Aerosol Chemistry

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6.1.1. Aerosol chemistry and physics

6.1.1.1. Chemistry: History and Context of the Different HPHCs Lists

6.1.1.1.1. Introduction

Cigarette smoke is a complex mixture in which more than 6000 constituents have been identified, representing nearly all known organic chemical classes (Rodgman and Perfetti, 2013). Within this complex mixture, several harmful and potentially harmful constituents (HPHCs) have been associated with the causation of disease in smokers, such as aromatic amines (Bartsch et al., 1993; Vineis and Pirastu, 1997), gas-phase constituents (Costa et al., 1986; Penn and Snyder, 1996; Witschi et al., 1997), oxygen-free radicals (Pryor, 1997; Valavanidis et al., 2009), polycyclic aromatic hydrocarbons (PAHs) (Penn et al., 1981; Smith et al., 2000), and tobacco-specific *N*-nitrosamines (TSNAs) (Hecht, 1998, 1999). However, a causal link between a specific smoke constituent and disease has not been conclusively established.

Since it is not possible to quantify all constituents present in cigarette smoke, various priority lists of smoke toxicants in mainstream cigarette smoke have been proposed for the evaluation of commercial market cigarettes based mainly on risk assessments (Cunningham et al., 2011; Fowles and Dybing, 2003; Haussmann, 2012; Hecht, 2006; Hoffmann et al., 1997; Pankow et al., 2007; Rodgman and Green, 2003; Smith and Hansch, 2000; Talhout et al., 2011; Vorhees and Dodson, 1982; Xie et al., 2012).

6.1.1.1.2. Smoke Constituent Reporting

Smoke constituent reporting and brand-by-brand disclosure is required by different regulatory authorities, either on an annual basis (Health Canada, British Columbia, Brazil, and Taiwan) or as a one-off disclosure (Massachusetts Department of Health, UK, and Australia) (Wright, 2015). The lists of smoke constituents to be reported show a great deal of similarity between different regulatory authorities (Table 1); however, with the exception of Health Canada (Health Canada, 2000), specific test methods have not been defined or validated.

6.1.1.1.3. World Health Organization Study Group on Tobacco Product Regulation – 2007

The World Health Organization (WHO) Study Group on Tobacco Product Regulation (TobReg), composed of leading public health experts and scientists, has proposed a scientific basis for tobacco product regulation (WHO, 2007). As part of their recommendation, this group concluded that chemical measurements of smoke constituents determined by a smoking machine is probably the most effective approach currently available for scientifically assessing differences between products for regulatory assessment of product toxicity (Burns et al., 2008). However, evaluating tobacco products using machine-measured "tar" (or using ISO 4387 terminology, Nicotine Free Dry Particulate Matter, NFDPM), nicotine, and carbon monoxide (CO) yields may be misleading to smokers and most regulators. It was concluded that the Health Canada intense (HCI) machine-smoking protocol (55 mL puff volume, 30 seconds puff interval, 2 seconds puff, 100% vent blocking, butt length 23 mm for non-filter cigarettes or the length of filter overwrap plus 3 mm for filter

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brands) (Health Canada, 2000) offered significant advantages over both the International Organization for Standardization (ISO)/Federal Trade Commission (FTC) standard machine-smoking regimen (35 mL puff volume, 60 second puff interval, 2 second puff, no vent blocking) (ISO: ISO, 1991; FTC: Federal Trade Commission, 1967) and the Massachusetts Department of Public Health machine-smoking regimen (45 mL puff volume, 30 seconds puff interval, 2 seconds puff, 50% vent blocking, butt length 23 mm for non-filter cigarettes or the length of filter overwrap plus 3 mm for filter brands). Cigarettes should be collected and sampled according to ISO 8243 (ISO, 2006) and conditioned prior to machine-smoking for at least 48 hours at 22 ± 1°C and a relative humidity of 60 ± 3% according to ISO 3402 (ISO, 1999). Using the HCI machine-smoking protocol, it was recommended that manufacturers of tobacco products report to the Member States of the WHO Framework Convention on Tobacco Control (FCTC) the yields of a priority list of 25 smoke constituents in mainstream smoke (Table 1) expressed on a per milligram (mg) NFDPM basis. Furthermore, it was proposed to regulate the presence of two TSNAs, namely *N*-nitrosonornicotine (NNN) and 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK) based on ceilings of 114 and 72 ng normalized per mg nicotine in smoke, respectively. Normalizing the levels of NNK and NNN per mg nicotine was considered to reduce the misleading differences between the levels of both toxicants when expressed on a per cigarette basis (Hammond et al., 2007).

6.1.1.1.4. World Health Organization Study Group on Tobacco Product Regulation – 2008

In 2008, TobReg (WHO, 2008) reduced the previous priority list from 25 to 18 toxicants in mainstream smoke and proposed that 9 priority toxicants (1,3-butadiene, acetaldehyde, acrolein, benzene, benzo[a]pyrene, CO, formaldehyde, NNK, and NNN) should be mandated for lowering and regulation (Table 1). The most important criterion for the selection of priority compounds for regulation was evidence of toxicity (Fowles and Dybing, 2003). It was proposed that cigarette samples should be obtained as part of a series of at least five sub-periods from either manufacturers/importers or from retail locations according to the ISO standard method 8243 for sampling of cigarettes (ISO, 2006). The ISO standard method 3402 for conditioning of cigarettes prior to smoking (ISO, 1999) and the HCI machine-smoking regimen (Health Canada, 2000) were proposed. It was also proposed that nicotine and CO yields should be determined by ISO standard methods 10315 and 8454, respectively (ISO, 2000, ISO 2007), while other toxicants should be determined by official methods recommended by Health Canada (2000) and expressed on a per mg nicotine basis.

6.1.1.1.5. World Health Organization Study Group on Tobacco Product Regulation – 2015

In 2015, TobReg identified 39 priority toxicants in mainstream cigarette smoke (WHO, 2015). The list of 39 priority toxicants was based primarily on lists of toxicants previously identified by Health Canada (Health Canada, 2000), the National Institute for Public Health and the Environment in the Netherlands (Talhout et al., 2011), and the U.S. Food and Drug Administration (FDA, 2012). Previous recommendations for standard cigarettes were extended to cover other smoked tobacco products, such as non-standard cigarettes (e.g.,

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'slims'), cigars, water pipes, roll-your-own and low ignition-propensity cigarettes. However, specific recommendations on machine-smoking regimens for these products were not detailed. It was, however, recommended that standardized testing methods validated by the WHO Tobacco Laboratory Network (TobLabNet), a global network of government, academic and independent laboratories should be used. At present, TobLabNet has validated methods for the determination of B[*a*]P, CO, humectants, nicotine, "tar", and TSNAs [*N*-nitrosoanabasine, *N*-nitrosoanatabine, NNK, and NNN] in mainstream smoke, while methods for the determination of ammonia, volatile organic compounds and aldehydes are in progress. TobReg also concluded that the same principles used to set upper limits of emissions to toxicants in foods and other consumer products should be applied to tobacco products and that "tar" need not be determined as it is not a sound basis for regulation.

6.1.1.1.6. Food and Drug Administration List of 93 - 2012

The U.S. FDA has established a list of 93 HPHCs in tobacco products and tobacco smoke (FDA, 2012a) and issued draft guidance on the reporting of an abbreviated list of 18 HPHCs in mainstream cigarette smoke and 9 HPHCs in smokeless tobacco products for which analytical protocols are well established and widely available (FDA, 2012b). The protocols recommend machine-smoking of cigarettes to be performed using both the ISO and HCI regimens (ISO, 1991; Health Canada, 2000) and seven replicates used for the determination of all HPHCs, except nicotine and CO where 20 replicates are recommended. HPHC quantities should be expressed on a per cigarette basis and reported by tobacco product manufacturers to the FDA. In addition, the FDA has encouraged tobacco product manufacturers to include HPHC data in new product applications.

6.1.1.1.7. Philip Morris International's Aerosol Chemistry List of 58

The list of constituents measured in the evaluation of the mainstream aerosol composition of THS 2.2 is presented in Table 1 and compared to lists of priority smoke constituents proposed by TobReg (WHO, 2007; WHO, 2008; WHO, 2015), Health Canada (Health Canada, 2000), and the FDA (FDA, 2012). The list of 58 constituents ('PMI-58 list') covers both smoke constituents and analytes determined by ISO standard methods (CO, nicotine, NFDPM, total particulate matter [TPM], and water) and chemical constituent representatives of all major toxicologically relevant chemical classes of compounds present in both the particulate-phase and gas/vapor-phase of cigarette smoke and was originally based on recommendations by the U.S. Consumer Product Safety Commission on smoke constituents presenting toxicological concerns in low ignition-potential cigarettes (US CPSC, 1993) and compounds reported in cigarette smoke which have been classified as either known or probable human carcinogens by the International Agency for Research on Cancer (IARC, 1985). Further additional HPHCs identified in mainstream cigarette smoke were considered and, if deemed relevant, included in the PMI-58 list of constituents requiring measurement for product evaluation. The PMI-58 list contains all constituents required for reporting by different regulatory authorities including the 18 HPHCs which are subject to reporting on the FDA's abbreviated list (FDA, 2012b), Health Canada (Health Canada, 2000), all smoke constituents identified as priority toxicants and proposed for reporting by TobReg (WHO, 2007; WHO 2008; WHO, 2015).

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All machine-smoking methods have their limitations (Borgerding and Klus, 2005; Dixon and Borgerding, 2006; Roemer and Carchman, 2011), particularly the inability to reflect the variation in human puffing patterns and exposure to smoke constituents (Hammond et al., 2007; Stratton et al., 2001). Compared to the ISO 3308 machine-smoking regimen (ISO, 1991), the more intense machine-smoking regimen proposed by Health Canada (2000) results in much higher aerosol constituent yields which are thought to more closely represent smoker exposure to smoke constituents (Hammond et al., 2007; Hammond and O'Conner, 2008). No single machine-smoking regimen can represent all human smoking behavior (Stratton et al., 2001); however, machine-smoking testing is useful for characterizing tobacco product emissions for design and regulatory purposes. Data on emissions from machine measurements may also be useful as inputs for product hazard assessment, but smoking machine-derived data are not intended to be, nor are they valid as, measures of human exposure or risks (Hatsukami et al., 2012; WHO, 2012).

