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# Nicotine content of electronic cigarettes, its release in vapour and its consistency across batches: regulatory implications

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## ABSTRACT

**Background and aims** Electronic cigarettes (EC) may have a potential for public health benefit as a safer alternative to smoking, but questions have been raised about whether EC should be licensed as a medicine, with accurate labelling of nicotine content. This study determined the nicotine content of the cartridges of the most popular EC brands in the United Kingdom and the nicotine levels they deliver in the vapour, and estimated the safety and consistency of nicotine delivery across batches of the same product as a proxy for quality control for individual brands and within the industry. **Methods** We studied five UK brands (six products) with high internet popularity. **Measurements** Two samples of each brand were purchased 4 weeks apart, and analysed for nicotine content in the cartridges and nicotine delivery in vapour. **Results** The nicotine content of cartridges within the same batch varied by up to 12% relative standard deviation (RSD) and the mean difference between different batches of the same brand ranged from 1% [95% confidence interval (CI) = −5 to 7%] to 20% (95% CI = 14–25%) for five brands and 31% (95% CI = 21–39%) for the sixth. The puffing schedule used in this study vaporized 10–81% of the nicotine present in the cartridges. The nicotine delivery from 300 puffs ranged from ~2 mg to ~15 mg and was not related significantly to the variation of nicotine content in e-liquid ($r = 0.06$, $P = 0.92$). None of the tested products allowed access to e-liquid or produced vapour nicotine concentrations as high as conventional cigarettes. **Conclusions** There is very little risk of nicotine toxicity from major electronic cigarette (EC) brands in the United Kingdom. Variation in nicotine concentration in the vapour from a given brand is low. Nicotine concentration in e-liquid is not well related to nicotine in vapour. Other EC brands may be of lower quality and consumer protection regulation needs to be implemented, but in terms of accuracy of labelling of nicotine content and risks of nicotine overdose, regulation over and above such safeguards seems unnecessary.

**Keywords** E-cigarette, electronic cigarette, electronic nicotine delivery devices, MHRA, nicotine.

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## INTRODUCTION

Electronic cigarettes (EC) are battery-powered devices that deliver a vaporized liquid nicotine solution in propylene glycol or glycerine. In addition to nicotine delivery, the vapour generated from EC also provides a flavour and physical sensation similar to that of inhaled tobacco smoke, but no tobacco, smoke or combustion is actually involved in its operation. (Note that 'aerosol' is a technically more accurate description because of the presence of liquid droplets suspended in air, but we use 'vapour' to comply with common usage.) Nicotine is a stimulant and has been shown to be the key addictive component of tobacco products, but the adverse health consequences of cigarette smoking are caused primarily by tobacco combustion products. Thus, EC may have a potential for public health benefit as a safer alternative to smoking [1–5].

Regarding nicotine content, existing data suggest that EC brands differ in nicotine delivery and that the accuracy of labelling of nicotine content varies by manufacturer [5–8]. Further data are needed to determine the most

appropriate regulatory approach for the best public health outcome [9]. The UK Medicine and Healthcare Products Regulatory Agency (MHRA) has decided that EC should be licensed as a medicine, with accurate labelling of nicotine content seen as one of the main objectives of such a provision.

The current study was set up to determine the nicotine content of the cartridges of the most popular EC brands on sale in the United Kingdom, the nicotine levels they deliver in the vapour, whether users can be exposed to toxic levels of nicotine, the degree to which the labelling of the nicotine content of the cartridges is informative for the consumer and to estimate the consistency of nicotine delivery across batches of the same product as a proxy for quality control for individual brands and within the industry.

## METHODS

We selected the most popular UK brands, purchased two samples of each 4 weeks apart, and analysed the products for nicotine content in the cartridges and nicotine delivery in vapour.

