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3.3 Product Performance Characterization

3.3.1 Introduction

This section provides a description of the characterization data for THS. The data provided in Table 1 is representative of the product manufactured under commercial manufacturing conditions, with an overview of the characteristics of these products. Multiple batch sizes were produced to demonstrate consistency of the product.

The results provided in this section are composed of data generated to meet regulatory requirements and PMI internal requirements for product characterization. Batch release testing confirms the product released is manufactured in accordance with quality requirements for product release. The FDA 18+6 and the ISO parameters are tested in accordance with regulatory requirements for reporting of HPHCs in the US. The PMI-58 parameters (the "PMI-58") are used to characterize the product and will be used for analysis and interpretation of the reduction of HPHCs against reference products. The stability data is provided to support the proposed shelf life of the commercial products. The Droplet Size Distribution (DSD) influences the deposition pattern in the respiratory tract of inhaled aerosols. This assay is used to determine the DSD of the aerosol generated from the THS product, and to ensure a DSD in the respirable range.

Table 1 Characterization Data Provided

Characterization Data	Regular Tobacco Sticks	Menthol 1 Tobacco Sticks	Menthol 2 Tobacco Sticks
Batch Release	Section 3.3.2.1.1	Section 3.3.2.2.1	Section 3.3.2.3.1
PMI list – PMI-58	Section 3.3.2.1.2	Section 3.3.2.2.2	Section 3.3.2.3.2
HPHCs – FDA Abbreviated List (18+6)	Section 3.3.2.1.3	Section 3.3.2.2.3	Section 3.3.2.3.3
Droplet Size Distribution	Section 3.3.2.1.4	Section 3.3.2.2.4	Section 3.3.2.3.4
ISO parameters (NFDPM, Nicotine and CO)	Section 3.3.2.1.5	Section 3.3.2.2.5	Section 3.3.2.3.5
Stability	Section 3.3.2.1.6	Section 3.3.2.2.6	Section 3.3.2.3.6

3.3.2 Characterization

The nine batches described in Table 2 (three Regular, three Menthol 1 and three Menthol 2) are made under commercial manufacturing conditions as described in Section 3.2.2.

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Table 2 Batches Analyzed

Product	Batch # PMI	Batch # PMMTB	Labstat Sample ID (FDA 18+6)		Composite Batch # (PMI-58)
			18	6	
Regular Dorado II Ron	B-25904	41-2397948	1680390	1680391	B-27846
	B-25905	41-2397950	1680388	1680392	
	B-25906	41-2382704	1680389	1680393	
Menthol 1 Dorado I Mint Vinny	B-25900	41-2381531	1680394	1680397	B-27845
	B-25901	41-2374718	1680395	1680398	
	B-25902	41-2379112	1680396	1680399	
Menthol 2 Dorado I Mint Vinny	B-31061	41-2572271	1682837	1682840	B-27850
	B-31062	41-2572272	1682838	1682841	
	B-31063	41-2572273	1682839	1682842	

3.3.2.1 Regular Tobacco Sticks

3.3.2.1.1 Batch Release – Regular Tobacco Sticks

To release the Regular Tobacco Sticks the following chemical analyses are performed: (b) (4) (Appendix A3.2.2-14). Physical testing for release includes (b) (4) r. Batch Release (BR) Specifications are provided in Appendix A3.2.1-3 and the methods used to analyse the batch release are described in Appendix A3.2.2-5. A batch analysis for three batches of Regular Tobacco Sticks, manufactured as described in Section 3.2.2, is provided in Table 3. The Batch Release Certificates are provided in Appendix A3.3-1.

(b) (4) The sampling pattern is clearly defined and documented prior to production of the Tobacco Sticks.

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Table 3 Batch Analysis Regular Tobacco Sticks

Parameter	Batch Number	B-25904 41-2397948	B-25906 41-2382704	B-25905 41-2397950
	Date of Manufacture	18 Jan 2016	15 Jan 2016	18 Jan 2016
	Batch Size	(b) (4)	(b) (4)	(b) (4)
	Acceptance Criteria	Results		
(b) (4)				

3.3.2.1.2 PMI list (PMI-58) – Regular Tobacco Sticks

A composite of the (b) (4) batches (see Table 2) is tested for the PMI-58 (which contains the FDA abbreviated list of 18 HPHCs)(b) (4) , see Section 3.2.1.4). A list of the PMI-58 is provided in Appendix A3.3-2. (b) (4) .

The PMI-58 results of Regular Tobacco Sticks in comparison to the 3R4F Reference Cigarette are provided in Section 7.1 Regular TC vs 3R4F_Labstat NS308_H.

Sufficient data are available(b) (4) therefore, routine evaluation of batches is based upon a(b) (4) For a justification of this approach, see Appendix A3.2.1-12. The PMI-58 are comprised of the main aerosol deliveries and a set of 54 Harmful or Potentially Harmful Constituents (HPHCs). A comparison of the results for the PMI-58 in

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Regular Tobacco Sticks vs. the 3R4F reference cigarette is provided in Table 4 for the main aerosol deliveries, and in Table 5 for the 54 HPHCs. The testing for this study was performed by LabStat (see Section 3.2.2). Based on the data, the average reduction of HPHCs of more than 93% (stick basis) and 88% (nicotine basis) for Regular Tobacco Sticks compared to 3R4F.

Table 4 Main Aerosol Deliveries for Regular Tobacco Sticks

Aerosol deliveries according to ISO 4387; 8454; 10315	Unit	3R4F			THS		
		Mean	SD	n	Mean	SD	n
Glycerol[1]	mg/stick	2.08	0.113	2	5.02	0.101	3
Nicotine	mg/stick	1.74	0.039	2	1.29	0.047	3
Nicotine Free Dry Particulate Matter (NFDPM)[2]	mg/stick	25.0	1.14	2	19.4	1.62	3
Total Particulate Matter (TPM)	mg/stick	41.4	3.28	2	50.9	2.90	3
Water[3]	mg/stick	14.7	2.10	2	30.2	2.17	3

SD = Standard Deviation; n = number of replicates

[1] *Product specific, not part of ISO parameter.*
[2] *The ISO terminology, NFDPM, is used to describe the aerosol collected mass from THS. The NFDPM of the THS has a very different constituent make-up in comparison to conventional cigarettes. The glycerol, reported separately, is part of the NFDPM.*
[3] *The water value reported here was determined according to ISO 4387, and it is underestimated compared to the true value, due to important water losses linked with the high water content of the THS 2.2 aerosol. Accurate water measurements can only be obtained with a modified procedure, not available in Labstat [see Ghosh, D. & Jeannet, C. (2014). An Improved Cambridge Filter Pad Extraction Methodology to Obtain More Accurate Water and "Tar" Values: In Situ Cambridge Filter Pad Extraction Methodology. Beiträge zur Tabakforschung / Contributions to Tobacco Research, 26(2), pp. 38-49]*

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Table 5 54 HPHCs Results – Regular Tobacco Sticks

HPHCs (alphabetical order)	Unit	3R4F			Regular Tobacco Stick (B-27846)			% On Stick Basis		% On Nicotine Basis	
		Mean	SD	n	Mean	SD	n	% of 3R4F	% of Reduction to 3R4F	% of 3R4F	% of Reduction to 3R4F
1,3-Butadiene	µg/stick	89.2	1.73	2	0.207	0.0160	3	0.2%	99.8%	0.3%	99.7%
1-Aminonaphthalene	ng/stick	20.9	0.145	2	0.0427	0.00513	3	0.2%	99.8%	0.3%	99.7%
2-Aminonaphthalene	ng/stick	17.5	0.497	2	0.0223	0.00321	3	0.1%	99.9%	0.2%	99.8%
3-Aminobiphenyl	ng/stick	4.60	0.137	2	0.0070	0.003	3	0.2%	99.8%	0.2%	99.8%
4-(Methyl-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK)	ng/stick	244.7	7.54	2	7.80	0.423	3	3.2%	96.8%	4.3%	95.7%
4-Aminobiphenyl	ng/stick	3.21	0.105	2	0.0087	0.0012	3	0.3%	99.7%	0.4%	99.6%
Acetaldehyde	µg/stick	1602	NA	1	192	11.6	3	12.0%	88.0%	16.2%	83.8%
Acetamide	µg/stick	13.0	0.501	2	2.96	0.134	3	22.7%	77.3%	30.7%	69.3%
Acetone	µg/stick	653	NA	1	30.7	1.86	3	4.7%	95.3%	6.4%	93.6%
Acrolein	µg/stick	158	NA	1	8.32	0.755	3	5.3%	94.7%	7.1%	92.9%
Acrylamide	µg/stick	4.50	0.294	2	1.58	0.0543	3	35.0%	65.0%	47.3%	52.7%
Acrylonitrile	µg/stick	21.2	1.44	2	0.145	0.0112	3	0.7%	99.3%	0.9%	99.1%
Ammonia	µg/stick	33.2	0.539	2	12.2	0.973	3	36.8%	63.2%	49.8%	50.2%
Arsenic	ng/stick	<7.49 (LOQ)	NA	2	<0.36 (LOD)	NA	3	NA	NA	NA	NA
Benz[a]anthracene	ng/stick	28.4	1.09	2	2.65	0.0647	3	9.3%	90.7%	12.6%	87.4%

(table continues)

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HPHCs (alphabetical order)	Unit	3R4F			Regular Tobacco Stick (B-27846)			% On Stick Basis		% On Nicotine Basis	
		Mean	SD	n	Mean	SD	n	% of 3R4F	% of Reduction to 3R4F	% of 3R4F	% of Reduction to 3R4F
Benzene	µg/stick	77.3	5.81	2	0.452	0.0395	3	0.6%	99.4%	0.8%	99.2%
Benzo[a]pyrene	ng/stick	13.3	0.660	2	0.736	0.0973	3	5.5%	94.5%	7.5%	92.5%
Butyraldehyde	µg/stick	81.3	NA	1	20.7	1.52	3	25.5%	74.5%	34.5%	65.5%
Cadmium	ng/stick	89.2	9.31	2	<0.28 (LOQ)	NA	3	<0.3%	>99.7%	<0.4%	>99.6%
Carbon monoxide (CO)[4]	mg/stick	29.4	1.35	2	0.347	0.0462	3	1.2%	98.8%	1.6%	98.4%
Catechol	µg/stick	84.1	9.36	2	14.0	0.522	3	16.7%	83.3%	22.5%	77.5%
Chromium	ng/stick	<11.9 (LOD)	NA	2	<11.0 (LOQ)	NA	3	NA	NA	NA	NA
Crotonaldehyde	µg/stick	49.3	NA	1	<3.29 (LOQ)	NA	3	<6.7%	>93.3%	<9.0%	>91.0%
Dibenz[a,h]anthracene	ng/stick	<0.689 (LOQ)	NA	2	<0.124 (LOD)	NA	3	NA	NA	NA	NA
Ethylene oxide	µg/stick	16.0	1.18	2	<0.119 (LOQ)	NA	3	<0.7%	>99.3%	<1.0%	>99.0%
Formaldehyde	µg/stick	79.4	NA	1	14.1	0.430	3	17.8%	82.2%	24.1%	75.9%
Hydrogen cyanide	µg/stick	329	16.2	2	<1.75 (LOQ)	NA	3	<0.5%	>99.5%	<0.7%	>99.3%

(table continues)

[4] *CO is an ISO parameter but reported as HPHC in order to report the reduction to 3R4F*

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HPHCs (alphabetical order)	Unit	3R4F			Regular Tobacco Stick (B-27846)			% On Stick Basis		% On Nicotine Basis	
		Mean	SD	n	Mean	SD	n	% of 3R4F	% of Reduction to 3R4F	% of 3R4F	% of Reduction to 3R4F
Hydroquinone	µg/stick	94.5	10.3	2	6.55	0.461	3	6.9%	93.1%	9.4%	90.6%
Isoprene	µg/stick	891	35.8	2	1.51	0.129	3	0.2%	99.8%	0.2%	99.8%
Lead	ng/stick	31.2	2.78	2	2.23	0.351	3	7.2%	92.8%	9.7%	90.3%
m-Cresol	µg/stick	4.24	0.461	2	0.0424	0.0045	3	1.0%	99.0%	1.4%	98.6%
Mercury	ng/stick	3.68	0.140	2	1.38	0.163	3	37.4%	62.6%	50.6%	49.4%
Methyl-ethyl-ketone (MEK)	µg/stick	183	NA	1	10.1	0.759	3	5.5%	94.5%	7.4%	92.6%
Nickel	ng/stick	<12.9 (LOD)	NA	2	<15.9 (LOD)	NA	3	NA	NA	NA	NA
Nitric oxide (NO)	µg/stick	484	7.20	2	12.6	0.418	3	2.6%	97.4%	3.5%	96.5%
Nitro benzene	µg/stick	<0.038 (LOD)	NA	2	<0.011 (LOD)	NA	3	NA	NA	NA	NA
Nitrogen oxides (NOx)	µg/stick	538	8.78	2	14.2	0.413	3	2.6%	97.4%	3.6%	96.4%
N-nitrosoanabasine (NAB)	ng/stick	29.0	1.08	2	2.35	0.0589	3	8.1%	91.9%	11.0%	89.0%
N-nitrosoanatabine (NAT)	ng/stick	254	17.4	2	14.7	1.25	3	5.8%	94.2%	7.9%	92.1%
N-Nitrosonornicotine (NNN)	ng/stick	271	8.49	2	10.1	0.205	3	3.7%	96.3%	5.0%	95.0%
o-Cresol	µg/stick	4.81	0.304	2	0.0779	0.0093	3	1.6%	98.4%	2.2%	97.8%
o-Toluidine	ng/stick	96.2	3.09	2	1.10	0.0243	3	1.1%	98.9%	1.5%	98.5%
p-Cresol	µg/stick	9.60	0.929	2	0.0706	0.00816	3	0.7%	99.3%	1.0%	99.0%
Phenol	µg/stick	15.6	1.75	2	1.47	0.206	3	9.4%	90.6%	12.7%	87.3%

(table continues)

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HPHCs (alphabetical order)	Unit	3R4F			Regular Tobacco Stick (B-27846)			% On Stick Basis		% On Nicotine Basis	
		Mean	SD	n	Mean	SD	n	% of 3R4F	% of Reduction to 3R4F	% of 3R4F	% of Reduction to 3R4F
Propionaldehyde	µg/stick	109	NA	1	10.8	0.675	3	9.9%	90.1%	13.4%	86.6%
Propylene oxide	ng/stick	896	82.5	2	142.3	6.67	3	15.9%	84.1%	21.5%	78.5%
Pyrene	ng/stick	79.2	3.58	2	8.20	0.152	3	10.3%	89.7%	14.0%	86.0%
Pyridine	µg/stick	30.9	1.64	2	6.58	0.185	3	21.3%	78.7%	28.8%	71.2%
Quinoline	µg/stick	0.434	0.0246	2	<0.011 (LOQ)	NA	3	<2.5%	>97.5%	<3.4%	>96.6
Resorcinol	µg/stick	1.72	0.168	2	<0.055 (LOQ)	NA	3	<3.2%	>96.8%	<4.3%	>95.7
Selenium[5]	ng/stick	<4.42 (LOD)	NA	2	1.27	0.0577	3	NA	NA	NA	NA
Styrene	µg/stick	13.9	1.72	2	0.577	0.0916	3	4.2%	95.8%	5.6%	94.4%
Toluene	µg/stick	129	1.17	2	1.42	0.162	3	1.1%	98.9%	1.5%	98.5%
Vinyl chloride	ng/stick	93.4	3.00	2	<0.657 (LOD)	NA	3	<0.7%	>99.3%	<1.0%	>99.0%

SD = Standard Deviation; n = number of replicates<mean value: detected below the limit of detection (LOD) or limit of quantification (LOQ). In this case LOD/LOQ is used to calculate the reduction to 3R4F

[5] In the case of selenium, the 3R4F is below the LOD while a value is reported for the THS. The LOD for 3R4F however, is higher than the value reported for the THS. In such a case, the reduction can not be quantified.

