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Aldehyde levels in e-cigarette aerosol: Findings from a replication study and from use of a new-generation device

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ABSTRACT

Purpose: A recent study identified high aldehyde emissions from e-cigarettes (ECs), that when converted to reasonable daily human EC liquid consumption, 5 g/day, gave formaldehyde exposure equivalent to 604–3257 tobacco cigarettes. We replicated this study and also tested a new-generation atomizer under verified realistic (no dry puff) conditions.

Design: CE4v2 atomizers were tested at 3.8 V and 4.8 V, and a Nautilus Mini atomizer was tested at 9.0 W and 13.5 W. All measurements were performed in a laboratory ISO-accredited for EC aerosol collection and aldehyde measurements.

Results: CE4v2 generated dry puffs at both voltage settings. Formaldehyde levels were > 10-fold lower, acetaldehyde 6–9-fold lower and acrolein 16–26-fold lower than reported in the previous study. Nautilus Mini did not generate dry puffs, and minimal aldehydes were emitted despite > 100% higher aerosol production per puff compared to CE4v2 (formaldehyde: 16.7 and 16.5 μg/g; acetaldehyde: 9.6 and 10.3 μg/g; acrolein: 8.6 and 11.7 μg/g at 9.0 W and 13.5 W, respectively). EC liquid consumption of 5 g/day reduces aldehyde exposure by 94.4–99.8% compared to smoking 20 tobacco cigarettes.

Conclusion: Checking for dry puffs is essential for EC emission testing. Under realistic conditions, new-generation ECs emit minimal aldehydes/g liquid at both low and high power. Validated methods should be used when analyzing EC aerosol.

1. Introduction

Electronic cigarettes (ECs) are currently seeing high popularity as replacements to combustible tobacco usage (Vardavas et al., 2015; Barbeau et al., 2013; Regan et al., 2013; Pearson et al., 2012). One of the main health concerns about EC usage is the potential for toxic aldehyde emissions, such as formaldehyde, acetaldehyde and acrolein, which are known to be formed from heating mixtures of propylene glycol and glycerol, typical carrier solvents for EC liquids (e-liquids), as thermal decomposition products (Paschke et al., 2014; Uchiyama et al., 2013). These aldehydes are potential irritants, such as acrolein, toxins and/or carcinogens, such as formaldehyde and acetaldehyde (US OSHA, 2007; US OSHA, 2011). They are also formed in high quantities from tobacco combustion (Counts et al., 2005). ECs, in contrast, have generally been shown to produce aldehydes at much lower levels compared to smoking (Goniewicz et al., 2014; Bekki et al., 2014). However, in 2015 a study that received much publicity reported that ECs can emit formaldehyde at levels far exceeding tobacco cigarettes (Jensen et al., 2015). That study, which used older, "top-coil" atomizer-tanks with silica wicks, was criticized for raising power levels too high (5.0 V, corresponding to 10.9 W) for the heating coils to be effectively replenished with e-liquid fast enough to avoid overheating the coil (Bates and Farsalinos, 2015; Nitzkin et al., 2015). Overheating of the liquid leads to the "dry-puff" phenomenon (Farsalinos et al., 2015), which is perceived by the user as unpleasant taste and, thus, is not representative of realistic user conditions. Moreover, the atomizer chosen for that study had a very inefficient design, with the coil and wick located just below the mouthpiece, making it quite prone to the generation of dry puffs even at relatively low power settings. That is why this design was largely abandoned years ago by consumers; in fact, they are not

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available in the European Union (EU) market any more, although they are still availability in other countries such as the US. Modern "bottom-coil" atomizers using cotton (instead of silica) wick, have been developed in recent years, which seem to have a more efficient design in terms of liquid replenishment to the coil and are used at higher power settings as recommended by the manufacturers of the devices. A recent replication study verified that formaldehyde emissions at 5.0 V from the same top-coil atomizer were very high but were associated with dry puffs and represented unrealistic conditions (Farsalinos et al., 2017a); however, even at realistic use conditions formaldehyde levels were higher than more recent, "bottom coil" atomizers (Gillman et al., 2016). In any case, verifying the absence of dry puffs during laboratory evaluation of EC emissions, irrespective of the type of product tested, is a necessity to ascertain that realistic conditions of use are examined, especially when making claims related to production of thermal decomposition products.

