ADDICTION
SSA SOCIETY FOR THE STUDY OF ADDICTION
RESEARCH REPORT
doi:10.1111/add.13299

Protocol proposal for, and evaluation of, consistency in nicotine delivery from the liquid to the aerosol of electronic cigarettes atomizers: regulatory implications

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ABSTRACT

Aims To propose a protocol and evaluate the consistency in nicotine delivery to the aerosol of different types of electronic cigarette (EC) atomizers, as required by regulatory authorities. **Design** Three cartomizer and four tank-type atomizer products were tested (three samples per product). The aerosol from three 20-puff sessions from each sample was collected using a smoke machine. Three cartridges from a nicotine inhaler and three tobacco cigarettes were also tested. **Setting** Analytical laboratory in Greece. **Measurements.** Aerosol nicotine levels were measured. Relative standard deviation (RSD, i.e. coefficient of variation) was calculated separately for each cartomizer and replacement atomizer head sample (intrasample RSD) and between different samples (intersample RSD). The percentage difference from the mean, which is used to assess the quality of medicinal nebulizers, was also calculated. **Findings** The aerosol nicotine levels were 1.01–10.61 mg/20 puffs for ECs, 0.12–0.18 mg/20 puffs for the nicotine inhaler and 1.76–2.20 mg/cigarette for the tobacco cigarettes. The intrasample RSDs were 3.7–12.5% for ECs and 14.3% for the nicotine inhaler and 11.1% for the tobacco cigarettes. The intersample RSDs were higher in cartomizers (range: 6.9–37.8%) compared with tank systems (range: 6.4–9.3%). All tank-type atomizers and one cartomizer were within 75–125% of the mean, as dictated for medicinal nebulizers. **Conclusions** Electronic cigarettes that use tank-type atomizers appear to deliver nicotine in more consistent quantities (within the acceptable limits for medicinal nebulizers and similar to the nicotine inhaler) than electronic cigarettes that use cartomizers. The protocol for testing nicotine delivery consistency described in this paper could be used effectively for regulatory purposes.

Keywords Aerosol, electronic cigarette, nicotine, regulation.

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Submitted 21 July 2015; initial review completed 27 October 2015; final version accepted 6 January 2016

INTRODUCTION

Electronic cigarettes (ECs) are a recent addition in the tobacco harm reduction strategy of providing alternative, less harmful, products to smokers. Until now they have been unregulated; however, in 2014 the European Union adopted a new Tobacco Products Directive (TPD) [1], which included rules for the marketing of EC products. The regulation will take effect in May 2016, and mandates that products are only placed on the market if they comply with this Directive. Among the requirements, the TPD states clearly that: 'electronic cigarettes deliver the nicotine doses at consistent levels under normal conditions of use'. This is a reasonable concern, not related to the safety but to the efficacy of ECs as smoking substitutes. One of the main expectations is that ECs will provide the amount of nicotine a smoker needs, and this will probably play an important role determining the success of ECs to substitute smoking. Studies have shown that there is a learning curve in EC use, with consumers (vapers) having different puffing patterns compared to smokers [2–4]. Another study found better nicotine absorption from EC use after consumers used the products for 4 weeks compared to baseline [5]. This is related to the different functional and performance characteristics, as well as different nicotine delivery patterns of ECs compared to tobacco cigarettes [3,4,6]. Similar adjustments are seen in smokers when switching from 'regular' to 'light' cigarettes (compensatory smoking) [7–9]. It is expected that consistency in nicotine delivery would prevent vapers from the need to adjust their EC use patterns continuously to compensate for the inconsistent nicotine delivery when using the same EC products repeatedly.

A previous study examined the nicotine delivery from the liquid to the aerosol using first-generation (cigarette-like) devices [10]. However, that study examined disposable devices equipped with prefilled cartomizers only. Moreover, the results were influenced by differences in the nicotine content of the liquid; thus it could not assess the consistency of the cartomizers only. Finally, the devices were tested at 150 and 300 puffs, evaluating the total nicotine delivery to the aerosol rather than the consistency in nicotine delivery to the aerosol from repeated use sessions, as it is highly unlikely for consumers to take 150 or 300 puffs within one session. Newer-generation atomizers are refillable, can be used with a large variety of battery devices and can be used long-term by changing the wick-coil head only; thus, a different protocol is needed to determine their consistency in nicotine delivery.

