

# **Electronic cigarettes:**

A briefing for stop smoking services



***NCSCT***

## **Electronic cigarettes: A briefing for stop smoking services**

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## Introduction

This briefing has been written to assist stop smoking services support people who want to use electronic cigarettes (e-cigarettes) to help them quit smoking. Such an approach brings together the most effective method of quitting (stop smoking services) with the most popular (e-cigarettes).

In August 2015 Public Health England published a comprehensive review of the latest evidence on e-cigarettes<sup>1</sup> and an accompanying document highlighting the implications of this evidence for policy and practice.<sup>2</sup> This briefing draws upon these documents to summarise what is currently known about nicotine delivery and the safety of e-cigarettes, and covers some of the issues that have been raised about the use of these devices.

We begin by acknowledging that e-cigarettes are considerably safer than smoking cigarettes, are popular with smokers and that they have a role to play in reducing smoking rates.

This briefing does not focus on the use of e-cigarettes in the general population for managing temporary abstinence, nor as part of an attempt to reduce the amount of cigarettes being smoked.

While the evidence base on e-cigarettes is growing, there are a limited number of good quality and reliable studies, especially on the subject of cessation which is the main driver for public health interventions.

In addition, this briefing is limited by the fact that the e-cigarette market is continuing to develop and that there is no single e-cigarette model. Many different forms exist, each with their own technology, delivery and nicotine concentrations; people also differ in how they use these devices.

This briefing makes recommendations for stop smoking practitioners and services, provides common questions and suggested answers about e-cigarettes, and summarises the evidence upon which these recommendations are drawn.

## Background

E-cigarettes are devices that deliver nicotine within an inhalable aerosol by heating a solution that typically contains nicotine, propylene glycol and/or glycerol, plus flavours.

This aerosol is commonly referred to as vapour and so the use of an e-cigarette is described as vaping. Unlike cigarettes, there is no combustion (burning) involved in e-cigarettes so there is no smoke and no other harmful products of combustion, such as tar and carbon monoxide.

The development of the first e-cigarette is generally attributed to Hon Lik at the Chinese company Ruyan in 2004.<sup>3</sup> E-cigarettes appeared in the UK a few years later and the number of people reporting using them was such that they began appearing in national surveys from 2011. It is currently estimated that there are 2.6 million e-cigarette users in Britain.

E-cigarettes generally consist of a battery, a heating element or coil (atomiser) and e-cigarette liquid (e-liquid). The e-liquid can be in sealed cartridges or added to a tank system. Some e-cigarettes use cartomisers that combine the atomiser and e-liquid in a single unit. Although some cartomisers are refillable, most are disposable and designed for single use.

### ***Is nicotine dangerous?***

*Nicotine does not cause smoking related disease, such as cancers and heart disease. These are caused by other chemicals found in tobacco smoke. Nicotine is addictive however and it is why people continue to smoke despite knowing about the harmful effects of tobacco. Nicotine in e-cigarettes poses little danger to adult users. In order to prevent accidental poisoning of children, e-cigarettes and liquids should be stored away safely (just as you would with household cleaning products and medicines, including NRT products).*

First generation e-cigarettes, sometimes called cigalikes, are designed to look like a cigarette and generally use cartomisers. When the user takes a puff (or presses a button on some models) a heating coil is activated to vapourise the e-liquid, creating a vapour that can be inhaled. Many first generation models have a light on the end of the device that also glows when a puff is taken.

More experienced e-cigarette users (vapers) prefer to use newer (second and third) generation e-cigarettes. Often called personal vaporisers, these are particularly popular with people who have completely replaced their cigarette smoking with e-cigarette use.

Second generation e-cigarettes are typically larger and have a more powerful battery linked to an atomiser and a 'tank'. The user fills the tank with their choice of e-liquid which may include flavours and contain nicotine in different concentrations. These devices often look like a fountain pen and can be used with a range of atomisers, cartomisers and tank systems. They typically use larger batteries and may have adjustable power settings.

Third generation e-cigarettes are usually larger still with a more powerful battery and adjustable air flow. They also allow the user to adjust the voltage or wattage applied to the atomiser (often referred to as 'variable voltage' or 'variable wattage' devices). Some come with 'puff counters' or downloadable software that allow users to program their own voltage and wattage level, and to monitor their patterns of use. Third generation devices are designed to allow modifications and substitution of individual components according to user preference.

***"Every time I see someone vaping I think: that's another person NOT smoking a cigarette."***

*Louise Ross, Leicester City Stop Smoking Service*

**Figure 1: The three generations of e-cigarettes**



Images courtesy of Anna Phillips

## E-cigarettes and stop smoking services

Public Health England recommends that stop smoking services should offer support to people who are using e-cigarettes in a quit attempt.<sup>2,4</sup> Clients using unlicensed nicotine containing products (NCP, usually e-cigarettes) can be included in the national data returns that stop smoking services submit.\*

Data from English stop smoking services for the year 2014–15 show that 2,221 smokers used an unlicensed NCP alone and 1,932 used an unlicensed NCP in combination with a licensed stop smoking medicine to support their quit attempt.<sup>5</sup> These are relatively small numbers of people, although there may be some underreporting, given that 450,582 quit attempts were made with the services during that 12 months.

\* providing they adhere to the national data definitions, based upon the Russell Standard, contained in the Local Stop Smoking Services: Service and delivery guidance: [www.ncsct.co.uk/usr/pub/LSSS\\_service\\_delivery\\_guidance.pdf](http://www.ncsct.co.uk/usr/pub/LSSS_service_delivery_guidance.pdf)

E-cigarettes can support people to quit smoking. Clients of stop smoking services who combined e-cigarettes with behavioural support had the highest quit-rates in 2014–15.<sup>5</sup> The four-week self-reported quit rates for these two groups, unlicensed NCP alone and NCP in combination with a stop smoking medication, were higher (66% and 63% respectively) than those seen in people who used combination nicotine replacement therapy (NRT) (48%, n=135,719). It is worth noting that the monitoring data doesn't allow us to control for things like tobacco dependence, and that the people using NCPs may differ from the rest of the smokers quitting with the services. It is also possible that some of the unlicensed NCP reported as being used were not e-cigarettes, although the assumption is that they were predominantly e-cigarettes.

