Addiction
RESEARCH REPORT
doi:10.1111/add.12235

Analysis of refill liquids for electronic cigarettes

Jean-François Etter[1], Eva Zäther[2] & Sofie Svensson[2]

Institute of Social and Preventive Medicine, Faculty of Medicine, University of Geneva, Geneva, Switzerland[1] and Analytical Development R&D, McNeil AB, Helsingborg, Sweden[2]

ABSTRACT

Aims To assess levels of nicotine, nicotine degradation products and some specific impurities in commercial refill liquids for electronic cigarettes. **Design and setting** We analyzed 20 models of 10 of the most popular brands of refill liquids, using gas and liquid chromatography. **Measurements** We assessed nicotine content, content of the known nicotine degradation products and impurities, and presence of ethylene glycol and diethylene glycol. **Findings** The nicotine content in the bottles corresponded closely to the labels on the bottles. The levels of nicotine degradation products represented 0–4.4% of those for nicotine, but for most samples the level was 1–2%. Cis-N-oxide, trans-N-oxide, myosmine, anatabine and anabasine were the most common additional compounds found. Neither ethylene glycol nor diethylene glycol were detected. **Conclusion** The nicotine content of electronic cigarette refill bottles is close to what is stated on the label. Impurities are detectable in several brands above the level set for nicotine products in the European Pharmacopoeia, but below the level where they would be likely to cause harm.

Keywords Electronic cigarette, electronic nicotine delivery systems, nicotine, quality control, smoking, tobacco.

Correspondence to: Jean-François Etter, Institut de médecine sociale et préventive, Université de Geneve, CMU, 1 rue Michel-Servet, CH-1211 Genève 4, Switzerland. E-mail: Jean-Francois.Etter@unige.ch
Submitted 22 October 2012; initial review completed 15 January 2013; final version accepted 25 April 2013

INTRODUCTION

Electronic cigarettes (e-cigarettes) usually look like regular cigarettes, cigars or pens, but do not contain tobacco. Instead, they comprise a battery-powered atomizer that produces vapor or a mist for inhalation from cartridges that contain propylene glycol or glycerol (or a mix of both), flavors, water, nicotine or—in some cases—other medications [1–3]. E-cigarettes (or 'personal vaporizers') are a new galenic form to administer a range of substances.

E-cigarettes are increasingly popular. *Google* searches for 'electronic cigarettes' have increased several fold in recent years and now surpass searches for nicotine medications [4]. Surveys show that 11–21% of adult smokers in the USA report having ever used e-cigarettes, which translates into several millions users [5–8]. Regulations for e-cigarettes vary widely across countries, from prohibition to unregulated marketing [9–11].

There are relatively few research reports on e-cigarettes [12–28]. In clinical studies conducted on *inexperienced* users, e-cigarettes appear to attenuate craving for tobacco despite delivering very little nicotine to the blood [16,17]. In contrast, *experienced* users can obtain amounts of nicotine similar to the amounts usually obtained by smokers from tobacco cigarettes, and twice as high as the amounts usually obtained by users of nicotine replacement therapy [22,23]. Laboratory testing has shown that some cartridges or refill liquids for e-cigarettes contain impurities and toxic components, or are not filled true to label [12,14,18,20,24,26,27,29]. Another concern is the lack of mandatory manufacturing standards for e-cigarettes. There are many manufacturers, largely in China, Europe and the USA, but the products are not manufactured along standards imposed on medications or drug delivery devices. There is no guarantee that cartridges are filled true to label and that the refill liquids (e-liquids) do not contain impurities or toxic elements [20,30].

The main alkaloid found in tobacco is nicotine, and the most abundant of the minor tobacco alkaloids are nornicotine, anatabine and anabasine. Several of the minor alkaloids are thought to arise by bacterial action or oxidation during tobacco processing, rather than by biosynthetic processes in the living plant [31,32]. Examples of other alkaloids present in tobacco are cotinine

(which is also the major metabolite of nicotine in humans), nicotine-N-oxides, myosmine, beta-nicotyrine and beta-nornicotyrine.

Nicotine is a toxic and potent substance that is quickly absorbed through the skin and mucous membranes in its base form. Qualitatively, many of the alkaloids listed above have similar actions to nicotine, but are generally less toxic and less potent.

Nicotine in medications and e-liquids is extracted from tobacco, and this extraction process may produce some impurities. Nicotine of pharmaceutical grade, in accordance with the European Pharmacopoeia [33], may, as a raw material, contain up to 0.3% of each of the specified nicotine impurities (anatabine, beta-nicotyrine, cotinine, myosmine, nicotine-N-oxide, nornicotine and anabasine) plus 0.1% each of unspecified impurities for a total of no more than 0.8%. For finished medicinal products, other limits can be justified with rationale and supportive data (i.e. stability data, relationship to the daily dose) [34].

Currently, very little is known about e-liquids, and it is not clear whether e-liquids fulfill European Union requirements for nicotine medications [33,34]. Thus, the objectives of this study were to assess levels of nicotine, nicotine degradation products and some specific impurities in commercial e-liquids.

