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Electronic cigarettes: human health effects

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ABSTRACT

Objective With the rapid increase in use of electronic nicotine delivery systems (ENDS), such as electronic cigarettes (e-cigarettes), users and non-users are exposed to the aerosol and product constituents. This is a review of published data on the human health effects of exposure to e-cigarettes and their components.

Methods Literature searches were conducted through September 2013 using multiple electronic databases.

Results Forty-four articles are included in this analysis.

E-cigarette aerosols may contain propylene glycol, glycerol, flavourings, other chemicals and, usually, nicotine. Aerosolised propylene glycol and glycerol produce mouth and throat irritation and dry cough. No data on the effects of flavouring inhalation were identified. Data on short-term health effects are limited and there are no adequate data on long-term effects. Aerosol exposure may be associated with respiratory function impairment, and serum cotinine levels are similar to those in traditional cigarette smokers. The high nicotine concentrations of some products increase exposure risks for non-users, particularly children. The dangers of secondhand and thirdhand aerosol exposure have not been thoroughly evaluated.

Conclusions Scientific evidence regarding the human health effects of e-cigarettes is limited. While e-cigarette aerosol may contain fewer toxicants than cigarette smoke, studies evaluating whether e-cigarettes are less harmful than cigarettes are inconclusive. Some evidence suggests that e-cigarette use may facilitate smoking cessation, but definitive data are lacking. No e-cigarette has been approved by FDA as a cessation aid. Environmental concerns and issues regarding non-user exposure exist. The health impact of e-cigarettes, for users and the public, cannot be determined with currently available data.

INTRODUCTION

Electronic cigarettes (e-cigarettes) are rapidly increasing in popularity in the USA. E-cigarettes purportedly do not involve tobacco combustion; rather, nicotine and the other components are aerosolised prior to inhalation. While the lack of combustion likely reduces toxicant exposure for e-cigarette users as compared to traditional cigarettes, users and others may experience secondhand or thirdhand exposures through direct physical contact with product components, or inhaling secondhand aerosol. Most of the available published data related to health effects do not include an evaluation of the effects on the population as a whole. This is a review of published data on the health effects associated with exposure to e-cigarettes with a focus on individual harm. Product addiction was not considered in this review of health effects.

METHODS

Systematic literature searches were conducted through September 2013 to identify research related to e-cigarettes and health effects. 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 '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 'toxicity' OR 'health effects' OR 'adverse effects' OR 'smoking cessation' OR 'smoking reduction' OR 'safety.'

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 health effects related to exposure to, or use of, electronic nicotine delivery systems (ENDS) or e-cigarettes. A total of 359 articles met the inclusion criteria. Article titles and abstracts (when titles provided insufficient detail) were then screened for potential relevance. This yielded 105 articles for full-text review, which included a manual search of the reference lists of selected articles to identify additional relevant publications.

Following the full-text review, 44 articles were deemed relevant for this analysis; articles selected for inclusion were published between 2009 and 2013. The validity and strength of each study were determined based on a qualitative assessment of study objectives and population, risk of bias, experience of subjects with e-cigarettes, and experimental details. Meaningful study limitations are noted in the analysis.

Although the vast majority of documents reviewed were found in the peer-reviewed literature, additional documents considered included one poster, results of a publicly available FDA analysis, and two theatre industry reports.¹

RESULTS**Health effects related to specific components of electronic cigarettes**

Eighteen reviewed publications evaluated the health effects related to specific e-cigarette components. Aerosolisation of e-cigarette liquid (most commonly composed of water, propylene glycol (PG), glycerin, nicotine and flavourings) produces the 'smoke' that users, and potentially non-users, inhale.¹ Factors which may contribute to inhalation effects of

¹The theater industry uses glycol and glycerin (common ingredient in e-cigarettes) to create artificial smoke.[END]



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e-cigarettes include climate conditions, air flow, room size, number of users in the vicinity, type(s) and age of systems being used, battery voltage, puff length, interval between puffs, and user characteristics (eg, age, gender, experience, health status). Additionally, particle size affects the site and effects of pulmonary absorption; details of e-cigarette aerosol particle size and absorption are unknown and likely vary depending on the product.²

Glycol and glycerol vapour are components of most e-cigarettes. Used in the theatre industry and for aviation emergency training, these are known upper airway irritants.³ Contact with glycol mist may also dry out mucous membranes and eyes.⁴ Glycerin is used therapeutically to increase the efficacy of inhalants; it has hygroscopic properties that draw water into bronchial secretions and reduces their viscosity. Glycerin and PG did not cause cytotoxic effects when human embryonic stem cells, mouse neural stem cells, and human pulmonary fibroblasts were exposed to several e-cigarette refill solutions.⁵ The repeated and potentially long-term inhalation of glycerol vapour associated with e-cigarette use, however, differs from exposure levels in the entertainment industry; currently available data are not sufficient to determine long-term safety.

