3. Clinical pharmacology of nicotine in electronic nicotine delivery systems

Armando Peruga, Centre of Epidemiology and Health Policies, School of Medicine, Clínica Alemana, University of Desarrollo, Chile

Thomas Eissenberg, Center for the Study of Tobacco Products, Department of Psychology, Virginia Commonwealth University, USA

Contents

3.1 Introduction

Electronic nicotine delivery systems (ENDS) are a heterogeneous class of products in which an electrically powered coil is used to heat a liquid matrix, or e-liquid, that contains nicotine, solvents (e.g. propylene glycol, vegetable glycerine) and, usually, flavourings. The user inhales the resulting aerosol, which contains variable concentrations of nicotine *(1)*, a dependence-producing central nervous system stimulant. In many countries and certainly in the two largest markets – the European Union and the USA – ENDS are regulated either as generic consumer products or as tobacco products *(2)*.

Products such as ENDS that are marketed to the public and contain drugs that act on the central nervous system, such as nicotine, ideally should have little potential for abuse or dependence for public health reasons. This is true, unless some level of abuse potential is desirable to maintain compliance and support substitution in place of a substance of greater potential abuse and harm. ENDS fall into this category on the basis of claims of a potential role in smoking cessation and reduction.

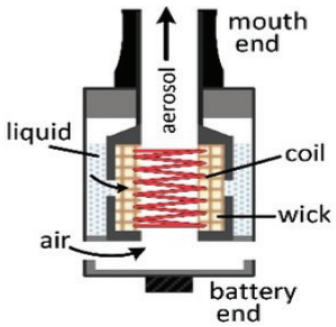
The purpose of this background paper is to review the literature at the time of writing with some additions after review between March and December 2018 on the nicotine content and nicotine delivery of ENDS and to explore factors that influence the emissions of nicotine and non-nicotine toxicants. In addition,

we review the potential role of ENDS in smoking cessation and the prospective population health impact. We also identify some relevant research gaps and make recommendations for policy.

3.2 ENDS operations

Understanding how ENDS operate is useful. Fig. 3.1 is a schematic drawing of a common ENDS configuration. The heating coil is attached to an electrical power source (usually a battery, not shown in the figure) enclosed in a fabric wick that is in turn surrounded by the nicotine-containing e-liquid that saturates the wick. When power is flowing, the coil heats and thus vaporizes some of the e-liquid from the wick. As the user draws air from the mouth-end of the ENDS, the vapour is carried away and re-condenses to form an aerosol, which is inhaled by the user.

Fig. 3.1. Schematic drawing of ENDS operation

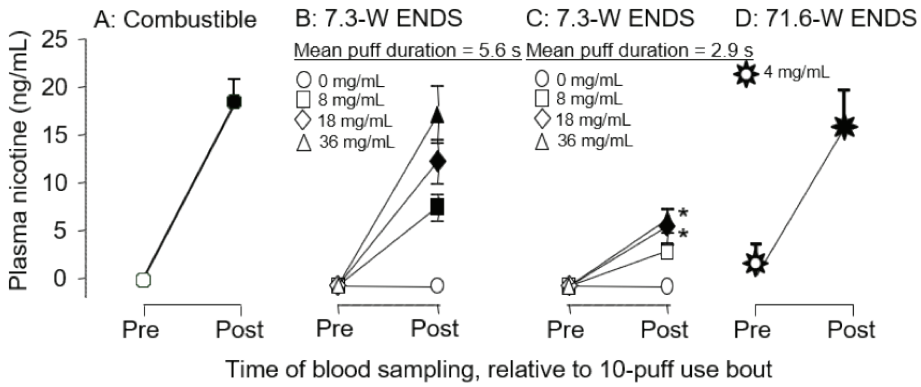


Source: Dr Alan Shihadeh, American University of Beirut, Lebanon.

Several factors influence the amount of nicotine carried by the aerosol, including the electrical power flowing through the ENDS, the inhalation behaviour (or "puff topography") of the user and the amount of nicotine in the e-liquid *(3)*. Electrical power (W) is a function of battery voltage (V) and coil resistance (Ω), such that $W = V^2/\Omega$. Early ENDS models were powered at ≤ 10 W, but the devices marketed currently are powered at ≥ 250 W *(4, 5)*. Higher power is often achieved with coils with low resistance (e.g. < 1 Ω), application of varying voltage to the coil or a combination.

Puff topography variables include puff number, duration and volume and the interval between puffs (inter-puff interval). User puff topography is highly individual. Experienced ENDS users, however, typically take longer puffs than ENDS-naive cigarette smokers *(6–9)* (see Fig. 3.2 and description below).

Fig. 3.2. Mean plasma nicotine concentrations before and after use of a combusted cigarette and of ENDS



Panel A, N=32 *(8)*; Panel B, N=33 *(8)*; Panel C, N=31 *(8)*; Panel D, N=11 *(4)* (puff topography not available). *Source*: Figure adapted from one published previously *(1)* by adding puff duration data and updating Panel D.

3.3 Nicotine concentration in e-liquids

The nicotine-containing e-liquid used in ENDS comes in prefilled cartridges or refill bottles, depending on the type of device used. The concentration of nicotine in marketed e-liquid can reach 36 mg/mL or more *(1)*, and users can choose from a wide range of concentrations at the point of sale; some manufacturers provide labelling information relevant to the e-liquid. There has been no comprehensive study, however, of the extent to which manufacturers accurately inform consumers of the nicotine concentration in a representative sample of e-liquids, globally or by country. Existing studies give a partial picture based on convenience samples. The proportion of e-liquids that have clear label information on the nicotine content is unknown. Some studies indicate that such information is not always available *(10, 11)* or interpretable *(12)* from the manufacturer's label. Nevertheless, the concentration of nicotine is usually reported on the label as a percentage of total volume or as mg/mL. Table 3.1 lists studies in which the concentration of nicotine was analysed in e-liquids that allegedly contained nicotine and compared with the concentration reported on the manufacturer's label.

Table 3.1. Comparison of labelled and measured concentrations of nicotine in e-liquids with declared nicotine

First author and reference number	Type of e-liquid container	Number of samples		
		Analysed	> ±10% of labelled concentration	> ±25% of labelled concentration
Beauval *(13)*	Refill bottle	2	0	0
Buettner-Schmidt *(14)*	Refill bottle	70	36	NA
Cameron *(15)*	Prefilled cartridge and refill bottle	21	13	7
Cheah *(10)*	Cartridge	8[a]	8[b]	7[b]
Davis *(16)*	Refill bottle	81	36	21
El-Hellani *(17)*	Prefilled cartridge	4	4	4
Etter *(18)*	Refill bottle	35	4	0
Etter *(19)*	Refill bottle	34	10	0
Farsalinos *(20)*	Refill bottle	21	9	0
Goniewiscz *(21)*	Refill bottle	62	25	7
Kim *(22)*	Refill bottle	13	7	2
Kirschner *(23)*	Refill bottle	6	6	4
Kosmider *(24)*	Refill bottle	9	2	0
Lisko *(25)*	Refill bottle	29	15	7
Pagano *(26)*	Prefilled cartridge	4	3	2
Peace *(27)*	Refill bottle	27	16	7
Rahman *(28)*	Refill bottle	69	65	53
Raymond *(29)*	Refill bottle	35	22	22
Trehy *(30)*	Prefilled cartridge	22	22	19
Trehy *(30)*	Refill bottle	17	8	6

NA: not available. [a] Number of brands analysed; number of samples analysed not provided. [b] Number of brands in which at least one sample had a nicotine concentration per cartridge above the criterion.

The majority of the studies showed nicotine concentrations below those reported by the manufacturer, and all except one indicated that the nicotine concentrations in some samples were at least 10% below or above that reported on the label of the product, meeting a quality criterion recommended by a United States manufacturers' association *(31)*. In a median of 53% of samples, the nicotine concentration was misreported on the label by at least 10%, and in a median of 26% of samples, the nicotine concentration was misreported by at least 25%.

We know of only three studies of the consistency of nicotine concentration in e-liquids in different batches of the same brand and model of e-liquid. The median variation among production batches was 0.5% in one *(19)* and 15% *(16)* and 16% *(32)* in the other two.

Other studies have shown that some products labelled as not containing nicotine do have measurable nicotine levels. Table 3.2 lists studies in which the concentration of nicotine in e-liquids was analysed and compared with a reported absence of nicotine on the label. Almost half the studies reported that small amounts of nicotine were present in some e-liquids advertised as not containing nicotine. Furthermore, in about 5% of samples of e-liquids allegedly without nicotine, the concentration of nicotine was significant.

Table 3.2. Labelled and measured nicotine concentrations in e-liquids with declared zero nicotine

First author and reference number	Samples			Nicotine concentration in samples containing > 0. 1 mg/mL
	Analysed	Nicotine > 0.1 mg/mL	Nicotine > 10 mg/mL	
Beauval *(13)*	2	0	0	–
Cheah *(10)*	2	0	0	–
Davis *(16)*	10	0	0	–
Goniewiscz *(21)*	28	3	0	0.8–0.9
Kim *(22)*	20	0	0	–
Lisko *(25)*	5	0	0	–
Omaiye *(33)*	125	17	2	0.4–20.4
Raymond *(29)*	35	6	6	5.7–23.9
Trehy *(30)*	8	2	2	12.9–24.8/cartridge
Trehy *(30)*	5	2	2	12–21
Westenberger *(34)*	5	0	0	–

3.4 Nicotine delivery to ENDS users

The nicotine delivery profile of ENDS may be an important determinant of how effectively the product can substitute for a cigarette for a long-term smoker. Fig. 3.2 demonstrates the influence of the nicotine concentration in e-liquid, user behaviour and device power on the nicotine delivery profile of ENDS relative to a cigarette. Panel A *(9)* shows the nicotine delivery profile of a cigarette when smokers take 10 puffs with a 30-s inter-puff interval. Panel B shows the nicotine delivery profile of a 7.3-W ENDS loaded with 0, 8, 18 or 36 mg/mL nicotine e-liquid when users took 10 puffs of an average length of 3.6 s at a 30-s inter-puff interval. Clearly, the e-liquid nicotine concentration influences delivery of nicotine to the users' blood. When the 7.3-W ENDS is paired with 36 mg/mL nicotine e-liquid and when users take 10 ~5.6-s puffs, the pairing can match or exceed the nicotine delivery profile of a combusted cigarette *(8)*.

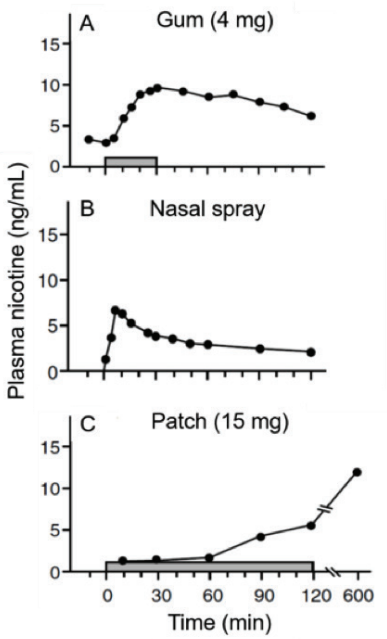
Puff duration is also a factor in ENDS nicotine delivery: Panel C *(8)* shows the same device and e-liquid nicotine concentration as in Panel B, but the study participants took shorter puffs (2.9 s on average). When the puff duration is shorter and all other device and e-liquid characteristics are constant, less nicotine is delivered. Panel D shows the nicotine delivery profile of higher-powered ENDS devices (mean power, 71.6 W) when users took 10 puffs at a 30-s inter-puff interval *(4)*. When these higher-powered devices were paired with 4 mg/mL nicotine liquid, they approximated the nicotine delivery profile of a combusted cigarette.

Overall, at least in some cases, these data suggest that some ENDS can deliver the same dose of nicotine, at the same rate as a cigarette, to venous blood. Unfortunately, few studies have been conducted to compare the ability of ENDS and cigarettes to deliver nicotine to arterial blood, an important indicator of exposure of the central nervous system to the drug *(35)*. In the only such comparison to date, 10 puffs (30-s inter-puff interval) from a 7.3-W ENDS

with 36 mg/mL liquid resulted in a lower mean arterial nicotine concentration (maximum, 12 ng/mL) than 10 puffs (30-s inter-puff interval) from a cigarette (maximum concentration, 27 ng/mL), although the time to peak concentration did not differ *(36)*. The sample was, however, small (four for ENDS; three for cigarettes), and puff duration was not measured. Under the controlled conditions of this study, positron emission tomography imaging showed that this ENDS effectively delivered nicotine to the central nervous system.

While the ENDS used to generate the data for Fig. 3.2 can deliver nicotine as effectively as a cigarette under some conditions, many ENDS cannot *(6, 9, 37–41)*. This heterogeneity in ENDS nicotine delivery is in contrast to regulated nicotine replacement products that deliver nicotine more reliably, although they often achieve lower plasma concentrations at a slower rate. For example, as shown in Panel A in Fig. 3.3 *(42)*, nicotine chewing-gum can take ≥ 30 min to achieve a peak plasma concentration, while Panel C shows that a nicotine patch can take > 2 h *(43, 44)*; other therapeutic products (e.g. nicotine lozenges) also deliver nicotine within this time frame *(43)*. Presumably, ENDS that deliver nicotine to the blood and brain as effectively as a cigarette are more likely to substitute for a cigarette, although this speculation has not been tested empirically, as the ENDS used in clinical trials on the question did not deliver nicotine effectively *(45)*.

Fig. 3.3. Plasma nicotine concentrations before, during and after administration of a single dose of nicotine in several therapeutic forms



Note: the grey bar indicates duration of product use. *Source*: reference *42*. Reprinted with permission from the Massachusetts Medical Society.

3.5 Toxicant content of ENDS emissions

ENDS toxicant emissions are a function of a variety of factors, including device construction, device power, liquid constituents and user behaviour. We review below the literature on ENDS toxicant emissions, beginning with nicotine and then moving to non-nicotine toxicants (for reviews of older literature, see Breland et al. *(1)* and Department of Health and Human Services *(46)*).