### Selection of EC brands and models

Because the internet is currently the main distribution channel for EC, we searched four price comparison websites (http://e-smokereviews.co.uk, http://which-electronic-cigarette.org.uk, http://uk.cigzag.com, http://ecigclick.co.uk), three online market-places (http://theelectroniccigarette.co.uk, http://e-fog.co.uk, http://ukecigstore.com) and three internet discussion forums for EC users (http://e-cigarette-forum.com, http://ukvapers.org, http://allaboute-cigarettes.proboards.com) to identify the most popular brands of EC distributed from within the United Kingdom. Twenty-five brands were identified.

The brands were entered into http://google.co.uk, and ranked according to the number of hits they generated. (Note: we could not use http://ebay.co.uk sales data because eBay does not allow sales of ECs.) Searches were performed on 5 September 2012.

Of the top seven brands, two (Sky and Gamucci) have already been tested in our previous study [5] and we focused on the remaining five (see the first five rows in Table 1). We also included two brands of disposable EC distributed within the United Kingdom which received the highest number of hits on http://google.ac.uk, one from a supplier already included in Table 1, and one from a different supplier (Totally Wicked). Disposable EC are a recent development of which we were unaware when planning the study initially. They are more user-friendly than models that require cartridge manipulation and charging and are likely to increase in popularity, as they allow consumers to try a brand before investing in the charging apparatus.

**Table 1** Electronic cigarette (EC) brands, models and labelling of nicotine content.

| *Brand* | *Model tested* | *Nicotine content* |
|---|---|---|
| Non-disposable ECs | | |
| Green Smoke | Only one model available | 2.4% |
| E-Lites | E200 | 2.4% |
| Vapouriz | Tank | 1.8% |
| Smokers Angel (Halo) | King size | High 1.8% |
| Smokers Angel (Halo) | King size | Extra High 2.4% |
| Vapestick | Max | 2.4% |
| Disposable ECs | | |
| Totally Wicked | Disposable | 18 mg |
| Vapouriz | Disposable | 2.4% |

We planned to test one model from each of the five brands. EC were purchased from online vendors. Where brands sell models with different nicotine content, cartridges with the highest declared nicotine content were purchased. One supplier sent two different types of cartridges (High 1.8% and Extra High 2.4%) and we tested both for nicotine content, but had enough cartridges of only one of them (High 1.8%) to test for nicotine in vapour.

To test the consistency of nicotine delivery within individual models, we purchased two samples of cartridges for non-disposable ECs 4 weeks apart. In two instances (Halo High and E-Lites) the cartridges were from the same batch number; for the other four brands the second supply of cartridges came from different batches. The consistency of drug content across batches is a proxy for variations in the quality of the machinery and stability of the ingredients and production routines.

### Laboratory procedures

#### *Testing nicotine in cartridges*

Three cartridges of the same batch and series of each brand were analysed. Nicotine was also analysed in used cartridges after 300 puffs had been taken. Comparing nicotine content of the new and used cartridges allowed an estimate of how much nicotine was released in the vapour. Each testing destroys the cartridge, so altogether five cartridges from each batch were used (three to analyse nicotine content and two to generate vapour).

Cartridges were analysed as described previously [5]. Briefly, nicotine from cartridges was extracted with 50 ml of ethyl acetate and 100-µl internal standard solution (quinoline 50 mg/ml in methanol) using an ultrasound bath for 30 minutes. Nicotine was analysed using gas

chromatography with the Thermionic Specific Detector (GC-TSD; Varian Inc., Palo Alto, CA, USA). Calibration solutions of nicotine in propylene glycol with a concentration range of 0.01–40 mg/ml were prepared by weighing various amounts of nicotine standard and dissolving them in solvent. Calibration and control cartridges were prepared by spiking empty cartridges with 0.5 ml of calibration solution. A calibration procedure was performed beforehand to validate the analytical method [10]. Precision of the method was 15%, mean recovery 98%, and quantitation limit 0.1 mg/cartridge.