Table 1 PMI-58 list of aerosol constituents compared to some proposed lists of harmful and potentially harmful constituents (HPHCs)

PMI-58 list	HC (2000)	WHO (2007)	WHO (2008)	FDA (2012)	WHO (2015)
ISO Parameters:					
1. Carbon monoxide	●*	●	●*	●*	●*
2. Nicotine	●*	●		●*	●*
3. NFDPM	●*	●			
4. Total Particulate Matter					
5. Water					
Aliphatic dienes:					
6. 1,3-Butadiene	●*	●	●*	●*	●*
7. Isoprene	●*			●*	●*

(table continues)

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PMI-58 list	HC (2000)	WHO (2007)	WHO (2008)	FDA (2012)	WHO (2015)
Carbonyls:					
8. Acetaldehyde	●*	●	●*	●*	●*
9. Acetone	●*			●	●*
10. Acrolein	●*	●	●*	●*	●*
11. Butyraldehyde	●*				●*
12. Crotonaldehyde	●*		●	●*	●*
13. Formaldehyde	●*	●	●*	●*	●*
14. Methyl ethyl ketone	●*			●	
15. Propionaldehyde	●*			●	●*
Acid derivatives:					
16. Acetamide				●	
17. Acrylamide				●	
18. Acrylonitrile			●	●*	●*
Epoxides:					
19. Ethylene oxide		●		●	
20. Propylene oxide				●	
Nitro compounds:					
21. Nitrobenzene				●	
Aromatic amines:					
22. 1-Aminonaphthalene	●*			●*	●*
23. 2-Aminonaphthalene	●*	●	●	●*	●*

(table continues)

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PMI-58 list	HC (2000)	WHO (2007)	WHO (2008)	FDA (2012)	WHO (2015)
24. 3-Aminobiphenyl	●*				●*
25. 4-Aminobiphenyl	●*	●	●	●*	●*
26. *o*-Toluidine				●	
***N*-Heterocyclic aromatics:**					
27. Pyridine	●*				●*
28. Quinoline	●*			●	●*
Halogen compounds:					
29. Vinyl chloride				●	
Inorganic compounds:					
30. Ammonia	●*			●*	●*
31. Hydrogen cyanide	●*	●	●	●	●*
32. Nitric oxide	●*		●[a]		●[a,*]
33. Nitrogen oxides	●*	●			
Monocyclic aromatic compounds:					
34. Benzene	●*	●	●*	●*	●*
35. Styrene	●*			●	
36. Toluene	●*			●*	●*
***N*-nitrosamines:**					
37. 4-(Methylnitrosamino)-1-(3-pyridyl)-1-butanone [NNK]	●*	●	●*	●*	●*
38. *N*-Nitrosoanabasine	●*	●			●*

(table continues)

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PMI-58 list	HC (2000)	WHO (2007)	WHO (2008)	FDA (2012)	WHO (2015)
39. *N*-Nitrosoanatabine	●*	●			●*
40. *N*-Nitrosonornicotine [NNN]	●*	●	●*	●*	●*
Phenols:					
41. *o*-Cresol	●*			●	●*
42. *m*-Cresol	●b,*			●	●*
43. *p*-Cresol				●	●*
44. Catechol	●*		●	●	●*
45. Hydroquinone	●*		●		●*
46. Phenol	●*			●	●*
47. Resorcinol	●*				●*
Polycyclic aromatic hydrocarbons:					
48. Benzo[*a*]pyrene	●*	●	●*	●*	●*
49. Benz[*a*]anthracene				●	
50. Dibenz[*a*,*h*]anthracene				●	
51. Pyrene					
Metals:					
52. Arsenic	●*	●		●	●*
53. Cadmium	●*	●	●	●	●*
54. Chromium	●*	●		●	
55. Lead	●*	●		●	●*
56. Mercury	●*	●		●	●*

(table continues)

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PMI-58 list	HC (2000)	WHO (2007)	WHO (2008)	FDA (2012)	WHO (2015)
57. Nickel	●*	●		●	
58. Selenium	●*	●		●	
Product specific:					
Glycerol					

Abbreviations and symbols: FDA, Food and Drug Administration; HC, Health Canada; WHO, World Health Administration; ●, listed constituent; ●*, listed constituent subject to reporting; [a], combined nitric oxide and nitrogen oxides; [b], combined *m*+*p* cresols

6.1.1.2. Aerosol physics

The physical property of an aerosol is characterized by two main parameters that are the Mass Median Aerodynamic Diameter (MMAD), a diameter which separates the mass size distribution into two equivalent portions, while the Geometric Standard Deviation (GSD) describes the distribution of the mass around the MMAD. The MMAD is a measure of the transport behavior of an aerosol by associating it to an equivalent sphere of unit density. Consequently, the MMAD is a key parameter that allows to determine how an aerosol of a known size is transported from its generation to its deposition in lungs.

From an inhalation standpoint, two main steps describe aerosol transport in lungs. The first step is linked to the aerosol inhalability corresponding to the fraction of droplets entering the mouth from an external source of aerosol. In general, the inhalable fraction (IF) is close to unity for submicron aerosols (IF > 97%). The inhalable fraction at the mouth level will be transported further in the direction of the trachea-brachial region and then in the alveolar region as defined by American Conference of Governmental Industrial Hygienists (ACGIH). Two definitions of the respirability are available. One considers droplets below or equal to 4 micrometers for which at least 50% of the aerosol is transported to the alveolar region. A second definition is linked to PM2.5, where 85% of an aerosol of a size below or equal to 2.5 micrometers is transported in the alveolar region.

6.1.1.3. Results

Table 2 shows an overview of the studies conducted in the context of the aerosol chemistry and physics.

For the aerosol chemistry, the studies were conducted by [redacted] (b) (4), according to their procedures and methods, while the aerosol physics studies were conducted at PMI R&D

[1] (b) (4) [redacted]

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laboratories in Neuchâtel, Switzerland. All methods (chemistry and physics) were accredited according to ISO 17025.

Table 2 Aerosol chemistry and physics assessment studies summary. For the PMI-58, a reference cigarette (3R4F) was smoked in parallel to the THS 2.2

Assay	Tobacco sticks	Batch number	Study number
PMI-58	THS Regular: (b) (4) / Dorado II / (b) (4) (b) (4)	B-27846 (composite of B-25904/ 41-2397948; B-25905/41-2397950; B-25906/41-2382704)	(b) (4) report NS308-H
	THS Menthol: (b) (4) /Dorado (b) (4) (b) (4)	B-27845 (composite of B-25900/ 41.2381531; B-25901/41.2374718; B-25902/41.2379112)	(b) (4) report NS309-H
DSD	THS Regular: (b) (4) / Dorado II /(b) (4) (b) (4)	B-25904/ 41-2397948 B-25905/ 41-2397950 B-25906/ 41-2382704	RLS-ZRH-2016-95
	THS Menthol: (b) (4) 1/Dorado (b) (4)	B-25900/ 41.2381531 B-25901/ 41.2374718 B-25902/ 41.2379112	RLS-ZRH-2016-94

6.1.1.3.1. Aerosol and smoke generation

Prior to conducting the aerosol generation experiment, all test items were conditioned according to ISO 3402 conditions (22°C ± 1°C and 60% ± 2%). The laboratory condition set during the aerosol generation was maintained at 22°C ± 2°C and 60% ± 5% relative humidity.

All aerosol and smoke collections were performed according to the Health Canada Intense (HCI) machine-smoking protocol (55 mL puff volume, 30 seconds puff interval, 2 seconds puff, 100% vent blocking, butt length 23 mm for non-filter cigarettes or the length of filter overwrap plus 3 mm for filter brands) (Health Canada, 2000) on a linear smoking machine.

For the THS 2.2, the vent blocking does not apply as the tobacco sticks are not ventilated (no perforation at the filter level). The butt length does not apply either, as the sticks are not consumed by combustion and remain of the same size throughout use. The beginning and the end of the aerosol collection for the tobacco sticks differs from what is applied to a cigarette, as there is not ignition and the stick is not consumed by combustion. The aerosol collection starts after the pre-heating period (30 seconds) and stops at 6 minutes, which is the end of the heating period. This results in exactly 12 puffs under HCI.

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6.1.1.3.2. PMI-58 for the proposed products - Tables and Graphs

Table 3 and Table 4: Summary of results of THS 2.2. Yields of the 3R4F reference cigarette from the same study are included for the comparison.

Figure 1 and Figure 2 show a graphical representation of the data of Table 4, showing, for each HPHC, their proportion (in %) compared to the 3R4F (set at 100 %) on a stick and nicotine basis respectively.

Table 3 Main aerosol deliveries for THS 2.2 Regular

Aerosol deliveries according to ISO 4387; 8454; 10315	Unit	3R4F			THS 2.2		
		mean	SD	n	mean	SD	n
Glycerol[2]	mg/stk	2.08	0.113	2	5.02	0.101	3
Nicotine	mg/stk	1.74	0.039	2	1.29	0.047	3
Nicotine Free Dry Particulate Matter (NFDPM)[3]	mg/stk	25.0	1.14	2	19.4	1.62	3
Total Particulate Matter (TPM)	mg/stk	41.4	3.28	2	50.9	2.90	3
Water[4]	mg/stk	14.7	2.10	2	30.2	2.17	3

[2] *Product specific not part of ISO parameter.*

[3] *We use here the ISO terminology NFDPM to describe the aerosol collected mass from THS 2.2. It should be noted that the NFDPM of the THS 2.2 has a very different constituent make-up in comparison to conventional cigarette. The glycerol, reported separately, is part of the NFDPM.*

[4] *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* (b) (4) *t [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 4 **HPHCs from the PMI-58 for THS 2.2 regular and the 3R4F (excluding main aerosol deliveries reported in Table 3). % of 3R4F and % reduction vs. 3R4F are calculated on stick basis and on nicotine basis. When HPHCs for both THS 2.2 and reference product were below LOD or LOQ, % is replaced by NA (as no reduction can be calculated). For HPHCs that were found below LOD or LOQ for the THS 2.2, the % of reduction was calculated with the LOD/LOQ value**

HPHCs (alphabetic order)		3R4F			THS 2.2			% on stick basis		% on nicotine basis	
	Unit	mean	SD	n	mean	SD	n	% of 3R4F	% of reduction to 3R4F	% of 3R4F	% of reduction to 3R4F
1,3-Butadiene	µg/stk	89.2	1.73	2	0.207	0.0160	3	0.2%	99.8%	0.3%	99.7%
1-Aminonaphthalene	ng/stk	20.9	0.145	2	0.0427	0.00513	3	0.2%	99.8%	0.3%	99.7%
2-Aminonaphthalene	ng/stk	17.5	0.497	2	0.0223	0.00321	3	0.1%	99.9%	0.2%	99.8%
3-Aminobiphenyl	ng/stk	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/stk	244.7	7.54	2	7.80	0.423	3	3.2%	96.8%	4.3%	95.7%
4-Aminobiphenyl	ng/stk	3.21	0.105	2	0.0087	0.0012	3	0.3%	99.7%	0.4%	99.6%
Acetaldehyde	µg/stk	1602	NA	1	192	11.6	3	12.0 %	88.0%	16.2%	83.8%
Acetamide	µg/stk	13.0	0.501	2	2.96	0.134	3	22.7 %	77.3%	30.7%	69.3%
Acetone	µg/stk	653	NA	1	30.7	1.86	3	4.7%	95.3%	6.4%	93.6%