3.5.1 Nicotine emissions

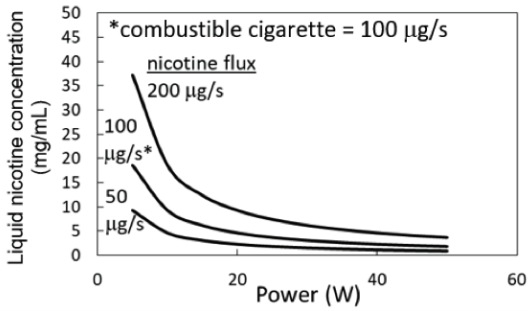
The "yield" of nicotine from ENDS is the amount (in mg) of nicotine in the aerosol produced by an ENDS under a specific puffing regimen. Knowing the yield of nicotine from ENDS has been considered important for understanding the pharmacokinetics of nicotine in ENDS users. One review of the literature *(47)* identified seven studies of nicotine yield *(30, 34, 48–52)*; since then, several other studies on this issue have been published *(3, 33, 53, 54)*.

The nicotine yields in these studies were highly variable, depending on the type of ENDS used, the nicotine concentration of the e-liquids and the puffing regime used to obtain the aerosol. Some methodological issues complicate the comparability of studies, including the fact that the ISO methods of machine-smoking ENDS fail to activate some ENDS models. Although the nicotine yields from ENDS in these studies are not fully comparable with those from machine-smoked cigarettes, they are usually much lower than those from cigarettes *(47)*. The literature is, however, limited, for two important reasons. First, nicotine yield does not capture the rate of nicotine emission, which is a measure not only of the amount but also of the speed at which nicotine is made available to the user. The rate of nicotine emission is almost certainly related to the rate of nicotine delivery, and the rate of nicotine delivery is probably a key factor in the capacity of a nicotine-containing product to substitute for cigarettes by providing nicotine that rapidly reaches peak levels in the bloodstream and enters the brain *(55)*. Secondly, ENDS and their e-liquids are so heterogeneous that the results of a study on a particular ENDS are probably not generalizable to another.

To address the first concern, there is growing interest in measuring nicotine "flux", the rate at which nicotine is emitted from ENDS *(56, 57)*. Nicotine flux can be measured (usually reported in μg/s) and can be compared among ENDS and with cigarettes. Those ENDS that mimic the flux of a cigarette may be more likely to substitute well for a cigarette than ENDS that do not. To address the second concern, a physics-based mathematical model has been developed to predict the nicotine flux of any ENDS *(58)* – even those that have not yet been constructed. The model accounts for the time it takes for the coil to heat up after electricity begins flowing and how much the coil cools down between puffs. It also accounts for the various ways in which heat can be transported away from the coil: by the air passing over it, by the latent heat of the e-liquid

as it evaporates, by conduction through the metal solder to the body of the device and by radiation to the surroundings. The inputs to the model are the length, diameter, electrical resistance and thermal capacitance of the heater coil; the composition and thermodynamic properties of the e-liquid (including nicotine concentration); puff velocity and duration and inter-puff interval; and the ambient air temperature. In a test of the model, the authors compared its predictions against actual nicotine flux measurements for 100 conditions in which power, puff topography, ENDS type (tank or cartomizer) and liquid composition were varied. The mathematically predicted nicotine flux was highly correlated to measured values (r = 0.85, P <.0001) *(58)*. In addition, the model accurately predicted the dependence of nicotine flux on device power and nicotine concentration (see Fig. 3.4), the ratio of propylene glycol and vegetable glycerine in the liquid and user puff duration. Fig. 3.4 shows that the higher the electrical power of the device, the lower the e-liquid nicotine concentration required to achieve a given flux. Cigarette flux is 100 µg/s, and the lines depict ENDS nicotine fluxes equivalent to twice, once and half that of a cigarette. Given the relation between ENDS power and liquid nicotine concentration shown in Fig. 3.4, a nicotine flux that is dramatically greater than that of a cigarette can be achieved by pairing a higher-powered ENDS with a higher concentration liquid. The figure does not show that some ENDS are powered well over 100 W *(4, 5)*.

Fig. 3.4. Relation between ENDS power and e-liquid nicotine concentration and effect on nicotine flux



Source: reference *58*, reproduced with permission from Dr Alan Shihadeh, American University of Beirut, Lebanon.

Another important issue with regard to ENDS nicotine emissions is the amount of nicotine in e-liquids and aerosols that is present in its more bioavailable, free-base form, as opposed to the less bioavailable protonated form *(17)*. Some studies of nicotine emissions from e-cigarettes have reported nicotine yields without determining whether the methods used resulted in quantification of total nicotine or only one of its forms *(38, 58)*, so that the reported results are difficult to compare or to evaluate with regard to nicotine delivery to the user. In an evaluation of this issue, the free-base nicotine fraction in 19 commercial

liquids varied widely (10–90%), and, importantly, the differences were also seen in the aerosol *(17, 59)*, suggesting another factor that probably influences ENDS nicotine delivery to the user. Thus, in addition to measuring nicotine flux, the form of the nicotine in the aerosol should be determined. Overall, as for nicotine delivery to the user, there is considerable variation in nicotine emissions from ENDS, which can be explained and predicted by careful consideration of the many factors that influence it, especially ENDS power, liquid constituents and user behaviour.

3.5.2 Emissions of non-nicotine toxicants

Non-nicotine toxicants in ENDS aerosols are either present in the liquid or formed when the liquid is heated. Those present in the liquid before heating include propylene glycol and vegetable glycerine, which together make up 80–97% of the content of most e-liquids *(60)*, flavourings and other compounds added intentionally and contaminants not added intentionally. Aerosolized propylene glycol is a respiratory irritant *(61–64)* and, when administered intravenously at high doses, can cause potentially fatal lactic acidosis *(65)*. Preclinical work also indicates that vegetable glycerine may be toxic at high doses *(66, 67)*. The health effects of long-term, daily, chronic inhalation of aerosolized propylene glycol and/or vegetable glycerine are unknown. The flavourings used in e-liquids are usually compounds that are added to food, and their effects on the human lung after having been heated and aerosolized are unknown *(68)*. At least three flavourings that have been found in e-liquids and aerosols have raised health concerns: diacetyl (buttery flavour), which causes bronchiolitis obliterans *(69)*; benzaldehyde (fruity flavour), which is cytotoxic and genotoxic *(70)*; and cinnamaldehyde (cinnamon flavour), which is also cytotoxic and genotoxic *(71)* and can cause an inflammatory response in lung cells *(72)*. The contaminants include diethylene glycol, ethylene glycol and ethanol *(73, 74)*. Even if rigorous quality controls are imposed to ensure contaminant-free e-liquids, the uncertain effects of long-term, daily, frequent inhalation of aerosolized propylene glycol and vegetable glycerine and the many chemical flavourings that are often combined in a single liquid pose a potential health threat for ENDS users.

The non-nicotine toxicants formed when the liquid is heated include metals, volatile aldehydes, furans and benzene. In one study of 11 "first-generation" ENDS brands (disposable ENDSs shaped like tobacco cigarettes), three of each brand were puffed for 4.3 s every 5 min for two series of 60 puffs, and the resulting aerosol was analysed for elements, including metals *(75)*. The results revealed substantial variation among brands, but many metals were found in the aerosol generated from most brands, "in some cases at concentrations that were significantly higher than in conventional cigarettes". The authors concluded that most of the elements and metals in ENDS aerosols probably originate from

components in the atomizer, such as the filament, solder joints, wick and sheath. These results show how ENDS construction can contribute to the non-nicotine toxicant profile of the aerosol.

In a study of an advanced-generation ENDS with a 1.5-Ω heating element and variable voltage battery (3.3–5.0 V), the aldehyde content of aerosols produced from a variety of liquids (all 6 mg/mL nicotine) was compared after 10 4-s puffs of 91 mL/puff *(76)*. Power was manipulated systematically from 9.1 to 16.6 W. Acetaldehyde, acetone, acrolein and formaldehyde were all present in ENDS aerosols, and aldehyde production increased proportionally as puff volume increased and dramatically when the power was > 11.7 W. The presence of aldehydes in ENDS aerosol is now well documented *(77–79)*, as is the role of device power in forming them: increasing ENDS power from 4.1 to 8.8 W approximately tripled volatile aldehyde emissions *(80–83)*. There also is some suggestion that flavourings contribute to non-nicotine toxicants formed during heating *(84–87)*. For example, heating sweeteners in e-liquids may expose users to furans, a toxic class of compounds. In one study *(88)*, a VaporFi platinum tank ENDS (2.3 Ω) was used to generate aerosol under various conditions, including power (4.2 and 10.8 W), puff duration (4 and 8 s) and sweetener (sorbitol, glucose and sucrose). The per-puff yield of some furans was comparable to values reported for combustible cigarettes, and, again, device power is a factor: increasing power from 4.3 to 10.8 W more than doubled furan emissions. With regard to benzene, increasing ENDS power from 6 to 13 W increased emissions of this carcinogen 100 times *(89)*, although the level remained far below those found in cigarette smoke. The fact that volatile aldehydes, furans and benzene are all formed by thermal degradation of the contents of e-liquids (e.g. propylene glycol, vegetable glycerine, sweeteners), coupled with the fact that increased device power increases the amount of these toxicants in ENDS aerosols, suggests that high-power ENDS are a particular public health concern. To date, most studies of the toxicant profile of ENDS aerosols have been limited to devices powered at 25 W or less (e.g. references *80, 83, 88, 90*), and much of the data reported here may not be relevant to the higher-powered devices common in some locations *(4, 5)*.

3.6 Potential role of ENDS in smoking cessation

Six narrative reviews *(91–96)* and six systematic reviews *(97)*, of which five were meta-analyses *(98–103)*, addressed the role of electronic nicotine and non-nicotine delivery systems (EN&NNDS) in smoking reduction and cessation. Two meta-analyses *(100, 102)* covered studies available up to January 2016.

All five systematic reviews of the quality of the evidence *(97, 98, 100, 102, 103)* concluded that the available studies provide evidence of low to very low certainty, due mainly to the limitations of the cross-sectional and cohort studies included in the reviews and the lack of detail in many of the published articles.

Given these limitations, El Dib et al. *(102)*, and Malas et al. *(97)* concluded that no credible inferences could be drawn from their reviews and that the evidence remains inconclusive. Similarly, a review of the systematic reviews concluded that "overall, there is limited evidence that e-cigarettes may be effective aids to promote smoking cessation" *(104)*. The other systematic reviews, however, came to a different conclusion. While Kalkhoran & Glantz *(101)* determined that "as currently used, e-cigarettes were associated with significantly less quitting among smokers", Hartmann-Boyce et al. *(100)* and Rahman et al. *(98)* concluded that use of e-cigarettes is associated with smoking cessation and reduction. Khoudigian et al. *(103)* included only randomized clinical trials. The striking disparity in the conclusions arises from differences in the criteria for selecting eligible studies and the availability of studies at the times at which the reviews were done. Table 3.3 summarizes the studies used in each review.

Table 3.3. Comparison of studies included in reviews of the effectiveness of electronic nicotine and non-nicotine delivery systems as quitting aids

	Review and cut-off date of literature review											
Studies available for review	Franck *(91)* Sep 2013	Harrell *(92)* Dec 2013	Rahman *(98)* May 2014	McRobbie *(99)* Aug 2014	Lam *(93)* Mar 2015	Ioakeimidis *(94)* Jun 2015	Kalkhoran *(101)* Jul 2015	Hartmann *(100)* Jan 2016	El Dib *(102)* Jan 2016	Malas *(97)* Feb 2016	Khoudigian *(103)* May 2016
Cohort studies											
Polosa, 2011	✓	✓		✓				✓			
Adkison, 2013		✓					✓			✓	
Caponnetto, 2013b	✓										
Ely, 2013				✓				✓			
Van Staden, 2013				✓				✓			
Vickerman, 2013 (*119*)		✓					✓		✓		
Borderud, 2014 (*123*)						✓	✓		✓		
Choi, 2014				✓			✓	✓			
Etter, 2014			✓	✓				✓			
Farsalinos, 2014 (*69*)						✓					
Grana, 2014				✓			✓	✓		✓	
Nides, 2014 (39)				✓				✓			
Pearson, 2014 (*122*)							✓				
Polosa, 2014	✓	✓	✓	✓		✓		✓		✓	
Prochaska, 2014							✓		✓		
Wagener, 2014		✓									
Al-Delaimy, 2015 (*120*)							✓		✓		
Biener, 2015						✓	✓		✓	✓	
Brose, 2015						✓			✓		
Harrington, 2015							✓		✓		
Hitchman, 2015 (*124*)							✓				
Manzoli, 2015						✓	✓		✓		
McRobbie, 2015				✓				✓			

Oncken, 2015								✓			
Pacifici, 2015								✓			
Pavlov, 2015							✓				
Polosa 2015								✓			
Shi, 2015							✓				
Sutfin, 2015							✓				
Cross-sectional studies											
Siegel, 2011		✓	✓								
Popova, 2013		✓									
Dawkins, 2013 (*37*)	✓									✓	
Goniewicz, 2013 (*32*)										✓	
Pokhrel, 2013		✓									
Brown, 2014			✓				✓			✓	
Christensen, 2014							✓			✓	
McQueen, 2015							✓				
Tackett, 2015										✓	
Randomized controlled trials with control group											
Bullen, 2010	✓				✓						✓
Bullen, 2013 (*45*)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Caponnetto, 2013a	✓	✓	✓	✓	✓	✓		✓	✓		✓
Caponnetto, 2014		✓		✓				✓			
Adriaens, 2014					✓				✓	✓	
Randomized controlled trials without control group											
Hajek, 2015							✓		✓		
Unknown											
Humair, 2014				✓				✓			

The differences in the conclusions do not arise from the evidence provided by the randomized clinical trials. Meta-analysis of the few existing trials showed that ENDS use increases the likelihood of quitting smoking by a factor of two when compared with placebo. Two meta-analyses *(98, 99)* provided an estimated risk ratio of 2.29 (95% CI. 1.05, 4.96) in favour of quitting, one meta-analysis *(102)* gave an estimate of 2.03 (95% CI, 0.94, 4.38) and another *(103)* an estimate of 2.02 (95% CI, 0.97, 4.22). The differences are due to slight variations in the weight attributed to the two randomized clinical trials analysed and treatment of missing data. The different conclusions arise, more specifically, from the conflicting evidence presented by the longitudinal and cross-sectional studies reviewed. Below, we concentrate on the evidence from the longitudinal studies, because it is difficult to interpret the direction of possible associations in cross-sectional studies.

