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## Chemical evaluation of electronic cigarettes

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Received 4 December 2013  
Revised 27 February 2014  
Accepted 28 February 2014

Documento scaricato dal sito [vapit.it](http://vapit.it)

L'ASSOCIAZIONE ITALIANA A TUTELA DEI DIRITTI DEI VAPER

## ABSTRACT

**Objective** To review the available evidence evaluating the chemicals in refill solutions, cartridges, aerosols and environmental emissions of electronic cigarettes (e-cigarettes).

**Methods** Systematic literature searches were conducted to identify research related to e-cigarettes and chemistry using 5 reference databases and 11 search terms. The search date range was January 2007 to September 2013. The search yielded 36 articles, of which 29 were deemed relevant for analysis.

**Results** The levels of nicotine, tobacco-specific nitrosamines (TSNAs), aldehydes, metals, volatile organic compounds (VOCs), flavours, solvent carriers and tobacco alkaloids in e-cigarette refill solutions, cartridges, aerosols and environmental emissions vary considerably. The delivery of nicotine and the release of TSNAs, aldehydes and metals are not consistent across products. Furthermore, the nicotine level listed on the labels of e-cigarette cartridges and refill solutions is often significantly different from measured values. Phenolic compounds, polycyclic aromatic hydrocarbons and drugs have also been reported in e-cigarette refill solutions, cartridges and aerosols. Varying results in particle size distributions of particulate matter emissions from e-cigarettes across studies have been observed. Methods applied for the generation and chemical analyses of aerosols differ across studies. Performance characteristics of e-cigarette devices also vary across and within brands.

**Conclusions** Additional studies based on knowledge of e-cigarette user behaviours and scientifically validated aerosol generation and chemical analysis methods would be helpful in generating reliable measures of chemical quantities. This would allow comparisons of e-cigarette aerosol and traditional smoke constituent levels and would inform an evaluation of the toxicity potential of e-cigarettes.

## INTRODUCTION

e-cigarettes are nicotine delivery devices designed to look and feel like a traditional cigarette, a pen or a fashion accessory. They are often marketed as tobacco-free nicotine delivery devices.<sup>1</sup> In a typical device configuration, instead of burning tobacco, a user draws air through the device; an airflow sensor or a physical power button activates a battery that powers an atomizer to produce an aerosol from liquid containing nicotine and flavourings. A high percentage of the liquid is composed of carrier solvents, such as glycerol and/or propylene glycol. Aerosol generated from an e-cigarette is commonly but inaccurately referred to as 'vapour.' Vapour refers to the gaseous state of a substance; in contrast, an aerosol is a suspension of fine particles of liquid, solid or both in a gas. Both the particulate and gas phases are mixtures of chemical

substances in e-cigarette aerosols. The e-cigarette aerosol simulates cigarette smoke.<sup>2</sup> Following a puff, the aerosol is delivered into the user's mouth and lungs by inhalation, after which the remaining aerosol is exhaled into the environment.<sup>1</sup> These products are commercialised in various forms (or 'models') with different design characteristics and generate different physical and chemical characteristics during operation.

e-cigarettes are becoming increasingly popular, a concerning trend given limited information about their chemistry. Marketers of e-cigarettes have made a variety of claims indicating that e-cigarettes are safer than conventional cigarettes and that their use facilitates smoking cessation.<sup>3</sup> However, e-cigarette manufacturers do not provide complete information on the chemicals used in the manufacturing process or the chemicals that may be released or synthesised during the aerosol generation process that occurs during use. Minimal valid chemistry data are available on e-cigarette emissions. Furthermore, nicotine levels are intentionally formulated to create target strengths, yet measured levels may not match the label claim.<sup>4</sup> Consequently, safety concerns exist regarding e-cigarette user exposure to harmful and potentially harmful constituents (HPHCs), including nicotine, which has the potential to cause addiction and other adverse events.<sup>5</sup> This paper summarises existing research findings related to e-cigarette chemical composition; it also highlights limitations and information gaps that are critical for reliable chemistry data collection necessary for e-cigarette hazard evaluation.

## METHODS

Systematic literature searches were conducted through September 2013 to identify research related to e-cigarettes and chemistry. Five reference databases (Web of Knowledge, PubMed, SciFinder, Embase and EBSCOhost) were searched using a set of relevant search terms used singly or in combination. Search terms included the following: 'electronic nicotine devices' OR 'electronic nicotine device' OR 'electronic nicotine delivery systems' OR 'electronic nicotine delivery system' OR 'electronic cigarettes' OR 'electronic cigarette' OR 'e-cigarettes' OR 'e-cigarette' OR 'e-cig' OR 'e-cigs' AND 'chemistry.' The search date range was restricted between January 2007, when the first study of chemicals in e-cigarettes was published, and September 2013.