The primary aim of the study was to propose a protocol for regulatory purposes and examine the consistency in nicotine delivery from different EC atomizer products. A secondary objective was to compare the nicotine consistency among the EC products tested and with a medicinal nicotine inhaler and tobacco cigarettes.

METHODS

Materials

Both first-generation (cigarette-like rechargeable batteries with cartomizers) and new-generation (so called 'tank-type atomizers') were examined in this study. To avoid inconsistencies in nicotine content of the EC liquid, a custom liquid composed of 45% propylene glycol, 45% glycerol, 8% deionized water and 2% nicotine was prepared and used with all products. This represents a common formulation for commercial EC liquids, and was prepared to avoid differences between labelled and true levels of nicotine that have been observed in commercial liquids.

Three brands of first-generation products were acquired from the United Kingdom (JacVapour V3i kit, Edinburgh, UK and Volcano Magma, New Malden UK) and from Prague, Czech Republic (Vapour2 cigs). They consisted of a rechargeable lithium battery and a cartomizer. The choice was based on the availability of empty cartomizers from these brands that can be filled with liquid by the consumer. This would allow us to use the prepared liquid, avoiding the possible variability in nicotine concentration in the pre-filled cartomizers which would affect consistency. Three samples of cartomizers and battery devices were obtained from each brand. Four brands of tank-type refillable atomizers were obtained from the market, representing two of the most popular atomizer manufacturers world-wide (Aspire Nautilus Mini and Aspire Atlantis, Aspire, Shenzhen, China; Kangertech EVOD Mega and Kangertech Subtank, KangerTech, Shenzhen, China). Instead of replacing the whole atomizer, they have replaceable wick-coil heads which need to be replaced regularly (usually every few days) by the vapers. We obtained three samples of wick-coil replacement heads for each atomizer. Two new-generation battery devices were used with the tank-type atomizers, depending on the power level setup: Innokin iTaste SVD2.0 and Innokin iTaste MVP3.0 Pro (Innokin, Shenzhen, China). These devices contain a rechargeable lithium battery with a capacity of 2400–2600 mAh and have integrated electronic circuits to adjust power (W) delivery. The former has a power delivery capacity of 5–20 W, while the latter has a power delivery capacity of 5–40 W. As a comparator, a pharmaceutical nicotine inhaler (Nicorette, Johnson & Johnson Hellas Consumer, Marousi, Greece) was obtained from a local pharmacy, consisting of a pipette and 42 replacement cartridges. According to the leaflet, each cartridge contained 10 mg of nicotine. Finally, one pack of tobacco cigarettes (Marlboro regular) was obtained from a local tobacco store.

Protocol design

Our purpose was to evaluate nicotine delivery consistency when the same equipment setup is used in different sessions (intrasample consistency), as well as when different replacement cartomizers or wick-coil replacement heads of the same product brand are used (intersample consistency). Therefore, three aerosol samples from 20-puff sessions (with a 5-minute period between sessions) would be collected using the same cartomizer and the same wick-coil replacement head. The comparison between these puff sessions would determine the intrasample consistency. The same procedure would be followed with two more cartomizers and wick-coil replacement heads. The comparison between the three cartomizers and between the three wick-coil replacement heads would determine the intersample consistency.