### ***Which e-cigarette should I start with?***

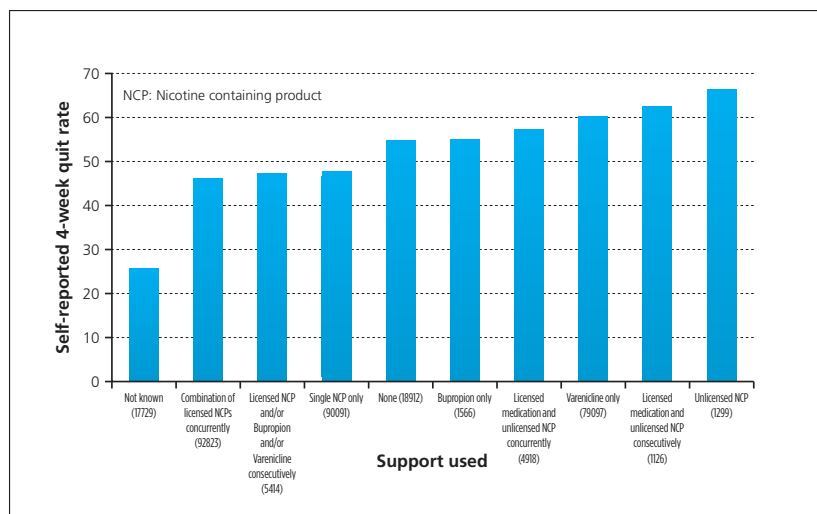
*This is very much a personal choice. The refillable tank system e-cigarettes (second and third generation) might take a bit of getting used to, but they allow the use of more flavours and a better sensation, and generally deliver more nicotine than the e-cigarettes that look like cigarettes. Specialist e-cigarette retailers can provide advice and there are also internet forums where e-cigarette users discuss the different product types.*

### ***How often should I use my e-cigarette to help me to stop smoking?***

*As often as you need to help manage nicotine withdrawal and urges to smoke. You will soon discover the best way for you of using your e-cigarette, and find that you're using it when you feel a need to top-up. It's not like a cigarette, which you would smoke from start to finish, with an e-cigarette you can sip on it once or twice, and then put it away. If you find you've got it in your mouth all the time, you might need to use a stronger e-liquid.*



**Figure 2: Four-week self-reported quit rates from English stop smoking services 2014–15<sup>5</sup>**



Based on a large number of people still accessing stop smoking services, and the current popularity of e-cigarettes as an aid to quitting, there is an opportunity to improve success rates by combining the most popular (e-cigarettes) with the most effective method of quitting (behavioural support from services).

***“I was waiting for this hard part to start that everyone talks about. It just didn’t happen.”***

*Service user and successful quitter using an e-cigarette,  
Leicester City Stop Smoking Service*

Many stop smoking services have declared themselves 'e-cigarette friendly' (see Box 1).

**Box 1: E-cigarette friendly stop smoking services**

**An e-cigarette friendly stop smoking service supports clients who want to use an e-cigarette to help them quit smoking and reaches out to smokers considering using an e-cigarette to come to the service for behavioural support.**

This may present a dilemma for practitioners who feel uncomfortable with this concept, or who feel they lack knowledge about e-cigarettes. These tips may help:

- **Don't be anxious about not being an expert.** It is unlikely that you will know, or be expected to know, everything about e-cigarettes – but what you do know is how to help people stop smoking. It may be that your service users will use NRT along with e-cigarettes; this can increase the likelihood of successful quitting.
- **Familiarise yourself with e-cigarettes.** Talk to experienced vapers, visit a reputable retailer and read posts on forums.
- **Be positive when speaking about e-cigarettes.** When you say: "We can't recommend e-cigarettes", people hear: "E-cigarettes are no good". Instead choose words that convey a positive message such as: "We can't supply them, but we can certainly offer the extra support that will help you stop smoking if you buy your own e-cigarette".
- **Don't push people to come off their e-cigarette.** Some practitioners feel it is important to get people off nicotine as soon as possible, but in fact longer-term e-cigarette use can be a protective factor against relapse back to smoking.

- **Don't be alarmed about recreational nicotine.** This is a choice some people make, and it is not the business of stop smoking services to make judgements about this. We are not a 'stop nicotine service' and if we think getting people off their e-cigarette is a good use of our time, we are ignoring a far more important opportunity to help people quit and to stay off cigarettes. Be open to their choices, and listen to them, especially when they say that they are doing really well with their e-cigarette.
- **Look forward to hearing people celebrate their success, and telling you that using an e-cigarette and receiving support was a revelation.**

One service in the City of London provided free e-cigarette starter packs in addition to standard stop-smoking medications as part of a research project.<sup>6</sup> Their experience suggests that such a provision can increase the attractiveness and efficacy of the service. Despite the extra cost of the e-cigarettes, this practice generated savings because e-cigarettes are typically cheaper than licensed stop smoking medicines and a proportion of clients found that they did not need any other medication.

### ***How much do e-cigarettes cost?***

*You can expect to pay around £20 for a good quality, and easy to use, refillable second generation starter kit. More advanced e-cigarettes for the adventurous or experienced user can range from £30 to several hundred pounds; although a decent third generation kit can be bought for about £70. As with other consumables, you will need to pay more for better quality products.*

### ***Will e-cigarettes be cheaper for me than smoking?***

*Yes. Once you have chosen your starter kit then you only need to replace the atomiser (heating coil or 'head') for a couple of pounds and purchase your e-liquid which can start at £3.00 for 10 ml. You will notice savings very quickly compared with buying cigarettes.*

Pregnant women are choosing to use e-cigarettes to help them stop smoking and they may also be useful as a means of reducing harm for those women unable or unwilling to quit abruptly.<sup>7</sup> E-cigarettes are a great deal safer than smoking but we don't know yet if there are any risks to the fetus from exposure to e-cigarette vapour, therefore licensed stop smoking medications are currently the recommended option. However, if a pregnant woman has chosen to use an e-cigarette to quit or to reduce the number of cigarettes that she smokes, she should not be discouraged from doing so. All pregnant smokers can be referred to their local stop smoking service, or a smoking in pregnancy specialist, for advice and support.

