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Selected Harmful and Potentially Harmful Constituents Levels in Commercial e-Cigarettes

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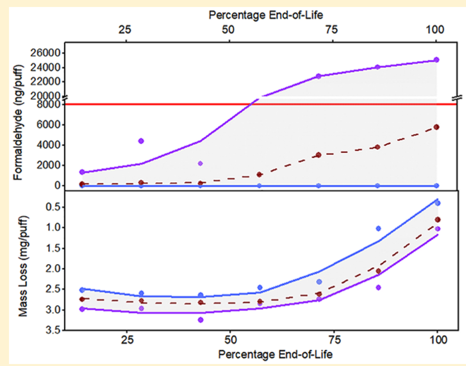
Supporting Information

ABSTRACT: A broad range of commercially available electronic cigarette (e-cigarette) systems were tested for levels of emissions of harmful and potentially harmful constituents (HPHC), with a particular focus on the carbonyls: acetaldehyde, acrolein, and formaldehyde. The tobacco-specific nitrosamines *N*′-nitrosonornicotine and 4-(methylnitrosamino)-1-(3-bipyridyl)-1-butanone; the elements arsenic, cadmium, chromium, lead, and nickel; benzene; 1,3-butadiene; and benzo(a)pyrene were also quantified. The results show that except for the levels of carbonyls, all types of e-cigarettes performed in a similar manner, and emission levels for HPHCs were generally not quantifiable. However, levels of carbonyls, especially formaldehyde, were highly variable. Overall, the lowest levels of formaldehyde were observed in cartridge systems, which generally achieved substantial reductions in yields in comparison with cigarette smoke. Formaldehyde levels in open tank systems were variable; however, the median formaldehyde levels across different brands were substantially lower than the formaldehyde levels in cigarette smoke. The results for variable-power devices operated at the highest voltage confirmed existing literature data regardless of orientation and differences in puffing regimes. Furthermore, our results show that many products deliver consistent HPHC yields over a broad range of testing conditions (with minimal variability from one device to another, under a range of puffing conditions). However, some products exhibit high variability in emissions of HPHCs. The use of air blanks is further highlighted to assess nonproduct-related contributions to HPHC levels to avoid misrepresentation of the data. Overall, our results highlight that some but not all electronic cigarettes deliver low levels of carbonyls consistently across the full e-liquid depletion cycle under different test conditions. The need for further research and standardization work on assessment of variable-voltage electronic cigarettes is emphasized.



1. INTRODUCTION

Electronic cigarettes (e-cigarettes) have been proposed as a safer alternative to cigarette smoking,[1−4] although the current state of understanding of the precise health benefits at the population level in comparison with continued cigarette smoking remains a subject of debate.[5] E-cigarettes are available in a wide variety of products in terms of e-liquids and device types,[6] including disposable or rechargeable cigarette-shaped devices, pen-style cartomizers with prefilled or refillable cartridges, and open tank-style devices and mods, where power and sometimes other settings can be adjusted by the consumer.

The ongoing debate about the potential harms and benefits of e-cigarettes[1,7−9] is partly due to the paucity of available toxicologically relevant data and the lack of an agreed assessment framework.[10,11] Even at the simplest level of toxicological assessment, namely the analysis of e-liquids, electronic devices, and their resulting aerosols, there are very few validated widely recognized methods or international quality standards.[12−15]

For example, concerns have been raised about the levels of harmful and potentially harmful constituents (HPHC) in e-cigarette aerosols, specifically carbonyl compounds, such as acetaldehyde, acrolein, and formaldehyde, resulting from the heating of the liquid in the device;[16−18] metals released by some device components;[19−25] impurities already present in the e-liquids and transferring into the aerosol, such as tobacco-specific nitrosamines (TSNA); aerosol former impurities; and flavor impurities.[26−32] The levels of the HPHCs in e-cigarette aerosols have generally been reported to be well below the levels observed in mainstream cigarette smoke in normal use conditions.[33−36] This has also been confirmed in clinical trials, where the levels of biomarkers of exposure to a number of toxicants, including acrolein, cadmium, and lead, were significantly lower in participants who switched to e-cigarettes than in control subjects who continued smoking cigarettes.[37−40]

The generation of carbonyls by e-cigarettes has been the focus of a number of studies, and concentrations of these compounds in the e-cigarette aerosols have been reported across a wide range of values, from hardly detectable amounts

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to concentrations exceeding those observed in mainstream cigarette smoke.[26,27,41−48] It is difficult to compare literature results, because the methods to generate the e-cigarette aerosols were not standardized. However, there is some consensus regarding the generation of carbonyls in e-cigarette aerosol: acetaldehyde, acrolein, and formaldehyde are mainly formed through a thermal decomposition of glycerol (G) and propylene glycol (PG), the two common aerosol formers present in e-liquids,[17,18,30,49,50] as investigated through theoretical simulations and confirmed experimentally.[51,52] The reaction is promoted by higher temperatures,[53] as observed by the increase of the carbonyl compounds in devices operating at higher voltage or higher power,[16,27,49,54,55] at different heating coil resistances[56] or by the impact of the dry puff effect on the carbonyl concentration when the e-liquid is close to depletion.[18,35,41,57] In a study performed in a tube reactor at increasing controlled temperatures with pure G and PG, significantly higher amounts of formaldehyde and acetaldehyde were generated from G than from PG at 270 °C, while the difference decreased at higher temperature, possibly indicating different kinetics in the thermal degradation of G and PG.[53] Acrolein was generated only from G. In recent publications,[58,59] the authors came to the conclusion that the flavoring compounds may also contribute to the generation of acetaldehyde, acrolein, and formaldehyde and other aldehydes in e-cigarette aerosol.

More importantly, carbonyl compounds have been measured in the exhaled breath of e-cigarette consumers:[60] Higher concentrations were observed in the e-cigarette users' breath samples than in the background breath samples. The authors concluded that the emission of carbonyls in e-cigarette aerosols is not limited to dry puff conditions[35] but also occurs in typical consumer vaping conditions.

