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Review

A systematic review of health effects of electronic cigarettes

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ABSTRACT

Objective: To provide a systematic review of the existing literature on health consequences of vaporing of electronic cigarettes (ECs).

Methods: Search in: PubMed, EMBASE and CINAHL. Inclusion criteria: Original publications describing a health-related topic, published before 14 August 2014. PRISMA recommendations were followed. We identified 1101 studies; 271 relevant after screening; 94 eligible.

Results: We included 76 studies investigating content of fluid/vapor of ECs, reports on adverse events and human and animal experimental studies. Serious methodological problems were identified. In 34% of the articles the authors had a conflict of interest. Studies found fine/ultrafine particles, harmful metals, carcinogenic tobacco-specific nitrosamines, volatile organic compounds, carcinogenic carbonyls (some in high but most in low/trace concentrations), cytotoxicity and changed gene expression. Of special concern are compounds not found in conventional cigarettes, e.g. propylene glycol. Experimental studies found increased airway resistance after short-term exposure. Reports on short-term adverse events were often flawed by selection bias.

Conclusions: Due to many methodological problems, severe conflicts of interest, the relatively few and often small studies, the inconsistencies and contradictions in results, and the lack of long-term follow-up no firm conclusions can be drawn on the safety of ECs. However, they can hardly be considered harmless.

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Introduction

The electronic cigarette (EC), also called e-cigarette, e-cig, electronic vaping device, personal vaporizer or electronic nicotine delivery system (ENDS) has been on the market for a decade. ECs are marketed as safe products providing a sensation of traditional smoking without the harmful effects, delivering pure nicotine and releasing harmless water vapor that vanishes in seconds (Anon, 2014; Smoke, 2014). Puffing activates the battery-operated heating element in the atomizer and the liquid. The liquid consists of various combinations of propylene glycol, glycerin, nicotine, tobacco extracts, flavorants and/or adulterants which vaporize to an aerosol/vapor. The newer generations of ECs seem to be very efficient nicotine delivery systems (Etter and Bullen, 2011a; Wall et al., 1988). Almost all regular users use ECs with nicotine Etter and Bullen, 2011b.

In the beginning, ECs were primarily produced by small manufacturers in China and sold on the Internet without drawing major attention. In the last few years, major tobacco companies such as Lorillard, British American Tobacco, Altria, Reynolds and Imperial Tobacco have launched their own EC brands and are buying up existing ones. Marketing and sale has exploded and EC-shops and -lounges pop-up everywhere. For the first time in more than 40 years tobacco companies are back on TV with cigarette ads CNN Money, 2014. Industrial economists project that the ECs will surpass conventional cigarettes (CC) in about three decades, and the global EC market is expected to hit $10 billion by 2017 (Lopes, 2013; Stocks, 2013).

The epidemic spread of this new product raises great concern in some health and public health professionals sglanz, 2014 and great enthusiasm in others, who support the idea of "harm reduction" and see the EC as a long-awaited alternative to the conventional cigarette. Tobacco is the most deadly product on the market, and it is estimated that it will cause 1 billion deaths in the 21st century Eriksen et al., 2012.

Discussions concerning this new product are characterized by strong feelings and beliefs, as well as strong economic interests, making it very difficult to obtain unbiased information. There are many important issues concerning the EC, the most important being their long-term health effects.

The aim of this article is to give a systematic and critical review of the existing literature on the health consequences of vaping of ECs and discuss the implications of our findings for public health. Furthermore, as a first, we want to investigate how many of the published articles have a conflict of interest.

Objectives

We examined the published data to:

- Identify original publications on ECs which describe a health-related topic.
- Examine critically the design of the studies, the funding and other conflicts of interest and their influence on conclusions drawn.
- Assess the existing evidence on the safety of ECs.

Methods

We have followed the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) guidelines whenever meaningful.

Eligibility criteria

Original articles or abstracts on ECs of any topic relevant to health. Published before 14 Aug 2014 — in any language.

Exclusion criteria

Recommendations, expert statements, reviews, technical reports and other non-original papers. Papers on smoking cessation, abuse liability, nicotine levels, withdrawal symptoms, poisonings, prevalence, attitudes and beliefs.

Search

A search was carried out in PubMed, EMBASE and CINAHL (Appendix 1, detailed search).

Keywords: "electronic cigarette" or "e-cigarette" or "electrically heated cigarette" or "ENDS and cigarette" or "electronic nicotine delivery system" or "electronic nicotine delivery device" or "e-liquid". No limits.

Study selection

We identified 2147 papers (Fig. 1).

Identification

Screening of title left 1101 articles on ECs. After reading the abstract, papers were rejected which did not report a health-related topic. Agreement of authors was necessary to exclude a paper. Papers on symptoms were included even if the main focus of the article was, for example, smoking cessation, leaving n = 271. Out of these, 177 were duplicates, described the same study population or did not report original data, leaving 94 papers. Full documents were obtained for the final inclusion. Additionally, we thoroughly looked through the reference lists of the articles for missed papers and investigated reports for overlooked papers (Anon, 2012, 2013a,b; Burstyn, 2013; Schaller et al., 2013). Eight studies were identified (Anon, 2009; Gennimata et al., 2014; Heavner et al., 2010; Laugesen et al., 2008; Lauterbach and Laugesen, 2012; Lauterbach et al., 2012; Trehy et al., 2011; U.S.Food and Drug Administration, 2009): one was a laboratory analysis (U.S.Food and Drug Administration, 2009)