Since the last systematic review, seven new longitudinal studies have been published on the difference in quitting smoking between users and non-users of EN&NNDS *(105–110)*, including an update of a previous one with a longer follow-up *(111)*. Table 3.4 summarizes the findings of longitudinal studies according to sample attributes, characteristics of EN&NNDS products used by

participants, measures used to typify ENDS use, criteria for nicotine dependence and abstinence and a summary of the results. It summarizes the seven studies that found a statistically significant positive or negative association between EN&NNDS use and smoking abstinence in systematic reviews. It also summarizes all seven longitudinal studies that were not included in the reviews, for a total of 16 studies. To select the best longitudinal studies for assessing the evidence, we considered that the association between ENDS use and quitting smoking as the outcome of interest should be measured under at least three conditions to obtain valid results:

- Criterion 1: It should be known whether the e-liquid used contains nicotine and the type (electrical power) of device used. Ideally, devices should be classified on the basis of their tested capacity to deliver nicotine, but this might prove difficult in population studies without laboratory testing of the devices used by participants. Otherwise, it is difficult to assess whether the association is linked to the potential role of ENDS as a nicotine replacement aid. We know that some ENDS devices can deliver cigarette-like amounts of nicotine in some instances *(4, 8)*; however, use of ENNDS or ENDS that cannot deliver nicotine because of low power and other factors is still common in the USA *(112)* and many other countries.
- Criterion 2: The analysis must discriminate between people who use ENDS to quit smoking and those who do not. Many use ENDS for reasons other than to quit, including reducing their smoking *(113)*, use indoors when smoking is not allowed or for recreational purposes *(114, 115)*. Conflating ENDS users who do and do not do so for quitting may bias the association towards the null if, as expected, the real effects on smoking cessation are different or even opposite.
- Criterion 3: The measures of ENDS use must be accurate and refined in order to distinguish between established and transient, erratic use to assess the effects of ENDS on population health *(116, 117)*. As ENDS use is a relatively new population behaviour, many people may experiment briefly with EN&NNDS but not adopt an established pattern of use. Comparisons of "ever use" with "never use" of ENDS, for example, might classify as users people who have used an ENDS only once in their lives, while it has been standard practice to consider people smokers if they have smoked at least 100 cigarettes in their lifetime. Conflating experimenters with steadier users may result in the biases described in the previous paragraph.

Table 3.4. Characteristics of longitudinal studies that showed a statistically significant positive or negative association between use of electronic nicotine and non-nicotine delivery systems and smoking abstinence in existing systematic reviews and more recent studies not included in those reviews

	Sample						Product		Measures						Results
									EN&NNDS use						
Reference no.	Year data collected	Country and baseline	Age range (years)	No. at baseline	Follow-up	Retention rate at follow-up	EN&NNDS type	Nicotine in e-liquid	Frequency	Quantity	Duration	Reasons	Nicotine dependence	Criterion for smoking abstinence	Association between EN&NNDS use and quitting smoking
118	2010	USA. Nationally representative sample of smokers in the general population	≥ 18	5255	1 year	63%	NM	NM	Ever used vs Never used	NM	NM	NM	M	SR 30 days at follow-up	Ever use of an e-cigarette to quit was associated with less success in quitting than those who had not, adjusted for use of pharmacological help in last attempt, age, sex, race, education, cigarettes smoked per day, nicotine dependence and early smoking initiation.
119	2011–2012	USA Smokers Quitline callers[a]	≥ 18	2758	7 months	35%	NM	NM	Ever use vs use for ≥ 1 month vs use for < 1 month	NM	NM	N NU	M NU	SR 30 days at follow-up	Never ENDS users, 31.3% Use < 1 month, 16.6% Use > 1 month, 21.7% (*P* <.001). Not adjusted for use of NRT.
120	2011–2012	USA. Current smokers at baseline	18–59	1000	1 year	23%	NM	NM	EN&NNDS users classified as: ever used might use will never	NM	NM	NM	M	SR 1 month at follow-up	Smokers who had ever used e-cigarettes at baseline (not during follow-up) were significantly less likely to be abstinent at follow-up (AOR=0. 41; 95% CI=0.186, 0. 93) than smokers who reported at baseline they would never use e-cigarettes, adjusted for addiction (time to first cigarette in the morning), age, gender, education, ethnicity, desire to quit smoking, and smoking status. "Have used" and "will never use" include only those respondents with consistent responses at baseline and follow-up.

									Ever used an e-cigarette or not; if so, on how many of the past 30 days Currently used e-cigarettes every day, some days or not at all. If not at all, ever used e-cigarettes "fairly regularly" E-cigarette use: intensive (daily ≥ 1 month); intermittent (≥ once but not daily for ≥ 1 month); no use or at most once or twice.				Intensive e-cigarettes users were more than six times as likely to have quit smoking as those who had never used e-cigarettes or used them only once or twice, after adjustment for gender, age group, race/ethnicity and education level as well as baseline smoking level. Intermittent users were three times more likely not to quit than non-users or experimenters, although the association was not statistically significant.		
121	2011–12	Representative sample of smokers in two United States metropolitan areas	18–65	1374	2 years	51%	NM	NM		M	NM	SR 1 month at follow-up			
122	2012	USA. Smokers on NRT recruited from a free, publicly available internet cessation programme. Randomized to social network integration or no social network × 2 (access to free NRT, no access)	30–52	3408	3 months	62%	NM	NM	Ever used during follow-up vs never used	NM	NM	NM	M	SR 1 month at follow-up	The odds of abstinence were lower among smokers who used e-cigarettes to quit than those who did not use e-cigarettes to quit, after adjustment for (measured at baseline) gender, age, race/ethnicity, education, parent, study treatment allocation, Fagerstrom score, number of quit attempts in the past year, cigarettes per day, self-efficacy to quit and stage of change. After further adjustment for use of other quit methods in the past 3 months and number of quit attempts in the past 3 months, the association was not significant.

123	2012–2013	USA In-treatment cancer patients who were current smokers and had received cessation treatment	NR	781	1 year	53%	NM	NM	Selection: 1 < puff Past 30 days at baseline, past 7 days use vs no use at follow-up	NM	NM	NM	M	SR 1 day at follow-up	After adjustment for nicotine dependence, number of past quit attempts and cancer diagnosis, current e-cigarette users were as likely to smoke non-users. Intention-to-treat analysis showed that non-users of e-cigarettes were twice as likely to abstain from smoking as e-cigarette users.
124	2012–2013	Great Britain. Current smokers	≥ 18	1759	1 year	44%	Ciga-like tanks	NM	Daily, less than daily but ≥ 1 weekly less than weekly but ≥ 1 monthly less than monthly not at all	NM	NM	NM[a]	NM[b]	SR "I stopped smoking completely in the past year"	In comparison with no e-cigarette use at follow-up: non-daily cigalike users were less likely to quit (P <.001), daily cigalike or non-daily tank users were no more likely to quit (P =.4 and P =.4, respectively), and daily tank users were more likely to quit (*P* =.0012). Adjusted for age, sex, education level, income, motivation to quit and strength of urge to smoke.
111	2013–2015	Italy. Convenience sample of daily smokers for ≥ 6 months, EN&NNDS users for ≥ 6 months	30–75	932	2 years	69%	NM	NM	EN&NNDS user: inhales ≥ 50 puffs/ week	No. of months of continued EN& NNDS use	NM	NM	SR 30 days at follow-up with CO-tested subsample	Dual use did not improve the chances of smoking cessation at follow-up but reduced smoking.	
110	2014	Canada. Smokers enrolled in cessation programme with access to free NRT and behavioural counselling	≥ 16	6526	6 months	–	NM	NM	Any EN&NNDS use in the 3 months before follow-up	NM	NM	M NU	M	SR 7-day point prevalence of abstinence	Any EN&NNDS use was associated with less quitting at 6-month follow-up (AOR=0.50; 0.39, 0.64). Adjusted for heaviness of smoking at baseline and confidence in ability to quit.

106	2014–2015	Hong Kong. Young current smokers from Quit line free counselling service not on other cessation programmes	18–25	190	6 months	99%	NM	NM	Ever tried	NM	NM	NM	M	7 days at 6-month follow-up Validated salivary cotinine	EN&NNDS ever users had nonsignificantly lower odds of quitting (AOR, 0. 56; 95% CI, 0.24, 1.35) than non-users after adjustment for sex, age, smoking friends, smoking family members, baseline quit attempts and nicotine dependence level. They tried quitting more frequently than non-users.
105	2014–2015	France. Exclusive smokers and dual users	15–85	2057	6 months	695	NM	NM	Use of e-cigarettes: regular use in past 30 days. No use: used e-cigarettes sometimes, rarely or never	NM	NM	NM	NM	SR 7 days at 6-month follow-up	Baseline dual users were not more likely than exclusive tobacco smokers to have quit smoking at follow-up (12.5% versus 9.5%, *P* =.18, AOR, 1.2; 95% CI, 0.8, 1.9) after adjustment for age, sex, intention to quit smoking in the next 6 months, attempt to quit for at least 24 h in the previous 30 days at baseline and heaviness of smoking. They were more likely to reduce their smoking by half and tried to quit.
107	2014	USA. Smokers seeking treatment enrolled in a quitline programme offering counselling and NRT	≥ 18	5672	NR	NR	NR	NR	Number of days used EN&NNDS in past 30 days Classified as 0, none 1–5 6–20 30, daily	NM	1 month before follow-up	NM	NM	Self-reported 30-day complete abstinence at follow-up	Quit rate of daily EN&NNDS users no different from that of non-users. Quit rate of non-daily users lower than that of non-users. Results were adjusted for age, sex, education level, tobacco use, type of quitline programme and counselling with NRT use.
108	2013–2015	USA. Current cigarette smokers with no current use of EN&NNDS at baseline	≥ 25	5124	1 year	83%	Reported use of cartridges, refills and tanks	NM	Number of days used EN&NNDS in past 30 days	NM	NM	NM	Time to first cigarette	Self-reported 30-day complete abstinence at follow-up	Daily EN&NNDS users were eight time more likely to quit than non-users when using non-cartridge, refillable tanks. Experimenters were half as likely as non-users to quit. Non-daily users tended to quit less than non-users, but the association was statistically nonsignificant. Less quitting seen mainly among users of cartridge, non-refillable devices.

109	2012–2015	USA. Hospital-discharged daily smokers who had received inpatient counselling plus encouragement to use NRT and who planned to stop smoking after discharge	≥ 18	Controls: 677, Intervention: 680	6 months	75% for controls 77% for intervention	NM	NM	Any use of EN&NNDS in past 7 and 30 days	NM	NM	All participants planned to quit smoking	No. of cigarettes per day and time to first cigarette	Cotinine-validated 7-day point prevalence of tobacco abstinence	Proportion of daily smokers motivated to quit who actually quit was slightly higher among EN&NNDS non-users than among users in the 7 days before follow-up, but the difference was statistically nonsignificant.
125	2014–2016	USA. Smokers of ≥S5 cigarettes/day for ≥ 1 year, ENDS-naive, not seeking treatment to quit	≥ 18	Control= 22; arm 1 = 25; arm 2= 21	3 months	Control= 73%; arm 1=76%; arm 2=71%. EMA compliance 58%	Cigalike	Arm 1= 3-week provision of 16 mg/mL nicotine Arm 2= 24 mg/mL nicotine Control = no provision of ENDS. No ENNDs provided but nor precluded from buying them	Number of days used EN&NNDS per week	Number of puffing sessions/day	From baseline to follow-up			CO-verified 7-day abstinence at follow-up	9.5% of users of 24 mg/mL nicotine e-liquid and 4.0% of 16 mg/mL users quit smoking vs 4.6% in controls. Difference was not statistically significant. No analysis by frequency of use of ENDS presented. Motivation to quit interacted, varying by group and over time within groups.

		Italy. Smokers of ≥ 10 cigarettes/day for ≥ 10 years highly motivated to quit but not quitting or using NRT at baseline.			Arm 1= ENDS plus support Placebo = ENNDS plus support Control = no EN&NNDS		Arm 1= ENDS plus support Placebo = ENNDS plus support Control = no EN&NNDS		
	2015–2016	ENDS-naive	≥ 55	70 per arm		eGO 3.3–4.2 V working voltage			Quitting rate higher among EN&NNDS users than in control group; however, there was no difference between ENDS and ENNDS users. Authors indicate that ENDS users had an e-liquid that delivered very little nicotine in the aerosol (0.1 mg/puff).
126									

AOR: adjusted odds ratio; CI: confidence interval; CO: carbon monoxide; EN&NNDS: electronic nicotine and non-nicotine delivery systems; M: measured; NM: not measured; NRT: nicotine replacement therapy; NU: not used in analysis; SR: self-reported; U, used in analysis. [a]The authors did not report whether a caller was abstinent when enrolled. Some of the participants attended multiple calls, and the authors do not indicate whether they were "new" callers. [a] Instead, they measured desire to quit. [b] Instead, they measured strength of urge to smoke.

With these criteria in mind, we find that, of the 14 studies examined,

- only two characterized the type of device used (criterion 1);
- 12 studies did not restrict by or analyse the reasons for use of EN&NNDS, although two included adjustment for or analysis of some variables that could be used as proxies for using EN&NNDS (criterion 2); and
- seven studies compared cessation only between ever and never users of EN&NNDS, three used a crude measure of current use, and six used a more elaborated measure of frequency (criterion 3).

Seven longitudinal studies met at least one of the three criteria; none met all three. The combined evidence from the seven studies suggests that their samples consisted of different subgroups that experienced different or opposing effects of EN&NNDS use on cigarette cessation. Consequently, it could be hypothesized that **some** smokers may successfully quit tobacco use by using **some** types of ENDS frequently or intensively, while others experience no difference or are even prevented from quitting. The findings of these studies are shown in Table 3.5.