Nicotine is readily absorbed through the airway, skin, mucous membranes and gastrointestinal tract. Acute exposure to inhaled nicotine may cause dizziness, nausea, or vomiting. Toxic reactions associated with dermal nicotine exposure have been described after spills of nicotine-containing liquids or occupational contact with tobacco leaves. Serious cases of nicotine poisoning due to cigarettes are relatively rare; spontaneous vomiting usually limits the absorption of swallowed tobacco.⁶ E-cigarettes, however, may pose increased risk of nicotine toxicity due to the availability of high nicotine concentrations in the cartridges.⁷ There are reports of completed and attempted suicide by intravenous injection and oral ingestion of liquid nicotine intended for e-cigarette cartridges.^{8–10} The level of nicotine exposure from use of electronic cigarettes is highly variable. Studies have found wide ranges in nicotine levels, variability in aerosolisation, inaccurate product labelling, and inconsistent nicotine delivery during product use. In one study, e-cigarette liquids were obtained in retail stores and via the Internet. Liquids tested contained between 14.8 and 87.2 mg/mL of nicotine and the measured concentration differed from the declared concentration by up to 50%.^{11–14} FDA's Division of Pharmaceutical Analysis conducted repeat testing of three different cartridges with the same label and found nicotine levels varying from 26.8 to 43.2 µg nicotine/100 mL puff.¹⁵ In the absence of quality standards, e-cigarette product consistency is a significant concern. Product labelling is also inconsistent and potentially misleading.

To date, evaluations of other e-cigarette components have not found serious health effects, but findings must be interpreted with caution due to limited data and lack of standardised testing methods. Analyses of flavourings used in e-cigarettes have shown brand-to-brand variability. Laugesen tested the Ruyan V8 e-cigarette for over 50 cigarette smoke toxicants with negative results.¹⁶ Other evaluations have found low levels of tobacco-specific nitrosamines (TSNA) and diethylene glycol, though, in most cases, the levels were minimal and similar to levels in a nicotine patch.¹⁷ Pellegrino *et al* evaluated particulate matter (PM) emissions from e-cigarettes and conventional cigarettes. PM emissions from e-cigarettes slightly exceeded WHO air quality guidelines, but were 15 times lower than emissions after use of traditional cigarettes.¹⁸ These data showing lower emissions from e-cigarettes could indicate less danger for secondhand and thirdhand exposure, but without a standardised testing method the studies are not conclusive.

Physiological effects observed in clinical studies

Nine studies evaluated the physiological effects of e-cigarette use. E-cigarettes are frequently marketed as 'safe' products. However, while the inhaled compounds associated with e-cigarettes may be fewer and less toxic than those from traditional cigarettes, data to establish whether e-cigarette use as a whole is less harmful to the individual user than traditional cigarettes are not conclusive. Studies reviewed noted the following observed physiologic effects associated with acute exposure to e-cigarettes or e-cigarette aerosols:

- ▶ mouth and throat irritation and dry cough at initial use, though complaints decreased with continuing use^{1 19}
- ▶ no change in heart rate, carbon monoxide (CO) level, or plasma nicotine level²⁰
- ▶ decrease in fractional exhaled nitric oxide (FeNO) and increase in respiratory impedance and respiratory flow resistance similar to cigarette use²¹
- ▶ no change in complete blood count (CBC) indices²²
- ▶ no change in lung function^{23 24}
- ▶ no change in cardiac function as measured with echocardiogram²⁵
- ▶ no increase in inflammatory markers²⁶

A summary of additional details and results of seven of the reviewed studies are presented in table 1.

Exposure risks for non-users

Five studies addressed exposure risks for non-users. E-cigarette refill cartridges may contain toxic amounts of nicotine. Nicotine from the aerosol or the liquid can remain on surfaces for weeks to months, and may react with ambient nitrous acid to produce TSNAs, leading to inhalation, ingestion, or dermal exposure to carcinogens.^{27 31} The primary indoor sources of ambient nitrous acid are gas appliances. Children are at risk of toxicity from refill cartridges; the flavourings may increase appeal while the total nicotine content is potentially life-threatening. The cytotoxic effects of refill solution components may be more pronounced on embryonic cells.⁵ Aerosol from e-cigarettes is only released during exhalation and content will vary depending on the users' technique or other conditions, such as temperature.²⁸ An evaluation of e-cigarette aerosol showed traces of TSNAs, but the levels were 9–450 times lower than in cigarette smoke, and generally comparable with amounts found in a prescription nicotine inhaler.^{29 30} However, these data may not reflect real-world use of e-cigarettes, where the human user is an intermediary between the aerosol and the environment. Persistent residual nicotine on indoor surfaces can lead to thirdhand exposure through the skin, inhalation and ingestion long after the aerosol has cleared the room.³¹

