

# Safety evaluation and risk assessment of electronic cigarettes as tobacco cigarette substitutes: a systematic review

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**Abstract:** Electronic cigarettes are a recent development in tobacco harm reduction. They are marketed as less harmful alternatives to smoking. Awareness and use of these devices has grown exponentially in recent years, with millions of people currently using them. This systematic review appraises existing laboratory and clinical research on the potential risks from electronic cigarette use, compared with the well-established devastating effects of smoking tobacco cigarettes. Currently available evidence indicates that electronic cigarettes are by far a less harmful alternative to smoking and significant health benefits are expected in smokers who switch from tobacco to electronic cigarettes. Research will help make electronic cigarettes more effective as smoking substitutes and will better define and further reduce residual risks from use to as low as possible, by establishing appropriate quality control and standards.

**Keywords:** electronic cigarettes, e-liquid, e-vapor, harm reduction, nicotine, safety, tobacco

## Introduction

Complete tobacco cessation is the best outcome for smokers. However, the powerful addictive properties of nicotine and the ritualistic behavior of smoking create a huge hurdle, even for those with a strong desire to quit. Until recently, smokers were left with just two alternatives: either quit or suffer the harmful consequences of continued smoking. This gloomy scenario has allowed the smoking pandemic to escalate, with nearly 6 million deaths annually and a predicted death toll of 1 billion within the 21st century [World Health Organization, 2013]. But a third choice, involving the use of alternative and much safer sources of nicotine with the goal to reduce smoking-related diseases is now available: tobacco harm reduction (THR) [Rodu and Godshall, 2006].

Electronic cigarettes (ECs) are the newest and most promising products for THR [Polosa *et al.* 2013b]. They are electrically-driven devices consisting of the battery part (usually a lithium battery), and an atomizer where liquid is stored and is aerosolized by applying energy and generating heat to a resistance encircling a wick. The liquid used mainly consists of propylene glycol, glycerol,

distilled water, flavorings (that may or may not be approved for food use) and nicotine. Consumers (commonly called ‘vapers’) may choose from several nicotine strengths, including non-nicotine liquids, and a countless list of flavors; this assortment is a characteristic feature that distinguishes ECs from any other THR products. Since their invention in 2003, there has been constant innovation and development of more efficient and appealing products. Currently, there are mainly three types of devices available [Dawkins, 2013], depicted in Figure 1. (1) First-generation devices, generally mimicking the size and look of regular cigarettes and consisting of small lithium batteries and cartomizers (i.e. cartridges, which are usually prefilled with a liquid that bathes the atomizer). Batteries may be disposable (to be used once only) or rechargeable. (2) Second-generation devices, consisting mainly of higher-capacity lithium batteries and atomizers with the ability to refill them with liquid (sold in separate bottles). In the most recent atomizers you can simply change the atomizer head (resistance and wick) while keeping the body of the atomizer, thus reducing the operating costs. (3) Third-generation devices (also called ‘Mods’, from modifications),

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**Figure 1.** Examples of electronic cigarette devices currently available on the market.

consisting of very large-capacity lithium batteries with integrated circuits that allow vapors to change the voltage or power (wattage) delivered to the atomizer. These devices can be combined with either second-generation atomizers or with rebuildable atomizers, where the consumers have the ability to prepare their own setup of resistance and wick.

Awareness and use (vaping) of ECs has increased exponentially in recent years. Data obtained from the HealthStyles survey showed that, in the US, awareness of ECs rose from 40.9–57.9% from 2010 to 2011, with EC use rising from 3.3–6.2% over the same time period [King *et al.* 2013]. In the United Kingdom, EC use in regular smokers increased from 2.7% in 2010 to 6.7% in 2012 [Dockrell *et al.* 2013]. Similar findings were obtained from the International Tobacco Control Four-Country Survey [Adkison *et al.* 2013]. A recent prospective study in Swiss army recruits showed that 12% of smokers who tried ECs progressed to daily use [Doupcheva *et al.* 2013]. It must be noted that this increase in EC use has occurred despite the concerns raised by public health authorities about the safety and appropriateness of using these products as alternatives to smoking [National Association of Attorneys General, 2013; Food and Drug Administration, 2009; Mayers, 2009].