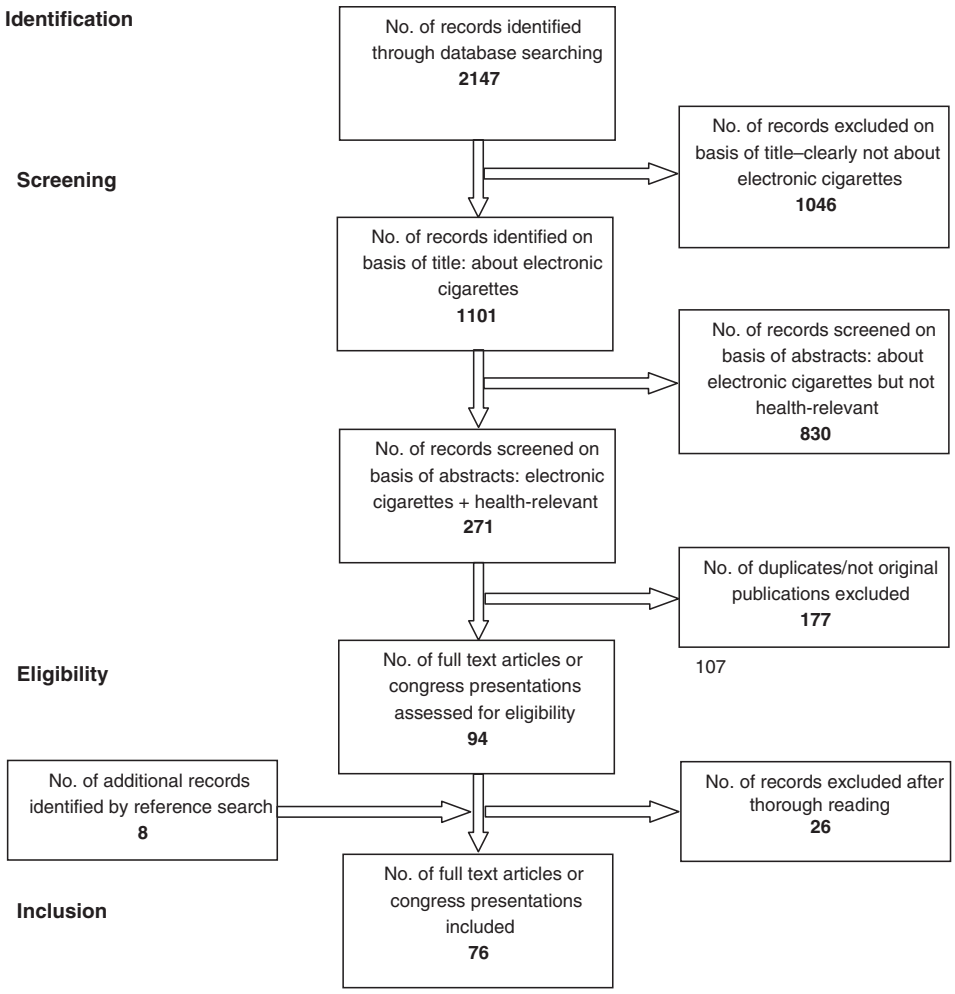

Fig. 1. Flowchart of publications included in the systematic review.

based on data from another identified source (Trehy et al., 2011). Twenty-six were excluded after reading the full text thoroughly (Farsalinos et al., 2013a; Frost-Pineda et al., 2008a,b,c; Horvath, 2012; Kouretas et al., 2012; Martin et al., 2012; Moennikes et al., 2008; Patskan and Reininghaus, 2003; Roemer et al., 2008; Roethig et al., 2005, 2007, 2008; Schorp et al., 2012; Stabbert et al., 2003; Terpstra et al., 2003; Tewes et al., 2003; Tricker et al., 2009, 2012a,b,c,d; Urban et al., 2012; Werley et al., 2008; Zenzen et al., 2012). Two abstracts were later published as a full article (Kouretas et al., 2012), and the remaining articles investigated electrically heated tobacco leaves. None of the additionally included studies have been published as full peer-reviewed articles.

Both authors read and discussed the articles. CP wrote the first draft of the paper. We investigated all papers for conflict of interest, funding and workplace of authors. If in doubt, we contacted the authors and asked about funding and conflict of interest and/or searched the Internet.

Results

Summarizing the evidence

We found 34 studies investigating content/effect of e-fluid or -vapor (Anon, 2009; Bahl et al., 2012; Behar et al., 2014; Bertholon et al., 2013; Cameron et al., 2013; Cervellati et al., 2014; Cheah et al., 2012; Czogala et al., 2014; Etter et al., 2013; Fuoco et al., 2014; Goniewicz et al., 2013a, b, 2014; Hadwiger et al., 2010; Hutzler et al., 2014; Ingebrethsen et al., 2012; Kim and Shin, 2013; Kosmider et al., 2014; Laugesen et al., 2008; Lauterbach and Laugesen, 2012; Lauterbach et al., 2012; McAuley et al., 2012; Park et al., 2014; Pellegrino et al., 2012; Romagna et al., 2013; Ruprecht et al., 2014; Schober et al., 2014; Schripp et al., 2013; Stepanov and Fujioka, 2014; Trehy et al., 2011; Uryupin et al., 2013; Westenberger, 2009; Williams et al., 2013; Zhang et al., 2013), 20 studies reporting adverse events (Bullen et al., 2010; Camus et al., 2014; Caponnetto et al., 2013a,b; Chen, 2013; Dawkins et al., 2013a; Etter, 2010; Farsalinos and Romagna, 2013; Farsalinos et al., 2013b, 2014; Heavner et al., 2010; Hua et al., 2013a; Hureaux et al., 2014; Lee et al., 2013a; McCauley et al., 2012; McQueen et al., 2011; Monroy et al., 2012; Polosa et al., 2011, 2014a; Thota and Latham, 2014), 21 human experimental studies (Battista et al., 2013; Chorti et al., 2012; Czogala et al., 2012; Dawkins and Corcoran, 2013; Dawkins et al., 2012, 2013b; Eissenberg, 2010; Etter and Bullen, 2011a; Farsalinos et al., 2012; Flouris et al., 2012, 2013; Gennimata et al., 2014; Marini et al., 2014; Palamidas et al., 2014; Polosa et al., 2014b; Tsikrika et al., 2014; Vakali et al., 2014; van Staden et al., 2013; Vansickel et al., 2010, 2012; Vardavas et al., 2012) and one animal experimental study (Lim and Kim, 2014). In total, 76 studies (Fig. 1).

Conflict of interest

In 26 studies (34%) the authors had a conflict of interest. Most studies were funded or otherwise supported/influenced by manufacturers of ECs, but several authors had also been consultants for manufacturers of medicinal smoking cessation therapy.

Table 1
Studies investigating the content/effect of fluid or vapor of electronic cigarettes (n = 34).