METHODS

Previous research enabled us to identify the most popular brands of e-liquids used in several countries (USA, UK, France, Switzerland) [19,25]. Where possible, we purchased these brands, and thus the brands analyzed here are among those that dominate the market in the USA and much of Western Europe [19,25]. Nevertheless, the sample of brands included in this study was not a representative sample of the most popular e-liquid brands because retailers of some popular brands did not mail their products outside the USA.

We obtained 20 bottles of 10 different brands. Nineteen bottles were purchased on the Internet and sent to us by mail by retailers, and one bottle was received directly (in person) from one of the largest manufacturers (Dekang, China), which supplies many retailers worldwide. Upon receipt in Geneva, the bottles were kept at room temperature and protected from the light until they were sent for analysis to McNeil R&D (Helsingborg, Sweden), where they were kept at room temperature until they were opened for analysis. During the analyses, which were performed in March and April 2012, the bottles were stored in a refrigerator at 6–8°C.

The analyses performed included nicotine content by ultra-high performance liquid chromatography (UHPLC), and content of the known nicotine degradation products and impurities, i.e. cotinine, myosmine, nicotine-N-oxides, beta-nicotyrine, nornicotine, anabasine and anatabine by UHPLC. Presence (but not quantification) of ethylene glycol and diethylene glycol by gas chromatography (GC), in accordance with current United States Pharmacopeial (USP) monograph for propylene glycol [35]. We used a limit test set by the USP and National Formulary (USP-NF) that was able to detect 0.1% of diethylene glycol or ethylene glycol in the liquids—levels that are considered acceptable and safe [36]. Based on the content of the degradation products and impurities, we determined whether these levels were within a normal range from a pharmaceutical perspective (i.e. compared with requirements for nicotine medications), based on the International Conference on Harmonisation guideline for new drug products and the European Pharmacopeia for active ingredients [33,34]. Finally, the nicotine concentration in the liquids was compared with the labels on the bottles.

Analysis of nicotine and nicotine-related substances

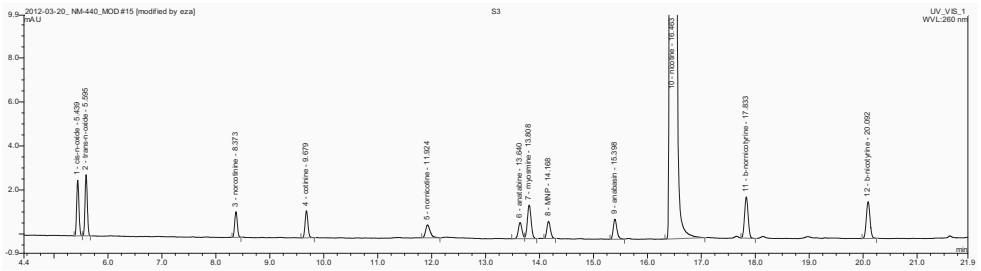
The e-liquids were diluted with 1 M ammonia solution to a concentration of about 150 μg/mL and analyzed with a gradient method using Dionex UltiMate 3000 RS UHPLC. Two replicates were prepared for each sample, and results for both replicates are presented. We used UHPLC with a combination of ultraviolet-vis and photo diode array detector, GC with flame ionization detector and GC–mass spectrometry (MS) with electron impact ionization mode.

The reference solutions, used for identification and quantification of the substances, contained known levels of nicotine, nicotine-cis-N-oxide, nicotine-trans-N-oxide, norcotinine, cotinine, nornicotine, anatabine, myosmine, MNP, anabasine, beta-nornicotyrine and beta-nicotyrine (Fig. 1). The specific spectra of the peaks in the standard were compared with the spectra of the peaks in the samples.

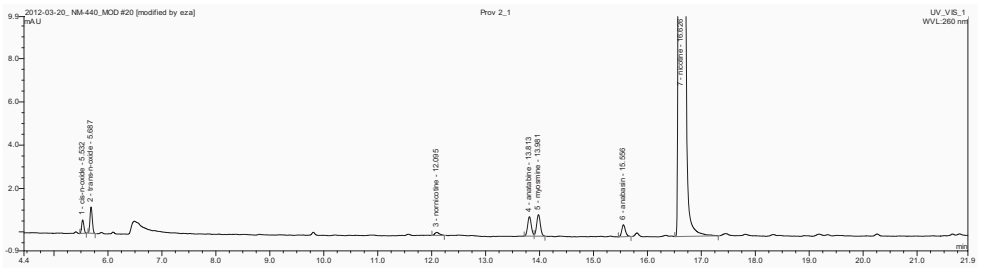
For these analyses, we used a method based on the European Pharmacopeia method for nicotine analysis, including all standards, but this method is not validated for e-cigarette refill solutions. The limit of detection is 0.01–0.03 μg/mL for the different nicotine-related substances analyzed here.

