Ammonia	µg/cig	10.6	1.44	9	12.2	0.973	3	-13.11
Arsenic	ng/cig	<1.2	NA	9	<0.36 (LOD)	NA	3	233.33
Benz[a]anthracene	ng/cig	2.07	0.0823	9	2.65	0.0647	3	-21.89
Benzene	µg/cig	0.491	0.0453	9	0.452	0.0395	3	8.63
Benzo[a]pyrene	ng/cig	0.75	0.0512	9	0.736	0.0973	3	1.90
Butyraldehyde	µg/cig	21.1	0.762	9	20.7	1.52	3	1.93
Cadmium	ng/cig	<0.09	NA	9	<0.28 (LOQ)	NA	3	-67.86

Carbon monoxide (CO)	mg/cig	0.379	0.0439	9	0.347	0.0462	3	9.22
Catechol	µg/cig	16.4	0.885	9	14	0.522	3	17.14
Chromium	ng/cig	<3.31	NA	9	<11.0 (LOQ)	NA	3	-69.91
Crotonaldehyde	µg/cig	<3.29	NA	9	<3.29 (LOQ)	NA	3	0.00
Dibenz[a,h]anthracene	ng/cig	<0.413	NA	9	<0.124 (LOD)	NA	3	233.06
Ethylene oxide	µg/cig	<0.119	NA	9	<0.119 (LOQ)	NA	3	0.00
Formaldehyde	µg/cig	7.5	0.585	9	14.1	0.43	3	-46.81
Glycerol	mg/cig	4.62	0.581	9	5.02	0.101	3	-7.97
Hydrogen cyanide	µg/cig	2.5	0.593	9	<1.75 (LOQ)	NA	3	42.86
Hydroquinone	µg/cig	7.39	0.47	9	6.55	0.461	3	12.82
Isoprene	µg/cig	1.66	0.135	9	1.51	0.129	3	9.93
Lead	ng/cig	<1.62	NA	9	2.23	0.351	3	-27.35
m-Cresol	µg/cig	0.0256	0.00392	9	0.0424	0.0045	3	-39.62
Mercury	ng/cig	2.04	0.0864	9	1.38	0.163	3	47.83
Methyl-ethyl-ketone (MEK)	µg/cig	7.72	0.548	9	10.1	0.759	3	-23.56
Nickel	ng/cig	<15.9	NA	9	<15.9 (LOD)	NA	3	0.00
Nicotine	mg/cig	1.32	0.108	9	1.29	0.047	3	2.33
Nitric oxide (NO)	µg/cig	8.63	0.675	9	12.6	0.418	3	-31.51
Nitro benzene	µg/cig	<0.011	NA	9	<0.011 (LOD)	NA	3	0.00
Nitrogen oxides (NOx)	µg/cig	9.84	0.734	9	14.2	0.413	3	-30.70
N-nitrosoanabasine (NAB)	ng/cig	2.05	0.23	9	2.35	0.0589	3	-12.77
N-nitrosoanatabine (NAT)	ng/cig	13.1	1.27	9	14.7	1.25	3	-10.88
N-Nitrosonornicotine (NNN)	ng/cig	4.83	0.319	9	10.1	0.205	3	-52.18
o-Cresol	µg/cig	0.0506	0.00569	9	0.0779	0.0093	3	-35.04
o-Toluidine	ng/cig	0.682	0.0729	9	1.1	0.0243	3	-38.00

p-Cresol	µg/cig	0.0565	0.00893	9	0.0706	0.00816	3	-19.97
Phenol	µg/cig	0.959	0.0892	9	1.47	0.206	3	-34.76
Propionaldehyde	µg/cig	12.8	0.897	9	10.8	0.675	3	18.52
Propylene oxide	ng/cig	133	12.3	9	142.3	6.67	3	-6.54
Pyrene	ng/cig	7.85	0.307	9	8.2	0.152	3	-4.27
Pyridine	µg/cig	7	0.399	9	6.58	0.185	3	6.38
Quinoline	µg/cig	<0.011	NA	9	<0.011	NA	3	0.00
Resorcinol	µg/cig	<0.055	NA	9	<0.055	NA	3	0.00
Selenium	ng/cig	<0.83	NA	9	1.27	0.0577	3	-34.65
Styrene	µg/cig	0.434	0.0254	9	0.577	0.0916	3	-24.78
Toluene	µg/cig	1.52	0.181	9	1.42	0.162	3	7.04
Total Particulate Matter (TPM)	mg/cig	54.6	2.03	9	50.9	2.9	3	7.27
Vinyl chloride	ng/cig	<2.19	NA	9	<0.657 (LOD)	NA	3	233.33

Note 1: When the HPHCs yields for both IQOS System and the reference 3R4F reference cigarette are below LOD or LOQ, percent reductions are not calculated and NA (Not Applicable) are reported. For HPHCs below LOD or LOQ in the IQOS Systems, but not in the 3R4F reference cigarette, the percent reductions are calculated using the LOD or LOQ values, respectively. SD – standard deviation; n – sample size.

