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OFFICIAL STATEMENT

Position statement on electronic cigarettes or electronic nicotine delivery systems

An official statement of the E-cigarette Working Group of the International Union Against Tuberculosis and Lung Disease*

T. S. Bam, W. Bellew, I. Berezhnova, A. Jackson-Morris, A. Jones, E. Latif, M. A. Molinari, G. Quan, R. J. Singh, M. Wisotzky

Tobacco Control Department, International Union Against Tuberculosis and Lung Disease, Paris, France

KEY MESSAGES

- The International Union Against Tuberculosis and Lung Disease (The Union) has issued this position statement based on a careful review of the scientific evidence; the position statement will be reviewed by mid-2015.
- The safety of electronic cigarettes (ECs) or electronic nicotine delivery systems (ENDS) has *not* been scientifically demonstrated.
- Adverse health effects for third parties exposed (second-hand exposure) cannot be excluded because the use of electronic cigarettes leads to emission of fine and ultrafine inhalable liquid particles, nicotine and cancer-causing substances into indoor air.
- The benefits of e-cigarettes have not been scientifically proven. To date, very few studies have assessed ECs/ENDS as a harm reduction and cessation aid, with conflicting findings.
- The Union is concerned that the marketing, awareness and use of ECs or ENDS is growing rapidly.
- A range of current and proposed legislative and regulatory options exists; some countries (such as Brazil, Norway, and Singapore) have banned ECs/ENDS completely.
- ENDS could undermine the implementation of the World Health Organization (WHO) Framework Convention on Tobacco Control (FCTC) Article 12 (denormalisation of tobacco use); use of ENDS could also hamper the implementation of Article 8 (protection from exposure to tobacco smoke), as ENDS users in public places may claim that their electronic cigarette does not contain tobacco and/or does not produce second-hand tobacco smoke.
- The Union strongly supports the regulation of the manufacture, marketing and sale of electronic cigarettes or ENDS; the preferred option is to regulate ECs or ENDS as medicines.
- If regulation as medicines is not feasible, the following measures should be considered, pending the availability of reliable evidence:
  - —a comprehensive ban on all advertising, promotion and sponsorship;
  - —promotion of ECs/ENDS for tobacco cessation to be prohibited;
  - —display of ECs/ENDS in retail stores to be prohibited;
  - —sale to minors (persons under the age of full legal responsibility) to be prohibited;
  - —ECs/ENDS and their refills should not be sold in flavours that are appealing to children;
  - —packaging and labelling of EC/ENDS cartridges and disposable ECs/ENDS should include a list of all ingredients, stipulate the quantity of nicotine and include appropriate warning labels;
  - —ECs/ENDS should not be used in public places, workplaces or on public transportation;
  - —consumer safety standards for EC cartridges should be established, including ensuring manufacturing consistency and regulating the maximum quantity/dosage of nicotine they may contain.

POSITION STATEMENT

1 **Electronic cigarettes (ECs) or electronic nicotine delivery systems (ENDS)** may be defined as devices whose function is to vaporise and deliver to the lungs of the user a chemical mixture typically composed of nicotine, propylene glycol and other

*Ratified by The Union Board of Directors on 1 November 2013. This statement is continued in the online version, available at http://www.ingentaconnect.com/content/iuatld/ijtld/2014/00000018/00000001/art00003

Correspondence to: Bill Bellew and Myra Wisotzky, Tobacco Control Department, International Union Against Tuberculosis and Lung Disease, 8 Ranolph Crescent, Edinburgh EH3 7TH, UK. e-mail: bbellew@theunion.org, mwisotzky@theunion.org

chemicals, although some products claim to contain no nicotine. Each device contains an electronic vaporisation system, rechargeable batteries, electronic controls and cartridges of the liquid that is vaporised. These products are not currently regulated or monitored, so the contents may vary between different e-cigarettes and may not be known to the consumer. ENDS initially emerged in China in 2003 and have since become widely available globally, particularly over the Internet.

2 **The safety of ECs or ENDS has *not* been scientifically demonstrated.** The potential risks they pose for the health of users remain undetermined. Furthermore, scientific testing indicates that the products vary widely in the amount of nicotine and other chemicals they deliver, and there is no way for consumers to find out what is actually delivered by the product they have purchased. As ENDS do not generate the smoke that is associated with the combustion of tobacco, their use is commonly believed by consumers to be safer than smoking tobacco. This illusive 'safety' of ENDS can be enticing to consumers; however, the chemicals used in electronic cigarettes have not been fully disclosed, and there are no adequate data on their emissions. Adverse health effects for exposed third parties (second-hand exposure) cannot be excluded because the use of electronic cigarettes leads to emission of fine and ultrafine inhalable liquid particles, nicotine and cancer-causing substances into indoor air.

3 **Awareness and use of ECs or ENDS is growing rapidly.** Population-based estimates of awareness (among current and former smokers) for the year 2010 are in the range of 32.2–40.9% for the United States; for the year 2011 estimates for the United States are 57.9–73.4%, for the United Kingdom 54.4%, for Canada 39.5%, for Australia 20% and for Indonesia 10.9%. Use of ENDS among current and former tobacco users in 2010–2011 was estimated at 6% for the United States, 4% for the United Kingdom, and 1% for both Canada and Australia, and use of ENDS among Indonesian men is 0.5%. However a recent report by the UK Medicines and Healthcare Products Regulatory Agency found that a tenth of UK smokers now use e-cigarettes; the number of UK users has risen to around 1.3 million in 2013, up from 700 000 in the previous year. A recent study by the US Centers for Disease Control and Prevention showed that e-cigarette experimentation and recent use doubled among US middle and high school students during 2011–2012, resulting in an estimated 1.78 million students ever having used e-cigarettes as of 2012. This is of serious concern because the overall impact of e-cigarette use on public health remains uncertain. In youths, concerns include the potential negative impact of nicotine on adolescent brain development as well as the risk of nicotine addiction and initiation of the use of conventional cigarettes or other tobacco products.

4 **The benefits of e-cigarettes have not been scientifically proven. To date, few studies have assessed ECs/ENDS as a harm reduction or cessation aid, with conflicting findings.** For example, one study, with positive findings, was based on a very small prospective study that monitored possible modifications in the smoking habits of 40 regular smokers; another with equivocal findings was based on a sample of 5939 current and former smokers across four countries. The all-important 'bottom line' from the 'four-country' study was that ENDS users were not more likely to quit smoking than non-users (further waves of research in this longitudinal study will yield important insights into this important question). More recently, a randomised controlled trial conducted in New Zealand found that e-cigarettes, with or without nicotine, were modestly effective at helping smokers to quit, with similar achievement of abstinence as with nicotine patches, and few adverse events.

5 **A range of proposals for legislative and regulatory approaches to ENDS currently exist.** Electronic cigarettes and other electronic products containing nicotine are to be regulated as medicines in the United Kingdom from 2016, to ensure their quality and safety. The United Kingdom's plans are aligned with forthcoming European legislation, so e-cigarettes would not be required to obtain a medicines licence until the European Commission's Tobacco Products Directive is agreed and becomes UK law in 2016. The United Kingdom's decision contrasts with those of some countries that have introduced restrictions on the sale and use of e-cigarettes and other countries that have banned them completely, such as Brazil, Norway and Singapore. In the United States, e-cigarettes that are marketed for therapeutic purposes are regulated by the US Food and Drug Administration (FDA) Center for Drug Evaluation and Research (CDER). The FDA Center for Tobacco Products (CTP) currently regulates cigarettes, cigarette tobacco, roll-your-own tobacco and smokeless tobacco. The FDA has stated its intention to issue a proposed rule that would extend the FDA's tobacco product authorities to products that meet the statutory definition of 'tobacco product'. The Food and Drug Monitoring Agency in Indonesia has warned the Indonesian people that electronic cigarettes could be more dangerous than regular cigarettes. ECs are illegal in Indonesia.