(table continues)

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HPHCs (alphabetic order)	Unit	3R4F			THS 2.2			% on stick basis		% on nicotine basis	
		mean	SD	n	mean	SD	n	% of 3R4F	% of reduction to 3R4F	% of 3R4F	% of reduction to 3R4F
Acrolein	µg/stk	158	NA	1	8.32	0.755	3	5.3%	94.7%	7.1%	92.9%
Acrylamide	µg/stk	4.50	0.294	2	1.58	0.0543	3	35.0 %	65.0%	47.3%	52.7%
Acrylonitrile	µg/stk	21.2	1.44	2	0.145	0.0112	3	0.7%	99.3%	0.9%	99.1%
Ammonia	µg/stk	33.2	0.539	2	12.2	0.973	3	36.8 %	63.2%	49.8%	50.2%
Arsenic	ng/stk	<7.49 (LOQ)	NA	2	<0.36 (LOD)	NA	3	NA	NA	NA	NA
Benz[a]anthracene	ng/stk	28.4	1.09	2	2.65	0.0647	3	9.3%	90.7%	12.6%	87.4%
Benzene	µg/stk	77.3	5.81	2	0.452	0.0395	3	0.6%	99.4%	0.8%	99.2%
Benzo[a]pyrene	ng/stk	13.3	0.660	2	0.736	0.0973	3	5.5%	94.5%	7.5%	92.5%
Butyraldehyde	µg/stk	81.3	NA	1	20.7	1.52	3	25.5 %	74.5%	34.5%	65.5%

(table continues)

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HPHCs (alphabetic order)	Unit	3R4F			THS 2.2			% on stick basis		% on nicotine basis	
		mean	SD	n	mean	SD	n	% of 3R4F	% of reduction to 3R4F	% of 3R4F	% of reduction to 3R4F
Cadmium	ng/stk	89.2	9.31	2	<0.28 (LOQ)	NA	3	<0.3 %	>99.7%	<0.4%	>99.6%
Carbon monoxide (CO)[5]	mg/stk	29.4	1.35	2	0.347	0.0462	3	1.2%	98.8%	1.6%	98.4%
Catechol	µg/stk	84.1	9.36	2	14.0	0.522	3	16.7 %	83.3%	22.5%	77.5%
Chromium	ng/stk	<11.9 (LOD)	NA	2	<11.0 (LOQ)	NA	3	NA	NA	NA	NA
Crotonaldehyde	µg/stk	49.3	NA	1	<3.29 (LOQ)	NA	3	<6.7 %	>93.3%	<9.0%	>91.0%
Dibenz[a,h]anthracene	ng/stk	<0.689 (LOQ)	NA	2	<0.124 (LOD)	NA	3	NA	NA	NA	NA
Ethylene oxide	µg/stk	16.0	1.18	2	<0.119 (LOQ)	NA	3	<0.7 %	>99.3%	<1.0%	>99.0%
Formaldehyde	µg/stk	79.4	NA	1	14.1	0.430	3	17.8 %	82.2%	24.1%	75.9%

(table continues)

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

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HPHCs (alphabetic order)	Unit	3R4F			THS 2.2			% 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/stk	329	16.2	2	<1.75 (LOQ)	NA	3	<0.5 %	>99.5%	<0.7%	>99.3%
Hydroquinone	µg/stk	94.5	10.3	2	6.55	0.461	3	6.9%	93.1%	9.4%	90.6%
Isoprene	µg/stk	891	35.8	2	1.51	0.129	3	0.2%	99.8%	0.2%	99.8%
Lead	ng/stk	31.2	2.78	2	2.23	0.351	3	7.2%	92.8%	9.7%	90.3%
m-Cresol	µg/stk	4.24	0.461	2	0.0424	0.0045	3	1.0%	99.0%	1.4%	98.6%
Mercury	ng/stk	3.68	0.140	2	1.38	0.163	3	37.4 %	62.6%	50.6%	49.4%
Methyl-ethyl-ketone (MEK)	µg/stk	183	NA	1	10.1	0.759	3	5.5%	94.5%	7.4%	92.6%
Nickel	ng/stk	<12.9 (LOD)	NA	2	<15.9 (LOD)	NA	3	NA	NA	NA	NA
Nitric oxide (NO)	µg/stk	484	7.20	2	12.6	0.418	3	2.6%	97.4%	3.5%	96.5%
Nitro benzene	µg/stk	<0.038 (LOD)	NA	2	<0.011 (LOD)	NA	3	NA	NA	NA	NA
Nitrogen oxides (NOx)	µg/stk	538	8.78	2	14.2	0.413	3	2.6%	97.4%	3.6%	96.4%
N-nitrosoanabasine (NAB)	ng/stk	29.0	1.08	2	2.35	0.0589	3	8.1%	91.9%	11.0%	89.0%

(table continues)

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HPHCs (alphabetic order)	Unit	3R4F			THS 2.2			% on stick basis		% on nicotine basis	
		mean	SD	n	mean	SD	n	% of 3R4F	% of reduction to 3R4F	% of 3R4F	% of reduction to 3R4F
N-nitrosoanatabine (NAT)	ng/stk	254	17.4	2	14.7	1.25	3	5.8%	94.2%	7.9%	92.1%
N-Nitrosonornicotine (NNN)	ng/stk	271	8.49	2	10.1	0.205	3	3.7%	96.3%	5.0%	95.0%
o-Cresol	µg/stk	4.81	0.304	2	0.0779	0.0093	3	1.6%	98.4%	2.2%	97.8%
o-Toluidine	ng/stk	96.2	3.09	2	1.10	0.0243	3	1.1%	98.9%	1.5%	98.5%
p-Cresol	µg/stk	9.60	0.929	2	0.0706	0.00816	3	0.7%	99.3%	1.0%	99.0%
Phenol	µg/stk	15.6	1.75	2	1.47	0.206	3	9.4%	90.6%	12.7%	87.3%
Propionaldehyde	µg/stk	109	NA	1	10.8	0.675	3	9.9%	90.1%	13.4%	86.6%
Propylene oxide	ng/stk	896	82.5	2	142.3	6.67	3	15.9 %	84.1%	21.5%	78.5%
Pyrene	ng/stk	79.2	3.58	2	8.20	0.152	3	10.3 %	89.7%	14.0%	86.0%
Pyridine	µg/stk	30.9	1.64	2	6.58	0.185	3	21.3 %	78.7%	28.8%	71.2%
Quinoline	µg/stk	0.434	0.0246	2	<0.011 (LOQ)	NA	3	<2.5 %	>97.5%	<3.4%	>96.6

(table continues)

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HPHCs (alphabetic order)	Unit	3R4F			THS 2.2			% on stick basis		% on nicotine basis	
		mean	SD	n	mean	SD	n	% of 3R4F	% of reduction to 3R4F	% of 3R4F	% of reduction to 3R4F
Resorcinol	µg/stk	1.72	0.168	2	<0.055 (LOQ)	NA	3	<3.2 %	>96.8%	<4.3%	>95.7
Selenium[6]	ng/stk	<4.42 (LOD)	NA	2	1.27	0.0577	3	NA	NA	NA	NA
Styrene	µg/stk	13.9	1.72	2	0.577	0.0916	3	4.2%	95.8%	5.6%	94.4%
Toluene	µg/stk	129	1.17	2	1.42	0.162	3	1.1%	98.9%	1.5%	98.5%
Vinyl chloride	ng/stk	93.4	3.00	2	<0.657 (LOD)	NA	3	<0.7 %	>99.3%	<1.0%	>99.0%

[6] 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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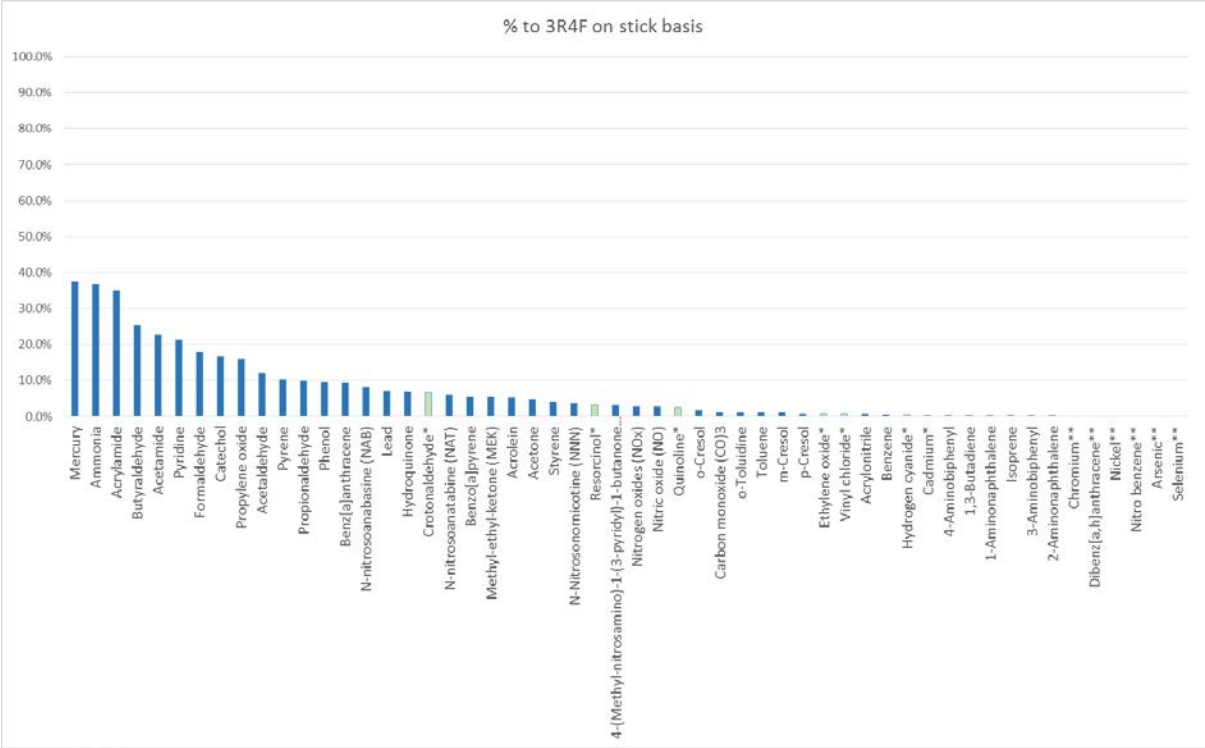