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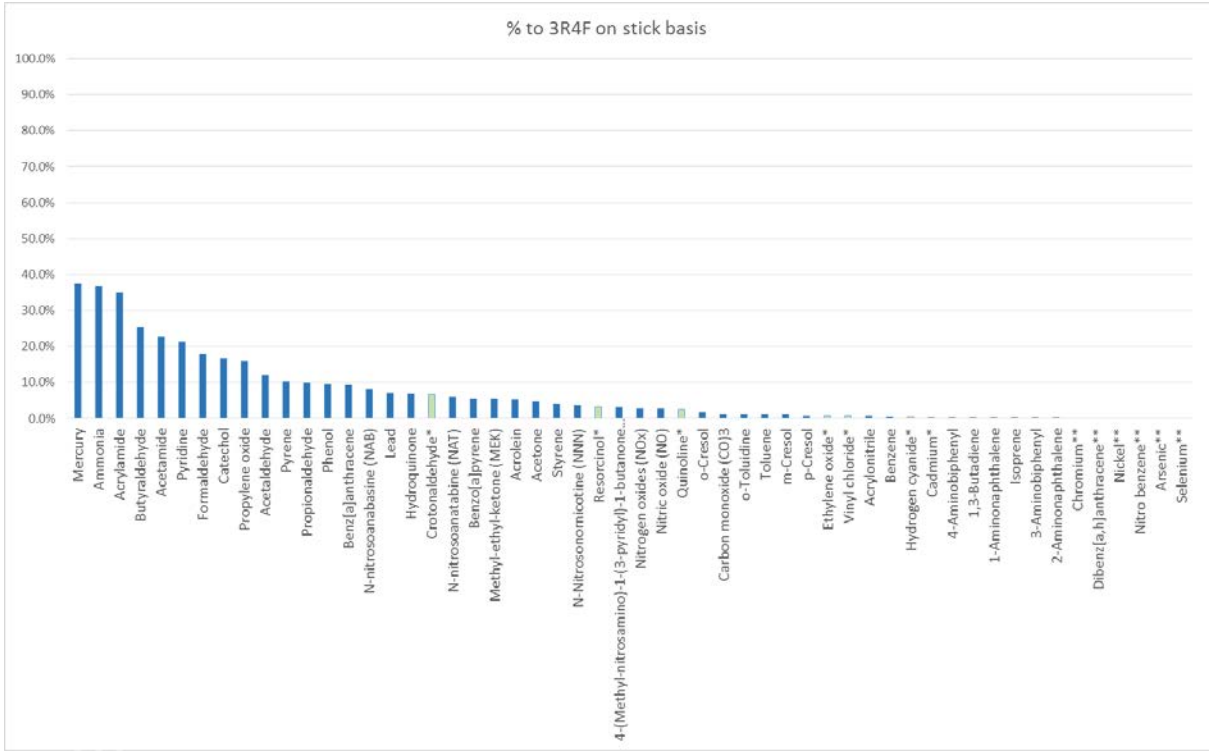


Figure 1 HPHCs of THS Regular vs. Reference 3R4F Cigarette; % on Stick Basis in Decreasing Order

Note: HPHCs marked with a "" and identified with light color bars were reported below LOD or LOQ in THS and relative % is based on LOD/LOQ value. HPHCs marked with a "**" were found below LOD or LOQ in both reference and THS and no relative % can be calculated (marked as NA in Table 5).*

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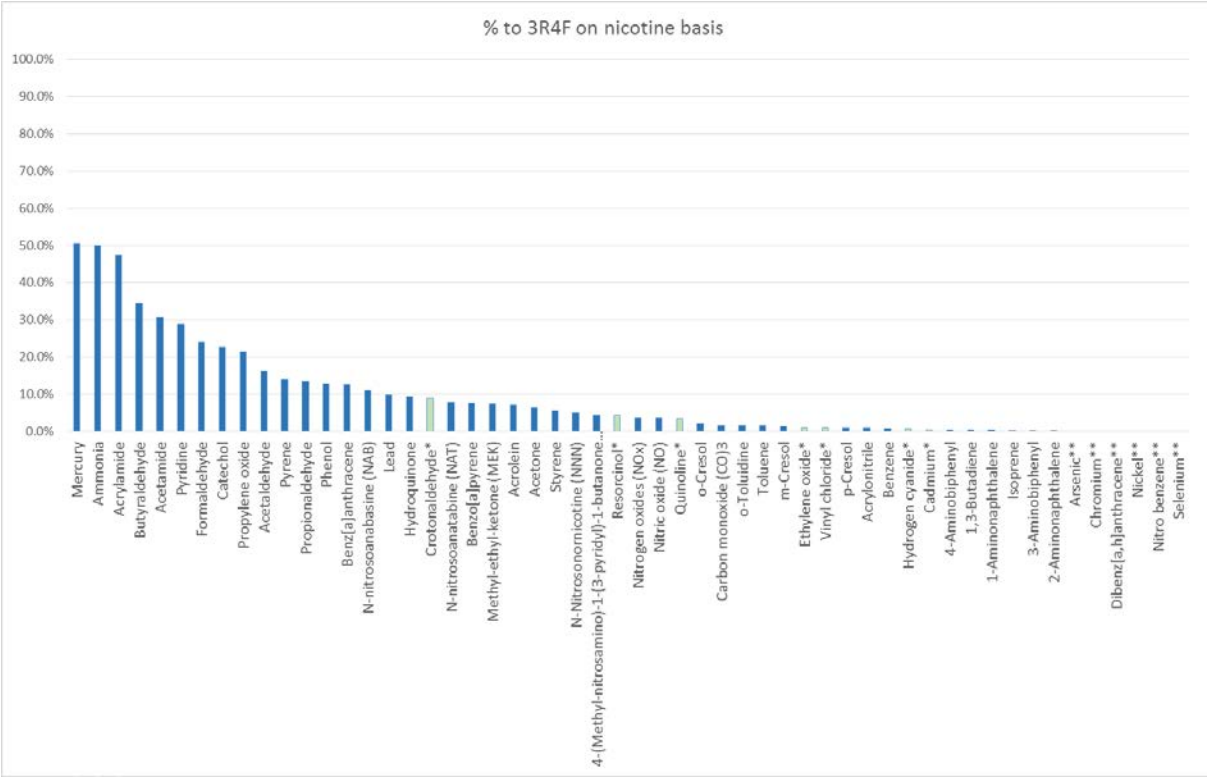


Figure 2 HPHCs of THS Regular vs. Reference 3R4F Cigarette; % on Nicotine Basis in Decreasing Order

Note: HPHCs marked with a "" and identified with light color bars were reported below LOD or LOQ in THS and relative % is based on LOD/LOQ value. HPHCs marked with a "**" were found below LOD or LOQ in both reference and THS and no relative % can be calculated (marked as NA in Table 5).*

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3.3.2.1.3 HPHCs – FDA List (18 + 6) – Regular Tobacco Sticks

Analysis of the FDA Abbreviated list of HPHCs, 18 in aerosol and 6 measured in the tobacco, was performed on Regular Tobacco Sticks by Labstat (Section 3.2.2) on 3 batches. Both the ISO (see results in Table 6) and Health Canada Intense (HCI) smoking regimes (see results in Table 7) were used for the FDA 18. The tobacco constituent results (FDA +6) are provided in Table 8.

A description of the analysis is provided in Section 7.1 NS298-H_Report Regular.

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Table 6 FDA Abbreviated HPHC List Results – ISO Conditions – Regular Tobacco Sticks

Aerosol Constituent Name	CAS no.	Unit of Measure	B-25905		B-25906		B-25904		Sample size per batch	Method
			Result	SD	Result	SD	Result	SD	Replicates	
Acetaldehyde	75-07-0	µg/stick	128	6	130	6	131	10	7	Labstat T-104
Acrolein	107-02-8	µg/stick	4.47	0.29	4.47	0.36	4.41	0.51	7	Labstat T-104
Acrylonitrile	107-13-1	µg/stick	<0.107 (LOQ)	NA	<0.107 (LOQ)	NA	<0.107 (LOQ)	NA	7	Labstat TMS-00124
4-aminobiphenyl	92-67-1	ng/stick	<0.005 (LOQ)	NA	<0.005 (LOQ)	NA	0.009	0.004	7	Labstat TMS-00128
1-Amino-naphthalene	134-32-7	ng/stick	<0.027 (LOQ)	NA	<0.027 (LOQ)	NA	0.035	0.019	7	Labstat TMS-00128
2-amino-naphthalene	91-59-8	ng/stick	<0.012 (LOQ)	NA	<0.012 (LOQ)	NA	0.034	0.027	7	Labstat TMS-00128
Ammonia	7664-41-7	µg/stick	2.41	0.44	2.68	0.40	2.49	0.39	7	Labstat T-101

(table continues)

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Aerosol Constituent Name	CAS no.	Unit of Measure	B-25905		B-25906		B-25904		Sample size per batch	Method
			Result	SD	Result	SD	Result	SD	Replicates	
Benzene	71-43-2	µg/stick	0.163	0.018	0.185	0.016	0.170	0.027	7	Labstat TMS-00124
Benzo(a)pyrene	50-32-8	ng/stick	0.359	0.359	<0.354 (LOQ)	NA	<0.354 (LOQ)	NA	7	Labstat TMS-00120
1,3 Butadiene	106-99-0	µg/stick	<0.095 (LOQ)	NA	<0.095 (LOQ)	NA	0.101	0.009	7	Labstat TMS-00124
Carbon Monoxide	630-08-0	mg/stick	<0.223 (LOQ)	NA	<0.223 (LOQ)	NA	<0.223 (LOQ)	NA	20	T-115*
Crotonaldehyde	4170-30-3	µg/stick	<3.29 (LOQ)	NA	<3.29 (LOQ)	NA	<3.29 (LOQ)	NA	7	T-104*
Formaldehyde	50-00-0	µg/stick	12.2	0.4	12.5	0.2	12.1	0.5	7	T-104*
Isoprene	78-79-5	µg/stick	0.694	0.076	0.857	0.080	0.766	0.098	7	Labstat TMS-00124
Nicotine (Total)	54-11-5	mg/stick	0.416	0.031	0.413	0.043	0.429	0.029	20	T-115*

(table continues)

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Aerosol Constituent Name	CAS no.	Unit of Measure	B-25905		B-25906		B-25904		Sample size per batch	Method
			Result	SD	Result	SD	Result	SD	Replicates	
4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)	64091-91-4	ng/stick	2.70	0.34	2.58	0.61	2.96	0.40	7	Labstat TMS-00135
N-nitrosonornicotine (NNN)	16543-55-8	ng/stick	3.49	0.33	3.29	0.65	3.82	0.45	7	Labstat TMS-00135
Toluene	108-88-3	µg/stick	0.512	0.062	0.562	0.067	0.548	0.100	7	Labstat TMS-00124

SD = Standard Deviation; > = below limit of quantitation with LOQ provided by Labstat; NA = Not Applicableno standard deviation can be calculated
*Canadian Tobacco Reporting Regulations: 2000-07-19 Canada Gazette Part II, Vol. 134, No. 15 Part 3: Emissions from Designated Tobacco Products.