6 **ENDS could undermine the implementation of the WHO Framework Convention on Tobacco Control Article 12 (denormalisation of tobacco use); use of ENDS could also hamper the implementation of Article 8 (protection from exposure to**

tobacco smoke), as ENDS users in public places may claim that their electronic cigarette does not contain tobacco and/or does not produce second-hand tobacco smoke. The WHO FCTC Secretariat has produced a report entitled 'Electronic nicotine delivery systems, including electronic cigarettes'.*

7 **The Union strongly supports the regulation of the manufacture, marketing and sale of electronic cigarettes or electronic nicotine delivery systems. The preferred option is to regulate ECs or ENDS as medicines.**

8 **If regulation as medicines is not feasible, the following measures should be considered, pending the availability of reliable evidence:**
- a comprehensive ban on all advertising, promotion and sponsorship;
- promotion of ECs/ENDS for tobacco cessation to be prohibited;
- display of ECs/ENDS in retail stores to be prohibited;
- sale to minors (persons under the age of full legal responsibility) should be prohibited;
- ECs/ENDS and their refills should not be sold in flavours that are appealing to children;
- packaging and labelling of EC/ENDS cartridges and disposable ECs/ENDS should include a list of all ingredients, stipulate the quantity of nicotine and include appropriate warning labels;
- ECs/ENDS should not be used in public places, workplaces or on public transportation;
- consumer safety standards for EC cartridges should be established, including ensuring manufacturing consistency and regulating the maximum quantity/dosage of nicotine they may contain.

* An excerpt from the report is featured in online Appendix A.

Continued: Position statement on electronic cigarettes or electronic nicotine delivery systems

DEFINITION

Electronic cigarettes (ECs) or electronic nicotine delivery systems (ENDS) are devices whose function is to vaporise and deliver to the lungs of the user a chemical mixture typically composed of nicotine, propylene glycol and other chemicals, although some products claim to contain no nicotine. A number of ENDS are offered in flavours that can be particularly attractive to adolescents. Electronic cigarettes are the most common prototype of ENDS. Each device contains an electronic vaporisation system, rechargeable batteries, electronic controls and cartridges of the liquid that is vaporised. The manufacturers report that the cartridges typically contain between 6 and 24 mg of nicotine, but sometimes can contain more than 100 mg. In the form of tobacco products, nicotine is an addictive chemical that in excessive amounts can be lethal (0.5–1.0 mg per kg of weight of the person). Most ENDS are shaped to look like their conventional (tobacco) counterparts (e.g., cigarettes, cigars, cigarillos, pipes, hookahs or shishas). They are also sometimes made to look like everyday items such as pens and USB memory sticks, for people who wish to use the product without other people noticing.[1] Where included, the levels of the nicotine can vary drastically and cartridges can also contain candy-like flavourings. These products are not currently regulated or monitored, so the contents may vary between different e-cigarettes and may not be known to the consumer.[2] ENDS initially emerged in China in 2003 and have since become widely available globally, particularly over the Internet.[3] Documents from the Legacy Tobacco Documents Library also show that the Philip Morris company was experimenting with ECs as early as the 1990s.[4]

CONSUMER SAFETY

The safety of ECs or ENDS has ***not*** been scientifically demonstrated.[1,2,5–8]

The health impact from long-term inhalation of propylene glycol through the lung is of particular concern and has not been fully investigated. The potential risks they pose for the health of users remain undetermined. Furthermore, scientific testing indicates that the products vary widely in the amount of nicotine and other chemicals they deliver, and there is no way for consumers to find out what is actually delivered by the product they have purchased.[1,9]

Most ENDS contain large concentrations of propylene glycol, which is a known irritant when inhaled. The testing of some of these products also suggests the presence of other toxic chemicals, aside from nicotine. In addition, use of these products—when they contain nicotine—can pose a risk for nicotine poisoning (i.e., if a child of 30 kilos of weight swallows the contents of a nicotine cartridge of 24 mg this could cause acute nicotine poisoning that most likely would cause his/her death) and a risk of addiction among non-smokers of tobacco products. Nicotine, inhaled, ingested or in direct contact with the skin, can be particularly hazardous to the health and safety of certain segments of the population, such as children, young people, pregnant women, nursing mothers, people with heart conditions and the elderly. ENDS and their nicotine cartridges and refill accessories must be kept out of the reach of young children at all times in view of the risk of choking or nicotine poisoning. Tests by the US Food and Drug Administration (FDA) on some ECs showed the presence of diethylene glycol, a chemical that has a history of mass poisonings and deaths when inadvertently substituted for propylene glycol in consumer products. The additional presence of irritants, solvents, genotoxins and animal carcinogens (e.g., butyl acetate, diethyl carbonate, benzoic acid, quinoline, dioctyl phthalate 2,6-dimethyl phenol) is of unclear significance but needs further consideration.[10] As ENDS do not, according to the World Health Organization (WHO), generate the smoke that is associated with the combustion of tobacco, their use is commonly believed by consumers to be safer than smoking tobacco. This illusive 'safety' of ENDS can be enticing to consumers; however, the chemicals used in electronic cigarettes have not been fully disclosed, and there are no adequate data on their emissions.[1]

Several laboratory type studies involving live human subjects,[11–14] or other models,[15–17] underline concerns about negative consequences for health. These concerns include the presence of metal and silicate particles in cartomiser* aerosol which demonstrate the need for improved quality control in EC design and manufacture,[18] nicotinergic dose and impact,[11] lung function,[12] the presence of chemicals such as glycerol and propylene glycol in the nicotine-containing liquid of cartridges, design flaws, lack of adequate labelling and quality control variation in contents and misleading information on product ingredients,[13,16] the need to fully assess the possible cytotoxic prenatal effect of EC refill fluids,[15] the decreasing amount of aerosol produced by e-cigarettes during smoking, which necessitates increasing puff strength to produce aerosol and the potential adverse effects of this on human health.[14,17] These design flaws, lack of adequate labelling and concerns about quality control and health issues have led some researchers to conclude the need for product regulation,[14] and that regulators

*A cartomiser is a device consisting of an atomiser and cartridge, all in one piece, that connects to the battery.

should consider removing ENDS from the market until their safety can be adequately evaluated.[16]

ECs/ENDS are not emission-free; they contain volatile organic substances, including propylene glycol, flavours and nicotine, and are emitted as mist or aerosol into indoor air. The substances emitted by ECs/ENDS may be inhaled by non-users, especially when used indoors. Adverse health effects for exposed third parties cannot be excluded, because the use of electronic cigarettes leads to emission of fine and ultrafine inhalable liquid particles, nicotine and cancer-causing substances into indoor air.[19]

PREVALENCE ESTIMATES OF EC/ENDS AWARENESS AND USE

A recent review found that a tenth of UK smokers now use e-cigarettes; the number of UK users has risen to around 1.3 million in 2013, up from 700 000 in the previous year. The vast majority of EC users were current or former smokers, and many feared that they would return to smoking tobacco if the products were banned. There was little evidence of use of e-cigarettes by children who weren't already smokers.[9]