The cartomizers and tank-type atomizers were filled with the prepared liquid. The nominal capacity of the cartomizers was 1 ml, but we filled them with 0.8 ml to avoid potential overfilling. A preliminary evaluation showed that 0.8 ml was enough for performing three 20-puff sessions. The tank-type atomizers were filled with 1 ml liquid. All products were attached to a custom-made smoke machine, and the aerosol was collected in 44-mm-diameter Cambridge filter pads. The batteries of the cartomizers were activated automatically when the puff was initiated by the machine. The tank-type atomizers were puffed with manually controlled batteries, so one of the researchers was responsible for pressing the button to activate the device for the time the puff was drawn. To facilitate coordination, the researcher activated the smoke machine manually to initiate each puff at the same time of activation of the battery device. All batteries were charged fully before use. For every cartomizer, 20 puffs were obtained, with the smoke machine programmed to a puffing pattern of 4-sec puffs, 30-sec interpuff interval and 60 ml puff volume. There was no possibility to adjust the power with the batteries used with the cartomizers. For every wick-coil replacement head of the tank-type atomizers, 20 puffs were obtained at different power levels. Power levels were chosen based on information from the retailers and preliminary testing by a vaper (member of the research team) who obtained few puffs from all tank-type atomizers at the chosen power settings to ensure that there was enough aerosol production. For Aspire Nautilus Mini and KangerTech EVOD Mega, puffs were obtained at 7 W using a puffing pattern of 4-sec puffs, 30-sec interpuff interval and 60 ml puff volume and at 10 W using a puffing pattern of 3-sec puffs, 30-sec interpuff interval and 60 ml puff volume. The manufacturer‘s instructions for Aspire Atlantis and KangerTech Subtank recommended that they should be used at 15–30 W power levels. A preliminary test by the vaper verified that there was almost no aerosol production when used at 10 W. Thus, puffs were obtained at 15 W, using a puffing pattern of 4-sec puffs, 30-sec interpuff interval and 60 ml puff volume, and at 25 W, using a puffing pattern of 3-sec puffs, 30-sec interpuff interval and 60 ml puff volume. The Innokin SVD2.0 device was used for the aerosol collection at 7 and 10 W, while Innokin iTaste MVP3.0 Pro was used at 15 and 25 W. The cartomizers and the tank-type atomizers were weighed with a precision scale before and after the aerosol collection to measure aerosol yield.

The nicotine inhaler was tested with the same smoke machine, using Health Canada Intense puffing patterns (2-sec puffs, 30-sec interpuff duration, 55 ml puff volume) [11]. Three 20-puff sessions were obtained with each of three cartridges. Finally, three tobacco cigarettes were puffed in the smoking machine using the same puffing pattern as with the nicotine inhaler.

Nicotine measurements

The aerosol from each session was collected in Cambridge glass-fibre filters. They were stored subsequently in freezing conditions (-20^{o}C) until analysed.

The Cambridge filter was transferred in a 50-ml volume centrifuge tube. Two per cent quinoline in n-Hexane was used as internal standard; 0.5 ml of internal standard and 19.5 ml of n-hexane were added to the centrifuge tube. The filter was well rinsed with the solvent by using a vortex. Finally the mixture was centrifuged for 5 minutes at 1712 g. The organic solvent layer was decanted quantitatively in another clean tube and 0.5 ml of the decanted liquid was diluted further with 9.5 ml n-hexane in a stoppered glass tube. Four µl of the diluted solution were injected in a gas chromatography equipped with a nitrogen–phosphorous detector (NPD). The analytical method was validated by using Cambridge filters spiked with known concentrations of nicotine. The limit of quantification of the method was 0.01 mg. Five samples of two different nicotine concentrations were analysed. The results of the validation analysis were: (a) nicotine concentration of 0.2%: accuracy = 90.5%, precision = 9.3%; (b) nicotine concentration of 0.001%: accuracy = 88.7%, precision = 9.8%; and (c) average linearity = 0.991 (from eight calibration curves).

STATISTICAL ANALYSIS

Values are reported as mean [standard deviation (SD)]. The association between aerosol yield and nicotine content in the aerosol was evaluated using Pearson‘s correlation coefficient. To evaluate consistency in nicotine delivery, the relative standard deviation [(RSD), coefficient of variation], expressed in %, was calculated using the equation: RSD = (SD/mean) × 100. To evaluate the consistency between the three puff sessions of the same cartomizer, wick-coil replacement head and nicotine inhaler cartridge, the intrasample RSDs were calculated. Each cartomizer and the nicotine inhaler had three RSD values, while tank-type atomizers had six RSDs (three per power setting). Comparisons in intrasample RSDs were performed between products (including nicotine inhaler, eight products in total) with one-way analysis of variance (ANOVA). For tobacco cigarettes, there was only one intrasample RSD calculated, and it was used for descriptive analysis. To evaluate the consistency between different cartomizers, wick-coil replacement heads and nicotine inhaler cartridges, the intersample RSDs were calculated. For cartomizers and the nicotine inhaler, the mean and SD of all measurements were calculated in order to derive the intersample RSD. For tank-type atomizers, a separate mean and SD was calculated for each power setting; thus, two RSDs per product were derived (one per power setting), and their average was considered as intersample RSD. No intersample RSD was calculated for tobacco cigarettes. Finally, considering that the medicinal products accuracy for nebulizers requires nine of 10 samples to lie between 75 and 125% of the average value (all must lie between 65 and 135%) [10,12], the % difference of each measurement from the mean of all measurements was calculated. A P-value of < 0.05 was considered statistically significant, and all analyses were performed using commercially available software (SPSS version 22; SPSS Inc., Chicago, IL, USA).