E-cigarettes could also have a significant role to play in managing temporary abstinence, and as part of a quit attempt, for those smokers entering institutions that are smokefree (e.g. in secondary care, mental health services and prisons).

### ***Is it OK to smoke and vape at the same time?***

*Yes. There is no evidence that smoking cigarettes and vaping at the same time increases health risks. However, the greatest health benefits are seen when people stop smoking tobacco completely, so quitting smoking should be the goal. Stop smoking services can provide advice and support to help.*

*Some people manage to switch completely to vaping quickly, whilst others take a little time. You may have to try a number of different e-cigarettes and e-liquids before you find the one that enables you to stop smoking completely, but this is quite normal.*

## Recommendations for practice

1. Be open to e-cigarette use in people keen to try them; especially in those who have tried and failed to stop smoking using licensed stop smoking medicines.
2. Provide advice on e-cigarettes that includes:
  - E-cigarettes provide nicotine in a form that is much safer than smoking.
  - Some people find e-cigarettes helpful for quitting, cutting down their nicotine intake and/or managing temporary abstinence.
  - There is a wide range of e-cigarettes and people may need to try various types, flavours and nicotine dosages before they find a product that they like.
  - E-cigarette use is not like smoking and people may need to experiment and learn to use them effectively (e.g. longer 'drags' may be required and a number of short puffs may be needed initially to activate the vaporiser and improve nicotine delivery). They may also need to recognise when atomisers need replacing.<sup>8</sup>
  - People previously using e-cigarettes while smoking (e.g. to reduce the number of cigarettes that they smoke) may need to consider changing devices and/or nicotine concentrations when making a quit attempt.<sup>9</sup>
  - Although some health risks from e-cigarette use may yet emerge, these are likely, at worst, to be a small fraction of the risks of smoking. This is because e-cigarette vapour does not contain the products of combustion (burning) that cause lung and heart disease, and cancer.
3. Multi-session behavioural support provided by trained stop smoking practitioners will improve the chances of successfully stopping smoking whether or not people use e-cigarettes. It may be useful to encourage clients to familiarise themselves with the use of their e-cigarette before setting a quit date.

4. Stop smoking services can provide behavioural support to clients who are using e-cigarettes and can include this in their national data returns.
5. Clients of stop smoking services who are using an e-cigarette and who also want to use NRT can safely use the two in conjunction. They do not need to have stopped using the e-cigarette before they can use NRT.

### ***Do I use e-cigarettes in the same way that I smoke cigarettes?***

*Using an e-cigarette is different to smoking a cigarette. This usually involves taking slower and longer puffs over a longer period of time; this is because e-cigarettes heat a coil in a liquid (think of a kettle). You may feel the need to take a few puffs on an e-cigarette at times when you would not have smoked; this is nothing to worry about and your pattern of e-cigarette use will develop over time.*

## Regulation

Most e-cigarettes are currently marketed by independent companies importing products from China, but some production is now based in the UK. In recent years several prominent brands of cigalikes have been purchased by tobacco companies and some are now investing in tank models.

At present, e-cigarettes are covered by general product safety legislation. This will change in May 2016 with the introduction of new regulations under the revised European Union Tobacco Products Directive (TPD).<sup>10</sup> Under the TPD e-cigarettes will either be licensed as medicines or, if unlicensed, will be subject to new quality and safety standards, packaging and labelling requirements, and restrictions on advertising. The new regulations include specification of ingredients, limits on nicotine concentration and on the size of tanks and refills, and child and tamper proof containers (see Box 2).

### **Box 2: Tobacco Products Directive**

From 20th May 2016 e-cigarettes containing nicotine will be regulated in the Europe Union under Article 20 of the Tobacco Products Directive (2014/40/EU).<sup>10</sup> The main changes to the current regulation status for unlicensed e-cigarettes are:

- A notification scheme where manufacturers have to provide a dossier of information six months before a product can be placed on the market. All existing products will need to notify by November 2016.
- Manufacturers will be required to submit data on product sales annually.
- Restrictions on advertising, sponsorship and promotion of e-cigarettes.
- Limiting the strength of nicotine in e-cigarette liquid (e-liquid) to 20mg/ml (2%).
- Restricting the size of e-liquid containers to 10ml. *Continued overleaf*

- Limiting the size of e-cigarette tanks to 2 ml.
- Banning additional ingredients such as vitamins, minerals, caffeine and taurine.
- Products must be child and tamper proof, protected against breakage and leakage and have a mechanism that ensures refilling without leakage.
- Mandatory health warnings that will cover at least 30% of the packaging and state either 'This product contains nicotine which is a highly addictive substance'.
- Product labelling that includes a list of all of the ingredients, nicotine content, batch number and recommendation to keep out of reach of children; use of certain descriptors (e.g. natural or organic) is also prohibited
- Products must include a leaflet containing information on instructions for use, contraindications (e.g. non-smokers and young people), warnings for specific groups, possible side effects, addictiveness and toxicity, and the contact details of the manufacturer or importer.
- Manufacturers to set up a system whereby consumers can notify them of suspected adverse events.

The TPD also gives Member States the mandate to take corrective action if there is reason to believe that products are not safe or of good quality or are not conforming to the Directive.



It is unclear what impact the TPD may have on the e-cigarette market and whether there will be any unintended consequences. A number of manufacturers have applied to the Medicines and Healthcare Products Regulatory Agency (MHRA) for licensing of their e-cigarettes. Medicines regulation enables high quality, safe and effective products to be made available by the NHS on prescription and the first licensed e-cigarettes may be available in the near future. However, it is also unclear how effective these licensed e-cigarettes will be compared with newer devices.

With effect from 1 October 2015, the sale of e-cigarette products to under-18s in England and Wales has been prohibited. It is also illegal for an adult to purchase e-cigarette products for someone under the age of 18.