Analysis of diethylene glycol and ethylene glycol (impurities of propylene glycol)

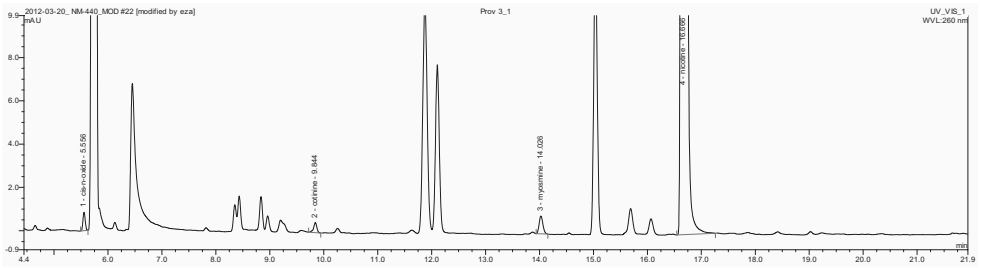
Nineteen solutions were tested for the propylene glycol impurities ethylene glycol and diethylene glycol, in accordance with the USP [35]. The Dekang sample was received too late to be included in this analysis. The solutions were solved in methanol, followed by GC analysis using an Agilent 7890 GC. The test method used was a limit test with 2, 2, 2-trichloroethanol as internal standard. In addition, GC-MS analysis was also conducted, which is a



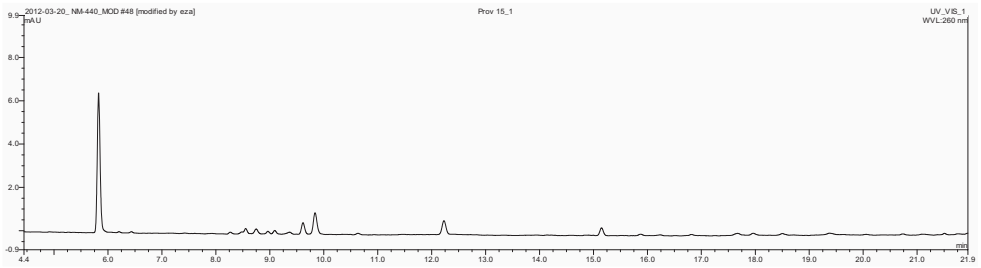
A: Reference solution



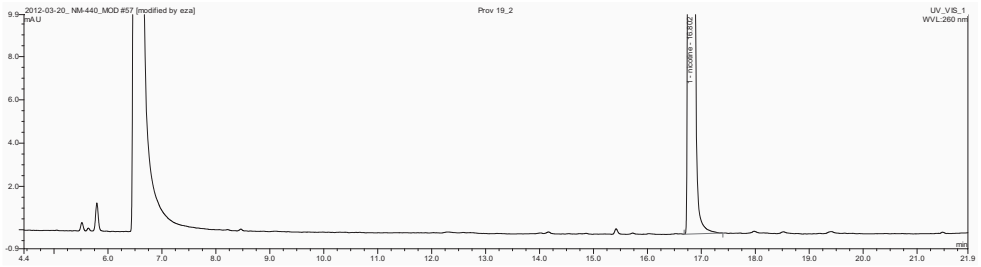
B: Sample 2 showed many known degradation products, not many other peaks



C: Sample 3 showed many other peaks, not many nicotine-related peaks



D: Sample 15, no nicotine.



E: Sample 19, nicotine but no nicotine-related substances.

Figure 1 Examples of chromatograms. (a) Reference solution; (b) sample 2 showed many known degradation products, not many other peaks; (c) sample 3 showed many other peaks, not many nicotine-related peaks; (d) sample 15, no nicotine; (e) sample 19, nicotine but no nicotine-related substances

specific technique based on molecular weight, to assess whether the e-liquids contained diethylene glycol.

RESULTS

Products analyzed

Twenty samples of 10 different brands of e-cigarette refill liquids were analyzed. The 20 samples are described in Table 1.

Nicotine and nicotine-related substances

Only nicotine, known degradation products and nicotine-related unidentified impurities were quantified in this analysis. Some samples contained most of the known degradation products of nicotine, while others mostly contained unidentified peaks. The unidentified peaks were judged to be nicotine-related or not based on a comparison with the spectra of the peaks in the reference standard. The unidentified non-nicotine-related peaks may be related to flavors or other excipients.

Table 2 presents the amount of nicotine in the samples and on the labels on the bottles. Within each brand there were some differences between the duplicates, possibly because the solutions were oily and viscous, which made it difficult to prepare the samples for analyses. The exact volume can be difficult to pipette and disperse when the samples are highly viscous, and a non-homogeneous sample can also produce differences in assay determinations. There was no nicotine amount specified on the labels for samples 14 and 15 (Sedansa), and results showed that these samples did not contain nicotine.