Another recent study by Sleiman et al. (2016) reported extremely high emissions of aldehydes from a top-coil EC atomizer at 3.8 V and 4.8 V, using a commercially-available flavored e-liquid, with aldehyde levels (in μg per gram of e-liquid) up to 48200 μg/g for formaldehyde, 19080 μg/g for acetaldehyde and 10060 μg/g for acrolein. Such levels far exceed the exposure from smoking. A study evaluating 50 tobacco cigarette brands found average formaldehyde emissions of 74 μg/cigarettes, under intense smoking conditions (Counts et al., 2005). Therefore, using the data from Sleiman et al. and calculating exposure for a daily liquid consumption of 5 g, daily EC use at low and high voltage settings would expose users to formaldehyde levels equivalent to smoking 604 to 3257 tobacco cigarettes respectively. Unfortunately, the authors did not assess for the generation of dry puffs, which can only be determined by getting feedback from experienced EC users actually using the devices at the same power settings and puffing regime as in the laboratory. Thus, the authors could not verify that the conditions tested were comparable to normal device usage and exclude the possibility for dry puff and overheating conditions. Given the exceedingly high aldehyde values reported, it is very probable that the data was generated under dry puff conditions.

Since the levels reported are so high that there are reasonable expectations of harm to consumers, it is important to assess these findings under verified realistic usage conditions which are relevant to human exposure. Therefore, the primary purpose of the current study was to replicate that study using the liquid with the highest levels of aldehyde emissions as reported by Sleiman et al. and the same equipment (EC battery and atomizer). Additionally, the same liquid was also tested with new-generation EC equipment with higher power settings. In our experiments, generation of dry puffs was assessed by two experienced EC users (members of the research team). Analytical testing was performed using validated methods and in testing facilities with accreditation for collecting EC aerosol and measuring aldehydes. Finally, a comparison of aldehyde emissions with literature data from tobacco cigarettes and with environmental levels and safety limits was performed.

2. Materials and methods

2.1. Equipment

The liquid used in this study was Apollo Classic Tobacco liquid (Apollo Ecigs, California, USA), which was tested by Sleiman et al. and emitted the highest levels of formaldehyde, acetaldehyde and acrolein. The flavored liquid, containing a carrier base of 50% propylene glycol/50% glycerol ratio and 18 mg/mL nicotine concentration, was purchased online. The EC device for the replication experiment was the same CE4v2 atomizers and eGo-type variable voltage battery used by Sleiman et al. The other atomizer used in the study by Sleiman et al. was also obtained for testing (Aerotank Mini, Kangertech, Shenzhen, China); however, we were unable to find the atomizer heads used in that study (2.0 Ohm silica wick coils), therefore we were unable to replicate the experiment with this atomizer. To further examine aldehyde emissions from the same EC liquid, a new-generation device, the EVIC VTC Mini variable-wattage battery device (Joyetech, Shenzhen, China) and the Nautilus Mini atomizer with 1.6 Ohm replacement coils and cotton wick (Aspire, Shenzhen, China), were used. All battery devices and atomizers were purchased online. An unflavored liquid, containing the same proportions of propylene glycol, glycerol and nicotine but no added flavoring, was prepared and tested under the same conditions as the flavored sample with the new-generation atomizer only.

2.2. HPLC analysis

The samples were analyzed using an Agilent Model 1100, High Performance Liquid Chromatograph equipped with an Ultraviolet (UV) Detector, operating at 365 nm, and a Brownlee Choice C18 column. The carbonyl compounds were treated with 2,4-dinitrophenylhydrazine (DNPH) as a derivatizing reagent to be able to detect the compounds at 365 nm on an HPLC-UV detector. All methods have been validated according to International Conference on Harmonization guidelines including for method specificity, linearity, accuracy and precision. The aerosol analysis method was validated for sample trapping efficiency. Analytical testing was performed using validated methods where the all test methods were included on the testing facilities with ISO 17025:2005 scope of accreditation (A2LA, 2017). This method is a validated modified version of the CORESTA assay for determining carbonyls in cigarette smoke (CORESTA, 2014).

2.3. Liquid analysis

EC liquid samples were derivatized directly in autosampler vials (ALS vials) with a saturated DNPH solution. A volume of 100 μL of the liquid sample was dispensed into a sample vial and 1 mL of the DNPH solution was added to the sample. A vortexer was used to ensure that the sample was well mixed into the DNPH solution. The sample was allowed to sit at room temperature for 20 ± 1 min to allow time for the derivatization process to complete. The reaction was then quenched with pyridine, 50 μL pyridine for every 1 mL of DNPH solution. Samples were analyzed by HPLC. The LOQs for the method were as follows: 0.27μg/mL for acetaldehyde and acrolein and 0.03μg/mL for formaldehyde. The LODs for were 0.03μg/mL for all compounds. Results were converted to μg/g based on the density of the liquid samples.