Several studies of prevalence have been conducted in the United States,[20–24] including a four-country survey which also examined prevalence in Canada, Australia and the United Kingdom.[3] Popova and colleagues' nationally representative probability-based cross-sectional survey of 1836 current or recently former adult smokers was completed in November 2011. Of smokers, 38% had tried an alternative tobacco product, most frequently e-cigarettes. Alternative tobacco product use was associated with having made a quit attempt, and those intending to quit were significantly more likely to have tried and to currently use the products than were smokers with no intention to quit. Use was not associated with successful quit attempts. Interest in future use of alternative tobacco products was low, except for e-cigarettes. The researchers concluded that these data did not indicate that alternative tobacco products promote cessation.[20]

Regan and colleagues conducted a consumer-based mail-in survey that was completed by 10 587 adults (⩾18 years) in 2009 and 10 328 adults in 2010. Data from these surveys were used to provide estimates of awareness, ever use and past month use of ENDS from 2009 to 2010 and to assess demographic characteristics and tobacco use of ENDS users. Awareness of ENDS doubled from 16.4% in 2009 to 32.2% in 2010; 'ever use' more than quadrupled, from 0.6% in 2009 to 2.7% in 2010. 'Ever use' of ENDS was most common among women and those with lower education, although these were not the groups who had heard of ENDS most often. Current smokers and tobacco users were most likely to try ENDS. Current smokers who had tried ENDS did not say they planned to quit smoking more often than smokers who had never tried them.[21]

King and colleagues conducted national consumer-based surveys of US adults aged ⩾18 years. In 2010, data collection was both mail-based (n = 4184) and web-based (n = 2505); in 2011, it was web-based (n = 4050) only. Estimates of awareness and ever-use of e-cigarettes were calculated overall and by sex, age, race/ethnicity, educational attainment, household income, region and smoking status. In 2010, overall awareness of e-cigarettes was 38.5% (mail survey) and 40.9% (web survey); in 2011, awareness was 57.9% (web survey). Ever-use of e-cigarettes among all respondents was 2.1% in the 2010 mail survey, 3.3% in the 2010 web survey, and 6.2% in the 2011 web survey. Ever-use of e-cigarettes was significantly higher among current smokers compared with both former and never-smokers, irrespective of survey method or year. During 2010–2011, ever-use increased among both sexes, those aged 45–54 years, non-Hispanic Whites, those living in the South, and current and former smokers. The researchers concluded that awareness and ever-use of e-cigarettes increased among US adults from 2010 to 2011. In 2011, approximately 1 in 5 current smokers reported ever having used e-cigarettes.[22]

Pearson and colleagues have reported data from two surveys conducted in 2010: a national online study (n = 2649) and the Legacy Longitudinal Smoker Cohort (n = 3658). Multivariate models were used to examine EC awareness, use, and harm perceptions. In the online survey, 40.2% (95%CI 37.3–43.1) had heard of ECs, with awareness highest among current smokers. Utilisation was higher among current smokers, estimated at 11.4% (95%CI 9.3–14.0), than in the total population—3.4% (95%CI 2.6–4.2]. The researchers found that 2.0% of former smokers (95%CI 1.0–3.8) and 0.8% of never-smokers (95%CI 0.35–1.7) reported ever using ECs. In both surveys, non-Hispanic Whites, current smokers, young adults, and those with at least a high-school diploma were most likely to perceive ECs as less harmful than regular cigarettes.[23]

McMillen and colleagues have reported what they describe as the 'first nationally representative estimates for use of four emerging products' (snus, waterpipe, dissolvable tobacco products and ENDS). A mixed-mode survey was used to obtain two representative samples of US adults. Of 3240 eligible respondents contacted, 74% completed the survey. In the weighted analysis, 13.6% of respondents had tried at least one emerging tobacco product: snus 5.1%, waterpipe 8.8%, dissolvable tobacco products 0.6% and ENDS 1.8%. Daily smokers (25.1%) and non-daily smokers (34.9%) were the most likely to have tried at least one of these products, compared to former smokers (17.2%) and never smokers (7.7%, $P <$ 0.001); 18.2% of young adults aged 18–24 years and

Table 1 Prevalence of ENDS awareness, trial and use among current and former tobacco users, % yes*

Country	Aware of ENDS (overall)	Tried ENDS (overall)	Tried ENDS (among aware)	Current ENDS user (overall)	Current ENDS user (among tried)
All countries	46.6	7.6	16.3	2.9	38.7
Canada	39.5	4.0	10.0	1.0	33.0
United States	73.4	14.9	20.4	6.0	37.0
United Kingdom	54.4	9.6	17.7	4.0	46.0
Australia	20.0	2.0	11.0	1.0	27.0

*Adapted from Adkison et al.[3]
ENDS = electronic nicotine delivery systems.

12.8% of those aged >24 had tried one of these products ($P < 0.01$). In multivariate analysis, current daily (odds ratio [OR] 5.5, 95% confidence interval [CI] 4.3–7.6), nondaily (OR 6.1, 95%CI 4.0–9.3), and former smoking status (OR 2.7, 95%CI 2.1–3.6) remained significant, as did young adults (OR 2.2, 95%CI 1.6–3.0), males (OR 3.5, 95%CI 2.8–4.5), higher educational attainment, some college (OR 2.7, 95%CI 1.7–4.2) and college degree (OR 2.0, 95%CI 1.3–3.3). The researchers concluded that use of these products raises concerns about non-smokers being at risk for nicotine dependence and current smokers maintaining their dependence.[24]

In 2013, the September 6th edition of MMWR reported that e-cigarette experimentation and recent use had doubled among US middle and high school students during 2011–2012, resulting in an estimated 1.78 million students having ever used e-cigarettes as of 2012. Moreover, in 2012, an estimated 160 000 students who reported ever using e-cigarettes had never used conventional cigarettes. This is of serious concern because the overall impact of e-cigarette use on public health remains uncertain. In youths, concerns include the potential negative impact of nicotine on adolescent brain development, as well as the risk for nicotine addiction and initiation of the use of conventional cigarettes or other tobacco products.[25]

A well-designed four-country survey conducted by Adkison and colleagues has reported prevalence of ENDS use in the United States, United Kingdom, Canada and Australia (Table 1).[3] Overall, 46.6% were aware of ENDS (United States 73%, United Kingdom 54%, Canada 40%, Australia 20%); 7.6% had tried ENDS (16% of those aware of ENDS); and 2.9% were current users (39% of triers). Awareness of ENDS was higher among younger, non-minority smokers with higher incomes who were heavier smokers. Prevalence of trying ENDS was higher among younger, nondaily smokers with a high income and among those who perceived ENDS as less harmful than traditional cigarettes. Current use was higher among both nondaily and heavy (⩾20 cigarettes per day) smokers. In all, 79.8% reported using ENDS because they were considered less harmful than traditional cigarettes; 75.4% stated that they used ENDS to help them reduce their smoking; and 85.1% reported using ENDS to help them quit smoking. The researchers concluded that because the trial was associated with nondaily smoking and a desire to quit smoking, ENDS may have the potential to serve as a cessation aid.[3] It is noteworthy that in an effort to evaluate claims of reduction in cigarette use, change in the number of cigarettes per day was assessed between Wave 7 and Wave 8 (of this cohort study). *Quitting did not differ between users and non-users*: χ^2 (2, n = 4136) = 0.422 (P = 0.516); this is a note emphasised by the reviewer and not by the researchers, although it was included in their paper and key findings. This aspect of the findings has also been noted by Chapman.[26]