To be considered for inclusion, the article had to (1) be written in English, (2) be publicly available, (3) be published in a peer-reviewed journal and (4) deal partly or exclusively with chemistry. Excluded sources included (1) indirect data sources, (2) patents and (3) conference presentations.



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To cite: Cheng T. *Tob Control* 2014;**23**:ii11–ii17.

**Table 1** Nicotine reported in refill solutions, cartridges, aerosols and environmental emission of e-cigarette products

Literature	Matrix	Units	Nicotine level	Deviation from label*
Goniewicz <i>et al</i> <sup>4</sup>	Refill solution	mg	0±0.0 to 25±1.1	-75 to 28%
	Cartridge	mg	0±0.0 to 19±0.5	-89 to 25%
	Aerosol	mg/150 puffs	0.3±0.2 to 8.7±1.0	N.A.
Etter <i>et al</i> <sup>13</sup>	Refill solution	mg/mL	N.D. to 29.0	-15 to 21%†
Kirschner <i>et al</i> <sup>16</sup>	Refill solution	mg/mL	14.8±0.2 to 87.2±2.7	-50 to 40%†
Cameron <i>et al</i> <sup>15</sup>	Refill solution	mg/mL	8.5±0.16 to 22.2±0.62	-66 to 42%†
Pellegrino <i>et al</i> <sup>6</sup>	Cartridge	% WW	<0.001 to 0.25	N.A.
	Aerosol	mg/m <sup>3</sup>	<0.01 to 6.21	N.A.
McAuley <i>et al</i> <sup>11</sup>	Indoor air	ng/L	538 to 8770	N.A.
Cheah <i>et al</i> <sup>17</sup>	Cartridge	mg/cartridge	0.00 to 15.3	-89 to 105%†
Trehay <i>et al</i> <sup>7</sup>	Refill solutions	mg/mL	0 to 25.6	-100 to 100%†
	Cartridge	mg/cartridge	0 to 21.8	-100 to 100%†
	Aerosol	µg/100 mL puff	0 to 43.2	N.A.
Cobb <i>et al</i> <sup>8</sup>	Cartridge	mg/cartridge	3.23±0.5 to 4.07±0.54	-80 to -77%†
	Aerosol	µg/35 mL puff	0.3 for puffs 11 to 50 to 1.0 for puffs 1 to 10	N.A.
Westenberger <sup>9</sup>	Cartridge	mg/cartridge	0.00 to 6.76	N.A.
	Aerosol	µg/100 mL puff	0.35 to 43.2	N.A.
Westenberger <sup>10</sup>	Refill solution	µg/mL	N.D. to 25.6	N.A.

\*Deviation from label=(measured value – labelled value) \* 100/labelled value.

†Calculation performed by this analysis based on reported data in each study.

N.A., not available; N.D., not detected.

The search yielded a total of 261 articles that met the inclusion criteria. Exclusion criteria reduced the number of articles to 158. The titles and abstracts (when titles provided insufficient detail) of these 158 articles were screened for relevance. This screening identified 36 articles for full-text review, including a manual search of the reference lists of selected articles to identify additional relevant publications.

Following the full-text review, 29 articles were deemed relevant for this analysis. The validity and strength of each study were determined based on a qualitative assessment of study scope objectives and research design. Meaningful study limitations are noted in the analysis.

## RESULTS

Chemical substances reported in studies of e-cigarette refill solutions, cartridges, aerosols and environmental emissions are provided in tables 1–7. The instrumental methods developed by each study for specific categories of chemicals are provided in tables 8 and 9. Methods, conditions and parameters for machine (laboratory device) aerosol generation reported in these studies are provided in tables 10 and 11. The combined results of these research studies are described below.

### Nicotine

Table 1 summarises the current research regarding the nicotine levels found in e-cigarette cartridges, refill solutions, aerosols