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Table 7 FDA Abbreviated HPHC List Results – Health Canada Intense – Regular Tobacco Sticks

Aerosol Constituent Name	CAS no.	Unit of Measure	B-25905		B-25906		B-25904		Sample size per batch	Method
			Result	SD	Result	SD	Result	SD	Replicates	
Acetaldehyde	75-07-0	µg/stick	187	6	190	12	203	19	7	Labstat T-104
Acrolein	107-02-8	µg/stick	8.86	0.74	9.15	0.70	11.5	5.9	7	Labstat T-104
Acrylonitrile	107-13-1	µg/stick	0.118	0.024	0.120	0.027	0.120	0.026	7	Labstat TMS-00124
4-aminobiphenyl	92-67-1	ng/stick	0.008	0.001	0.009	0.001	0.010	0.005	7	Labstat TMS-00128
1-Amino-naphthalene	134-32-7	ng/stick	0.034	0.014	0.036	0.014	0.040	0.019	7	Labstat TMS-00128
2-amino-naphthalene	91-59-8	ng/stick	0.022	0.008	0.022	0.007	0.030	0.032	7	Labstat TMS-00128
Ammonia	7664-41-7	µg/stick	10.8	0.9	10.9	10.9	10.8	0.6	7	Labstat T-101

(table continues)

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Aerosol Constituent Name	CAS no.	Unit of Measure	B-25905		B-25906		B-25904		Sample size per batch	Method
			Result	SD	Result	SD	Result	SD	Replicates	
Benzene	71-43-2	µg/stick	0.432	0.028	0.474	0.099	0.450	0.064	7	Labstat TMS-00124
Benzo(a)pyrene	50-32-8	ng/stick	0.662	0.063	0.673	0.049	0.627	0.037	7	Labstat TMS-00120
1,3 Butadiene	106-99-0	µg/stick	0.206	0.018	0.224	0.007	0.226	0.027	7	Labstat TMS-00124
Carbon Monoxide	630-08-0	mg/stick	0.318	0.035	0.328	0.042	0.318	0.036	20	T-115*
Crotonaldehyde	4170-30-3	µg/stick	<3.29 (LOQ)	NA	<3.29 (LOQ)	NA	<3.29 (LOQ)	NA	7	T-104*
Formaldehyde	50-00-0	µg/stick	14.0	1.0	13.0	1.5	13.4	1.4	7	T-104*
Isoprene	78-79-5	µg/stick	1.36	0.10	1.58	0.14	1.54	0.20	7	Labstat TMS-00124
Nicotine (Total)	54-11-5	mg/stick	1.19	0.06	1.15	0.08	1.17	0.10	20	T-115*

(table continues)

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Aerosol Constituent Name	CAS no.	Unit of Measure	B-25905		B-25906		B-25904		Sample size per batch	Method
			Result	SD	Result	SD	Result	SD	Replicates	
4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)	64091-91-4	ng/stick	8.56	0.48	8.08	0.86	8.01	0.076	7	Labstat TMS-00135
N-nitrosonornicotine (NNN)	16543-55-8	ng/stick	9.91	0.62	8.65	0.42	9.10	0.085	7	Labstat TMS-00135
Toluene	108-88-3	µg/stick	1.36	0.10	1.40	0.34	1.39	0.29	7	Labstat TMS-00124

SD = standard deviation; < = below limit of quantitation with LOQ provided by Labstat; NA = Not Applicable no standard deviation can be calculated
*Canadian Tobacco Reporting Regulations: 2000-07-19 Canada Gazette Part II, Vol. 134, No. 15 Part 3: Emissions from Designated Tobacco Products.

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Table 8 FDA Abbreviated HPHC List Tobacco Constituents Results – Regular Tobacco Sticks

Constituent	CAS No.	Unit	B-25904		B-25905		B-25906		Sample Size	Method
			Mean	SD	Mean	SD	Mean	SD		
Ammonia	7664-41-7	µg/unit	105.3	1.5	110.5	1.0	104.8	2.4	7	T-302*
Arsenic	7440-38-2	ng/unit	34.3	0.9	36.0	0.5	36.8	0.6	7	T-306*
Cadmium	7440-43-9	ng/unit	160.2	1.0	166.9	1.2	162.5	1.7	7	T-306*
Nicotine	54-11-5	mg/unit	4.4	0.1	4.5	0.05	4.5	0.04	7	T-301*
NNK	64091-91-4	ng/unit	44.9	4.1	46.2	2.6	24.7	2.7	7	Labstat TWT-00333
NNN	16543-55-8	ng/unit	88.4	12.2	104.1	14.3	95.4	16.1	7	Labstat TWT-00333

SD = standard deviation *Canadian Tobacco Reporting Regulations: 2000-07-19 Canada Gazette Part II, Vol. 134, No. 15 Part 3: Emissions from Designated Tobacco Products.

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3.3.2.1.4 Droplet Size Distribution – Regular Tobacco Sticks

The Droplet Size Distribution (DSD) influences the deposition pattern in the respiratory tract of inhaled aerosols. This assay is used to determine the DSD of the aerosol generated from the THS product. This assay is based on the use of a cascade impactor to gravimetrically determine the DSD.

Table 9 shows the Mass Median Aerodynamic Diameter (MMAD) and Geometric Standard Deviation (GSD) for all replicates on the 3 tested batches for the Regular Tobacco Sticks.

Figure 3 shows a plot of the same data, where MMAD are plotted as a function of the GSD. The dotted line defines the respirability upper limit, based on the MMAD value and its distribution (GSD), based on the respirability upper threshold defined at 2.5 µm. All measured THS data fall within the respirability region.

Table 9 MMAD and GSD Values for Regular Tobacco Sticks

Replicate	Day 1 B-25904		Day 2 B-25905		Day 3 B-25906	
	MMAD [µm]	GSD	MMAD [µm]	GSD	MMAD [µm]	GSD
1	0.61	1.37	0.63	1.34	0.71	1.42
2	0.60	1.38	0.71	1.45	0.65	1.35
3	0.71	1.07	0.60	1.36	0.69	1.41
4	0.58	1.40	0.65	1.33	0.69	1.41
5	0.55	1.39	0.65	1.28	0.67	1.44
6	0.61	1.37	0.64	1.33	0.69	1.40
7	0.60	1.38	0.63	1.34	0.68	1.44
8	0.62	1.36	0.60	1.37	NA[6]	NA
9	0.65	1.34	0.63	1.36	0.69	1.40
10	0.65	1.33	0.64	1.32	0.66	1.36

[6] *No sufficient mass was accumulated in the PIXE cascade impactor for replicate 8 to obtain a MMAD and a GSD value.*

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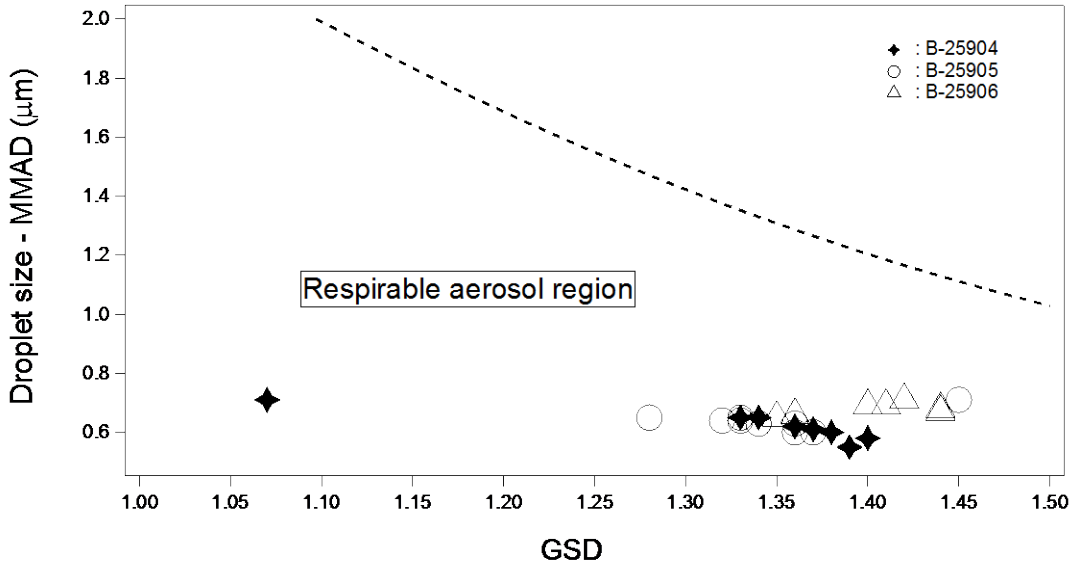


Figure 3 MMAD Plotted as a Function of GSD Values.

Note: The dotted line separates the respirable (below the curve) from the non-respirable aerosol (above the curve).

3.3.2.1.5 Nicotine Free Dry Particulate Matter (NFDPM), Nicotine, Carbon Monoxide (ISO) – Regular Tobacco Sticks

Table 10 shows the results of ISO parameters (NFDPM, Nicotine and Carbon monoxide [CO]) determined in mainstream aerosol under ISO methodology for three batches of Dorado II Ron (Regular) Tobacco Sticks using Tobacco Heating Device (THD) 2.4. The detailed results are available in Section 7.1 PT_SR_ISO parameters Regular.

ISO standards prescribe methods for the quantification of certain analytes and constituents in conventional cigarette smoke, such as nicotine, water, CO, benzo[a]pyrene, TPM and NFDPM, and menthol (see ISO standards references below).

However, these methods were developed specifically for conventional cigarette smoke, which is fundamentally distinct from a heated tobacco product aerosol. A critical distinction is the fact that aerosol generated by THS is approximately 80% water, while conventional cigarette smoke contains only about 10% water. Standardized testing and quantification methods such as the ISO and HCI methods were not developed to measure aerosols containing principally water, which evaporates rapidly or is absorbed during the measurement process. High levels of evaporation and absorption result in substantially inaccurate measurements of the total levels of water in the aerosol. In turn, the calculations of other analytes that are based on the amount of water in the aerosol are also inaccurate.

To address this issue, PMI has developed and validated a modified methodology that traps the aerosol particulate matter in the same way as the standard method but where the filter pad can be extracted *in situ* without opening the filter pad holder, thus avoiding water losses. The filter pad holder is hermetically sealed and solvent is flushed through the holder for a defined

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period of time. This method is described in detail by Ghosh and Jeannet (Ghosh and Jeannet 2014).

Using the *in situ* method results in NFDPM measurements (calculated by subtracting the mass of water and nicotine from the mass of the TPM) for the aerosol generated by THS of 4.7 mg under the ISO method and 10.2 mg under the Health Canada Intense method. Even these values should be interpreted in light of the high levels of glycerol, approximately 30% to 45% of the NFDPM.

Table 10 ISO Parameters – Regular Tobacco Sticks

Constituent	Unit	B-25904		B-25905		B-25906	
		Result	SD	Result	SD	Result	SD
Nicotine	mg/stick	0.46	0.022	0.47	0.023	0.46	0.033
NFDPM	mg/stick	4.6	1.13	4.6	0.90	4.9	0.78
CO	mg/stick	0.3	0.07	0.3	0.04	0.3	0.03

SD = Standard Deviation

3.3.2.1.6 Stability – Regular Tobacco Sticks

Stability Specifications

The stability specifications for the Regular Tobacco Stick are identical to those described in Table 3 with the following exception:

- (b) (4)

(b) (4)

Stability Summary

Three batches of Regular Tobacco Sticks manufactured at the proposed site of commercial manufacture were placed on stability using the protocol provided in Table 11. A matrix approach was used for the stability studies. Detailed information regarding the stability studies is provided in Appendix A3.3-3.

(b) (4) The batches remained within the stability specifications at all storage conditions. Stability data and statistical analysis are provided in Appendix A3.3-4.

Complete results for the stability studies will provided to the Agency when they become available. PMI anticipates that these data will be available during the review process.

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Table 11 Stability Protocol for Regular Tobacco Sticks

Batch	Storage Conditions	Analysis Time points (months)
(b) (4)		(b) (4)

Shelf Life

Based on the available stability data (6 months) and the anticipated availability of acceptable 12 months data during the review process, a shelf life of 12 months is proposed for the Regular Tobacco Sticks.

Ongoing Stability Program

Stability will be performed on the Regular Tobacco Sticks using the protocol provided in Table 12. Details of the post-approval protocol are provided in Appendix A3.3-5.

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Table 12 Post Approval Stability Protocol for Regular Tobacco Stick

Storage Conditions	Analysis Time points (months)
(b) (4)	(b) (4)

Stability Commitment

The stability studies described in this document will be continued throughout the proposed shelf life.

Analytical Methods used for Stability

Reference is made to Section 3.2.2.5 for information pertaining to the analytical methods used for stability.

Stability Data

Reference is made to Appendix A3.3-4 for the stability data.

3.3.2.2 Menthol 1 Tobacco Stick

3.3.2.2.1 Batch Release – Menthol 1 Tobacco Sticks

(b) (4) (see Section 3.3.2.1.1) (b) (4) l. In addition, (b) (4) . Batch Release (BR) Specifications are provided in Appendix A3.2.1-3 and the methods used to analyse the batch release are described in Appendix A3.2.2-5 A batch analysis for three batches of Menthol 1 Tobacco Sticks, manufactured as described in this submission, is provided in Table 13. Batch Release certificates are provided in Appendix A3.3-6.

(b) (4) .

The sampling pattern is clearly defined and documented prior to production iof the Tobacco Sticks.

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Table 13 Batch Analysis Menthol 1 Tobacco Sticks

Parameter	Batch Number	B-25900 41-2381531	B-25901 41-2374718	B-25902 41-2379112
	Date of Manufacture	21 Dec 2015	22 Dec 2015	17 Dec 2015
	Batch Size	(b) (4)		
	Acceptance* Criteria	Results		
(b) (4)				

3.3.2.2.2 PMI list (PMI-58) – Menthol 1 Tobacco Sticks

A composite batch of the (b) (4) batches (see Table 2) are tested for the PMI-58 (which contains the FDA abbreviated list of 18 HPHCs) (b) (4) (see Section 3.2.1.4). A list of the PMI-58 is provided in Appendix A3.3-2.(b) (4) .

A comparison of the PMI-58 results of Menthol 1 Tobacco Sticks in comparison to the 3R4F Reference Cigarette is provided in Section 7.1 Menthol TC vs 3R4F_Labstat NS309+H.

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As stated in Section 3.3.2.1.2, sufficient data is available t (b) (4) , and routine evaluation of batches is based upon a (b) (4) . For a justification of this approach, see Appendix A3.2.1-12. The PMI 58 are comprised of the main aerosol deliveries and a set of 54 Harmful or Potentially Harmul Constituents (HPHCs). A comparison of the results for the PMI-58 in Menthol 1 Tobacco Sticks vs. the 3R4F reference cigarette is provided in Table 14 for the main aerosol deliveries, and in Table 15 for the 54 HPHCs. The testing for this study was performed by LabStat. Based on the data, there is an average reduction of HPHCs of more than 92% (stick basis) and 89% (nicotine basis) for Menthol 1 Tobacco Sticks compared to 3R4F.