The Global Adult Tobacco Survey 2011 for Indonesia shows that, overall, 10.9% of adults had heard about electronic cigarettes, but only 0.3% had used them (in males 0.5%). More men than women had heard about electronic cigarettes (16.8% and 5.1%, respectively), as well as those in the age groups 15–24 and 25–44 years (14.4% and 12.4%, respectively), those living in urban areas (15.3%), people with higher levels of education (secondary 11.5%, high school 20.3%, and college and university 29.4%), those who are employed (16.3%) and students (19.1%).[27]

By the end of 2012, according to estimates by Euromonitor International, the EC/ENDS market was worth in excess of US$2 billion globally (about the size of the global small cigars market).[28]

EVIDENCE ABOUT EC/ENDS AND HARM REDUCTION

To date, few studies of acceptable quality have assessed ENDS as a harm reduction and cessation aid. In September 2013, Bullen and colleagues reported on the findings from a randomised controlled trial conducted in New Zealand, in which 657 people were randomised (289 to nicotine e-cigarettes, 295 to nicotine patches, and 73 to placebo e-cigarettes) and included in an intention-to-treat analysis. At 6 months, verified abstinence was 7.3% (21 of 289) with nicotine e-cigarettes, 5.8% (17 of 295) with patches, and

4.1% (three of 73) with placebo e-cigarettes (risk difference for nicotine e-cigarette vs. patches 1.51 [95%CI −2.49–5.51]; for nicotine e-cigarettes vs. placebo e-cigarettes 3.16 [95%CI −2.29–8.61]). Achievement of abstinence was substantially lower than the researchers anticipated for the power calculations, and they thus had insufficient statistical power to conclude superiority of nicotine e-cigarettes over patches or placebo e-cigarettes. No significant differences in adverse events were identified.[29]

Adkison and colleagues have reported data from Wave 8 of the International Tobacco Control (ITC) Four-Country Survey conducted from July 2010 to June 2011 in the United States, United Kingdom, Canada and Australia, via telephone interviews and web surveys. Data were collected for 5939 respondents across the four countries: United States (n = 1520), United Kingdom (n = 1325), Canada (n = 1581), Australia (n = 1513). Nearly three quarters (70.4%) of this sample reported that they used ENDS as a way to obtain nicotine in smokefree spaces, indicating that ENDS were being used also to satisfy nicotine addiction during periods of temporary abstinence. Current ENDS use was associated with a greater reduction in cigarettes per day over time, compared to non-ENDS users (among cohort participants, where data were available). *The all-important 'bottom line' was that ENDS users were not more likely to quit smoking than non-users*. With the addition of future International Tobacco Control survey waves, it will be possible to track whether those self-selecting to use ENDS compared to those not using ENDS are more or less successful with their efforts to abstain from smoking. Limitations of the study include sampling of only current and former cigarette smokers (understanding the awareness, trial, and use of ENDS among non-smokers, in particular adolescents, is of great importance to understanding their potential impact on public health).[3]

Caponnetto and colleagues reported in 2013 on a study designed to evaluate smoking reduction/abstinence in 300 smokers 'not intending to quit', experimenting with two different nicotine strengths of a popular e-cigarette model ('Categoria'; Arbi Group Srl, Italy) compared to its non-nicotine choice. The authors concluded that '*in smokers not intending to quit*' (author's emphasis), the use of e-cigarettes, with or without nicotine, reduced cigarette consumption and elicited enduring tobacco abstinence without causing significant side effects.[30]

Polosa and colleagues reported in 2013 on a small (n = 40) prospective observational study that evaluated smoking reduction/abstinence in smokers *not intending to quit* using an e-cigarette[31] (also the Categoria brand—and very similar research team membership to Caponnetto et al.[30]). Of the 40 subjects, 17 were lost to follow-up at 24 months. Despite this 42% drop-out rate, the researchers felt able to conclude that long-term e-cigarette use can substantially reduce cigarette consumption in smokers not willing to quit, and is well tolerated.[31] In an earlier report of this same study, Polosa and colleagues reported in 2011 that the use of EC substantially reduced cigarette consumption without causing significant side effects in smokers not intending to quit; they also acknowledge that as this was a small and uncontrolled study, the results observed may be due to a chance finding and not to a true effect.[32]

In 2010, Eissenberg reported on a laboratory study that examined how two brands of electronic nicotine delivery devices (e-cigarettes) influence plasma nicotine levels, heart rate and cigarette craving in cigarette smokers, and compared these effects to those produced by smokers' usual brand of cigarettes (own brand). Relative to a tobacco cigarette, 10 puffs from either of the electronic nicotine delivery devices (e-cigarettes) with a 16 mg nicotine cartridge delivered little to no nicotine and suppressed craving less effectively. Importantly, these results were from two specific products tested under acute conditions in which puff number was controlled. The author concluded that, at the least, consumers should be aware that unlike several regulated nicotine products (e.g., gum, patch), these putative drug delivery systems do not deliver nicotine effectively after acute administration.[14]

WHO FRAMEWORK CONVENTION ON TOBACCO CONTROL

The Framework Convention on Tobacco Control (FCTC) Conference of the Parties' fifth session published a report in June 2012 inviting further comment on ENDS, including electronic cigarettes.[33] The report concluded that the popularity of ENDS was growing rapidly, that health and safety concerns have not been resolved and that more research must be conducted, especially with regard to their safety and the marketing claims made by the manufacturers. Parties were advised that to prevent the further spread of ENDS, a number of FCTC provisions could be used. Detailed advice derived from the FCTC Secretariat report is included in Appendix A.

LEGISLATIVE AND REGULATORY RESPONSES

Electronic cigarettes and other electronic products containing nicotine are to be regulated as medicines in the United Kingdom from 2016, to ensure their quality and safety. The move comes after an investigation into the products by the Medicines and Healthcare Products Regulatory Agency (MHRA).[34] This MHRA investigation included a public consultation; a review of existing studies and the MHRA's own commissioned research into the quality, safety, marketing,

and use of the products; and an impact analysis on the consequences of regulation.[9]

Once the MHRA licenses e-cigarettes and other nicotine containing products, health care professionals will be able to recommend them for the first time to smokers who want to quit or to reduce the harm caused to them by tobacco. However, as the MHRA's plans are aligned with forthcoming European legislation, e-cigarettes would not be required to obtain a medicines licence until the European Commission's Tobacco Products Directive is agreed and becomes UK law in 2016. The revision of the European Commission's Directive is expected to address the following main issues:

— how to regulate products that do not contain tobacco, but which are closely linked to smoking or tobacco consumption, for example electronic and herbal cigarettes;
— labelling and packaging of tobacco products;
— additives, such as flavourings, used in tobacco products;
— internet sales of tobacco products; and
— tracking and tracing of these products.