In the present study, we report on the product performance of a range of e-cigarettes, under standardized conditions to be able to compare them, on the basis of the analysis of compounds (carbonyl compounds, TSNAs, elements, volatiles, benzo(a)pyrene [BaP]) recommended by the World Health Organization (WHO) for cigarette emissions[61] and the European Committee for Standardization (CEN) for e-cigarette aerosols.[62] Analyses were performed from the beginning of the aerosol generation, when the maximum amount of e-liquid was present in the devices, until full e-liquid depletion, with a standardized aerosol generation and collection protocol, as recently published by CORESTA.[12] More intense aerosol-generating regimes were also used to evaluate the robustness of the electronic nicotine delivery systems in terms of aerosol HPHC delivery, as recommended by the U.S. Food and Drug Administration (FDA).[63]

2. METHODS

2.1. Commercial Devices and e-Liquid Samples. Thirty-four samples of commercial e-cigarette devices and 57 e-liquids were purchased in 2015, 2017, and 2018 at the point of sale or through Internet channels in U.K., Poland, France, South Africa, and Canada. Brands were selected to capture as much as possible the market diversity in terms of different manufacturers, device types (closed systems, such as disposable "cigalike" products or cartridge systems, and open systems with tanks and mods), and e-liquid designs.

In addition, a reference e-liquid was prepared internally and used in combination with a number of commercial e-cigarette open systems. The reference e-liquid formulation was made of 39.1% PG, 39.1% G, 1.8% nicotine, and 20% water.

2.2. Analyses of Aerosol Constituents. The analyses of the aerosol constituents were conducted under contract to Philip Morris International by Labstat International (Kitchener, Ont., Canada), an ISO 17025-accredited laboratory. The generation of the e-cigarette aerosol was performed according to the CORESTA CRM No. 81,[12] with the devices in horizontal position, with the combinations of e-liquids and e-cigarettes devices provided in the Supporting Information. More intense aerosol-generating regimes were also applied to selected devices. Devices with variable temperature or variable power were analyzed at the highest temperature or power setting, according to recommendations of governmental agencies in the U.S.A.[63] and U.K.[64] Groups of 50 puffs were collected for further analysis of TSNAs (*N*′-nitrosonornicotine [NNN] and 4-(methylnitrosamino)-1-(3-bipyridyl)-1-butanone [NNK]), BaP, volatiles (benzene and 1,3-butadiene), selected elements (arsenic [As], cadmium [Cd], chromium [Cr], lead [Pb], and nickel [Ni]), and carbonyl compounds (acetaldehyde, acrolein, and formaldehyde).

Carbonyl compounds (acetaldehyde, acrolein, and formaldehyde) were analyzed by high-performance liquid chromatography with an ultraviolet detector (HPLC-UV) according to the Labstat internal method T-104/TMS-00104. E-cigarettes were puffed on 12 alternate ports of a standard 20-port linear smoking machine that was fitted with Drechsel-type bottles or traps with fritted impingers, with one cartridge per port. The unfiltered e-cigarette aerosol was scrubbed of volatile carbonyls by passing each puff through an impinger into a trap containing 80 mL of an acidified solution of 2, 4-dinitrophenylhydrazine (DNPH) in acetonitrile. An aliquot of the reacted DNPH-aerosol extract was then syringe-filtered and diluted with 1% Trizma base in aqueous acetonitrile. The samples were analyzed by HPLC-UV. For the samples analyzed in 2017 and later, the carbonyl compounds were measured by gas chromatography−mass spectrometry (GC/MS) according to Labstat internal method TMS-155. The mainstream aerosol of e-cigarettes was trapped on a 44 mm glass fiber disc (pad) and a cryogenic trap (<−35 °C) containing acetonitrile. The pad was extracted with the liquid trap solution. Then 1 mL of the extract was transferred into a glass tube containing 5 mL of water. A mixed internal standard solution containing deuterated acetaldehyde, acetone, methyl−ethyl ketone and 2, 3-butanedione was added as well as an aqueous solution of *O*-(2,3,4,5,6-pentafluorobenzyl)-hydroxylamine. The glass tube was capped and placed in the dark for 24 h. Five drops of concentrated H_2SO_4 were added, and the solution was extracted with 2 mL of toluene. The extract was analyzed by GC/MS using selected ion monitoring. Four replicates per analysis were performed. A discussion of the merit of the two methods has been presented by Labstat co-workers.[65]

For TSNAs, the mainstream e-cigarette aerosol was collected onto glass fiber filter discs (pads). The pads were spiked with an internal standard solution containing four deuterium-labeled TSNA analogues and extracted into an aqueous ammonium acetate solution. The extract was filtered and analyzed by liquid chromatography−tandem mass spectrometry (LC-MS/MS) using positive electrospray ionization (ESI). Four replicates per analysis were performed.

The elements (As, Cd, Cr, Pb, and Ni) were measured by inductively coupled plasma mass spectrometry (ICP-MS). E-cigarettes were puffed on a rotary smoking machine. An electrostatic precipitation generator was used to precipitate the particulate matter onto a glass tube. The collected mass was extracted in methanol, evaporated, and subjected to microwave digestion. The gaseous phase metals were trapped in an impinger containing a 10% v/v nitric acid solution. The impinger solution was added to the same vessel and subjected to microwave digestion. The analysis of trace elements was performed on ICP-MS, according to the Health Canada method T-109. Four replicates per analysis were performed.

For the volatiles (benzene and 1,3-butadiene), the e-cigarette aerosol was generated on a linear smoking machine, trapped on a Cambridge filter pad, and concentrated into a cryogenic trap containing methanol. A solution of internal standards is added to the methanol and analyzed by GC/MS for quantification. Four replicates per analysis were performed.

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For BaP, the e-cigarette aerosol was generated on a linear smoking machine and trapped on a Cambridge filter pad. A solution of internal standard was added to the pad. The pad was extracted with methanol. The extraction solution was filtered and cleaned up using solid-phase extraction. The resulting solution was analyzed by GC/MS for quantification. Four replicates per analysis were performed.

2.3. Robustness of Carbonyls Yields. To assess whether the e-cigarette products designs were robust in relation to slight changes in the aerosol-generating regime, we modified either the puff duration or the puff volume for some closed systems. Carbonyl yields in the e-cigarette products aerosols were measured in a number of closed systems with the aerosol generated under different conditions: (a) puff volume 55 mL, puff duration 4 s, puff interval 30 s; (b) puff volume 80 mL, puff duration 3 s, puff interval 30 s; and (c) puff volume 80 mL, puff duration 4 s, puff interval 30 s in addition to the CRM 81[12] used for all products.