Table 14 Main Aerosol Deliveries for THS – Menthol 1 Tobacco Sticks

Aerosol deliveries according to ISO 4387; 8454; 10315	Unit	3R4F			THS Menthol 1		
		Mean	SD	n	Mean	SD	n
Glycerol[7]	mg/stick	2.15	0.11	2	4.41	0.10	3
Nicotine	mg/stick	1.84	0.11	2	1.19	0.05	3
Nicotine Free Dry Particulate Matter (NFDPM)[8]	mg/stick	24.8	1.0	2	19.5	1.3	3
Total Particulate Matter (TPM)	mg/stick	41.9	2.39	2	56.3	0.93	3
Water[9]	mg/stick	15.3	1.55	2	35.6	0.59	3

SD = Standard Deviation; n = number of replicates

[7] *Product specific not part of ISO parameter*
[8] *The ISO terminology, NFDPM, is used to describe the aerosol collected mass from THS. The NFDPM of the THS has a very different constituent make-up in comparison to conventional cigarettes. The glycerol, reported separately, is part of the NFDPM.*
[9] *The water value reported here was determined according to ISO 4387, and it is underestimated compared to the true value, due to important water losses linked the high water content of the THS 2.2 aerosol. Accurate water measurements can only be obtained with a modified procedure, not available in Labstat [see Ghosh, D. & Jeannet, C. (2014). An Improved Cambridge Filter Pad Extraction Methodology to Obtain More Accurate Water and "Tar" Values: In Situ Cambridge Filter Pad Extraction Methodology. Beiträge zur Tabakforschung / Contributions to Tobacco Research, 26(2), pp. 38-49].*

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Table 15 54 HPHCs Results – Menthol 1 Tobacco Sticks

HPHCs (alphabetical order)	Unit	3R4F			Menthol 1 Tobacco Stick (B-27845)			% On Stick Basis		% On Nicotine Basis	
		Mean	SD	n	Mean	SD	n	% of 3R4F	% of Reduction to 3R4F	% of 3R4F	% of Reduction to 3R4F
1,3-Butadiene	µg/stick	92.8	3.1	2	0.223	0.030	3	0.2%	99.8%	0.4%	99.6%
1-Aminonaphthalene	ng/stick	20.9	0.8	2	0.043	0.012	3	0.2%	99.8%	0.3%	99.7%
2-Aminonaphthalene	ng/stick	17.3	0.5	2	0.022	0.007	3	0.1%	99.9%	0.2%	99.8%
3-Aminobiphenyl	ng/stick	4.61	0.24	2	0.008	0.001	3	0.2%	99.8%	0.3%	99.7%
4-(Methyl-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK)	ng/stick	256	8	2	6.63	0.53	3	2.6%	97.4%	4.0%	96.0%
4-Aminobiphenyl	ng/stick	3.21	0.22	2	0.009	0.002	3	0.3%	99.7%	0.5%	99.5%
Acetaldehyde	µg/stick	1612	NA	1	206	6	3	12.8%	87.2%	19.9%	80.1%
Acetamide	µg/stick	14.0	1.2	2	2.98	0.06	3	21.2%	78.8%	32.9%	67.1%
Acetone	µg/stick	648	NA	1	37.8	2.2	3	5.8%	94.2%	9.0%	91.0%
Acrolein	µg/stick	144	NA	1	9.79	1.66	3	6.8%	93.2%	10.6%	89.4%
Acrylamide	µg/stick	4.67	0.32	2	1.64	0.001	3	35.1%	64.9%	54.4%	45.6%
Acrylonitrile	µg/stick	22.1	0.3	2	0.127	0.017	3	0.6%	99.4%	0.9%	99.1%
Ammonia	µg/stick	32.2	1.3	2	11.1	1.1	3	34.6%	65.4%	53.6%	46.4%
Arsenic	ng/stick	<7.49 (LOQ)	NA	2	<1.2 (LOQ)	NA	3	NA	NA	NA	NA
Benz[a]anthracene	ng/stick	26.5	0.5	2	1.80	0.03	3	6.8%	93.2%	10.6%	89.4%

(table continues)

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HPHCs (alphabetical order)	Unit	3R4F			Menthol 1 Tobacco Stick (B-27845)			% On Stick Basis		% On Nicotine Basis	
		Mean	SD	n	Mean	SD	n	% of 3R4F	% of Reduction to 3R4F	% of 3R4F	% of Reduction to 3R4F
Benzene	µg/stick	79.7	2.9	2	0.453	0.046	3	0.6%	99.4%	0.9%	99.1%
Benzo[a]pyrene	ng/stick	12.5	0.3	2	0.539	0.081	3	4.3%	95.7%	6.7%	93.3%
Butyraldehyde	µg/stick	83.4	NA	1	21.1	0.4	3	25.3%	74.7%	39.2%	60.8%
Cadmium	ng/stick	89.2	9.3	2	<0.28 (LOQ)	NA	3	<0.3%	>99.7%	<0.5%	>99.5%
Carbon monoxide (CO)[10]	mg/stick	30.8	1.7	2	0.320	0.000	3	1.0%	99.0%	1.6%	98.4%
Catechol	µg/stick	92.8	6.8	2	11.5	1.0	3	12.4%	87.6%	19.3%	80.7%
Chromium	ng/stick	<11.9 (LOD)	NA	2	<3.31 (LOD)	NA	3	NA	NA	NA	NA
Crotonaldehyde	µg/stick	48.2	NA	1	<3.29 (LOQ)	NA	3	<6.8%	>93.2%	<10.6%	>89.4%
Dibenz[a,h]anthracene	ng/stick	<0.689 (LOQ)	NA	2	<0.124 (LOD)	NA	3	NA	NA	NA	NA
Ethylene oxide	µg/stick	19.0	2.8	2	<0.119 (LOQ)	NA	3	<0.6%	>99.4%	<1.0%	>99.0%
Formaldehyde	µg/stick	67.9	NA	1	15.2	0.0	3	22.3%	77.7%	34.6%	65.4%

(table continues)

[10] *CO is an ISO parameter but reported as HPHC in order to report the reduction to 3R4F*

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HPHCs (alphabetical order)	Unit	3R4F			Menthol 1 Tobacco Stick (B-27845)			% On Stick Basis		% On Nicotine Basis	
		Mean	SD	n	Mean	SD	n	% of 3R4F	% of Reduction to 3R4F	% of 3R4F	% of Reduction to 3R4F
Hydrogen cyanide	µg/stick	331	10	2	<1.75 (LOQ)	NA	3	<0.5%	>99.5%	<0.8%	>99.2%
Hydroquinone	µg/stick	97.2	7.0	2	4.99	0.50	3	5.1%	94.9%	8.0%	92.0%
Isoprene	µg/stick	956	11	2	1.51	0.31	3	0.2%	99.8%	0.2%	99.8%
Lead	ng/stick	31.2	2.8	2	1.87	0.06	3	6.0%	94.0%	9.3%	90.7%
m-Cresol	µg/stick	4.23	0.11	2	0.027	0.002	3	0.6%	99.4%	1.0%	99.0%
Mercury	ng/stick	3.70	0.32	2	1.32	0.09	3	35.8%	64.2%	55.5%	44.5%
Methyl-ethyl-ketone (MEK)	µg/stick	178	NA	1	13.9	0.2	3	7.8%	92.2%	12.1%	87.9%
Nickel	ng/stick	<43.1 (LOQ)	NA	2	<15.9 (LOD)	NA	3	NA	NA	NA	NA
Nitric oxide (NO)	µg/stick	500	9	2	13.0	0.4	3	2.6%	97.4%	4.0%	96.0%
Nitro benzene	µg/stick	<0.038 (LOD)	NA	2	<0.011 (LOD)	NA	3	NA	NA	NA	NA
Nitrogen oxides (NOx)	µg/stick	554	11	2	14.5	0.5	3	2.6%	97.4%	4.1%	95.9%
N-nitrosoanabasine (NAB)	ng/stick	31.1	2.5	2	2.29	0.21	3	7.4%	92.6%	11.4%	88.6%
N-nitrosoanatabine (NAT)	ng/stick	248	15	2	12.8	1.4	3	5.1%	94.9%	8.0%	92.0%
N-Nitrosonornicotine (NNN)	ng/stick	274	8	2	7.01	0.51	3	2.6%	97.4%	4.0%	96.0%
o-Cresol	µg/stick	4.58	0.30	2	0.048	0.005	3	1.0%	99.0%	1.6%	98.4%
o-Toluidine	ng/stick	102	1	2	0.936	0.041	3	0.9%	99.1%	1.4%	98.6%

(tablecontinues)

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HPHCs (alphabetical order)	Unit	3R4F			Menthol 1 Tobacco Stick (B-27845)			% On Stick Basis		% On Nicotine Basis	
		Mean	SD	n	Mean	SD	n	% of 3R4F	% of Reduction to 3R4F	% of 3R4F	% of Reduction to 3R4F
p-Cresol	µg/stick	9.83	0.71	2	0.047	0.007	3	0.5%	99.5%	0.7%	99.3%
Phenol	µg/stick	17.1	0.9	2	0.953	0.045	3	5.6%	94.4%	8.6%	91.4%
Propionaldehyde	µg/stick	108	NA	1	12.0	0.6	3	11.1%	88.9%	17.2%	82.8%
Propylene oxide	ng/stick	1066	28	2	111	5	3	10.5%	89.5%	16.2%	83.8%
Pyrene	ng/stick	74.8	2.5	2	5.81	0.19	3	7.8%	92.2%	12.1%	87.9%
Pyridine	µg/stick	26.8	2.7	2	6.22	0.25	3	23.2%	76.8%	35.9%	64.1%
Quinoline	µg/stick	0.450	0.048	2	<0.011 (LOQ)	NA	3	<2.4%	>97.6%	<3.8%	>96.25
Resorcinol	µg/stick	1.86	0.23	2	<0.055 (LOQ)	NA	3	<3.05	>97.0%	<4.6%	>95.4%
Selenium[11]	ng/stick	<4.42 (LOD)	NA	2	1.21	0.63	3	NA	NA	NA	NA
Styrene	µg/stick	12.3	2.3	2	0.457	0.070	3	3.7%	96.3%	5.8%	94.2%
Toluene	µg/stick	137	4	2	1.28	0.12	3	0.9%	99.1%	1.4%	98.6%
Vinyl chloride	ng/stick	92.5	7.7	2	<2.19 (LOQ)	*	3	<2.4%	>97.6%	<3.7%	>96.3%

SD = Standard Deviation; n = number of replicates
<mean value: detected below the limit of quantification (LOQ). In this case LOQ is used to calculate the reduction to 3R4F

[11] In the case of selenium, the 3R4F is below the LOD while a value is reported for the THS. The LOD for 3R4F however, is higher than the value reported for the THS. In such a case, the reduction can not be quantified.

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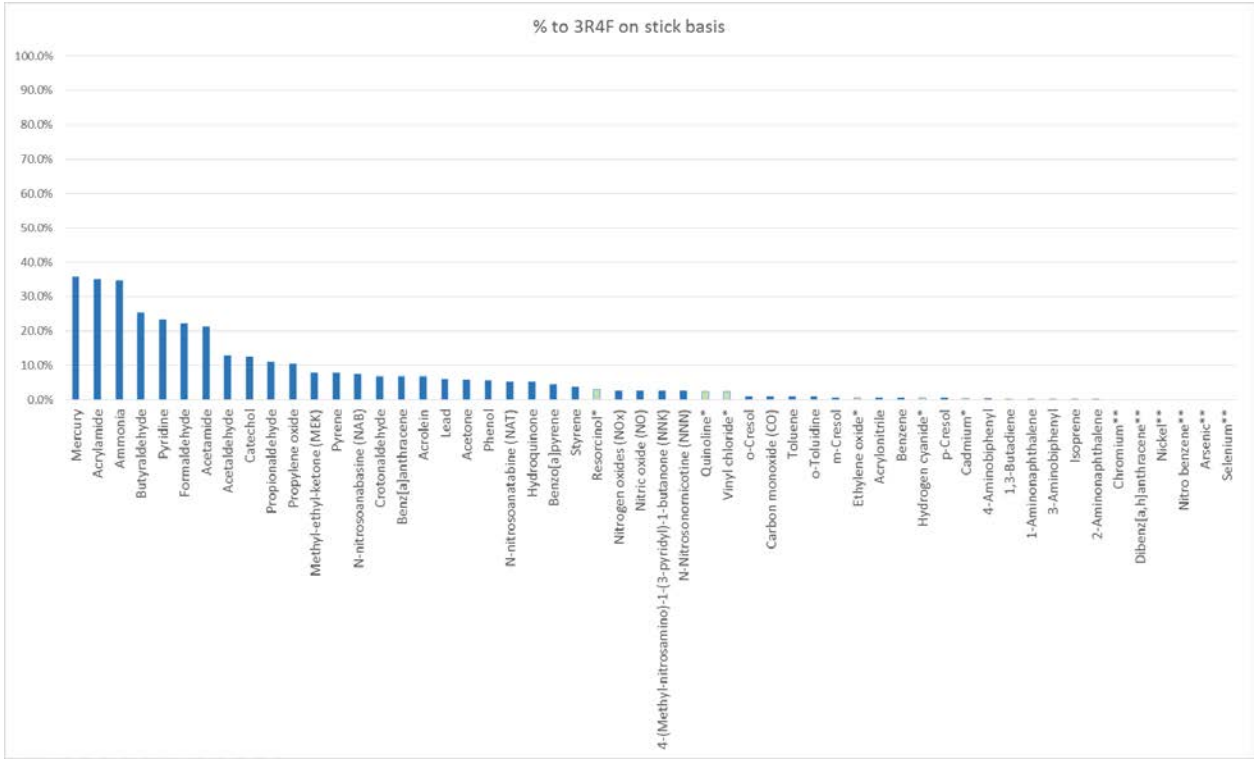


Figure 4 HPHCs of THS Menthol 1 vs. Reference 3R4F Cigarette; % on Stick Basis in Decreasing Order