The United Kingdom's decision contrasts with those of some countries that have introduced restrictions on the sale and use of e-cigarettes and other countries that have banned them completely, such as Brazil, Norway and Singapore.[34] In Indonesia, the Food and Drug Monitoring Agency has warned the Indonesian people that electronic cigarettes could be more dangerous than regular cigarettes; ECs are illegal in Indonesia.[35]

In the United States, e-cigarettes that are marketed for therapeutic purposes are currently regulated by the US FDA Center for Drug Evaluation and Research (CDER). The FDA Center for Tobacco Products (CTP) currently regulates cigarettes, cigarette tobacco, roll-your-own tobacco, and smokeless tobacco. FDA has stated its intent to issue a proposed rule that would extend the FDA's tobacco product authorities to products that meet the statutory definition of 'tobacco product'.[36] The background to this is that the US Court of Appeals for the DC Circuit, in Sottera, Inc. *v.* Food & Drug Administration, 627 F.3d 891 (DC Cir. 2010), issued a decision with regard to e-cigarettes and other products 'made or derived from tobacco' and the jurisdictional line that should be drawn between 'tobacco products' and 'drugs', 'devices', and combination products, as the terms are defined in the FD&C Act. The court held that e-cigarettes and other products made or derived from tobacco can be regulated as 'tobacco products' under the Act and are not drugs/devices unless they are marketed for therapeutic purposes. The government decided not to seek further review of this decision, and the FDA will comply with the jurisdictional lines established by the Sottera case.[37]

In the Philippines, the Food and Drug Administration has issued a 2013 advisory notice on secondary exposure to EC/ENDS emissions. Citing the review published by the German Cancer Research Centre,[19] the advisory states that 'second-hand exposure to e-cigarette emission which may lead to adverse health effects cannot be excluded'. It goes on to recommend that: 'The public, especially the youth sector, is advised NOT to start smoking at all and to stop using cigarettes, cigars or e-cigarettes. Consistent with the mandate of the DOH and as provided by the TA No. 7394, otherwise known as the Consumer Act of the Philippines, the local government units (LGUs) shall be guided by this advisory in strengthening their ordinances against smoking in public places and on second-hand exposure to harmful substances'.[38]

STRUCTURED EVIDENCE REVIEW

Search strategy

Unless otherwise stated, the search period was January 2008 to August 2013, inclusive. Resources used were Medline/PreMedline, AMED (Allied and Complementary Medicine), Cochrane Database of Systematic Reviews to July 2013, Database of Abstracts of Reviews of Effects 3rd Quarter 2013, Cochrane Central Register of Controlled Trials to July 2013, Cochrane Methodology Register to 3rd Quarter 2012, Health Technology Assessment to 3rd Quarter 2013, National Health Service Economic Evaluation Database to 3rd Quarter 2013, Centers for Disease Control and Prevention Guide to Community Preventive Services, International Pharmaceutical Abstracts and PsycINFO. Search terms used were: electronics; electrical equipment and supplies; nicotine/*administration & dosage/*therapeutic use; smoking; smoking cessation; and tobacco products. Secondary sources were also searched for a selection of papers using a 'snowballing' technique. Internet searches were conducted using the search terms electronic cigarette, electronic nicotine delivery system, position statement and policy. After removal of duplicates, the database comprised 111 records, of which 13 were from the 'grey' literature. A tabulation of selected studies is featured in Appendix B.

Classification of retrieved studies

Classification of retrieved database records* resulted in the following:

2 were classified as 'meta-analysis'[39,40]
4 were classified as 'randomised controlled trial'[29,30,41,42]
2 were classified as 'cohort study'[3,31,32]

*Note that a paper may be classified in more than one category, for example a cross-sectional report from a cohort design.

22 were classified as 'cross-sectional study,'[3,20–25,43–57] [of which 4 were classified as 'cross-sectional analytic study'[23,44,50,55]]
9 were classified as 'position statement'[1,2,5–8,58–60]
3 were classified as 'technical report'[19,61,62]
4 records were classified as 'review: non- or semi-systematic'[9,63–65]
3 were classified as 'observational study'[66–68]
31 were classified as 'journal article–general'[10,26,34,69–96]
24 were classified as 'laboratory study'[11–18,97–112] (of which half were classified as 'laboratory study–human subjects'[11,12,14,98,102,104,105,108–112])
4 were classified as 'clinical case study'[113–116]
3 were classified as 'qualitative'[117–119]
4 were classified as 'public information bulletin'[9,36,37,120]

The evolution of evidence on ECs/ENDS is in a very early stage, and may currently be characterised as 'weak' (in terms of study designs capable of determining causality). General journal articles (including 'expert opinion' pieces) made up the largest proportion (27%), followed by laboratory studies (21%), cross-sectional studies (19%) and position statements (8%). Only four records categorised as 'Randomised controlled trial' were retrieved,[30,41,42,121] and of these, one described the study protocol rather than results of a trial.[41] Only two records classified as 'cohort study' were retrieved,[3,32] of which one involved only 40 subjects over a 24-week period.[32] Whilst two retained studies were classified as 'meta-analysis', these dealt with nicotine replacement therapy for smoking cessation[39] and use of smokeless tobacco and risk of myocardial infarction and stroke.[40] These were included for completeness, to note that 1) ECs/ENDS are not covered in the relevant Cochrane review, and 2) an association between use of smokeless tobacco products and risk of fatal myocardial infarction and stroke has been detected which does not seem to be explained by chance. In the absence of higher-quality study designs, there was of course no possibility for the availability of systematic reviews dealing specifically with ECs/ENDS (see Figure).

ANALYSIS OF POSITION STATEMENTS FROM SELECTED HEALTH AGENCIES

As part of the structured evidence review, an analysis was undertaken of key elements in EC/ENDS position statements from selected national/ international health agencies (see Table 2).[1,2,5–8,58,60] The most commonly included elements in organisational position statements on this issue were as follows:

1 Definition of EC/ENDS
2 Assessment of safety
3 Assessment of effectiveness as cessation aid
4 Assessment of effectiveness in harm reduction
5 General public health risk assessment
6 Recommendation for urgent (federal) regulation of the manufacture, marketing and sale of e-cigarettes and for states to apply laws governing cigarettes also to ECs
7 Recommendation for risk management of EC potential to undermine progress in tobacco control (TC Risk Management): regulate—sale of ECs to minors should be banned (Federal/State legislation)
8 TC Risk Management Recommendation: regulate —ECs cannot be sold in flavours that are appealing to children

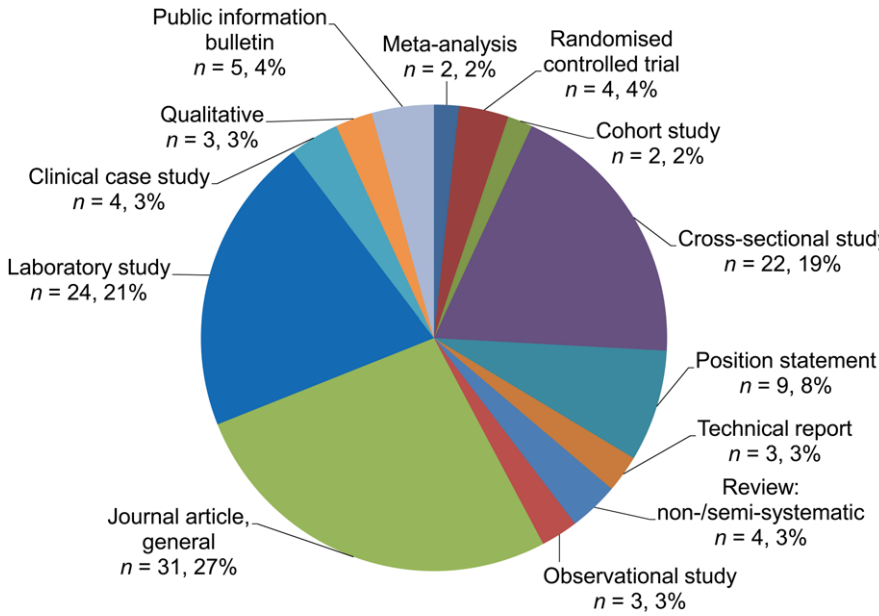

Figure Classification of retrieved studies (structured evidence review).