2.4. Aerosol collection and analysis

CE4v2 atomizers were tested at 3.8 V and 4.8 V with a puffing protocol of 50 mL puff volume, 5 s puff duration and 30 s interpuff interval (from the beginning of one puff to the beginning of the next puff). Three different atomizers were tested, with one aerosol collection from each at 3.8 V and 4.8 V. The Nautilus Mini atomizer was tested at 9 W and 13.5 W with a puffing protocol of 50 mL puff volume, 4 s puff duration and 30 s interpuff interval, since a 5 s puff duration exceeds the typical human puff duration as observed in EC use topography studies (Farsalinos et al., 2013a) A different replacement atomizer head was used for flavored and unflavored liquid. Before performing the laboratory collections, two experienced vapers (members of the research team) tested all equipment for generation of dry puffs, using different atomizers from those used in the aerosol collection.

Aerosol collections were performed using a Cerulean SM450 smoking machine. One coarse-fritted impinger was connected to the smoking machine and was submerged in ice water to allow aerosol condensation and no loss of volatile compounds. Aerosol was generated through an automatic trigger activating the EC battery device, using the puffing patterns mentioned above. Sleiman et al. reported that at "steady-state" conditions (collecting puffs after performing 30 "warm-up" puffs) the levels of aldehydes were increased by 60%. However, in that study, only 1–5 puffs were collected in DNPH cartridges and analyzed while we collected 50 puffs per sample. Despite that, the "warm-up" procedure of obtaining 30 puffs before collecting the aerosol was also followed herein. After the 30 "warm-up puffs, 50 puffs were collected through the impinger, constituting one "puff block". The atomizer was weighed before and after the puff block collection session to determine liquid consumption. Weight loss of the atomizer was considered as liquid consumption; thus, aldehyde levels could be reported as μg/g of liquid consumption.

The aerosol was directed into an impinger that contained 35 mL of a DNPH trapping solution. The combined aerosol and trapping solution mixture was left to react for 20 min so that the DNPH was able to form a complex with the carbonyl compounds. After derivatizing, a 5 mL aliquot of the impinger contents was retained and quenched with 0.25 mL of pyridine. These aliquots were the samples transferred into vials to be analyzed on the HPLC instrument. The aerosol samples were analyzed for formaldehyde, acetaldehyde and acrolein by HPLC.

Validation for aldehyde collection in one impinger was performed by adding a second impinger in series and measuring aldehyde levels separately in each impinger. Aldehydes were not detected in the second impinger. The limits of quantification (LOQs) for the method were as follows: 1.72 μg/puff block (0.049 μg/mL DNPH solution) for acetaldehyde and acrolein, and 0.53 μg/puff block (0.015 μg/mL DNPH solution) for formaldehyde. The limits of detection (LODs) for the method were as follows: 0.86 μg/puff block (0.025 μg/mL DNPH solution) for acetaldehyde, 1.0 μg/puff block (0.029 μg/mL DNPH solution) for acrolein and 0.46 μg/puff block (0.013 μg/mL DNPH solution) for formaldehyde.

2.5. Statistical analyses

Aldehyde levels were presented as mean and standard error (SE) for CE4v2 (due to high variability between measurements), and standard deviation (SD) for Nautilus Mini. Comparison between low and high power setting and between flavored and unflavored liquid (for the Nautilus Mini) was performed with independent-samples *t*-test separately. A P value of < 0.05 was considered statistically significant, and all analyses were performed using SPSS v23 (Chicago, Illinois, USA).

3. Results

3.1. Aldehyde emissions in flavored and unflavored liquid

No formaldehyde, acetaldehyde and acrolein were detected from analysis of the flavored liquid itself. The amount of liquid consumption and levels of aldehyde emissions to the aerosol are presented in Table 1. The results of the Sleiman et al. study are also displayed for comparison, using data from Table S1 of that study (battery setting: 3.8 V and 4.8 V; clearomizer: EGO; liquid: CT; regime: st-state). The "clearomizer" mentioned in the Sleiman et al. table is the CE4-type atomizer used herein, "CT" liquid is the Apollo Classic Tobacco liquid and "st-state" refers to aerosol collected after 30 "warm-up" puffs were obtained.

Dry puffs were detected at both 3.8 V and 4.8 V with the CE4v2 atomizer. Specifically, the burning taste of dry puffs was discernible (although not unbearable) at 3.8 V, and was particularly aversive and unpleasant at 4.8 V even with shorter puff duration (no attempt was made to use it at 5 s puff duration). Liquid consumption ranged from 5.2 to 7.0 mg and was very close to the values reported by Sleiman et al. At 3.8 V, formaldehyde was detected at levels 11.2-fold lower, acetaldehyde 5.6-fold lower and acrolein 24.6-fold lower compared to the study by Sleiman et al. At 4.8 V, the respective levels were 11.3-fold, 8.8-fold and 16.1-fold lower.