Note: HPHCs marked with a "" and identified with light color bars were reported below LOD or LOQ in THS and relative % is based on the LOD/LOQ value. HPHCs marked with a "**" were found below LOD or LOQ in both reference and THS and no relative % can be calculated (marked as NA in Table 15).*

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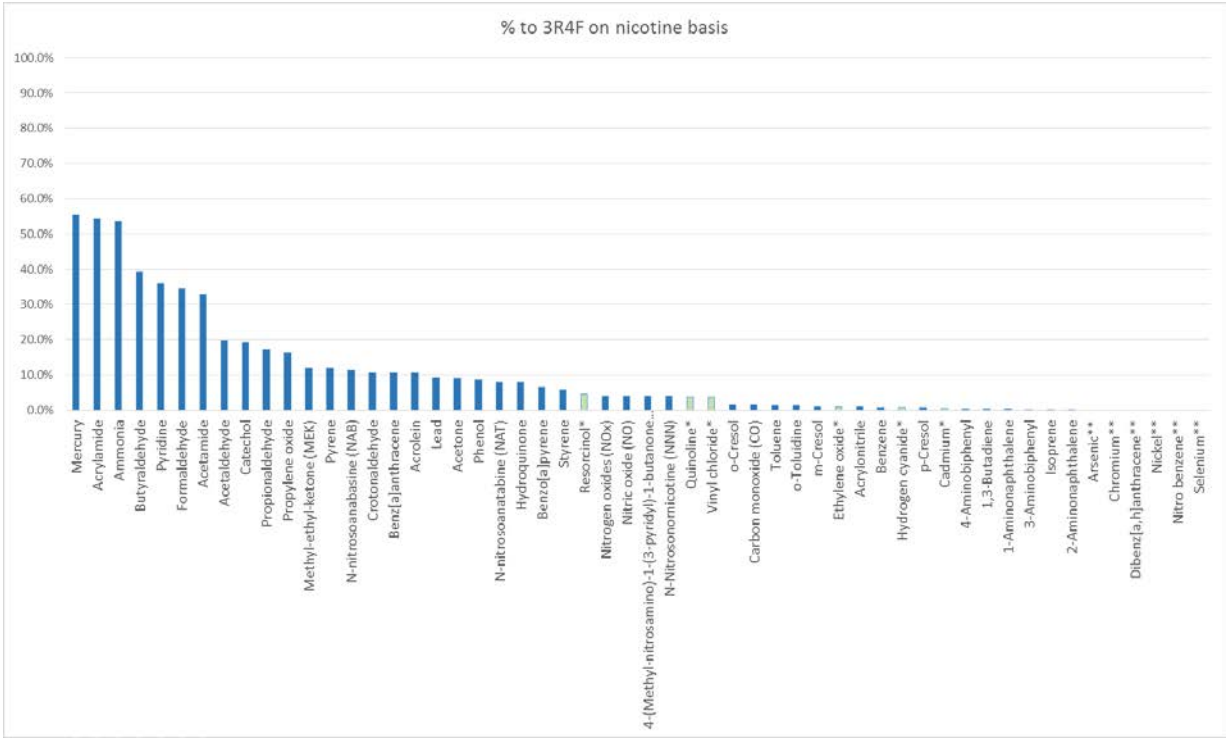


Figure 5 HPHCs of THS Menthol 1 vs. Reference 3R4F Cigarette; % on Nicotine Basis in Decreasing Order

Note: HPHCs marked with a "" and identified with light color bars were reported below LOD or LOQ in THS 2.2 and relative % is based on the LOD/LOQ value. HPHCs marked with a "**" were found below LOD or LOQ in both reference and THS and no relative % can be calculated (marked as NA in Table 15).*

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3.3.2.2.3 HPHCs – FDA List (18 + 6) – Menthol 1 Tobacco Sticks

Analysis of the FDA Abbreviated list of HPHCs, 18 in aerosol and 6 measured in the tobacco, was performed on Menthol 1 Tobacco Sticks by Labstat. Both the ISO (see results in Table 16) and Health Canada Intense (HCI) smoking regimes (see results in Table 17) were used. The tobacco constituent results are provided in Table 18.

A description of the analysis is provided in Section 7.1NS298-H_Report Menthol.

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Table 16 FDA Abbreviated HPHC List Results – ISO Conditions – Menthol 1 Tobacco Sticks

Aerosol Constituent Name	CAS no.	Unit of Measure	B-25900		B-25901		B-25902		Sample size per batch	Method
			Result	SD	Result	SD	Result	SD	Replicates	
Acetaldehyde	75-07-0	µg/stick	125	5	129	6	126	4	7	Labstat T-104
Acrolein	107-02-8	µg/stick	4.06	0.253	3.93	0.42	3.92	0.20	7	Labstat T-104
Acrylonitrile	107-13-1	µg/stick	<0.107 (LOQ)	NA	<0.107 (LOQ)	NA	<0.107 (LOQ)	NA	7	Labstat TMS-00124
4-aminobiphenyl	92-67-1	ng/stick	0.006	0.003	0.006	0.002	0.005	0.001	7	Labstat TMS-00128
1-Amino-naphthalene	134-32-7	ng/stick	0.034	0.019	0.028	0.017	<0.027 (LOQ)	NA	7	Labstat TMS-00128
2-amino-naphthalene	91-59-8	ng/stick	0.022	0.016	0.021	0.019	<0.012 (LOQ)	NA	7	Labstat TMS-00128
Ammonia	7664-41-7	µg/stick	1.47	0.30	1.40	0.23	1.23	0.09	7	Labstat T-101

(table continues)

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Aerosol Constituent Name	CAS no.	Unit of Measure	B-25900		B-25901		B-25902		Sample size per batch	Method
			Result	SD	Result	SD	Result	SD	Replicates	
Benzene	71-43-2	µg/stick	0.294	0.104	0.287	0.124	0.230	0.053	7	Labstat TMS-00124
Benzo(a)pyrene	50-32-8	ng/stick	<0.354 (LOQ)	NA	<0.354 (LOQ)	NA	<0.354 (LOQ)	NA	7	Labstat TMS-00120
1,3 Butadiene	106-99-0	µg/stick	0.121	0.05	0.115	0.013	0.110	0.010	7	Labstat TMS-00124
Carbon Monoxide	630-08-0	mg/stick	<0.223 (LOQ)	NA	<0.223 (LOQ)	NA	<0.223 (LOQ)	NA	20	T-115*
Crotonaldehyde	4170-30-3	µg/stick	<3.29 (LOQ)	NA	<3.29 (LOQ)	NA	<3.29 (LOQ)	NA	7	T-104*
Formaldehyde	50-00-0	µg/stick	11.9	0.3	12.2	0.4	12.0	0.2	7	T-104*
Isoprene	78-79-5	µg/stick	1.06	0.12	0.997	0.181	0.929	0.061	7	Labstat TMS-00124
Nicotine (Total)	54-11-5	mg/stick	0.393	0.034	0.392	0.031	0.381	0.031	20	T-115*

(table continues)

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Aerosol Constituent Name	CAS no.	Unit of Measure	B-25900		B-25901		B-25902		Sample size per batch	Method
			Result	SD	Result	SD	Result	SD	Replicates	
4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)	64091-91-4	ng/stick	2.83	0.41	3.08	0.29	2.88	0.27	7	Labstat TMS-00135
N-nitrosonornicotine (NNN)	16543-55-8	ng/stick	3.19	0.63	3.45	0.34	3.27	0.24	7	Labstat TMS-00135
Toluene	108-88-3	µg/stick	0.921	0.318	0.845	0.322	0.658	0.219	7	Labstat TMS-00124

SD = standard deviation; < = below limit of quantitation with LOQ provided provided by Labstat; NA = Not applicable no standard deviation can be calculated
*Canadian Tobacco Reporting Regulations: 2000-07-19 Canada Gazette Part II, Vol. 134, No. 15 Part 3: Emissions from Designated Tobacco Products.

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Table 17 FDA Abbreviated HPHC List Results – Health Canada Intense – Menthol 1 Tobacco Sticks

Aerosol Constituent Name	CAS no.	Unit of Measure	B-25900		B-25901		B-25902		Sample size per batch	Method
			Result	SD	Result	SD	Result	SD	Replicates	
Acetaldehyde	75-07-0	µg/stick	186	5	199	12	199	7	7	Labstat T-104
Acrolein	107-02-8	µg/stick	9.16	0.62	9.49	1.25	9.31	0.68	7	Labstat T-104
Acrylonitrile	107-13-1	µg/stick	0.121	0.025	0.128	0.029	0.139	0.025	7	Labstat TMS-00124
4-aminobiphenyl	92-67-1	ng/stick	0.010	0.002	0.009	0.002	0.008	0.002	7	Labstat TMS-00128
1-Amino-naphthalene	134-32-7	ng/stick	0.040	0.013	0.036	0.009	0.036	0.006	7	Labstat TMS-00128
2-amino-naphthalene	91-59-8	ng/stick	0.025	0.006	0.017	0.006	0.017	0.007	7	Labstat TMS-00128
Ammonia	7664-41-7	µg/stick	12.5	1.6	11.8	1.0	11.0	0.8	7	Labstat T-101

(table continues)

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Aerosol Constituent Name	CAS no.	Unit of Measure	B-25900		B-25901		B-25902		Sample size per batch	Method
			Result	SD	Result	SD	Result	SD	Replicates	
Benzene	71-43-2	µg/stick	0.509	0.075	0.476	0.050	0.518	0.069	7	Labstat TMS-00124
Benzo(a)pyrene	50-32-8	ng/stick	0.512	0.038	0.585	0.044	0.521	0.059	7	Labstat TMS-00120
1,3 Butadiene	106-99-0	µg/stick	0.230	0.028	0.218	0.024	0.237	0.030	7	Labstat TMS-00124
Carbon Monoxide	630-08-0	mg/stick	0.338	0.035	0.331	0.041	0.324	0.008	20	T-115*
Crotonaldehyde	4170-30-3	µg/stick	<3.29 (LOQ)	NA	<3.29 (LOQ)	NA	<3.29 (LOQ)	NA	7	T-104*
Formaldehyde	50-00-0	µg/stick	14.4	0.4	15.4	1.4	14.8	0.6	7	T-104*
Isoprene	78-79-5	µg/stick	1.69	0.24	1.50	0.22	1.68	0.22	7	Labstat TMS-00124
Nicotine (Total)	54-11-5	mg/stick	1.07	0.05	1.14	0.06	1.10	0.05	20	T-115*

(table continues)

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Aerosol Constituent Name	CAS no.	Unit of Measure	B-25900		B-25901		B-25902		Sample size per batch	Method
			Result	SD	Result	SD	Result	SD	Replicates	
4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)	64091-91-4	ng/stick	6.51	0.57	7.66	0.48	6.34	0.051	7	Labstat TMS-00135
N-nitrosonornicotine (NNN)	16543-55-8	ng/stick	7.95	0.37	8.87	0.53	7.77	0.071	7	Labstat TMS-00135
Toluene	108-88-3	µg/stick	1.38	0.23	1.31	0.13	1.55	0.29	7	Labstat TMS-00124

SD = Standard Deviation < = below limit of quantitation with LOQ provided provided by Labstat; NA = Not applicable no standard deviation can be calculated
*Canadian Tobacco Reporting Regulations: 2000-07-19 Canada Gazette Part II, Vol. 134, No. 15 Part 3: Emissions from Designated Tobacco Products.

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Table 18 FDA Abbreviated HPHC List Tobacco Constituents Results – Menthol 1 Tobacco Sticks

Constituent	CAS No.	Unit	B-25900		B-25901		B-25902		Sample Size	Method
			Mean	SD	Mean	SD	Mean	SD		
Ammonia	7664-41-7	µg/unit	112.6	2.3	106.3	5.1	105.0	1.2	7	T-302*
Arsenic	7440-38-2	ng/unit	40.5	1.1	39.5	1.6	43.2	1.4	7	T-306*
Cadmium	7440-43-9	ng/unit	158.3	1.6	149.0	1.7	148.8	2.4	7	T-306*
Nicotine	54-11-5	mg/unit	4.8	0.08	4.6	0.07	4.7	0.1	7	T-301*
NNK	64091-91-4	ng/unit	61.0	3.1	54.9	3.2	49.7	2.4	7	Labstat TWT-00333
NNN	16543-55-8	ng/unit	95.6	6.7	82.6	11.4	79.7	13.0	7	Labstat TWT-00333

SD = standard deviation

*Canadian Tobacco Reporting Regulations: 2000-07-19 Canada Gazette Part II, Vol. 134, No. 15 Part 3: Emissions from Designated Tobacco Products.

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3.3.2.2.4 Droplet Size Distribution – Menthol 1 Tobacco Sticks

The Droplet Size Distribution (DSD) influences the deposition pattern in the respiratory tract of inhaled aerosols. This assay is used to determine the DSD of the aerosol generated from the THS product. This assay is based on the use of a cascade impactor to gravimetrically determine the DSD.

Table 19 shows the MMAD and GSD for all replicates on the 3 tested batches for the mentholated Tobacco Sticks.

Figure 6 shows a plot of the same data, where MMAD are plotted as a function of the GSD. The dotted line defines the respirability upper limit, based on the MMAD value and its distribution (GSD), based on the respirability upper threshold defined at 2.5 µm. Similarly to the regular, all measured THS data fall within the respirability region.