Table 2 Analysis of key elements in EC/ENDS position statements from selected national/international health agencies

Position statements – selection of the key elements	WHO	Scottish Directors of Public Health	NSRA (Canada)	CTFK (USA)	NACCHO (USA)	Canada Lung Association (Canada)	Cancer Society (NZ)	ACS, AHA, ALA, CTFK (USA)	The Union (proposed)
Definition of EC/ENDS	•	•	•			•	•	•	•
Assessment of safety	•	•	•	•		•	•	•	•
Assessment of effectiveness as cessation aid	•	•		•		•	•	•	•
Assessment of effectiveness in harm reduction	•	•		•			•		•
General public health risk assessment			•	•		•	•		•
Recommendation for urgent (federal) regulation of the manufacture, marketing and sale of ECs and for states to apply laws governing cigarettes also to ECs			•	•	•	•		•	•
Recommendation for risk management of EC potential to undermine progress in tobacco control (TC Risk Management): regulate – sale of ECs to minors should be banned (Federal/State legislation)			•	•	•				•
TC Risk Management recommendation: regulate – ECs cannot be sold in flavours that are appealing to children			•	•	•				•
TC Risk Management recommendation: regulate – ECs may not be used in indoor public places and workplaces			•	•		•			•
TC Risk Management recommendation: regulate – display of ECs in retail stores to be prohibited			•						•
TC Risk Management recommendation: regulate – ECs cannot be promoted except in adult-only venues and in direct mail to a named adult/restrict marketing that appeals to youth			•	•					•
Recommendation for consumer safety standards for EC cartridges, including ensuring manufacturing consistency and regulating the maximum quantity/ dosage of nicotine they may contain			•	•					•
Recommendation that packaging of EC cartridges and disposable ECs should include a list of all ingredients, as well as stipulating the quantity of nicotine/ appropriate warning labels			•						•
Explicit statement that consumers should avoid ECs	•	•							
Recommendation that health claims about ECs, including their effectiveness in helping smokers quit, should be illegal, and this measure actively enforced, until there is adequate scientific evidence to support such claims			•	•					•
Recommendation that sale of ECs should *not* be banned			•		•				
TC Risk Management recommendation: regulate – ECs may not be sold wherever the sale of tobacco is already prohibited			•						
TC Risk Management recommendation: regulate – ECs may not be used on school grounds			•						
Recommendation that sale of bottled e-liquid to consumers should be banned			•						
Recommendation that regulatory provisions governing manufacture, sale and use of ECs be reviewed within 5 years or sooner if significant new research becomes available			•						

EC = electronic cigarette; ENDS = electronic nicotine delivery systems; WHO = World Health Organization (International); NSRA = Non-Smokers' Rights Association (Canada); CTFK = Campaign for Tobacco Free Kids (USA); NACCHO = National Association of City and County Health Officials (USA); ACS = American Cancer Society (USA); AHA = American Heart Association (USA); ALA = American Lung Association (USA); The Union = International Union Against Tuberculosis and Lung Disease (International); TC = tobacco control.

9 TC Risk Management Recommendation: regulate —ECs may not be used in indoor public places and workplaces

Not included as position 'statements', but nonetheless very useful 'technical reports' and/or 'public information bulletins' were made available by the WHO[62] and by the US FDA.[36,37,120]

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APPENDIX A
ECS/ENDS AND THE WHO FCTC IN DETAIL

This is an excerpt from the FCTC Secretariat Report *Electronic Nicotine Delivery Systems, Including Electronic Cigarettes*.[33] The full Report by the Convention Secretariat is available at: http://apps.who.int/gb/fctc/PDF/cop5/FCTC_COP5_13-en.pdf.

ENDS and the WHO FCTC

1 It should be noted that ENDS are products resembling cigarettes and could therefore undermine the denormalisation of tobacco use upheld by the WHO FCTC. One of the guiding principles of the guidelines for implementation of Article 12 (Education, communication, training and public awareness) is Norm change. It stipulates that it is 'essential to change social, environmental and cultural norms and perceptions regarding the acceptability of the consumption of tobacco products, exposure to tobacco smoke . . .'*

   Parties are therefore invited to consider that a ban of ENDS as already undertaken by some Parties would contribute to changing the social norms regarding the consumption of tobacco products.

2 Another aspect to consider is that if ENDS are regarded as imitation tobacco products and banned, all ENDS would be covered, regardless of whether or not they contain nicotine, tobacco extracts, or make health claims. Parties may wish to consider that strong measures to prevent further spread of ENDS could be considered under a number of provisions of the WHO FCTC, including Article 5.2(b) which requires Parties to 'adopt and implement effective . . . measures . . . for preventing and reducing . . . nicotine addiction . . .' Most ENDS contain nicotine, and would therefore contribute to maintaining an addiction to nicotine.

3 Furthermore, under Article 13.2, Parties have an obligation to undertake a comprehensive ban of all tobacco advertising, promotion and sponsorship. 'Tobacco advertising and promotion' is defined in Article 1(c) as 'any form of commercial communication, recommendation or action with the aim, effect or likely effect of promoting a tobacco product or tobacco use either directly or indirectly'. Therefore, Parties may also wish to consider whether the sale, advertising, and even the use of electronic cigarettes can be considered as promoting tobacco use, either directly or indirectly. Regardless of whether or not ENDS contain nicotine or tobacco extracts, they are used to mimic smoking, which could be considered as a (direct or indirect) promotion of tobacco use. Article 16.1(c) could also be relevant since it requires Parties to prohibit 'the manufacture and sale of . . . any other objects in the form of tobacco products which appeal to minors'.

4 Additionally, the use of ENDS could hamper the implementation of Article 8 (Protection from exposure to tobacco smoke) as ENDS users in public places may claim that their electronic cigarette does not contain tobacco and/or does not produce second-hand tobacco smoke. Parties may also wish to note that Article 14 (Demand reduction measures concerning tobacco dependence and cessation) and its guidelines for implementation refer to evidence-based treatment for tobacco dependence and tobacco cessation, and to making available medications that have been clearly shown by scientific evidence to increase the chances of tobacco cessation.

5 If ENDS are not banned, a two-pronged strategy —regulating ENDS as both a tobacco and a medical product—could close potential loopholes in their regulation. However, Parties may again wish to consider the desirability of allowing the sale of new products that may have the capacity to maintain a nicotine addiction.

6 If a Party decided to categorise and regulate ENDS as tobacco products, all provisions of the WHO FCTC would also apply to ENDS. However, Parties may wish to consider that as ENDS are new products resembling tobacco products that would maintain a nicotine addiction, regulating them rather than banning them could grant these new products a level of legitimacy in terms of market access, even though they may be subject to the provisions of the WHO FCTC or to regulation as medical products. Parties may wish to consider that admitting such new products would not support the objective of the WHO FCTC as stated in Article 3, which is to '. . . reduce continually and substantially the prevalence of tobacco use . . .'

7 Regulating ENDS as medical products would most likely be the case for ENDS that are marketed with health or therapeutic claims. In this case, ENDS would be subject to the Party's relevant regulations, most notably the requirement to provide data substantiating those claims in order to obtain market authorisation.

8 In summary, ENDS are a new type of product entering the market with or without regulation by Parties. Specific complexities as derived from the review above could be summarised as follows:
   a there are many different product categories (with or without tobacco, with or without nicotine, with cartridge or single use, battery driven or chargeable);
   b the market for ENDS has increased significantly;

*The Guidelines for implementation of Article 12 of the WHO Framework Convention on Tobacco Control are available at: http://www.who.int/fctc/protocol/guidelines/adopted/article_12/en/index.html.

c Parties regulate ENDS differently, resulting in legal complexity, possible uncertainty and a regulatory gap in most countries;
d health and safety concerns have not been resolved;
e products may be subject to heavy marketing, including promotion to young people and use of flavourings;
f the role of ENDS is not clearly established: they are perceived in some quarters as smoking cessation aids, and in others as a starter or dual-use (to maintain nicotine addiction) product.