2.4. Analyses of e-liquids. Selected e-liquids were analyzed for their content in elements and TSNAs.

The analysis of elements was performed as follows: 0.5 g of the liquid sample was extracted in a mixture of HCl, HNO_3, and hydrogen peroxide and subjected to microwave digestion. The analysis of the elements was performed on ICP-MS. Four replicates per analysis were performed.

The TSNAs were measured by LC-MS/MS using positive ESI after spiking 500 mg of an e-liquid sample with four deuterium-labeled TSNA analogues. Four replicates per analysis were performed.

2.5. Data Treatment for Comparison Between Test Systems. While it is well established that cigarettes are consumed in about 10 puffs under standard analytical smoking machine conditions,[66] e-cigarettes systems may continue to operate for several hundred puffs (more than 1000 puffs for some open systems). As a consequence, for direct comparison of emission yields between products tested under unique testing conditions, the data are presented here on a per-puff basis, by dividing the results reported by the number of puffs collected per puff segment, according to the aerosol generation regime.[15] For direct comparison of products assessed under alternative aerosol generating conditions (increasing the puffing volume for example from 55 to 80 mL), the results are expressed per a constant volume of 100 cm^3 of aerosol, multiplying the results per-puff by the ratio 100/testing puffing volume.

For many constituents measured in the aerosol of e-cigarette products at each puff segment, the emissions were below the limit of detection (LOD) and/or limit of quantification (LOQ). To enable further computational and comparative assessment, the < LOD and < LOQ values were replaced by their respective LOD, and LOQ numbers.

For each e-cigarette product, four replicates were performed for each analysis. Each replicate corresponds to a unique and new device, tested up to e-liquid depletion. The emissions lifetime average yields (LAY) are then calculated as the weighted average of the emissions levels measured across all collected blocks of puffs and replicates; and the device to device (DV-DV) variability expressing emission system consistency is calculated by the between replicate standard deviation.

3. RESULTS

3.1. Concept of End-of-Life. The products analyzed in the frame of this study cover a wide range of designs, delivering different numbers of puffs (200−1,700) until depletion of the e-liquid. Therefore, to allow a direct comparison of products analyzed in the frame of our study, we measured the constituents (carbonyls, TSNAs, and elements) in blocks of 50 puffs until mass loss was below 12.5 mg per collection (puff block), as a marker of the exhaustion of the liquid in the e-cigarette product. The limit of 12.5 mg/collection was chosen in accordance with what was selected by the CORESTA e-vaping Sub-Group in a proficiency trial related to e-cigarette aerosol analysis as a marker of liquid full depletion.[67] Using this way to estimate the end-of-life, we avoided the dry puff phenomenon[35] as much as possible. The average until end-of-life among all blocks was then calculated to be able to compare all products, as provided in Tables 1−5. An example of the end-of-life concept for one open e-cigarette product is provided in Figure 1 for formaldehyde.

Table 1. TSNA Levels in e-Liquids and e-Cigarette Aerosols (Average until End of Life)

sample	results in e-liquid (ng/g)			results in aerosol (ng/puff)		
	NNN	NNK	NAT	NNN	NNK	NAT
liquid A	<3.28	<5.02	<6.50	<0.033	<0.050	<0.065
liquid B	<3.28	<5.02	<6.50	<0.033	<0.050	<0.065
liquid C	9.80	<5.02	11.84	0.055	0.056	0.073
liquid D	<3.28	<5.02	<6.50	<0.033	<0.050	<0.065
liquid E	<3.28	<5.02	<6.50	<0.033	<0.050	<0.065
liquid F	<3.28	<5.02	23.96	<0.033	<0.050	0.081
liquid G	<3.28	<5.02	<6.50	<0.033	<0.050	<0.065
liquid H	<3.28	<5.02	22.35	0.042	<0.050	0.077
liquid I	<3.28	<5.02	<6.50	0.062	0.111	<0.065
liquid J	<3.28	<5.02	<6.50	<0.033	<0.050	<0.065
liquid K	<3.28	<5.02	<6.50	<0.033	<0.050	<0.065
liquid L	<3.28	<5.02	<6.50	0.043	<0.050	<0.065

3.2. TSNAs. TSNAs were analyzed in a subset of 12 e-liquids and in the aerosol of the same liquids when added to one reference device.

All results for the e-liquids were below the limit of quantification (LOQ) for the individual TSNAs (*N*-nitrosoanabasine [NAB]: 1.79 ng/g; *N*′-nitrosoanatabine [NAT]: 6.5 ng/g; NNK: 5.02 ng/g; NNN: 3.28 ng/g), except for Liquid C (NAT: 11.84 ng/g; NNN: 9.80 ng/g), liquid F (NAT: 23.96 ng/g), and liquid H (NAT: 22.35 ng/g).

In the e-cigarette aerosols, all results were below the LOQ of the individual TSNAs (NAB: 0.893 ng/50 puffs; NAT: 3.25 ng/50 puffs; NNK: 2.51 ng/50 puffs; NNN: 1.64 ng/50 puffs), with the exception of the results provided in Table 1.

The results are in line with what has been previously observed in commercial e-cigarette products,[28,34,68−70] where TSNAs were found in trace amounts only in some of the analyzed products.

3.3. Elements. Selected elements (As, Cd, Cr, Pb, and Ni) were analyzed in a subset of 12 e-liquids and the aerosol of the same liquids when added to one reference device. The purpose of the study was not to examine if metals originated from the devices, but rather to check the impact of the reporting requirements in Europe for suppliers of e-liquids aimed to be used for open and mod systems, which are supposed to use the most appropriate device for their reporting to authorities.[64]

In the e-liquids, all results were below the LOQ of the respective elements (As: 47.8 ng/g; Cd: 10.9 ng/g; Cr: 87.6 ng/g; Pb: 192 ng/g; Ni: 90.4 ng/g).

In the e-cigarettes aerosols, results above the LOQ (As: 0.12 ng/puff; Cd: 0.06 ng/puff; Cr: 0.09 ng/puff; Pb: 0.05 ng/puff; Ni: 1.08 ng/puff) are provided in Table 2.

The LOQs are well below the values obtained for the blanks (obtained the same day, with the same volume of air puffed with blank samples than the samples). Only two results for arsenic content are above the air blanks.