No dry puffs were detected with the Nautilus Mini atomizer at any power settings. Liquid consumption ranged from 8.0 mg/puff at low power to 16.6 mg/puff at high power setting for the flavored liquid, and from 8.5 mg/puff to 21.0 mg/puff for the unflavored liquid respectively. The liquid consumption per puff for the flavored liquid was > 50% higher at low power and > 100% higher at high power compared to the CE4v2 atomizer, while for the unflavored liquid consumption per puff was about 200% higher.

Aldehyde levels were lower in unflavored compared to flavored liquid ($P < 0.05$ for all aldehydes tested at both power settings). For all measurements, the levels of aldehydes were very low, thus the absolute difference between flavored and unflavored liquid was minimal. In fact, in several collection samples carbonyls were measured at levels between the LODs and LOQs of the method. Compared to Sleiman et al., the levels of formaldehyde emissions were > 500-fold lower at the low power and almost 3000-fold lower at the high power setting for the flavored liquid, and > 650-fold and > 4500-fold lower for the unflavored liquid respectively. For acetaldehyde, our findings were lower by almost 200-fold and 2000-fold for the flavored liquid, and by > 500-fold and > 10,000-fold for the unflavored liquid at low and high power settings, respectively. For acrolein, our findings were lower by almost 200-fold and > 850-fold for the flavored liquid, and by > 400-fold and > 5500-fold for the unflavored liquid at low and high power settings respectively.

3.2. Comparison between different power settings

Since only the Nautilus Mini performed under realistic (no dry puff) conditions at both power settings, the differences between low and high power settings with this atomizer only are displayed in Fig. 1 (for μg/g) and Fig. 2 (for μg/puff), separately for flavored and unflavored liquid. No statistically significant difference in emissions per g of liquid was observed between low and high power settings for the flavored liquid, while a statistically significant decrease in acetaldehyde and acrolein emissions was observed for the unflavored sample at high compared to low power setting. The latter should be attributed to the very low levels detected, which were below the LOQ levels of the analytical method.

Table 1
Aldehyde emissions (μg/g) and liquid consumption per puff (mg) for the Ce4v2 and the Nautilus Mini atomizer, with the latter tested with flavored and unflavored liquid. The findings by Sleiman et al. (2016) for Ce4v2 and the same flavored liquid are also displayed for comparison.

Measurements	CE4v2 Flavored liquid[a,b]		Sleiman et al. (CE4v2-Flavored liquid)		Nautilus Mini Flavored liquid		Nautilus Mini Unflavored liquid	
	Low voltage (3.8 V)	High voltage (4.8 V)	Low voltage (3.8 V)	High voltage (4.8 V)	Low power (9 W)	High power (13.5 W)	Low power (9 W)	High power (13.5 W)
Aldehydes, μg/g (SD)								
Formaldehyde	796.7 (449.3)	4259.6 (2405.6)	8950	48200	16.7 (0.7)	16.5 (1.4)	13.5 (0.4)	9.9 (2.3)
Acetaldehyde	320.6 (178.5)	2156.2 (1313.9)	1820	19080	9.6 (1.3)	10.3 (1.5)	3.2 (0.2)	1.8 (0.2)
Acrolein	69.1 (34.8)	623.6 (464.2)	1700	10060	8.6 (1.3)	11.7 (2.0)	4.1 (0.2)	1.8 (0.3)
Liquid per puff, mg	5.2 (3.2)	7.0 (0.6)	5.1	7.1	8.0 (0.2)	16.6 (1.3)	8.5 (0.3)	21.0 (2.1)

[a] Standard error of mean presented for aldehydes.
[b] Dry puffs were detected at both 3.8 V and 4.8 V with the CE4v2 atomizer.