Table 3 presents the concentration of nicotine-related substances expressed as percentage of the area for nicotine. Quantification of the known degradation products and of nicotine-related unidentified impurities was made by comparison with the peak area for nicotine in the samples. Across all samples analyzed, the area for the degradation products represented between 0 and 4.4% of the area for nicotine, but for most samples the level of degradation products represented 1–2% of the nicotine content. Cis-N-oxide, trans-N-oxide, myosmine, anatabine and anabasine were the most common substances found. Sample 19 (Intellicig, 'made in the UK') was the cleanest sample and contained only nicotine, without any nicotine-related substances. Empty cells in Table 3 mean that the substances were not present in these samples.

Ethylene glycol and diethylene glycol

All solutions contained a mixture of propylene glycol and glycerol, with the exception of sample 19 (Intellicig), which contained only glycerol. None of the solutions analyzed contained either ethylene glycol or diethylene glycol (the Dekang sample was not included in this analysis).

DISCUSSION

Nicotine and nicotine-related substances

We analyzed 20 samples of 10 brands of refill liquids for e-cigarettes and found that the content of nicotine degradation products and nicotine impurities represented between 0% and 4.4% of the nicotine content, but for the majority of e-liquids, the level was 1–2%. Nicotine-cis-N-oxide, nicotine-trans-N-oxide, myosmine, anatabine and anabasine were the most common nicotine degradation or nicotine-related substances in the solutions. Cotinine and nicotine-N-oxide are also created during the body's metabolism of nicotine. These metabolites are less potent and less toxic than nicotine itself [37], and their presence in e-liquids at authorized levels might therefore be acceptable. However, the presence of high levels of other degradation products or impurities would be justified only if toxicology studies showed that they did not convey any additional risks to the users. As with previous reports, our analysis showed differences in quality between brands, but also differences across models within the same brands [20,24]. The origin of the nicotine and its manufacturing process are difficult to determine based on these data. Regarding the content of nicotine and nicotine-related substances, half of the e-liquids in our analysis could be acceptable as medicinal products, but all regulations for manufacturing medicinal products were probably not fulfilled. The other half of the liquids analyzed contained up to five times the maximum amount of impurities specified in the European Pharmacopoeia [33].

High amounts of nicotine-related impurities suggest that oxidative degradation of nicotine occurred either during the manufacturing of the ingredient or during the manufacturing of the final liquids, or owing to an unstable formulation. Other reasons may include non-desirable interactions with the packaging material, inadequate handling and storage, or some other problems. For a high quality product, it is critical to use raw material of good quality, and that the composition of the product is stable and non-reactive. Flavor is a parameter known to affect the stability of products. For example, nicotine is often easily oxidized by common substances found in mint, vanilla and fruit flavors.

The production process and content of medicinal products are strictly regulated, and the dose must be proven to be safe and to have a clinical effect. Medications must be produced in a strictly controlled and regulated manner in accordance with good manufacturing

Table 1 Description of the e-liquids analyzed.

No.	*Brand name*	*Model name*	*Bottle capacity (mL)*	*Labeled content*	*Ordered on website*	*'Made in' label*	*Country sent from (label on mail package)*	*Expiry or 'use by' date*
1	Forever Vapor	USA Mix	10	24 mg	forevervapor.com		China (Beijing)	01/11/2013
2	Forever Vapor	Menthol	10	24 mg	forevervapor.com		China (Beijing)	05/10/2013
3	Ecigexpress	Premium Tobacco	10	18 mg/mL	Ecigexpress.com	USA	USA (WA)	Not stated
4	Ecigexpress	USA Mix	10	24 mg	Ecigexpress.com		USA (WA)	Not stated
5	Ecigexpress	Minty Menthol	30	18 mg/mL	Ecigexpress.com	USA	USA (WA)	Not stated
6	Ecigexpress	Unflavored PG base	30	6 mg	Ecigexpress.com		USA (WA)	Not stated
7	Janty	Orange	15	16 mg	france.jantyworld.com		France	05/2013
8	Janty	Flavorless	15	24 mg	france.jantyworld.com		France	05/2013
9	Janty	TXS-H	15	16 mg (in order form)	france.jantyworld.com		France	04/2011–10/2012
10	Totally Wicked	Pillbox 38—High 18 mg	10	18 mg	Totallywicked-eliquid.co.uk	China	UK	Not stated
11	Totally Wicked	Pillbox 38—Patriot Range, tobacco flavor	10	18 mg	Totallywicked-eliquid.co.uk	USA	UK	Not stated
12	Vapor4Life	V4L-555 Nobacco Juice	30	24 mg	v4l.com		USA (IL)	22/08/2013
13	Vapor4Life	V4L-Nobacco Juice—Gunslinger	30	24 mg	v4l.com	USA	USA (IL)	10/10/2012
14	Sedansa	Turkish Blend	10	None specified	Sedansa.be	China	Belgium	Not stated
15	Sedansa	Anatolia	10	None specified	Sedansa.be	China	Belgium	Not stated
16	Johnson Creek	JC Original	15	24 mg	Johnsoncreeksmokejuice.com	USA	USA (WI)	Date not found
17	Johnson Creek	Tennessee Cured	15	24 mg	Johnsoncreeksmokejuice.com	USA	USA (WI)	Not stated
18	Tecc	Titan Fluid, Flavor M/Borough	10	18 mg	theelectroniccigarette.co.uk	China	UK	09/2011–03/2013
19	Intellicig	Refill liquid, Rich X-high	10	30 mg	Intellicig.com	UK	UK	12/2013
20	Dekang	Western Conqueror	10	12 mg	(in person)	PRC (= China)	China: in person	04/01/2014

Table 2 Amount of nicotine in the samples.