In addition, nine open and mods systems in combination with the reference liquid mentioned in the experimental part were analyzed as well for the same elements in their aerosols, using CRM 81 puffing conditions.[12] Only the first block of 50

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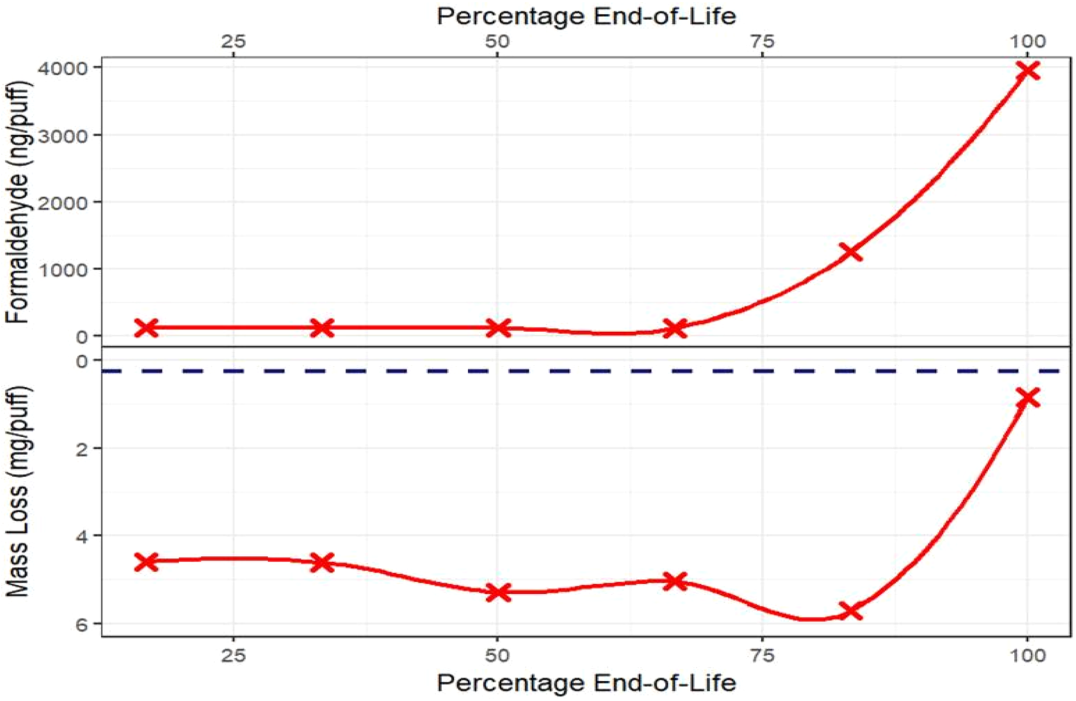

Figure 1. End-of-life concept illustrated for one commercial product (open system). The upper part of the figure provides the concentration of formaldehyde in ng/puff. The lower part of figure provides, on a reverse scale, the yield of mass loss in mg/puff. In order to be able to standardize across different products, the blocks of 50 puffs collected during the aerosol-generating process were transformed into percentages. In this case, there were six blocks of 50 puffs before end-of-life, resulting in the first block being 16.67% of the total. The seventh block (not represented in the figure) had a mass loss below the lower limit of 12.5 mg and was not considered for the analysis and the calculation of the average yield of formaldehyde. The horizontal dashed line is the lower limit of the mass loss (mg/puff) considered for the end-of-life, at 12.5 mg/collection corresponding to 0.25 mg/puff. The crosses illustrate the level of formaldehyde and mass loss for the individual blocks of 50.

Table 2. Elements in the Aerosols (Average until End of Life)

product	As (ng/puff)	Cd (ng/puff)	Cr (ng/puff)	Pb (ng/puff)	Ni (ng/puff)
blank	0.97	<0.06	1.80	0.13	2.08
liquid A	<0.12	<0.06	<0.09	<0.05	<1.08
liquid B	<0.12	<0.06	<0.09	<0.05	<1.08
liquid C	0.54	<0.06	1.03	0.07	<1.08
liquid D	<0.12	<0.06	<0.09	<0.05	<1.08
liquid E	0.89	<0.06	0.97	0.07	<1.08
liquid F	<0.12	<0.06	0.85	0.09	<1.08
liquid G	<0.12	<0.06	<0.09	<0.05	<1.08
liquid H	1.33	<0.06	1.46	0.08	1.54
liquid I	1.17	<0.06	1.58	0.08	<1.08
liquid J	<0.12	<0.06	<0.09	<0.05	<1.08
liquid K	<0.12	<0.06	<0.09	<0.05	<1.08
liquid L	0.50	<0.06	<0.09	0.12	<1.08

puffs was analyzed. No result was above the blank values obtained the same day.

3.4. Additional HPHCs. For six closed systems bought in 2018, we additionally performed the analysis of the following HPHC: benzene, 1,3-butadiene, and Benzo(a)pyrene (BaP).

Their amounts were below the LOQ (benzene: 0.011 μg/puff; 1,3-butadiene: 0.019 μg/puff; BaP: 0.035 ng/puff) in the subset of combinations of e-liquids and devices in which those compounds were measured.

3.5. Carbonyls. The lifetime average yield and the device to device variability of carbonyl (acetaldehyde, acrolein, and formaldehyde) deliveries are provided in Table 3 for closed e-cigarette systems (disposable or cartridge) and in Table 4 for open systems. The puff block to puff block result dynamic up to e-liquid depletion, and the average yield distribution obtained for closed and open systems, respectively, are depicted in Figures 2–5. The results for mod systems are provided in the Supporting Information.

The obtained results for the disposable e-cigarettes are within a relatively small range, with the exception of one product. When compared with all types of devices, the lifetime average for the carbonyl concentrations in the aerosol of disposable devices is generally toward the lower values. This is most probably due to the relatively low power and relatively low temperatures obtained with these products.[71] The absolute values observed for disposable e-cigarettes are below the target values in e-cigarette aerosols (acetaldehyde (16 000 ng/puff), acrolein (80 ng/puff), and formaldehyde (1,000 ng/puff)) proposed in the Association Française de Normalization (AFNOR) experimental voluntary standard,[72] with the exception of two products for the amount of acrolein only. For the other closed systems, a wide range of values is observed. All values are below the target values for acetaldehyde,[72] and six of the 16 products are below the target values for the three carbonyl compounds.

The range observed for the lifetime averages for carbonyl compounds against the value obtained for 3R4F cigarettes is provided in Figure 2. The individual results are also provided in Table 4.