Table 3.5. Results of seven longitudinal studies of the efficacy of use of EN&NNDS for quitting tobacco use

Reference	Results by criterion: Frequency of use	Type of device used	Use for quitting smoking
Berry *(108)*	More daily users of EN&NNDS quit smoking than users, especially if they used refillable tank devices; however, the quit rate of experimenters with EN&NNDS and non-daily users of non-refillable cartridge devices was lower than that of non-users.		

EN&NNDS use	AOR[a]	95% CI	P
Non-users	Reference		
Experimenters	0.5	0.26, 1.00	0.05
Current users (not daily)	0.5	0.17, 1.47	0.21
Current users (daily)	7.9	4.45, 13.95	< 0.001

EN&NNDS use by type of device			
Non-users			
Daily users of:			
non-cartridge	10.1	5.4, 10.1	< 0.001
refillable	9.1	4.9, 17.0	< 0.001
tank	10.2	5.4, 19.4	< 0.001
non-tank	3.6	1.04, 12.2	0.04
Experimental or not daily users of:			
cartridge	0.3	0.1, 0.9	0.03
non-refillable	0.25	0.1, 0.9	0.04
non-tank	0.34	0.1, 0.8	0.02

[a] Adjusted for age, sex, race, region, income, frequency, intensity of cigarette use, nicotine dependence and previous quit attempts.

<table>
<tr><td></td><td>Smokers who were daily tanks users were more likely to quit smoking than non-users of EN&NNDS, while non-daily users of cigalikes were less likely to quit.
<table><tr><th>EN&NNDS use</th><th>AOR*</th><th>95% CI</th><th>P</th></tr><tr><td>Non-users</td><td>Reference</td><td></td><td></td></tr><tr><td>Non-daily cigalike</td><td>0.35</td><td>0.20, 0.60</td><td>0.002</td></tr><tr><td>Daily cigalike</td><td>0.74</td><td>0.39, 1.42</td><td>0.36</td></tr><tr><td>Non-daily tank</td><td>0.7</td><td>0.29, 1.68</td><td>0.42</td></tr><tr><td>Daily tank</td><td>2.7</td><td>1.48, 4.89</td><td>0.001</td></tr></table>*Adjusted for gender, age, education, income, motivation to stop smoking, strength of urge to smoke.</td><td>Although motivation to quit was measured, no information was collected on whether ENNDS were used specifically to quit.</td></tr>
<tr><td>Hitchman (124)</td><td></td><td></td></tr>
<tr><td></td><td>Smokers who used EN&NNDS daily were more likely to quit smoking than those who never used EN&NNDS. Non-daily users, however, were less likely to quit than non-users, although the association was not statistically significant.
<table><tr><th>EN&NNDS USE</th><th>AOR*</th><th>95% CI</th></tr><tr><td>Non-users</td><td>Reference</td><td></td></tr><tr><td>Current non-daily</td><td>0.31</td><td>0.04, 2.80</td></tr><tr><td>Current daily</td><td>6.07</td><td>1.15, 24.4</td></tr></table>*Adjusted for gender, age, race, education and baseline level of smoking</td><td>Motivation to quit with EN&NNDS was measured as two variables: expectation to be smoking in 1 year and plans to quit within 6 months. Smokers who were not daily EN&NNDS users were six times more likely to expect to continue smoking in 1 year than smokers who were non-users. The expectation to continue smoking was similar for daily users and non-users. Smokers who did not use EN&NNDS were less like to have plans to quit smoking than smokers who were EN&NNDS users, but the differences were not statistically significant.</td></tr>
<tr><td>Biener (121)</td><td></td><td></td></tr>
<tr><td></td><td>Smokers who used ENDS or ENNDS regularly (inhaled ≥ 50 puffs/week) quit at the same rate as smokers who did not use EN&NNDS (AOR = 1.25; 95% CI, 0.85, 1.84.) Adjustment for baseline age, gender, body mass index, marital status, educational level, occupation, alcohol use, hypertension, hypercholesterolaemia, diabetes, self-reported health, years of tobacco smoking (former smoking for e-cigarette users), number of tobacco cigarettes smoked per day (or puffs per day for smokers of e-cigarettes only).</td><td></td></tr>
<tr><td>Manzoli (111)</td><td></td><td></td></tr>
</table>

<table>
<tr><td></td><td>The quitting behaviour of daily and non-daily users of EN&NNDs was different from that of non-users. While the rate of quitting was no different for daily users and non-users, non-daily users quit at a lower rate than non-users.
<table><tr><th>EN&NNDS use in past 30 days</th><th>AOR</th><th>95% CI</th><th>P</th></tr><tr><td>Non-users</td><td>Reference</td><td></td><td></td></tr><tr><td>Infrequent (1–5 days)</td><td>0.35</td><td>0.20, 0.59</td><td>< 0.001</td></tr><tr><td>Intermediate (6–29 days)</td><td>0.50</td><td>0.32, 0.80</td><td>0.004</td></tr><tr><td>Daily (30 days)</td><td>1.16</td><td>0.71, 1.70</td><td>0.453</td></tr></table></td><td></td></tr>
<tr><td>Nowariak (107)</td><td>Adjusted for age, gender, education, tobacco type, advice from health professional, state programme and medication use.</td><td></td></tr>
<tr><td>Rigotti (109)</td><td>The quitting rate of smokers was 13.7% among those who had used EN&NNDS in the past 7 days and 17.9% among those who had not used them. The difference in risk was–4.3% (95% CI, –13.6, 5.1), which was not statistically significant. Quitting was therefore slightly but not statistically significantly lower among ENNDS users.</td><td></td></tr>
<tr><td>Zawartalio (110)</td><td></td><td>At the 6-month follow-up, the quit rate of EN&NNDS users (measured crudely as at least once in the past 3 months) who did not use them for smoking cessation was similar to that of non-users (37.6% vs 42.0%; P = 0.43), while the quit rate of EN&NNDS users who reported using them to help them quit smoking cigarettes was significantly lower than that of non-users.</td></tr>
</table>

AOR: adjusted odds ratio; CI: confidence interval; ENDS: electronic nicotine delivery systems; ENNDS: electronic non-nicotine delivery systems; EN&NNDS: electronic nicotine and non-nicotine delivery systems.

A cross-sectional study by Giovenco et al. *(127)* of current and former smokers who had quit since 2010, as reported in the 2014–2015 National Health Interview in the USA, lends some support to this hypothesis. The prevalence of quitting smoking tripled among daily ENDS users as compared with those who had never used ENDS, in line with the findings of Zhu et al. *(128)*. Interestingly, Giovenco et al. found the opposite effect among non-daily ENDS users and former experimenters, with a prevalence of quitting smoking of 2.6 and 1.5 times less than those who had never used ENDS, respectively. Success or failure in quitting in different subgroups may be influenced by:

- motivation to use EN&NNDS, including for quitting smoking;
- patterns of quantity, frequency and duration of ENDS use;
- technology used, including type of devices and e-liquids;
- type of smoker, including level of nicotine dependence and history of previous successful and unsuccessful quit attempts; and
- the regulatory environment for ENDS and tobacco use *(131-133)*.

Further support for the possibility that some smokers may successfully quit smoking by using ENDS includes the fact that ENDS may be economic substitutes for cigarettes *(134–136)* and the absence of a reversal in the decreasing rate of smoking rate in the two major EN&NNDS markets. Current cigarette smoking among adults in the USA decreased from 20.9% in 2005 to 15.1% in 2015, a 27.7% decrease (*P* for trend, < 0.05) *(137)*. The decrease includes a significant 1-year drop between 2014 and 2015 of 1.7 percentage points, which coincided with a notable increase in the cessation rate in 2014–2015, attributed by the authors partly to use of EN&NNDS. The results were adjusted for other changes to the policy environment that might affect quit attempts, such as tax increases and the "Tips from former smokers" media campaign of the Centers for Disease Control and Prevention in the USA.

In the United Kingdom, the proportion of current adult (≥ 18 years) smokers in 2016 was 15.8%, the lowest prevalence recorded since the start of the Annual Population Survey in 2010 *(138)*. At the same time, the increase in the use of EN&NNDS in England has been associated with the increasing success of quit attempts *(139)*.

These data in themselves do not prove that use of EN&NNDS by the population is an effective quitting aid. They do show, however, that use of EN&NNDS is at least not changing the trend to a decreasing prevalence of smoking in the United Kingdom.

3.7 Potential health impact of ENDS

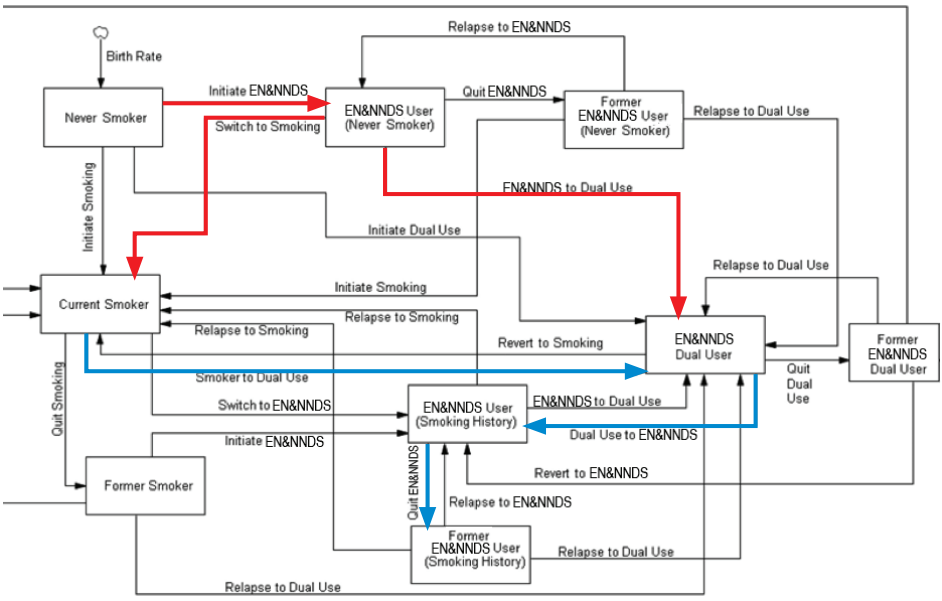
As some ENDS may help some smokers to quit, what is their potential health benefit for the population? The overall impact of using ENDS on population

health depends primarily on two factors. One is the capacity of ENDS to help prevent smoking, and the other is the relative risk associated with their use in comparison with a defined alternative, such as smoking *(140)*.

3.7.1 Behavioural trajectories associated with use of ENDS

If ENDS prevent smoking, they do not entice nonsmokers into smoking but instead lure smokers into quitting smoking and, ideally, abstaining from nicotine. In other words, whatever the initial status of a person – never, current or former smoker – behavioural paths or trajectories associated with ENDS use must lead away from smoking and ultimately from nicotine dependence. Fig. 3.5 presents the 27 possible paths from an initial state of never, current or former smoker into one of four possible final states: exclusive smoker, exclusive ENDS user, dual user or dual abstainer. The web of trajectories in Fig. 3.5 represents only the behavioural paths between two nicotine products. In reality, it may be complicated by competition among more than two products, be they pharmaceutical, tobacco or consumer products.

Fig. 3.5. Web of trajectories associated with ENDS use



EN&NNDS, electronic nicotine and non-nicotine delivery systems. *Source*: Modified from reference *141*.

The first step in understanding the effect on population health of using ENDS is, therefore, to estimate the probability that people in each initial state will end over time in one of the four final states. The probabilities are context sensitive

and therefore cannot be transferred among different cultural and regulatory environments for EN&NNDS and tobacco. Estimating the probabilities is complex, especially in light of the scant empirical evidence for characterizing them. The discussion has focused on the two most relevant combinations of trajectories in which EN&NNDS can play a role for or against health. One is the combination that leads smokers to quit smoking (blue lines in the figure), and the other is that which leads never smokers to smoke (red lines in the figure).

Trajectories that lead smokers to quit smoking

We discussed above the evidence for the role of EN&NNDS in quitting smoking. Contrary to the polarized discussion on whether ENNDS support or dissuade quitting, we concluded that the effects of EN&NNDS use on smoking cessation might depend on individual patterns of use and smoking, attitudes and behaviour, technology and the regulatory environment. The overall usefulness of ENDS for quitting might depend on the predominance of the subgroups for whom ENDS use might have an effect. For example, Giovenco et al. *(127)* showed that daily ENDS users quit smoking 3.2 times more often than never users; however, daily users represented only 5.1% of the sample. Non-daily ENDS users and former attempters, who represented 9.8% and 33.1% of the sample, respectively, however, quit smoking 2.6 and 1.5 times less often than those who had never used ENDS. Overall, the adjusted percentage of the total sample that quit is 26.5% with EN&NNDS and 28.2% without (Table 3.6). Given the predominance of non-daily EN&NNDS users and former experimenters in the population, preventing quitting predominated over promoting quitting among daily users.

Table 3.6. Theoretical impact on the prevalence of population quitting among smokers who use and do not use electronic nicotine and non-nicotine delivery systems (EN&NNDS) by type of user

Type of EN&NNDS user	Prevalence of EN&NNDS use (%)	Rate attributable to EN&NNDS use (%)	Adjusted[a] prevalence of quitting attributable to EN&NNDS use (%)	Prevalence in the absence[b] of EN&NNDS use (%)
Daily	5.1	52.2	4.6	1.4
Non-daily	9.8	12.1	1.1	2.8
Former	33.1	20.2	6.3	9.3
Non-user	51.9	28.2	14.7	14.7
Total	100	--	26.5	28.2

[a] Quit rate adjusted for a prevalence rate for daily and non-daily users, former experimenters and non-users of 3.18, 0.38, 0.67 and 1, respectively. [b] If the whole population were non-users at a quit rate of 28.2%.

Trajectories of never smokers to smoking

Young never smokers who experiment with ENDS are more likely to experiment with smoking later. A meta-analysis *(142)* of three longitudinal studies in the

USA *(143–145)* showed that young people who had used ENDS even once in their lives at baseline were twice as likely to experiment later with smoking than those who had never used ENDS. A more recent meta-analysis *(146)* that included the three previously mentioned studies and six additional ones *(147)* concluded that the likelihood of subsequent smoking initiation by young people who had ever used ENDS was about 3.5 times higher than that of never ENDS users. The authors also reported that using ENDS during the previous 30 days increased the chance of smoking at least once in the next 30 days by four. Two longitudinal studies in the United Kingdom *(148, 149)* showed a similar association between experimental use of ENDS and subsequent experimental smoking. The data available so far do not, however, prove that this evident association is causal or due mostly to ENDS use.