Sample no.	*Brand and model*	*Nicotine (mg/mL)*	*Labeled nicotine content*	*% of label*
1	Forever Vapor USA Mix	20.3	24 mg	85
		25.3	24 mg	106
2	Forever Vapor Menthol	24.6	24 mg	102
		26.8	24 mg	112
3	Ecigexpress Premium Tobacco	21.8	18 mg/mL	121
		18.0	18 mg/mL	100
4	Ecigexpress USA Mix	25.7	24 mg	107
		23.7	24 mg	99
5	Ecigexpress Minty Menthol	17.8	18 mg/mL	99
		17.8	18 mg/mL	99
6	Ecigexpress Unflavored PG base	6.0	6 mg	101
		6.0	6 mg	100
7	Janty Orange	15.2	16 mg	95
		15.0	16 mg	94
8	Janty Flavorless	23.5	24 mg	98
		22.2	24 mg	93
9	Janty TXS-H	16.1	16 mg	101
		15.9	16 mg	99
10	Totally Wicked Pillbox 38—High 18 mg	17.7	18 mg	98
		18.4	18 mg	102
11	Totally Wicked Pillbox 38—Patriot Range	16.1	18 mg	90
		16.7	18 mg	93
12	Vapor4life V4L-555 Nobacco Juice	22.3	24 mg	93
		23.6	24 mg	98
13	Vapor4life V4L-Nobacco Juice Gunslinger	22.9	24 mg	95
		25.1	24 mg	105
14	Sedansa Turkish Blend	nd	ns	na
		nd	ns	na
15	Sedansa Anatolia	nd	ns	na
		nd	ns	na
16	Johnson Creek JC Original	25.7	24 mg	107
		25.4	24 mg	106
17	Johnson Creek Tennessee Cured	24.5	24 mg	102
		25.0	24 mg	104
18	Tecc Titan Fluid, Flavor M/Borough	17.5	18 mg	97
		17.2	18 mg	96
19	Intellicig Rich X-high	29.0	30 mg	97
		28.4	30 mg	95
20	Dekang Western Conqueror	11.7	12 mg	98
		12.5	12 mg	104

nd = not detected; ns = nicotine content not specified on label; na = not applicable. Results for two replicates are presented for each sample.

practice, and all excipients must show proof of good quality and well-established characteristics. The container must be tested and made of inert material. Most e-liquids probably do not fulfill these requirements, but e-liquids are currently marketed as alternatives to tobacco, rather than medications. Our analysis did not investigate how the solutions, or the nicotine or other excipients, were produced, how the solutions might be affected when added to the e-cigarette, long-term stability, in-use stability, or how the solutions are affected when heated, vaporized and inhaled.

The nicotine content in the samples generally corresponded to the labels on the bottles, and differences between content and labels were smaller than previously reported [20,24], which suggests that the manufacturing processes has improved over time. The bottles of e-liquid are dangerous as they contain up to 720 mg of nicotine, which is several times the fatal dose of nicotine (and larger bottles are available online). The acute minimum lethal oral dose of nicotine is 40–60 mg in children (oral intake of tobacco from cigarettes) or 0.8–1.0 mg/kg of body weight in adult non-smokers [38].

Table 3 Amount of nicotine-related substances (NRS), expressed as % of nicotine content.