Name of first author (reference year)	Conflict of interest (yes = ▲)	Reference product	Fluid/ vapor	Conclusion
Bahl et al. (2012)	No	No	○ Fluid	○ Approx. one third of samples were highly cytotoxic to human embryonic stem cells and mouse neural stem cells
Behar et al. (2014)	No	No	○ Fluid	○ Cinnamon flavorings in refill fluids are linked to cytotoxicity
Bertholon et al. (2013)	No	CC and water pipe	○ Vapor	○ Contrary to CC smoke, which has a half-life in air of 19 to 20 min, the half-life of EC is very short and risk of passive "smoking" exposure from EC is modest
Cameron et al. (2013)	No	No	○ Fluid	○ Large variability in nicotine concentrations was found
Cervellati et al. (2014)	No	CC	○ Vapor	○ Exposure to EC vapors is far less toxic than exposure to CC smoke
Cheah et al. (2012)	No	No	○ Fluid	○ Contained nicotine even though they claimed to be nicotine free ○ Significant difference in the nicotine content across EC with same label, brand-to-brand and cartridge-to-cartridge variations ○ Polycyclic aromatic hydrocarbons and TSNAs compounds were not found
Czogala et al. (2014)	▲	CC	○ Vapor	○ Using EC in indoor environments may involuntarily expose non-users to nicotine but not to toxic tobacco-specific combustion products
Etter et al. (2013)	▲Yes	No	○ Fluid	○ Half of the liquids analyzed contained up to five times the maximum amount of impurities specified in the European Pharmacopoeia
Fuoco et al. (2014)	No	CC	○ Vapor	○ Particle number distribution modes of the EC-generated vapor were similar to the CC ○ ECs were found to be a major particle source, which can lead to significantly high deposition in vapers
Gennimata et al. (2014)	▲	CC	○ Fluid and vapor	○ There is very little risk of nicotine toxicity from major EC brands in the United Kingdom. ○ Nicotine concentration in e-liquid is not well related to nicotine in vapor ○ None of the tested products reached nicotine concentrations as high as CC
Goniewicz et al. (2013a)	▲Yes	Medicinal nicotine inhalator, CC	○ Vapor	○ Toxic compounds: metals, carbonyls and volatile organic compounds were found in almost all EC, but much lower levels than in CC smoke ○ Vapor of some EC contains traces of carcinogenic nitrosamines ○ Exposure to carcinogenic formaldehyde comparable with CC smoking
Goniewicz et al. (2013b)	▲Yes	No	○ Vapor	○ Vapor contains nicotine, but EC brands and models differ in their efficacy and consistency of nicotine vaporization
Hadwiger et al. (2010)	No	No	○ Fluid	○ Presence of unapproved active pharmaceutical ingredients ○ Nicotine-free products contained nicotine
Hutzler et al. (2014)	No	No	○ Fluid and vapor	○ Many ECs labeled as 'nicotine free' contained nicotine ○ Release of aldehydes is strongly enhanced in the second half of the vaping period ○ The occurrence of aldehydes seems to be associated with lower liquid levels within the cartridges (overheating of the wire?)
Ingebrethsen et al. (2012)	▲Yes	CC	○ Vapor	○ Particle diameters and particle number conc. as in CC smoke
Kim and Shin (2013)	No	No	○ Fluid	○ Almost all fluids contained carcinogenic compounds, tobacco specific nitrosamines ○ High maximum conc. of total tobacco specific nitrosamines ○ Great variability in content of the four measured tobacco specific nitrosamines
Kosmider et al. (2014)	▲	Glycerin, PPG/ mixture of both	○ Vapor	○ ECs might expose their users to the same or even higher levels of carcinogenic formaldehyde than CC smoke ○ Vapors from EC contain toxic and carcinogenic carbonyl compounds ○ Both solvent and battery output voltage significantly affect levels of carbonyl compounds in EC vapors
Anon (2009) (2 versions)	▲Yes	CC	○ Fluid and vapor	○ Very low score for toxic emissions (based on >50 toxicants) ○ Small particle size ○ Mercury detected
Laugesen et al. (2008)	▲Yes	CC	○ Fluid	○ Acetaldehyde, benzene, acrolein and tobacco specific nitrosamines detected at low levels ○ Metals, CO and other VOCs at lower limits than detection
Lauterbach and Laugesen (2012)	▲Yes	CC	○ Vapor	○ Acetaldehyde, formaldehyde, TSNs and mercury detected ○ Compared to CC level of toxins and carcinogens was reduced by >90%
Lauterbach et al. (2012)	▲Yes	CC	○ Vapor	○ Tobacco specific nitrosamines, tar, formaldehyde, acetaldehyde, acrolein, and other toxins found in vapor ○ Most toxicants were reduced by over 98% compared with CC
McAuley et al. (2012)	▲Yes	CC	○ Vapor	○ Ethylbenzene, benzene, toluene, and m/p xylenes acetone, formaldehyde, and acetaldehyde detected ○ Tobacco specific nitrosamines: typically found at lower levels than tobacco smoke ○ Conc. of pollutants were generally orders of magnitude lower than in CC smoke
Park et al. (2014)	No	CC	○ Vapor	○ Preliminary analyses indicate the observed that EC-specific gene expression changes were concordantly changed following CC-conditioned media exposure
Pellegrino et al. (2012)	No	CC	○ Fluid and vapor	○ PG and VG are major ingredients — other ingredients = traces ○ PM in vapor: fine + ultrafine particles ○ PM emissions are significantly lower than in CC smoke
Romagna et al. (2013)	▲Yes	CC	○ Vapor	○ Vapor from 1 out of 21 EC liquids examined had cytotoxic effects on cultured fibroblast ○ CC: significantly higher cytotoxicity
Ruprecht et al. (2014)	No	CC	○ Vapor	○ EC produce less PM than CC and therefore may be less hazardous in terms of secondhand exposure
Schober et al. (2014)	No	No vaping	○ Vapor	○ EC are not emission-free — could be of health concern for users and secondhand smokers ○ Ultrafine particles can be deposited in the lung ○ Release of inflammatory signaling molecule NO
Schripp et al. (2013)	No	CC	○ Vapor	○ Prominent components in the gas-phase: 1,2-propanediol, 1,2,3-propanetriol, diacetin, flavorings, and traces of nicotine ○ Passive vaping must be expected

(continued on next page)