and environmental emissions. Nicotine is the primary addictive substance in tobacco products. The data indicate that the nicotine levels in e-cigarettes vary considerably. e-cigarette brands and models differ in the efficacy and consistency of nicotine yields, and the delivery of nicotine is not uniform either from puff-to-puff or across products of the same brand.<sup>4 6–11</sup> Furthermore, the level of nicotine listed on the labels of e-cigarette cartridges and refill solutions is often significantly different from measured values<sup>4 7 8 12–18</sup> and labelling may not adequately convey the amount or concentration of nicotine.<sup>19</sup> For example, Goniewicz *et al* conducted a quantitative analysis of nicotine in aerosols generated from 15 e-cigarette brands (16 products) that were selected based on their market popularity. They found that total nicotine in aerosol varied by brand from 0.5 to 15.4 mg per 300 puffs (20 series of 15 puffs, 70 mL/puff, triplicate tests of each product) and that the nicotine in aerosol varied from 21% to 85% of the nicotine present in the cartridge. Westenberger repeatedly tested three individual cartridges with the same label and obtained results varying from 26.8 to 43.2 µg nicotine per 100 mL puff (estimated to be 8.04–13.0 mg nicotine per 300 puffs). Consequently, environmental nicotine emissions from e-cigarettes differ across brands. For example, McAuley studied nicotine emissions from aerosols of four different high-nicotine content e-liquids in cartridges and found 538–8770 ng/L of nicotine in indoor air compared with 5039 to 48050 ng/L from conventional cigarette smoke.<sup>11</sup>

**Table 2** Aldehydes reported in refill solutions and aerosols of e-cigarettes

Literature	Matrix	Units	Formaldehyde	Acetaldehyde	Acrolein	o-Methyl benzaldehyde	Acetone
Goniewicz <i>et al</i> <sup>20</sup>	Aerosol	µg/150 puffs	3.2±0.8 to 56.1±1.4	2.0±0.1 to 13.6±2.1	N.D. to 41.9±3.4	1.3±0.8 to 7.1±0.4	N.T.
Lim and Shin <sup>25</sup>	Refill solution	mg/L	0.02 to 10.09	0.10 to 15.63	N.D.	N.T.	N.T.
Ohta <i>et al</i> <sup>23</sup>	Aerosol	mg/m <sup>3</sup>	260	<LOQ	<LOQ	N.T.	N.T.
Uchiyama <i>et al</i> <sup>24</sup>	Aerosol	mg/m <sup>3</sup>	8.3	11	9.3	N.T.	2.9
Laugesen <sup>22</sup>	Aerosol	ppm/38 mL puff	0.25	0.34	N.D. to 0.33	N.T.	0.16

&lt;LOQ, below the limit of quantitation but above the limit of detection; N.D., not detected; N.T., not tested by the study.

**Table 3** Tobacco-specific nitrosamines reported in aerosols, refill solutions and cartridges of e-cigarettes

Literature	Matrix	Units	NNN	NNK	NAT	NAB
Goniewicz <i>et al</i> <sup>20</sup>	Aerosol	µg/150 puffs	N.D. to 4.3±2.4	N.D. to 28.3±13.2	N.T.	N.T.
Kim and Shin <sup>21</sup>	Refill solution	µg/L	0.34 to 60.08	0.22 to 9.84	0.09 to 62.19	0.11 to 11.11
Westenberger <i>et al</i> <sup>9</sup>	Cartridge	mg/cartridge	N.D. to <LOQ	N.D. to <LOQ	N.D. to <LOQ	N.D. to <LOQ
Laugesen <sup>22</sup>	Cartridge	ng/cartridge	BDL to 3.87	0.26 to 1.46	BDL to 2.16	N.Q. to 0.69

<LOQ, below the limit of quantitation but above the limit of detection; BDL, below detection limit; N.D., not detected; N.Q., not quantifiable; N.T., not tested by the study. NNN, N-nitrosanornicotine; NNK, 4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone; NAT, N-nitrosoanatabine; NAB, N-nitrosoanabasine.

Given these issues with nicotine content variability, all studies recommend that e-cigarette manufacturers implement quality standards regarding nicotine content.

### Other chemical substances

Quantitative and qualitative studies have identified a wide variety of chemical components in the cartridges, refill solutions and aerosols of e-cigarettes. Tables 2–7 summarise the chemical substances that have been detected and/or quantified in e-cigarette refill solutions, cartridges and aerosols. Substances identified include tobacco-specific nitrosamines (TSNAs),<sup>9 20–22</sup> aldehydes,<sup>20 22–25</sup> metals,<sup>20 22 26</sup> volatile organic compounds (VOCs),<sup>6 20 22 27</sup> phenolic compounds,<sup>22</sup> polycyclic aromatic hydrocarbons (PAHs),<sup>22 28</sup> flavours,<sup>6 22</sup> solvent carriers,<sup>6 22 27</sup> tobacco alkaloids,<sup>7 9 10 13</sup> and drugs (amino-tadalafil and rimonabant).<sup>18</sup>