### ***Can I use e-cigarettes in places where I cannot smoke?***

*There is currently no legislation preventing or restricting the use of e-cigarettes. Some places do not allow vaping whilst others do; if there is no signage then you should ask.*

## **Summary of evidence on e-cigarettes**

- E-cigarettes are predominantly used by smokers who want to reduce the number of cigarettes that they smoke; they are also used by smokers who want an alternative for when they cannot or do not want to smoke, or by those who want to quit.
- E-cigarette technology continues to evolve and the quality of devices has improved. With experience, users can achieve blood nicotine levels similar to those achieved with smoking cigarettes.
- E-cigarettes can reduce urges to smoke and can help smokers quit and reduce cigarette consumption; although data on the effectiveness for quitting are not yet as robust as those for medicines licensed for smoking cessation.

- Taken together, data from two randomised controlled trials shows that old (and now obsolete) brands of e-cigarette were more effective than 'placebo' versions that did not deliver any nicotine. The effect size was similar to what is found with licensed nicotine products when prescribed by a health professional. A large observational study of e-cigarettes in the 'real world' found similar effectiveness to licensed stop smoking medicines obtained on prescription, and greater than licensed nicotine products bought from a shop.
- Short-term exposure to e-cigarettes appears to pose few if any risks. Mouth and throat irritation are most commonly reported symptoms and these subside over time. There are no high quality safety data from long-term e-cigarette use, but there is no good reason to expect that their use would be anywhere near as risky as smoking.
- Low levels of toxicants and carcinogens have been detected in e-cigarette liquid and vapour, but these are much lower than those found in cigarette smoke.
- The concentration of toxins in exhaled vapour is much lower than that in side-stream and exhaled cigarette smoke, and is expected to pose no measurable health risk to bystanders.
- Concurrent (dual) use of cigarettes and e-cigarettes has been associated with increased motivation to quit, and to a reduction in the number of cigarettes smoked.
- Use of e-cigarettes by never smokers remains negligible and evidence does not support the view that e-cigarettes are acting as a gateway into smoking among young people.

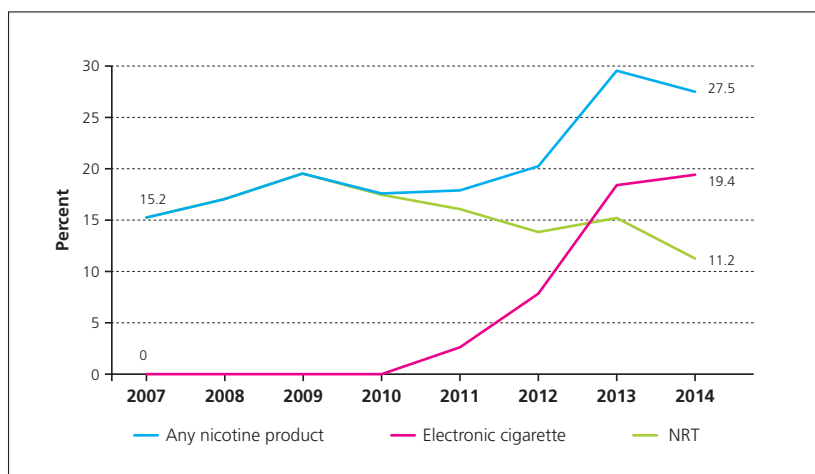
## Prevalence and epidemiology

Awareness of e-cigarettes is high in countries where e-cigarettes are available, especially among current and ex-smokers.<sup>11</sup> Survey data shows that use of e-cigarettes by smokers in Britain increased from 2.7% in 2010 to 6.7% in 2012.<sup>12</sup> By 2013, 11% of smokers reported ever using e-cigarettes.<sup>13</sup> This had risen to almost 20% in 2014 and 2015 data suggests that use has plateaued at around 21%. Data from the Smoking Toolkit Study<sup>14</sup> shows a similar picture (see Figure 2).

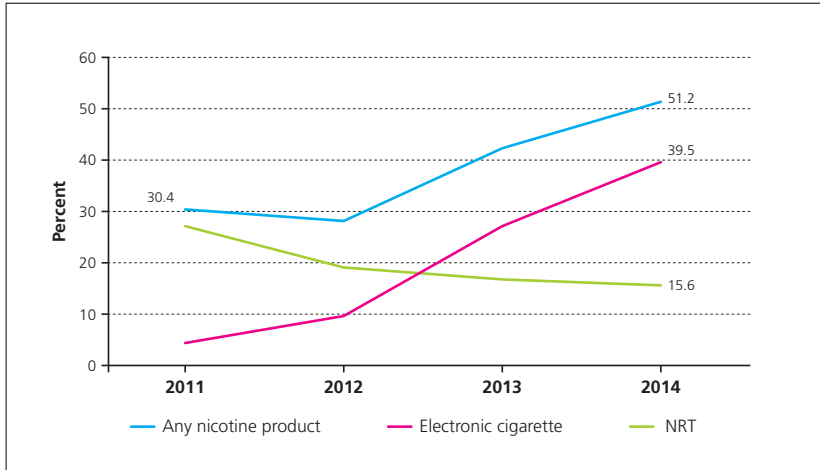
Almost 40% of recent ex-smokers use e-cigarettes (see Figure 3).

Use of e-cigarettes by never smokers is very rare. In 2014 only 0.2% of never smokers reported using an e-cigarette, the same proportion who report using NRT.

**Figure 2: Prevalence of use of NRT, e-cigarettes or any non-tobacco nicotine products among current cigarette smokers in England 2007–14**



**Figure 3: Prevalence of use of NRT, e-cigarettes or any non-tobacco nicotine products among recent ex-smokers in England 2011–14**



***“E-cigarettes offer a potentially useful way out of smoking, especially for those people who have not succeeded with tried and tested methods.”***

*Professor Robert West, University College London*

In some surveys, use of e-cigarettes is defined as 'ever having used' which includes people who have had just a single try of an e-cigarette. Data suggest that around one third of people who report ever using e-cigarettes are current users<sup>12</sup> and some 10–15% are daily users.<sup>15,16</sup> Studies that have specifically assessed daily e-cigarette use in people who have never smoked tobacco (never smokers)<sup>13,15,17</sup> found no progression from experimentation to daily e-cigarette use.