Table 1 *(continued)*

Name of first author (reference year)	Conflict of interest (yes = ▲)	Reference product	Fluid/ vapor	Conclusion
				○ The aerosol size distribution alters in the human lung and leads to an exhalation of smaller particles
Stepanov and Fujioka (2014)	No	No	○ Fluid	○ ECs with the same nicotine content, but different pH, may deliver different doses of nicotine to users ○ Most of the tested brands have basic pH — the long-term effect of chronic aero-digestive tract exposure is not known
Trehy et al. (2011)	No	CC	○ Fluid	○ Some products were found to contain high conc. of nicotine when labeled not to contain nicotine ○ The actual amount of nicotine delivered is likely to be highly variable ○ Transfer of rimonabant and amino-tadalafil to the vapor phase is low ○ Impurity level is lower than for CC
Uryupin et al. (2013)	No	No	○ Fluid	○ The main components of mixtures were non-tobacco products
Westenberger (2009) (FDA)	No	Medicinal nicotine inhalator	○ Fluid	○ Diethylene glycol in one cartridge ○ Detectable levels of carcinogens and toxic chemicals
Williams et al. (2013)	No	CC	○ Fluid and vapor	○ Harmful or potentially harmful elements detected ○ Aerosol: significant amounts of tin and other metals, silicate beads, and nanoparticles, mostly higher than or equal to corresponding conc's in CC smoke ○ Fluid with tin particles was cytotoxic
Zhang et al. (2013)	No	CC	○ Vapor	○ CC produce more particles initially, but particle counts converge to a similar scale as the aerosols condense ○ EC and CC produce aerosols having generally similar particle sizes

CC	conventional cigarette
EC	electronic cigarette
FDA	US Food and Drug Administration
NO	nitric oxide
PM	particular matter
PPG	propylene glycol
TSNAs	tobacco specific nitrosamines
UFP	ultra fine particles
VG	vegetable glycerin
VOCs	volatile organic compounds

Studies reporting content/effect of fluid and/or vapor (Table 1, for details see Appendix 2)

Most studies used CCs as reference and investigated concentrations of several substances known to be toxic/carcinogenic in CCs. Many studies found that the product labels did not show the concentrations of solvents and flavorings.

Glycols

These are the major components in ECs. High amounts of propylene glycol (also called 1,2-propandiol) and glycerin were found in studies testing for these substances (Cheah et al., 2012; Etter et al., 2013; Pellegrino et al., 2012; Schripp et al., 2013; Uryupin et al., 2013).

Nicotine

Several studies found a large variability in nicotine concentrations across brands, labels and cartridges (Cameron et al., 2013; Cheah et al., 2012; Goniewicz et al., 2013b; Hadwiger et al., 2010; Schober et al., 2014; Trehy et al., 2011; Westenberger, 2009), others found smaller variability (Goniewicz et al., 2014). Nicotine-free products were found to contain nicotine, sometimes in high concentrations (Cheah et al., 2012, 2014; Hadwiger et al., 2010; Hutzler et al., 2014; Trehy et al., 2011), while others found that nicotine content corresponded to labels on the bottles (Etter et al., 2013; Laugesen et al., 2008). One study found the concentration of nicotine in vapor to be much lower than in tobacco smoke (Czogala et al., 2014).

Particles

Some studies found that ECs and CCs produce aerosols with comparable particle sizes (Fuoco et al., 2014; Ingebrethsen et al., 2012; Zhang et al., 2013) with fine and ultrafine particles in vapor (Pellegrino et al., 2012), but one study found particles from ECs much smaller (Anon, 2009) and another much bigger (Bertholon et al., 2013) than in tobacco smoke. A study showed that the vapor size distribution alters in the human lung and leads to exhalation of smaller particles (Schripp et al., 2013). Regarding particle concentration, two studies found this to be the same as in tobacco smoke (Fuoco et al., 2014; Ingebrethsen et al., 2012), while three found the concentration to be lower, up to an order of magnitudes lower, than in smoke (Czogala et al., 2014; McAuley et al., 2012; Pellegrino et al., 2012) and one study found that CCs produce more particles initially, but particle counts converge to a level comparable to the condensed vapor Zhang et al., 2013. Two 'real-life' condition studies found that vaping ECs with nicotine showed only marginal particulate matter production in indoor air, while it was much higher after vaping ECs without nicotine (Ruprecht et al., 2014; Schober et al., 2014). The half-life of vapor was found to be very short – seconds – due to rapid evaporation (Bertholon et al., 2013).

Cytotoxicity

One study found that several samples were highly cytotoxic to human embryonic and mouse neural stem cells, and cytotoxicity was due to flavors. Cinnamon had a strong cytotoxic effect (Bahl et al., 2012). E-fluid containing tin particles was found to be cytotoxic on human pulmonary fibroblasts (Williams et al., 2013). However, other studies found that vapor from only one out of 21 e-fluids had cytotoxic effects on cultured murine fibroblasts Romagna et al., 2013 and CCs had significantly higher cytotoxicity (Cervellati et al., 2014; Romagna et al., 2013).

Metals

A study found that concentrations of lead and chromium in vapor were within the range of CCs, while nickel was up to 100 times higher than in CCs Williams et al., 2013. One puff of EC-vapor contained numerous particles, mainly tin, silver, nickel and aluminum. Tin, chromium, and nickel were found as nano-particles. Another study found cadmium, nickel and lead in almost all vapors of 12 brands but the amounts of toxic metals were low, comparable with amounts contained in a nicotine inhaler (nicotine replacement treatment, NRT) (Goniewicz et al.,

2013a). Finally, some studies found metals in fluid at lower limits than detection (Laugesen et al., 2008) and trace quantity of mercury in vapor (Anon, 2009). A 'real-life' study showed a 2-fold increase of aluminum in indoor air after vaping (Schober et al., 2014).

Tobacco-specific nitrosamines (TSNAs)

Some studies found high maximum concentrations of total TSNAs in the vapor of most (Goniewicz et al., 2013a), or almost all fluids (Kim and Shin, 2013). Other studies found carcinogenic TSNAs present in vapor at lower levels than tobacco smoke (McAuley et al., 2012) or at trace levels (Lauterbach and Laugesen, 2012; Lauterbach et al., 2012). Some studies detected TSNAs with no/weak carcinogenic effect or no TSNAs in the fluid (Cheah et al., 2012; Etter et al., 2013; Schober et al., 2014; Westenberger, 2009).

Carbonyls

In one study the potential human carcinogens formaldehyde, acetaldehyde and acrolein were detected in the vapors of almost all ECs (Goniewicz et al., 2013a). Exposure to formaldehyde was comparable with smoking (Goniewicz et al., 2013a), as was also the case with vapor from high-voltage devices (Kosmider et al., 2014). The highest levels of carbonyls were observed in vapors generated from propylene glycol-based solutions (Kosmider et al., 2014) or in the second half of a vaping period, indicating overheating of wires (Hutzler et al., 2014). A study concluded that most carbonyls were detected at low concentrations in vapor, with the exception of acetone, formaldehyde, and acetaldehyde (McAuley et al., 2012). Formaldehyde, acetaldehyde and acrolein were also found in another study, at concentrations approx. 1/10 of those in smoke from CCs (Lauterbach et al., 2012). One study found acetaldehyde and formaldehyde at low levels (Lauterbach and Laugesen, 2012) and another found acetaldehyde and acrolein in vapor at low levels (Laugesen et al., 2008). The same author presented similar findings in another study, but in a newer version of the same abstract, acetaldehyde and acrolein were not mentioned (Anon, 2009). Finally, one study found that the release of formaldehyde was below the limit of detection (Schripp et al., 2013).