RESULTS

Aerosol nicotine content

Table 1 shows the mean (SD) aerosol nicotine content per 20 puffs from all products tested. There was a wide range of nicotine delivery from different EC products, from 1.01 to 3.01 mg/20 puffs for cartomizers and from 2.72 to 10.61 mg/20 puffs for tank-type atomizers. The nicotine inhaler delivered very low levels of nicotine (0.12-0.18 mg/20 puffs). Tobacco cigarette smoke

Table 1 Aerosol nicotine levels per puff session for the products tested.

	Aerosol nicotine levels (mg)		
Product	*Puff session 1*	*Puff session 2*	*Puff session 3*
Aspire Nautilus Mini (7 W)			
Wick-coil head 1	3.13	3.07	3.12
Wick-coil head 2	3.11	3.09	3.12
Wick-coil head 3	3.02	2.72	2.90
Aspire Nautilus Mini (10 W)			
Wick-coil head 1	4.18	4.40	4.21
Wick-coil head 2	3.99	4.54	4.26
Wick-coil head 3	3.42	3.80	3.98
Aspire Atlantis (15 W)			
Wick-coil head 1	3.88	3.68	3.74
Wick-coil head 2	3.66	3.74	3.97
Wick-coil head 3	3.11	3.26	4.12
Aspire Atlantis (25 W)			
Wick-coil head 1	5.83	6.15	6.32
Wick-coil head 2	6.94	6.22	5.74
Wick-coil head 3	6.24	6.14	6.45
KangerTech EVOD Mega (7 W)			
Wick-coil head 1	3.69	3.45	3.56
Wick-coil head 2	3.20	3.17	3.15
Wick-coil head 3	3.36	3.41	3.25
KangerTech EVOD Mega (10 W)			
Wick-coil head 1	4.42	3.98	4.16
Wick-coil head 2	3.75	3.38	4.04
Wick-coil head 3	4.02	4.14	4.09
KangerTech Subtank (15 W)			
Wick-coil head 1	8.02	8.28	8.13
Wick-coil head 2	8.95	8.73	8.49
Wick-coil head 3	8.76	7.79	7.35
KangerTech Subtank (25 W)			
Wick-coil head 1	8.34	7.26	8.36
Wick-coil head 2	10.33	10.37	10.61
Wick-coil head 3	10.11	9.59	10.09
Volcano Magma			
Cartomizer 1	3.00	2.61	2.16
Cartomizer 2	1.14	1.10	1.10
Cartomizer 3	3.01	2.23	2.13
Vapour 2 cigs			
Cartomizer 1	2.08	2.23	2.30
Cartomizer 2	2.02	2.02	2.21
Cartomizer 3	1.38	1.64	1.01
JacVapour V3i kit			
Cartomizer 1	2.13	2.05	2.15
Cartomizer 2	2.02	2.46	2.32
Cartomizer 3	2.31	2.40	2.20
Nicotine inhaler			
Cartridge 1	0.15	0.12	0.13
Cartridge 2	0.18	0.14	0.13
Cartridge 3	0.14	0.12	0.12
Tobacco cigarette	1.76	2.20	2.03

delivered 1.76–2.20 mg/cigarette, which was expected, considering that they were puffed using the Health Canada Intense puffing regimen. A significant correlation was found between aerosol yield and aerosol nicotine content ($r = 0.985$, $P < 0.001$).