Potential for reduced harm or cigarette smoking cessation

Twelve studies and surveys evaluated the patterns of e-cigarette use including the reasons for initiating or continuing use and the potential for e-cigarettes to facilitate smoking cessation.

Marketing information frequently includes a stated or implied claim that using e-cigarettes will help smokers quit or reduce cigarette use. Supporting data, however, are quite limited. Several small studies have demonstrated short-term reduction in cigarette smoking while using e-cigarettes.^{32–34 36} Smokers also report fewer withdrawal symptoms when using e-cigarettes while quitting.^{32 34 35} Many cigarette smokers also report attraction to e-cigarettes due to reduced cost, perceived reduced toxicity, and more freedom of use. Users acknowledge that e-cigarettes may 'not be completely safe' and are 'addictive' but believe they are safer and less addictive than cigarettes.³⁷ Studies attempting to show efficacy of e-cigarettes as a cessation therapy

Table 1 Physiological effects following acute exposure to electronic cigarettes

Reference	Study population	Study groups	Summary of results
Vansickel <i>et al</i> ²⁰	32 smokers e-cig naive; two cigs (10 puffs) each type	Own brand cig 18 mg e-cig 16 mg e-cig Sham cig	Increased heart rate, plasma nicotine & CO No measurable increase in heart rate, plasma nicotine or CO level
Vardavas <i>et al</i> ²¹	30 healthy adult smokers (e-cig status unknown); Used e-cig for 5 minutes	Nicotine-containing e-cig No-cartridge e-cig	Decrease in FeNO; Increase in respiratory impedance and respiratory flow resistance (similar to cigarette use) Control
Flouris <i>et al</i> ^{22 24}	15 smokers # puffs adjusted for smoking history	Active cig Active e-cig Passive e-cig Passive cig	Increase in WBC, lymphocyte, granulocyte counts; cotinine increased; FEV1/FVC decreased CBC indices unchanged; cotinine increased; FEV1/FVC unchanged Increase in WBC, lymphocyte, granulocyte counts; cotinine increased; FEV1/FVC unchanged
Chorti <i>et al</i> ²³	15 cigarette smokers; used one e-cig	Passive smoking Smoke 2 usual brand cigs Active e-cig Passive e-cig	Increased CO and cotinine Decreased FEV1, FEV1/FVC, & FeNO; increased cotinine and CO Lung function unchanged; cotinine increased Reduced FEV1/FVC; increased cotinine
Farsalinos <i>et al</i> ²⁵	22 ex-cigarette e-cig users 20 current cigarette users	Baseline cardiac echo, repeat study after one cig or e-cig	No change in cardiac echo parameters Measurable decrease in LV function
Tzatzarakis, <i>et al</i> ²⁶	10 smokers Brief active e-cig session 10 never-smokers; 1 h exposure	Active cig Active e-cig Passive cig Passive e-cig	Increased interleukins and epidermal growth factor No increase in assessed inflammatory markers Increased tumour necrosis factor alpha No increase in assessed inflammatory markers

CBC, complete blood count; CO, carbon monoxide; e-cig, electronic cigarette; FeNO, fractional exhaled nitric oxide, FEV1, forced expiratory volume in 1 s; FVC, forced vital capacity; LV, left ventricle; WBC, white blood count.

have had mixed results, with generally low sustained cessation rates (self-reported or verified).^{19 36 38–42} Adverse events, when reported, were not serious.^{37 39–42}

A summary of the reviewed surveys and studies is presented in table 2.

CONCLUSIONS

Although e-cigarettes have potential advantages over traditional cigarettes, there are many deficiencies in the available data.¹ Differences in product engineering, components and potential toxicities make it difficult to discuss e-cigarettes as a single device.⁴³ E-cigarettes may be useful in facilitating smoking cessation, but definitive data is lacking. E-cigarettes may provide a less harmful source of nicotine than traditional cigarettes, but evidence of decreased harm with long-term use is not available. It is encouraging that few serious adverse events have been reported related to e-cigarette use during the years the products have been available, but without a specific reporting mechanism, adverse event data may not be comprehensive. There is continued concern about the attractiveness of these products for tobacco-naïve individuals. The novelty of the new technology and the variety of flavouring options may be appealing to younger users.