Volatile organic compounds (VOCs) such as toluene Czogala et al. (2014) and p,m-xylene were identified in almost all vapors (Goniewicz et al., 2013a). In one study, the concentrations were below the level of detection (McAuley et al., 2012).

Polycyclic aromatic hydrocarbons (PAHs)

Studies found either no PAHs in fluid (Cheah et al., 2012), or that most PAHs were below detection level (Lauterbach and Laugesen, 2012; McAuley et al., 2012) or as traces, only (Lauterbach et al., 2012). However, probably carcinogenic PAHs in indoor air increased by 20% after vaping (Schober et al., 2014).

Other measures

Human bronchial cells that contained mutations found in smokers at risk of lung cancer were grown in a culture medium that had been exposed to vapor. The researchers found that cells exposed to high-nicotine vapor showed a similar pattern of gene expression to those exposed to tobacco smoke (Park et al., 2014). A study found that vapor induced the release of cytokines and pro-inflammatory mediators (Cervellati et al., 2014). Another study found that half of the liquids analyzed contained up to five times the maximum amount of impurities specified in the European Pharmacopoeia (Etter et al., 2013). The highly toxic diethylene glycol was found in one cartridge in one study (Westenberger, 2009) but not in another (Etter et al., 2013). One study found potentially harmful additives, such as coumarin (Hutzler et al., 2014). Products advertised as containing tadalafil contained amino-tadalafil (Hadwiger et al., 2010; Trehy et al., 2011). Products advertised as containing rimonabant, contained rimonabant plus an oxidative impurity of rimonabant (Hadwiger et al., 2010). One study found significant amounts of silicate beads in the aerosol (Williams et al., 2013). Most nicotine-containing ECs have a basic pH > 9, which seems to influence the doses of nicotine delivered (Stepanov and Fujioka, 2014).

Studies reporting adverse events (Appendix 3)

Reports on AE were often flawed by selection bias. In most cases of the reporting of adverse events causality could not be confirmed. Therefore, and due to limited space, we present details on AE in Appendix 3 only. No serious AE were reported in controlled prospective studies. Most AE have been from the mouth/throat and the respiratory system, but symptoms from many organ systems have been reported. On the other hand, many regular EC users reported decrease in respiratory symptoms and improvements in general health.

Human experimental studies (Table 2, for details see Appendix 4)

Most studies included smokers as volunteers and compared with a reference, mostly own-brand CCs.

Adverse events (AE)

These were very similar to those reported in Appendix 3. There was low reporting of AE in regular users, who were EC-naïve before study start, with the most frequent being light-headedness, throat irritation, dizziness, cough (Dawkins and Corcoran, 2013; Vakali et al., 2014; van Staden et al., 2013).

Pulmonary system

Studies in EC-naïve smokers found that the same particle dose was received as with smoking and vaping (Marini et al., 2014), increased airway resistance (Marini et al., 2014; Palamidas et al., 2014; Vardavas et al., 2012) and a concomitant decrease in specific airway conductance (Palamidas et al., 2014), an increase in impedance and overall peripheral airway resistance (Vardavas et al., 2012); effects that are reminiscent of those seen with tobacco smoking. Two studies found immediate reductions in exhaled nitric oxide, similar to smoking (Marini et al., 2014; Vardavas et al., 2012) and increased the release of the inflammatory signaling molecule NO upon inhalation (FeNO) (Schober et al., 2014) while another study found a decrease in FeNO (Vakali et al., 2014). A study including both healthy volunteers and patients with asthma and chronic obstructive pulmonary disease also showed that 10 min of vaping caused immediate significant airway obstruction (Gennimata et al., 2014) which is in contrast with a retrospective review finding objective and subjective improvements in asthma outcomes (Polosa et al., 2014b.) Another study found that short-term usage was associated with increased flow resistance even though spirometry-assessed lung function was deemed normal (Chorti et al., 2012). Passive, but not active vaping of one EC resulted in short-term lung obstruction, indicating insufficient inhalation by EC-naïve smokers (Chorti et al., 2012). The last study found that short-term vaping of ECs generated non-significant decrease in lung function; approx. half of what was seen in smoking (Flouris et al., 2013).

Cardiovascular system

Some studies in EC-naïve smokers found that short-term vaping resulted in increased heart rate (Battista et al., 2013; Czogala et al., 2012; Tsikrika et al., 2014; Vakali et al., 2014; Vansickel et al., 2012), an elevation in diastolic blood pressure (Battista et al., 2013; Czogala et al., 2012), and a decrease in oxygen saturation (Vakali et al., 2014). Other studies found no increase in heart rate (Eissenberg, 2010; van Staden et al., 2013; Vansickel et al., 2010) or in blood pressure (van Staden et al., 2013) but an increase in oxygen saturation (van Staden et al., 2013). Active and passive vaping in EC-naïve smokers did not influence the complete blood count (Flouris et al., 2012). One study using experienced EC-users found a slight elevation in diastolic blood pressure, but no effect on cardiac function (Farsalinos et al., 2012).

Table 2
Human experimental studies reporting health effects (n = 21).

