Supplementary Section

Heated Tobacco products: Insights into composition and toxicity.

Swapna Upadhyay[1*], Mizanur Rahman[1], Gunnar Johanson[1], Lena Palmberg[1], Koustav Ganguly[1*]

[1]Unit of Integrative Toxicology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, 171 77, Sweden.

Name	Email	ORCID ID
Swapna Upadhyay	swapna.upadhyay@ki.se	0000-0003-4699-4082
Mizanur Rahman	mizanur.rahman@ki.se	0000-0003-4129-9822
Gunnar Johanson	gunnar.johanson@ki.se	0000-0002-8759-9567
Lena Palmberg	lena.palmberg@ki.se	0000-0001-5650-4484
Koustav Ganguly	koustav.ganguly@ki.se	0000-0001-8531-8154

All authors contributed equally.

*Correspondence

Koustav Ganguly (koustav.ganguly@ki.se)

Unit of Integrative Toxicology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, 171 77, Sweden

Swapna Upadhyay (swapna.upadhyay@ki.se)

Unit of Integrative Toxicology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, 171 77, Sweden

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Supplementary table S1: Concentration of harmful and potentially harmful constituents (per cigarette) present in heated tobacco product mainstream aerosol (HTP aerosol) and mainstream smoke of traditional combustible cigarettes (TCC smoke). Reported HTP aerosol data was obtained from tobacco/regular and menthol flavoured HTP sticks, TCC smoke data was obtained from reference grade (3R4F, 1R5F) cigarettes. Values are mean (standard deviation). Source: Bekki et al. 2017 [1].

	HTP sticks	**TCC cigarette**
Nicotine (mg)	4.7 (0.1) - regular 5.1 (0.2) - menthol	15.0 (0.1) - 3R4F 8.7 (0.1) -1R5F
Tobacco specific nitrosamines (TSNAs)		
N-nitrosonornicotine (NNN) (ng)	94.4(1.4) - regular 101.0 (2.8) - menthol	1899.0 (66.0) - 3R4F 1691.0 (67.0) - 1R5F
N´-nitrosoanatabine (NAT) (ng)	99.8 (1.46) - regular 94.5 (2.0) - menthol	1341.0 (43.0) - 3R4F 913.0 (30.0) -1R5F
N-nitrosoanabasine (NAB) (ng)	5.6 (0.8) - regular 2.6 (0.4) - menthol	65.0 (1.0) - 3R4F 46.0 (1.0) - 1R5F
Nicotine derived nitrosoamine ketone (NNK) (ng)	51.1 (0.3) - regular 58.2 (2.0) - menthol	532.0 (24.0) - 3R4F 412.0 (10.0) - 1R5F
Total of TSNA (ng)	250.8.1 (2.7) - regular 258.9 (4.0) - menthol	3826.0 (63.1) - 3R4F 3061.0 (92.0) - 1R5F

	HTP aerosol	**TCC smoke**
Total particulate matter (mg)	44.0 (11.4) - regular 49.9 (8.6) - menthol	36.9 (1.9) - 3R4F 28.9 (2.3) - 1R5F
Tar (mg)	9.8 (3.0) - regular 13.4 (2.2) - menthol	25.2 (1.5) - 3R4F 19.2 (1.3) - 1R5F
Nicotine (mg)	1.1 (0.1) - regular 1.2 (0.1) - menthol	1.7 (0.1) - 3R4F 1.0 (0.1) - 1R5F
Carbonmonoxide (mg)	0.4 (0.04) - regular 0.4 (0.04) - menthol	33.0 (1.8) - 3R4F 29.7 (1.7) - 1R5F
TSNAs (ng)		
NNN (ng)	19.2 (2.1) - regular 24.9 (3.5) - menthol	311.1 (24.3) - 3R4F 240.7 (6.6) - 1R5F
NAT (ng)	34.0 (3.1) - regular 37.2 (3.9) - menthol	246.4 (16.9) - 3R4F 183.1 (6.0) - 1R5F
NAB (ng)	4.5 (0.5) - regular 5.5 (0.6) - menthol	30.4 (2.0) - 3R4F 26.2 (0.5) - 1R5F
NNK (ng)	12.3 (1.5) - regular 13.8 (2.6) - menthol	250.4 (13.7) - 3R4F 107.0 (5.0) - 1R5F
Total of TSNA (ng)	70.0 (7.2) - regular 81.4 (10.4) - menthol	838.2 (53.7) - 3R4F 557.1 (15.7) - 1R5F