These TSNAs, aldehydes, metals, VOCs, phenolic compounds, PAHs and tobacco alkaloids are harmful or potentially harmful constituents released during the smoking of conventional cigarettes, and their public health risks have been the focus of many studies. In contrast, e-cigarettes use solvent carriers, such as propylene glycol and glycerol, as humectants in e-cigarette solutions to produce aerosols that simulate conventional cigarette smoke. These humectants are oxidised to form the same aldehydes found in conventional cigarette smoke when a heating voltage greater than 3 V is used during the aerosol generation process.<sup>23 25 26</sup> The data reported by Goniewicz

*et al* indicate that e-cigarette brands and product models differ in yields of TSNAs, aldehydes, metals and VOCs.<sup>20</sup> For example, the acrolein level in the aerosol generated from two different product models within the same brand is reported to be 4.4±2.5 µg/150 puffs for one model and 16.6±2.5 µg/150 puffs for the other model. An even greater variance in the acrolein level is observed when comparing products across brands, where an acrolein level was determined to be as large as 41.9±3.4 µg/150 puffs in aerosol of a product from a different brand. The relative standard deviations (SDs) reported for all measurements range from 0% to 100% of the mean values, indicating inconsistencies in the release of these chemicals across products. Similarly, in 2013 Etter *et al* found that e-cigarette sub-brands differ in levels of tobacco alkaloids.<sup>13</sup> Within a brand, nicotine-N-oxide (one of the tobacco alkaloids) is at 0.16% (of nicotine content) in a tobacco-flavoured sub-brand, 0.09% in a menthol-flavoured sub-brand and 0.03% in an unflavoured sub-brand.

Nevertheless, analytical methods applied in these studies are inconsistent. Tables 8 and 9 summarise the instrumental methods developed for specific categories of target analytes by each study. Analytical methodology for qualitative and/or quantitative determination of a constituent in cigarette smoke generally encompasses two areas of effort: sample preparation and instrumental analysis. Sample preparation involves smoke/aerosol generation, sample extraction and sample collection. Instrumental analysis involves analysing the sample to identify

**Table 4** Metals reported in aerosols and cartridges of e-cigarettes

Literature	Units	Cadmium	Nickel	Lead	Chromium	Arsenic
Goniewicz <i>et al</i> <sup>20</sup>	µg/150 puffs	N.D. to 0.22±0.16	0.11±0.05 to 0.29±0.08	0.03±0.03 to 0.57±0.28	N.T.	N.T.
Williams <i>et al</i> <sup>26</sup>	µg/10 puffs	N.T.	0.005	0.017	0.007	N.T.
Laugesen <sup>22</sup>	µg/cartridge	N.D.	N.D.	N.D.	N.D.	N.D.

N.D., not detected; N.T., not tested by the study.

**Table 5** Tobacco alkaloids reported in refill solutions, cartridges and aerosols of e-cigarettes

Literature	Matrix	Units	Cotinine	Myosmine	Anatabine	Anabasine	β-Nicotyrine	Nornicotine
Etter <i>et al</i> <sup>13</sup>	Refill solution	% of nicotine	0.04 to 0.21	0.05 to 0.42	0.13 to 1.56	0.04 to 0.45	0.06	0.02 to 0.10
Trehay <i>et al</i> <sup>7</sup>	Cartridge	mg/cartridge	N.D.	<LOQ to 0.08	N.D. to 0.82	N.D. to <LOQ	N.D. to <LOQ	N.T.
	Aerosol	mg/30×100 mL puffs	N.D.	N.D.	N.D. to <LOQ	N.D.	N.D.	N.T.
Westenberger <sup>9</sup>	Cartridge	mg/cartridge	N.D. to <LOQ	N.D. to <LOQ	N.A.	N.D. to <LOQ	N.D. to <LOQ	N.A.
	Aerosol	µg/100 mL puff	N.D. to 0.4	N.T.	N.T.	N.T.	N.D. to D.	N.T.
Westenberger <sup>10</sup>	Refill solution	µg/mL	N.D. to 178	36 to 71	18 to 57	N.D.	1 to 6	N.T.

<LOQ, below the limit of quantitation but above the limit of detection; D., detected; N.A., not available; N.D., not detected; N.T., not tested by the study.

**Table 6** Polycyclic aromatic hydrocarbons and cresol reported in aerosols from one e-cigarette cartridge

Literature	Cresol	PAHs				Others
		Anthracene	Phenanthrene	1-Methyl phenanthrene	Pyrene	
Laugesen <sup>22</sup>	0.16 ppm/38 mL puff	7 ng/cartridge	48 ng/cartridge	5 ng/cartridge	36 ng/cartridge	N.D.

N.D., not detected.