Name of first author (reference year)	Conflict of interest ▲ = Yes	Reference product	Method Length of exposure	Numbers of participants	Conclusions
Battista et al. (2013)	No	CC	○ Experimental study ○ Exposure: 4 min of smoking/ vaping	○ 12 regular users of EC	○ EC inhalation produces the same patho-physiological cardiovascular effects of CC smoking
Chorti et al. (2012)	No	CC	○ Volunteers in CC group smoked 2 CC ○ Volunteers in EC group puffed 1 EC	○ 15 EC naive heavy-smokers	○ Passive but not active EC vaping resulted in short-term lung obstruction and increased cotinine
Czogala et al. (2012)	No	CC	○ A repeated measures design ○ Exposure: 5 min of smoking/ vaping	○ 42 EC naive daily smokers	○ Slight non-sign elevation in diastolic blood pressure, pulse and carboxyhemoglobin
Dawkins and Corcoran (2013)	▲	No	○ A repeated measures design ○ Exposure: 1) Ten puffs 2) 1 h ad lib use	○ 14 regular EC users	○ Low reporting of AE in regular users. Most frequent: light-headedness, throat irritation and dizziness
Dawkins et al. (2013b)	▲	0 mg nicotine EC	○ Within-subjects design ○ Exposure: 10 min ad lib use	○ 20 EC naive smokers	○ EC can effectively deliver nicotine to impact on cognitive performance; improved time-based memory
Dawkins et al. (2012)	▲	0 mg nicotine EC	○ Mixed experimental design ○ Exposure: 5 min ad lib use	○ 86 EC naive smokers	○ Improved nicotine withdrawal impaired concentration/ memory
Eissenberg (2010)	No	CC	○ Hemodynamic measurements ○ Exposure: Puffed ad libitum 10 times	○ 16 EC naive smokers	○ No increase in heart rate
Etter and Bullen (2011a)	No	No	○ Saliva sampling in current vapers ○ Exposure: daily vaping	○ 31 current users (30 daily users) of EC	○ Cotinine levels in experienced vapers were similar to levels previously observed in smokers and higher than in users of nicotine replacement therapy
Farsalinos et al. (2012)	No?	CC	○ Hemodynamic measurements + echocardiogram at baseline and after smoking/vaping ○ Exposure: 1 CC or 7 min of vaping of EC	○ 20 EC naive smokers and 20 EC users	○ Slight elevation in diastolic blood pressure but no effect on cardiac function in experienced EC users
Flouris et al. (2013)	No	CC	○ Repeated-measures controlled study ○ Exposure: 30 min of active/passive smoking or vaping	○ 15 EC naive smokers and 15 never-smokers	○ Short term passive vaping generated small non-sign decrease in lung function, approx. the half of smoking ○ Similar nicotinergic impact to CC
Flouris et al. (2012)	No	CC	○ Three experimental sessions; active and passive exposure ○ Exposure: 2 CC within 30 min or 'a number of puffs' within 30 min	○ 15 EC naive smokers and 15 never-smokers	○ Acute active and passive vaping did not influence complete blood count indices in smokers and never smokers
Gennimata et al. (2014)	No?	?	○ Exposure: vaping for 10 min	○ 8 never smokers and 24 EC naive smokers	○ Short-term exposure caused immediate airway obstruction
Marini et al. (2014)	No	CC	○ Experimental study ○ Exposure: 4 puffs	○ 25 smokers	○ Similar effect on human airways, and same particle dose received with smoking and vaping
Palamidas et al. (2014)	No	No	○ Experimental study ○ Exposure: Gr. A: vaping in 10 min	○ 70 volunteers (27 with asthma/COPD). Smokers + never smokers	○ Increased airway resistance and a concomitant decrease in specific airway conductance
Polosa et al. (2014b)	▲	No	○ Retrospective review of changes in lung function and asthma control ○ Exposure: 6 and 12 months follow-up	○ 18 smoking asthmatics who switched to regular EC use	○ Study indicates that regular use of EC to substitute smoking is associated with objective and subjective improvements in asthma outcomes
Tsikrika et al. (2014)	No	No	○ Experimental study ○ Exposure: vaping in 10 min	○ 62 volunteers, non-smokers + smokers: 28 with COPD/asthma	○ Increased heart rate and symptoms like cough and sore throat
Vakali et al. (2014)	No	No	○ Experimental study ○ Exposure: vaping in 10 min	○ 64 volunteers, non-smokers + smokers	○ Increased heart rate, palpitations and a decrease in SpO_2 ○ A decrease in fraction of exhaled nitric oxide
van Staden et al. (2013)	▲	No	○ A single group within-subject design ○ Exposure: switch to EC vaping in 2 weeks	○ 15 smokers switched to EC, 2 drop-outs	○ Increase in oxygen saturation, no changes in blood pressure and pulse rate, cough worse/improved ○ Phlegm increased in some but decreased in more
Vansickel et al. (2010)	No	CC	○ Repeated-measures controlled study ○ Exposure: two, 10-puff EC bouts	○ 32 EC naive heavy smokers	○ No changes in plasma nicotine and heart rate ○ No increase in CO
Vansickel et al. (2012)	No	CC	○ 4 within-subject sessions ○ Exposure: six 10-puff bouts-separated by 30-mins	○ 20 EC naive heavy smokers	○ Increase in heart rate
Vardavas et al. (2012)	No	EC with cartridge removed	○ Exposure: ad lib use for 5 min	○ 30 EC naive smokers of at least 5 pack years	○ Increased flow resistance ○ Immediate adverse effects on the airways after short-term use; similar to some of the effects seen with smoking

EC = electronic cigarette; CC = conventional cigarette.

Cognitive function

Two studies found improved time-based but not event-based prospective memory (Dawkins et al., 2013b) and improved nicotine withdrawal impaired concentration/memory (Dawkins et al., 2012).

Other

A metabolite of the pyrolysis product acrolein was found in urine, after vaping ECs with nicotine (Schober et al., 2014).

Animal study (Table 3, for detail see Appendix 5)

One study in mice treated intratracheally with EC fluid increased the infiltration of inflammatory cells, aggravated asthmatic airway inflammation and airway hyper-responsiveness, and stimulated the production of cytokines and ovalbumin-specific IgE production (Lim and Kim, 2014).

Discussion

Interpreting the findings

Our review included 76 studies investigating the health effects of ECs. We included studies investigating content of ECs, reports on adverse events, animal experiments and human experimental studies. Due to the many methodological problems, severe conflicts of interest, the relatively few and often small studies, the inconsistencies and contradictions in results and the lack of long-term follow-up, no firm conclusions can be drawn on the safety of ECs, and much is left to subjective interpretations.