The evolution of formaldehyde levels versus mass loss during the full aerosol generation procedure is shown in Figure 3. Formaldehyde increases as of about 50% of the depletion of the liquid in the liquid reservoir.

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Table 3. Closed Systems: Carbonyls in Aerosols[a]

system	device	liquid	year	acetaldehyde (ng/puff) LAY	acetaldehyde (ng/puff) DV-DV variability	acetaldehyde (ng/puff) air blank	formaldehyde (ng/puff) LAY	formaldehyde (ng/puff) DV-DV variability	formaldehyde (ng/puff) air blank	acrolein (ng/puff) LAY	acrolein (ng/puff) DV-DV variability	acrolein (ng/puff) air blank
closed	brand A	liquid M	2015	2880	2460	43.8	4580	3700	52.6	810	858	11.18
	brand B	liquid N		200	16.52		173	120		35.2	8.58	
	brand C	liquid O		876	438		588	164.4		94.8	7.32	
	brand C	liquid P		492	308		360	160.6		50.8	7.1	
	brand D	liquid Q		234	48.4		232	36.2		51.8	27.6	
	brand D	liquid R		396	144.6		526	194.4		108.8	38.4	
	brand E	liquid S	2017	540	302		466	228		336	171	
	brand F	liquid T		346	18.62		936	128.2		123.2	3.94	
	brand G	liquid U		3600	61.4		3780	65.8		2160	93.8	
	brand H	liquid V	2018	50	9.79	19.25	92.9	50.7	29.39	<30.92	N/A	9.64
	brand I	liquid W		72.8	25.2		105	41.1		36.8	11.6	
	brand J	liquid X		13600	3330		10700	2790		848	174	
	brand K	liquid Y		6550	4320		4840	2380		388	65.4	
	brand L	liquid Z		223	81.6		99.6	98.6		427	216	
	brand M	liquid AA		5320	3920		6910	3470		1900	1930	
	brand M2	liquid AA1		<33.17	N/A		18.9	0.636		<9.28	N/A	
disposable	brand N	liquid AB	2015	338	75.8	43.8	140	32	52.6	109.2	16.06	11.18
	brand O	liquid AC		194.8	60.6		121.6	28.8		61.8	23.4	
	brand P	liquid AD		756	592		688	722		216	176.8	
	brand P	liquid AE		232	49.2		135.2	52.2		42.4	21.4	
	brand P	liquid AF		206	56.8		107.8	31.8		50.8	20.2	

[a]DV-DV variability, device-to-device variability; LAY: lifetime average yield.

The device-to-device variability varies from one commercial product to the other, with, a range of 20−100% relative for the lifetime average of formaldehyde, acetaldehyde and acrolein (see Table 3).

For open systems, the range observed for the lifetime averages for carbonyls compounds against the value obtained for 3R4F cigarettes is provided in Figure 4.

The formaldehyde versus mass loss during the full aerosol-generating regime is given in Figure 5. Formaldehyde increases as of about 50% of the depletion of the liquid in the liquid reservoir.

One open system device provides much lower carbonyl concentrations than the others (Table 4) and is in line with the limits proposed in the AFNOR experimental standard.[72] The other products deliver results above the target values for acrolein and formaldehyde and below the limit for acetaldehyde (with one exception). Device-to-device variability for a given brand also covers a wide range, from less than 1% relative to 120% relative. This possibly reflects the accuracy of temperature control from one device (whether it is an open or a closed system) to another. It was recently demonstrated that the temperatures measured in the heating coils of commercially available devices are more or less variable, depending on the commercial device brand,[73] and therefore result in different levels of device-to-device variability for the carbonyl concentrations in their aerosols due to the impact of temperature on carbonyl formation.

In addition, for open systems, we used one standard liquid in combination with different commercial devices on one hand and one standard open device with different commercial e-liquids (see the Supporting Information for the list of combinations of devices and liquids).

The carbonyl emissions of one standard e-liquid in combination with commercial devices were analyzed in the resulting aerosols. The approach to use a standard e-liquid to be able to report data has been proposed within various standardization committees, such as AFNOR[72] or CEN. It is observed that the amounts of acetaldehyde, acrolein, and formaldehyde cover a wide range of concentrations in the e-cigarette aerosols. For example, there are almost 3 orders of magnitude between the highest and the lowest formaldehyde concentrations, while the liquid was the same in all devices. These results possibly reflect the absolute temperature to which the liquid is exposed to in the different devices,[16,30,41] in addition to a possible dry puff effect for some of the devices.[46] The observed results are above the target values proposed in the AFNOR experimental voluntary standard[72] for acetaldehyde, acrolein, and formaldehyde in e-cigarette aerosols, in most cases for acrolein and formaldehyde and in a few cases also for acetaldehyde.

For suppliers of e-liquids, UK authorities[64] recommend using a reference device for the reporting of aerosol component data. We therefore additionally arbitrarily selected a reference device (widely available commercial open tank system) and assessed it for carbonyl emissions in combination with a number of commercially available e-liquids from different suppliers. The range observed for the results was lower than the range observed for a reference liquid used in different commercial devices, with, for example, a factor of 2.7 from the lowest to the highest lifetime average yield (LAY) for formaldehyde between different e-liquids. This most likely reflects the fact that a lower temperature range is observed when comparing the aerosol obtained with different e-liquids added to a single reference device than different devices with the same liquid. The differences observed for different e-liquids may be due to differences in the composition of the e-liquids, especially in terms of the proportion of PG and G, which are known to result in different acetaldehyde, acrolein, and formaldehyde concentrations.[46,50−53] All results are above the target values proposed in the AFNOR experimental standard[72]