APPENDIX B
TABULATION OF SELECTED STUDIES

Details of study, reference, country	Study type and purpose	Key findings/key summary points
Caponnetto,[30] Italy	Randomised, controlled trial Designed to evaluate smoking reduction/abstinence in 300 smokers not intending to quit experimenting two different nicotine strengths of a popular e-cigarette model ('Categoria'; Arbi Group Srl, Italy) compared to its non-nicotine choice. Group A ($n = 100$) received 7.2 mg nicotine cartridges for 12 weeks; Group B ($n = 100$), a 6-week 7.2 mg nicotine cartridges followed by a further 6-week 5.4 mg nicotine cartridges; Group C ($n = 100$) received no-nicotine cartridges for 12 weeks. The study consisted of nine visits during which cigarette/day use and exhaled carbon monoxide levels were measured. Smoking reduction and abstinence rates were calculated. Adverse events and product preferences were also reviewed	Declines in cigarette/day use and eCO levels were observed at each study visits in all three study groups ($P < 0.001$ vs. baseline), with no consistent differences among study groups. Smoking reduction was documented in 22.3% and 10.3% at week 12 and week 52, respectively. Complete abstinence from tobacco smoking was documented in 10.7% and 8.7% at week 12 and week 52, respectively. A substantial decrease in adverse events from baseline was observed and withdrawal symptoms were infrequently reported during the study. Participants' perception and acceptance of the product under investigation was satisfactory. In smokers not intending to quit, the use of ECs, with or without nicotine, decreased cigarette consumption and elicited enduring tobacco abstinence without causing significant side effects
Bullen,[29] New Zealand	Randomised, controlled trial This study investigated whether ECs are more effective than nicotine patches at helping smokers to quit; 657 adults (⩾18 years) smokers wanting to quit were randomised in a 4:4:1 ratio to 16 mg nicotine ECs, nicotine patches (21 mg patch, one daily) or placebo ECs (no nicotine)	6-month verified abstinence was 7.3% (21/289) with nicotine ECs, 5.8% (17/295) with patches and 4.1% (3/73) with placebo ECs (risk difference for nicotine EC vs. patches 1.51, 95%CI −2.49–5.51); for nicotine ECs vs. placebo ECs 3.16 (95%CI −2.29–8.61). Insufficient statistical power to conclude superiority of nicotine ECs to nicotine patches
Adkison,[3] USA, Canada, UK, Australia	Prospective cohort (longitudinal study) Wave 8 of the International Tobacco Control Four-Country Survey, collected July 2010 to June 2011 and analysed through June 2012 Data on ENDS usage patterns are limited. The current paper examines patterns of ENDS awareness, use and product-associated beliefs among current and former smokers in four countries	Awareness of ENDS is high, especially in countries where they are legal (i.e., the U.S. and UK). Because trial was associated with nondaily smoking and a desire to quit smoking, ENDS may have the potential to serve as a cessation aid; however, there was no difference in quit rate for users/non-users in this study sample. Overall, 46.6% were aware of ENDS (U.S.: 73%; UK: 54%; Canada: 40%; Australia: 20%); 7.6% had tried ENDS (16% of those aware of ENDS); and 2.9% were current users (39% of triers). Awareness of ENDS was higher among younger, non-minority smokers with higher incomes who were heavier smokers. Prevalence of trying ENDS was higher among younger, nondaily smokers with a high income and among those who perceived ENDS as less harmful than traditional cigarettes. Current use was higher among both nondaily and heavy (⩾20 cigarettes per day) smokers. In all, 79.8% reported using ENDS because they were considered less harmful than traditional cigarettes; 75.4% stated that they used ENDS to help them reduce their smoking; and 85.1% reported using ENDS to help them quit smoking
Polosa,[32] Italy	Cohort study (24 weeks, $n = 40$) This small, 24 week cohort study was designed to monitor possible modifications in smoking habits of 40 regular smokers (unwilling to quit) experimenting the 'Categoria' e-cigarette with a focus on smoking reduction and smoking abstinence	Sustained 50% reduction in the number of cigarette/day at week-24 was reported in 13/40 (32.5%) participants; their median of 25 cigarettes/day decreasing to 6 cigarettes/day ($P < 0.001$). Sustained 80% reduction was reported for 5/40 (12.5%) participants; their median of 30 cigarettes/day decreasing to 3 cigarettes/day ($P = 0.043$). Sustained smoking abstinence at week 24 was observed in 9/40 (22.5%) participants, with 6/9 still using the e-cigarette by the end of the study. Combined sustained 50% reduction and smoking abstinence was reported for 22/40 (55%) participants, with an overall 88% fall in cigs/day. Study authors concluded that use of e-cigarette substantially decreased cigarette consumption without causing significant side effects in smokers not intending to quit

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APPENDIX B (*Continued*)

Details of study, reference, country	Study type and purpose	Key findings/key summary points
Williams,[18] USA	Laboratory study Study tested the hypothesis that EC aerosol contains metals derived from various components in EC. Cartomizer contents and aerosols were analysed using light and electron microscopy, cytotoxicity testing, X-ray microanalysis, particle counting, and inductively coupled plasma optical emission spectrometry	The aerosol contained particles >1 micron comprised of tin, silver, iron, nickel, aluminium, and silicate and nanoparticles (<100 nm) of tin, chromium and nickel. The concentrations of nine of eleven elements in EC aerosol were higher than or equal to the corresponding concentrations in conventional cigarette smoke. Many of the elements identified in EC aerosol are known to cause respiratory distress and disease. Study authors concluded that the presence of metal and silicate particles in cartomiser aerosol demonstrates the need for improved quality control in EC design and manufacture and for studies on how EC aerosol impacts the health of users and bystanders
Flouris,[11] Greece	Laboratory study [human subjects] Stated objective was to conduct the first comprehensive and standardised assessment of the acute impact of active and passive e-cigarette smoking on serum cotinine and lung function, as compared to active and passive tobacco cigarette smoking.	E-cigarettes and tobacco cigarettes generated similar ($P > 0.001$) effects on serum cotinine levels after active (60.6 ± 34.3 versus 61.3 ± 36.6 ng/ml) and passive (2.4 ± 0.9 versus 2.6 ± 0.6 ng/ml) smoking. Neither a brief session of active e-cigarette smoking (indicative: 3% reduction in FEV_1/FVC) nor a 1 h passive e-cigarette smoking (indicative: 2.3% reduction in FEV_1/FVC) significantly affected the lung function ($P > 0.001$). In contrast, active (indicative: 7.2% reduction in FEV_1/FVC; $P < 0.001$) but not passive (indicative: 3.4% reduction in FEV_1/FVC; $P = 0.005$) tobacco cigarette smoking undermined lung function. Study authors concluded, for short-term usage, that the studied e-cigarettes generate smaller changes in lung function but similar nicotinergic impact to tobacco cigarettes. Future research should target the health effects of long-term e-cigarette usage, including the effects of nicotine dosage
Vardavas,[12] Greece	Laboratory study [human subjects] This study aimed to assess whether using an e-cigarette for 5 min has an impact on the pulmonary function tests and fraction of exhaled nitric oxide of healthy adult smokers. study sample was composed of 30 adults (14 men, 16 women) of a mean age of 34.8 years (range 19–56 years) recruited from a community setting in Athens, Greece	Using an e-cigarette for 5 min led to an immediate decrease in fraction of exhaled nitric oxide [Feno] within the experimental group by 2.14 ppb ($P = 0.005$) but not in the control group ($P = 0.859$). Total respiratory impedance at 5 Hz in the experimental group was found to also increase by 0.033 kPa/(L/s; $P < 0.001$), and flow respiratory resistance at 5 Hz, 10 Hz, and 20 Hz also statistically increased. Regression analyses controlling for baseline measurements indicated a statistically significant decrease in Feno and an increase in impedance by 0.04 kPa/(L/s; $P = 0.003$), respiratory resistance at 5 Hz by 0.04 kPa/(L/s; $P = 0.003$), at 10 Hz by 0.034 kPa/(L/s; $P = 0.008$), at 20 Hz by 0.043 kPa/(L/s; $P = 0.007$), and overall peripheral airway resistance (beta, 0.042 kPa/[L/s]; $P = 0.024$), after using an e-cigarette. Study authors concluded that e-cigarettes assessed in the context of this study had immediate adverse physiologic effects after short-term use that are similar to some of the effects seen with tobacco smoking. The long-term health effects of e-cigarette use are unknown but potentially adverse and worthy of further investigation
Cheah,[13] Singapore	Laboratory study Identification of the nicotine, glycerol and propylene glycol contents using gas chromatography mass spectrometry with quantification performed using flame ionisation techniques. ENDS samples were evaluated for design features, including nicotine and glycols content; this could be useful in developing a legal framework to handle ENDS [Many ENDS are marketed as safer tobacco alternative products or effective cessation therapies]	Varying nicotine amounts were found in ENDS cartridges which were labelled with the same concentration. Chemicals such as PPG and glycerol were found to be present in the nicotine-containing liquid of the cartridges. ENDS varied in their contents and packaging information. Limited information was available on the contents of nicotine and other chemicals present in a variety of ENDS sampled. Based on samples tested in this study, the authors concluded that many contain misleading information on product ingredients. The results show poor consistency between actual nicotine content analysed on ENDS cartridges and the amount labelled. The findings raise safety and efficacy concerns for current and would-be recreational users or those trying to quit smoking
Bahl,[15] USA	Laboratory study On the basis that EC and refill fluids are distributed with little information on their pre- and postnatal health effects. This study compared the cytotoxicity of EC refill fluids using embryonic and adult cells and examines the chemical characteristics of refill fluids using HPLC. Refill solutions were tested on human embryonic stem cells, mouse neural stem cells, and human pulmonary fibroblasts	Human embryonic stem cells (hESC) and mouse neural stem cells (mNSC) were generally more sensitive to refill solutions than human pulmonary fibroblasts (hPF). All products from one company were cytotoxic to hESC and mNSC, but non-cytotoxic to hPF. Cytotoxicity was not due to nicotine, but was correlated with the number and concentration of chemicals used to flavour fluids. Study authors concluded that additional studies are needed to fully assess the prenatal effect of refill fluids