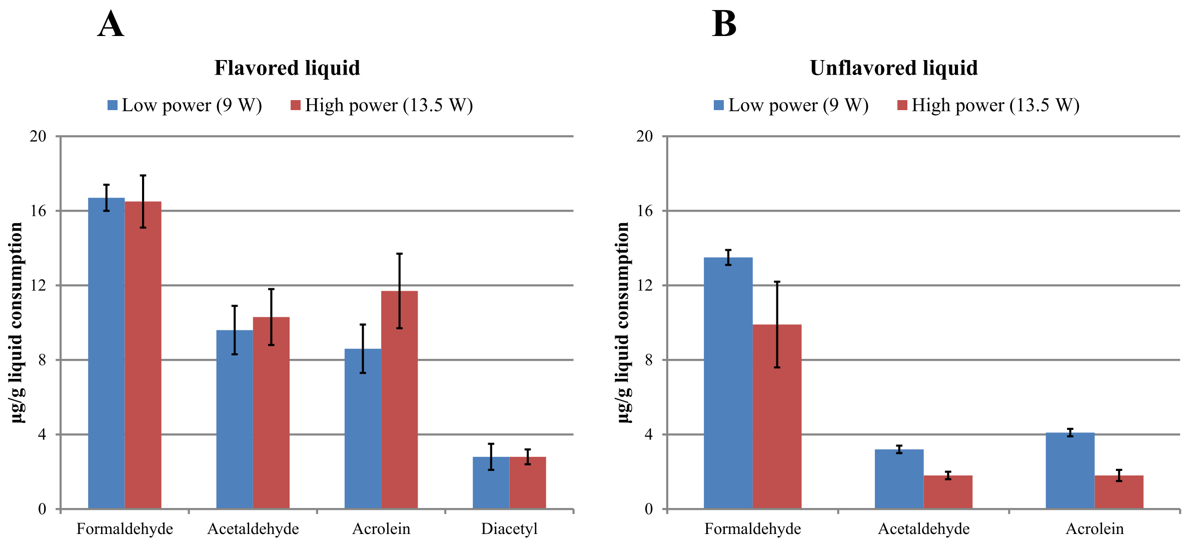

Fig. 1. Aldehyde emissions (μg/g) at low and high power settings for the flavored (A) and the unflavored (B) liquids tested.

For the levels per puff, statistically significant elevation in all aldehyde emissions was observed in high power setting compared to low power setting for both flavored and unflavored liquid ($P < 0.05$ for all differences besides formaldehyde for the unflavored sample for which $P = 0.052$).

3.3. Comparison with tobacco cigarette smoke and environmental levels

Table 2 displays the comparison between 10 puffs of EC and 1 tobacco cigarette, as well as a daily consumption of 5 g EC liquid compared to 20 tobacco cigarettes. The data from the flavored liquid using the Nautilus Mini atomizer at the higher power setting were used in the comparison since they represent realistic use. The choice for the daily EC consumption was slightly higher than reported in large surveys of consumers (Farsalinos et al., 2013b, 2014). Data for tobacco cigarettes were derived from a study by Counts et al. (2005) by averaging aldehyde emissions from 50 products tested under Health Canada Intense puffing regime. Large differences in emitted aldehydes were observed between EC use and smoking. Daily exposure to formaldehyde was calculated to be 18-fold lower, acetaldehyde > 450-fold lower and acrolein > 40-fold lower from use of the flavored liquid tested herein at high power setting compared to tobacco cigarette use. This represents a reduction in daily exposure of 94.4% for formaldehyde, 99.8% for acetaldehyde, and 97.6% for acrolein (Supplementary Fig. 1). In contrast, Sleiman et al. found > 150-fold higher formaldehyde, almost 4-fold higher acetaldehyde and 20-fold higher acrolein levels from 5 g of liquid consumption compared to smoking 20 cigarettes. In fact, the findings by Sleiman et al. showed that consuming 5 g EC liquid would be equivalent to approximately 604–3257 tobacco cigarettes for formaldehyde, 7–77 tobacco cigarettes for acetaldehyde and 71–418 tobacco cigarettes for acrolein at low and high voltage settings respectively.

According to the World Health Organization (2010) indoor air of homes can have up to 250 μg/m^3 formaldehyde, although on average levels of < 50 μg/m^3 are found. Considering a daily ventilation volume of 20 m^3, the daily formaldehyde exposure from breathing indoor air is approximately 1000 μg, by far higher than the total exposure from consuming 5 g of the liquid tested. The European Union (2005) reports that the median levels of acetaldehyde in European homes are 10–20 μg/m^3. Additionally, an Indoor Air Quality guideline of 200 μg/m^3 has been set as the upper safety limit. Therefore, staying at home for 24 h would result in acetaldehyde exposure of 200–400 μg, with an upper safety limit of 4000 μg. Both values are by far higher than the total exposure from consuming 5 g of the liquid tested. The National