Table 19 MMAD and GSD Values for Menthol 1 Tobacco Sticks

Replicate	B-25902		B-25901		B-25900	
	MMAD [µm]	GSD	MMAD [µm]	GSD	MMAD [µm]	GSD
1	0.57	1.40	0.66	1.32	0.64	1.33
2	0.62	1.36	0.60	1.37	0.66	1.30
3	0.60	1.38	0.69	1.38	0.73	1.36
4	0.62	1.39	0.75	1.34	0.63	1.25
5	0.62	1.36	0.73	1.38	0.74	1.36
6[12]	NA	NA	0.73	1.37	0.66	1.31
7	0.54	1.39	0.72	1.37	0.66	1.33
8	0.56	1.41	0.64	1.33	0.67	1.35
9	0.58	1.37	0.66	1.41	0.73	1.36
10	0.60	1.37	0.70	1.37	0.69	1.34

[12] *No sufficient mass was accumulated in the PIXE cascade impactor for replicate 6 to obtain a MMAD and a GSD value.*

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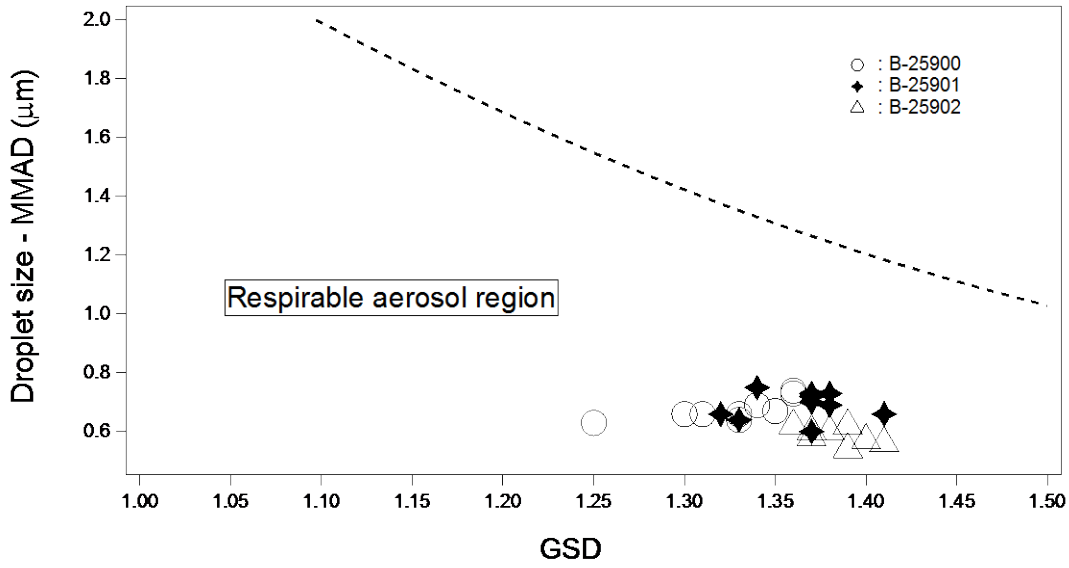


Figure 6 MMAD Plotted as a Function of GSD Values.

Note: The dotted line separates the respirable (below the curve) from the non-respirable aerosol (above the curve).

3.3.2.2.5 Nicotine Free Dry Particulate Matter (NFDPM), Nicotine, Carbon Monoxide (ISO) – Menthol 1 Tobacco Sticks

We use here the ISO terminology NFDPM to describe the aerosol collected mass from THS. It should be noted that the NFDPM of the THS has a very different constituent make-up in comparison to conventional cigarettes. The glycerol, reported separately, is part of the NFDPM, as further described in Section 3.3.2.1.5.

Table 20 shows the results of ISO parameters (NFDPM, Nicotine and Carbon monoxide) determined in mainstream aerosol under ISO methodology for three batches of Menthol 1 Tobacco Sticks, using the Tobacco Heating Device. The detailed results are available in Section 7.1 PT_SR_ISO parameters Menthol.

Table 20 ISO Parameters – Menthol 1 Tobacco Sticks

Constituent	Unit	B-25902		B-25901		B-25900	
		Result	SD*	Result	SD	Result	SD
Nicotine	mg/stick	0.41	0.031	0.43	0.029	0.43	0.024
NFDPM	mg/stick	5.1	0.84	4.9	0.88	5.2	1.11
CO	mg/stick	0.3	0.02	0.3	0.02	0.3	0.02

SD = Standard Deviation

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3.3.2.2.6 Stability Menthol 1 Tobacco Sticks

Stability Specifications

The stability specifications for the Menthol 1 Tobacco Stick are identical to those described in Table 13 with the following exceptions:

(b) (4)

(b) (4)

The proposed stability specifications for Menthol 1 Tobacco Sticks are based on that for conventional cigarettes. The maximum internal level for menthol in CC is 2.0 mg/cigarette in the ISO smoking regime. This translates into 4.0 mg/stick in the Health Canada Intense smoking regime, which supports the proposed upper limit.

Stability Summary

Three batches of Menthol 1 Tobacco Sticks manufactured at the proposed site of commercial manufacture were placed on stability using the protocol provided in Table 21. A matrix approach was used for the stability studies. Detailed information regarding the stability study are provided in Appendix A3.3-7.

(b) (4) The batches remained within the stability specifications at all storage conditions. Stability data and statistical analysis are provided in Appendix A3.3-8.

Complete results for the stability studies will provided to the Agency when they become available. PMI anticipates that these data will be available during the review process.

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Table 21 Stability Protocol for Menthol 1 Tobacco Sticks

Batch	Storage Conditions	Analysis Time points (months)
(b) (4)		(b) (4)

Shelf Life

Based on the available stability data (6 months) and the anticipated availability of acceptable 12 months data during the review process, a shelf life of 12 months is proposed for the Menthol 1 Tobacco Sticks.

Ongoing Stability Program

Stability will be performed on the Menthol 1 Tobacco Sticks using the protocol described in Table 12 with the addition of testing for menthol at all time points. Details of the post-approval protocol are provided in Appendix A3.3-5.

Stability Commitment

The stability studies described in this document will be continued throughout the proposed shelf life.

Analytical Methods used for Stability

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Reference is made to Section 3.2.2.5 for information pertaining to the analytical methods used for stability.

Stability Data

Reference is made to Appendix A3.3-8 for the stability data.

3.3.2.3 Menthol 2 Tobacco Stick

3.3.2.3.1 Batch Release – Menthol 2 Tobacco Sticks

(b) (4) (see Section 3.3.2.2.1). (b) (4) Batch Release (BR) Specifications are provided in Appendix A3.2.1-3 and the methods used to analyse the batch release are described in Appendix A3.2.2-5. A batch analysis for three batches of Menthol 2 Tobacco Sticks, manufactured as described in this submission, is provided in Table 13. Batch Release certificates are provided in Appendix A3.3-9.

(b) (4)

The sampling pattern is clearly defined and documented prior to production iof the Tobacco Sticks.

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Table 22 Batch Analysis Menthol 2 Tobacco Sticks

Parameter	Batch Number	B-31061 41-2572271	B-31062 41-2572272	B-31063 41-2572273
	Date of Manufacture	15th July 2016	16th July 2016	16th July 2016
	Batch Size	(b) (4)		
	Acceptance Criteria*	Results		
(b) (4)				

3.3.2.3.2 PMI list (PMI-58) – Menthol 2 Tobacco Sticks

A(b) (4) (see Table 2) are tested for the PMI-58 (which contains the FDA abbreviated list of 18 HPHCs)(b) (4) (see Section 3.2.1.4). A list of the PMI-58 is provided in Appendix A3.3-2. (b) (4)

A comparison of the PMI-58 results of Menthol 2 Tobacco Sticks in comparison to the 3R4F Reference Cigarette is provided in Section 7.1 Menthol 2 TC vs 3R4F_Labstat NS336_H.

As stated in Section 3.3.2.1.2, sufficient data is available (b) (4), and routine evaluation of batches is based upon a (b) (4)

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(b) (4) For a justification of this approach, see Appendix A3.2.1-12. The PMI 58 are comprised of the main aerosol deliveries and a set of 54 Harmful or Potentially Harmul Constituents (HPHCs). A comparison of the results for the PMI-58 in Menthol 2 Tobacco Sticks vs. the 3R4F reference cigarette is provided in Table 23 for the main aerosol deliveries, and in Table 24 for the 54 HPHCs. The testing for this study was performed by LabStat. Based on the data, there is an average reduction of HPHCs of more than 93% (stick basis) and 88% (nicotine basis) for Menthol 2 Tobacco Sticks compared to 3R4F.

Table 23 Main Aerosol Deliveries for THS – Menthol 2 Tobacco Sticks

Aerosol deliveries according to ISO 4387; 8454; 10315	Unit	3R4F			THS Menthol 2		
		Mean	SD	n	Mean	SD	n
Glycerol[13]	mg/stick	2.32	NA	1	4.49	0.23	3
Nicotine	mg/stick	1.93	NA	1	1.17	0.03	3
Nicotine Free Dry Particulate Matter (NFDPM)[14]	mg/stick	28.5	NA	1	18.1	1.1	3
Total Particulate Matter (TPM)	mg/stick	44.9	NA	1	55.3	0.83	3
Water[15]	mg/stick	14.5	NA	1	36.0	0.49	3

SD = Standard Deviation; n = number of replicates, NA = Not Applicable

[13] *Product specific not part of ISO parameter*
[14] *The ISO terminology, NFDPM, is used to describe the aerosol collected mass from THS. The NFDPM of the THS has a very different constituent make-up in comparison to conventional cigarettes. The glycerol, reported separately, is part of the NFDPM.*
[15] *The water value reported here was determined according to ISO 4387, and it is underestimated compared to the true value, due to important water losses linked the high water content of the THS 2.2 aerosol. Accurate water measurements can only be obtained with a modified procedure, not available in Labstat [see Ghosh, D. & Jeannet, C. (2014). An Improved Cambridge Filter Pad Extraction Methodology to Obtain More Accurate Water and "Tar" Values: In Situ Cambridge Filter Pad Extraction Methodology. Beiträge zur Tabakforschung / Contributions to Tobacco Research, 26(2), pp. 38-49].*

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Table 24 54 HPHCs Results – Menthol 2 Tobacco Sticks

HPHCs (alphabetical order)	Unit	3R4F			Menthol 2 Tobacco Stick (B-27850)			% On Stick Basis		% On Nicotine Basis	
		Mean	SD	n	Mean	SD	n	% of 3R4F	% of Reduction to 3R4F	% of 3R4F	% of Reduction to 3R4F
1,3-Butadiene	µg/stick	93.0	19.7	3	0.192	0.006	3	0.2%	99.8%	0.3%	99.7%
1-Aminonaphthalene	ng/stick	21.7	0.7	3	0.060	0.003	3	0.3%	99.7%	0.5%	99.5%
2-Aminonaphthalene	ng/stick	17.0	0.3	3	0.031	0.009	3	0.2%	99.8%	0.3%	99.7%
3-Aminobiphenyl	ng/stick	4.51	0.14	3	0.009	0.001	3	0.2%	99.8%	0.3%	99.7%
4-(Methyl-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK)	ng/stick	282	28	3	5.52	0.34	3	2.0%	98.0%	3.2%	96.8%
4-Aminobiphenyl	ng/stick	3.02	0.12	3	0.010	0.002	3	0.3%	99.7%	0.5%	99.5%
Acetaldehyde	µg/stick	1656	42.3	3	192	9	3	11.6%	88.4%	19.1%	80.9%
Acetamide	µg/stick	14.2	1.18	3	2.94	0.215	3	20.8%	79.2%	34.2%	65.8%
Acetone	µg/stick	658	14.3	3	38.7	2.29	3	5.9%	94.1%	9.7%	90.3%
Acrolein	µg/stick	161	5.22	3	9.32	0.569	3	5.8%	94.2%	9.5%	90.5%
Acrylamide	µg/stick	5.00	0.18	3	1.68	0.099	3	33.5%	66.5%	55.2%	44.8%
Acrylonitrile	µg/stick	23.5	4.0	3	<0.107 (LOQ)	NA	3	<0.5%	>99.5%	<0.7%	>99.3%
Ammonia	µg/stick	26.7	3.7	2	10.7	0.943	3	40.1%	59.9%	66.0%	34.0%
Arsenic	ng/stick	<7.49 (LOQ)	NA	3	<1.20 (LOQ)	NA	3	NA	NA	NA	NA

(table continues)

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HPHCs (alphabetical order)	Unit	3R4F			Menthol 2 Tobacco Stick (B-27850)			% On Stick Basis		% On Nicotine Basis	
		Mean	SD	n	Mean	SD	n	% of 3R4F	% of Reduction to 3R4F	% of 3R4F	% of Reduction to 3R4F
Benz[a]anthracene	ng/stick	25.6	1.92	3	1.51	0.177	3	5.9%	94.1%	9.7%	90.3%
Benzene	µg/stick	73.5	10.1	3	0.473	0.036	3	0.6%	99.4%	1.1%	98.9%
Benzo[a]pyrene	ng/stick	14.4	1.08	3	0.448	0.073	3	3.1%	96.9%	5.1%	94.9%
Butyraldehyde	µg/stick	79.6	1.17	3	18.9	0.821	3	23.7%	76.3%	39.0%	61.0%
Cadmium	ng/stick	104	7.16	3	0.301	0.235	3	0.3%	99.7%	0.5%	99.5%
Carbon monoxide (CO)[16]	mg/stick	33.3	NA	1	0.480	0.000	3	1.4%	98.6%	2.4%	97.6%
Catechol	µg/stick	101	4.48	3	14.1	0.211	3	14.0%	86.0%	23.1%	76.9%
Chromium	ng/stick	<11.9 (LOD)	NA	3	<11.0 (LOQ)	NA	3	NA	NA	NA	NA
Crotonaldehyde	µg/stick	49.9	1.13	3	<3.29 (LOQ)	NA	3	<6.6%	>93.4%	<10.9%	>89.1%
Dibenz[a,h]anthracene	ng/stick	1.02	0.121	3	<0.124 (LOD)	NA	3	<12.1%	>87.9%	<20.0%	>80.0%
Ethylene oxide	µg/stick	15.7	0.628	3	0.125	0.041	3	0.8%	99.2%	1.3%	98.7%
Formaldehyde	µg/stick	92.9	4.75	3	10.0	0.773	3	10.7%	89.3%	17.7%	82.3%
Hydrogen cyanide	µg/stick	378	13.0	3	2.71	0.191	3	0.7%	99.3%	1.2%	98.8%

(table continues)

[16] *CO is an ISO parameter but reported as HPHC in order to report the reduction to 3R4F*