This association is difficult to understand, for several reasons *(150, 151)*. In most of the longitudinal studies, use of these products was measured as at least once in either a lifetime or in the previous 30 days. These recall periods cover a mixture of behaviour in the formative years of young people, including more frequent experimental use of ENDS and smoking, which is tentative and volatile, and also less prevalent established behaviour. It can be assumed that established ENDS use patterns better define the likelihood of future smoking than volatile, tentative ENDS use, such as having a puff once in a while.

Furthermore, there are three theoretical explanations for the association. The first is the "common liability conjecture". According to this theory, ENDS use and smoking are initiated independently of each other because they are the result of a common latent propensity to risky behaviour. Thus, it has been suggested that a large proportion of the young people who try ENDS and then smoke would have tried smoking regardless of the existence of ENDS. The fact that ENDS are used before smoking and not the other way around is due to several factors, including the novelty of ENDS. The second theory is the "renormalization" hypothesis, by which ENDS use is widespread and frequent among young people, and the devices and mannerisms of its use remind them of smoking. The similarity between ENDS use and smoking facilitates the trajectory from one product to the other within a social learning framework. The third theory is the "catalyst" theory, which comprises six hypotheses for initiation of ENDS use: flavour, health, price, role model, concealment and acceptance. Another three hypotheses are proposed to explain the transition to smoking: addiction, accessibility and experience *(152)*. Proving any of these theories will face critical methodological challenges *(153)*. In some longitudinal studies, adjustment has been made for variables to measure common susceptibility traits; however, residual confounding always muddles the association between ENDS use and smoking, and no one has proven beyond doubt which hypothesis or combination best explains the transition from never using nicotine to ENDS use and later to smoking.

The fact that some "never smokers" who experiment with ENDS end up smoking must be reconciled with the fact that the prevalence of current smoking among young people in the two countries with the most prominent ENDS markets continues to decrease. One review *(142)* shows that the prevalence of use of ENDS at least once a month increased quickly in some countries like the USA *(154)* (probably EN&NNDS), while in others such as the United Kingdom the rate among nonsmokers has been stable at very low levels.

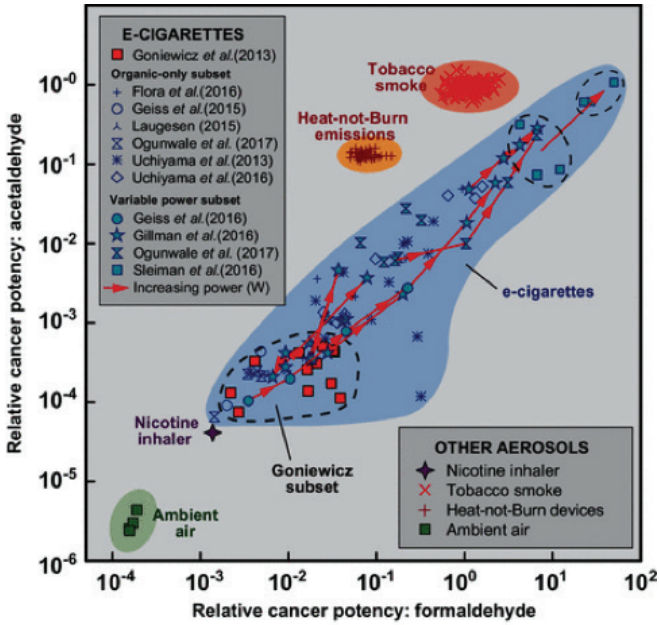
3.7.2 Harm from ENDS and electronic non-nicotine delivery systems

Although EN&NNDS may route the population through trajectories in and out of smoking, the overall health impact of use of ENDS depends on the health risks associated with their use. The long-term health effects of EN&NNDS use are still unknown, and determination of such effects with some degree of certainty will require investigations of the health outcomes of large cohorts of well-characterized users who are followed for many years. In the meantime, conclusions about the toxicity of EN&NNDS are based mainly on empirical evidence from chemical and toxicological studies and, to a lesser degree, clinical studies. Reviews of these studies have led various authors to conclude, with more or fewer caveats, that EN&NNDS are not harmless but are generally less dangerous than cigarettes *(155–160)*, especially with regard to death from diseases associated with cigarette use. Efforts have been made to specify and characterize the health risks of EN&NNDS use by type of health condition.

Cancer risk

Ideal combinations of EN&NNDS device power settings, liquid formulation and use should produce an aerosol containing carcinogenic chemicals at a potency < 1% that of tobacco smoke and two orders of magnitude higher than that of a medicinal nicotine inhaler. As shown in Fig. 3.6, however, some products and circumstances can increase the cancer risk of EN&NNDS aerosol considerably, sometimes close to that of tobacco smoke *(161)*. Aerosols with higher carcinogenic potency appear to be formed when the user applies excessive power to the atomizer coil *(76)*. It has been argued that this occurs only under "dry puff" conditions *(162)* – brief situations that are readily detectable by EN&NNDS users. There is no empirical evidence, however, that this is due only to dry puff conditions or, if so, how often such conditions occur.

Fig. 3.6. Carcinogenic potency of formaldehyde and acetaldehyde in aerosol from electronic nicotine and non-nicotine delivery systems and in tobacco smoke, heat-not-burn devices, a nicotine inhaler and ambient air



Source: reproduced from reference *161* with permission from BMJ Publishing Group Ltd.

Cardiovascular risk

There is controversy about whether the risk for cardiovascular events associated with use of EN&NNDS is as low as its carcinogenic potential. Some consider that the main cardiovascular risk of ENDS aerosol is due to the toxicity of nicotine, which appears to pose a low short-term cardiovascular risk in healthy users *(163)*. A review of clinical and cell culture studies conducted in 2015–2017 addressed the relation between ENDS use and indicators of risk for cardiovascular disease, including heart rate, blood pressure, and vagal tone; platelet aggregation and adhesion; aortic stiffness and endothelial function; expression of genes for antioxidant defence and immune system function; and indices of oxidative stress. Of the six studies reviewed that showed significant adverse cardiovascular effects, three found that ENDS had less effect on physiological cardiovascular risk indicators than cigarettes, and the other three found that ENDS had the same effect as cigarette smoking. Some studies indicated that these adverse cardiovascular effects are independent of nicotine, although adding nicotine may enhance them *(164)*.

Pulmonary risk

While EN&NNDS aerosol is probably less toxic than tobacco smoke and causes less mortality than cigarettes, the reduction in toxicity in the lung remains unknown for both long-term users who quit smoking and dual users. The authors of a review on the topic concluded that the induction of inflammation by EN&NNDS might differentially affect the risks for lung cancer and chronic obstructive pulmonary disease *(165)*. Thus, the most recent empirical evidence suggests that EN&NNDS aerosol is less toxic than cigarette smoke; however, there are no empirical data to quantify the relative risks of exposure to EN&NNDS aerosol and tobacco smoke.

Several efforts have been made to model the potential population impact of EN&NNDS *(166–168)*; however, the results are only as good as the data put into the model. Given the paucity of data, it is unclear which should be included in calculating the benefits of ENDS in worst- and best-case scenarios *(169, 170)*, especially for variables such as the efficacy of ENDS in helping people quit smoking and their safety relative to cigarettes.

Quantifying the effects of ENDS use on the health of the population is highly complex, as many variables must be taken into account. The available evidence indicates a possible positive effect of ENDS on population health, particularly if appropriate ENDS regulation is enacted to maximize their benefits and minimize their risks.

3.8 Summary of evidence, research gaps and policy issues derived from the evidence

ENDS are a heterogeneous class of products, with various profiles of nicotine and non-nicotine toxicants, which depend on factors including their construction, power, liquid constituents, nicotine concentration and user behaviour. The amount of nicotine delivered can range from none to doses that exceed those delivered by tobacco cigarettes in the same number of puffs. Nicotine from ENDS reaches users' blood faster than from most types of nicotine replacement therapy (NRT), and, at least with some ENDS, at higher concentrations. ENDS could be effective in cessation for some smokers under some circumstances, while, for other smokers, in different circumstances, it might have the opposite effect. Whether an ENDS has beneficial or detrimental effects on smoking cessation appears to depend on the technology, the motivation and consumer behaviour of the ENDS user, the type of smoker who seeks ENDS use and the regulatory environment for ENDS and tobacco use.

Translating the evidence into a potential role of EN&NNDS in smoking cessation is difficult. The evidence does not allow a blanket policy recommendation for or against general use of ENDS and ENNDS as cessation aids. Nevertheless, it points to four areas for regulatory consideration by policy-makers.

The concept of nicotine flux in ENDS regulation: regulators who wish to maximize the potential of the ENDS technology for nicotine substitution should

consider the rate at which nicotine is emitted (i.e. nicotine flux) as a primary factor in their decision. In practical terms, factors that influence nicotine flux should not be regulated in isolation. ENDS nicotine flux can be modelled mathematically for product standards for regulatory purposes, although such standards should also be based on a clinical evaluation (i.e. effects in humans who are and are not ENDS users).

The relation between nicotine flux and toxicant profile: a corollary to the above is that the conditions under which different nicotine fluxes are obtained may affect the toxicant profile, because some of the same factors that increase the nicotine flux, such as power, also increase the concentrations of some toxicants in the aerosol, such as aldehydes. Therefore, regulators might consider how the manufacturers and the government should inform users of the balance between creating an adequate nicotine flux and the associated toxicant delivery.

Nicotine e-liquid concentration: despite some industry guidelines on labelling nicotine concentrations, the labels on many e-liquids do not indicate the concentration, are difficult to interpret or, most often, do not provide accurate information. Depriving ENDS users of accurate information on the nicotine concentration in e-liquids denies them important information for controlling their self-administration of nicotine.

Labelling and quality control for ENDS devices and e-liquids: the labels on all e-liquids should display the total amount of nicotine per receptacle, the ratio of free-base to protonated nicotine and the liquid concentration in mg/mL, visibly and understandably; otherwise, they should indicate that the e-liquids do not contain nicotine at a concentration above, for example, 0.1 mg/mL. Quality control must be used to ensure the veracity of labelling information and conformity to production standards.

Although the topic is not reviewed in this paper, there is conclusive evidence that exposure to nicotine in e-liquids other than through aerosol inhalation can harm health, sometimes fatally *(171)*. In order to avoid accidental exposure to nicotine, regulators should consider requiring child-resistant containers for all e-liquid receptacles.

The development of adequate policies and regulations on the ENDS issues described in this paper would benefit from disclosure requirements for manufacturers and effective, organized, systematic national surveillance. Key disclosure data to be requested from manufacturers include the voltage, resistance and power of marketed devices and the e-liquid constituents. In addition, monitoring should be conducted to determine consumer behaviour towards ENDS, such as who uses them, for what purpose, what and how products are used and the frequency of use.

Table 3.7 summarizes the evidence on the delivery of nicotine by ENDS, their effect on smoking cessation and their prospective impact on population health. The table also lists gaps in research and policy issues for each element of the evidence.

Table 3.7. Summary of evidence, research gaps and policy issues

Topic	Evidence	Research gaps	Policy and regulatory issues
Effective nicotine delivery	**Technology** A nicotine flux similar to that of cigarettes with regard to the levels and speed of nicotine delivery can be produced. The flux is influenced by: • the voltage applied to a coil of a given resistance: the higher the power, the higher the concentration of nicotine in the aerosol in a range of values between a threshold and a ceiling; • the concentration of nicotine in e-liquid: the higher the concentration in the e-liquid the higher concentration in aerosol at a given power value; and • the puffing behaviour of the user: the longer the puff, the more nicotine is delivered.	ENDS differ widely in device technology and e-liquid components. Although the technological characteristics of ENDS that govern the delivery of nicotine are known, further research is needed to generalize the findings to the whole class of ENDS, beyond individual products. Programmatic and transdisciplinary research is required, combining aerosol research, analytical chemistry and clinical laboratory methods to complete the mathematical model for predicting nicotine flux and to begin to describe similar models for predicting non-nicotine toxicants to the extent possible. The relation between nicotine flux and smoking cessation must be characterized at population level. Characterizing the relation between nicotine flux and potential abuse might help to explain and prevent initiation of cigarette smoking by non-tobacco users via ENDS.	The concept of nicotine flux in ENDS regulation As nicotine flux is the primary determinant of the capacity of ENDS to substitute for nicotine from cigarettes, regulators should consider this factor in endeavours to maximize the nicotine substitution potential of ENDS technology. Regulation of only one of the factors that influence nicotine flux (e.g. concentration in e-liquids) might result in changes to other factors by ENDS users (e.g. increased power). Such changes may or may not increase nicotine flux but may increase health risks (e.g. by increasing volatile aldehyde emissions at higher power values). ENDS that cannot deliver nicotine at a speed and concentration similar to those of cigarettes should, at a minimum, bear a warning that they cannot assist in smoking cessation.
	Relation between toxicant profile of ENDS emissions and nicotine flux Some of the factors that increase the nicotine flux, such as power, also increase the concentrations of some toxicants in the aerosol, such as aldehydes.	Further research is needed to characterize the association between the toxicant profile of ENDS emissions and the factors that influence nicotine flux, under a variety of conditions, such as: e-liquid composition: types of solvents and flavourings. Many flavourings used in ENDS liquids are intended to be consumed orally and have not been tested for safety after heating and inhalation. device construction: including general design, metals used, wicking materials.	Toxicant profile information Regulators might consider how to make users aware of the factors that influence the balance between creating an adequate nicotine flux and the associated toxicant delivery.

Concentration of nicotine in e-liquid

Despite some industry guidelines on labelling of e-liquids for nicotine concentration, many do not carry such a label, it is difficult to interpret or, most often, does not provide accurate information.

Depriving ENDS users of accurate information on the nicotine concentration in e-liquids denies them adequate information for deciding whether to self-administer nicotine.

A major research gap is how to communicate this information in a manner that is useful to the consumer and increases the chance that ENDS will be used to increase cessation rates. The same applies to ENDS power. Some ENDS users may not realize that they are using an ENDS that cannot deliver nicotine effectively, no matter what strength of nicotine liquid it contains.