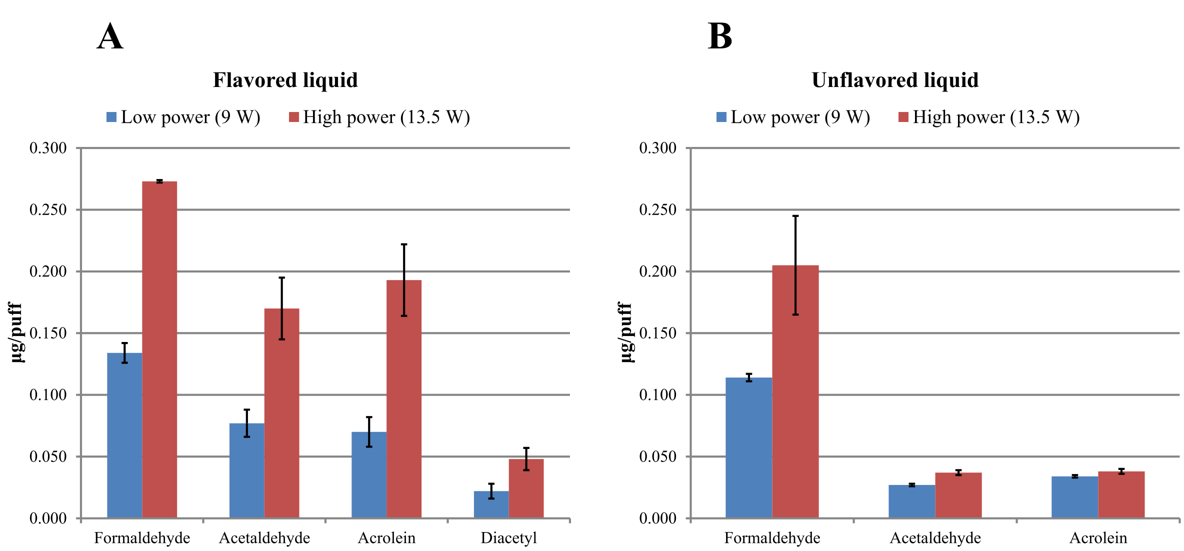

Fig. 2. Aldehyde emissions (μg/puff) at low and high power settings for the flavored (A) and the unflavored (B) liquids tested.

Table 2
Aldehyde emissions per 1 and 20 tobacco cigarettes, and per 10 puffs and 5 g of flavored and unflavored e-cigarette liquids tested with Nautilus Mini. Standard deviation (SD) for each measured value is given in parentheses.

	Formaldehyde[a]	Acetaldehyde[a]	Acrolein[a]
	μg/10 puffs or μg/cigarette (SD)	μg/10 puffs or μg/cigarette (SD)	μg/10 puffs or μg/cigarette (SD)
Unflavored liquid			
9 W	0.9 (0.1)	0.3 (0.1)	–
13.5 W	1.4 (0.0)	0.5 (0.0)	–
Flavored liquid			
9 W	1.3 (0.1)	0.8 (0.1)	0.7 (0.1)
13.5 W	2.7 (0.0)	1.7 (0.2)	1.9 (0.3)
Sleiman et al. flavored liquid[b]			
3.8 V	456.5	92.8	86.7
4.8 V	3422.2	1354.7	714.3
Tobacco cigarette	74.0 (23.7)	1240.3 (147.7)	120.4 (14.7)
	μg/5g or μg/20 cigarettes (SD)		
Unflavored liquid			
9 W	46.4 (3.0)	18.6 (3.0)	–
13.5 W	35.8 (4.2)	12.9 (1.5)	–
Flavored liquid			
9 W	83.3 (3.4)	48.0 (6.3)	43.2 (6.6)
13.5 W	82.5 (6.8)	51.3 (7.3)	58.3 (9.8)
Sleiman et al. flavored liquid			
3.8 V	44750	9100	8500
4.8 V	241000	95400	50300
Tobacco cigarette	1480.7 (474.3)	24806.0 (2954.3)	2408.0 (294.3)

[a] Data on emissions of formaldehyde, acetaldehyde and acrolein from tobacco cigarettes were derived from Counts et al. (2005).
[b] Levels calculated from the reported emissions per g and the liquid consumption per puff as reported in Table S1 of the study by Sleiman et al. (2016) for the same flavored liquid as tested herein.

Institute of Occupational Safety and Health (2015) has set an occupational setting Recommended Exposure Limit of 0.25 mg/m^3 for acrolein. Therefore, an 8 h occupational exposure (ventilation volume of 6.7 m^3/8 h) would result in acrolein exposure of 1675 μg. Again, this is by far higher than the total exposure from consuming 5 g of the liquid tested.