The popularity of ECs may be due to their ability to deal both with the physical (i.e. nicotine) and the behavioral component of smoking addiction. In particular, sensory stimulation [Rose and Levin, 1991] and simulation of smoking behavior and cigarette manipulation [Hajek *et al.* 1989] are important determinants of a product's effectiveness in reducing or completely substituting smoking. These features are generally absent in nicotine replacement therapies (NRTs) and oral

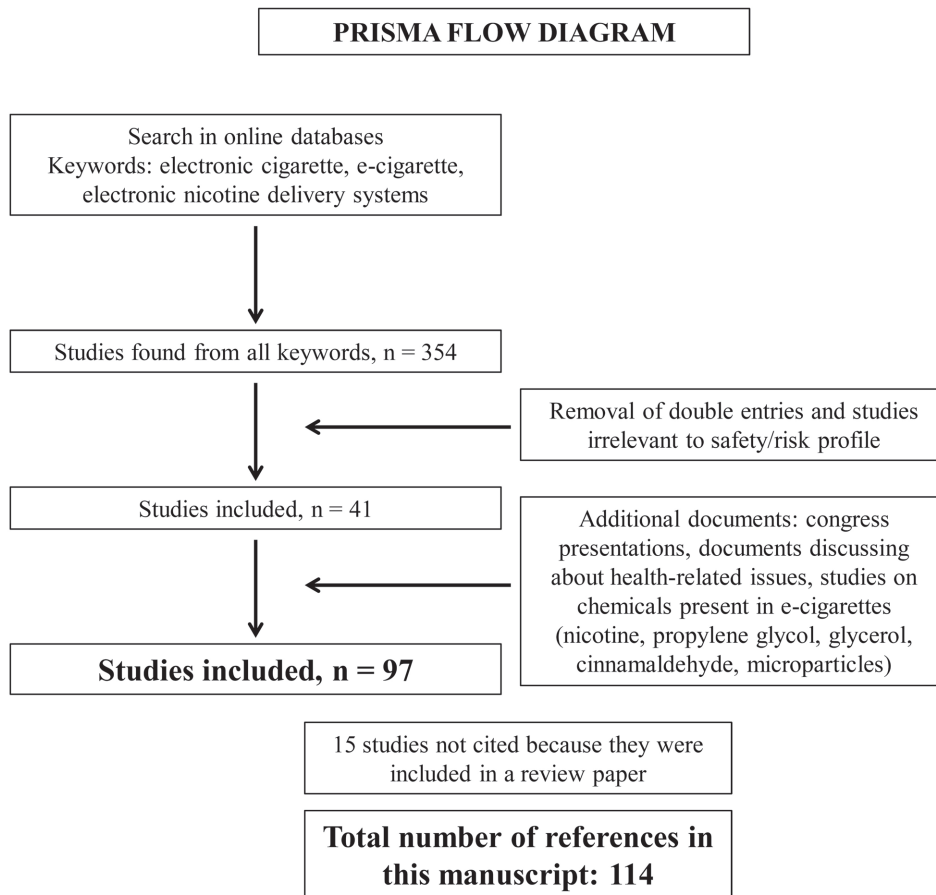
medications for nicotine dependence, whereas ECs are unique in that they provide rituals associated with smoking behavior (e.g. hand-to-mouth movement, visible 'smoke' exhaled) and sensory stimulation associated with it [Farsalinos *et al.* 2013b]. This explains why these products can be effective in reducing consumption of tobacco smoking [Bullen *et al.* 2013; Caponnetto *et al.* 2013b; Polosa *et al.* 2011] and are efficient as long-term substitutes of conventional cigarettes [Farsalinos *et al.* 2013b].

### Methods

For this systematic review (Figure 2), we searched the PubMed electronic database by using keywords related to ECs and/or their combination (e-cigarette, electronic cigarette, electronic nicotine delivery systems). We obtained a total of 354 results, and selected 41 studies we judged relevant to research on EC safety/risk profile. Reference lists from these studies were also examined to identify relevant articles. We searched additional information in abstracts presented at scientific congresses (respiratory, cardiovascular, tobacco control, toxicology), and in reports of chemical analyses on EC samples that were available online. We also looked for selected studies on chemicals related to EC ingredients (e.g. nicotine, propylene glycol, glycerol, cinnamaldehyde, microparticles emission, etc.), but not specifically evaluated in EC research. In total, 97 publications were found, from which 15 chemical analyses of single or a limited number of EC samples were excluded because they were discussed in a review paper [Cahn and Siegel, 2011]. In total, 114 studies are cited in this paper.

### Risk differences compared with conventional cigarettes and the issue of nicotine

Conventional cigarettes are the most common form of nicotine intake. Smoking-related diseases are pathophysiologically attributed to oxidative stress, activation of inflammatory pathways and the toxic effect of more than 4000 chemicals and carcinogens present in tobacco smoke [Environmental Protection Agency, 1992]. In addition, each puff contains  $>1 \times 10^{15}$  free radicals [Pryor and Stone, 1993]. All of these chemicals are emitted mostly during the combustion process, which is absent in ECs. Although the addictive potential of nicotine and related compounds is largely documented [Guillem *et al.*