Range of nicotine concentration in e-liquids

Regulation of a minimum and a maximum amount and concentration of nicotine in e-liquids should ensure a balance between:

- ensuring a sufficient concentration to reach an adequate flux for nicotine replacement; and
- the risk of accidental exposure to e-liquid containing nicotine.

The total amount of nicotine per e-liquid container should be small enough to avoid the risk of lethal or serious cases of accidental nicotine poisoning if packaging safeguards fail.

The nicotine concentration should be high enough to provide an adequate nicotine flux and to limit production of toxicants when the coil is heated too much to obtain more nicotine aerosol.

Labelling and quality control of ENDS devices and e-liquids

Consumers must have accurate, reliable information on product design characteristics and e-liquid ingredients, including:

- the ingredients listed comprise all liquid constituents (i.e. no contaminants); and
- all e-liquid containers are labelled to provide accurate information on the amount of nicotine, the ratio of free-base to protonated nicotine and the concentration.

E-liquid contaminants known to pose a severe risk should be banned (e.g., diethylene glycol, diacetyl).

Quality control must be used ensure the veracity of labelling information and implementation of production standards.

Effectiveness of ENDS as a smoking cessation aid	ENDS can be effective for cessation for some smokers under some circumstances. It may have the opposite effect for other smokers under different circumstances.		

	The conditions that appear to affect the potential of ENDS as a smoking cessation aid include:
	- the appropriate combination of ENDS device and e-liquid to deliver nicotine at levels and speed similar to those of cigarettes;
	- use of ENDS for quitting smoking with a minimal pattern of quantity, frequency and duration of use;
	- the type of smoker, including level of nicotine dependence and history of previous successful and unsuccessful attempts to quit; and
	- the regulatory environment of ENDS and tobacco use.
		Better understanding is needed of the circumstances in which ENDS use can promote or be detrimental to smoking cessation, including:
		- features of ENDS that facilitate cessation:
		  - the nicotine delivery profiles most strongly associated with quitting;
		  - whether flavours are necessary and, if so, which and how many will maximize quitting; and
		  - which user behaviour and use frequencies are most strongly associated with quitting and avoiding relapse to cigarettes;
		- the subpopulations of smokers in whom ENDS are likely to be effective for cessation and those in whom they are not;
		- the features of ENDS that maintain dual cigarette and ENDS use and how they could be manipulated to encourage cigarette cessation; andhe features of ENDS that maintain dual cigarette and ENDS use and how they could be manipulated to encourage cigarette cessation; and
		- how to help long-term ENDS users to cease ENDS use, should they desire that outcome.
			Regulators should be aware that ENDS use may have opposite effects on smoking cessation. Without further research, however, it is not possible to recommend policies to maximize their potential to help quit smoking and to minimize their detrimental effects on cessation.

Potential health impact of ENDS	The overall population health effects of using ENDS depends primarily on: the capacity of ENDS to lead smokers away from smoking, while dissuading never smokers from starting to smoke and ex-smokers from relapsing; and the health risks associated with their use relative to defined alternatives such as never using ENDS or smoking.	The gaps in research on the effectiveness of ENDS as smoking cessation aid are described above. Further research is needed on the long-term health consequences of ENDS use in comparison with non-use and with cigarette smoking in: smokers, including adults, children and pregnant women; and nonsmokers.	Development of adequate policies and regulations on the ENDS issues described in this paper would benefit from effective, organized national and global surveillance of the types of ENDS marketed and their use. More specifically, information is required on who is using them, for what purpose (including to deliver other drugs of abuse) and the products being used (including measures of voltage, resistance, power, liquid constituents, use frequency).
		In some cases, in-vitro (e.g. cell preparations) or in-vivo (e.g. animal models) methods may be appropriate for addressing these questions or to guide subsequent clinical investigation. For human studies, any diseases associated with ENDS use may not necessarily be those associated with cigarette smoking. Thus, particular attention must be paid to disease states and biomarkers of disease that might be associated with ENDS use, with an initial focus on known ENDS emissions that include propylene glycol, vegetable glycerine, flavourings, sweeteners and by-products of these liquid constituents that are produced when they are heated.	

3.9 References

1. Breland A, Soule E, Lopez A, Ramôa C, El-Hellani A, Eissenberg T et al. Electronic cigarettes: what are they and what do they do? Ann N Y Acad Sci. 2016;1394:5–30.
2. Kennedy RD, Awopegba A, De León E, Cohen JE. Global approaches to regulating electronic cigarettes. Tob Control 2016;26:440–5.
3. Talih S, Balhas Z, Eissenberg T, Salman R, Karaoghlanian N, El Hellani H et al. Effects of user puff topography, device voltage, and liquid nicotine concentration on electronic cigarette nicotine yield: measurements and model predictions. Nicotine Tob Res. 2014;17:150–7.
4. Wagener T, Floyd E, Stepanov I, Driskill LM, Frank SG, Meier E et al. Have combustible cigarettes met their match? The nicotine delivery profiles and harmful constituent exposures of second-generation and third-generation electronic cigarette users. Tob Control. 2016;26:e23–8.
5. Rudy A, Leventhal A, Goldenson NI, Eissenberg T. Assessing electronic cigarette effects and regulatory impact: challenges with user self-reported device power. Drug Alcohol Depend. 2017;179:337–40.
6. Farsalinos K, Spyrou A, Stefopoulos C, Tsimopoulou K, Kourkoveli P, Tsiapris D et al. Nicotine absorption from electronic cigarette use: comparison between experienced consumers (vapers) and naïve users (smokers). Sci Rep. 2015;5:11269.
7. Hua M, Yip H, Talbot P. Mining data on usage of electronic nicotine delivery systems (ENDS) from YouTube videos. Tob Control. 2011;22:103–6.
8. Hiler M, Breland A, Spindle T, Maloney S, Lipato T, Karaoghlanian N et al. Electronic cigarette user plasma nicotine concentration, puff topography, heart rate, and subjective effects: the influence of liquid nicotine concentration and user experience. Exp Clin Psychopharmacol. 2017;25(5):380–92.
9. Vansickel A, Cobb C, Weaver M, Eissenberg T. A clinical laboratory model for evaluating the acute effects of electronic "cigarettes": nicotine delivery profile and cardiovascular and subjective effects. Cancer Epidemiol Biomarkers Prev. 2010;19:1945–53.
10. Cheah N, Chong N, Tan J, Morsed FA, Yee SK. Electronic nicotine delivery systems: regulatory and safety challenges: Singapore perspective. Tob Control. 2012;23:119–25.
11. Chaudhry IW, Leigh NJ, Smith DM, O'Connor RJ, Goniewicz ML. Labeling information on electronic nicotine delivery systems. Tob Regul Sci. 2017;3:3–9.
12. Buonocore F, Marques Gomes ACN, Nabhani-Gebara S, Barton SJ, Calabrese G. Labelling of electronic cigarettes: regulations and current practice. Tob Control. 2016;26:46–52.
13. Beauval N, Antherieu S, Soyez M, Gengler N, Grova N, Howsam M et al. Chemical evaluation of electronic cigarettes: multicomponent analysis of liquid refills and their corresponding aerosols. J Anal Toxicol. 2017;41:670–8.
14. Buettner-Schmidt K, Miller DR, Balasubramanian N. Electronic cigarette refill liquids: child-resistant packaging, nicotine content, and sales to minors. J Pediatric Nurs. 2016;31:373–9.
15. Cameron JM, Howell DN, White JR, Andrenyak DM, Layton ME, Roll JM. Variable and potentially fatal amounts of nicotine in e-cigarette nicotine solutions: Table 1. Tob Control 2013;23:77–8.
16. Davis B, Dang M, Kim J, Talbot P. Nicotine concentrations in electronic cigarette refill and do-it-yourself fluids. Nicotine Tob Res. 2014;17:134–41.
17. El-Hellani A, El-Hage R, Baalbaki R, Salman R, Talih S, Shihadeh A et al. Free-base and protonated nicotine in electronic cigarette liquids and aerosols. Chem Res Toxicol. 2015;28:1532–7.
18. Etter J, Zäther E, Svensson S. Analysis of refill liquids for electronic cigarettes. Addiction. 2013;108:1671–9.
19. Etter J, Bugey A. E-cigarette liquids: constancy of content across batches and accuracy of labeling. Addictive Behav. 2017;73:137–43.
20. Farsalinos KE, Gillman IG, Melvin MS, Paolantonio AR, Gardow WJ, Humphries KE et al. Nicotine

levels and presence of selected tobacco-derived toxins in tobacco flavoured electronic cigarette refill liquids. Int J Environ Res Public Health. 2015;12:3439–52.
21. Goniewicz ML, Gupta R, Lee YH, Reinhardt S, Kim S, Kim B et al. Nicotine levels in electronic cigarette refill solutions: a comparative analysis of products from the US, Korea, and Poland. Int J Drug Policy. 2015;26:583–8.
22. Kim S, Goniewicz M, Yu S, Kim B, Gupta R. Variations in label information and nicotine levels in electronic cigarette refill liquids in South Korea: regulation challenges. Int J Environ Res Public Health. 2015;12:4859–68.
23. Kirschner RI, Gerona R, Jacobitz KL. Nicotine content of liquid for electronic cigarettes. Clin Toxicol. 2013;51:684–4.
24. Kosmider L, Sobczak A, Szołtysek-Bołdys I, Prokopowicz A, Skórka A, Abdulafeez O et al. Assessment of nicotine concentration in electronic nicotine delivery system (ENDS) liquids and precision of dosing to aerosol. Przegl Lek. 2015;72:500–4.
25. Lisko JG, Tran H, Stanfill SB, Blount BC, Watson CH. Chemical composition and evaluation of nicotine, tobacco alkaloids, pH, and selected flavors in e-cigarette cartridges and refill solutions. Nicotine Tob Res. 2015;17:1270–8.
26. Pagano T, DiFrancesco AG, Smith SB, George J, Wink G, Rahman I et al. Determination of nicotine content and delivery in disposable electronic cigarettes available in the United States by gas chromatography–mass spectrometry. Nicotine Tob Res. 2015;18:700–7.
27. Peace MR, Baird TR, Smith N, Wolf CE, Poklis JL, Poklis A. Concentration of nicotine and glycols in 27 electronic cigarette formulations. J Anal Toxicol. 2016;40:403–7.
28. Rahman A, Nik Mohamed MH, Mahmood S. Nicotine estimations in electronic cigarette e-liquids among Malaysian marketed samples. Anal Chem Lett. 2018;8:54–62.
29. Raymond BH, Collette-Merrill K, Harrison RG, Jarvis S, Rasmussen RJ. The nicotine content of a sample of e-cigarette liquid manufactured in the United States. J Addict Med. 2018;12:127–31.
30. Trehy ML, Ye W, Hadwiger ME, Moore TW, Allgire JF, Woodruff JT et al. Analysis of electronic cigarette cartridges, refill solutions, and smoke for nicotine and nicotine related impurities. J Liquid Chromatogr Relat Technol. 2011;34:1442–58.
31. E-liquid manufacturing standards 2017 version 2.3.2. Mooresville (NC): American E-liquid Manufacturing Standards Association; 2017 (http://www.aemsa.org/standards/, accessed 19 September 2017).
32. Goniewicz ML, Hajek P, McRobbie H. Nicotine content of electronic cigarettes, its release in vapour and its consistency across batches: regulatory implications. Addiction. 2013;109:500–7.
33. Omaiye E, Cordova I, Davis B, Talbot P. Counterfeit electronic cigarette products with mislabeled nicotine concentrations. Tob Regul Sci. 2017;3:347–57.
34. Westenberger B. Evaluation of e-cigarettes. St Louis (MO): Center for Drug Evaluation and Research, Office of Pharmaceutical Science, Office of Testing and Research; 2009 (https://www.fda.gov/AboutFDA/CentersOffices/OfficeofMedicalProductsandTobacco/CDER/ucm088761.htm, accessed 1 October 2018).
35. Henningfield J, London E, Benowitz N. Arterial–venous differences in plasma concentrations of nicotine after cigarette smoking. JAMA. 1990;263:2049–50.
36. Baldassarri SR, Hillmer AT, Anderson JM, Jatlow P, Nabulsi N, Labaree D et al. Use of electronic cigarettes leads to significant beta2-nicotinic acetylcholine receptor occupancy: evidence from a PET imaging study. Nicotine Tob Res. 2018;20(4):425–33.
37. Dawkins L, Corcoran O. Acute electronic cigarette use: nicotine delivery and subjective effects in regular users. Psychopharmacology. 2013;231:401–7.
38. Hajek P, Goniewicz ML, Phillips A, Myers Smith K, West O, McRobbie H. Nicotine intake from electronic cigarettes on initial use and after 4 weeks of regular use. Nicotine Tob Res. 2014;17:175–9.
39. Nides MA, Leischow SJ, Bhatter M, Simmons M. Nicotine blood levels and short-term smoking