Sample no.	*Brand and model*	*Cis-N-oxide*	*Trans-N-oxide*	*Cotinine*	*Nornicotine*	*Anatabine*	*Myosmine*	*Anabasine*	*Beta-nicotyrine*	*Unidentified*	*Total NRS*
1	Forever Vapor USA Mix	0.14	0.36	–	–	0.38	0.18	0.17	–	–	1.22
		0.14	0.36	–	–	0.39	0.18	0.17	–	–	1.24
2	Forever Vapor Menthol	0.14	0.27	–	0.06	0.32	0.36	0.20	–	–	1.35
		0.13	0.28	–	0.06	0.33	0.37	0.21		–	1.37
3	Ecigexpress Premium	0.16	–	0.12	–	–	0.25	–	–	–	0.54
	Tobacco	0.16	–	0.12	–	–	0.25	–	–	–	0.53
4	Ecigexpress USA Mix	0.37	0.99	–	–	1.56	0.21	0.33	–	–	3.46
		0.37	0.89	–	–	1.54	0.20	0.33	–	–	3.34
5	Ecigexpress Minty	0.09	0.20	0.10	–	–	0.24	–	–	–	0.63
	Menthol	0.09	0.20	0.10		–	0.25	–	–	–	0.65
6	Ecigexpress Unflavored	0.03	0.06	–	–	–	0.14	–	–	–	0.23
	PG base	0.03	0.06	–	–	–	0.14	–	–	–	0.23
7	Janty Orange	0.19	1.06	0.06	0.10	0.95	0.20	0.20	–	0.07	2.82
		0.18	1.06	0.06	0.10	0.94	0.19	0.18	–	–	2.71
8	Janty Flavorless	0.11	–	–	–	0.77	0.21	0.17	–	0.12	1.37
		0.11	–	–	–	0.77	0.21	0.16	–	0.13	1.38
9	Janty TXS-H	0.15	0.31	0.07	–	0.25	0.22	0.13	–	–	1.11
		0.15	0.30	0.06	–	0.22	0.20	0.12	–	–	1.07
10	Totally Wicked Pillbox	0.24	0.52	0.06	–	0.43	0.28	0.45	–	–	1.97
	38-High 18 mg	0.23	0.51	0.06	–	0.43	0.29	0.45	–	–	1.97
11	Totally Wicked Pillbox	0.09	0.23	0.21	–	–	0.42	–	–	–	0.96
	38-Patriot Range	0.09	0.25	0.21	–	–	0.42	–	–	0.05	1.01
12	Vapor4life V4L—555	0.43	2.68	0.12	–	0.41	0.34	0.18	0.06	0.12	4.35
	Nobacco Juice	0.42	2.69	0.13	–	0.42	0.35	0.17	0.06	0.12	4.36
13	Vapor4life V4L -	–	1.16	–	–	0.32	0.24	0.16	–	–	1.87
	Nobacco Juice Gunslinger	–	1.16	–		0.31	0.24	0.16	–	–	1.88
14	Sedansa Turkish Blend	–	–	–	–	–	–	–	–	–	nd
		–	–	–	–	–	–	–	–	–	nd
15	Sedansa Anatolia	–	–	–	–	–	–	–	–	–	nd
		–	–	–	–	–	–	–	–	–	nd
16	Johnson Creek JC	–	0.67	–	–	–	0.10	–	–	–	0.76
	Original	–	0.68	–	–	–	0.09	–	–	–	0.78
17	Johnson Creek Tennessee	–	0.32	0.04	–	–	0.08	–	–	–	0.44
	Cured	–	0.34	0.05	–	–	0.08	–	–	–	0.46
18	Tecc Titan Fluid	0.12	0.26	0.06	–	0.57	0.27	0.23	–	–	1.51
		0.12	0.26	0.05	–	0.57	0.28	0.23	–	–	1.51
19	Intellicig Rich X-high	–	–	–	–	–	–	–	–	–	nd
		–	–	–	–	–	–	–	–	–	nd
20	Dekang Western	0.03	0.04	–	0.02	0.13	0.05	0.04	–	–	0.31
	Conqueror	0.03	0.04	–	0.03	0.14	0.05	0.05	–	–	0.34

nd = not detected. Empty cells mean that the substances were not present in these samples. Results for two replicates are presented for each sample.

Ethylene glycol and diethylene glycol

We did not find either ethylene glycol or diethylene glycol in the liquids analyzed (the Dekang sample was not included in this analysis), which is an indicator of the quality of the e-liquids, and is reassuring. The minimum toxic dose of diethylene glycol is 0.14 mg/kg of body weight and the lethal dose is 1 g/kg of body weight [39,40].

Study strengths and limitations

Strengths of our study included the analysis of a large number of brands and models (one of the largest to date), and the inclusion of some of the most popular brands of e-liquids. From a public health perspective, analyses should include the brands that most 'vapers' (i.e. users of e-cigarettes) are exposed to. In contrast, some previously published analyses omitted several of the most popular brands [20,24,27,28]. Other study strengths include analysis of most of the known impurities and degradation products of nicotine: levels of cis-N-oxide, trans-N-oxide and nornicotine in e-liquids have not previously been reported, and levels of the other substances included in our analyses have been reported in only one paper for just three brands of e-cigarettes [20]. One limitation is that, for practical reasons, some popular brands were not included in our analyses. Another limitation is that we tested only one batch of liquid per brand/model and therefore could not assess whether there were variations from batch to batch within a given brand or within a given model obtained from different sources. Finally, our analyses were limited to a few substances, and analyses of other substances, in both the liquids and in the vapor, are necessary. These substances include flavors and fragrances, aroma transporters (acetin, diacetin, solanone), food dyes, carcinogenic tobacco-specific nitrosamines, oil (as an impurity in glycerol)—since inhaled oil can cause lipoid pneumonia [41]—phthalates and plasticizers (that can migrate from the container during heating and vaporization), aldehydes (formaldehyde, acetaldehyde), metal particles [27], allergens and infectious agents. We analyzed refill liquids only, but future studies should analyze the vapor because new substances may be created during the heating and vaporization processes. In addition, because e-liquids are intended to be vaporized and inhaled, they should be tested for delivered dose uniformity and aerodynamic particle size distribution. These tests are mandatory for medications intended to be inhaled.