Supplementary table S2: Nicotine **c**oncentration present in heated tobacco product mainstream aerosol (HTP aerosol), mainstream smoke of traditional combustible cigarettes (TCC smoke), and mainstream electronic cigarette aerosol (ECIG aerosol). Health Canada Intense puffing regime was used. Reported HTP aerosol data was obtained from tobacco/regular/menthol flavoured HTP sticks. TCC smoke data was obtained from Marlboro Red 100 and Marlboro regular cigarettes. ECIG aerosol data was obtained from tobacco flavoured ECIG-liquid using 1st and 2nd generation ECIG devices. Values are mean (standard deviation). Sources: Leigh et al. 2018, Farsalinos et al. 2018 [2,3].

	HTP aerosol (12 puffs) (Tobacco flavor)	**TCC smoke (8 puffs) (Marlboro Red 100)**	**ECIG aerosol (55 puffs) (MarkTen, 3-5% nicotine, tobacco flavor)**
Nicotine (mg/cigarette)	1.4 (0.2)	2.1 (0.1)	1.3 (0.2)
	HTP aerosol	**TCC smoke** (Marlboro regular)	**ECIG aerosol** (2% nicotine)
Nicotine (mg/12 puffs)	1.40 (0.16) - regular 1.38 (0.11) - menthol	1.99 (0.20)	2 s puff: 0.46 (0.06) - 0.51 (0.05) 4 s puff: 0.86 (0.08) - 1.73 (0.20) 1st generation: cigaLike/ 2nd generation: eGO

Supplementary table S3: Comparative range of harmful and potentially harmful constituents (per cigarette) present in mainstream heated tobacco product mainstream aerosol (HTP aerosol) and mainstream smoke of traditional combustible cigarettes (TCC smoke). Blanks indicate not reported/not quantified/below level of detection. Single values are provided where range could not be obtained. ISO-International Organization for Standardization and HCI-Health Canada Intense regimes were used. Reported HTP aerosol data was obtained from tobacco flavoured HTP sticks, TCC smoke data was obtained from Marlboro Red cigarettes and reference grade (3R4F) cigarettes. Values are mean (standard deviation wherever available). Sources: Salman et al. 2019, Li et al. 2019 [4,5].

	HTP aerosol		**TCC smoke (Marlboro Red)**	
Smoking/Vaping regime	ISO	HCI	ISO	HCI
Total particulate matter (mg)	12.93 (0.25)	27.17 (2.08)	10.03 (0.65)	37.5 (2.96)
Nicotine (mg)	0.77 (0.06)	1.50 (0.2)	0.80 (0.05)	1.80 (0.11)
% Free Base	13.6 (1.4)	5.7 (2.2)	14.5 (1.9)	5.8 (1.7)
Propylene glycol/ glycerol	-	8/92	-	-
Reactive Oxygen Species nmol H_2O_2/cigarette				
Gas phase	1.93 (0.95)	2.25 (0-74)	22.10 (0.74)	-
Particle phase	4.34 (1.8)	7.78 (1.46)	24.74 (4.18)	-
Total	6.26 (2.72)	10.74 (2.12)	46.83 (9.6)	-
Carbonyls (µg)				
Formaldehyde	-	0.85 (0.28)	-	3.17 (0.33)
Acetaldehyde	-	301.46 (15.8)	-	1059 (9.03)
Acetone	-	48.37 (2.73)	-	775.6 (28.42)
Propionaldehyde	-	22.25 (0.6)	-	47.89 (1.04)
Crotonaldehyde	-	5.52 (0.55)	-	40.42 (0.69)
Methacrolein	-	6.53 (0.37)	-	85.46 (3.85)
Butyraldehyde	-	30.73 (1.89)	-	22.19 (2.91)
Valeraldehyde	-	20.11 (1.48)	-	-
Glyoxal	-	3.11 (0.18)	-	-
Methyl glyoxal	-	33.51 (1.23)	-	-
Sum of carbonyls	-	472.4 (19.35)	-	2033 (35.72)