Significant gaps exist in the health-effects data for e-cigarettes.² Product standards including criteria for ingredients, quality and manufacturing have not been developed. There are limited data on the effects of recurrent long-term exposures to aerosolised nicotine, flavourings and PG. The effects of an aerosol delivery system on the quantity of nicotine consumed by users are unknown. Health effects may be influenced by the 'learning curve' for e-cigarette use; many of the currently published studies were conducted in e-cigarette-naïve subjects, which may influence study results.⁴⁴ Studies have shown large individual differences in nicotine levels in subjects using the same product. Stronger puffing is required for most e-cigarettes, and the puff strength needs to increase as cartridge liquid

volume decreases. The average vacuums for 10 puffs for the tested e-cigarettes ranged from 25 to 153 mm H₂O; all tested brands of e-cigarettes required a vacuum above that needed to smoke conventional cigarettes.⁴⁵ Aerosol density decreases as puff number increases, and the smoking characteristics vary considerably within and between e-cigarette brands, making data comparison and interpretation difficult.⁴⁶

Another significant issue related to health effects is the risk associated with the use and abuse of nicotine refill bottles. Poison control centre reports of unintentional nicotine ingestion, usually by children, are increasing. Of 79 total exposures, 2 were reported in 2009, 6 in 2010, 11 in 2011, 43 in 2012 and 17 in the first 3 months of 2013. Most (80%) of the exposures were unintentional.⁷ Finally, the likelihood that non-tobacco users will begin using e-cigarettes and transition to other nicotine-containing products due to addiction development should be thoroughly evaluated. Future studies assessing the human health effects of e-cigarettes should include the effects of e-cigarettes on tobacco use patterns, quit attempts and quit rates; preferred brands; satisfaction rates; and the effects of secondhand and thirdhand exposures to exhaled aerosol.

E-cigarettes have the potential for significant impact on public health. The regulation of e-cigarettes varies from country to country. Of the 33 countries that responded to a 2011 WHO survey about regulation and availability of e-cigarettes within their country, 13 reported no availability, 16 reported they were available (nine unregulated, seven with some type of regulation), and four were unsure.⁴⁷ Although the sale, use and advertising of e-cigarettes are permitted in the USA, some individual states have imposed restrictions. As noted by Trtchounian and Talbot, the effects of policies, regulations, healthcare costs and any health benefit for users or the general population will be difficult to assess unless e-cigarettes are a regulated product.⁴⁸ At this time, data are not sufficient to confirm a long-term benefit for users or a public health benefit for the population at large.