*Generation and testing of vapour from ECs*

Vapour from ECs was generated using a smoking machine [5]. The puffing set-up included puff duration 1.8 seconds, puff volume 70 ml and puff intervals of 10 seconds. A total of 300 puffs were taken from each EC in 20 series of 15 puffs with 5-minute intervals between series. Each EC was tested twice on 2 consecutive days with different cartridges from the same batch after the batteries in the core unit were recharged overnight.

Nicotine from EC vapour was absorbed using a liquid extraction to organic solvent technique. EC were connected with a set of two 200-ml gas washing bottles. Each washing bottle contained 100 ml of methanol with quinoline as an internal standard (10 µg/ml). Both washing bottles were immersed in an acetone–dry ice bath. The development and validation of the testing protocol has been described previously [5]. Seven 0.25-ml samples were collected from each washing bottle: at the baseline, post-15, -30, -60, -90, -150 and -300 puffs. Nicotine was analysed using gas chromatography with the Thermionic Specific Detector (GC-TSD; Varian Inc.). We used the modified standard National Institute for Occupational Safety and Health (NIOSH) 2551 method for determination of nicotine in air [11]. A calibration curve was generated to cover a range in nicotine concentration from 0.5 to 100 µg/ml, which corresponds to cumulative nicotine levels in EC vapour from 0.2 to 40 mg. The method was validated earlier as per the International Conference on Harmonization guideline Q2 R1 [10]. Precision of the method was 8% and the quantitation limit was 0.05 µg/ml.

**Statistical analysis**

Amounts of nicotine in unused cartridges of two different batches were compared using *t*-tests. For each EC, a nicotine delivery profile was generated. The profiles represent the relationship between the mean cumulative dose of nicotine released from two cartridges to vapour and number of puffs. For all tests, Statistica version 10.0 (Statsoft, Bedford, UK) software was used.

## RESULTS

Table 2 shows the consistency of nicotine content across three cartridges from each batch and the difference between batches. The nicotine content of the three cartridges within the same batch varied by up to 12%, calculated as the relative standard deviation (RSD) and expressed as a percentage, and the difference between batches was up to 31% [95% confidence interval (CI) = 21–39%), calculated as the mean of the percentage difference of each cartridge from the overall mean of the brand.

**Table 2** Consistency of nicotine content in EC cartridges.

| | *Detected nicotine content mg, (SD; RSD), 95% CI* | | | *Mean difference between batches mg (95% CI) [% difference;[b] 95% CI]* |
|---|---|---|---|---|
| *Brand* | *Batch 1* | *Batch 2* | *Overall* | |
| Non-disposable ECs | | | | |
| Green Smoke | 23.9 (1.1; 4%) | 27.7 (0.8; 3%) | 25.8 (2.2) | 3.8 (95% CI: 1.7 to 5.9) |
| | 95% CI: 21.2–26.6 | 95% CI: 25.8-29.6 | 95% CI: 23.4-28.2 | [15%; 95% CI: 7 to 23] |
| E-Lites[a] | 19.7 (0.4; 2%) | 20.6 (2.4; 12%) | 20.2 (1.6) | 0.9 (95% CI: –3.0 to 4.9) |
| | 95% CI: 18.7 – 20.7 | 95% CI: 14.7 – 26.7 | 95% CI: 18.5-21.9 | [5%; 95% CI: –15 to 24] |
| Halo High[a] | 26.5 (0.8; 3%) | 21.7 (0.4; 2%) | 24.1 (2.7) | 4.8 (95% CI: 3.4 to 6.1) |
| | 95% CI: 24.6 – 28.4 | 95% CI: 20.7 – 22.7 | 95% CI: 21.3-26.9 | [20%; 95% CI: 14 to 25] |
| Halo X High | 33.0 (1.1; 4%) | 32.6 (0.7; 2%) | 32.8 (0.8) | 0.4 (95% CI: –1.6 to 2.4) |
| | 95% CI: 30.3 – 35.8 | 95% CI: 31.0 – 34.2 | 95% CI: 32.0-33.7 | [1%; 95% CI: –5 to 7] |
| Vapestick | 23.6 (1.0; 4%) | 23.3 (2.0; 8%) | 23.4 (1.4) | 0.3 (95% CI: –3.2 to 3.8) |
| | 95% CI: 21.0 – 26.1 | 95% CI: 18.4 – 28.1 | 95% CI: 21.9–24.9 | [1%; 95% CI: –14 to 16] |
| Vapouriz | 12.8 (0.1; <1%) | 17.5 (0.9; 5%) | 15.2 (2.6) | 4.7 (95% CI: 3.3 to 6.0) |
| | 95% CI: 12.7 – 13.0 | 95% CI: 15.4 – 19.6 | 95% CI: 12.4–17.9 | [31%; 95% CI: 21 to 39] |