reduction with an electronic nicotine delivery system. Am J Health Behav. 2014;38:265–74.
40. St Helen G, Havel C, Dempsey DA, Jacob P 3rd, Benowitz NL. Nicotine delivery, retention and pharmacokinetics from various electronic cigarettes. Addiction. 2015;111:535–44.
41. Yan XS, D'Ruiz C. Effects of using electronic cigarettes on nicotine delivery and cardiovascular function in comparison with regular cigarettes. Regul Toxicol Pharmacol 2015;71:24–34.
42. Henningfield JE. Nicotine medications for smoking cessation. N Engl J Med. 1995;333:1196–203.
43. Choi JH, Dresler CM, Norton MR, Strahs KR. Pharmacokinetics of a nicotine polacrilex lozenge. Nicotine Tob Res. 2003;5:635–44.
44. Evans SE, Blank M, Sams C, Weaver MF, Eissenberg T. Transdermal nicotine-induced tobacco abstinence symptom suppression: nicotine dose and smokers' gender. Exp Clin Psychopharmacol. 2006;14:121–35.
45. Bullen C, Howe C, Laugesen M, McRobbie H, Parag V, Williman J et al. Electronic cigarettes for smoking cessation: a randomised controlled trial. Lancet 2013;382:1629–37.
46. E-Cigarette use among youth and young adults. A report of the Surgeon General. Atlanta (GA): Department of Health and Human Services, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2016.
47. Schroeder MJ, Hoffman AC. Electronic cigarettes and nicotine clinical pharmacology. Tob Control 2014;23:ii30–5.
48. Cobb NK, Byron MJ, Abrams DB, Shields PG. Novel nicotine delivery systems and public health: the rise of the "e-cigarette". Am J Public Health. 2010;100:2340–2.
49. McAuley TR, Hopke PK, Zhao J, Babaian S. Comparison of the effects of e-cigarette vapor and cigarette smoke on indoor air quality. Inhal Toxicol. 2012;24:850–7.
50. Pellegrino RM, Tinghino B, Mangiaracina G, Marani A, Vitali M, Protano C et al. Electronic cigarettes: an evaluation of exposure to chemicals and fine particulate matter (PM). Ann Ig. 2012;24:79–88.
51. Goniewicz ML, Kuma T, Gawron M, Knysak J, Kosmider L. Nicotine levels in electronic cigarettes. Nicotine Tob Res. 2012;15:158–66.
52. Farsalinos KE, Romagna G, Tsiapras D, Kyrzopoulos S, Voudris V. Evaluation of electronic cigarette use (vaping) topography and estimation of liquid consumption: implications for research protocol standards definition and for public health authorities' regulation. Int J Environ Res Public Health 2013;10:2500–14.
53. Laugesen M. Nicotine and toxicant yield ratings of electronic cigarette brands in New Zealand. NZ Med J. 2015;128:77–82.
54. Tayyarah R, Long GA. Comparison of select analytes in aerosol from e-cigarettes with smoke from conventional cigarettes and with ambient air. Regul Toxicol Pharmacol. 2014;70:704–10.
55. Henningfield JE, Keenan RM. Nicotine delivery kinetics and abuse liability. J Consult Clin Psychol 1993;61:743–50.
56. Shihadeh A, Eissenberg T. Electronic cigarette effectiveness and abuse liability: predicting and regulating nicotine flux. Nicotine Tob Res. 2014;17:158–62.
57. Eissenberg T, Shihadeh A. Nicotine flux: a potentially important tool for regulating electronic cigarettes. Nicotine Tob Res. 2014;17:165–7.
58. Talih S, Balhas Z, Salman R, El-Hage R, Karaoghlanian N, El-Hellani A et al. Transport phenomena governing nicotine emissions from electronic cigarettes: model formulation and experimental investigation. Aerosol Sci Technol. 2016;51:1–11.
59. Stepanov I, Fujioka N. Bringing attention to e-cigarette pH as an important element for research and regulation. Tob Control. 2014;24:413–4.
60. Han S, Chen H, Zhang X, Liu T, Fu Y. Levels of selected groups of compounds in refill solutions for electronic cigarettes. Nicotine Tob Res. 2015;18:708–14.
61. Burr GA, Van Gilder TJ, Trout BD, Wilcox TC, Driscoll R. Health hazard evaluation report HETA

90-0355-2449, Actors' Equity Association/The League of American Theatres and Producers, Inc. Washington (DC): National Institute for Occupational Safety and Health, Hazard Evaluations and Technical Assistance Branch Division of Surveillance, Hazard Evaluations, and Field Studies; 1994 (http://www.cdc.gov/niosh/hhe/reports/pdfs/1990-0355-2449.pdf, accessed 1 October 2018).

62. Moline JM, Golden AL, Highland JH, Wilmarth KR, Kao AS. Health effects evaluation of theatrical smoke, haze, and pyrotechnics. Report to Equity-League Pension and Health Trust Funds, 2000.
63. Varughese S, Teschke K, Brauer M, Chow Y, van Netten C, Kennedy SM. Effects of theatrical smokes and fogs on respiratory health in the entertainment industry. Am J Ind Med. 2005;47:411–8.
64. Wieslander G. Experimental exposure to propylene glycol mist in aviation emergency training: acute ocular and respiratory effects. Occup Environ Med. 2001;58:649–55.
65. Neale BW, Mesler EL, Young M, Rebuck JA, Weise WJ. Propylene glycol-induced lactic acidosis in a patient with normal renal function: a proposed mechanism and monitoring recommendations. Ann Pharmacother. 2005;39:1732–6.
66. Deichmann W. Glycerol:–effects upon rabbits and rats–. Am Ind Hyg Assoc Q 1941;2:5–6.
67. Hine CH, Anderson HH, Moon HO, Dunlop MK, Morse MS. Comparative toxicity of synthetic and natural glycerin. Arch Ind Hyg Occup Med. 1953;7:282–91.
68. Safety assessment and regulatory authority to use flavors: focus on electronic nicotine delivery systems and flavored tobacco products. Washington (DC): Federal Emergency Management Agency; 2013 (https://www.femaflavor.org/safety-assessment-and-regulatory-authority-use-flavors-focus-electronic-nicotine-delivery-systems, accessed 18 Oct 2017).
69. Farsalinos KE, Kistler KA, Gillman G, Voudris V. Evaluation of electronic cigarette liquids and aerosol for the presence of selected inhalation toxins. Nicotine Tob Res. 2014;17:168–74.
70. Kosmider L, Sobczak A, Prokopowicz A, Kurek J, Zaciera M, Knysak J et al. Cherry-flavoured electronic cigarettes expose users to the inhalation irritant, benzaldehyde. Thorax. 2016;71:376–7.
71. Behar RZ, Luo W, Lin SC, Wang Y, Valle J, Pankow JE et al. Distribution, quantification and toxicity of cinnamaldehyde in electronic cigarette refill fluids and aerosols. Tob Control 2016;25:ii94–102.
72. Gerloff J, Sundar IK, Freter R, Sekera ER, Friedman AE, Robinson R et al. Inflammatory response and barrier dysfunction by different e-cigarette flavoring chemicals identified by gas chromatography–mass spectrometry in e-liquids and e-vapors on human lung epithelial cells and fibroblasts. Appl In Vitro Toxicol. 2017;3:28–40.
73. Hutzler C, Paschke M, Kruschinski S, Henkler F, Hahn J, Luch A. Chemical hazards present in liquids and vapors of electronic cigarettes. Arch Toxicol. 2014;88:1295–308.
74. Varlet V, Farsalinos K, Augsburger M, Thomas A, Etter JF. Toxicity assessment of refill liquids for electronic cigarettes. Int J Environ Res Public Health. 2015;12:4796–815.
75. Williams M, Bozhilov K, Ghai S, Talbot P. Elements including metals in the atomizer and aerosol of disposable electronic cigarettes and electronic hookahs. PLoS One. 2017;12:e0175430.
76. Ogunwale MA, Li M, Ramakrishnam Raju MV, Chen Y, Nantz MH, Conklin DJ et al. Aldehyde detection in electronic cigarette aerosols. ACS Omega 2017;2:1207–14.
77. Herrington JS, Myers C. Electronic cigarette solutions and resultant aerosol profiles. J Chromatogr A 2015;1418:192–9.
78. Talih S, Balhas Z, Salman R, Karaoghlanian N, Shihadeh A. "Direct dripping": a high-temperature, high-formaldehyde emission electronic cigarette use method. Nicotine Tob Res. 2015;18:453–9.
79. Bekki K, Uchiyama S, Ohta K, Inaba Y, Nakagome H, Kunugita N. Carbonyl compounds generated from electronic cigarettes. Int J Environ Res Public Health. 2014;11:11192–200.

80. Sleiman M, Logue JM, Montesinos VN, Russell ML, Litter MI, Gundel LA et al. Emissions from electronic cigarettes: key parameters affecting the release of harmful chemicals. Environ Sci Technol. 2016;50:9644–51.
81. Wang P, Chen W, Liao J, Matsuo T, Ito K, Fowles J et al. A device-independent evaluation of carbonyl emissions from heated electronic cigarette solvents. PLoS One. 2017;12:e0169811.
82. Havel CM, Benowitz NL, Jacob P 3rd, St Helen G. An electronic cigarette vaping machine for the characterization of aerosol delivery and composition. Nicotine Tob Res. 2017;19(10):1224–31.
83. Geiss O, Bianchi I, Barrero-Moreno J. Correlation of volatile carbonyl yields emitted by e-cigarettes with the temperature of the heating coil and the perceived sensorial quality of the generated vapours. Int J Hyg Environ Health. 2016;219:268–77.
84. Khlystov A, Samburova V. Flavoring compounds dominate toxic aldehyde production during e-cigarette vaping. Environ Sci Technol. 2016;50:13080–5.
85. Farsalinos K, Gillman G, Kistler K, Yannovits N. Comment on "Flavoring compounds dominate toxic aldehyde production during e-cigarette vaping". Environ Sci Technol. 2017;51:2491–2.
86. Khlystov A, Samburova V. Response to comment on "Flavoring compounds dominate toxic aldehyde production during e-cigarette vaping". Environ Sci Technol. 2017;51:2493–4.
87. Tierney P, Karpinski C, Brown J, Luo W, Pankow JF. Flavour chemicals in electronic cigarette fluids. Tob Control. 2015;25:e10–5.
88. Soussy S, EL-Hellani A, Baalbaki R, Salman R, Shihadeh A, Saliba NA. Detection of 5-hydroxymethylfurfural and furfural in the aerosol of electronic cigarettes. Tob Control. 2016;25:ii88–93.
89. Pankow JF, Kim K, McWhirter KJ, Luo W, Escobedo JO, Strongin RM et al. Benzene formation in electronic cigarettes. PLoS One. 2017;12:e0173055.
90. Gillman I, Kistler K, Stewart E, Paolantonio AR. Effect of variable power levels on the yield of total aerosol mass and formation of aldehydes in e-cigarette aerosols. Regul Toxicol Pharmacol. 2016;75:58–65.
91. Franck C, Budlovsky T, Windle S, Filion KB, Eisenberg MJ. Electronic cigarettes in North America: history, use, and implications for smoking cessation. Circulation. 2014;129:1945–52.
92. Harrell PT, Simmons VN, Correa JB, Padhya TA, Brandon TH. Electronic nicotine delivery systems ("e-cigarettes"): review of safety and smoking cessation efficacy. Otolaryngol Head Neck Surg. 2014;151:381–93.
93. Lam C, West A. Are electronic nicotine delivery systems an effective smoking cessation tool? Can J Resp Ther. 2015;51:93–8.
94. Ioakeimidis N, Vlachopoulos C, Tousoulis D. Efficacy and safety of electronic cigarettes for smoking cessation: a critical approach. Hell J Cardiol. 2016;57:1–6.
95. Waghel RC, Battise DM, Ducker ML. Effectiveness of electronic cigarettes as a tool for smoking cessation or reduction. J Pharm Technol. 2014;31:8–12.
96. Orr KK, Asal NJ. Efficacy of electronic cigarettes for smoking cessation. Ann Pharmacother 2014;48:1502–6.
97. Malas M, van der Tempel J, Schwartz R, Mimichiello A, Lightfoot C, Noormohamed A et al. Electronic cigarettes for smoking cessation: a systematic review. Nicotine Tob Res. 2016;18:1926–36.
98. Rahman MA, Hann N, Wilson A, Mnatzganian G, Worrell-Carter L. E-cigarettes and smoking cessation: evidence from a systematic review and meta-analysis. PLoS One. 2015;10:e0122544.
99. McRobbie H, Bullen C, Hartmann-Boyce J, Hajek P. Electronic cigarettes for smoking cessation and reduction. Cochrane Database Syst Rev. 2014;(12):CD010216.
100. Hartmann-Boyce J, McRobbie H, Bullen C, Begh R, Stead LF, Hajek P. Electronic cigarettes for smoking cessation. Cochrane Database Syst Rev. 2016;9:CD010216.
101. Kalkhoran S, Glantz SA. E-cigarettes and smoking cessation in real-world and clinical settings: a systematic review and meta-analysis. Lancet Resp Med. 2016;4:116–28.
102. El Dib R, Suzumura EA, Akl EA, Gomaa H, Agarwal A, Chang Y et al. Electronic nicotine delivery

systems and/or electronic non-nicotine delivery systems for tobacco smoking cessation or reduction: a systematic review and meta-analysis. BMJ Open. 2017;7:e012680.
103. Khoudigian S, Devji T, Lytvyn L, Campbell K, Hopkins R, O'Reilly D. The efficacy and short-term effects of electronic cigarettes as a method for smoking cessation: a systematic review and a meta-analysis. Int J Public Health. 2016;61:257–67.
104. Stratton K, Kwan LY, Eaton DL, editors. Smoking cessation among adults. Chapter 17. In: Public health consequences of e-cigarettes. Washington (DC): National Academies Press;2018;541–88 (http://nationalacademies.org/hmd/Reports/2018/public-health-consequences-of-e-cigarettes.aspx, accessed 20 April 2018).
105. Pasquereau A, Guignard R, Andler R, Nguyen-Thanh V. Electronic cigarettes, quit attempts and smoking cessation: a 6-month follow-up. Addiction. 2017;112:1620–8.
106. Wang M, Li W, Wu Y, Lam TH, Chan SS. Electronic cigarette use is not associated with quitting of conventional cigarettes in youth smokers. Pediatric Res. 2017;82:14–8.
107. Subialka Nowariak EN, Lien RK, Boyle RG, Amato MS, Beebe LA. E-cigarette use among treatment-seeking smokers: moderation of abstinence by use frequency. Addict Behav 2018;77:137–42.
108. Berry KM, Reynolds LM, Collins JM, Siegel MB, Fetterman JL, Hamburg NM et al. E-cigarette initiation and associated changes in smoking cessation and reduction: the Population Assessment of Tobacco and Health Study, 2013–2015. Tob Control 2018; doi:10.1136/tobaccocontrol-2017-054108.
109. Rigotti NA, Chang Y, Tindle HA, Kalkhoran SM, Levy DE, Regan S et al. Association of e-cigarette use with smoking cessation among smokers who plan to quit after a hospitalization. Ann Internal Med. 2018;168(9):613–20..
110. Zawertailo L, Pavlov D, Ivanova A, Ng G, Baliunas D, Selby P. Concurrent e-cigarette use during tobacco dependence treatment in primary care settings: association with smoking cessation at three and six months. Nicotine Tob Res. 2016;19:183–9.
111. Manzoli L, Flacco ME, Ferrante M, La Vecchia C, Siliquini R, Ricciardi W et al. Cohort study of electronic cigarette use: effectiveness and safety at 24 months. Tob Control 2017;26:284–92.
112. Barrington-Trimis JL, Gibson LA, Halpern-Felsher B, Harrell MB, Kong G, Krishnan-Sarin S et al. Type of e-cigarette device used among adolescents and young adults: findings from a pooled analysis of 8 studies of 2,166 vapers. Nicotine Tob Res. 2018;20(2):271–4.
113. Hummel K, Hoving C, Nagelhout GE, de Vries H, van den Putte B, Candel MJJM et al. Prevalence and reasons for use of electronic cigarettes among smokers: findings from the International Tobacco Control (ITC) Netherlands Survey. Int J Drug Policy. 2014;26(6):601–8.
114. Attitudes of Europeans towards tobacco and electronic cigarettes (Special Eurobarometer 458). Brussels: European Union; 2017.
115. Ayers JW, Leas EC, Allem JP, Benton A, Dredze M, Althouse BM et al. Why do people use electronic nicotine delivery systems (electronic cigarettes)? A content analysis of Twitter, 2012–2015. PLoS One. 2017;12(3):e0170702.
116. Pearson JL, Hitchman SC, Brose LS, Bauld L, Glasser AM, Vilanti AC et al. Recommended core items to assess e-cigarette use in population-based surveys. Tob Control. 2018;27(3):341–6.
117. Amato MS, Boyle RG, Levy D. How to define e-cigarette prevalence? Finding clues in the use frequency distribution. Tob Control. 2015;25:e24–9.
118. Shi Y, Pierce J, White M, Vijayaraghavan M, Compton W, Conway K et al. E-cigarette use and smoking reduction or cessation in the 2010/2011 TUS-CPS longitudinal cohort. BMC Public Health. 2016;16(1):1105.
119. Vickerman K, Carpenter K, Altman T, Nash CM, Zbikowski SM. Use of electronic cigarettes among state tobacco cessation quitline callers. Nicotine Tobacco Res. 2013;15:1787–791.
120. Al-Delaimy W, Myers M, Leas E, Strong DR, Hofstetter CR. E-Cigarette use in the past and quit-