**Figure 2.** Methodology for literature research and selection of studies.

2005], much less dissemination has been given to the notion that nicotine does not contribute to smoking-related diseases. It is not classified as a carcinogen by the International Agency for Research on Cancer [WHO-IARC, 2004] and does not promote obstructive lung disease. A major misconception, commonly supported even by physicians, is that nicotine promotes cardiovascular disease. However, it has been established that nicotine itself has minimal effect in initiating and promoting atherosclerotic heart disease [Ambrose and Barua, 2004]. It does not promote platelet aggregation [Zevin *et al.* 1998], does not affect coronary circulation [Nitenberg and Antony, 1999] and does not adversely alter the lipid profile [Ludviksdottir *et al.* 1999]. An observational study of more than 33,000 smokers found no evidence of increased risk for myocardial infarction or acute stroke after NRT subscription, although follow up was only 56 days [Hubbard *et al.* 2005]. Up to 5 years of nicotine gum use in the Lung Health Study was unrelated

to cardiovascular diseases or other serious side effects [Murray *et al.* 1996]. A meta-analysis of 35 clinical trials found no evidence of cardiovascular or other life-threatening adverse effects caused by nicotine intake [Greenland *et al.* 1998]. Even in patients with established cardiovascular disease, nicotine use in the form of NRTs does not increase cardiovascular risk [Woolf *et al.* 2012; Benowitz and Gourlay, 1997]. It is anticipated that any product delivering nicotine without involving combustion, such as the EC, would confer a significantly lower risk compared with conventional cigarettes and to other nicotine containing combustible products.

The importance of using nicotine in the long-term was recognized several years ago by Russell, indicating that the potential of nicotine delivery systems as long-term alternatives to tobacco should be explored in order to make the elimination of tobacco a realistic future target [Russell, 1991]. However, current regulations restrict the

long-term use of pharmaceutical or recreational nicotine products (such as snus) [Le Houezec *et al.* 2011]. In other words, nicotine intake has been demonized, although evidence suggests that, besides being useful in smoking cessation, it may even have beneficial effects in a variety of disorders such as Parkinson's disease [Nielsen *et al.* 2013], depression [McClernon *et al.* 2006], dementia [Sahakian *et al.* 1989] and ulcerative colitis [Guslandi, 1999]. Obviously, the addictive potential is an important factor in any decision to endorse nicotine administration; however, it should be considered as slight 'collateral damage' with minimal impact to vapers' health compared with the tremendous benefit of eliminating all disease-related substances coming from tobacco smoking. In fact, smokers are already addicted to nicotine; therefore the use of a 'cleaner' form of nicotine delivery would not represent any additional risk of addiction. Surveys have shown that ECs are used as long-term substitutes to smoking [Dawkins *et al.* 2013; Etter and Bullen, 2012]. Although consumers try to reduce nicotine use with ECs, many are unable to completely stop its intake, indicating an important role for nicotine in the ECs' effectiveness as a smoking substitute [Farsalinos *et al.* 2013b].

Nicotine overdose or intoxication is unlikely to occur with vaping, since the amount consumed [Farsalinos *et al.* 2013c] and absorbed [Nides *et al.* 2014; Dawkins and Corcoran, 2013] is quite low. Moreover, although not yet proven, it is expected that vapers will self-titrate their nicotine intake in a similar way to tobacco cigarettes [Benowitz *et al.* 1998]. Last, but not least, there is evidence suggesting that nicotine cannot be delivered as fast and effectively from ECs compared to tobacco cigarettes [Farsalinos *et al.* 2014]. Therefore, it seems that ECs have a huge theoretical advantage in terms of health risks compared with conventional cigarettes due to the absence of toxic chemicals that are generated in vast quantities by combustion. Furthermore, nicotine delivery by ECs is unlikely to represent a significant safety issue, particularly when considering they are intended to replace tobacco cigarettes, the most efficient nicotine delivery product.

#### Studies on the safety/risk profile of ECs

Findings on the safety/risk profile of ECs have just started to accumulate. However, this research must be considered work in progress given that the safety/risk of any product reflects an evolving

body of knowledge and also because the product itself is undergoing constant development.

Existing studies about the safety/risk profile of ECs can be divided into chemical, toxicological and clinical studies (Table 1). Obviously, clinical studies are the most informative, but also the most demanding because of several methodological, logistical, ethical and financial challenges. In particular, exploring safety/risk profile in cohorts of well-characterized users in the long-term is required to address the potential of future disease development, but it would take hundreds of users to be followed for a substantial number of years before any conclusions are made. Therefore, most research is currently focused on *in vitro* effects, with clinical studies confined into evaluation of short-term use or pathophysiological mechanisms of smoking-related diseases.