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HPHCs (alphabetical order)	Unit	3R4F			Menthol 2 Tobacco Stick (B-27850)			% On Stick Basis		% On Nicotine Basis	
		Mean	SD	n	Mean	SD	n	% of 3R4F	% of Reduction to 3R4F	% of 3R4F	% of Reduction to 3R4F
Hydroquinone	µg/stick	92.9	8.47	3	6.48	0.220	3	7.0%	93.0%	11.5%	88.5%
Isoprene	µg/stick	927	88.6	3	1.27	0.281	3	0.1%	99.9%	0.2%	99.8%
Lead	ng/stick	30.2	0.459	3	<1.62 (LOQ)	NA	3	<5.4%	>94.6%	<8.8%	>91.2%
m-Cresol	µg/stick	4.14	0.558	3	<0.019 (LOQ)	NA	3	<0.5%	>99.5%	<0.8%	>99.2%
Mercury	ng/stick	4.13	0.283	2	1.89	0.066	3	45.6%	54.4%	75.2%	24.8%
Methyl-ethyl-ketone (MEK)	µg/stick	168	3.69	3	7.37	0.417	3	4.4%	95.6%	7.2%	92.8%
Nickel	ng/stick	<12.9 (LOD)	NA	3	<15.9 (LOD)	NA	3	NA	NA	NA	NA
Nitric oxide (NO)	µg/stick	471	36.5	3	12.8	1.04	3	2.7%	97.3%	4.5%	95.5%
Nitro benzene	µg/stick	<0.038 (LOD)	NA	3	<0.011 (LOD)	NA	3	NA	NA	NA	NA
Nitrogen oxides (NOx)	µg/stick	523	37.5	3	13.9	1.14	3	2.7%	97.3%	4.4%	95.6%
N-nitrosoanabasine (NAB)	ng/stick	33.9	1.03	3	2.19	0.442	3	6.5%	93.5%	10.6%	89.4%
N-nitrosoanatabine (NAT)	ng/stick	314	29.6	3	15.4	2.61	3	4.9%	95.1%	8.1%	91.9%
N-Nitrosonornicotine (NNN)	ng/stick	274	22.4	3	7.75	0.766	3	2.8%	97.2%	4.7%	95.3%
o-Cresol	µg/stick	4.98	0.525	3	0.043	0.005	3	0.9%	99.1%	1.4%	98.6%
o-Toluidine	ng/stick	106	3.14	3	0.982	0.083	3	0.9%	99.1%	1.5%	98.5%

(table continues)

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HPHCs (alphabetical order)	Unit	3R4F			Menthol 2 Tobacco Stick (B-27850)			% On Stick Basis		% On Nicotine Basis	
		Mean	SD	n	Mean	SD	n	% of 3R4F	% of Reduction to 3R4F	% of 3R4F	% of Reduction to 3R4F
p-Cresol	µg/stick	10.1	1.21	3	<0.034 (LOQ)	NA	3	<0.3%	>99.7%	<0.6%	>99.4%
Phenol	µg/stick	16.7	1.39	3	0.927	0.072	3	5.5%	94.5%	9.1%	90.9%
Propionaldehyde	µg/stick	118	3.35	3	11.8	0.662	3	10.0%	90.0%	16.4%	83.6%
Propylene oxide	ng/stick	921	64.6	3	119	6.27	3	12.9%	87.1%	21.3%	78.7%
Pyrene	ng/stick	93.8	4.95	3	7.55	0.552	3	8.0%	92.0%	13.2%	86.8%
Pyridine	µg/stick	27.0	1.45	3	6.05	0.326	3	22.4%	77.6%	36.9%	63.1%
Quinoline	µg/stick	0.410	0.004	3	<0.011 (LOQ)	NA	3	<2.7%	>97.3%	<4.4%	>95.6%
Resorcinol	µg/stick	1.93	0.130	3	<0.055 (LOQ)	NA	3	<2.9%	>97.1%	<4.7%	>95.3%
Selenium	ng/stick	<4.42 (LOD)	NA	3	<0.83 (LOQ)	NA	3	NA	NA	NA	NA
Styrene	µg/stick	11.9	1.08	3	0.460	0.080	3	3.9%	96.1%	6.3%	93.7%
Toluene	µg/stick	119	8.39	3	1.03	0.272	3	0.9%	99.1%	1.4%	98.6%
Vinyl chloride	ng/stick	101	13.9	3	<0.657 (LOD)	NA	3	<0.7%	>99.3%	<1.1%	>98.9%

SD = Standard Deviation; n = number of replicates
<mean value: detected below the limit of quantification (LOQ). In this case LOQ is used to calculate the reduction to 3R4F

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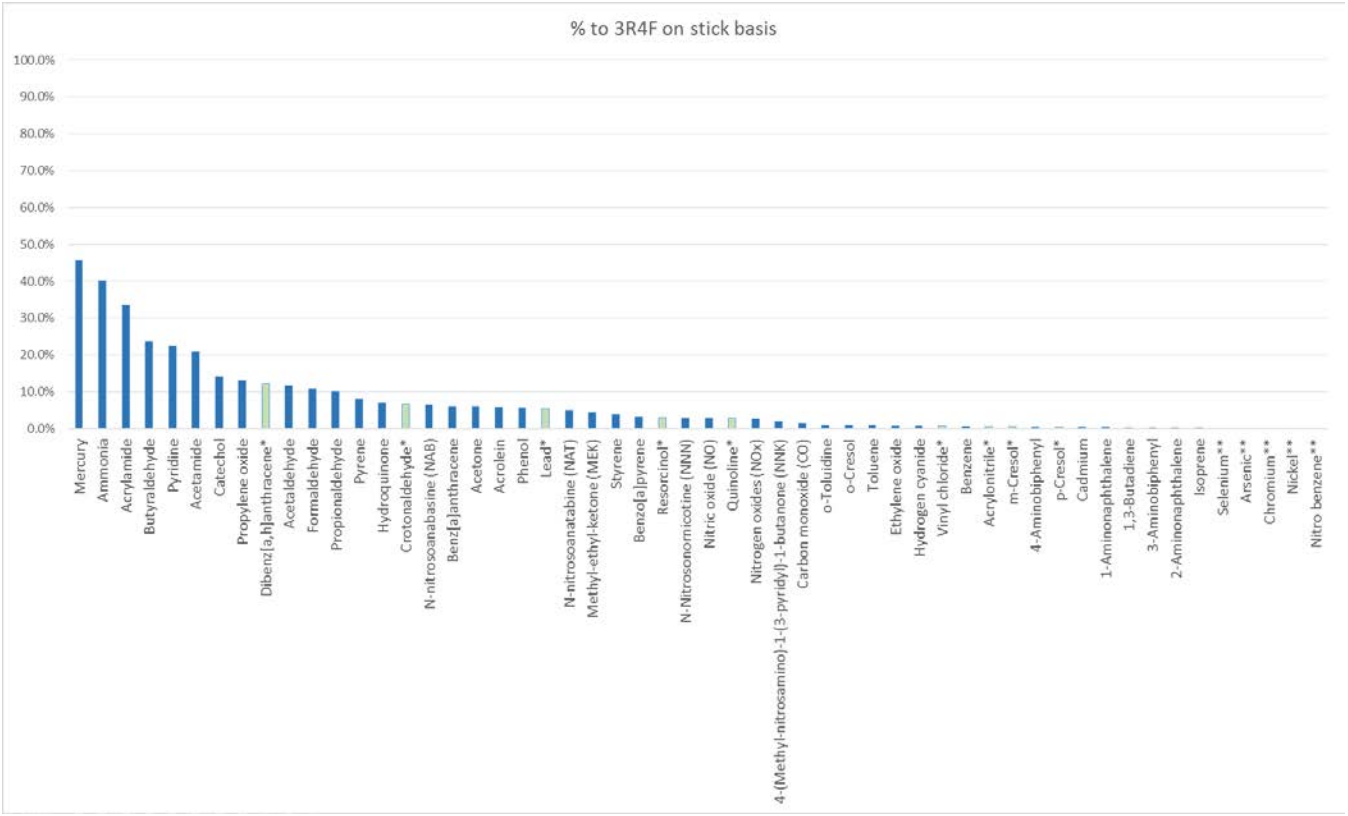


Figure 7 HPHCs of THS Menthol 2 vs. Reference 3R4F Cigarette; % on Stick Basis in Decreasing Order

Note: HPHCs marked with a "" and identified with light color bars were reported below LOD or LOQ in THS and relative % is based on the LOD/LOQ value. HPHCs marked with a "**" were found below LOD or LOQ in both reference and THS and no relative % can be calculated (marked as NA in Table 15).*

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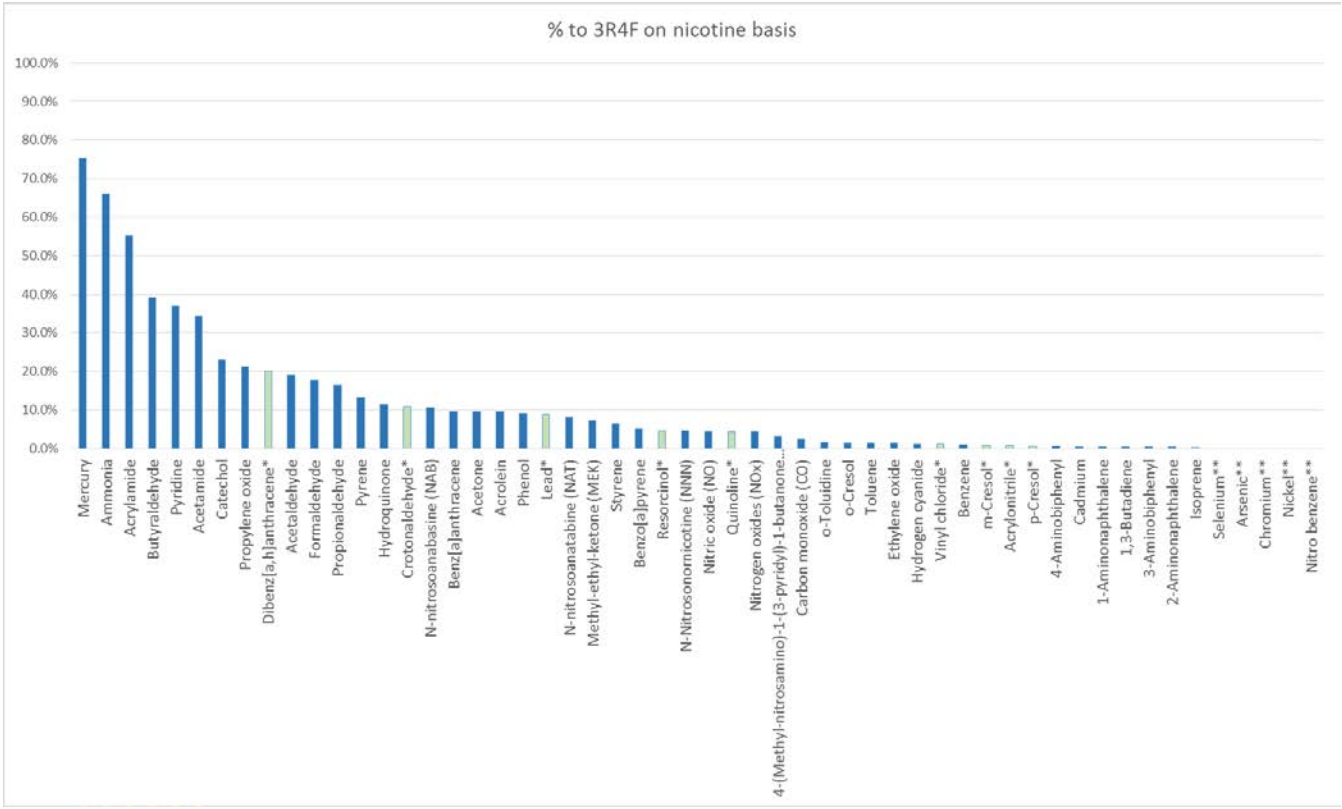


Figure 8 HPHCs of THS Menthol 2 vs. Reference 3R4F Cigarette; % on Nicotine Basis in Decreasing Order

Note: HPHCs marked with a "" and identified with light color bars were reported below LOD or LOQ in THS 2.2 and relative % is based on the LOD/LOQ value. HPHCs marked with a "**" were found below LOD or LOQ in both reference and THS and no relative % can be calculated (marked as NA in Table 24).*

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3.3.2.3.3 HPHCs – FDA List (18 + 6) – Menthol 2 Tobacco Sticks

Analysis of the FDA Abbreviated list of HPHCs, 18 in aerosol and 6 measured in the tobacco, was performed on Menthol 2 Tobacco Sticks by Labstat. Both the ISO (see results in Table 25) and Health Canada Intense (HCI) smoking regimes (see results in Table 26) were used. The tobacco constituent results are provided in Table 27.

A description of the analysis is provided in Section 7.1 NS335-H_Report_Menthol 2.