Figure 1 HPHCs of THS 2.2 Regular vs. reference 3R4F cigarette. % on stick basis in decreasing order

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 2.2 and no relative % can be calculated (marked as NA in Table 4).**

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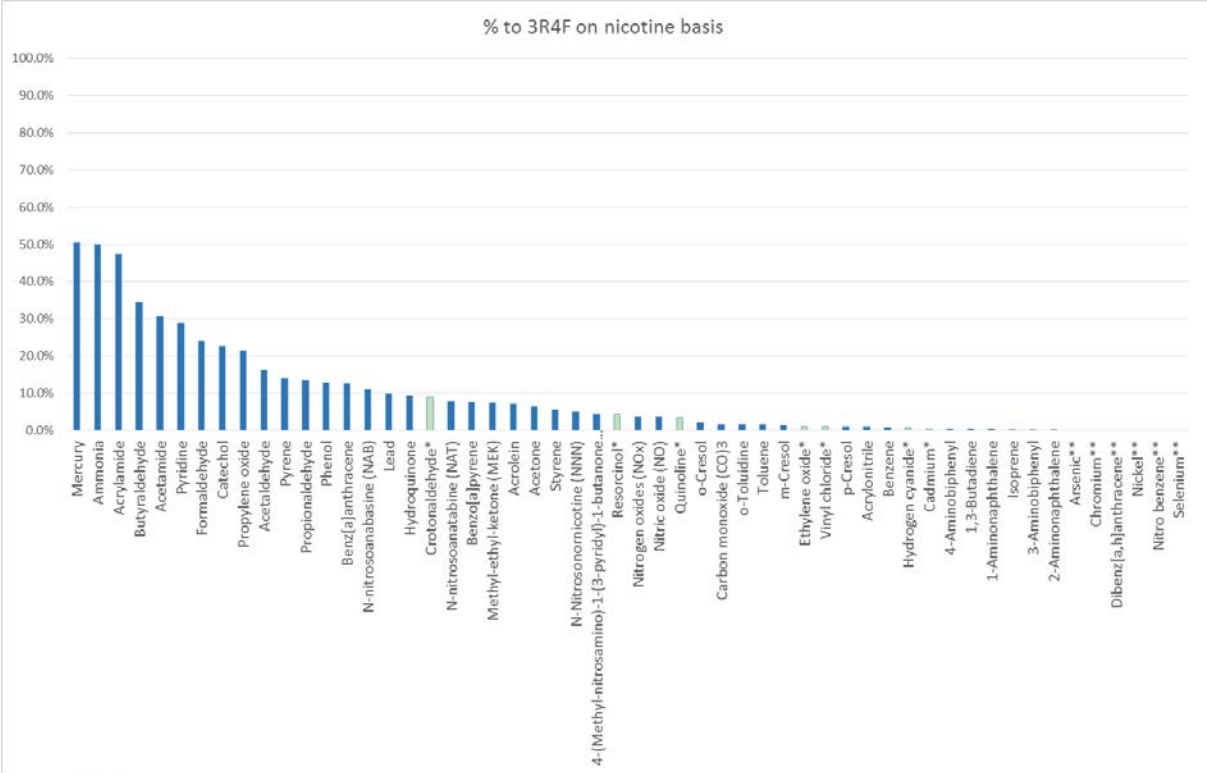


Figure 2 HPHCs of THS 2.2 Regular vs. reference 3R4F cigarette. % on nicotine basis in decreasing order

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 2.2 and no relative % can be calculated (marked as NA in Table 4).**

Table 5 and Table 6: summary of results of THS 2.2 Menthol. Yields of the 3R4F reference cigarette from the same study are included for the comparison.

Figure 3 and Figure 4 show a graphical representation of the data of Table 6, showing, for each HPHC, their proportion (in %) compared to the 3R4F (set at 100 %) on a stick and nicotine basis respectively.

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Table 5 Main aerosol deliveries for THS 2.2 Menthol

Aerosol deliveries according to ISO 4387; 8454; 10315	Unit	3R4F			THS 2.2 Menthol		
		mean	SD	n	mean	SD	n
Glycerol[7]	mg/stk	2.15	0.11	2	4.41	0.10	3
Nicotine	mg/stk	1.84	0.11	2	1.19	0.05	3
Nicotine Free Dry Particulate Matter (NFDPM)[8]	mg/stk	24.8	1.0	2	19.5	1.3	3
Total Particulate Matter (TPM)	mg/stk	41.9	2.39	2	56.3	0.93	3
Water[9]	mg/stk	15.3	1.55	2	35.6	0.59	3

[7] *Product specific not part of ISO parameter*

[8] *We use here the ISO terminology NFDPM to describe the aerosol collected mass from THS 2.2. It should be noted that the NFDPM of the THS 2.2 has a very different constituent make-up in comparison to conventional cigarette. 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*(b) (4)*t [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 6 **HPHCs from the PMI-58 for THS 2.2 Menthol and the 3R4F (excluding main aerosol deliveries reported in Table 5). % of 3R4F and % reduction vs. 3R4F are calculated on stick basis and on nicotine basis. When HPHCs for both THS 2.2 and reference product were below LOD or LOQ, % is replaced by NA (as no reduction can be calculated). For HPHCs that were found below LOD or LOQ for the THS 2.2, the % of reduction was calculated with the LOD/LOQ value**

HPHCs (alphabetic order)	Unit	3R4F			THS 2.2 menthol			% 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/stk	92.8	3.1	2	0.223	0.030	3	0.2%	99.8%	0.4%	99.6%
1-Aminonaphthalene	ng/stk	20.9	0.8	2	0.043	0.012	3	0.2%	99.8%	0.3%	99.7%
2-Aminonaphthalene	ng/stk	17.3	0.5	2	0.022	0.007	3	0.1%	99.9%	0.2%	99.8%
3-Aminobiphenyl	ng/stk	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/stk	256	8	2	6.63	0.53	3	2.6%	97.4%	4.0%	96.0%
4-Aminobiphenyl	ng/stk	3.21	0.22	2	0.009	0.002	3	0.3%	99.7%	0.5%	99.5%
Acetaldehyde	µg/stk	1612	NA	1	206	6	3	12.8%	87.2%	19.9%	80.1%
Acetamide	µg/stk	14.0	1.2	2	2.98	0.06	3	21.2%	78.8%	32.9%	67.1%
Acetone	µg/stk	648	NA	1	37.8	2.2	3	5.8%	94.2%	9.0%	91.0%

(table continues)

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HPHCs (alphabetic order)	Unit	3R4F			THS 2.2 menthol			% on stick basis		% on nicotine basis	
		mean	SD	n	mean	SD	n	% of 3R4F	% of reduction to 3R4F	% of 3R4F	% of reduction to 3R4F
Acrolein	µg/stk	144	NA	1	9.79	1.66	3	6.8%	93.2%	10.6%	89.4%
Acrylamide	µg/stk	4.67	0.32	2	1.64	0.001	3	35.1%	64.9%	54.4%	45.6%
Acrylonitrile	µg/stk	22.1	0.3	2	0.127	0.017	3	0.6%	99.4%	0.9%	99.1%
Ammonia	µg/stk	32.2	1.3	2	11.1	1.1	3	34.6%	65.4%	53.6%	46.4%
Arsenic	ng/stk	<7.49 (LOQ)	NA	2	<1.2 (LOQ)	NA	3	NA	NA	NA	NA
Benz[a]anthracene	ng/stk	26.5	0.5	2	1.80	0.03	3	6.8%	93.2%	10.6%	89.4%
Benzene	µg/stk	79.7	2.9	2	0.453	0.046	3	0.6%	99.4%	0.9%	99.1%
Benzo[a]pyrene	ng/stk	12.5	0.3	2	0.539	0.081	3	4.3%	95.7%	6.7%	93.3%
Butyraldehyde	µg/stk	83.4	NA	1	21.1	0.4	3	25.3%	74.7%	39.2%	60.8%

(table continues)

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HPHCs (alphabetic order)	Unit	3R4F			THS 2.2 menthol			% on stick basis		% on nicotine basis	
		mean	SD	n	mean	SD	n	% of 3R4F	% of reduction to 3R4F	% of 3R4F	% of reduction to 3R4F
Cadmium	ng/stk	89.2	9.3	2	<0.28 (LOQ)	NA	3	<0.3%	>99.7%	<0.5%	>99.5%
Carbon monoxide (CO)[10]	mg/stk	30.8	1.7	2	0.320	0.000	3	1.0%	99.0%	1.6%	98.4%
Catechol	µg/stk	92.8	6.8	2	11.5	1.0	3	12.4%	87.6%	19.3%	80.7%
Chromium	ng/stk	<11.9 (LOD)	NA	2	<3.31 (LOD)	NA	3	NA	NA	NA	NA
Crotonaldehyde	µg/stk	48.2	NA	1	<3.29 (LOQ)	NA	3	<6.8%	>93.2%	<10.6%	>89.4%
Dibenz[a,h]anthracene	ng/stk	<0.689 (LOQ)	NA	2	<0.124 (LOD)	NA	3	NA	NA	NA	NA
Ethylene oxide	µg/stk	19.0	2.8	2	<0.119 (LOQ)	NA	3	<0.6%	>99.4%	<1.0%	>99.0%
Formaldehyde	µg/stk	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 (alphabetic order)	Unit	3R4F			THS 2.2 menthol			% 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/stk	331	10	2	<1.75 (LOQ)	NA	3	<0.5%	>99.5%	<0.8%	>99.2%
Hydroquinone	µg/stk	97.2	7.0	2	4.99	0.50	3	5.1%	94.9%	8.0%	92.0%
Isoprene	µg/stk	956	11	2	1.51	0.31	3	0.2%	99.8%	0.2%	99.8%
Lead	ng/stk	31.2	2.8	2	1.87	0.06	3	6.0%	94.0%	9.3%	90.7%
m-Cresol	µg/stk	4.23	0.11	2	0.027	0.002	3	0.6%	99.4%	1.0%	99.0%
Mercury	ng/stk	3.70	0.32	2	1.32	0.09	3	35.8%	64.2%	55.5%	44.5%
Methyl-ethyl-ketone (MEK)	µg/stk	178	NA	1	13.9	0.2	3	7.8%	92.2%	12.1%	87.9%
Nickel	ng/stk	<43.1 (LOQ)	NA	2	<15.9 (LOD)	NA	3	NA	NA	NA	NA
Nitric oxide (NO)	µg/stk	500	9	2	13.0	0.4	3	2.6%	97.4%	4.0%	96.0%
Nitro benzene	µg/stk	<0.038 (LOD)	NA	2	<0.011 (LOD)	NA	3	NA	NA	NA	NA
Nitrogen oxides (NOx)	µg/stk	554	11	2	14.5	0.5	3	2.6%	97.4%	4.1%	95.9%