[a]Brands which had both sets of samples from a batch with the same number. [b]Calculated as the mean of the % difference of each cartridge from the overall mean of the brand. CI = confidence interval; RSD = relative standard deviation.

**Table 3** Nicotine levels released to vapour after 150 and 300 puffs.

| *Brand name* | *Nicotine in unused cartridges (mg) Mean (range), 95% CI, percentage of total* | *Nicotine released to vapour (mg) Mean (range), 95% CI, percentage of total* | | *Nicotine released with 300 puffs estimated from nicotine left in used cartridges (mg) Mean (range), 95% CI, percentage of total* |
|---|---|---|---|---|
| | | *With 150 puffs* | *With 300 puffs* | |
| Non-disposable ECs | | | | |
| Green Smoke | 23.9 (22.7–24.8)<br>95% CI = 21.2–26.6<br>100% | 4.6 (4.3–4.9)<br>95% CI = 1.1 to 8.1<br>19% | 8.6 (7.9–9.3)<br>95% CI = 0–17.2<br>36% | 11.7 (10.2–13.2)<br>95% CI = −7.1 to 30.4<br>49% |
| E-Lites | 19.7 (19.5–20.2)<br>95% CI = 18.7–20.7<br>100% | 1.1 (0.9–1.2)<br>95% CI = −0.8 to 2.9<br>6% | 2.1 (1.7–2.5)<br>95% CI = −3.1 to 7.3<br>11% | 1.9 (1.4–2.3)<br>95% CI = −4.0 to 7.8<br>10% |
| Halo | 26.5 (25.7–27.2)<br>95% CI = 24.6–28.4<br>100% | 2.2 (1.8–2.6)<br>95% CI = −2.7 to 7.1<br>8% | 3.9 (3.6–4.2)<br>95% CI = 0.2 to 7.6<br>15% | 6.3 (5.9–6.7)<br>95% CI = 0.8 to 11.8<br>24% |
| Vapestick | 23.6 (22.7–24.7)<br>95% CI = 21.0–26.1<br>100% | 9.6 (8.1–11.1)<br>95% CI = −9.0 to 28.2<br>41% | 15.1 (13.9–16.3)<br>95% CI = 0 to 30.2<br>64% | 19.0 (18.7–19.3)<br>95% CI = 15.4 to 22.6<br>81% |
| Vapouriz | 12.8 (12.8–12.9)<br>95% CI = 12.7–13.0<br>100% | 5.7 (5.6–5.8)<br>95% CI = 4.2 to 7.2<br>45% | 7.9 (7.4–8.4)<br>95% CI = 1.4 to 14.4<br>62% | 9.9 (9.8–10.1)<br>95% CI = 8.4 to 11.5<br>77% |
| Disposable ECs[a] | | | | |
| Totally Wicked | NA | 7.0 (6.0–8.7)<br>95% CI = 5.1 to 8.9 | 13.0 (11.3–16.1)<br>95% CI = 9.5 to 16.6 | NA |
| Vapouriz | NA | 2.4 (2.0–2.8)<br>95% CI = 1.9 to 3.0 | 4.4 (3.6–5.0)<br>95% CI = 3.5 to 5.3 | NA |

[a]Cartridge analyses were not possible for disposable products. EC = electronic cigarette; CI = confidence interval; NA = not applicable.