ting behavior in the future: a population-based study. Am J Public Health. 2015;105:1213–9.
121. Biener L, Hargraves JL. A longitudinal study of electronic cigarette use among a population-based sample of adult smokers: association with smoking cessation and motivation to quit. Nicotine Tob Res. 2014;17:127–33.
122. Pearson J, Stanton C, Cha S, Niaura RS, Luta G, Graham AL. E-Cigarettes and smoking cessation: insights and cautions from a secondary analysis of data from a study of online treatment-seeking smokers. Nicotine Tob Res. 2014;17:1219–27.
123. Borderud S, Li Y, Burkhalter J, Sheffer CE, Ostroff JS. Electronic cigarette use among patients with cancer: Characteristics of electronic cigarette users and their smoking cessation outcomes. Cancer. 2014;120:3527–35.
124. Hitchman SC, Brose LS, Brown J, Robson D, McNeill A. Associations between e-cigarette type, frequency of use, and quitting smoking: findings from a longitudinal online panel survey in Great Britain. Nicotine Tob Res. 2015;17:1187–94.
125. Carpenter M, Heckman B, Wahlquist A, Wagener TL, Goniewicz ML, Gray KM et al. A naturalistic, randomized pilot trial of e-cigarettes: uptake, exposure, and behavioral effects. Cancer Epidemiol Biomarkers Prev. 2017;26:1795–803.
126. Masiero M, Lucchiari C, Mazzocco K, Veronesi G, Maisonneuve P, Jemos C et al. E-Cigarettes may support smokers with high smoking-related risk awareness to stop smoking in the short run: preliminary results by randomized controlled trial. Nicotine Tob Res. 2018. doi:10.1093/ntr/nty175.
127. Giovenco DP, Delnevo CD. Prevalence of population smoking cessation by electronic cigarette use status in a national sample of recent smokers. Addict Behav. 2017;76:129–34.
128. Zhu S, Zhuang Y, Wong S, Cummins SE, Tedeschi GJ. E-cigarette use and associated changes in population smoking cessation: evidence from US current population surveys. BMJ. 2017;358:j3262.
129. Cho HJ, Dutra LM, Glantz SA. Differences in adolescent e-cigarette and cigarette prevalence in two policy environments: South Korea and the United States. Nicotine Tob Res. 2018;20(8):949–53.
130. Benmarhnia T, Leas E, Hendrickson E, Trinidad DR, Strong DR, Pierce JP. The potential influence of regulatory environment for e-cigarettes on the effectiveness of e-cigarettes for smoking cessation: different reasons to temper the conclusions from inadequate data. Nicotine Tob Res. 2018;20(5):659.
131. Yong HH, Hitchman S, Cummings K, Borland R, Gravely SML, McNeill A et al. Does the regulatory environment for e-cigarettes influence the effectiveness of e-cigarettes for smoking cessation? Longitudinal findings from the ITC four country survey. Nicotine Tob Res. 2017;19(11):1268–76.
132. Yong HH, Borland R, Balmford J, McNeill A, Hitchman S, Driezen P et al. Trends in e-cigarette awareness, trial, and use under the different regulatory environments of Australia and the United Kingdom. Nicotine Tob Res. 2015;17:1203–11.
133. Yong HH, Borland R, Hitchman SCB, Cummings KM, Gravely SML, McNeill AD et al. Response to letter to the Editor by Benmarhnia T, Leas E, Hendrickson E, Trinidad D, Strong D, Pierce J. The potential influence of regulatory environment for e-cigarettes on the effectiveness of e-cigarettes for smoking cessation: different reasons to temper the conclusions from inadequate data. Nicotine Tob Res. 2017;20(5):660–1.
134. Grace RC, Kivell BM, Laugesen M. Estimating cross-price elasticity of e-cigarettes using a simulated demand procedure. Nicotine Tob Res. 2014;17:592–8.
135. Johnson MW, Johnson PS, Rass O, Pacek LR. Behavioral economic substitutability of e-cigarettes, tobacco cigarettes, and nicotine gum. J Psychopharmacol. 2017;31:851–60.
136. Snider SE, Cummings KM, Bickel WK. Behavioral economic substitution between conventional cigarettes and e-cigarettes differs as a function of the frequency of e-cigarette use. Drug Al-

cohol Depend. 2017;177:14–22.
137. Jamal A, King BA, Neff LJ, Whitmill J, Babb SD, Graffunder CM. Current cigarette smoking among adults – United States, 2005–2015. Morbid Mortal Wkly Rep. 2016;65:1205–11.
138. Adult smoking habits in the UK: 2016. Cigarette smoking among adults including the proportion of people who smoke, their demographic breakdowns, changes over time, and e-cigarettes. Lonson: Office for National Statistics; 2017 (https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/healthandlifeexpectancies/bulletins/adultsmokinghabitsingreatbritain/2016#toc, accessed October 2018).
139. Beard E, West R, Michie S, Brown J. Association between electronic cigarette use and changes in quit attempts, success of quit attempts, use of smoking cessation pharmacotherapy, and use of stop smoking services in England: time series analysis of population trends. BMJ 2016;354:i4645.
140. McRobbie H. Modelling the population health effects of e-cigarettes use: current data can help guide future policy decisions. Nicotine Tob Res. 2016;19:131–2.
141. Hill A, Camacho OM. A system dynamics modelling approach to assess the impact of launching a new nicotine product on population health outcomes. Regul Toxicol Pharmacol 2017;86:265–78.
142. Yoong S, Tzelepis F, Wiggers JH, Oldmeadow C, Chai K, Paul CL et al. Prevalence of smoking-proxy electronic inhaling system (SEIS) use and its association with tobacco initiation in youths: a systematic review. Geneva: World Health Organization; 2015 (http://who.int/tobacco/industry/product_regulation/BackgroundPapersENDS2_4November.pdf?ua=1, accessed 3 October 2017).
143. Leventhal AM, Strong DR, Kirkpatrick MG, Unger JB, Sussman S, Riggs NR et al. Association of electronic cigarette use with initiation of combustible tobacco product smoking in early adolescence. JAMA. 2015;314:700.
144. Primack B, Soneji S, Stoolmiller M, Fine MJ, Sargent JD. Progression to traditional cigarette smoking after electronic cigarette use among US adolescents and young adults. JAMA Pediatrics. 2015;169:1018–23.
145. Wills T, Knight R, Sargent J, Gibbons FX, Pagano I, Williams RJ. Longitudinal study of e-cigarette use and onset of cigarette smoking among high school students in Hawaii. Tob Control 2016;26:34–9.
146. Soneji S, Barrington-Trimis J, Wills T, Leventhal AM, Unger JB, Gibson LA et al. Association between initial use of e-cigarettes and subsequent cigarette smoking among adolescents and young adults. JAMA Pediatrics. 2017;171:788.
147. Miech R, Patrick M, O'Malley P et al. E-cigarette use as a predictor of cigarette smoking: results from a 1-year follow-up of a national sample of 12th grade students. Tobacco Control 2017. doi:10.1136/tobaccocontrol-2016-053291.
148. Best C, Haseen F, Currie D, Ozakinci G, MacKintosh AM, Stead M et al. Relationship between trying an electronic cigarette and subsequent cigarette experimentation in Scottish adolescents: a cohort study. Tob Control. 2017. doi:10.1136/tobaccocontrol-2017-053691.
149. Conner M, Grogan S, Simms-Ellis R, Flett K, Sykes-Muskett B, Cowap L et al. Do electronic cigarettes increase cigarette smoking in UK adolescents? Evidence from a 12-month prospective study. Tob Control. 2017. doi:10.1136/tobaccocontrol-2016-053539.
150. Kozlowski LT, Warner KE. Adolescents and e-cigarettes: Objects of concern may appear larger than they are. Drug Alcohol Depend. 2017;174:209–14.
151. Gartner CE. E-cigarettes and youth smoking: be alert but not alarmed. Tob Control 2017. doi:10.1136/tobaccocontrol-2017-054002.
152. Schneider S, Diehl K. Vaping as a catalyst for smoking? An initial model on the initiation of electronic cigarette use and the transition to tobacco smoking among adolescents. Nicotine Tob Res 2015;18:647–53.

153. Lee PN. Appropriate and inappropriate methods for investigating the "gateway" hypothesis, with a review of the evidence linking prior snus use to later cigarette smoking. Harm Reduction J. 2015;12:8.
154. Jamal A, Gentzke A, Hu SS, Cullen KA, Apelberg BJ, Homa DM et al. Tobacco use among middle and high school students – United States, 2011–2016. Morb Mortal Wkly Rep. 2017;66:597–603.
155. Dinakar C, O'Connor GT. The health effects of electronic cigarettes. N Engl J Med. 2016;375:1372–81.
156. Hua M, Talbot P. Potential health effects of electronic cigarettes: a systematic review of case reports. Prev Med Rep. 2016;4:169–78.
157. Farsalinos KE, Polosa R. Safety evaluation and risk assessment of electronic cigarettes as tobacco cigarette substitutes: a systematic review. Ther Adv Drug Saf. 2014;5:67–86.
158. Burstyn I. Peering through the mist: systematic review of what the chemistry of contaminants in electronic cigarettes tells us about health risks. BMC Public Health. 2014;14:18.
159. Pisinger C. A systematic review of health effects of electronic cigarettes. Geneva: World Health Organization; 2017 (http://www.who.int/tobacco/industry/product_regulation/BackgroundPapersENDS3_4November-.pdf, accessed 30 September 2017).
160. Glasser AM, Collins L, Pearson JL, Abudayyeh H, Niaura RS, Abrams DB et al. Overview of electronic nicotine delivery systems: a systematic review. Am J Prev Med. 2017;52:e33–66.
161. Stephens WE. Comparing the cancer potencies of emissions from vapourised nicotine products including e-cigarettes with those of tobacco smoke. Tob Control. 2017. doi:10.1136/tobaccocontrol-2017-053808.
162. Farsalinos KE, Voudris V, Poulas K. E-cigarettes generate high levels of aldehydes only in "dry puff" conditions. Addiction. 2015;110:1352–6.
163. Benowitz NL, Burbank AD. Cardiovascular toxicity of nicotine: implications for electronic cigarette use. Trends Cardiovasc Med. 2016;26:515–23.
164. Shields PG, Berman M, Brasky TM, Freudenheim JL, Mathe E, McElroy JP et al. A review of pulmonary toxicity of electronic cigarettes in the context of smoking: a focus on inflammation. Cancer Epidemiol Biomarkers Prev. 2017;26:1175–91.
165. Levy DT, Borland R, Villanti AC, Niaura R, Yuan Z, Zhang Y et al. The application of a decision–theoretic model to estimate the public health impact of vaporized nicotine product initiation in the United States. Nicotine Tob Res 2016;19:149–59.
166. Kalkhoran S, Glantz SA. Modeling the health effects of expanding e-cigarette sales in the United States and United Kingdom. JAMA Internal Med. 2015;175:1671.
167. Levy D, Borland R, Lindblom E, Goniewicz ML, Meza R, Holford TR et al. Potential deaths averted in USA by replacing cigarettes with e-cigarettes. Tob Control 2017. doi:10.1136/tobaccocontrol-2017-053759.
168. Soneji S, Sung H, Primack B, Pierce JP, Sargent J. Problematic assessment of the impact of vaporized nicotine product initiation in the United States. Nicotine Tob Res 2016;19:264–5.
169. Glantz SA. Need for examination of broader range of risks when predicting the effects of new tobacco products. Nicotine Tob Res. 2016;19:266–7.
170. Levy DT, Borland R, Fong GT, Vilanti AC, Niaura R, Meza R et al. Developing consistent and transparent models of e-cigarette use: reply to Glantz and Soneji et al. Nicotine Tob Res. 2016;19:268–70.
171. Stratton K, Kwan LY, Eaton DL, editors. Injuries and poisonings. Chapter 14. In: Public health consequences of e-cigarettes. Washington (DC): National Academies Press;2018;541–88 (http://nationalacademies.org/hmd/Reports/2018/public-health-consequences-of-e-cigarettes.aspx, accessed 20 April 2018).