4. Discussion

This replication study sought to examine whether ECs emit high aldehyde levels exceeding tobacco cigarette smoke under realistic use conditions that could have clinical relevance in terms of human exposure. Sleiman et al. (2016) reported extreme aldehyde emissions, which in high voltage were comparable to thousands of tobacco cigarettes, making it essential to verify those findings because they could represent a substantial potential health hazard for users. Using the same equipment and puffing regime, high aldehyde emissions were found from the CE4v2 atomizer. However, the findings herein were substantially lower compared to those reported by Sleiman et al., while dry puffs were detected at both voltage settings. More importantly, using the same liquid with a new-generation atomizer at realistic (no dry puff) conditions, aldehyde levels were extremely low and unlikely to cause any substantial health harm to EC users.

The substantial differences in aldehyde emissions between the two atomizers tested indicate that the liquid was not the culprit for the extremely high aldehyde levels reported by Sleiman et al. Also, power setting was irrelevant because the new-generation atomizer was tested at sufficiently high power to deliver substantial aerosol yield per puff. It has been previously explained that there is no specific power level at which all atomizers overheat and generate dry puffs; it is the design of the atomizer, related to the coil mass and adequate supply of liquid to the wick and coil area, which influences the power needs and enables the application of high power levels without generating dry puffs (Farsalinos et al., 2015). New-generation battery devices can deliver very high power levels, but this does not mean that such power levels are usable with all available atomizers. The CE4v2 atomizer is an old design with at least two main design flaws: 1. It is a top-coil atomizer (meaning that the atomizer coil and wick are located just below the mouthpiece) which makes the supply of liquid largely inefficient (liquid travels towards the coil against gravity). 2. It uses a silica wick, which has substantially less sorptivity than cotton used in the Nautilus Mini atomizer (and all new-generation atomizers). Due to these characteristics, it is much easier to generate overheating and dry puffs with that atomizer. It was previously demonstrated that a similar atomizer generated dry puffs at high voltage settings and released substantial amounts of formaldehyde (Farsalinos et al., 2017a). Additionally, inconsistent performance of the atomizer was observed herein, with large variability in aldehyde emissions. Similar variability was observed with this atomizer in previous studies (Farsalinos et al., 2017a; Gillman et al., 2016; Jensen et al., 2015). Even at normal vaping conditions (no dry puffs), the levels of formaldehyde emissions were higher with this atomizer compared to new-generation, better designed, atomizers, even when the latter were tested at high power settings (Gillman et al., 2016). Herein we identified once again that such atomizers have a flawed design and easily generate dry puffs. Therefore, we repeat a previous recommendation that such atomizers should not be used by consumers, and in fact they are not available any more in the EU (Farsalinos et al., 2017a). However, it should be noted that Sleiman et al. reported unusually high aldehyde emissions, several-fold higher than found in the study herein using the same voltage settings and puffing regime. This raises the possibility for experimental error. Such error could be related to the use of DNPH-impregnated cartridges, some of which were found to create substantial pressure drop (Geiss et al., 2016) and thus impede airflow through the atomizer, or to false positives through interference with other aldehydes present in the EC liquid. It is also possible that defective devices were used in the experiment, which has been reported previously (Farsalinos et al., 2017a). More importantly however, Sleiman et al. did not check for the presence of unrealistic (dry puff) conditions. Of note, since the dry puff phenomenon is an organoleptic parameter, it can only be detected by experienced e-cigarette users (Farsalinos et al., 2015, 2017a). This represents a serious omission that can result in experimental conditions and findings which are irrelevant to human exposure. In fact, the majority of studies evaluating aldehyde emissions in e-cigarettes fail to control for dry puffs, and this omission has been noticed recently in another replication study (Farsalinos et al., 2017a; Jensen et al., 2015).

Recently, a study performed a risk assessment analysis, assessing EC users' intake of toxic compounds and second-hand exposure, using the findings by Sleiman et al. (Logue et al., 2017). The authors found extreme levels of exposure despite assuming low daily EC consumption (up to 49 mg formaldehyde and 10 mg acrolein from 250 puffs per day). Even if we assume no experimental error was made in the aerosol testing, the risk assessment analysis was based on findings associated with unrealistic use conditions and with the use of an outdated atomizer. Thus, this analysis does not present the risk of true exposure of EC consumers, and, in fact, may have created misleading conclusions about the relative risk of ECs compared to smoking. Herein, we assumed a 5 g liquid consumption per day and found that, under verified realistic conditions, with high power settings and substantial aerosol yield per puff from a new-generation atomizer, total exposure to aldehydes was substantially lower compared to smoking, regulatory safety limits and environmental levels. Unlike Sleiman et al., our findings are in agreement with three studies evaluating biomarkers of aldehyde exposure (urinary 3-HPMA levels, a biomarker of acrolein exposure) in EC users, which found levels significantly lower than smokers and similar to non-smokers (Shahab et al., 2017; Hecht et al., 2015;

McRobbie et al., 2015). These studies provide further and stronger evidence that the aldehyde levels reported by Sleiman et al. (2016) and the risk assessment analysis by Logue et al. (2017) are not relevant to true exposure of consumers.

