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Electronic cigarettes in the USA: a summary of available toxicology data and suggestions for the future

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ABSTRACT

Objective To review the available evidence evaluating the toxicological profiles of electronic cigarettes (e-cigarettes) in order to understand the potential impact of e-cigarettes on individual users and the public health.

Methods Systematic literature searches were conducted between October 2012 and October 2013 using five electronic databases. Search terms such as 'e-cigarettes' and 'electronic delivery devices' were used to identify the toxicology information for e-cigarettes.

Results As of October 2013, the scientific literature contains very limited information regarding the toxicity of e-cigarettes commercially available in the USA. While some preliminary toxicology data suggests that e-cigarette users are exposed to lower levels of toxicants relative to cigarette smokers, the data available is extremely limited at this time. At present, there is insufficient toxicological data available to perform thorough risk assessment analyses for e-cigarettes; few toxicology studies evaluating e-cigarettes have been conducted to date, and standard toxicological testing paradigms have not been developed for comparing disparate types of tobacco products such as e-cigarettes and traditional cigarettes.

Conclusions Overall, the limited toxicology data on e-cigarettes in the public domain is insufficient to allow a thorough toxicological evaluation of this new type of tobacco product. In the future, the acquisition of scientific datasets that are derived from scientifically robust standard testing paradigms, include comprehensive chemical characterisation of the aerosol, provide information on users' toxicant exposure levels, and from studies replicated by independent researchers will improve the scientific community's ability to perform robust toxicological evaluations of e-cigarettes.

INTRODUCTION

The impact of e-cigarettes on public health in the USA is not clear. Assessing the potential harm associated with e-cigarette use requires detailed analyses of various aspects of these products, including their toxicological profiles. This review summarises the current publicly available toxicology information for e-cigarettes in order to improve our understanding of the potential toxicological liabilities associated with this class of tobacco products.

The toxicity profile of e-cigarettes will depend upon the product's design and contents. E-cigarettes include two parts. A cartridge that looks like a conventional cigarette filter containing an atomisation chamber and a liquid (called 'e-liquid'), which typically contains nicotine, glycerin, propylene glycol, flavours and water. The

second part of an e-cigarette looks like the white part of a cigarette and contains the electronics, including the controller, battery assembly, and light-emitting diode (LED) light. The e-liquid is atomised into an aerosol, which is inhaled by the consumer ad libitum. E-cigarette users are exposed to nicotine (when the e-liquid contains nicotine) and other compounds and toxicants through the respiratory tract, similar to conventional cigarette smokers. However, it is also possible that some of the nicotine may be absorbed in the mouth via buccal absorption in addition to the respiratory tract. The absorption, metabolism, distribution and excretion of nicotine, compounds and toxicants will be similar for e-cigarettes and cigarettes, as both types of products involve a respiratory administration route. E-cigarettes and cigarettes may share similar toxicokinetic properties for compounds/toxicants inhaled by the tobacco product consumer. Unfortunately, the empirical data to confirm this assumption is not available in the public domain at this time. A major difference between e-cigarettes and conventional cigarettes is that e-cigarette users are exposed to toxicants via inhalation of a heated aerosol while conventional cigarette smokers' exposure to toxicants is from the inhalation of the smoke produced by burning the tobacco.

A number of obstacles to e-cigarette toxicology analyses exist. One challenge is that topography data for e-cigarette use is extremely limited. It is probable that the toxicant exposure will be dependent on the individual use pattern, most notably an individual's titration to his or her desired nicotine level. However, the lack of topography data prevents an accurate determination of the quantities of compounds and toxicants to which the average user may be exposed, as well as the duration of exposure. Exposure data is needed to inform an accurate toxicological evaluation of this class of products; nevertheless, it is still possible to calculate worst-case exposure levels and make comparisons with other tobacco products, such as smokeless tobacco and cigarettes, once the appropriate scientific information becomes available to conduct these analyses.