Nicotine content can be expressed in weight, as mg/cartridge, or as the percentage of volume if the volume of nicotine solution in each cartridge is fixed. Only one disposable product indicated weight, while the percentage volume was provided for all cartridges and the second disposable EC. Without information about the exact cartridge volume and density of nicotine solution, this does not allow a precise assessment of accuracy. Brands labelled as containing 1.8–2.4% nicotine contained 12.8–33.0 mg nicotine. The outlier value (33.0 mg) was from the largest of the cartridges labelled as Extra High. All the cartridges were sealed.

Table 3 shows nicotine concentration in the vapour after 150 and 300 puffs and an estimate of total nicotine released from the cartridge after 300 puffs based on the difference between nicotine content of the cartridges before and after 300 puffs. Figure 1 shows nicotine delivery profiles (mean and range) of the individual brands. The puffing schedule used in this study vaporized 10–81% of nicotine present in the cartridges. The tracking of nicotine delivery in vapour over different numbers of puffs confirmed the differences between products. The relationship between the nicotine content of e-liquid and nicotine concentration in vapour was non-significant ($r = 0.06$, $P = 0.92$).

A single puff of 70 ml can be estimated to deliver a maximum of 63 µg, so 15 puffs are needed to deliver up to 1 mg nicotine, i.e. less than a typical conventional cigarette (from 1.54 to 2.60 mg in a study using individualized puffing protocols derived from puffing characteristics of 133 smokes with an average of 12 puffs of 46 ml over 4 minutes) [12].

## DISCUSSION

All the EC models tested deliver less nicotine per puff than conventional cigarettes. Although an unsubstantiated claim is often repeated that 30–60 mg of nicotine is fatal, several suicide attempts have been recorded where people drank up to 1500 mg of nicotine in e-liquid (i.e. 50× the presumed lethal dose) without any consequence other than abdominal pain and 'voluminous vomiting' [13]. A recent study managed to trace the statement concerning the lethal toxicity of nicotine to dubious self-experiments in the 19th century [14]. It has been repeated uncritically ever since. Given the low toxicity of nicotine at the doses