An important finding of our study was that aldehyde levels per puff increased at high compared to low power, but aldehydes per gram liquid consumption were similar at both power settings. Previous studies have reported that aldehyde emissions increase at higher power settings when reporting emissions per puff (Farsalinos et al., 2015; Jensen et al., 2015; Kosmider et al., 2014). Geiss et al. (2016) also showed that there was a correlation between power settings and aldehyde emissions. However, all these studies reported aldehyde emissions per puff. Gillman et al. reported aldehyde levels per gram of liquid consumption and found no increase at high power settings with new-generation devices. Aerosol yield per puff positively correlates with power settings and energy delivery to the atomizer (Gillman et al., 2016). Herein, aerosol yield per puff increased by > 100% for a 50% increase in power and energy. The increase in aldehyde emissions per puff at high power can easily be explained by the increase in aerosol yield. Even if the thermal degradation rate of the liquid (% of evaporated liquid that degrades to aldehydes) is identical, higher liquid consumption per puff at increased power settings will result in higher amount of aldehyde emissions per puff. When levels of aldehydes emissions were reported per amount of liquid consumption, no increase was observed. Reporting emissions per gram of liquid is important because EC users measure consumption as amount of liquid consumed daily rather than number of puffs (Farsalinos et al., 2014), and thus is a better metric for evaluating daily exposures. It should be noted that aldehyde emissions per amount of liquid consumption is expected to increase under dry puff conditions because liquid consumption per puff is not linearly increased as a function of power at such conditions (Farsalinos et al., 2017a). Additionally, the thermal degradation rate is expected to increase because the delivered energy is higher than needed to evaporate the amount of liquid on the coil and is thus transformed to heat and results in temperature elevation. In fact, dry puffs are caused by the imbalance between energy delivery to the atomizer coil and liquid amount available to be evaporated. A previous study showed that there is an exponential increase in aldehyde emissions once dry puffs are generated (Farsalinos et al., 2015), while a similar exponential increase in aldehyde emissions at very high temperature (350 °C) was reported recently by Flora et al. (2017).

Recently, a study by Khlystov and Samburova (2016) reported that flavoring compounds were the main source of aldehyde emissions in EC aerosol. Up to 10,000-fold higher levels of aldehydes were reported for flavored compared to unflavored liquid (Farsalinos et al., 2017b). Herein, unflavored liquid emitted lower levels of aldehydes compared to the flavored sample but the absolute difference was minimal and of questionable clinical significance. However, we tested just one flavored liquid and it is possible that other flavors could contribute to higher aldehyde emissions. Since the vast majority of EC consumers use flavored liquids (Farsalinos et al., 2013b), it is essential to replicate the study by Khlystov and Samburova (2016) and further examine this issue using different flavors.

In conclusion, the study findings show that controlling for, and avoiding, dry puffs is important for the laboratory assessment of e-cigarette aerosol emissions in order to examine realistic human exposure. EC battery devices can deliver high power levels, but such levels are appropriate for specific atomizer designs and unusable for other types of atomizers. The ability to deliver high power levels means that ECs can be easily abused in the laboratory setting resulting in experimental conditions that do not represent exposure of consumers from routine use. This study found high levels of aldehyde emissions from an old-generation atomizer, but failed to reproduce previously reported extreme levels and clarified that the conditions of use were associated with dry puffs. Testing on a new-generation atomizer showed that high power levels within realistic (no dry puff) conditions are not associated with a significant increase in aldehyde emissions when the latter are reported per amount of liquid consumption. Reporting emissions per puff when comparing different power settings can be misleading because liquid consumption per puff increases at higher power.

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Conflicts of interest

In the past 3 years, KF has published 2 studies funded by the non-profit association AEMSA and 1 study funded by the non-profit association Tennessee Smoke-Free Association. KK, AP, AS, KP and GG have no conflict of interest to report. Enthalpy Analytical is a for-profit CRO involved in analytical testing of tobacco and e-cigarette products.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.fct.2017.11.002.

Transparency document

Transparency document related to this article can be found online at http://dx.doi.org/10.1016/j.fct.2017.11.002.

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