Many studies have defined current use of e-cigarettes as any use in the past 30 days. However, because e-cigarettes are a novel product, this definition includes lots of experimenters who are unlikely to continue their use and is of questionable value in estimating prevalence. One survey in 2014 found that among those with any use in the past 30 days, a large proportion of current (59%), never smokers (90%), and former smokers (43%) had used an e-cigarette for just five days or fewer during this time.<sup>18</sup>

British survey data shows that about 60% of current e-cigarette users (1.4 million people) are also current smokers ('dual users') and 40% (1.1 million people) are ex-smokers.<sup>19</sup> Use of e-cigarettes by never smokers is very rare and estimated to be 0.2% or less.<sup>14,19</sup>

Data collected between 2010 and 2012 showed that e-cigarette users tended to be younger, better educated and from higher socioeconomic groups than non-users.<sup>20–22</sup> However, data from a 2015 survey showed that adults from lower socio-economic groups, compared to those from higher socio-economic groups, were slightly more likely to have tried (19% vs. 13%) and still be using (6% vs. 5%) e-cigarettes.<sup>19</sup>

Young people are also experimenting with e-cigarettes. In a 2013 survey 4.5% of 16–18 year olds had tried an e-cigarette.<sup>23</sup> In 2015 the rate of experimentation by 11–18 year olds was 12.7%<sup>24</sup> and, as might be expected, was higher among 18 year olds (20%) compared with 11 year olds (3%). It is important to stress that a greater proportion of young people experiment with smoking cigarettes (4% and 41% of 11 and 18 year olds respectively).

Regular use of e-cigarettes is much lower than ever use. In 2014, for example, 1.6% of young people reported using e-cigarettes on at least a monthly basis. In 2015 this proportion was still only 1.7%. Regular use of e-cigarettes was almost exclusively confined to current and ex-smokers in England; similar findings have been reported in Scotland<sup>25</sup> and Wales.<sup>26</sup>

Concern has been expressed that e-cigarette use may act as a 'gateway' to tobacco smoking.<sup>27,28</sup> However, establishing that e-cigarette use leads to tobacco use is very difficult as there are other factors that might lead someone to smoke tobacco (e.g. their genetic predisposition or environmental factors) that may also increase their chance of trying an e-cigarette. To date there is no evidence that e-cigarettes lead adolescents to start smoking. Conversely, adolescents who smoke and have tried e-cigarettes are more likely to intend to quit smoking.<sup>29</sup>

### Why are people using e-cigarettes?

The most commonly reported reasons for using e-cigarettes are to assist with stopping smoking or to reduce cigarette consumption.<sup>19</sup> Other reasons include seeing them as a safer and cheaper alternative to smoked tobacco, and helping to manage urges to smoke and other tobacco withdrawal symptoms.<sup>11,19,30,31</sup>

#### ***How will I know when I need to change the atomiser in my e-cigarette?***

*The life of your atomiser (heating coil) will depend on how much you use your e-cigarette and the quality of your device; typically it should last up to two weeks but it could be a lot longer than this. Low vapour production, a 'burnt' taste or poor / reduced flavour are signs that your atomiser needs to be replaced.*

## Why do so few people who try e-cigarettes go on to use them regularly?

As already described, the rates of ever use are much greater than current use of e-cigarettes. Surveys seem to show that only a minority of people who try e-cigarettes go on to use them for longer.<sup>32,33</sup> A major contributing factor is likely to be unrealistic expectations (e.g. that e-cigarettes will provide the same experience as smoking), and also possibly because first generation e-cigarettes (cigalikes) do not generally deliver sufficient nicotine nor provide a pleasant experience. The mistaken fear that e-cigarettes may be as hazardous as cigarette smoking may also be a barrier to ongoing use.

A recent survey showed that 2% of current and ex-smokers surveyed thought that e-cigarettes were more harmful than cigarettes and 20% believed them to be equally harmful.<sup>19</sup> Surveys in England show that only 44% of current smokers in England believed that e-cigarettes were less harmful than cigarettes.<sup>14</sup>

## What products are people using?

The majority of e-cigarette users (65%) start on a cigalike, but few continue to use them. Among current e-cigarette users, only 31% were still using cigalikes and most (66%) use tank systems (either second or third generation e-cigarettes).<sup>19</sup>

## E-cigarette liquid and vapour

E-cigarette liquid (e-liquid) comes in various concentrations of nicotine. The liquid is often labelled as weight (mg) per millilitre (ml), or as a percentage of volume (%). Sometimes a descriptive label is used such as 'high strength' or 'extra high strength'. A concentration of 18mg/ml (1.8%) is most commonly used.<sup>30,34</sup>

E-liquid is currently available in strengths ranging from 0mg/ml to 36mg/ml, although it will soon be limited to a maximum of 20mg/ml (2.0%) under the Tobacco Products Directive.

The amount of nicotine in e-cigarette vapour will depend on a number of factors. These include: nicotine concentration of the e-liquid, efficiency of the e-cigarette and technique of the user. One review of nicotine delivery found that approximately 15 x 70ml puffs are needed to deliver up to 1mg nicotine.<sup>35</sup> This is less than a typical cigarette, where an average of 12 x 46ml puffs are needed to deliver 1.5 to 2.6mg of nicotine.<sup>36</sup>

### ***What nicotine strength e-liquid should I go for?***

*How much nicotine you require will depend upon how much nicotine you are getting from your cigarettes. And of course how much nicotine you get from your e-liquid will depend upon the type of e-cigarette that you use and how you use it. As a rough guide, most 20-a-day smokers find that 18mg/ml (1.8%) is sufficient, so you could start with this and see how you get on.*

A wide range of flavours of e-liquid is available. The most popular flavour among British adults who have tried and are still using e-cigarettes is tobacco flavour, followed by fruit and menthol flavours.<sup>19</sup> New users of e-cigarettes tend to choose tobacco flavour, with more experienced vapers gravitating towards fruit flavours and using on average three different types of e-liquid flavours.<sup>37</sup>