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Table 4. Open Systems: Carbonyls in Aerosols[a]

				acetaldehyde (ng/puff)			formaldehyde (ng/puff)			acrolein (ng/puff)		
system	device	liquid	year	LAY	DV-DV variability	air blank	LAY	DV-DV variability	air blank	LAY	DV-DV variability	air blank
	open tank reference	liquid A	2015	4300	2920	43.8	2820	1362	52.6	504	248	11.18
	open tank reference	liquid B		3780	2880		4140	2780		716	528	
	open tank reference	liquid C		2660	1380		3320	1102		512	118.8	
	open tank reference	liquid D		4180	2160		5440	1664		814	284	
	open tank reference	liquid E		2580	468		2020	132.4		396	100.4	
	open tank reference	liquid F		3140	2180		2280	1282		382	226	
	open tank reference	liquid G		4540	894		4260	994		936	230	
	open tank reference	liquid H		3620	2540		2640	1840		392	304	
	open tank reference	liquid I		3960	1518		2260	546		248	99.6	
	open tank reference	liquid J		4560	1976		3580	1306		1108	484	
	open tank reference	liquid K		4920	2180		3840	1058		1220	750	
	open tank reference	liquid L		3300	1360		3240	908		1628	848	
	brand Q	reference liquid		1398	782		950	548		440	260	
	open tank reference	reference liquid		202	160.6		338	135		76.2	31.8	
	brand R	reference liquid		4600	2160		3320	1722		798	492	
	brand S	reference liquid		4420	4340		3060	3240		1110	1232	
	brand T	reference liquid		5640	6060		4040	4240		1822	2100	
	brand U	reference liquid	2017	354	396		570	360		97.8	118.2	
	brand V	reference liquid		48200	18780		53400	16660		9180	3580	
	brand W	reference liquid		12720	3740		13960	3900		3120	856	
	brand X	reference liquid		2580	648		1484	364		126.2	30.4	
	brand Y	reference liquid		26200	18160		21200	13920		5260	3820	
	brand Z	reference liquid		8700	2380		13300	118.4		2880	688	
	brand AA	liquid AG		5120	1952		16280	10120		3340	1080	
	brand AB	liquid AH		50	6.18		484	300		31.6	1.024	
	brand AC	liquid AI		26800	6480		31400	3820		8700	820	
	brand Y	liquid AJ		8340	5420		10580	8880		2040	1932	
	brand Z	liquid AK		10120	1084		19380	2080		2900	181.6	
	brand AD	liquid AL		3840	1600		10120	5420		1586	512	
	brand AD	reference liquid		1440	422		4060	3660		758	42.8	
	brand AA	reference liquid		18240	2160		24400	2440		4920	786	

[a]DV-DV variability, device-to-device variability; LAY: lifetime average yield.

for formaldehyde and acrolein and below the corresponding limit for acetaldehyde.

3.6. Robustness. We examined whether the device designs were robust in relation to slight changes in the aerosol-generating regime and modified either the puff duration or the puff volume for some closed systems. The robustness was checked with the concentration of acetaldehyde, acrolein, and formaldehyde as markers of temperature fluctuations in the e-cigarette devices. The results are provided in Table 5.

For the closed systems we examined, slight variations of the puff volume or the puff duration had different impacts upon variations in carbonyl emissions: While some of the products tested were extremely consistent in their deliveries, other products showed differences in their performance.

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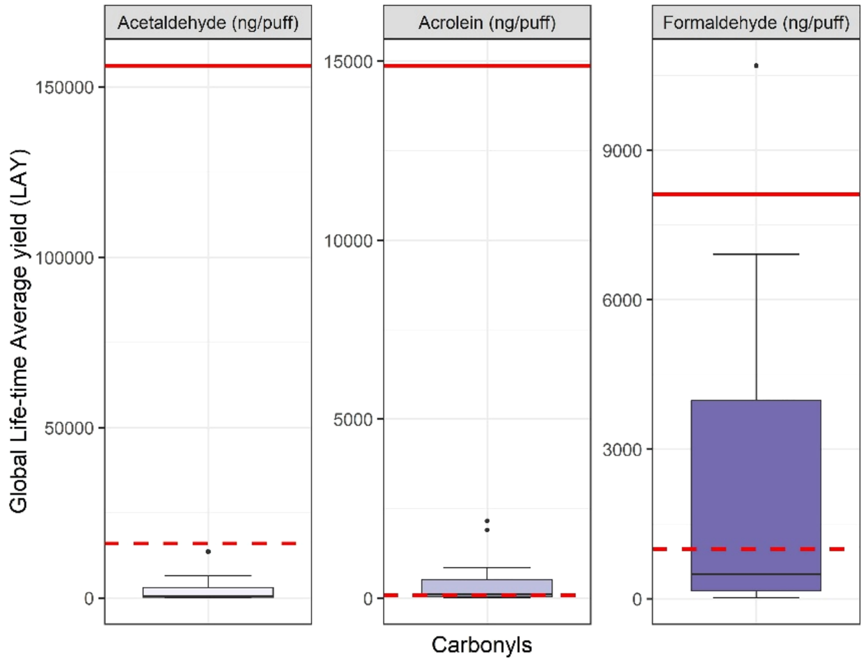

Figure 2. Boxplots representing the global lifetime average yield (LAY) of carbonyls in aerosol for 16 closed systems (excluding disposable systems). The horizontal line represents the levels observed for 3R4F cigarettes with an intense smoking regime ISO 20778. The horizontal dashed line represents the target values proposed in the AFNOR voluntary experimental standard.[72]

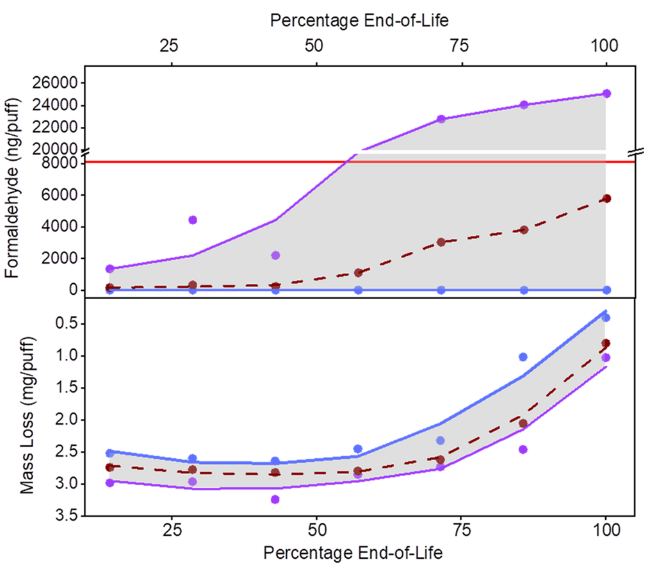

Figure 3. End-of-life of formaldehyde in aerosol for 16 closed systems (excluding disposable systems). The horizontal line shows the 3R4F level as a reference with an intense smoking regime ISO 20778. The upper solid, middle dashed, and bottom solid lines illustrate the max, average, and min yield, respectively, across all products. These are the best polynomial fit to the raw data.