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APPENDIX B (*Continued*)

Details of study, reference, country	Study type and purpose	Key findings/key summary points
Trtchounian,[16] USA	Laboratory study To evaluate five brands of ENDS for design features, accuracy and clarity of labelling and quality of instruction manuals and associated print material supplied with products or on manufacturers' websites	The basic design of ENDS was similar across brands, but specific design features varied significantly. Fluid contained in cartridge reservoirs readily leaked out of most brands, and it was difficult to assemble or disassemble ENDS without touching nicotine-containing fluid. Two brands had designs that helped lessen this problem. Labelling of cartridges was very poor; labelling of some cartridge wrappers was better than labelling of cartridges. In general, packs of replacement cartridges were better labelled than the wrappers or cartridges, but most packs lacked cartridge content and warning information, and sometimes packs had confusing information. Used cartridges contained fluid, and disposal of nicotine-containing cartridges was not adequately addressed on websites or in manuals. Orders were sometimes filled incorrectly, and safety features did not always function properly. Print and internet material often contained information or made claims for which there is currently no scientific support. The study authors concluded that design flaws, lack of adequate labelling and concerns about quality control and health issues indicate that regulators should consider removing ENDS from the market until their safety can be adequately evaluated
Trtchounian,[17] USA	Laboratory study The smoking properties of conventional and e-cigarettes were compared by examining the vacuum required to produce smoke (conventional cigarettes) or aerosol (e-cigarettes) and the density of the smoke/aerosol over time Vacuum was measured using a manometer coupled to a smoking machine. The density of aerosol or smoke was measured spectrophotometrically. E-cigarettes were subjected to smoke-out experiments in which vacuum and aerosol density were measured until each cartridge was exhausted	The vacuum required to smoke conventional cigarettes varied among the eight brands tested. Lights and ultra-light brands required stronger vacuums to smoke than unfiltered and regular filtered brands. Except for one brand, higher vacuums were required to smoke e-cigarettes than conventional brands. Smoke/aerosol density was stable for conventional brands and for e-cigarettes over the first 10 puffs; however, aerosol density of e-cigarettes dropped during subsequent smoking, and higher vacuums were required to produce aerosol as the puff number increased. While conventional cigarettes were uniform in their smoking behaviour within brands, vacuum and density varied within brands of e-cigarettes. The authors concluded that generally, e-cigarettes required stronger vacuums (suction) to smoke than conventional brands, and the effects of this on human health could be adverse. The amount of aerosol produced by e-cigarettes decreased during smoking, which necessitated increasing puff strength to produce aerosol. The decreased efficiency of aerosol production during e-cigarette smoking makes dosing non-uniform over time and calls into question their usefulness as nicotine delivery devices
Eissenberg,[14] USA	Laboratory study [human subjects] This study examined how two brands of electronic nicotine delivery devices (e-cigarettes) influence plasma nicotine levels, heart rate and cigarette craving in cigarette smokers, and compared these effects to those produced by smokers' usual brand of cigarettes (own brand)	Hydro and NPRO failed to increase nicotine levels significantly and NPRO decreased craving significantly 5 min after bout 2 only ($P < 0.05$). Mean plasma nicotine levels in the sham condition never were greater than 2.0. After bout 1, own brand plasma nicotine level was significantly greater than either Hydro or NPRO. For heart rate, a significant condition $\times$ bout $\times$ time interaction was observed. Relative to before bout 1, significant increases in heart rate were observed 5 and 15 min after bouts 1 and 2 for own brand only ($P < 0.05$) Relative to a tobacco cigarette, 10 puffs from either of these electronic nicotine delivery devices (e-cigarettes) with a 16 mg nicotine cartridge delivered little to no nicotine and suppressed craving less effectively. Importantly, these results were from two specific products tested under acute conditions in which puff number was controlled. Variability in product design may influence vapour content and chronic use and/or more intensive puffing (i.e., more puffs, greater puff volume) may influence nicotine delivery. The author concluded that given these and other factors, there is an ongoing need to evaluate electronic nicotine delivery devices (e-cigarettes). These evaluations should be conducted in a manner that takes into account variability in design (including cartridge nicotine content), examines the effects of user behaviour over time and compares these products to existing methods of delivering therapeutic nicotine safely and effectively Taken together, the well-known lethality of nicotine, variability in cartridge/vapour content, and the results reported here all support the notion that electronic nicotine delivery devices (e-cigarettes) and their nicotine-containing solution should be evaluated, regulated, labelled and packaged in a manner consistent with cartridge content and product effect. At the least, consumers should be aware that unlike several regulated nicotine products (e.g., gum, patch), these putative drug delivery systems do not delivery nicotine effectively after acute administration

EC = electronic cigarette; CI = confidence interval; ENDS = electronic nicotine delivery systems; FEV_1 = forced expiratory volume in 1 second; FVC = forced vital capacity; HPLC = high-performance liquid chromatography.