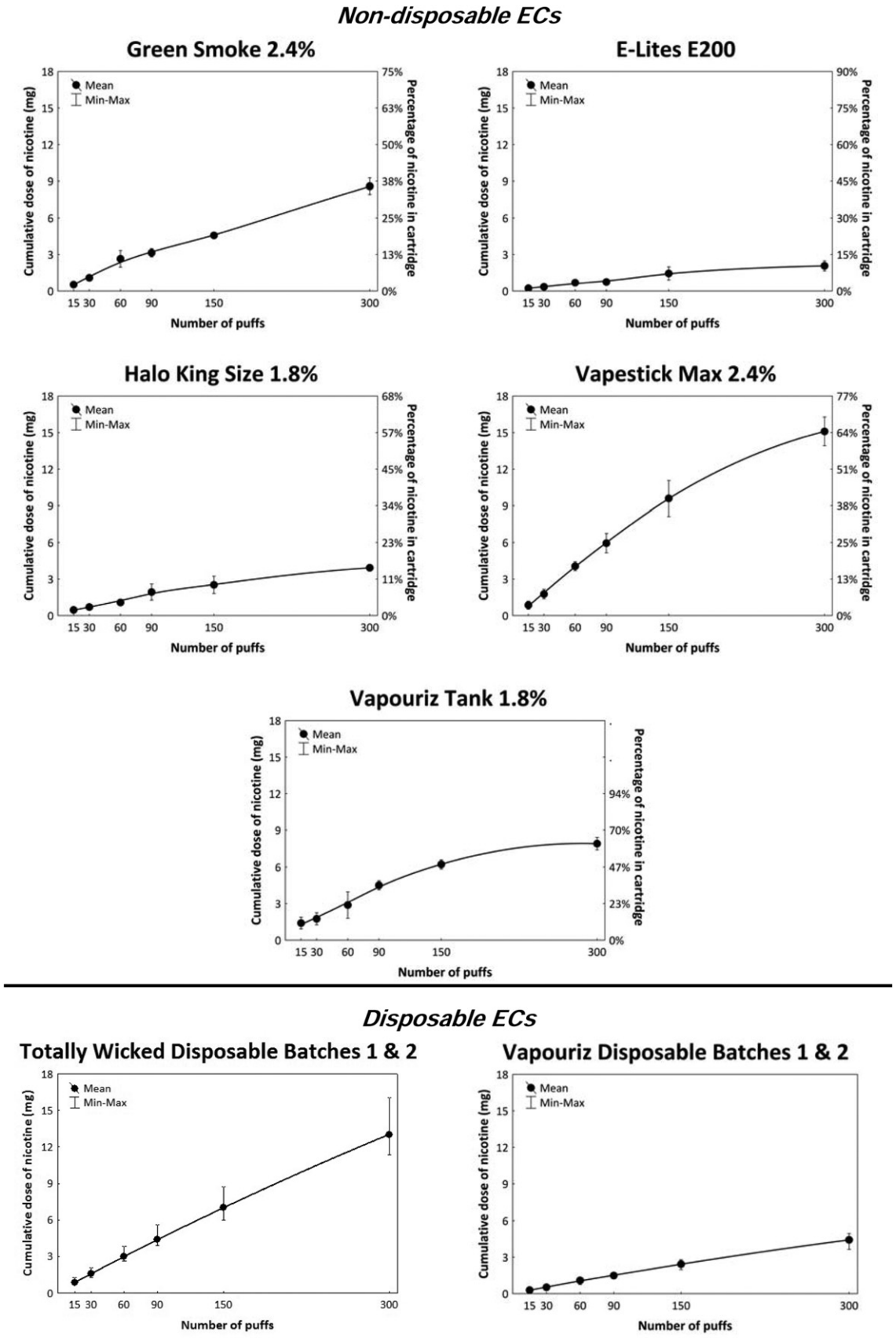


**Figure 1** Nicotine delivery profiles for tested ECs

observed and the fact that, long before any dangerous levels of nicotine concentration could be reached, an over-enthusiastic user would be warned by nausea, there is little concern that e-cigarettes can harm their users by delivering toxic nicotine levels. All tested products used sealed cartridges, but some EC models use e-liquid refills and these should, of course, use child-proof packaging.

Previous studies of e-liquid mainly analysed only one or two cartridges or fluid samples per product [7,8,15]. We used six cartridges across two batches for each brand, but this is still a relatively small sample and limits the reliability of the estimates of nicotine content and its consistency.

Using an analytical method with a variation of ~15%, the nicotine content of cartridges within the same batch varied by up to 12% RSD, and the difference between different batches of the same brand was up to 20% for five brands and 31% for the sixth (Vapouriz). The medicinal products accuracy for nebulizers require nine out of 10 samples to lie between 75 and 125% of the average value (all must lie between 65 and 135%) [16]. The consistency of nicotine content in EC cartridges we tested is not perfect, but it is well within this range and seems acceptable overall, especially given the fact that there are other major determinants of nicotine delivery to vapour and to the user, as discussed below.

One of the two products that had both batches with the same number (Halo High) had good within-batch consistency at both tests, but there was 20% less nicotine in the later batch. It is likely that longer storage with possible exposure to heat and light reduces nicotine content. This would correspond with anecdotal reports from long-term users of nicotine nasal spray in two of our studies [17,18] who detect weaker effects of some batches, and have linked this to the proximity of the expiry date.