A second challenge is that researchers, manufacturers and other stakeholders have not yet developed standardised research protocols for comparing toxicant levels in e-cigarette aerosol with toxicant levels in cigarette smoke. One question is whether the comparison should be made based on equivalent nicotine levels delivered to the consumer (compound level per nicotine level), or whether standard ISO¹ or Health



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Canada² methods of reporting toxicants should be used. Currently, there are no standardised methodologies for generating e-cigarette aerosol for compound/toxicant testing as there are for cigarettes. Additionally, chemical characterisations of e-cigarette aerosols have been limited. Until further data is collected, it is not known which chemicals and toxicants should be monitored and what magnitude of toxicant change will significantly impact public health.

A third challenge is that the e-cigarette device design is a major factor in the production of different types and levels of compounds and toxicants in the aerosol; given the wide variety of e-cigarette devices commercially available, toxicant profiles will also vary considerably. The toxicant fingerprint and levels will vary depending on the type of device and e-liquid formulation used by the consumer. For example, levels and types of metals in the aerosol may vary depending on the material used to construct the heating elements. From a nicotine formulation perspective, the use of US Pharmacopeia (USP)-grade nicotine in the e-liquid will have limited levels of impurities and may have a toxicity profile similar to nicotine replacement products, while non-pharmaceutical-grade nicotine may have higher levels of toxicants such as tobacco-specific nitrosamines (TSNA). Standards for ingredients, such as flavours and other additives in e-liquid production and the implementation of good manufacturing processes have the potential to improve this class of consumer products. As a result of the diversity of e-cigarette device designs, it may be difficult to extrapolate toxicity findings between different commercially available e-cigarette brands until researchers have a better understanding of the key design features that modulate toxicant production in the aerosol.

METHODS

Systematic literature searches were conducted in March 2012 and October 2013 to identify research related to e-cigarettes and toxicology. 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' OR 'toxicity' OR 'toxicology'. The search date range was unrestricted.

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 toxicity issues. Articles that did not identify the source of the test material (ie, the commercial brand of the e-cigarette or e-liquid used to generate study data) were excluded from this review since these studies cannot be replicated by other researchers due to the lack of test article identifiers.

The search yielded a total of 364 articles that met the inclusion criteria. Article titles and abstracts (when titles provided insufficient detail) were then screened for relevance. This yielded 20 articles for full-text review, which included a manual search of the reference lists of selected articles to identify additional relevant publications. Three additional documents not published in a peer-reviewed journal were considered relevant and were included in this review. Articles and publicly available information selected for inclusion were published or present in the public domain between 2008 and 2013.

RESULTS

Toxicant levels in tobacco products

One of the most thorough evaluations of the possible risks associated with e-cigarette use was conducted by the consulting firm Health New Zealand, which evaluated Ruyan e-cigarettes.³ Study limitations were as follows: (1) the evaluation was conducted on only one product, which limits the generalisability of findings, and (2) the study was funded by the e-cigarette manufacturer (Ruyan Holdings, Hong Kong). The evaluation report, produced in 2008, was designed to assist regulators in assessing the safety of Ruyan e-cigarettes; the report provided a safety evaluation of both the aerosol and the e-liquid.

The consulting firm evaluated the TSNA levels in a Ruyan e-cigarette with a 16 mg cartridge dated November 2007 (see table 1).³ The TSNA levels for the nicotine replacement products, smokeless tobacco and cigarettes are displayed in table 1 and were from the article by Stepanov *et al.*⁴ The total TSNA level in the cartridge was 8.18 ng/g, which was approximately four times higher than the levels contained in the Nicorette gum (4 mg/piece), almost identical to the levels in the NicoDerm CQ patch (4 mg/patch), 22 times lower than Ariva hard snuff, 246 times lower than the level in Swedish Snus (2010 ng/g), and 765 times lower than a Marlboro cigarette (see table 1). The TSNA levels in the other tobacco products studied ranged from 184 ng/g to 9290 ng/g. It should be noted that the product comparisons were not provided on a nicotine-equivalent basis: most nitrosamine levels were measured as ng/g of product, except for the gum (ng/piece) and patch (ng/patch). The researchers indicated that one puff of e-cigarette aerosol contains one-third to one-half the nicotine in a tobacco cigarette puff.³ The most effective method for cross-product comparisons for tobacco products is currently unclear.