A substantial number of studies were funded or otherwise supported by manufacturers of ECs. Conflict of interest seems to influence the conclusions of these papers. The content of e-liquid and vapor is characterized by high amounts of propylene glycol, and sometimes glycerin, nicotine and flavors. Many ECs contain misleading/missing information on product ingredients, especially nicotine, and many studies found harmful substances: fine/ultrafine particles, cytotoxicity, harmful metals, carcinogenic tobacco-specific nitrosamines and carbonyls — some in most samples, others in few. Some studies found a high concentration of harmful substances, as high as in CCs or higher, but more studies found low or trace levels. Some flavors, such as cinnamon were found to have strong cytotoxic effects. One experimental in vitro study found that EC vapor can change gene expression in a similar way to tobacco. Higher battery-output voltage increased the production of harmful substances substantially, which was also the case with propylene glycol-based solutions and when e-liquid levels decreased. The dangers of secondhand exposure have not been thoroughly evaluated. A potentially carcinogenic pyrolysis product was found in urine. Lungs are the primary target organ and experimental studies have found effects after very short-term exposure that are reminiscent of the obstructive effects seen with smoking, even though the impact on lung function was smaller than with smoking. An animal study found that EC fluid can exacerbate allergy-induced asthma symptoms. A few experimental studies have shown that ECs can effectively deliver nicotine to impact on cognitive performance and the heart. Case reports on different lung diseases and atrial fibrillation found time association and/or reversibility, but causality can only be hypothesized. No serious AE were reported in controlled prospective studies. No serious AE were reported in controlled prospective studies. Most AE have been from the mouth/throat and the respiratory system, but symptoms from many organ systems have been reported. Regular EC users often reported improvements in respiratory symptoms and general health. Findings were flawed by selection-bias.

This research field is new and very challenging. Serious methodological problems were identified. Core problems are: 1) Any research only applies to the specific EC brand, model and batch tested, with no certainty that the findings will apply to other or future brands, models or batches. ECs are subject to frequent modifications, and there are currently more than 460 brands. 2) Almost all studies have compared concentrations of harmful substances in CCs with concentrations in ECs, but health hazards may be different than from smoking. 3) EC-use topography is significantly different than smoking (Hua et al., 2013a). When vaping, you are sucking harder and have longer puffing duration, approx. double of smoking, especially if the fluid content in the cartridge is low (Hua et al., 2013b). Therefore, the real uptake of harmful substances might be underestimated when testing on EC-naïve volunteers or standard smoking machines. Also, studies show significant variations in puffing topography among users of various EC models (Farsalinos et al., 2013a), that production of harmful substances is influenced by both battery voltage output (Kosmider et al., 2014) and e-liquid levels left (Hutzler et al., 2014), and that pH may influence the doses of nicotine delivered to users (Stepanov and Fujioka, 2014) — this complicates the research even more. 4) Human experiments were mostly based on very short-term exposure, e.g. vaping for a few minutes — not reflecting real-life exposure.

Of special concern are compounds *not* found in CCs: the glycols, propylene glycol and glycerin, major ingredients of ECs. Propylene glycol, which creates the visible fume, is a solvent used in pharmaceutical products and is "generally recognized as safe" (Anon, 2011). An internal technical report commissioned by vapers and vendors of ECs concluded that estimated levels of exposure to propylene glycol and glycerin are close enough to threshold-limit values to warrant concern and that the threshold-limit values are based on uncertainty rather than knowledge (Burstyn, 2013). Volunteers exposed to propylene glycol mist for 1 min developed a slight airway obstruction and increased self-rated severity of dyspnea (Wieslander et al., 2001). Long-term exposure to propylene glycol has been found to exacerbate and/or induce multiple allergic symptoms in children (Choi et al., 2010). Experimental studies show moderate cytotoxic effect on skin fibroblasts (Ponec et al., 1990), irritation to the upper respiratory tract and squamous metaplasia of the epiglottis following exposure at concentrations present in ECs (Renne et al., 1992). Ethylene glycol, associated with pronounced toxicological risks (Hess et al., 2004), has been found to replace glycerol/

Table 3
Animal experimental studies reporting health effects (n = 1).

Name of first author (reference year)	Conflict of interest ▲=Yes	Reference product	Animal type and number	Exposure	Conclusions
Lim and Kim (2014)	No	CC	○ 24 five-week-old female BALB/c mice	○ Diluted solution was intra-tracheally instilled to ovalbumin -sensitized mice two times a week for 10 weeks	○ Suggest that the inhalation of EC solutions can function as an important factor to exacerbate the allergy-induced asthma symptoms

EC = electronic cigarette; CC = conventional cigarette.

propylene glycol in several brands (Hutzler et al., 2014). Other concerns are flavors, metals, rubber, silicone and ceramics. Significant amounts of metals (probably originating from solder joints, wires etc.) and silicate beads (probably from fiberglass wicks) have been found in ECs (Williams et al., 2013). Occupational exposure to silicate dusts can cause extensive pulmonary damage (Elmore, 2003). Lead and chromium concentrations were found within the range of CCs, nickel was up to 100 times higher than in CCs and e-fluid containing tin was found to be cytotoxic (Williams et al., 2013). These metals appear on the U.S. Food and Drug Administration's "Harmful and Potentially Harmful Chemicals" list (FDA, 2014).

Many of the harmful substances detected were identified at very low concentrations but we are dealing with intense and chronic exposure. Values below the threshold limit don't necessarily protect against the health effect of 200–300 daily inhalations (Goniewicz et al., 2013b) over decades — harm might accumulate over years/decades, as with CCs. Further, the presence of, for example, ten substances below the official threshold-limit values may add up in a synergic way and the safety of the combination of substances has not been evaluated. The inhaled aerosol may undergo changes in the human lung (Schripp et al., 2013). Long-term inhalation of an aerosol may increase the risk of tuberculosis, as observed in tobacco smoking (Bates et al., 2007). Additionally, there is enough heat generated during puffing (Schripp et al., 2013) to cause the fluid to decompose and/or components of the device to pyrolyze, whereby toxic/carcinogenic substances may be formed. Flavors are also known to affect the stability of products.

Discussions about levels of potentially harmful compounds in ECs often remove the focus from the fact that we are dealing with a very efficient nicotine delivery system. Almost all regular users report that they use ECs with nicotine (Etter and Bullen, 2011b), with levels in EC users (Etter and Bullen, 2011a) as in smokers (Etter et al., 2000), and higher than in NRT users (Benowitz et al., 1997). It is well established that nicotine is highly addictive (Benowitz, 1999; Picciotto and Corrigall, 2002). More than 60% of smokers wish to quit because they don't like being dependent (Pisinger et al., 2011) and switching to ECs does not break the nicotine addiction.