Using the same puffing protocol, different EC models and cartridges have different nicotine delivery in vapour that corresponded roughly to the descriptive indications of strength. The range was from ~2 mg of nicotine delivered in 300 puffs from the E-Light cartridge to ~15 mg delivered by the Vapestick Extra High cartridge. Our study provides the first data on disposable EC. They delivered nicotine to vapour within the range of the re-chargeable ECs.

The fact that the variation of nicotine content of the cartridges has little bearing on nicotine in vapour is the most striking finding of this study. This is due probably to different heater types reacting differently to the spacing and frequency of puffs employed in this study, and due to various other product characteristics such as cartridge size, battery strength, draw resistance, etc. For example, some brands may require stronger flow rates than others to activate vapour production [19] and different puffing schedules may produce different results [20]. For example, a brand suggesting low nicotine delivery (E-Lites) has cartridges that contain levels of nicotine similar to other brands, but its vapour contains substantially lower levels. Across brands, a cartridge containing 26 mg of nicotine delivered 4 mg after 300 puffs, while a cartridge containing 13 mg delivered 8 mg. In addition to these machine-derived values that are dependent upon the machine's puffing schedule and the elements listed above, as with conventional cigarettes, different users are likely to employ different frequency, depth and intensity of puffing and derive different levels of nicotine from the same product. The nicotine content of the cartridges is thus only one of the factors contributing to nicotine levels delivered to users.

The nicotine content of conventional cigarettes is known to have little association with blood nicotine levels of the smoker [21]. In fact, the Framework Convention for Tobacco Control Article 11 Guidelines recommend prohibition of the display of nicotine emission yields because they do not provide valid estimates of human exposure [22]. Our finding that the nicotine content of e-liquid has little, if any, relationship to nicotine content in vapour (let alone nicotine intake by users) suggests that a pharmaceutical level of accuracy of labelling of the nicotine content in EC cartridges is also unlikely to be informative for the user. It would appear that a general indication of strength such as that used, for example, on the packaging of coffee, would provide sufficient guidance to buyers.

Although, as in the previous study [15], the quality of the tested products seems adequate, this does not guarantee that all EC are of acceptable quality. In Europe, there are some 15 consumer protection directives and regulations that apply to EC, such as General Product Safety Directive and Classification, Labelling and Packaging of Substances and Mixtures Regulation, etc. These provisions cover general safety, packaging and labelling, chemical safety, electrical safety, weight and measures and commercial practice [23]. The consumer protection regulations need to be implemented strictly to ensure that EC are safe, fit for purpose and 'as described'. Specific directives may also be needed concerning childproof containers, regulation of advertising and sales to minors. In terms of product quality and risks of nicotine overdose, however, regulation of EC over and above such consumer protection safeguards seems unnecessary.

EC are an evolving product driven by market competition and consumer demand. EC cartridges from only a few years ago typically leaked fluid, deficient batteries were common, etc. [24]. This is less common now, and future products are likely to continue to improve, in

the same way that early versions of cars or mobile phones have improved, until EC catch up with conventional cigarettes and hopefully replace them completely. A concern has been expressed that medicinal licensing would stop this evolution and freeze EC in their current 'not-yet-very-good' format and thus protect the market monopoly of the deadly conventional cigarettes [25].

In summary, the maximum variation of nicotine content between two different batches of cartridges for the same EC model and between individual cartridges across the two batches was 31%. Given the large variation in how nicotine is delivered to vapour and how EC are used, the consistency seems adequate. Different EC models provide different nicotine delivery to vapour which is not directly related to variation of nicotine content in the cartridges. Consumers need to find models that suit their needs.

## Declaration of interests

None of the authors has any links with any e-cigarette manufacturers. All three authors received research funding from and/or provided consultancy to manufacturers of smoking cessation medications.

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