Note 2: * "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.

Note 3: ** 3R4F reference cigarette values from a research study (NS407) conducted in 2018 at Labstat International ULC

CONFIDENTIAL APPENDIX 3: Market Volume Projections for the new and the authorized tobacco products

Product	Unit	Market Volume Projections		
			First-Year	Fifth-Year
Marlboro Bronze HeatSticks	Individual HeatStick	NA	(b) (4)	
Marlboro Sienna HeatSticks	Individual HeatStick	NA		
Marlboro Amber HeatSticks (PM0000424; Authorized product)	Individual HeatStick	(b) (4)		
Total				

CONFIDENTIAL APPENDIX 4: Heavy Metals within IQOS HeatSticks

Summary of results of the heavy metals measured in the cast leaf of each single batch of Sienna and Bronze HeatSticks

Tobacco Constituent	Unit	Marlboro Sienna - Batch# 1			Marlboro Sienna - Batch# 2			Marlboro Sienna - Batch# 3		
		Mean	SD	n	Mean	SD	n	Mean	SD	n
(b) (4)	ng/g	(b) (4)								
(b) (4)	ng/g									

Tobacco Constituent	Unit	Marlboro Bronze - Batch# 1			Marlboro Bronze - Batch# 2			Marlboro Bronze - Batch# 3		
		Mean	SD	n	Mean	SD	n	Mean	SD	n
(b) (4)	[ng/g]	(b) (4)								
(b) (4)	[ng/g]									

Tobacco Constituent	Unit	Marlboro Amber ("Authorized HeatSticks") - Batch# 1			Marlboro Amber ("Authorized HeatSticks") - Batch# 2			Marlboro Amber ("Authorized HeatSticks") - Batch# 3		
		Average	*SD*	*n*	*Average*	*SD*	*n*	*Average*	*SD*	*n*
(b) (4)	[ng/g]	(b) (4)								
(b) (4)	[ng/g]									

Note: Note: SD – standard deviation; n – sample size.

CONFIDENTIAL APPENDIX 5: Screening-level risk assessments of nicotine and heavy metals in IQOS HeatSticks for aquatic animals

The agency calculated risk quotients for nicotine, cadmium, and arsenic using estimated aquatic expected introduction concentration (EIC) and acute toxicity endpoint data (EC_{50}/LC_{50}) as shown in the table below.

Chemical	Product	Aquatic Environmental Introduction Concentration (µg/L)[1]	Lowest Acute Toxicity Endpoint Value (EC_{50}/LC_{50}) (µg/L)[2]	Species	Risk Quotient[3]
(b) (4)	Marlboro Bronze HeatSticks	(b) (4)			
	Marlboro Sienna HeatSticks				
	Marlboro Amber HeatSticks (Authorized product)				
	Total				
(b) (4)	Marlboro Bronze HeatSticks				
	Marlboro Sienna HeatSticks				
	Marlboro Amber HeatSticks (Authorized product)				
	Total				
(b) (4)	Marlboro Bronze HeatSticks				
	Marlboro Sienna HeatSticks				
	Marlboro Amber HeatSticks (Authorized product)				
	Total				

[1] Expected Introduction Concentration (EIC)-aquatic (ppb or µg/L)=A*B*C*D; where A=kg/yr shipped quantity, B=1/1.214x10$_{11}$ L/day entering POTW (*Source*: 1996 Needs Survey, Report to Congress), C=year/365, D=10^9 µg/kg (Source of EIC estimation equation: Guidance for Industry Environmental Assessment of Human Drug and Biologics Applications, 1998)

[2] Lowest acute toxicity endpoint value and the corresponding species for each chemical obtained from U. S. Environmental Protection Agency's ECOTOXicology Knowledgebase (ECOTOX) available at https://cfpub.epa.gov/ecotox/search.cfm (retrieved December 22, 2021).

[3] Risk Quotient (RQ) calculated as Expected Environmental Concentration (EEC)/LC_{50} or EC_{50} per U. S. Environmental Protection Agency methodology (https://www.epa.gov/pesticide-science-and-assessing-pesticide-risks/technical-overview-ecological-risk-assessment-risk). For calculating the RQ, the Agency assumed a worse-case scenario that the EEC is the same as the EIC.