**Table 7** Volatile organic compounds reported in aerosols of e-cigarettes

Literature	Units	Toluene	p,m-Xylene	Propylene Glycol	Glycerin	3-Methylbutyl-3-methylbutanoate
Schripp <i>et al</i> <sup>27</sup>	µg/puff	N.A.	N.A.	1673 to 5525	5 to 15	0.1 to 1.1
Goniewicz <sup>20</sup>	µg/150 puffs	N.D. to 6.3±1.5	N.D. to 0.2±0.1	N.T.	N.T.	N.T.
Pellegrino <i>et al</i> <sup>6</sup>	mg/m <sup>3</sup>	N.T.	N.T.	1660	610	N.T.
Laugesen <sup>22</sup>	ppm/38 mL puff	N.T.	0.18	32	N.T.	N.T.

N.A., not available; N.D., not detected; N.T., not tested by the study.

and quantify analytes of interest. The instrument is commonly selected based on the scientific characteristics of the target analyte, the applicable features of the instrument and the instrument accessibility.

Taking instrumental TSNA analysis as an example, ultra-performance liquid chromatography coupled with mass spectrometry (LCMS) was used in Goniewicz's research,<sup>20</sup> whereas high-performance liquid chromatography coupled with tandem mass spectrometry (LCMSMS) was used in Kim's study.<sup>21</sup> The two instruments differ in performance characteristics such as detection limit, resolution and linear dynamic range.

By instrumental design, LCMSMS uses two mass spectrometers connected in series, as opposed to one mass spectrometer for LCMS. LCMSMS provides increased sensitivity and resolution when detecting an analyte in a complex sample matrix, such as smoke, by mass filtering and fragmentation pattern recognition of a specific target mass that undergoes inert gas fragmentation in the collision chamber. This also results in LCMSMS having a wider linear dynamic range than LCMS. These advantages of LCMSMS are beneficial to the analysis of a cigarette smoke/aerosol sample because the target analyte levels are frequently near the limit of quantitation for LCMS, and the

**Table 8** Instrumental methods developed for nicotine, TSNA, aldehydes, metals, VOCs and phenols

Literature	Nicotine	TSNAs	Aldehydes	Metals	VOCs	Phenols
Cameron <i>et al</i> <sup>15</sup>	LC/MS/MS					
Etter <i>et al</i> <sup>13</sup>	UHPLC/DAD, GC/FID, GC/MS					
Goniewicz <i>et al</i> <sup>4</sup>	GC/TSD					
Goniewicz <i>et al</i> <sup>20</sup>		UPLC/MS	HPLC/DAD	ICP/MS	GC/MS	
Kim and Shin <sup>21</sup>		LC/MS/MS				
Kubica <i>et al</i> <sup>14</sup>	LC/MS/MS/trap					
Lim and Shin <sup>25</sup>			HS GC/MS			
Kirschner <i>et al</i> <sup>16</sup>	LC/TOF					
Schripp <i>et al</i> <sup>27</sup>			HPLC/UV		GC/MS	
Uryupin <i>et al</i> <sup>30</sup>	NMR					
Williams <i>et al</i> <sup>26</sup>				ICP/OES		
Cheah <i>et al</i> <sup>17</sup>	GC/FID, GC/MS					
McAuley <i>et al</i> <sup>11</sup>	GC/NPD	GC/MS	HPLC/UV		HS GC/MS	
Ohta <i>et al</i> <sup>23</sup>			HPLC/UV			
Trehy <i>et al</i> <sup>7</sup>	HPLC/DAD					
Uchiyama <i>et al</i> <sup>24</sup>			HPLC/UV			
Westenberger <sup>9</sup>	HPLC/UV, GC/MS	LC/MS/MS				
Westenberger <sup>10</sup>	HPLC/UV	LC/MS/MS				
Laugesen <sup>22</sup>		LC/MS/MS	SIFTMS	ICP/MS	SIFTMS	SIFTMS

GC/FID, gas chromatography coupled with flame ionization detector; GC/MS, gas chromatography coupled with mass spectrometry; GC/NPD, gas chromatography coupled with nitrogen-phosphorus detector; GC/TSD, gas chromatography coupled with thermionic specific detector; HPLC/DAD, high-performance liquid chromatography coupled with diode array detector; HPLC/UV, high-performance liquid chromatography coupled with ultraviolet/visible spectroscopic detector; HS GC/MS, head space gas chromatography coupled with mass spectrometry; ICP/MS, inductively coupled plasma coupled with mass spectrometry; ICP/OES, inductively coupled plasma coupled with optical emissions spectroscopy; LC/MS/MS, liquid chromatography coupled with tandem mass spectrometry; LC/TOF, liquid chromatography coupled with time-of-flight mass spectrometry; NMR, nuclear magnetic resonance; SIFTMS, selected ion flow tube and mass spectrograph; Trap, ion trap; TSNAs, tobacco-specific nitrosamines; UHPLC/DAD, ultra high-performance liquid chromatography coupled with diode array detector; VOCs, volatile organic compounds.