(table continues)

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HPHCs (alphabetic order)	Unit	3R4F			THS 2.2 menthol			% on stick basis		% on nicotine basis	
		mean	SD	n	mean	SD	n	% of 3R4F	% of reduction to 3R4F	% of 3R4F	% of reduction to 3R4F
N-nitrosoanabasine (NAB)	ng/stk	31.1	2.5	2	2.29	0.21	3	7.4%	92.6%	11.4%	88.6%
N-nitrosoanatabine (NAT)	ng/stk	248	15	2	12.8	1.4	3	5.1%	94.9%	8.0%	92.0%
N-Nitrosonornicotine (NNN)	ng/stk	274	8	2	7.01	0.51	3	2.6%	97.4%	4.0%	96.0%
o-Cresol	µg/stk	4.58	0.30	2	0.048	0.005	3	1.0%	99.0%	1.6%	98.4%
o-Toluidine	ng/stk	102	1	2	0.936	0.041	3	0.9%	99.1%	1.4%	98.6%
p-Cresol	µg/stk	9.83	0.71	2	0.047	0.007	3	0.5%	99.5%	0.7%	99.3%
Phenol	µg/stk	17.1	0.9	2	0.953	0.045	3	5.6%	94.4%	8.6%	91.4%
Propionaldehyde	µg/stk	108	NA	1	12.0	0.6	3	11.1%	88.9%	17.2%	82.8%
Propylene oxide	ng/stk	1066	28	2	111	5	3	10.5%	89.5%	16.2%	83.8%
Pyrene	ng/stk	74.8	2.5	2	5.81	0.19	3	7.8%	92.2%	12.1%	87.9%
Pyridine	µg/stk	26.8	2.7	2	6.22	0.25	3	23.2%	76.8%	35.9%	64.1%
Quinoline	µg/stk	0.450	0.048	2	<0.01 1 (LOQ)	NA	3	<2.4%	>97.6%	<3.8%	>96.25

(table continues)

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HPHCs (alphabetic order)	Unit	3R4F			THS 2.2 menthol			% on stick basis		% on nicotine basis	
		mean	SD	n	mean	SD	n	% of 3R4F	% of reduction to 3R4F	% of 3R4F	% of reduction to 3R4F
Resorcinol	µg/stk	1.86	0.23	2	<0.055 (LOQ)	NA	3	<3.05	>97.0%	<4.6%	>95.4%
Selenium[11]	ng/stk	<4.42 (LOD)	NA	2	1.21	0.63	3	NA	NA	NA	NA
Styrene	µg/stk	12.3	2.3	2	0.457	0.070	3	3.7%	96.3%	5.8%	94.2%
Toluene	µg/stk	137	4	2	1.28	0.12	3	0.9%	99.1%	1.4%	98.6%
Vinyl chloride	ng/stk	92.5	7.7	2	<2.19 (LOQ)	*	3	<2.4%	>97.6%	<3.7%	>96.3%

[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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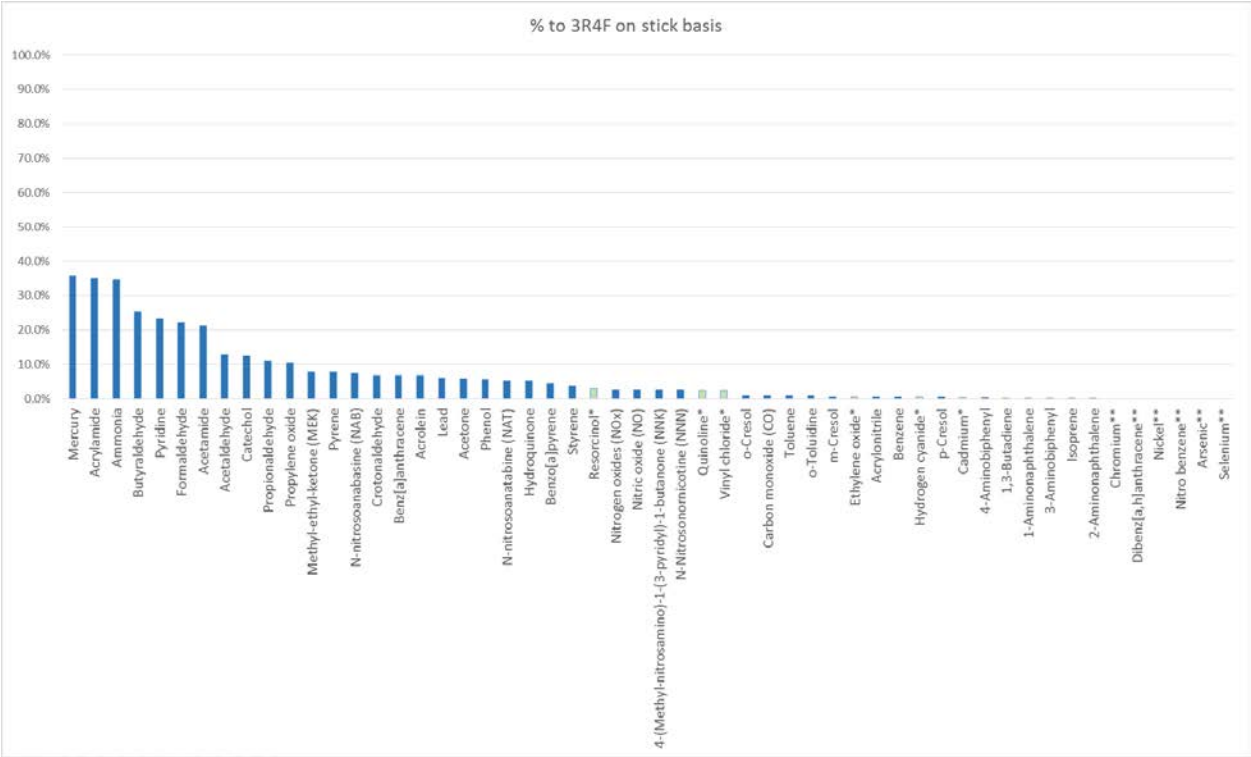


Figure 3 HPHCs of THS 2.2 Menthol vs. reference 3R4F cigarette. % on stick basis in decreasing order

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 2.2 and no relative % can be calculated (marked as NA in Table 6)**

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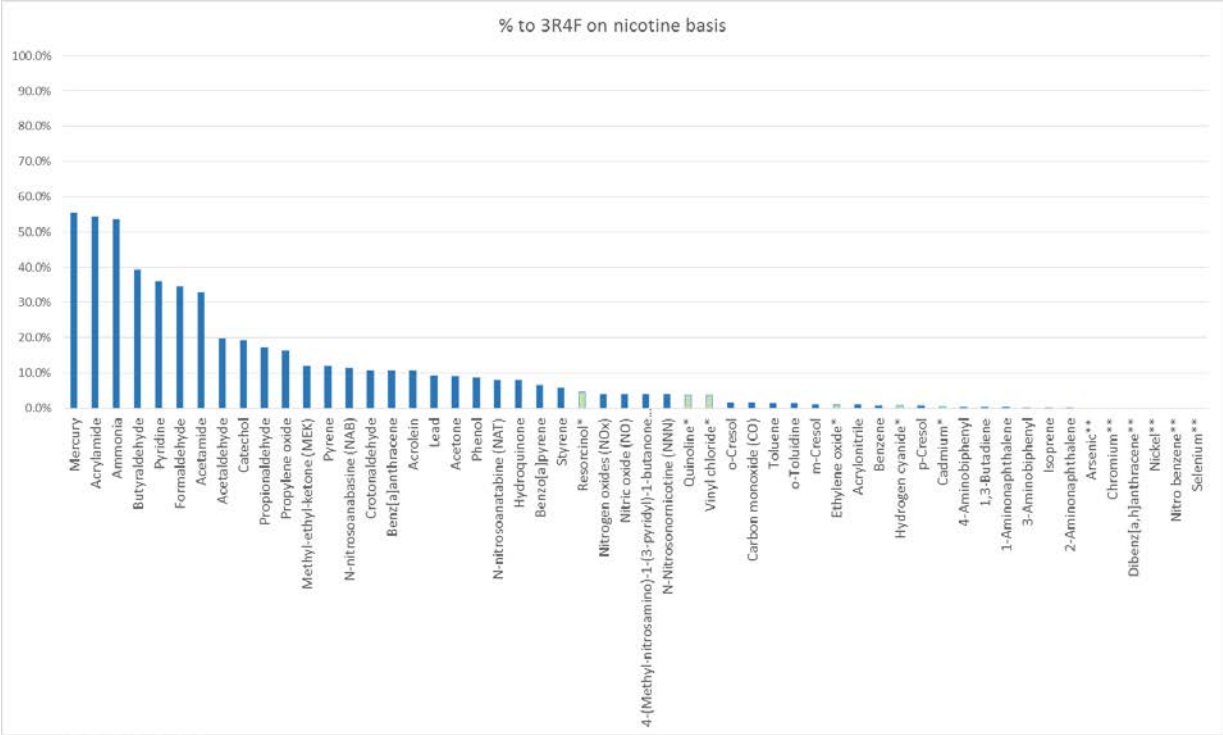


Figure 4 HPHCs of THS 2.2 Menthol vs. reference 3R4F cigarette. % on nicotine basis in decreasing order

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 2.2 and no relative % can be calculated (marked as NA in Table 6)**

6.1.1.3.3. Droplet Size Distribution - Tables and Graphs

Table 7, Table 8 and Table 9 show the MMAD and GSD for all replicates on the 3 tested batches for the regular tobacco sticks.

Figure 5 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 (see Section 6.1.1.2). All measured THS 2.2 data fall within the respirability region.