### ***How many bottles of e-liquid will I need in a week?***

*As a rough guide, for a 20-a-day smoker two 10ml bottles of 18mg/ml e-liquid will usually last a week. However this will depend on the quality of your e-cigarette and your puffing technique; with better devices and experience, e-liquid use will often reduce. You'll soon get to know how much you need.*

A number of toxicants have been found in e-liquid and vapour. A 2009 US report found the presence of diethylene glycol (a toxin at high doses) in e-liquid,<sup>38</sup> but at very low levels and this result has not been found in subsequent research.<sup>39,40</sup> Toxicants including acrolein and acetaldehyde, metal and silicate particles, and tobacco-specific nitrosamines (TSNAs) have also been found in vapour, but all at much lower levels than in cigarette smoke.<sup>41–54 55</sup>

Concern has been expressed about high levels of formaldehyde and other aldehydes that are generated when e-cigarettes are operated at high temperatures in laboratory studies.<sup>56,57</sup> However, in real world use when an e-liquid is heated at high temperatures it produces an unpleasant taste (known as a 'dry puff').

Vapers dislike this taste and do their best to avoid producing it.<sup>57,58</sup> Smokers who switch to vaping show significant reductions in exposure to the aldehyde acrolein, even in those who do not stop smoking completely (i.e. dual users).<sup>59</sup>

### ***How do I choose a flavour?***

*This is a personal choice. Some people start with tobacco flavour, or menthol flavour if they smoke mentholated cigarettes, but one of the advantages of e-cigarettes is that you can experiment and try new flavours. People usually try a few different flavours until they find the one that suits them. Some people choose to move away completely from tobacco flavours, preferring sweet and fruit flavours for example.*

## Quality control

The quality of e-cigarettes has been criticised and there are reports of devices that have leaked and malfunctioned.<sup>60,61</sup>

There has also been concern that labelling of nicotine content may not be accurate. Indeed there have been reports of cartridges labelled as 'no nicotine' that contained nicotine.<sup>38,62</sup> In a study of five popular brands of e-cigarette available in the UK, brands labelled as containing 18–24mg of nicotine actually contained between 12.8mg and 33mg of nicotine.<sup>35</sup> However, more recent data suggest that poorly labelled e-liquid mostly contained nicotine at lower concentrations than specified.<sup>42</sup> Quality control is improving and so there is better consistency in labelling the nicotine content of e-cigarette liquid.

Whilst there is a need for quality production of e-liquid, labelling the nicotine concentration may not be that useful in terms of nicotine delivery and absorption (much the same as with nicotine labelling on cigarettes packs). This is because it is only the nicotine contained in the vapour that can be absorbed and the nicotine cartridge content may have little relationship to nicotine levels in vapour.<sup>35,63</sup> Other factors such as heating of the liquid, voltage and amperage resistance, and how the user puffs on the e-cigarette also have a role to play. E-cigarettes usually require more 'suck' than regular cigarettes<sup>64</sup> and the puff duration of e-cigarette use is typically longer than that when smoking cigarettes (e.g. 2.4 seconds for conventional cigarettes versus 4.3 seconds for e-cigarettes).<sup>65</sup>

### ***Are e-cigarettes dangerous, do they blow up or catch fire?***

*As with any rechargeable device, like mobile phones and laptops, it is important to charge with the correct charger and not to leave an e-cigarette unattended whilst charging. Ensure that you buy from reputable suppliers and avoid generic charging equipment. There have been reported cases of e-cigarettes causing fires at a rate of around two per week in the UK, this is far fewer than the number of fires caused by cigarettes.*

*“Smokers binge on nicotine, vapers graze.”*

*Sarah Jakes, New Nicotine Alliance*

## Nicotine delivery

The early, first generation (cigalike) e-cigarettes delivered little or no nicotine.<sup>66–68</sup> One study in 2010 showed that e-cigarettes produced a maximum blood nicotine concentration of 1.3ng/ml, compared to 13.4ng/ml achieved with smoking a cigarette. This was less than the maximum blood nicotine concentration achieved with the Nicorette® nicotine inhalator: 2.1 ng/ml.<sup>66</sup>

As e-cigarette technology has improved, so also has nicotine delivery. This has produced blood nicotine levels that are similar to those obtained from oral NRT products (e.g. 4–6ng/ml)<sup>69,70</sup> but achieved significantly faster (e.g. peak blood nicotine levels were reached within five minutes after starting to use the device<sup>71</sup>).

Higher peak blood concentrations have been found in experienced e-cigarette users (e.g. 13–14ng/ml) after an hour of ad lib (as they wished) use.<sup>72,73</sup> This is similar to the changes seen after smoking a cigarette.<sup>74</sup> E-cigarette users can have similar levels of cotinine, a metabolite of nicotine, in saliva as regular smokers.<sup>75–77</sup>

A UK study found that among naive users, five minutes ad lib use of an e-cigarette containing 24mg/ml of nicotine produced a peak plasma concentration of 4.6ng/ml within five minutes; after four weeks of practice these users achieved levels of 5.7ng/ml.<sup>78</sup> Practice in the technique of using e-cigarettes is therefore clearly important, but it is likely to be subconscious ‘practice’ involving simply using and getting better at using devices.

Using e-liquids with higher nicotine concentration increases nicotine delivery and propylene glycol in e-liquid may also aid nicotine delivery.<sup>79</sup> Propylene glycol has a lower boiling point (187.6 °C) than glycerine (290 °C), which may account for a better delivery of nicotine in solutions that contain it.