4. DISCUSSION

4.1. Metals, TSNAs, and Other Priority HPHCs. Our analysis of e-liquids and e-cigarette aerosols was focused on the products recommended to be analyzed in such matrices in standardization documents,[62,72,74] namely elements, carbonyls, and TSNAs. We analyzed 12 e-liquids and their aerosols for their content of five elements (As, Cd, Cr, Pb, and Ni) using a standardized aerosol-generating regime.[12] The main source of metals in e-cigarettes has been identified to be the composition of the coils and other parts of the e-cigarette devices.[21,22,25] In the present study, none of these five elements were observed above the LOQ in the liquids, and only two e-liquid aerosols when combined with the reference device had as reported As content above air blank samples. The use of air blanks in the interpretation of results was found to be critical when analyzing e-liquid aerosols for metals, given the rather high volume of air puffed through the product when analyzing e-cigarette aerosols on an analytical puffing machine, using standard conditions, as provided in CRM 81 (typically 50 puffs × 55 mL = 2.75 L of air). Our results are also in line with results obtained for other commercial products, where no metals were detected[30,33] or where the maximum results for the same elements in commercial e-liquids were in the 1−12 ppb range.[19] They are also in line with the results of a cross-sectional survey, in which cigarette smokers who switched to e-cigarettes significantly reduced their exposure to Cd and Pb.[40]

The same 12 liquids and their aerosols, as obtained using a single reference device, were analyzed for their TSNA content. Very few results were above the LOQ in the liquids or in their aerosols. This corresponds to observations by other authors for commercial products[28,30,33,34,68,70] and is also reflected in the reduction of TSNA biomarkers for cigarette smokers who switch to e-cigarettes.[37−39,75]

The content of benzene, 1,3-butadiene, and BaP in the analyzed subset of combinations of liquids and devices was below the LOQ in all cases, in line with the observation of other authors for commercial closed systems products[30,32,76] and with the reduction of biomarkers of benzene and 1,3-butadiene exposure for cigarette smokers who switch to e-cigarettes.[38,39] However, benzene was found in the aerosol of some mod systems operated at high power, while it was not detected in a closed cartridge system.[77]

4.2. Carbonyls. The concentrations of the carbonyl compounds acetaldehyde, acrolein, and formaldehyde in e-cigarette aerosols has been the subject of numerous

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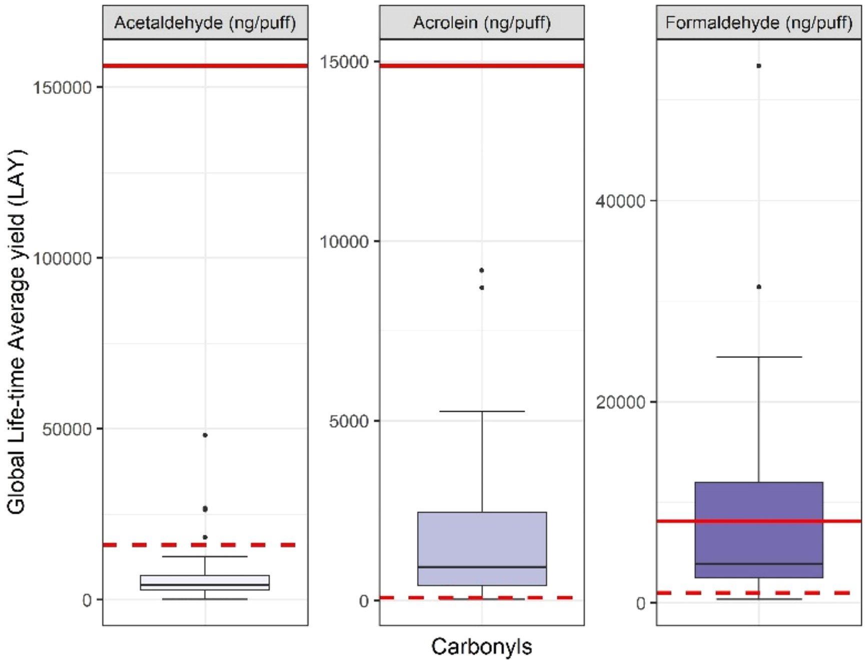

Figure 4. Boxplots representing the global lifetime average yield (LAY) of carbonyls in aerosol for 31 open systems. The horizontal line represents the levels observed for 3R4F cigarettes with an intense smoking regime ISO 20778. The horizontal dashed line represents the target values proposed in the AFNOR voluntary experimental standard.[72]

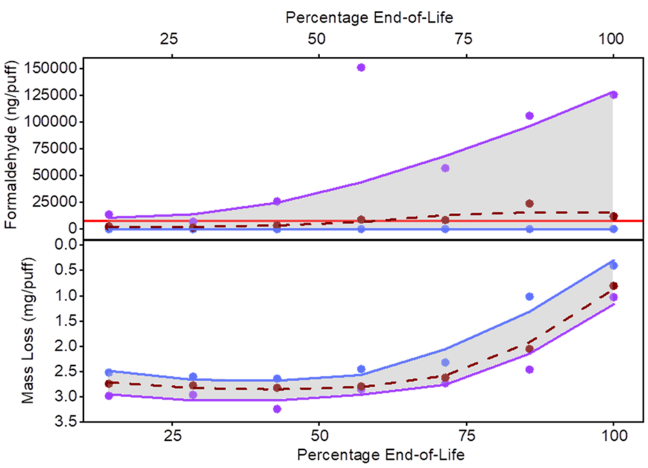

Figure 5. End-of-life of formaldehyde in aerosol for 31 open systems. The horizontal line shows the 3R4F level with an intense smoking regime ISO 20778. The upper solid, middle dashed, and bottom solid lines illustrate the max, average, and min yield, respectively, across all products. These are best polynomial fit to the raw data.

publications, as reviewed by Farsalinos.[46] They result mainly from the thermal degradation of PG and G, used as aerosol formers in the e-liquids.[51,52] The results obtained by different authors with different products are difficult to compare due to the use of different conditions (aerosol-generating regime, end of aerosol-generating process). It is known however that an increase of the coil temperature results in an increase of carbonyls in e-cigarette aerosols[16,53] and that an increase of the power for systems with variable output also results in an increase of carbonyl concentrations.[45,49,55] Nevertheless, in clinical trials in which cigarette smokers switched to a specific e-cigarette commercial product, there was a reduction of exposure to acrolein for e-cigarette users when compared with cigarette smokers, according to the concentration of the biomarker for acrolein.[38,39]

In this work, we used the same aerosol-generating conditions for all devices/e-liquids to overcome the issue mentioned above and to be able to compare the different devices and liquids in the same conditions.