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Table 7 MMAD and GSD values for Day 1 - 21.03.2016 for THS 2.2 Regular (B-25904 / 41-2397948)

Replicate	MMAD [µm]	GSD [-]
1	0.61	1.37
2	0.60	1.38
3	0.71	1.07
4	0.58	1.40
5	0.55	1.39
6	0.61	1.37
7	0.60	1.38
8	0.62	1.36
9	0.65	1.34
10	0.65	1.33

Table 8 MMAD and GSD values for Day 2 – 29.03.2016 for THS 2.2 Regular (B-25905 / 41-2397950)

Replicate	MMAD [µm]	GSD [-]
1	0.63	1.34
2	0.71	1.45
3	0.60	1.36
4	0.65	1.33
5	0.65	1.28
6	0.64	1.33
7	0.63	1.34
8	0.60	1.37
9	0.63	1.36
10	0.64	1.32

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Table 9 MMAD and GSD values for Day 3 – 05.04.2016 for THS 2.2 Regular (B-25906 / 41-2382704)

Replicate	MMAD [µm]	GSD [-]
1	0.71	1.42
2	0.65	1.35
3	0.69	1.41
4	0.69	1.41
5	0.67	1.44
6	0.69	1.40
7	0.68	1.44
8[12]	NA	NA
9	0.69	1.40
10	0.66	1.36

[12] *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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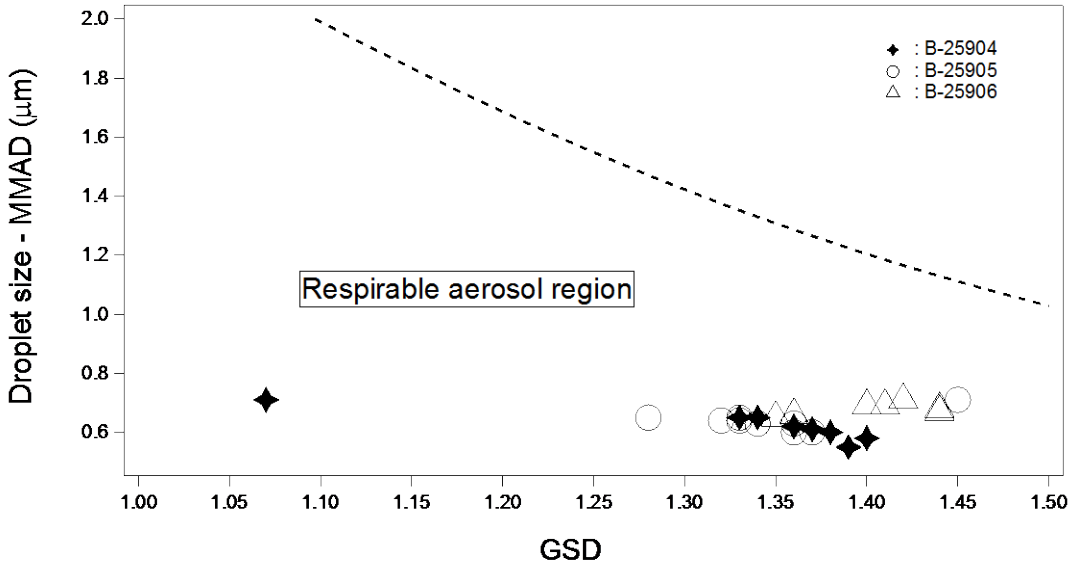


Figure 5 **MMAD plotted as a function of GSD values. The dotted line separates the respirable (below the curve) from the non-respirable aerosol (above the curve)**

Table 10, Table 11 and Table 12 show 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 define the respirability upper limit, based on the MMAD value and its distribution (GSD), based on the respirability upper threshold defined at 2.5 µm (see Section 6.1.1.2). Similarly to the regular, all measured THS 2.2 data fall within the respirability region.

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Table 10 MMAD and GSD values for Day 1 - 08.04.2016 for THS 2.2 Menthol (B-25902 / 412379112)

Replicate	MMAD [µm]	GSD [-]
1	0.57	1.40
2	0.62	1.36
3	0.60	1.38
4	0.62	1.39
5	0.62	1.36
6[13]	NA	NA
7	0.54	1.39
8	0.56	1.41
9	0.58	1.37
10	0.60	1.37

[13] *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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Table 11 MMAD and GSD values for Day 2 – 15.04.2016 for THS 2.2 Menthol (B-25901 / 412374718)

Replicate	MMAD [µm]	GSD [-]
1	0.66	1.32
2	0.60	1.37
3	0.69	1.38
4	0.75	1.34
5	0.73	1.38
6	0.73	1.37
7	0.72	1.37
8	0.64	1.33
9	0.66	1.41
10	0.70	1.37

Table 12 MMAD and GSD values for Day 3 – 18.04.2016 for THS 2.2 Menthol (B-25900 / 412381531)

Replicate	MMAD [µm]	GSD [-]
1	0.64	1.33
2	0.66	1.30
3	0.73	1.36
4	0.63	1.25
5	0.74	1.36
6	0.66	1.31
7	0.66	1.33
8	0.67	1.35
9	0.73	1.36
10	0.69	1.34

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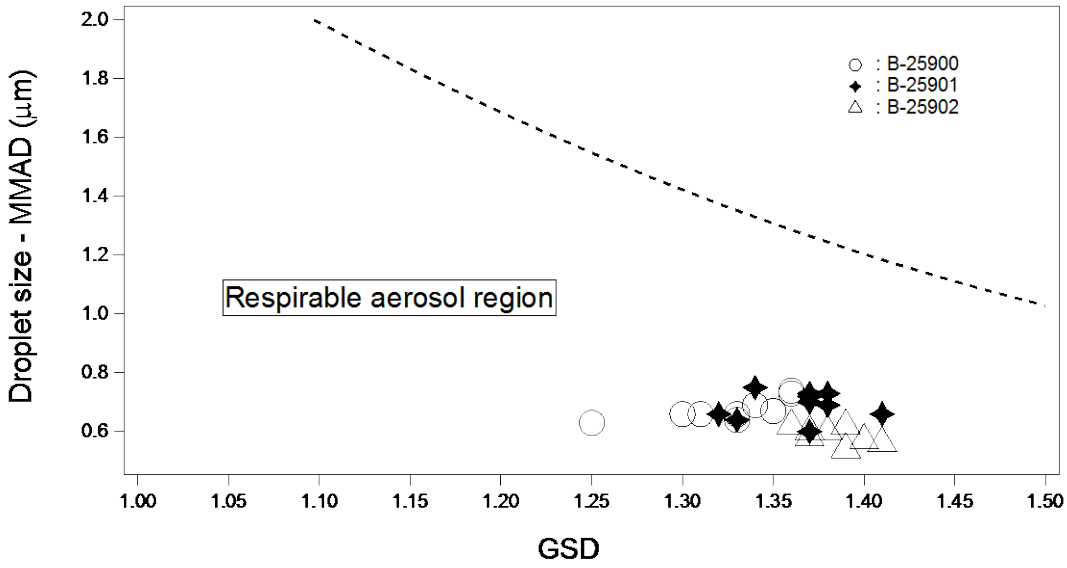


Figure 6 **MMAD plotted as a function of GSD values. The dotted line separates the respirable (below the curve) from the non-respirable aerosol (above the curve)**

6.1.1.3.4. FDA 18 HPHCs List versus market map USA (Altria Client Services) - Tables and Graphs. HCI regimen

Using the same data set shown in Table 4 and Table 6, we can compare the FDA 18 HPHCs levels in the THS 2.2 aerosol to the median levels measured in smoke from cigarette brands commercially available in the U.S. The data for the commercial cigarettes was provided to PMP by Altria Client Services under the terms of the existing agreements and comprises smoke chemistry data for the 31 brands[14] shown in Table 13.

[14] The 31 brands are Philip Morris USA brands which are a representative sample of US marketed cigarettes.

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Table 13 List of the 31 commercially available cigarette brands used for the THS 2.2 comparision for the levels of FDA-18 HPHCs

Basic Blue Pack Box	Marlboro Gold Pack Box	Marlboro Virginia Blend Box
Basic Box	Marlboro Menthol Blue Pack 100's Box	Merit Bronze Pack Box
Basic Gold Pack Box	Marlboro Menthol Blue Pack Box	Merit Gold Pack Box
Basic Non-Filter Soft Pack	Marlboro Menthol Box	Parliament Menthol (Green Pack) Box
L&M Turkish Blend Box	Marlboro Menthol Gold Pack Box	Parliament Menthol (White Pack) 100's Box
Marlboro 100's Box	Marlboro Red Label Box	Parliament Menthol Silver Pack Box
Marlboro 72's Silver Pack Box	Marlboro Silver Pack 100's Box	Parliament Silver Pack Box
Marlboro Blend No. 27 Box	Marlboro Silver Pack Box	Virginia Slims 120's Gold Pack Box
Marlboro Box	Marlboro Skyline Box	Virginia Slims Silver Pack Box
Marlboro Craft Blend Reserve Box	Marlboro Special Blend (Gold Pack) 100's Box	Virginia Slims Superslims Box
Marlboro Gold Pack 100's Box		

For the commercial cigarette brands, the yields of different constituents were measured between two different laboratories. To account for potential interlaboratory differences which can lead to systematic differences in reported yield values, normalization to the laboratory specific 3R4F research cigarette results was performed prior to the comparison.

For the baseline comparator, the median of the mean yields of each of the 31 cigarette brands was calculated on stick basis (referred to as "US market map Median (stick basis)". These results were further normalized to the results obtained for the 3R4F research cigarette in the same laboratories ("Altria 3R4F"). The same logic was applied for the THS 2.2 results (normalization to the 3R4F results performed during the THS 2.2 study) to eliminate as much as possible the inter-laboratory and/or long term analytical variability. The % of reduction of HPHCs for the THS 2.2 vs. the US market map median was then calculated on a stick basis and on a nicotine basis (each HPHCs normalized by the corresponding nicotine delivery). The results are shown in Table 14 (regular) and Table 15 (menthol), and illustrated in Figure 7 and Figure 8 (HPHCs reductions for the regular, on a stick and nicotine basis respectively), Figure 9 and Figure 10 (HPHCs reductions for the menthol, on a stick and nicotine basis respectively).