#### Chemical studies

Chemical studies are relatively simple and cheap to perform and provide quick results. However, there are several disadvantages with this approach. Research is usually focused on the known specific chemicals (generally those known to be toxic from studies of cigarette smoke) and fails to address unknown, potentially toxic contaminants that could be detected in the liquid or the emitted aerosol. Problems may also arise from the detection of the chemicals in flavors. Such substances, although approved for use in the food industry, have largely unknown effects when heated and inhaled; thus, information on the presence of such substances is difficult to interpret in terms of *in vivo* effects. In fact, chemical studies do not provide any objective information about the effects of use; they can only be used to calculate the risk based on theoretical models and on already established safety levels determined by health authorities. An overview of the chemical studies performed on ECs is displayed in Table 2.

Laugesen performed the first studies evaluating the chemical composition of EC aerosols [Laugesen, 2008, 2009]. The temperature of the resistance of the tested EC was 54°C during activation, which is approximately 5–10% of the temperature of a burning tobacco cigarette. Toxic chemicals such as heavy metals, carcinogenic polycyclic aromatic hydrocarbons and phenols were not detected, with the exception of trivial amounts of mercury (0.17 ng per EC) and traces of formaldehyde and acetaldehyde. Laugesen

**Table 1.** Types of studies performed to determine safety and to estimate risk from EC use.

Type of studies	Research subject	Advantages	Disadvantages
Chemical studies	Evaluate the chemical composition of liquids and/or aerosol. Examine environmental exposure (passive 'vaping').	Easier and faster to perform. Less expensive. Could realistically be implemented for regulatory purposes.	Usually targeted on specific chemicals. Unknown effects of flavorings when inhaled. No validated protocols for vapor production. Provide no objective evidence about the end results (effects) of use (besides by applying theoretical models).
Toxicological studies	Evaluate the effects on cell cultures or experimental animals.	Provide some information about the effects from use.	Difficult to interpret the results in terms of human <i>in vivo</i> effects. More expensive than chemical studies. Need to test aerosol and not liquid. Standards for exposure protocols have not been clearly defined.
Clinical studies	Studies on human <i>in vivo</i> effects.	Provide definite and objective evidence about the effects of use.	Difficult and expensive to perform. Long-term follow up is needed due to the expected lag from initiation of use to possible development of any clinically evident disease. For now, limited to acute effects from use.

evaluated emissions based on a toxicant emissions score and reported a score of 0 in ECs compared with a score of 100–134 for tobacco cigarettes (Figure 3). The US Food and Drug Administration (FDA) also performed chemical analyses on 18 commercially available products in 2009 [Westenberger, 2009]. They detected the presence of tobacco-specific nitrosamines (TSNAs) but did not declare the levels found. Small amounts of diethylene glycol were also found in one sample, which was unlikely to cause any harm from normal use. Another study identified small amounts of amino-tandafil and rimonabant in EC liquids [Hadwiger *et al.* 2010]. Subsequently, several laboratories performed similar tests, mostly on liquids, with Cahn and Siegel publishing a review on the chemical analyses of ECs and comparing the findings with tobacco cigarettes and other tobacco products [Cahn and Siegel, 2011]. They reported that TSNA levels were similar to those measured in pharmaceutical NRTs. The authors concluded that, based on chemical analysis, ECs are far less harmful compared with tobacco cigarettes. The most comprehensive study on TSNAs has been performed recently by a South Korean group, evaluating 105 liquids obtained from local retailers [Kim and Shin, 2013]. On average, they found 12.99 ng TSNAs per ml of liquid, with the amount of daily exposure to the users estimated to be similar to users of NRTs [Farsalinos *et al.* 2013d]. The estimated daily exposure to nitrosamines from tobacco cigarettes (average consumption of 15 cigarettes per day) is estimated to be up to 1800 times higher

compared with EC use (Table 3). Etter and colleagues evaluated the accuracy of nicotine labeling and the presence of nicotine impurities and degradation products in 20 EC liquid samples [Etter *et al.* 2013]. They found that nicotine levels were 85–121% of what was labeled, while nicotine degradation products were present at levels of 0–4.4%. Although in some samples the levels were higher than those specified in European Pharmacopoeia, they are not expected to cause any measurable harm to users.

Besides the evaluation for the presence of TSNAs, analyses have been performed for the detection of carbonyl compounds. It is known that the thermal degradation of propylene glycol and glycerol can lead to the emission of toxic compounds such as aldehydes [Antal *et al.* 1985; Stein *et al.* 1983]. Goniewicz and colleagues evaluated the emission of 15 carbonyls from 12 brands of ECs (mostly first-generation) [Goniewicz *et al.* 2013]. In order to produce vapor, researchers used a smoking machine and followed a regime of 1.8-second puffs with a very short 10-second interpuff interval, which does not represent realistic use [Farsalinos *et al.* 2013c]; although the puff duration was low, interpuff interval was remarkably short, which could potentially lead to overheating. In addition, the same puff number was used in all devices tested, although there was a significant difference in the design and liquid content between devices. Despite these limitations, out of 15 carbonyls, only 3 were detected (formaldehyde, acetaldehyde and acrolein); levels were

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