Nicotine is referred to by some health professionals as harmless, whereas others do not share this view (National Center for Chronic Disease Prevention and Health Promotion, 2014). A meta-analysis found no increased risk of serious adverse events (Moore et al., 2009). To our knowledge, only one study has investigated the health effects of long-term pure nicotine/NRT use, finding no increase in the risk of cancer (Murray et al., 2009). However, nicotine has a significant biologic activity: in the central nervous system nicotine stimulates the release of important neurotransmitters and hormones (Balfour, 1982), and in the peripheral system it stimulates the release of catecholamines, with effects such as vasoconstriction, increase in heart rate and myocardial contractility (Kilaru et al., 2001). Animal studies suggest that nicotine accelerates atherosclerosis (Kilaru et al., 2001), reduces sperm quality (Condorelli et al., 2013), promotes growth of cancer cells and the proliferation of endothelial cells, reduces the responsiveness of several cancers to chemotherapy (Al-Wadei et al., 2009; Banerjee et al., 2013; Catassi et al., 2008; Dinicola et al., 2013; Petros et al., 2012), and fetal and neonatal nicotine exposure leads to widespread adverse postnatal physical and mental health consequences (Bruin et al., 2010; Dwyer et al., 2009; Gao et al., 2008). The applicability to human beings may be questioned. Poison centers are receiving many calls regarding e-fluid (Kilaru et al., 2001); mostly exposures have resulted in minimal toxicity (Vakkalanka et al., 2014), but a case of fatal nicotine poisoning in a child has been reported (Kloosterman, 2013).

Health professionals who advocate "harm reduction" compare ECs with CCs, focus on smokers only, believe that ECs have no negative long-term health effects, that nicotine is a harmless recreational drug and that smokers are unwilling/unable to quit. These views are strongly supported by the EC/tobacco industry. On the other hand, health professionals working with public health point out that CCs are the most harmful legal products on the market (everything seems safe compared to smoking) and fear potential long-term health hazards. Other major concerns are that the product is spreading to never-smokers and ex-smokers, citizens unexposed to CCs, that many smokers have dual use (using both products) or switch instead of quitting, and that widespread EC-use will re-normalize smoking. This view is supported by the medical industry producing smoking cessation products.

Are there good reasons for concern? It would be naïve not to expect that the manufacturers will try hard to spread the use of their product to as many consumers as possible; it is a billion dollar business and history has shown that the tobacco industry has no ethical constraints and has used every iteration of cigarette design to undermine prevention and cessation (Bero, 2005; Proctor, 2011).

For several years ECs have been used as a healthier alternative to smoking or as an aid to cut down or quit (Adkison et al., 2013; Etter and Bullen, 2011b; Goniewicz et al., 2013c). Some prospective studies were very promising about ECs' effect as a smoking reduction/cessation aid (Caponnetto et al., 2013a,b), and a recent 'real-life' study showed that ECs increased cessation rates more than no aid/NRT bought over the counter (Kotz et al., 2014). However, a meta-analysis based on population studies found that EC users were significantly less likely than non-users to have stopped smoking (Grana et al., 2014), a longitudinal study in cancer patients showed that EC-users were twice as likely to be smoking at the time of follow-up as non-users (Borderud et al., 2014), and the only existing randomized smoking cessation study showed that ECs were not significantly more effective than nicotine patch therapy (Bullen et al., 2013). A survey sponsored by EC manufacturers found that only 1% of EC users achieved permanent abstinence by the use of ECs (Heavner et al., 2010); this study is not cited by harm reduction advocates. There is evidence that ECs are often used for dual use (Adkison et al., 2013; Etter, 2010; Etter and Bullen, 2011b; Lee et al., 2013b), as a supplement to CCs e.g. in places with a smoking ban, by ex-smokers (Adkison et al., 2013; Anon, 2013c; Etter, 2010; Etter and Bullen, 2011b) and by smokers who planned to quit but instead switched to long-term use of ECs, thereby undermining complete cessation (Bullen et al., 2013). An experimental study showed that EC exposure may evoke smoking urges in young adult daily smokers (King et al., 2014). The last few years EC-use has spread to minors and experimental use has doubled within one year (Anon, 2013c; Anon, 2013d; Camenga et al., 2014). Surveys show that a high proportion of adolescents have tried ECs (Goniewicz and Zielinska-Danch, 2012; Dautzenberg et al., 2013; Czoli et al., 2014), even children as young as 12–14 years (Dautzenberg et al., 2013). Of special concern is that young never-smokers are experimenting with ECs (Anon, 2013c,d; Czoli et al., 2014; Dautzenberg et al., 2013; Goniewicz and Zielinska-Danch, 2012). A survey found that every fifth of those who were non-smokers when they started using ECs were also smoking at time of survey, but there was no information as to whether they were never-smokers or ex-smokers at initiation of EC-use (Goniewicz et al., 2013c). To our knowledge, no studies have investigated whether ECs are a gateway to smoking.

It is necessary to include all users and modes of use when discussing benefits or risks of ECs. Additionally, the use of ECs might undermine decades of efforts to denormalize smoking (Choi et al., 2012).

We find that it is of concern that the safety, manufacture, quality control, labeling, sales and marketing of a product with unknown long-term health consequences and exploding sales is more or less unregulated. Authorities have a responsibility to ensure that EC-users can buy safe high-quality products with contents corresponding to the label, and they also have the responsibility to prevent the spread of the use of ECs to minors and non-smokers. Also, they must keep in mind that the impact of a product on public health is determined by two factors: 1) the degree of toxicity/harm of the substance; and 2) how widespread the exposure is. Even if ECs are less harmful than CCs, the product may have a very negative impact on public health if the use is spread to a large part of the population; ECs might achieve popularity as high as that of CCs in the 1950s or 60s, before evidence

and an awareness of harm became widespread in the population. Health professionals and decision-makers must exercise the utmost caution in trusting conclusions of studies/reviews where there is a conflict of interest (Bero, 2005; Brezis, 2008; Proctor, 2011). Systematic research is urgently needed (Etter et al., 2011).

Conclusion

Due to the many methodological problems, the relatively few and often small studies, the inconsistencies and contradictions in results and the lack of long-term results, no firm conclusions can be drawn on the safety of ECs. A substantial number of studies were published by authors with a conflict of interest and we must exercise the utmost caution in trusting their conclusions. Based on 76 studies, ECs cannot be regarded as safe, even though they probably are less harmful than CCs. The "harm reduction" strategy might be a gain for smokers reluctant to quit but ex- and never-smokers probably have an increased risk by using ECs. Combined with the imminent risk of undermining smoking cessation and the renormalization of smoking the total risk on public health from widespread use of ECs might be substantial. Their use should, so far, be restricted to smokers unwilling/unable to quit. Systematic research is urgently needed.

Conflict of interest
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Contributors

CP and MD were responsible for the conception and design. Both authors analyzed and interpreted the data and revised the article for important intellectual content. CP drafted the article and is guarantor.

Competing interests

Both authors declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous three years, no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval

Not required.

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