	HTP aerosol		**TCC smoke** (3R4F)	
Smoking/Vaping regime	ISO	HCI	ISO	HCI
Total particulate matter (mg)	25.70 (0.84)	55.82 (1.10)	9.77	37.70
Nicotine (mg)	0.50 (0.03)	1.35 (0.07)	0.71	1.90
Tar (mg)	7.47 (0.42)	16.60 (0.42)	7.98	25.50
Propylene glycol (mg)	0.23 (0.01)	0.63 (0.05)	-	-
Glycerin (mg)	1.59 (0.02)	3.84 (0.12)	0.80	2.34
CO (mg)	0.25 (0.06)	0.52 (0.04)	11.20	32.70
Volatile organic compounds (µg)	1.54	6.77	579.20	1318.50
1,3-butadiene	-	0.45 (0.03)	38.50	76.50
Isoprene	0.58 (0.06)	3.02 (0.25)	395.00	863.00
Acrylonitrile	-	0.21 (0.01)	26.40	67.00

Benzene	0.12 (0.01)	0.61 (0.04)	45.70	104.00
Toluene	0.84 (0.05)	2.48 (0.18)	73.60	208.00
Carbonyls (µg)	191.27	308.24	948.80	2899.73
Formaldehyde	8.84 (0.43)	21.87 (0.81)	20.00	68.10
Acetaldehyde	128.50 (9.96)	210.00 (21.71)	567.00	1534.00
Acetone	18.83 (0.48)	26.59 (1.17)	210.00	690.00
Acrolein	4.01 (0.15)	6.37 (0.31)	56.70	155.00
Propionaldehyde	9.59 (0.19)	11.76 (0.38)	48.40	124.00
Crotonaldehyde	2.39 (0.09)	6.42 (0.28)	10.10	43.10
Butanal	14.87 (0.22)	18.77 (0.53)	25.60	65.03
2-Butanone	4.24 (0.46)	6.46 (0.33)	11.00	220.50
Aromatic Amines (ng)	-	-	19.36	38.12
1-Aminonaphthalene	-	-	10.62	21.60
2-Aminonaphthalene	-	-	5.69	10.10
3-Aminobiphenyl	-	-	2.04	4.18
4-Aminobiphenyl	-	-	1.01	2.24
Hydrogen Cyanide (µg)	-	-	70.90	319.00
Ammonia (µg)	2.41(0.44)	10.50 (1.62)	11.10	28.70
Tobacco specific nitrosamines (TSNAs) (ng)	17.20	41.50	280.10	794.00
N-nitrosonornicotine (NNN)	5.00 (0.32)	10.50 (0.46)	92.10	276.00
Nicotine derived nitrosoamine ketone (NNK)	3.50 (0.17)	7.30 (0.34)	85.50	243.00
N´-nitrosoanatabine (NAT)	6.10 (0.42)	18.10 (0.67)	92.90	251.00
N-nitrosoanabasine (NAB)	2.60 (0.15)	5.60 (0.31)	9.60	24.00
Phenol (µg)	-	1.20 (0.05)	7.04	14.80
Polycyclic aromatic hydrocarbon (ng) Benzo(a)pyrene	-	-	6.73	16.20

Supplementary table S4: Comparative range of harmful and potentially harmful constituents (per cigarette) present in heated tobacco product mainstream aerosol (HTP aerosol), mainstream smoke of traditional combustible cigarettes (TCC smoke) and mainstream electronic cigarette aerosol (ECIG aerosol). HCI-Health Canada Intense and CORESTA- Cooperation Centre for Scientific Research Relative to Tobacco puffing regimes were used. Reported HTP aerosol data was obtained from tobacco/regular and menthol flavoured HTP sticks. TCC smoke data was obtained from reference grade (1R6F) and Marlboro Red cigarettes. ECIG-aerosol data was obtained from tobacco flavoured ECIG-liquid using 1st and 2nd generation ECIG devices at 10 and 14 wattage. Values are mean (standard deviation wherever available). **PR:** puffing regime. Sources: Farsalinos et al. 2018, Bitzer et al. 2020 [6,7]