CONCLUSIONS

About half of the e-liquids analyzed in this study contained acceptable levels of nicotine-related impurities, the nicotine content corresponded, in general, to the labels on the bottles and no diethylene glycol was found in a sample of some of the most popular brands of e-liquids. Thus, the quality of most of these products was surprisingly good. However, some brands had levels of impurities above accepted limits for pharmaceutical products. To ensure that e-liquids meet acceptable quality standards required to ensure the safety of nicotine medications, all the manufacturing processes should be controlled, particularly the choice of excipients, and standard testing and quality control procedures should be implemented. In the current legal situation in most countries, manufacturers and distributors of e-liquids are not controlled by the agencies that otherwise control medications. For some brands of e-liquids at least, the manufacturing process or control systems are probably below required standards for nicotine medications.

As this new market has largely developed outside an appropriate regulatory framework, some manufacturers and vendors apparently lack adequate know-how about safety, and most do not provide information about their products and manufacturing processes. However, no country currently regulates e-cigarettes and e-liquids as medications. Rather, they are regulated as tobacco products or consumer products. In this case, they should be compared with tobacco, not with nicotine medications, and the presence of impurities in e-liquids is less relevant, because even if e-liquids contained impurities, vaping would still be much less dangerous than smoking. The success of e-cigarettes challenges current legislation, which allows nicotine only in tobacco and in nicotine medications. This new situation requires a substantive discussion on the place of nicotine in our society and a reconsideration of the regulation of nicotine in all products, including tobacco.

Declarations of interests

JFE was reimbursed by a manufacturer of e-liquids for traveling to London and to China, but he received no honoraria for these meetings aimed at mutual information. EZ and SS are employed by McNeil, a manufacturer of medicinal products for smoking cessation.

Acknowledgements

The authors thank Adriana Ionescu, McNeil AB, who performed analytical work.

References

1. Flouris A. D., Oikonomou D. N. Electronic cigarettes: miracle or menace? *BMJ* 2010; **340**: c311.
2. Hadwiger M. E., Trehy M. L., Ye W., Moore T., Allgire J., Westenberger B. Identification of amino-tadalafil and rimonabant in electronic cigarette products using high pressure liquid chromatography with diode array and tandem mass spectrometric detection. *J Chromatogr A* 2010; **1217**: 7547–55.