Second and third generation e-cigarettes deliver more nicotine to the user than first generation devices. One study showed that a prescribed five-minute puffing regimen on a second generation device produced significantly greater rises in plasma nicotine concentration at the end of puffing than the use of a first generation device (4 ng/ml vs. 2 ng/ml).<sup>80</sup>

The latest data suggests that e-cigarettes can deliver levels of nicotine that are similar to those obtained from smoking cigarettes.<sup>71</sup>

### ***Will I end up using more nicotine with my e-cigarette and overdosing?***

*This is a common misconception around e-cigarettes. Much the same as with NRT, if you have more nicotine than you are used to then you might feel a little nauseous or lightheaded, both of which pass quickly. If this happens you can just reduce the level of nicotine in the e-liquid that you buy, or use the e-cigarette less. You are in no danger of poisoning yourself and there have been no cases of overdose from inhaling e-liquid.*

## Do e-cigarettes alleviate withdrawal symptoms?

E-cigarette use can reduce urges to smoke in inexperienced users,<sup>66-68,70,81,82</sup> in those who have had some practice in using e-cigarettes<sup>69</sup> and in experienced users.<sup>72,73</sup>

In studies that used a non-nicotine e-cigarette as a control,<sup>66,81,82</sup> both the nicotine and non-nicotine e-cigarettes reduced urges to smoke but the reduction was larger with e-cigarettes that contained nicotine.

The acute effect on other tobacco withdrawal symptoms was less pronounced with studies finding little or no significant effect,<sup>66-69</sup> or only showing an effect in subgroups.<sup>81</sup> One study found that second generation e-cigarettes seem to be more effective in reducing symptoms of nicotine withdrawal than do first generation e-cigarettes.<sup>83</sup> Another found that first and second generation e-cigarettes appear to be similarly effective in reducing urges to smoke during abstinence, but second-generation devices appear to be more satisfying to users.<sup>84</sup> In a small study of long-term NRT and e-cigarette users (all ex-smokers) e-cigarettes were more effective for controlling withdrawal symptoms than NRT.<sup>85</sup>

## Do e-cigarettes help people reduce or quit smoking?

Most of the studies reported in this section make the distinction between people who want to stop smoking completely and abruptly, and those who initially use e-cigarettes to reduce their smoking and who do not necessarily intend to quit.

E-cigarette users consistently report that these devices help them to either quit or cut down smoking,<sup>19,31,34,60,86</sup> although these respondents may not necessarily be representative of all e-cigarette users.

More robust survey data collected from representative groups of smokers present mixed results. One showed that among people who were using e-cigarettes and smoking, 46% had stopped smoking cigarettes at one-year follow-up.<sup>87</sup> Another found that in a sample of UK smokers who were trying to stop smoking, those using e-cigarettes were more likely to quit smoking than those who used NRT purchased over the counter. E-cigarettes were found to have similar effectiveness to licensed stop smoking medicines obtained on prescription.<sup>88</sup>

Other surveys have found that e-cigarette users are no more likely to quit smoking than non users. Data from the UK show that smokers using e-cigarettes daily when first surveyed were more likely to make a quit attempt over the following year, but were no more likely to actually quit smoking than non-e-cigarette users.<sup>89</sup> Further analysis of these data showed that the type and frequency of e-cigarette used affected the likelihood of quitting.<sup>90</sup> Smokers who used a cigalike device on a non-daily basis were less likely to have quit smoking over the year of follow-up than people who did not use an e-cigarette. Smokers who used cigalike e-cigarettes daily, or tank systems non-daily, were no more likely to have quit than people who did not use an e-cigarettes. Importantly however, those who were daily users of tank system e-cigarettes reported higher rates of quitting.

Similar findings have been reported in the USA where intensive use of e-cigarettes (e.g. daily for at least a month) is associated with a greater chance of quitting smoking.<sup>91</sup> Others have reported that smokers who use e-cigarettes may be less likely to quit than non-e-cigarette users.<sup>92–94</sup> However, these data are difficult to interpret because of limitations such as the definition of e-cigarette use (e.g. ever use vs. daily use) and not controlling for potential confounding factors (smoking history and environmental factors).

A small number of prospective cohort studies have described the effect of e-cigarette use in smokers who were not ready to quit smoking.<sup>95–97</sup> In one study,<sup>40</sup> highly dependent middle-aged smokers were provided with e-cigarettes for up to six months. The abstinence rates at six and 18 months were 23% and 15% respectively. Two years after enrolment, 13% achieved at least six months of carbon monoxide (CO)-validated abstinence from smoking and 28% had achieved a sustained reduction ( $\geq 50\%$ ) in their baseline cigarette consumption.<sup>95,96</sup> Another study tested the same approach with 14 smokers with schizophrenia<sup>97</sup> and reported 14% 30-day CO-validated abstinence at one year.

*“Many of my patients with complex COPD use a vaporiser to stop smoking. One man on assessment could hardly walk, was deathly white and had beads of sweat forming on his face when he tried to talk. Within two weeks he had less shortness of breath on exertion, within eight weeks he had been able to reduce his meds, and within 16 weeks he said he was reaping the benefits.”*

*Specialist advisor in acute care, Leicester City Stop Smoking Service*

To date there have been three randomised controlled trials that have directly examined the effects of e-cigarette use in people who did,<sup>98</sup> and in those who did not,<sup>99,100</sup> want to quit.

In one study the effect of e-cigarette use (two groups using different nicotine doses for 12 weeks) was compared to non-nicotine e-cigarettes in 300 smokers who were not intending to quit. The biochemically validated six-month abstinence rates at one-year follow-up were 13%, 9% and 4% in the three groups (differences were not significant).<sup>99</sup> There was also no significant difference between the three groups in the proportion of participants that achieved  $\geq 50\%$  cigarette reduction. Unfortunately the study was underpowered (i.e. it did not have enough subjects to be able to detect a statistically significant difference between groups). It also lacked a ‘non e-cigarette’ group, which makes the results only tentative. In addition, the brand of e-cigarette used in this study had poor nicotine delivery and often malfunctioned.

***“E-cigarettes are different to NRT and as such smokers should have different expectations of what e-cigarettes can offer.”***

*Lorien Jollye, New Nicotine Alliance*

In another smoking cessation study,<sup>98</sup> nicotine-containing e-cigarettes were compared with 21 mg nicotine patches and with non-nicotine e-cigarettes. Participants were provided with a referral to a telephone quitline but not given any face-to-face contact. In this minimal support setting there were no significant differences in validated continuous abstinence at six months (7.3% nicotine e-cigarette, 5.8% nicotine patch and 4.1% non-nicotine e-cigarette). Participants who received nicotine e-cigarettes reported significantly higher smoking reduction, and higher user endorsements, than those who received nicotine patches. Again, the study was underpowered and used e-cigarettes with low nicotine delivery.