The researchers also tested the levels of heavy metal concentrations (arsenic, cadmium, chromium, nickel and lead) from 300 puffs (one cartridge) of the e-cigarette using inductively coupled plasma mass spectrometry. Heavy metal levels were below the limits of detection (<1 part per million (ppm)). The authors also tested the e-cigarette liquid for a panel of polycyclic aromatic hydrocarbons (PAH); low levels of four compounds (anthracene, phenanthrene, 1-methyl phenanthrene and pyrene) were detected. Finally, the researchers evaluated toxicological data on propylene glycol, which comprises 89–90% of the e-liquid; based on this evaluation, which included data from rat, monkey and human studies, the researchers concluded that propylene glycol is non-toxic. Safety evaluations from multiple government agencies support the concept that propylene glycol presents a very low risk to human health.^{3–5} However, there was only one chronic inhalation study in monkeys available for review and the study was published in 1947; furthermore, the monkeys had an underlying parasitic nematode infection present at study initiation. Testing propylene glycol in chronic inhalation studies using rodent and non-rodent species is needed to improve the current understanding of the toxicological liabilities associated with long-term inhalation of propylene glycol.

Overall, the report provides evidence that the TSNA levels for this e-cigarette are slightly greater than levels in the two nicotine replacement products, but considerably lower relative to smokeless tobacco and cigarettes as measured by Stepanov *et al.*⁴

Aerosol toxicants

One study on aerosol toxicants was included in this review. While there are several published studies on this topic, some did

Table 1 Comparison of tobacco-specific nitrosamine levels from nicotine replacement products and tobacco products (ng/g of product wet weight), except for nicotine gum (ng/piece), nicotine patch (ng/patch), e-Cigarette (ng per 16 mg cartridge)

Product Type	Product Brand	NNN	NNK	NAT	NAB	Total
Nicotine replacement product	Nicorette gum (4 mg) ⁴	2.00	ND	ND	ND	2.00
	NicoDerm CQ patch (4 mg) ⁴	ND	8.00	ND	ND	8.00
E-cigarette	Ruyan (16 mg cartridge) ³	3.87	1.46	2.16	0.69	8.18
Smokeless tobacco	Ariva hard snuff ⁴	19	37	120	8	184
	Stonewall hard snuff ⁴	56	43	170	7	276
	Revel packets (wintergreen) ⁴	640	32	310	17	999
	Swedish snus ⁴	980	180	790	60	2010
	Kodiak (wintergreen) ⁴	2200	410	1800	150	4560
	Copenhagen snuff ⁴	2200	750	1800	120	4870
	Skoal (long cut straight) ⁴	4500	470	4100	220	9290
Cigarette	Quest 1 low-nicotine cigarette ⁴	930	170	310	13	1423
	Winston cigarette (full) ⁴	2200	580	560	25	3365
	Newport cigarette (full) ⁴	1100	830	1900	55	3885
	Marlboro cigarette (ultra light) ⁴	2900	750	1100	58	4808
	Marlboro cigarette (ultra light) ⁴	2800	770	1200	55	4825
	Camel cigarette (ultra light) ⁴	2500	900	1700	91	5191
	Camel cigarette (full) ⁴	2900	960	2300	100	6260
	Marlboro cigarette (full) ⁴					

NAB: N'-nitrosoanabasine; NAT: N'-nitrosoanatabine; NNK: N'-nitrosornicotine; NNN: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone. ND, not detected.

not identify e-cigarette brands or evaluated e-cigarettes that are not commercially available; these studies were excluded from this review.

The study evaluated the contents of the aerosols produced by 12 brands of e-cigarettes, smoke from a conventional tobacco cigarette, and a nicotine inhaler (nicotine replacement product; Nicorette Inhalator) in controlled conditions using a smoking machine.⁶ Investigators measured four groups of potentially toxic and carcinogenic compounds: carbonyls, volatile organic compounds (VOC), TSNA and heavy metals. Eleven of the e-cigarette brands were the most popular brands distributed in Poland, and the twelfth brand was distributed in the UK. The investigators reported that toxicant levels were 9–450 times lower in e-cigarette aerosol than in conventional mainstream cigarette smoke.⁶ The Nicorette Inhalator contained trace amounts of carbonyl compounds and metals. For the VOCs and TSNA measured, the compounds were not detected in the Nicorette Inhalator in this study.⁶