RSDs

The intrasample RSDs for each product are displayed in Fig. 1. Statistically significant differences in intrasample RSDs between products were observed ($F = 2.41$, $P = 0.046$). For tank-type atomizers, the intrasample RSD ranged from 3.7 to 6.5%, while for cartomizers it ranged from 5.5 to 12.5%. The intrasample RSD for the nicotine inhaler was 14.3% and for the tobacco cigarette 11.11%.

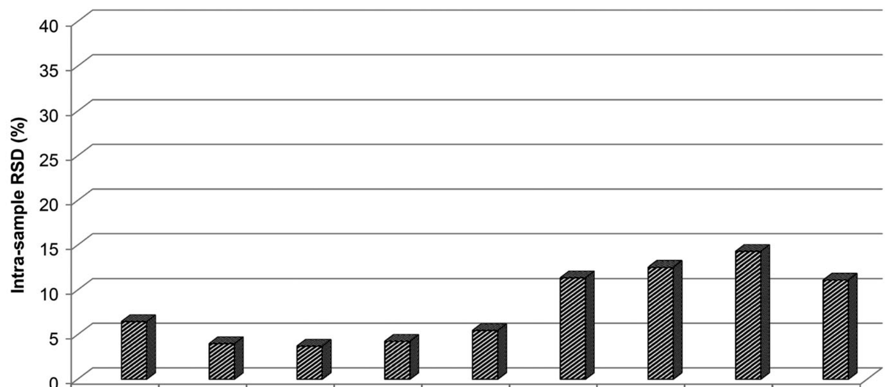
The intersample RSDs for each product are displayed in Fig. 2. For tank-type atomizers, the intersample RSD ranged from 6.4 to 9.3%, while for cartomizers it ranged from 6.9 to 37.8%. The high intersample RSDs in two of the three cartomizers (Vapour 2 and Volcano Magma) were due to one of the cartomizer samples delivering significantly lower levels of nicotine to the aerosol compared to the other two samples. The intersample RSD for the nicotine inhaler was 14.2%.

Difference from the mean

The % difference of every measurement of aerosol nicotine content from the mean of all measurements is shown in Table 2. For tank-type atomizers, it ranged from a lowest value of 76.8% to the highest value of 112.3% (both for KangerTech Subtank at 25 W). All tank-type atomizer products complied with the standards for medicinal nebulizers. For cartomizers, only one product complied with the nebulizer standards (JacVapour V3i), while the other two products showed significant deviations, which were again associated with one of the cartomizer samples delivering lower nicotine levels to the aerosol compared with the other two samples.

Discussion

This is the first study evaluating consistency in nicotine delivery from the liquid to the aerosol of ECs. Both first-generation (cigarette-like) devices and new-generation (tank-type) atomizers were tested. The main findings were that tank-type atomizers delivered nicotine from the liquid to the aerosol with acceptable consistently, similar to a pharmaceutical nicotine inhaler and to tobacco cigarettes, and within the acceptable limits for medicinal nebulizers. Consistency was observed both when the same setup was used in different sessions and when changing wick-coil replacement heads. Two of three cartomizers had poor performance in intersample consistency and in the percentage difference from the mean, due mainly to lower nicotine delivery with one of the cartomizer samples. Of note, nicotine delivery is enhanced significantly with new-generation (tank-type) atomizers, especially at high power levels. This protocol could be used for regulatory



	Aspire Atlantis	Aspire Nautilus Mini	KangerTech EVOD Mega	KangerTech SubTank	Jack Vape	Vapour 2	Volcano Magma	Nicotine inhaler	Tobacco cigarette
Aspire Nautilus Mini									
KangerTech EVOD Mega									
KangerTech Subtank									
Jack Vape									
Vapour 2									
Volcano Magma		*	*	*					
Nicotine inhaler	*	*	*	*					

Figure 1 Intrasample relative standard deviation (RSD) in aerosol nicotine content of all products. The table provides the one-way analysis of variance (ANOVA) *post-hoc* results for differences between individual products (asterisk indicates $P < 0.05$)