3. Etter J. F., Bullen C., Flouris A. D., Laugesen M., Eissenberg T. Electronic nicotine delivery systems: a research agenda. *Tob Control* 2011; **20**: 243–8.
4. Yamin C. K., Bitton A., Bates D. W. E-cigarettes: a rapidly growing Internet phenomenon. *Ann Intern Med* 2010; **153**: 607–9.
5. Regan A. K., Promoff G., Dube S. R., Arrazola R. Electronic nicotine delivery systems: adult use and awareness of the 'e-cigarette' in the USA. *Tob Control* 2013; **22**: 19–23.
6. Pearson J. L., Richardson A., Niaura R. S., Vallone D. M., Abrams D. B. e-cigarette awareness, use, and harm perceptions in US adults. *Am J Public Health* 2012; **102**: 1758–66.
7. King B. A., Alam S., Promoff G., Arrazola R., Dube S. R. Awareness and ever use of electronic cigarettes among U.S. adults, 2010–2011. *Nicotine Tob Res*; Epub ahead of print; 2013.
8. Adkison S. E., O'Connor R. J., Bansal-Travers M., Hyland A., Borland R., Yong H. H. *et al*. Electronic nicotine delivery systems: international tobacco control four-country survey. *Am J Prev Med* 2013; **44**: 207–15.
9. OFSP. Lettre d'information n°146: cigarettes électroniques. Office fédéral de la santé publique, Berne, May 2009.
10. Sottera, Inc. v. FDA (United States Court of Appeals, District of Columbia Circuit). 2010.
11. World Health Organization. WHO Study Group on Tobacco Product Regulation: report on the scientific basis of tobacco product regulation: third report of a WHO Study Group. *World Health Organ Tech Rep Ser* 2009; **955**.
12. Laugesen M. Safety report on the Ruyan e-cigarette cartridge and inhaled aerosol. (Christchurch, New Zealand, Health New Zealand Ltd). 2008.
13. Laugesen M. Ruyan e-cigarette bench-top tests, Poster presented at the Conference of the Society for Research on Nicotine and Tobacco, Dublin, April 27–30, 2009.
14. FDA. *Summary of Results: Laboratory Analysis of Electronic Cigarettes Conducted by FDA*. Silver Spring, MD: Food and Drug Administration (FDA), 2009. Available at: http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm173146.htm (accessed 15 May 2013) (Archived at http://www.webcitation.org/6GbsIQ1fZ).
15. Eissenberg T. Electronic nicotine delivery devices: ineffective nicotine delivery and craving suppression after acute administration. *Tob Control* 2010; **19**: 87–8.
16. Vansickel A. R., Cobb C. O., Weaver M. F., Eissenberg T. E. A clinical laboratory model for evaluating the acute effects of electronic 'cigarettes': nicotine delivery profile and cardiovascular and subjective effects. *Cancer Epidemiol Biomarkers Prev* 2010; **19**: 1945–53.
17. Bullen C., McRobbie H., Thornley S., Glover M., Lin R., Laugesen M. Effect of an electronic nicotine delivery device (e cigarette) on desire to smoke and withdrawal, user preferences and nicotine delivery: randomised cross-over trial. *Tob Control* 2010; **19**: 98–103.
18. Cahn Z., Siegel M. Electronic cigarettes as a harm reduction strategy for tobacco control: a step forward or a repeat of past mistakes? *J Public Health Policy* 2010; **32**: 16–31.
19. Etter J. F., Bullen C. Electronic cigarette: users profile, utilization, satisfaction and perceived efficacy. *Addiction* 2011; **106**: 2017–28.
20. Trehy M., Ye W., Hadwiger M., Moore T., Allgire J., Woodruff J. *et al*. Analysis of electronic cigarette cartridges, refill solutions, and smoke for nicotine and nicotine related impurities. *J Liq Chromatogr Relat Technol* 2011; **34**: 1442–58.
21. McQueen A., Tower S., Sumner W. Interviews with 'vapers': implications for future research with electronic cigarettes. *Nicotine Tob Res* 2011; **13**: 860–7.
22. Etter J., Bullen C. Cotinine levels in users of electronic cigarettes. *Eur Respir J* 2011; **38**: 1219–20.
23. Vansickel A. R., Eissenberg T. Electronic cigarettes: effective nicotine delivery after acute administration. *Nicotine Tob Res* 2013; **15**: 267–70.
24. Goniewicz M. L., Kuma T., Gawron M., Knysak J., Kosmider L. Nicotine levels in electronic cigarettes. *Nicotine Tob Res* 2013; **15**: 158–66.
25. Etter J. F. Electronic cigarettes: a survey of users. *BMC Public Health* 2010; **10**: 231.
26. Goniewicz M. L., Knysak J., Gawron M., Kosmider L., Sobczak A., Kurek J. *et al*. Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. *Tob Control*; Epub ahead of print; 2013.
27. Williams M., Villarreal A., Bozhilov K., Lin S., Talbot P. Metal and silicate particles including nanoparticles are present in electronic cigarette cartomizer fluid and aerosol. *PLoS ONE* 2013; **8**: e57987.
28. Trtchounian A., Williams M., Talbot P. Conventional and electronic cigarettes (e-cigarettes) have different smoking characteristics. *Nicotine Tob Res* 2010; **12**: 905–12.
29. Uchiyama S., Inaba Y., Kunugita N. Determination of acrolein and other carbonyls in cigarette smoke using coupled silica cartridges impregnated with hydroquinone and 2,4-dinitrophenylhydrazine. *J Chromatogr A* 2010; **1217**: 4383–8.
30. Haller C. Made in China. *J Med Toxicol* 2008; **4**: 141–2.
31. Gorrod J. W., Jacob P. *Analytical Determination of Nicotine and Related Compounds and Their Metabolites*. Amsterdam: Elsevier; 1999.
32. Hukkanen J., Jacob P. 3rd, Benowitz N. L. Metabolism and disposition kinetics of nicotine. *Pharmacol Rev* 2005; **57**: 79–115.
33. European Directorate for the Quality of Medicines and Healthcare. European Pharmacopeia 7.0. European Directorate for the Quality of Medicines and Healthcare. 2012.
34. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. ICH Topic Q 3 B (R2) Impurities in New Drug Products. *International Conference on Harmonisation*. 2006.
35. US Pharmacopeial Convention. *USP35-NF30*. Rockville, MD: US Pharmacopeial Convention; 2012.
36. US Pharmacopeial Convention. *The United States Pharmacopeia: The National Formulary*. Rockville, MD: United States Pharmacopeial Convention; 2008.
37. Gorrod J. W., Tsai M. C. Nicotine and the tobacco alkaloids. In: Waring R. H., Steventon G. B., Mitchell S. C., editors. *Molecules of Death*. London: Imperial College Press; 2007, p. 233–52.
38. Salomon M. E. Nicotine and tobacco preparations. In: Flomenbaum N. E., Goldfrank L. R., Hoffman R. S., editors. *Goldfrank's Toxicologic Emergencies*, 8th edn. New York: McGraw-Hill; 2006, p. 1221–30.
39. Schep L. J., Slaughter R. J., Temple W. A., Beasley D. M. Diethylene glycol poisoning. *Clin Toxicol (Phila)* 2009; **47**: 525–35.
40. Kraut J. A., Kurtz I. Toxic alcohol ingestions: clinical features, diagnosis, and management. *Clin J Am Soc Nephrol* 2008; **3**: 208–25.
41. McCauley L., Markin C., Hosmer D. An unexpected consequence of electronic cigarette use. *Chest* 2012; **141**: 1110–3.