**Table 9** Instrumental methods developed for PAHs, flavours, solvents, alkaloids, drugs and particles

Literature	PAHs	Flavours	Solvents	Alkaloids	Drugs	Particles
Etter <i>et al</i> <sup>13</sup>			GC/FID, MS-EI			
Schripp <i>et al</i> <sup>27</sup>						EMA
Uryupin <i>et al</i> <sup>30</sup>			ESI/MS, NMR			
Williams <i>et al</i> <sup>26</sup>						SMPS-CPC
Zhang <i>et al</i> <sup>31</sup>						SMPS
Cheah <i>et al</i> <sup>17</sup>			GC/FID, GC/MS			
Ingebretsen <i>et al</i> <sup>29</sup>						ST
McAuley <i>et al</i> <sup>11</sup>	GC/MS		GC/MS			WPS
Pellegrino <i>et al</i> <sup>6</sup>		GC/MS	GC/MS			Aerocet
Trehy <i>et al</i> <sup>7</sup>				HPLC/DAD		
Hadwiger <i>et al</i> <sup>18</sup>					HPLC/DAD or MSMS	
Westenberger <sup>9</sup>			NMR, GC/MS	HS GC/MS or MSMS		
Westenberger <sup>10</sup>			GC/MS	HPLC/UV, GC/MS		
Laugesen <sup>22</sup>	GC/MS		SIFTMS			

Aerocet, aerosol mass analyzer; Drugs, amino-tadalafil and rimonabant; EMA, electrical mobility analyzer; ESI/MS, electro-spray ionization mass spectrometry; GC/FID, gas chromatography coupled with flame ionization detector; GC/MS, gas chromatography coupled with mass spectrometry; GC/NPD, gas chromatography coupled with nitrogen-phosphorus detector; GCTSD, gas chromatography coupled with thermionic specific detector; HPLC/DAD, high-performance liquid chromatography coupled with diode array detector; HPLC/UV, high-performance liquid chromatography coupled with ultraviolet/visible spectroscopic detector; HS GC/MS, head space gas chromatography coupled with mass spectrometry; MS-EI, electron impact mass spectrometry; MSMS, tandem mass spectrometry; NMR, nuclear magnetic resonance; PAHs, polycyclic aromatic hydrocarbons; SIFTMS, selected ion flow tube and mass spectrograph; SMPS, scanning mobility particle sizer; SMPS-CPC, scanning mobility particle sizer and condensation particle counter; ST, spectral transmission method; WPS, wide range particle spectrometer.

complex sample matrix is not well resolved by LCMS unless additional sample clean-up is completed before analysis. Such differences are expected to contribute to variations in quantitative and qualitative results.

Another noteworthy concern is that many of the analytical methods used in these studies have not been validated. Method validation is generally an important part of good laboratory practice (GLP) and good manufacture practice (GMP). It ensures good science, consistent application of method and comparability of data. Therefore, it would be helpful to develop validated analytical test methods to measure chemicals of interest in e-cigarettes.

### Aerosol generation

The sample preparation for analysis of smoke/aerosol involves generation of the smoke/aerosol. The factors influencing e-cigarette aerosol generation include human use topography, machine aerosol generation parameters and aerosol generation techniques. Human use topography is important in determining true levels of human exposure to constituents in e-cigarettes. Smoking machine parameters for laboratory studies are important in understanding the way that constituent yields delivered by a tobacco product can change over a range of different smoking conditions. Studies of aerosol generation characteristics reveal that, compared with conventional cigarettes, e-cigarettes require a higher airflow rate and longer puff durations to produce aerosols. Furthermore, pressure drop (mm H<sub>2</sub>O across e-cigarettes during each puff) varies greatly across cartridges in

models across brands and within a brand.<sup>1 4 7 12 20</sup> Hua *et al* determined electronic nicotine delivery systems (ENDS) require longer puff durations with large variation (1.9–8.3 s).<sup>32</sup> Hua's result is consistent with Farsalinos' research, which reported puff durations of 4.2±0.7 s.<sup>33</sup> The results suggest that standard protocols used to test conventional cigarettes are not necessarily applicable to e-cigarettes. Table 10 presents a side-by-side comparison of e-cigarette and conventional cigarette smoking parameters<sup>1</sup> that clearly indicates the remarkable difference between e-cigarettes and conventional cigarettes regarding the vacuum and pump speed applied for aerosol generation in a laboratory-built device. Table 11 summarises the parameters and instrumentation used for aerosol generation in the chemistry studies. The wide range in smoking parameters and instrumentation demonstrate the lack of standardisation in methodologies for aerosol generation used for e-cigarette analyses.