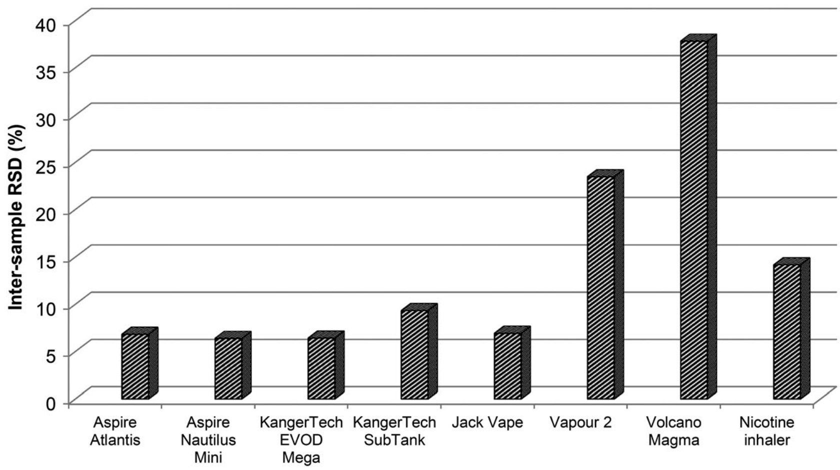


Figure 2 Intersample relative standard deviation (RSD) in aerosol nicotine content of all products

purposes, considering that there is a requirement by the authorities that ECs should deliver nicotine consistently.

The 2014 TPD is the first regulatory standard for ECs proposed by the European Union [1]. The directive will be enforced in May 2016 and requires that EC products deliver nicotine consistently. However, there is currently no proposal on how this should be determined. There has been a debate and a letter exchange among scientists and regulators concerning the need to perform pharmacokinetic studies to determine consistent nicotine delivery [9]. This would be similar to evaluating a pharmaceutical product and, considering the huge variability of EC battery devices and atomizers, it would be unrealistic, impractical and expensive. Herein, we propose a protocol which could examine the consistency of cartomizers and newer generation (tank-type) atomizers in nicotine delivery to the aerosol, both when the same equipment is used in multiple sessions and when different cartomizers or wick-coil replacement heads are used. A similar protocol could be used for examining the consistency of battery devices. The protocol is practical, feasible and financially sustainable. Moreover, it provides valuable information about the performance and quality of the products in terms of delivering nicotine from the EC liquid to the aerosol.

There was a large range of nicotine delivery potential among products. Cartomizers delivered less nicotine to the aerosol than tobacco cigarettes (on a puff-by-puff basis), but some tank-type atomizers exceeded tobacco cigarettes in nicotine delivery. This is related to different design characteristics of the products and power delivery potential of the battery device.

Cartomizers are composed of an absorbent material surrounding a wick-coil setup [13], while tank-type atomizers are composed of a chamber which contains the liquid and a wick-coil head which obtains liquid from the chamber through holes. Moreover, cartomizers are used with low-capacity batteries which reduce power delivery to the cartomizer as they are discharged and do not have

Table 2 Mean aerosol nicotine levels and % deviation from the mean for the products tested.

Product	*Mean (SD) aerosol nicotine content (mg/20 puffs)*	*% Difference from the mean*[a]
Aspire Nautilus Mini (10 W)	4.09 (0.34)	92.9–107.6
Aspire Atlantis (15 W)	3.68 (0.62)	84.5–112.0
Aspire Atlantis (25 W)	6.31 (0.31)	92.4–110.0
KangerTech EVOD Mega (7 W)	3.36 (0.19)	93.8–109.8
KangerTech EVOD Mega (10 W)	4.0 (0.29)	93.8–110.5
KangerTech Subtank (15 W)	8.28 (0.51)	94.1–108.1
KangerTech Subtank (25 W)	9.45 (1.18)	76.8–112.3
Volcano Magma	2.05 (0.78)	53.6–146.8
Vapour 2 cigarettes	1.88 (0.44)	53.7–118.6
JacVapour V3i kit	2.23 (0.15)	90.6–110.3
Nicotine inhaler	0.14 (0.02)	85.7–128.6
Tobacco cigarette	2.00 (0.22)[b]	88.0–110.0

[a]Range of % difference from the mean of all puffs performed by the particular product. For medicinal nebulizers, the acceptable deviation from the mean is 75–125% [10]. [b]Amount per one cigarette using Health Canada Intense puffing regimen. SD = standard deviation.