Table 2 Surveys and studies evaluating cigarette reduction or smoking cessation

Reference	Study design and population	Summary of results	Limitations of study
Etter ³²	Internet survey of 81 ever-users of e-cigs; 37% dual cigarette and e-cig users	Reasons for e-cig use were to quit smoking (53%), health (49%), cost (26%), freedom to use in smoke-free places (21%), and to avoid disturbing others (20%)	Self-selected sample of internet users
Siegel <i>et al</i> ³³	Online survey of all first-time purchasers of particular e-cigs over 2-week period; 222 respondents (response rate 4.5%)	Reported six-month point prevalence of smoking abstinence of 31%; 66.8% reported a reduction in cigarette smoking	Low response rate; only 1 brand; self-reported abstinence rate
Etter and Bullen ³⁴	Self-selected Internet survey of 3587 visitors to e-cigarette websites; 70% former smokers; Of current smokers 60% responded 'trying to quit' and 84% 'trying to reduce'	Reasons for e-cig use were: less perceived toxicity (84%), to quit smoking or avoid relapsing (77%), tobacco craving (79%), withdrawal symptoms (67%), and decreased cost (57%)	Self-selected sample; respondents may have adjusted answers to justify opinions on cessation or safety
Bullen <i>et al</i> ³⁵	40 e-cig-naïve smokers randomized to use nicotine-containing e-cig, nicotine-free e-cig, Nicorette nicotine inhaler, or usual cigarette	Smoking desire and withdrawal symptoms were most effectively alleviated after the usual cigarette but the 16 mg e-cig and the Nicorette inhaler had similar results and both of these were more effective than the placebo e-cig	Small sample size; limited to smokers not intending to quit; subjects e-cig naïve
Popova and Ling ³⁶	Survey of 1836 current or recently (<2 years) former smokers	Of the smokers, 38% had tried an alternative tobacco product, most commonly e-cigarettes. Use of alternative tobacco products was associated with making a quit attempt but not with successful quitting	Internet survey; all results self-reported; unable to link use of specific product(s) with cessation
Goniewicz <i>et al</i> ³⁷	On-line recruiting of Polish e-cig users; 179 of 203 survey completers provided usable data	Self-reported results: 66% had quit smoking; additional 25% reported <5 cigarettes per day (CPD); 82% believed e-cigs 'not completely safe but better than cigarettes'. 60% believed e-cigs addictive but less than cigarettes.	Internet survey; subjects recruited from on-line groups; not a general population; self-reported results
Polosa <i>et al</i> ³⁸	Six-month pilot study of 7.4 mg nicotine e-cigs; 40 subjects not interested in quitting; CC smoking allowed though use of e-cigs encouraged; subjects completed diary	67.5% completed the program. Thirteen of 40 subjects had self-reported 50% reduction in CPD at 24 weeks. Nine subjects (22.5%) self-reported quitting by the end of the study; six of them were still using the e-cigs. eCO measured to verify reduction or abstinence	Small study; no control arm; 32.5% did not come to final follow-up visit; self-reported results; technical difficulty with e-cig (older product)
Polosa <i>et al</i> ¹⁹	24-month prospective observational continuation of above study; e-cigs not provided after first 6 months but subjects could purchase	23 completed all follow-up visits. At 24 months, >50% reduction in CPD was self-reported in 11 of the 40 participants, with a median decrease from 24 to 4 CPD. Smoking abstinence was self-reported in 5 of 40 participants. eCO measured to verify reduction or abstinence. No serious AEs reported; predominant complaints were mouth and throat irritation and dry cough; withdrawal symptoms uncommon	Same as above; 42.5% failed to attend final follow-up visit; assessment of withdrawal symptoms not rigorous; cannot make direct comparison with other cessation products
Caponnetto <i>et al</i> ³⁹	12-month prospective trial; 300 smokers not intending to quit received e-cigs (cartridges contained 7.2 mg, 5.4 mg, or 0 mg nicotine); study product provided for 12 weeks; double-blind, controlled, randomized	75% of the subjects returned at week 12, 70.3% at week 24, and 61% at week 52. No significant changes in heart rate, blood pressure, or weight were found over the study duration. Smokers in all three groups reduced diary (self)-recorded CPD by more than 50%; this was associated with reduction in measured eCO levels and was not related to cartridge nicotine content. The subject-reported abstinence rate at 52 weeks was 8.7%. Of the quitters, 26.9% reported still using e-cigarettes; no significant AEs	Cannot compare with other cessation programs since subjects not intending to quit; self-reported results; 40% did not attend final follow-up visit; technical issues with e-cig (older model product)
Caponnetto <i>et al</i> ⁴⁰	14 smokers with schizophrenia; 52 week follow-up; study product provided for 12 weeks; maximum 4 cartridges/day	Sustained 50% reduction in self-reported CPD (14 to 7). Two of 14 self-reported sustained abstinence at 52 weeks. eCO measured to verify reduction or abstinence. AEs included nausea, throat irritation, headache, and dry cough	Small uncontrolled study; assessment of withdrawal symptoms not rigorous
Bullen <i>et al</i> ⁴¹	657 adult smokers wanting to quit were given nicotine e-cigs, patch, or placebo e-cigs; product was supplied for 13 weeks; subjects were followed for 6 months	Self-reported abstinence rates at 6 months were 7.3% for nicotine e-cig users, 5.8% for patch users, and 4.1% for placebo e-cig users; eCO measured to verify abstinence; no difference in AEs	Study size not optimal for statistical analysis; more dropouts in patch group; low abstinence rates possibly due to inadequate nicotine replacement
Farsalinos <i>et al</i> ⁴²	Personal interviews of 111 former smokers who completely switched to e-cigs for >1 month	81% used e-cig with >15 mg/mL nicotine; few non-serious AEs (cough, throat irritation) Self-reported abstinence verified by blood carboxyhaemoglobin	May not reflect general population; majority male subjects

AE, adverse event; CC, conventional cigarette; eCO, exhaled carbon monoxide; e-cig, electronic cigarette.

What this paper adds

- ▶ This review summarises the available data related to health effects from use or exposure to electronic cigarettes.
- ▶ Studies have revealed variability in e-cigarette products including nicotine content. Evaluations of other e-cigarette components have not identified serious health effects. Impact on smoking cessation is unclear. Overall, the wide variability in products and lack of standardised testing methods makes evaluation of the available data challenging.
- ▶ There are not adequate data to support the safety of long-term use of electronic cigarettes at this time.

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