E-cigarette aerosol extract: cell-based assay data

Three studies investigated the cytotoxicity of e-cigarette aerosol. In one study, investigators tested four different e-cigarette liquids in human embryonic stem cells, human pulmonary fibroblasts and mouse neural stem cells using the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay (which measures the mitochondrial function of cells) as the end-point for cell viability.⁷ The authors tested different concentrations of e-liquids from different manufacturers in the three cell systems. The researchers observed differences in sensitivity to the e-liquids based on the cell type used in the experiment. Additionally, the authors concluded that the cytotoxicity was not due to nicotine. Cytotoxicity was correlated with types and quantities of flavours in the e-liquid. For example, the authors indicated that Cinnamon Ceylon (#22) had high cytotoxicity while Bubblegum (#18) was non-cytotoxic at the highest dose tested in the three cell types used in the study.⁷ The humectants vegetable glycerin and propylene glycol were both determined to be non-cytotoxic at the highest doses tested in the study.⁷

Two additional studies compared the cytotoxicity of e-cigarette aerosol and cigarette smoke extract. Both studies concluded that e-cigarette aerosol is significantly less cytotoxic than cigarette smoke extract in a variety of cell types.^{8,9} These results provide data supporting that e-cigarette aerosol extracts are significantly less cytotoxic than cigarette smoke extracts based on testing in cells.

Nicotine, TSNA and diethylene glycol

The US Food and Drug Administration (FDA) performed an evaluation of 18 e-cigarettes; analyses were conducted on Njoy e-cigarettes with different cartridges, Smoking Everywhere Electronic Cigarettes with different cartridges, and a Nicotrol Inhaler as a control.¹⁰ The goal of the study was to quantify the amount of nicotine and TSNA levels and identify the presence of ethylene glycol and diethylene glycol (DEG) in each brand evaluated. The authors concluded that nicotine was present in both products but TSNA levels were very low. DEG was detected in only one of the 18 e-cigarette cartridges (Smoking Everywhere 555 High); however, the quantities of DEG were not provided, which limits the ability to evaluate its toxicity potential. It is worth noting that the US Code of Federal Regulations allows up to 0.2% of DEG in polyethylene glycol when polyethylene glycol is used as a food additive (see 21CFR172.820)¹¹; however, this applies to oral exposure and not exposure via inhalation.

Overall, the report provides more evidence that TSNA levels are very low in e-cigarette cartridges tested in the study: in many cases N-nitrosanabasine (NAB), N-nitrosoanatabine (NAT), N-nitrosornicotine (NNK), and 4-methylnitrosamino-1-(3-pyridyl)-1-butanone (NNN) were not detected. While measuring TSNA in cigarettes and e-cigarettes is a good start for characterising differences between the two products, scientific consensus on the most appropriate compounds/toxicants/biomarkers to measure has not been reached. Potential biomarkers include harmful and potentially harmful constituents (HPHC)¹² and other tobacco-specific biomarkers of exposure/toxicity, such as a full panel of PAHs, VOCs, carbonyl

compounds and other types of compounds unique to e-cigarettes or present in both e-cigarette aerosol and cigarette smoke.

Risk assessment

A technical report by a Drexel University researcher presented results from a systematic review of peer-reviewed and 'grey' literature in an attempt to summarise all the available chemistry data on e-cigarette aerosols and e-liquids.¹³ The compilation of the chemistry information was used to determine potential user exposure to a number of toxicants, as well as whether these exposure levels were above the threshold limit values used to minimise workplace exposure. Based on the currently available information on e-cigarette aerosol compounds and toxicants and potential exposure levels, the author concluded that the levels of exposure to toxicants in the aerosol would not pose health concerns. However, the author did concede that the quality of the data assessed was poor, and that improving data quality would improve risk assessment. The funding for the work was provided by the Consumer Advocates for Smoke-free Alternatives Association (CASAA) research fund.