electronic circuits to adjust power levels. Conversely, tank-type atomizers can be used with more advanced battery devices, such as the ones used in this protocol, which maintain stable power levels throughout their working period. Such differences in design and characteristics could contribute to the lower consistency observed in two of the three cartomizers, which was due mainly to one cartomizer sample having poor performance in nicotine delivery. Among tank-type atomizers tested, there was a large range of nicotine delivery potential which, again, could be related to different design, wicking material, coil characteristics (thickness and length) and higher power settings. As expected, elevated nicotine yield was observed at higher power levels; similar findings were reported in a study by Talih *et al.* [14]. Such variability in performance may be important in order to satisfy the different needs and preferences of consumers [15]. Moreover, the high levels of nicotine in the aerosol from new-generation tank-type atomizers could enhance nicotine absorption, considering that several studies using older atomizers have found that plasma nicotine levels are lower from EC use compared to smoking tobacco cigarettes [4,6,16–18], or could satisfy nicotine craving without the need to obtain prolonged or more frequent puffs. This is even more important considering that the European Union TPD will limit the availability of nicotine concentration to a maximum of 20 mg/ml. Although some concerns have been raised about the delivery of high nicotine levels from ECs [19], nicotine intoxication through inhalation is highly unlikely (due to self-titration), and any improvement in the nicotine delivery potential of ECs may enhance their efficacy as smoking substitutes [15]. Finally, the tank-type atomizers tested herein delivered nicotine from the liquid to the aerosol with consistency similar to medicinal nebulizers. This ensures that the consumers can experience similar and consistent effects on repetitive use of the equipment. Of note, all tank-type atomizers tested were made in China. There is some (anecdotal) controversy about the quality of equipment made in China. Our findings show that Chinese products can be of high quality in terms of nicotine delivery.

Some limitations apply to this study. A limited number of EC products were evaluated; therefore, our findings cannot be extrapolated to all products. This protocol could be used not only for regulatory purposes but also by the manufacturing companies to examine the production quality. The very strong correlation between aerosol yield and aerosol nicotine content implies that the potential of the atomizer to deliver nicotine could be calculated by measuring aerosol yield. However, this needs to be verified by measuring aerosol nicotine content using liquids with different nicotine concentrations. For tank-type atomizers, the battery devices were activated manually. This could affect reproducibility if coordination with the puffing machine was not accomplished during the aerosol collection. We did our best to avoid this by activating the smoke machine manually at the same time of activation of the device. Improvements should be made, by integrating an automatic mechanism which will push the EC device button when the smoke machine takes a puff. The amount of nicotine delivery to the aerosol from tank-type atomizers should be interpreted with caution, because the use conditions were not verified by experienced consumers. It is possible that the puff duration was too high for the power levels selected. However, there is no reason to believe that different puff durations would alter the consistency in nicotine delivery. Finally, the protocol did not assess the effect of ageing of the atomizers. Use of the same wick-coil atomizer head for several days could affect performance and consistency in nicotine delivery. However, some compromise is needed when addressing testing for regulatory purposes, as it is impossible to replicate all potential use conditions and patterns.

CONCLUSIONS

Nicotine delivery to the aerosol from the tank-type atomizers tested was consistent and within the acceptable limits for medicinal nebulizers. Two of the three cartomizer products had low intersample consistency, probably related to design and battery limitations. There is a large range of nicotine delivery potential among different products, with some products capable of delivering higher levels of nicotine compared to tobacco cigarettes. The protocol designed to test the nicotine delivery consistency could be used for regulatory purposes because, unlike pharmacokinetic studies, it is feasible, practical and financially sustainable.

Funding

The study was funded by an unrestricted grant from Tennessee Smoke Free Association (TSFA), a non-profit consumer advocacy group with a focus on tobacco harm reduction. TSFA was not involved in protocol design, conduct of the study, product choice, data collection, analysis and interpretation. TSFA did not review the manuscript and did not participate in the decision to submit the study for publication.

Declaration of interests

Two studies by K.F. and V.V. were performed using unrestricted funds provided to the institution (Onassis Cardiac Surgery Center) by two electronic cigarette companies in 2013.

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