### Performance

The performance of e-cigarettes depends fundamentally on the physical and electronic design of the device. Performance properties include airflow, pressure drop, aerosol density, puff strength (ie, vacuum required to produce aerosol) and number of puffs. Studies of e-cigarette devices have found that aerosol generation performance varies by brand and even by product within a specific brand.<sup>1 4 12</sup> Evidence of this is demonstrated by Trtchounian's 2010 study showing that the total puff number ranges from 30±43 for one brand to 313±115 for another brand.<sup>1</sup> The relatively high SD (±43 and ±115, respectively) from each mean (30 and 313, respectively) indicates large performance variance by product within a specific brand. Furthermore, in 2011, Williams *et al*<sup>12</sup> recorded aerosol density for every other puff during the first 10 puffs of four e-cigarette models. They observed dissimilarity in aerosol density among models and between two samples of one model. Therefore, variations observed in these properties appear to be associated with both e-cigarette design and e-cigarette product qualities, suggesting a need for improved quality control during manufacture.

**Table 10** Machine-smoking parameters used by Trtchounian<sup>1</sup> in a lab-built device

Smoking properties	e-cigarettes	Conventional cigarettes
Pump speed	250±0 to 725±40 rpm	250±0 rpm
Vacuum	25±3 to 153±12 mm H <sub>2</sub> O	30±3 to 80±5 mm H <sub>2</sub> O
Aerosol density	0.1±0.1 to 0.5±0.2	0.2±0.1 to 0.9±0.4

**Table 11** Summary of reported e-cigarette machine (lab device) smoking parameters

Literature	Puff volume (mL)	Puff interval (s)	Puff duration(s)	Puffs/session	Total puffs	Series	Series interval (min)	Smoking machine
Goniewicz <i>et al</i> <sup>4</sup>	70	10	1.8	15	300	20	5	Palaczbot*
Goniewicz <i>et al</i> <sup>20</sup>	70	10	1.8	15	150	10	N.A.	Palaczbot*
Pellegrino <i>et al</i> <sup>6</sup>	498	8	3	16	N.A.	N.A.	N.A.	Aspiration
Ingebretsen <sup>29</sup>	55	30	2 to 4	10	N.A.	N.A.	N.A.	Lab-built device
McAuley <i>et al</i> <sup>11</sup>	50	30	4	50	N.A.	N.A.	N.A.	SCSM†
Trehy <i>et al</i> <sup>7</sup>	100	60	2	30	N.A.	N.A.	N.A.	Lab-built device
Williams and Talbot <sup>12</sup>	N.A.	60	2.2	10/11	N.A.	N.A.	N.A.	Lab-built device
Cobb <i>et al</i> <sup>8</sup>	35	60	2	≥50	N.A.	N.A.	N.A.	Machine ISO
Trtchounian <i>et al</i> <sup>1</sup>	N.A.	60	2.2	10	30 to 313	3	15	Lab-built Puff box
Uchiyama <i>et al</i> <sup>24</sup>	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	Plemium Smoker‡
Westenberger <sup>9</sup>	100	60	N.A.	N.A.	N.A.	N.A.	N.A.	Lab-built device
Laugesen <sup>22</sup>	38, 58	N.A.	N.A.	N.A.	N.A.	N.A.	N.A.	Syringe

\*Palaczbot, Technical University of Lodz, Poland, <http://mechaniczny.p.lodz.pl/strona%20kola/palaczbot.html>

†Single Cigarette Smoking Machine: CH Technology, Westwood, NJ.

‡Plemium smoker: EPI International Co., Ltd., Tokyo, Japan.

N.A., not available.