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Table 14 FDA abbreviated list of 18 HPHCs of THS 2.2 Regular compared to US market map

Aerosol deliveries according to ISO 4387; ISO 8454; ISO 10315	Unit	US Market map stick basis	THS 2.2 stick basis			% on stick basis		% on nicotine basis	
		Median	Mean	SD	n	% of US market map	% of reduction compared with US market map	% of US market map	% of reduction to US market map
Nicotine	mg/stk	2.00	1.29	0.047	3	NA	NA	NA	NA

HPHCs	Unit	US Market map stick basis	THS 2.2 stick basis			% on stick basis		% on nicotine basis	
		Median	Mean	SD	n	% of US market map	% of reduction compared with US market map	% of US market map	% of reduction to US market map
1,3-Butadiene	µg/stk	117.0	0.207	0.0160	3	0 2%	99.8%	0.3%	99.7%
1-Aminonaphthalene	ng/stk	32.1	0.0427	0.00513	3	0 2%	99.8%	0.3%	99.7%
2-Aminonaphthalene	ng/stk	20.1	0.0223	0.00321	3	0 1%	99.9%	0.2%	99.8%
4-(Methyl-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK)	ng/stk	128.0	7.80	0.423	3	5.7%	94.3%	8.5%	91.5%
4-Aminobiphenyl	ng/stk	3.43	0.0087	0.0012	3	0 3%	99.7%	0.4%	99.6%
Acetaldehyde	µg/stk	1467	192	11.6	3	13.2%	86.8%	20.4%	79.6%
Acrolein	µg/stk	159	8.32	0.755	3	5.7%	94.3%	8.6%	91.4%
Acrylonitrile	µg/stk	23.6	0.145	0.0112	3	0.7%	99.3%	1.1%	98.9%
Ammonia	µg/stk	31.0	12.2	0.973	3	30.7%	69.3%	46.4%	53.6%
Benzene	µg/stk	87.0	0.452	0.0395	3	0.6%	99.4%	0.9%	99.1%
Benzo[a]pyrene	ng/stk	15.3	0.736	0.0973	3	5.8%	94.3%	9.0%	91.0%

(table continues)

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HPHCs	Unit	US Market map stick basis	THS 2.2 stick basis			% on stick basis		% on nicotine basis	
		Median	Mean	SD	n	% of US market map	% of reduction compared with US market map	% of US market map	% of reduction to US market map
Carbon monoxide (CO)	mg/stk	28.0	0.347	0.0462	3	1 2%	98.8%	1.8%	98.2%
Crotonaldehyde	µg/stk	51.1	<3.29 (LOQ)	*	3	<7.3%	>92.7%	<11.0%	>89.0%
Formaldehyde	µg/stk	91.5	14.1	0.430	3	19.3%	80.7%	29.0%	71.0%
Isoprene	µg/stk	1005	1.51	0.129	3	0 2%	99.8%	0.2%	99.8%
N-Nitrosonornicotine (NNN)	ng/stk	184	10.1	0.205	3	5.0%	95.0%	7.2%	92.8%
Toluene	µg/stk	149	1.42	0.162	3	1 2%	98.8%	1.8%	98.2%

**no standard deviation can be calculated*
<mean value: detected below the limit of quantification (LOQ). In this case, the LOQ value is used to calculate the reduction vs. US market map

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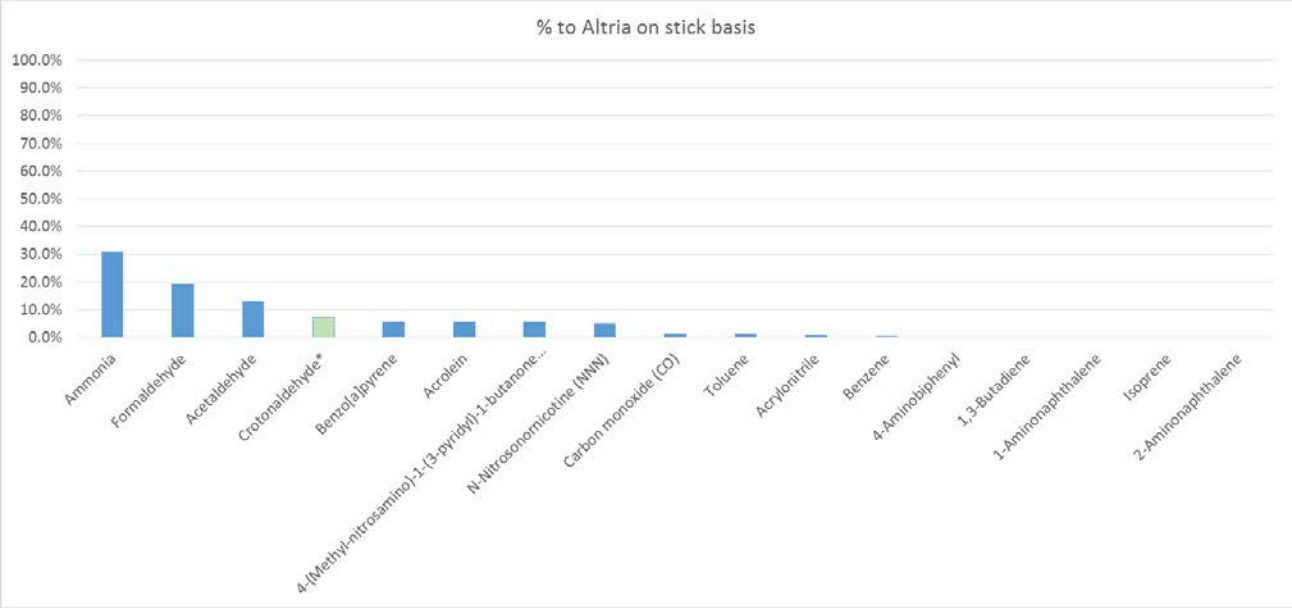


Figure 7 FDA abbreviated list of 18 HPHCs of THS 2.2 Regular vs. US market map cigarette. % on stick basis in decreasing order

HPHCs marked with a "*" and identified with light color bars were reported below LOQ in THS 2.2 and relative % is based on LOQ.

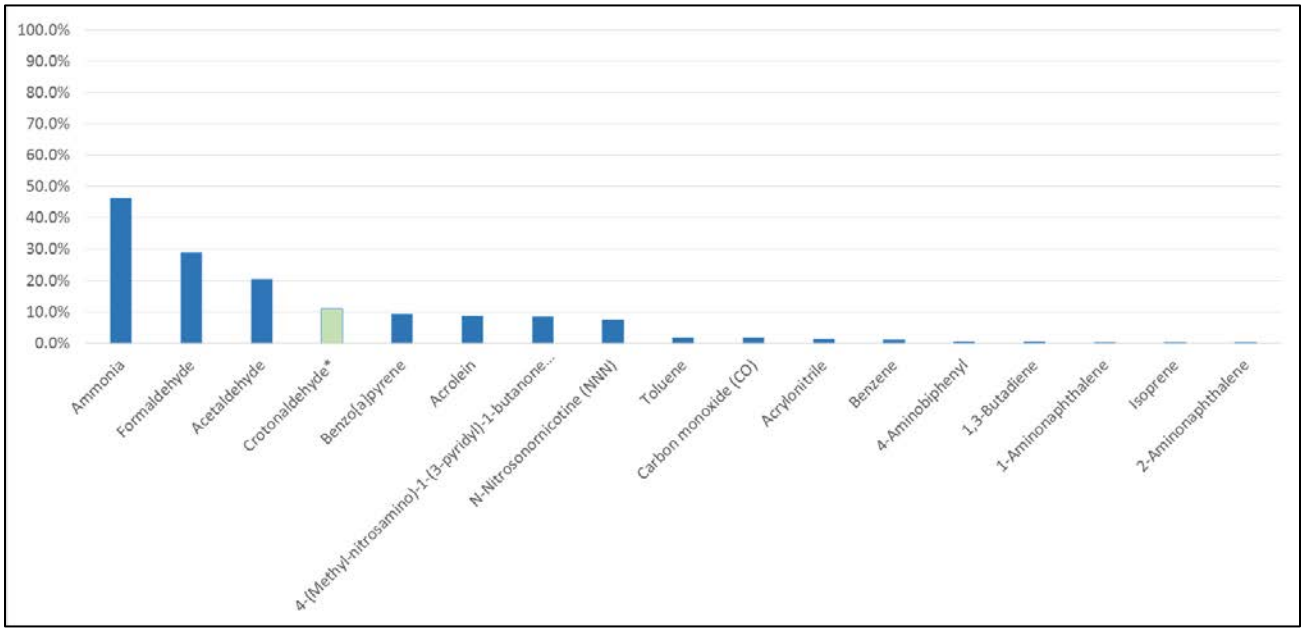


Figure 8 FDA abbreviated list of 18 HPHCs of THS 2.2 Regular vs. US market map cigarette. % on nicotine basis in decreasing order

HPHCs marked with a "*" and identified with light color bars were reported below LOQ in THS 2.2 and relative % is based on LOQ.

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Table 15 FDA abbreviated list of 18 HPHCs of THS 2.2 Menthol compared to US market map

Aerosol deliveries according to ISO ISO 4387; ISO 8454; ISO 10315	**Unit**	US Market map stick basis	THS 2.2 stick basis			% on stick basis		% on nicotine basis	
		Median	Mean	SD	n	% of US market map	% of reduction to of US market map	% of of US market map	% of reduction compared with US market map
Nicotine	mg/stk	2.00	1.19	0.05	3	NA	NA	NA	NA

HPHCs	**Unit**	US market map stick basis	THS 2.2 stick basis			% on stick basis		% on nicotine basis	
		Median	Mean	SD	n	% of US market map	% of reduction to US market map	% of US market map	% of reduction compared with US market map
1,3-Butadiene	µg/stk	117.0	0.223	0.030	3	0.2%	99.8%	0.4%	99.6%
1-Aminonaphthalene	ng/stk	32.1	0.043	0.012	3	0.2%	99.8%	0.3%	99.7%
2-Aminonaphthalene	ng/stk	20.1	0.022	0.007	3	0.1%	99.9%	0.2%	99.8%
4-(Methyl-nitrosamino)-1-(3-pyridyl)-1-butanone (NNK)	ng/stk	128	6.63	0.53	3	4.8%	95.2%	7.8%	92.2%
4-Aminobiphenyl	ng/stk	3.43	0.009	0.002	3	0.3%	99.7%	0.5%	99.5%
Acetaldehyde	µg/stk	1467	206	6	3	14.2%	85.8%	23.8%	76.2%
Acrolein	µg/stk	159	9.79	1.66	3	6.8%	93.2%	11.0%	89.0%

(table continues)