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Table 25 FDA Abbreviated HPHC List Results – ISO Conditions – Menthol 2 Tobacco Sticks

Aerosol Constituent Name	CAS no.	Unit of Measure	B-31061		B-31062		B-31063		Sample size per batch	Method
			Result	SD	Result	SD	Result	SD	Replicates	
Acetaldehyde	75-07-0	µg/stick	150	11	151	7	149	6	7	Labstat T-104
Acrolein	107-02-8	µg/stick	5.10	0.47	5.13	0.33	4.95	0.37	7	Labstat T-104
Acrylonitrile	107-13-1	µg/stick	<0.032 (LOD)	NA	<0.107 (LOQ)	NA	<0.032 (LOD)	NA	7	Labstat TMS-00124
4-aminobiphenyl	92-67-1	ng/stick	0.006	0.004	0.008	0.004	0.006	0.004	7	Labstat TMS-00128
1-Amino-naphthalene	134-32-7	ng/stick	<0.027 (LOQ)	NA	<0.027 (LOQ)	NA	0.030	0.015	7	Labstat TMS-00128
2-amino-naphthalene	91-59-8	ng/stick	0.022	0.023	0.020	0.010	0.025	0.021	7	Labstat TMS-00128
Ammonia	7664-41-7	µg/stick	2.71	0.77	3.08	0.93	2.09	0.4	7	Labstat T-101

(table continues)

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Aerosol Constituent Name	CAS no.	Unit of Measure	B-31061		B-31062		B-31063		Sample size per batch	Method
			Result	SD	Result	SD	Result	SD	Replicates	
Benzene	71-43-2	µg/stick	0.194	0.038	0.224	0.051	0.193	0.038	7	Labstat TMS-00124
Benzo(a)pyrene	50-32-8	ng/stick	<0.354 (LOQ)	NA	<0.354 (LOQ)	NA	<0.354 (LOQ)	NA	7	Labstat TMS-00120
1,3 Butadiene	106-99-0	µg/stick	0.120	0.045	0.114	0.044	0.141	0.056	7	Labstat TMS-00124
Carbon Monoxide	630-08-0	mg/stick	<0.223 (LOQ)	NA	<0.223 (LOQ)	NA	<0.223 (LOQ)	NA	20	T-115*
Crotonaldehyde	4170-30-3	µg/stick	<3.29 (LOQ)	NA	<3.29 (LOQ)	NA	<3.29 (LOQ)	NA	7	T-104*
Formaldehyde	50-00-0	µg/stick	7.50	0.39	7.47	0.39	7.23	0.57	7	T-104*
Isoprene	78-79-5	µg/stick	1.05	0.39	0.943	0.141	1.17	0.28	7	Labstat TMS-00124
Nicotine (Total)	54-11-5	mg/stick	0.463	0.030	0.465	0.027	0.474	0.026	20	T-115*

(table continues)

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Aerosol Constituent Name	CAS no.	Unit of Measure	B-31061		B-31062		B-31063		Sample size per batch	Method
			Result	SD	Result	SD	Result	SD	Replicates	
4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)	64091-91-4	ng/stick	1.83	0.32	1.61	0.29	1.69	0.20	7	Labstat TMS-00135
N-nitrosonornicotine (NNN)	16543-55-8	ng/stick	3.03	0.23	3.02	0.27	3.20	0.27	7	Labstat TMS-00135
Toluene	108-88-3	µg/stick	0.655	0.243	0.926	0.306	0.686	0.245	7	Labstat TMS-00124

SD = standard deviation; < = below limit of quantitation/detection with LOQ/LOD provided provided by Labstat; NA = Not applicable no standard deviation can be calculated *Canadian Tobacco Reporting Regulations: 2000-07-19 Canada Gazette Part II, Vol. 134, No. 15 Part 3: Emissions from Designated Tobacco Products.

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Table 26 FDA Abbreviated HPHC List Results – Health Canada Intense – Menthol 2 Tobacco Sticks

Aerosol Constituent Name	CAS no.	Unit of Measure	B-31061		B-31062		B-31063		Sample size per batch	Method
			Result	SD	Result	SD	Result	SD	Replicates	
Acetaldehyde	75-07-0	µg/stick	202	12	212	10	213	9	7	Labstat T-104
Acrolein	107-02-8	µg/stick	9.83	1.13	10.6	0.8	10.7	0.6	7	Labstat T-104
Acrylonitrile	107-13-1	µg/stick	0.120	0.039	0.150	0.050	0.122	0.062	7	Labstat TMS-00124
4-aminobiphenyl	92-67-1	ng/stick	0.009	0.005	0.009	0.002	0.009	0.002	7	Labstat TMS-00128
1-Amino-naphthalene	134-32-7	ng/stick	<0.027 (LOQ)	NA	0.029	0.005	0.029	0.010	7	Labstat TMS-00128
2-amino-naphthalene	91-59-8	ng/stick	0.017	0.007	0.017	0.003	0.018	0.007	7	Labstat TMS-00128
Ammonia	7664-41-7	µg/stick	12.0	0.9	11.3	1.0	11.3	1.5	7	Labstat T-101

(table continues)

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Aerosol Constituent Name	CAS no.	Unit of Measure	B-31061		B-31062		B-31063		Sample size per batch	Method
			Result	SD	Result	SD	Result	SD	Replicates	
Benzene	71-43-2	µg/stick	0.473	0.075	0.473	0.033	0.491	0.035	7	Labstat TMS-00124
Benzo(a)pyrene	50-32-8	ng/stick	0.553	0.112	0.544	0.029	0.514	0.064	7	Labstat TMS-00120
1,3 Butadiene	106-99-0	µg/stick	0.212	0.061	0.204	0.017	0.225	0.071	7	Labstat TMS-00124
Carbon Monoxide	630-08-0	mg/stick	0.476	0.018	0.480	0.000	0.480	0.026	20	T-115*
Crotonaldehyde	4170-30-3	µg/stick	<3.29 (LOQ)	NA	<3.29 (LOQ)	NA	<3.29 (LOQ)	NA	7	T-104*
Formaldehyde	50-00-0	µg/stick	9.84	0.99	10.5	0.9	10.2	0.7	7	T-104*
Isoprene	78-79-5	µg/stick	1.74	0.58	1.90	0.44	1.63	0.44	7	Labstat TMS-00124
Nicotine (Total)	54-11-5	mg/stick	1.25	0.06	1.30	0.05	1.28	0.07	20	T-115*

(table continues)

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Aerosol Constituent Name	CAS no.	Unit of Measure	B-31061		B-31062		B-31063		Sample size per batch	Method
			Result	SD	Result	SD	Result	SD	Replicates	
4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK)	64091-91-4	ng/stick	5.67	0.55	6.22	0.55	5.73	0.54	7	Labstat TMS-00135
N-nitrosonornicotine (NNN)	16543-55-8	ng/stick	7.44	0.38	8.69	0.52	7.74	0.49	7	Labstat TMS-00135
Toluene	108-88-3	µg/stick	1.48	0.23	1.36	0.20	1.35	0.3	7	Labstat TMS-00124

SD = Standard Deviation < = below limit of quantitation with LOQ provided provided by Labstat; NA = Not applicable no standard deviation can be calculated
*Canadian Tobacco Reporting Regulations: 2000-07-19 Canada Gazette Part II, Vol. 134, No. 15 Part 3: Emissions from Designated Tobacco Products.

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Table 27 FDA Abbreviated HPHC List Tobacco Constituents Results – Menthol 2 Tobacco Sticks

Constituent	CAS No.	Unit	B-31061		B-31062		B-31063		Sample Size	Method
			Mean	SD	Mean	SD	Mean	SD		
Ammonia	7664-41-7	µg/unit	421	17	427	13	426	7	7	T-302*
Arsenic	7440-38-2	ng/unit	143	5	138	4	141	11	7	T-306*
Cadmium	7440-43-9	ng/unit	708	20	682	19	688	16	7	T-306*
Nicotine	54-11-5	mg/unit	18000	406	17591	689	17759	272	7	T-301*
NNK	64091-91-4	ng/unit	204	12	198	11	196	8	7	Labstat TWT-00333
NNN	16543-55-8	ng/unit	242	27	255	16	247	10	7	Labstat TWT-00333

SD = standard deviation

*Canadian Tobacco Reporting Regulations: 2000-07-19 Canada Gazette Part II, Vol. 134, No. 15 Part 3: Emissions from Designated Tobacco Products.

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3.3.2.3.4 Droplet Size Distribution – Menthol 2 Tobacco Sticks

The Droplet Size Distribution (DSD) influences the deposition pattern in the respiratory tract of inhaled aerosols. This assay is used to determine the DSD of the aerosol generated from the THS product. This assay is based on the use of a cascade impactor to gravimetrically determine the DSD.

Table 28 shows the MMAD and GSD for all replicates on the 3 tested batches for the mentholated Tobacco Sticks.

Figure 6 shows a plot of the same data, where MMAD are plotted as a function of the GSD. The dotted line defines the respirability upper limit, based on the MMAD value and its distribution (GSD), based on the respirability upper threshold defined at 2.5 µm. Similarly to the regular, all measured THS data fall within the respirability region.

Table 28 MMAD and GSD Values for Menthol 2 Tobacco Sticks

Replicate	B-31061		B-31062		B-31063	
	MMAD [µm]	GSD	MMAD [µm]	GSD	MMAD [µm]	GSD
1	0.88	1.23	0.86	1.27	0.88	1.29
2	0.81	1.31	0.75	1.36	NA	NA
3	0.83	1.31	0.81	1.32	0.83	1.33
4	0.66	1.32	0.88	1.21	0.88	1.29
5	0.66	1.31	0.88	1.14	0.85	1.29
6	0.66	1.31	NA	NA	0.87	1.23
7	0.67	1.33	0.88	1.25	0.86	1.26
8	0.72	1.43	0.88	1.27	0.89	1.29
9	NA	NA	0.68	1.47	0.88	1.33
10	0.73	1.39	0.74	1.36	0.90	1.23

NA = No sufficient mass was accumulated in the PIXE cascade impactor for replicate 6 to obtain a MMAD and a GSD value.

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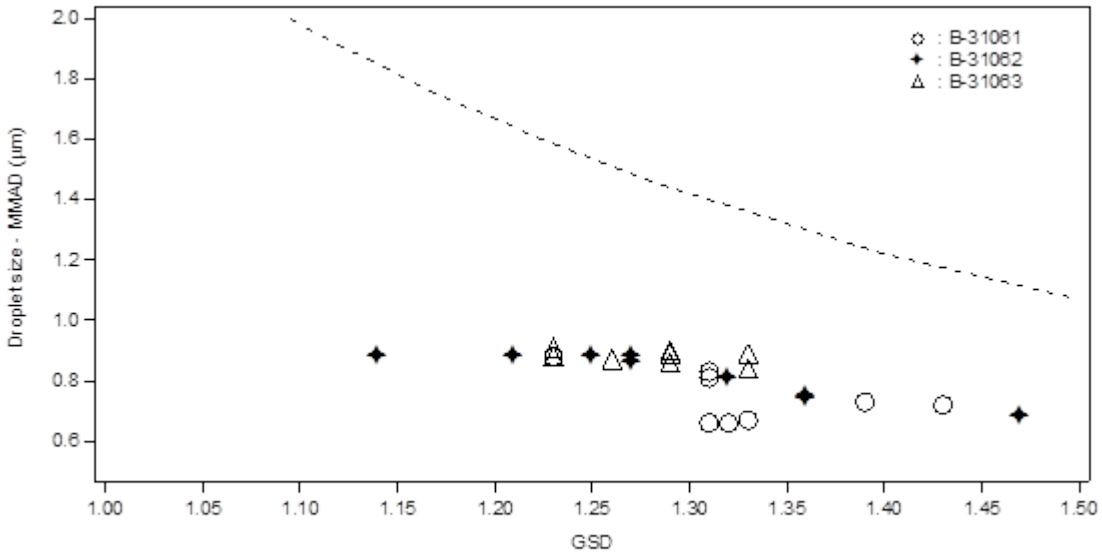


Figure 9 MMAD Plotted as a Function of GSD Values.

Note: The dotted line separates the respirable (below the curve) from the non-respirable aerosol (above the curve).

3.3.2.3.5 Nicotine Free Dry Particulate Matter (NFDPM), Nicotine, Carbon Monoxide (ISO) – Menthol 2 Tobacco Sticks

We use here the ISO terminology NFDPM to describe the aerosol collected mass from THS. It should be noted that the NFDPM of the THS has a very different constituent make-up in comparison to conventional cigarettes. The glycerol, reported separately, is part of the NFDPM, as further described in Section 3.3.2.1.5

Table 29 shows the results of ISO parameters (NFDPM, Nicotine and Carbon monoxide) determined in mainstream aerosol under ISO methodology for three batches of Menthol 2 Tobacco Sticks, using the Tobacco Heating Device. The detailed results are available in Section 7.1 PT_SR_ISO parameters Menthol 2.

Table 29 ISO Parameters – Menthol 2 Tobacco Sticks

Constituent	Unit	B-31061		B-31062		B-31063	
		Result	SD	Result	SD	Result	SD
Nicotine	mg/stick	0.45	0.029	0.46	0.026	0.47	0.034
NFDPM	mg/stick	5.3	0.83	5.3	0.83	5.3	0.79
CO	mg/stick	0.2	0.04	0.2	0.04	0.2	0.04

SD = Standard Deviation

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3.3.2.3.6 Stability Menthol 2 Tobacco Sticks

Stability Specifications

The stability specifications for the Menthol 2 Tobacco Stick are identical to those described in Table 22 with the following exceptions:

(b) (4)

(b) (4)

The proposed stability specifications for Menthol 2 Tobacco Sticks are based on that for conventional cigarettes. The maximum internal level for menthol in CC is 2.0 mg/cigarette in the ISO smoking regime. This translates into 4.0 mg/stick in the Health Canada Intense smoking regime, which supports the proposed upper limit.

Stability Summary

Three batches of Menthol 2 Tobacco Sticks manufactured at the proposed site of commercial manufacture were placed on stability using the protocol provided in Table 30. A matrix approach was used for the stability studies. Detailed information regarding the stability study are provided in Appendix A3.3-10.

Complete results for the stability studies will provided to the Agency when they become available. PMI anticipates that these data will be available during the review process.

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Table 30 Stability Protocol for Menthol 2 Tobacco Sticks

Batch	Storage Conditions	Analysis Time points (months)
		(b) (4)
(b) (4)		

Shelf Life

Based on the available stability data from a corresponding product and the anticipated availability of data during the review process, a shelf life of 12 months is proposed for the Menthol 2 Tobacco Sticks.

Ongoing Stability Program

Stability will be performed on the Menthol 2 Tobacco Sticks using the protocol described in Table 12 with the addition of testing for menthol at all time points. Details of the post-approval protocol are provided in Appendix A3.3-5.

Stability Commitment

The stability studies described in this document will be continued throughout the proposed shelf life.

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Analytical Methods used for Stability

Reference is made to Section 3.2.2.5 for information pertaining to the analytical methods used for stability.

3.3.3 References

Ghosh D., Jeannet C., Philip Morris International. 2014. An Improved Cambridge Filter Pad Extraction Methodology to Obtain More Accurate Water and "Tar" Values. In Situ Cambridge Filter Pad Extraction Methodology. Beiträge zur Tabakforschung International/Contributions to Tobacco Research. Volume 26 (2)

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