### Aerosol particle size distribution

Pellegrino *et al* measured the ultrafine particulate matter (PM) fraction yield of e-cigarettes. Data showed that the PM emission values were lower in e-cigarettes compared with the conventional cigarette (eg, PM<sub>1</sub>=14 vs 80 µg/m<sup>3</sup> and PM<sub>10</sub>=52 vs 922 µg/m<sup>3</sup>; PM<sub>1</sub> and PM<sub>10</sub> are particulate matter emission with particle size lower than 1 or 10 µm).<sup>6</sup> Ingebretsen *et al* discovered that aerosol dilution, which is necessary for detection of aerosol particle size when using an electrical mobility analyser, results in average particle diameters in the 50 nm range, compared with the 250–450 nm range determined by spectral transmission measurement, due partially to aerosol particle evaporation at the dilution levels. The authors suggested measuring e-cigarette aerosols in an undiluted state by using the spectral transmission method.<sup>29</sup> A recent in vitro study by Zhang *et al* demonstrated that under the conditions of a single puff experiment, during which the aerosol does not reach steady state, an e-cigarette generates an aerosol having particle sizes in the range 100–600 nm, which is similar to that of conventional cigarettes.<sup>31</sup> The authors noted that the single puff experiment generates much smaller particles than would be expected if the aerosol approached steady state; they also suggested that future studies could assay aerosols generated by human users. In another recent study by Schripp *et al*, the investigators concluded that the inhaled “aerosol size distribution alters in the human lung and leads to an exhalation of smaller particles. The effect is caused by the evaporation of the liquid particles in the lung and also in the environment after exhalation.”<sup>27</sup> Varying results in particle size distributions of PM emissions from e-cigarettes across studies indicate that standardised and valid determination methods are necessary in order to evaluate the real exposure to users and the mechanisms (such as the evaporation of solvents and the agglomeration and deposition of particles) underlying such exposure.

### CONCLUSION

As of September 2013, 29 published non-clinical studies evaluated the chemistry of e-cigarettes. Various chemical substances and ultrafine particles known to be toxic, carcinogenic and/or to

cause respiratory and heart distress have been identified in e-cigarette aerosols, cartridges, refill liquids and environmental emissions. In addition to the uniqueness of the liquid compositions in each brand, inconsistency of both the device performance properties and the data collection methodologies used by researchers contribute to the observed variation in constituent levels and to the range of particle size distributions among products. Moreover, few of these methods are well validated. In addition, e-cigarette use behaviours have only been taken into account for aerosol generation in two publications. Therefore, additional studies based on scientifically validated aerosol generation methods, aerosol physical property measurement methods and chemical analysis methods would be helpful in generating reliable estimates of chemical quantities and, thus, the toxic potential of e-cigarettes.

### CRITICAL INFORMATION GAPS

Overall, existing studies provide certain insights about e-cigarettes, but study limitations exist and critical information gaps remain. Limitations include a clear lack of uniformity in methods used to produce aerosols and to analyse target constituents in e-cigarettes. Furthermore, half of the studies identified (the most recent ones) evaluated e-cigarettes sold in foreign markets (eg, Poland, Korea, Italy, New Zealand, Japan), indicating a strong need for evaluation of products currently on the US market. Limited attention has been focused on e-cigarette device designs, design evolution (both manufacturer and user-initiated) and the corresponding alteration of chemical substance release patterns. Finally, the effects of carrier solvents and additives, including flavour ingredients, on aerosol generation, aerosol physical properties and the chemical profile of e-cigarette emissions have not been reported.

### OTHER RECOMMENDED RESEARCH ACTIVITIES

Subsequent studies of e-cigarettes should be developed to evaluate human use factors, levels of human external and internal exposure, and health effects. Data collected from these studies will inform the science base needed to effectively evaluate and regulate e-cigarettes.

## What this paper adds

- ▶ This is a systematic and comprehensive review of published studies related to the chemistry of e-cigarettes.
- ▶ e-cigarette brands and models differ in nicotine yield efficacy and consistency, and nicotine delivery is not uniform between puffs, brands or within a brand; furthermore, actual nicotine levels may not match labelled amounts.
- ▶ Wide ranges in the levels of chemical substances such as tobacco-specific nitrosamines, aldehydes, metals, volatile organic compounds, phenolic compounds, polycyclic aromatic hydrocarbons, flavours, solvent carriers, tobacco alkaloids and drugs have been reported in e-cigarette refill solutions, cartridges, aerosols and environmental emissions.
- ▶ Ultrafine particulate matter with different particle size distribution ranges has been reported in e-cigarette aerosols and environmental emissions.
- ▶ Standards of e-cigarette aerosol generation and validation of chemical testing would be helpful in generating reliable estimates of chemical quantities and, therefore, the toxic potential of e-cigarettes.

**Acknowledgements** The author would like to thank Dr Matthew Holman, Dr Michael Koenig and Dr Thomas Eads for the discussions and reviews during the research process, and Mr. Paul Aguilar, Ms. Deborah Neveleff, Dr Elizabeth Durmowicz, Dr Carolyn Dresler, Dr Cathy Backinger, Dr Candice Jongsma and Dr Corinne Husten for their support in the preparation of this article.

**Contributors** TC conducted the literature search, reviewed abstracts and composed this paper. She is the guarantor.

**Competing interests** None.

**Patient consent** No.

**Provenance and peer review** Not commissioned; externally peer reviewed.

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*Tob Control* 2014 23: ii11-ii17

doi: 10.1136/tobaccocontrol-2013-051482

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