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HPHCs	Unit	US market map stick basis	THS 2.2 stick basis			% on stick basis		% on nicotine basis	
		Median	Mean	SD	n	% of US market map	% of reduction to US market map	% of US market map	% of reduction compared with US market map
Acrylonitrile	µg/stk	23.6	0.127	0.017	3	0.6%	99.4%	1.0%	99.0%
Ammonia	µg/stk	31.0	11.1	1.1	3	28.0%	72.0%	45.8%	54.2%
Benzene	µg/stk	87.0	0.453	0.046	3	0.6%	99.4%	1.0%	99.0%
Benzo[a]pyrene	ng/stk	15.3	0.539	0.081	3	4.2%	95.8%	7.2%	92.8%
Carbon monoxide (CO)	mg/stk	28.0	0.320	0.000	3	1.1%	98.9%	1.8%	98.2%
Crotonaldehyde	µg/stk	51.1	<3.29 (LOQ)	*	3	<7.3%	>92.7%	<11.9%	>88.1%
Formaldehyde	µg/stk	91.5	15.2	0.035	3	20.7%	79.3%	33.7%	66.3%
Isoprene	µg/stk	1005	1.51	0.31	3	0.2%	99.8%	0.3%	99.7%
N-Nitrosonornicotine (NNN)	ng/stk	184	7.01	0.51	3	3.5%	96.5%	5.4%	94.6%
Toluene	µg/stk	149	1.28	0.12	3	1.1%	98.9%	1.8%	98.2%

**no standard deviation can be calculated*
<mean value: detected below the limit of quantification (LOQ). In this case, the LOQ value is used to calculate the reduction vs. US market map

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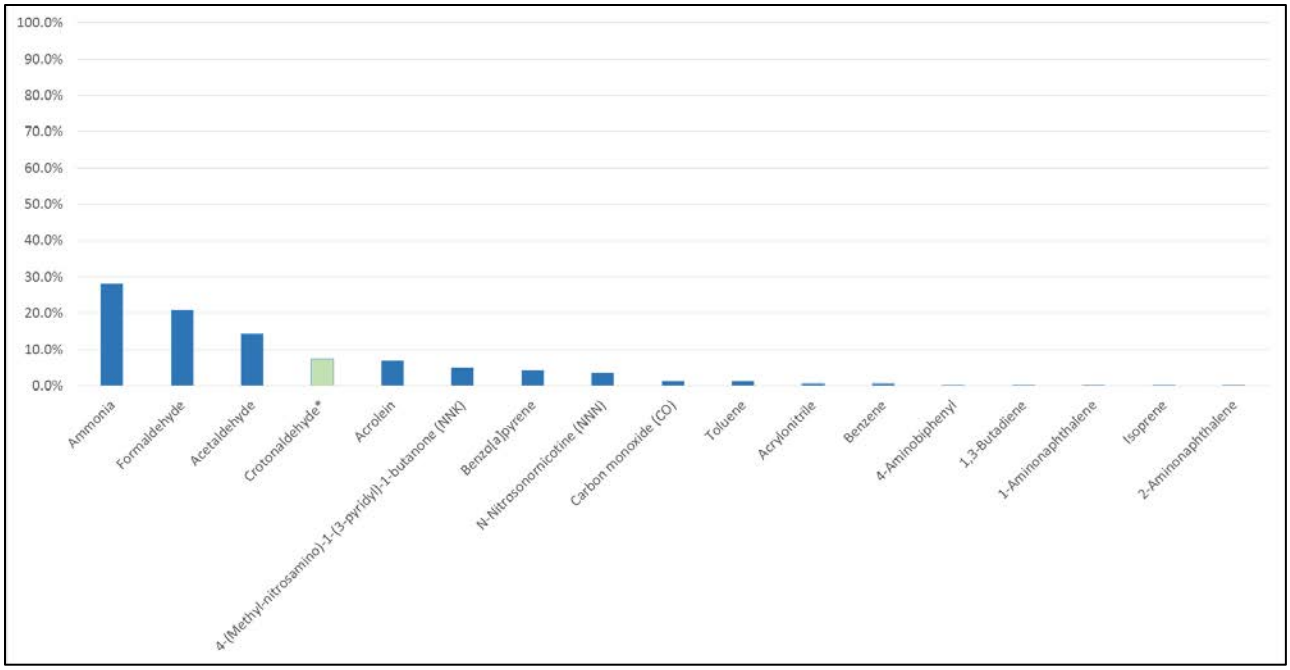


Figure 9 FDA abbreviated list of 18 HPHCs of THS 2.2 Menthol vs. US market map cigarette. % on stick basis in decreasing order

HPHCs marked with a "*" and identified with light color bars were reported below LOQ in THS 2.2 and relative % is based on LOQ.

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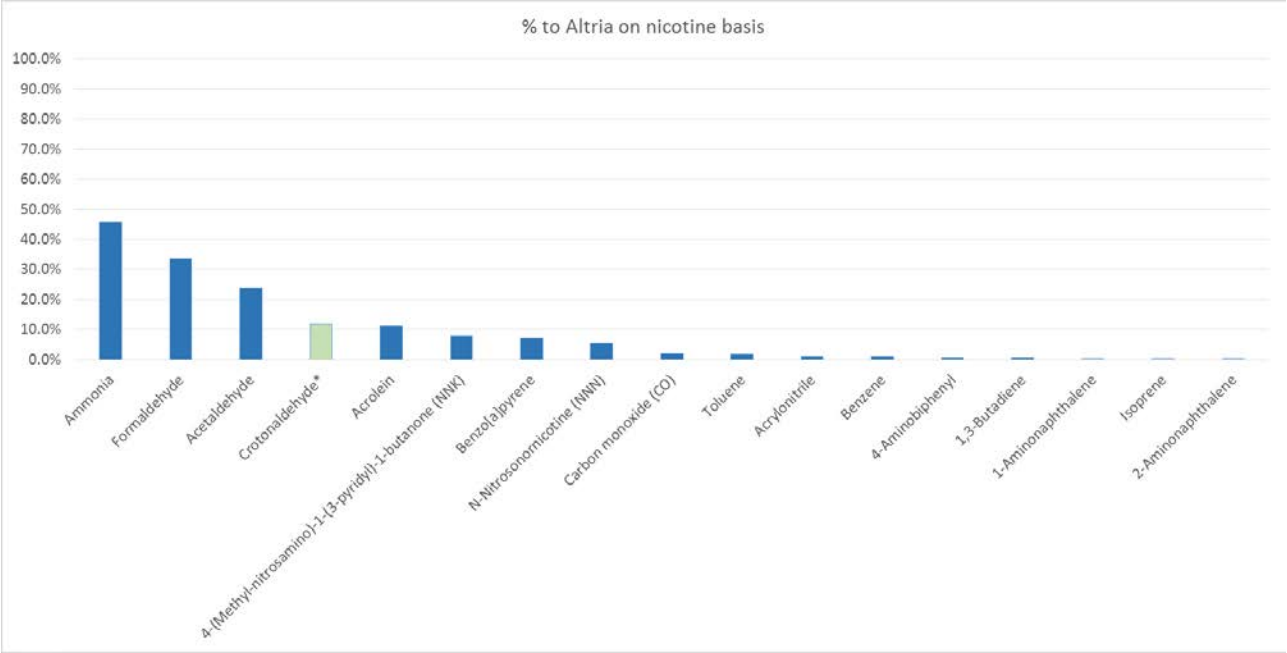


Figure 10 FDA abbreviated list of 18 HPHCs of THS 2.2 Menthol vs. US market map cigarette. % on nicotine basis in decreasing order

HPHCs marked with a "*" and identified with light color bars were reported below LOQ in THS 2.2 and relative % is based on LOQ.

6.1.1.4. Discussion on Reduced Emissions Based on the Results

The underlying principles of heat-not-burn concept is that a number of chemical processes occurring in a combustible cigarette, linked to the high temperatures resulting from the tobacco combustion, do not take place or are significantly reduced when the tobacco is heated to approximately 300°C. These chemical processes, in a combustible cigarette, are linked to the formation of a number of HPHCs, that are not originally present in tobacco, but formed by pyrolysis. Moreover, the transfer to the aerosol of some HPHCs known to be present in the cured tobacco leaves (such as TSNAs), will also be reduced compared to a cigarette, because of the reduced temperature.

The lower operating temperature of the tobacco translates into a range of reduction for all measured HPHCs when comparing the THS 2.2 vs. a reference cigarette (3R4F), either on a stick basis or on a nicotine basis. This range of reduction (compared to 3R4F, on a stick basis, reductions from 62.6 % for Mercury to more than 99 % for Aromatic Amines, 1,3-Butadiene, Acrylonitrile, Benzene, Cadmium, Ethylene Oxide, Hydrogen Cyanide, Isoprene, m-Cresol and p-Cresol are observed) reflects the different mechanisms involved in the generation of HPHCs, or their volatility for those already present in tobacco.

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Overall, compared to the 3R4F reference cigarette, the average reduction in the levels of HPHCs (from the PMI 58) for the THS 2.2 is >92 % on a stick basis and >89 % on a nicotine basis for the regular tobacco stick, and >93 % on a stick basis and >88 % on a nicotine basis for the mentholated tobacco stick.

With respect to commercial cigarettes, the range of reductions and the order of HPHCs, from less to more reduced is similar to what is observed with the 3R4F. Overall, compared to the US market map cigarettes, the average reduction of 18 HPHCs from the FDA abbreviated list for the THS 2.2 is >94 % on a stick basis and >91 % on a nicotine basis for the regular tobacco stick, and >94 % on a stick basis and >91 % on a nicotine basis for the mentholated tobacco stick. It is worth noting that the presence of menthol has no impact on the performance of the stick, as shown by the similar levels of reductions of HPHCs for both the regular and the menthol variants, compared to the 3R4F.

The aerosol content of THS 2.2 was also studied for its particulate nonvolatile content vs. cigarette smoke. To that end a thermodenuder (a heated tube at 300 °C) was used to strip the smoke/aerosol of its volatile content and the remaining fraction was collected on an impactor, and the impactor was scanned with an electron microscope to identify the potential remaining content. This study (Pratte et al., 2016) revealed that cigarettes smoke contains carbon based particles in the sub-micron range, while the aerosol of the THS is exempt of any such species, confirming that heating tobacco only produces an aerosol composed of liquid droplets, unlike combustion that also produces a solid fraction.

The impact of using THS 2.2. on indoor air quality was also experimentally assessed. Different scenario, based on different air renewal and room occupancy were experimentally assessed in a furnished control room, using validated methods quantifying relevant air quality markers (selected carbonyls and VOCs, carbon and nitrogen oxides, and Environmental Tobacco Smoke markers). This study (Mitova et al., 2016) showed that most measured analytes remained at background levels after the use of THS, with the exception of nicotine and acetaldehyde, for which measured levels remain significantly below defined levels in air quality guidelines.

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6.1.1.5. References

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