CONCLUSIONS

An evaluation of the literature reveals that peer-reviewed toxicology information on top-selling, commercially available e-cigarette brands is very limited. Currently, standardised testing paradigms for the e-liquid and e-cigarette aerosols have not been determined. The development of a scientific consensus on the most appropriate testing paradigms to be used for comparative analyses of e-cigarette products is critical. Additionally, the development of scientifically vetted standardised testing paradigms for comparing e-cigarettes with other types of tobacco products, such as conventional cigarettes, is necessary for robust scientific evaluation of the similarities and differences among the disparate types of tobacco products available today.

Scientifically robust methods for comparing e-cigarettes relative to traditional cigarettes need to be identified and implemented in future scientific studies. Very few studies have involved complete analytical chemistry analyses of the compounds in e-cigarette aerosols and compared this list to compounds in cigarette smoke. A thorough comparison of the chemical constituent levels found in different e-cigarettes would be very informative and improve future toxicological evaluations. Understanding e-cigarette toxicity profiles would allow scientists and regulators to confirm the toxicological liabilities associated with e-cigarettes.

E-cigarette toxicity profiles may fluctuate due to design features in the delivery device, type and source of ingredients used in the product, and the manufacturing and quality control measures employed by the manufacturer. Since the toxicity profile is dependent on e-cigarette design, it is necessary to identify the key design features that affect the production and levels of aerosol toxicants. Additionally, an understanding of toxicant exposure variability depending on use or non-use of good manufacturing practices needs to be determined. Studies on lot-to-lot e-cigarette variability should be conducted. Furthermore, e-cigarette ingredients play a significant role in that product's toxicity profile; studies are needed to evaluate how much the toxicity profile will vary between products that utilise USP-grade ingredients (including nicotine) versus those that do not, and whether the toxicity profile varies considerably between tobacco products that have a long and complex ingredient list versus products with a limited number of ingredients.

Additional parameters that affect the toxicity profile of e-cigarettes may also be identified through research.

Overall, limited toxicology data on e-cigarettes in the public domain is insufficient to allow a thorough toxicological evaluation of this new type of tobacco product. In the future, the acquisition of scientific datasets that are derived from scientifically robust standard testing paradigms, include comprehensive chemical characterisation of the aerosol, provide information on users' toxicant exposure levels, and are from scientifically robust standard testing paradigms with comprehensive chemical characterisation of the aerosol, a clear understanding of the individual's toxicant exposure levels, and the acquisition of datasets that are from studies replicated by independent researchers, will improve the scientific community's ability to perform robust toxicological evaluations of e-cigarettes.

Appropriate scientific datasets, and thorough toxicology evaluations, are required to inform an adequate understanding of the absolute and relative harm associated with e-cigarettes. Below are some questions that could clarify the potential toxicological liabilities associated with e-cigarettes:

- ▶ What e-cigarette design features alter the production of and user exposure to different compounds and toxicants?
- ▶ Are e-cigarette users exposed to higher or lower levels of toxicants than conventional cigarette smokers?
- ▶ Are e-cigarette users exposed to higher or lower levels of toxicants than smokeless tobacco product users?
- ▶ Are e-cigarette users exposed to higher or lower levels of toxicants than users of nicotine replacement products, which are considered to be the safest nicotine delivery device (eg, containing the least quantity of toxicants) on the US market today?
- ▶ What panel of exposure biomarkers should be used to determine e-cigarettes toxicant exposure, disease risk, morbidity and mortality?
- ▶ What panel of exposure biomarkers should be used to compare different classes of tobacco products between tobacco product users and also non-users?

What this paper adds

- ▶ This review highlights the lack of publicly available high-quality scientific data on e-cigarettes marketed in the USA.
- ▶ Very few commercially marketed e-cigarettes have undergone a thorough toxicology evaluation.
- ▶ Currently, standardised testing paradigms for evaluating the e-cigarette toxicity across brands and in comparison to other tobacco products do not exist.
- ▶ There is no scientific consensus on the appropriate datasets (eg, chemical lists, toxicants and biomarkers of exposure) and testing paradigms (eg, e-cigarette aerosol production) for use in comparing e-cigarettes with cigarettes, other tobacco products, or nicotine replacement products.
- ▶ E-cigarettes and e-liquid toxicity profiles may vary considerably within the USA commercial market and worldwide due to the potential diversity of delivery device construction and materials, type and source of ingredients in the e-liquid, and the use/non-use of good manufacturing practices and quality control measures.

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