It appears that carbonyl emissions are generally the lowest in closed systems and higher in open systems. There are relatively few products that are in line with the target limit values proposed by AFNOR in an experimental voluntary standard.[72] There is a wide range of device-to-device variability, reflecting the accuracy of the coil temperature control from device-to-device[73] and the resulting differences in thermal degradation of aerosol formers. The need to have a technical system integrated in e-cigarette devices to prevent overheating, as suggested by Hutzler et al.,[41] proved to be successful in one closed e-cigarette device having a built-in system detecting dry puff, which is among the devices delivering the lowest amount of carbonyls.

We also examined carbonyl emissions with different aerosol-generating regimes for seven closed systems, fulfilling the need to analyze e-cigarette emissions not only with a standardized regime but also with more intense conditions expressed by FDA.[78] While some of the products tested were extremely consistent in their deliveries, other products showed differences in their performance.

We tested as well mod type devices under CRM 81 conditions[12] and with full power mode for their yields in carbonyls compounds in aerosols. The results (provided in the Supporting Information) were higher than the ones obtained for 3R4F cigarettes. It confirmed previously obtained results.[45,48,55] Product orientation and slight changes in puffing conditions (higher puff duration and/or puff volume) did not substantially impact these findings. For those products, the use of such puffing regimes is possibly not adequate, and alternative aerosol-generating regimes may need to be

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Table 5. Closed Systems[a]

product	parameter (ng/100 cm^3)	55 mL/3 s/30 s	55 mL/4 s/30 s	80 mL/3 s/30 s	80 mL/4 s/30 s
brand E	acetaldehyde	145.27	168.36	72.13	116.75
	acrolein	72.55	67.45	14.38	50.00
	formaldehyde	190.91	216.36	173.75	190.00
brand H	acetaldehyde	115.09	142.73	46.13	33.38
	acrolein	4.67	7.49	<LOQ	<LOQ
	formaldehyde	169.09	289.09	95.75	141.25
brand J	acetaldehyde	24727	98000	25875	38875
	acrolein	1800	17872	2113	8313
	formaldehyde	19455	60182	19250	25500
brand K	acetaldehyde	11909	23273	5788	10588
	acrolein	694.6	1476.4	680.0	816.3
	formaldehyde	8800	15709	4263	7713
brand M2	acetaldehyde	<LOQ	<LOQ	<LOQ	<LOQ
	acrolein	<LOQ	<LOQ	<LOQ	<LOQ
	formaldehyde	<LOQ	37.45	35.25	45.00
brand L	acetaldehyde	405.5	1520	330.0	897.5
	acrolein	780.0	1496	502.5	1155
	formaldehyde	181.8	240.0	312.5	455.0
brand M	acetaldehyde	9673	18363	7938	10000
	acrolein	4236	9382	3525	4463
	formaldehyde	12563	18727	13000	16750

[a]Carbonyl lifetime average emissions with various aerosol-generating regimes. Note: The LOQs for formaldehyde were 33.27 ng/100 cm^3 and 22.87 ng/100 cm^3 for regimes with a puff volume of 55 and 80 mL, respectively. The LOQs for acetaldehyde were 60.31 ng/100 cm^3 and 41.46 ng/100 cm^3 for regimes with a puff volume of 55 and 80 mL, respectively. The LOQs for acrolein were 56.21 ng/100 cm^3 and 38.65 ng/cm^3 for regimes with a puff volume of 55 and 80 mL, respectively.

explored. It was observed for example that consumers using mod systems tend to have larger puffing volumes.[79] An alternative standardized aerosol-generating regime for mods may possibly be proposed by CORESTA and/or the European Technical Committee in charge of e-cigarettes in the future, according to their working programs.

Additionally, the use of the full power mode for mods may possibly not correspond to realistic use conditions[42] and represent a misuse of those products.[46] The goal in the present work was to check the emissions of aldehydes from these products under the full range of manufacturer-provided conditions in line with recommendations from governmental agencies[63,64] and in absence of reliable product use behavior data. Especially considering the proliferation of subohm coils, it is important that manufacturers consider limiting the power flow to the coil on the devices to avoid the potential for misuse of these products by the consumers and a potential exposure to high amounts of formaldehyde, acetaldehyde and acrolein.

5. CONCLUSIONS

A systematic investigation of emissions from a broad range of commercially available e-cigarettes revealed major differences in product performance and emission consistency. It was shown that the levels of TSNAs and heavy metals in product emissions are only dependent on the presence of these substances in e-liquids; the potential for leaching heavy metals from the device should also be considered. TSNAs and heavy metals could be quantified in very few products; notably for heavy metals, however, no nicotine salt e-liquids were assessed in the present study, and this may require further investigation, specifically with regard to potential contribution of e-cigarette devices to heavy metal emissions. On the contrary, the levels of carbonyls were highly variable, especially formaldehyde, which seems to be a good marker of product performance.

With respect to emission consistency, large differences were observed between products in terms of device-to-device consistency, while the puffing regime-to-puffing regime consistency was generally better. Some products, achieved very high consistency of emissions regardless of test conditions.

Finally, for products with very low levels of carbonyl emissions and a high degree of emission consistency, a limitation of existing testing protocols was identified, whereby the contribution of the laboratory blank exceeds the product-relevant contribution to the overall result. It is therefore important that blank results are systematically reported by the laboratories performing these assessments and that these results are taken into account in the interpretation of results and any comparative assessments of emissions between different products.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.chemrestox.9b00470.

List of devices and liquids used in the project: Table S1
Results related to mods systems: Tables S2−S3, Figure S1 (PDF)

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■ ABBREVIATIONS

AFNOR, Association Française de Normalization; G, glycerol; HPHC, harmful and potentially harmful constituents; NNK, 4-(methynitrosamino)-1(3-pyridyl)-1-butanone; NNN, *N*-nitrosonornicotine; PG, propylene glycol; TSNA, tobacco specific nitrosamines; WHO, World Health Organisation

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