Puffing regime: HCI		**HTP aerosol**		**TCC smoke**	**ECIG aerosol (ECIG liquid: 18mg/ml nicotine; Evic VTC mini**	
PR1: 55 ml puff volume, 2 s puff duration, 3 s inter puff interval (12 puffs); PR2: 80 ml puff volume, 3 s puff duration, 30 s inter puff interval (12 puffs); PR3: 90 ml puff volume, 3 s puff duration, 25 s inter puff interval (14 puffs)						
	Puffing regime	Regular	Menthol	Marlboro red	ECIG power 10 watt	ECIG power 14 watt
Formaldehyde (µg)	PR1	6.4 (1.8)	5.0 (1.4)	67.2 (14.0)	0.5 (0.2)	1.0 (0.2)
	PR2	9.1 (3.7)	13.6 (5.3)	74.4 (24.2)	2.8 (0.9)	3.1 (0.4)
	PR3	17.1 (2.4)	22.6 (4.8)	71.4 (15.4)	3.6 (1.7)	3.7 (6.6)
Acetaldehyde (µg)	PR1	144.1 (23.3)	176.7 (32.6)	1062.2 (161.4)	0.8 (0.3)	1.5 (0.3)
	PR2	146.8 (22.3)	187.8 (61.8)	1372.9 (191.2)	1.9 (0.6)	1.9 (03.3)
	PR3	165.1 (10.5)	187.1 (13.4)	1212.6 (144.2)	1.7 (0.4)	2.9 (0.6)
Acrolein (µg)	PR1	10.8 (4.0)	10.4 (1.9)	112.7 (14.2)	0.3 (0.1)	0.4 (0.1)
	PR2	8.1 (2.0)	10.6 (6.1)	156.8 (32.1)	0.5 (0.3)	1.0 (0.1)
	PR3	10.4 (1.8)	13.1 (1.2)	160.9 (19.3)	0.9 (0.1)	1.1 (0.1)
Propionaldehyde (µg)	PR1	12.8 (3.7)	11.0 (2.4)	108.6 (17.9)	-	-
	PR2	8.8 (4.6)	13.2 (4.0)	113.7 (14.1)	-	-
	PR3	11.8 (1.5)	13.5 (1.3)	117.1 (15.4)	-	-
Crotonaldehyde (µg)	PR1	2.0 (0.4)	1.9 (0.2)	41.1 (14.6)	-	-
	PR2	1.4 (0.5)	2.4 (0.9)	65.7 (9.5)	-	-
	PR3	3.0 (0.7)	3.3 (0.6)	40.5 (8.6)	-	-

Table S4 continued

Puffing regime: CORESTA	**HTP aerosol**		**TCC smoke**	**HTP aerosol (Hybrid)**	**ECIG aerosol**		
Puff volume 75ml, puff duration: 2.5 s, inter puff interval: 30 s	IQOS 12 puffs	Glo 7 puffs	1R6F 11 puffs (1 cigarette)	Ploom 10 puffs	JUUL 10puffs	SREC 10puffs	Mod 10 puffs
Nicotine (µg)	122.2 (9.6)	72.1 (10.6)	189.5 (7.9)	18.0 (0.0)	155.7 (44.6)	71.0 (8.2)	Nicotine free
Particulate phase radicals (pmol)	-	-	79.39 (7.5)	-	-	-	-
Total gas phase radicals (pmol)	12.6 (1.1)	12.5 (0.3)	567.6 (78.3)	12.1 (1.4)	5.3 (0.5)	39.6 (0.8)	47.8 (1.8)
Non-polar characteristics gas phase radicals (pmol)	13.9 (0.9) - 110%	14.3 (2.8) - 115%	449.9 (86.9) - 78%	11.3 (2.2) - 93%	2.4 (1.4) - 46%	14.4 (0.7) - 36%	19.2 (0.3) - 40%
Polar characteristics gas phase radicals (pmol)	6.8 (1.6) - 54%	8.2 (1.9) - 66%	9.6 (2.8) -2%	7.0 (1.0) - 58%	5.9 (1.1) - 113%	39.2 (0.9) - 99%	43.3 (2.9) - 91%

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