A 2014 Cochrane Review of these trials concluded that they demonstrated that e-cigarettes with nicotine help smokers stop smoking compared with placebo (no nicotine e-cigarettes).<sup>101</sup> The effect size was broadly similar to what is found with licensed nicotine products when prescribed by a health professional.<sup>102</sup> The review however gives these findings a ‘low’ confidence rating because there are only two studies.

Since the Review, another randomised controlled trial (RCT) has been published that randomised 48 smokers who did not want to quit to use either an e-cigarette (a tank system device) or no intervention.<sup>100</sup> At eight-week follow-up, 34% of those given an e-cigarette had quit smoking and none of the smokers in the no intervention control group had stopped. Smokers in the control group were then given an e-cigarette and everyone was followed up at eight months. At this time point 19% of smokers given e-cigarettes at the beginning of the study, and 25% who received e-cigarettes at week eight, had quit smoking.



## Are there any adverse health effects of e-cigarettes?

Although e-cigarettes are not completely risk free, experts agree that they are substantially less harmful than smoking.

E-cigarettes primarily deliver two substances: 1) nicotine and 2) the vapour, which is usually formed from propylene glycol or glycerol and flavourings.

There is good evidence from the use of NRT, and from the long term use of snus (a type of oral tobacco) in Sweden,<sup>103</sup> that nicotine is associated with few health risks in smokers.<sup>104</sup> It is the tar and toxicants in smoke rather than nicotine that causes the adverse health effects of smoking. However there are some data, for example, that suggest that nicotine might have adverse effects in pregnancy.<sup>105</sup>

Some commentators have raised concerns over the potential for nicotine poisoning of children if they ingest e-liquid containing nicotine. Cases of poisoning have been reported in the scientific literature, both accidental in children<sup>106–108</sup> and intentional in adults;<sup>109,110</sup> all but one (a suicide attempt in an adult who ingested more than 10g of nicotine in e-liquid<sup>110</sup>) recovered without any lasting illness. However, to manage the risk of accidental poisoning e-cigarettes and e-liquid should be kept out of the reach of children, as is the case with NRT.

The US Food and Drug Administration has classified propylene glycol as an additive that is “generally recognized as safe”. It has been used as an excipient in some old and new pulmonary (lung) inhalation devices,<sup>111,112</sup> as well as in food and cosmetics. Mild adverse effects (e.g. throat irritation) have been documented.<sup>52</sup> Studies that have subjected animals to short-term (1 month)<sup>113</sup> and long-term (12–18 months)<sup>114</sup> exposure have not demonstrated any adverse effects. Data on the long-term health risks of repeated vapour exposure in humans are lacking.

A number of studies have reported on the acute effects of e-cigarettes. No adverse effects of short-term e-cigarette use have been found on haematological or blood chemistry parameters, nor cardiovascular function in smokers or ex-smokers.<sup>115–118</sup>

The exception is that e-cigarette use increases heart rate after overnight abstinence,<sup>70,72</sup> in much the same way that smoking cigarettes after overnight abstinence does.<sup>119</sup>

Two studies examined acute effects of e-cigarette use on respiratory function. One reported a small, and not clinically relevant, increase in airways resistance post-e-cigarette use.<sup>120</sup> The other showed no significant adverse effect of e-cigarettes on lung function.<sup>77</sup> By comparison, smoking a conventional cigarette significantly reduced a measure of lung function (FEV1/FV). Cigarette smoking is associated with an increased risk of a number of respiratory illnesses, so stopping smoking can result in an improvement in respiratory symptoms. This was demonstrated in a small study of patients with asthma whose symptoms and respiratory function improved after switching from smoking to vaping.<sup>121</sup> One animal study reported that e-cigarette vapour delayed recovery from influenza infection,<sup>122</sup> but the relevance to humans is not clear.

As already noted, various toxicants have been found in e-cigarette vapour but at very low levels.<sup>40</sup> We do not know the effects of long-term exposure to these toxicants, even at low levels, and so there may be some degree of health risk. However, given what is known about the exposure to toxicants in tobacco smoke, the magnitude of any risks that may emerge from long-term e-cigarette use is likely to be small.

### ***Are e-cigarettes safer for me than smoking?***

*Yes. Experts estimate that e-cigarettes are, based on what we know so far, around 95% safer than cigarettes. Smoking is associated with a number of very serious health risks to both the smoker and to others around them. Therefore smokers who switch from smoking tobacco to e-cigarettes substantially reduce a major risk to their health.*

The authors of a comprehensive review of the latest evidence on e-cigarettes, commissioned by Public Health England, concluded that, based on the peer-reviewed literature, e-cigarette use is around 95% less harmful than smoking.<sup>1</sup>

In an authors' note to accompany their report,<sup>123</sup> they explained that this estimate is based on the facts that:

- the constituents of cigarette smoke that harm health, including carcinogens, are either absent in e-cigarette vapour or, if present, are mostly at levels significantly below 5% of doses from smoking (mostly below 1%) and far below safety limits for occupational exposure
- the main chemicals present in e-cigarettes only have not been associated with any serious risk

Although we cannot be certain on the exact degree of risk or safety of e-cigarettes, and it may be slightly more or slightly less than 95%, the obvious conclusion is that they are substantially less harmful than cigarettes.<sup>124</sup>

The other main component of e-liquids is flavourings. These flavourings are considered safe for oral ingestion, but the risks of their inhalation are largely unknown.<sup>125</sup> There are some flavours where a degree of risk is established and so these flavours should be avoided. For example, chronic exposure to diacetyl which gives a buttery flavour (butterscotch flavour has already been voluntarily withdrawn by some manufacturers), caused irreversible bronchiolitis in workers at a microwave popcorn plant.<sup>126</sup> There is also some evidence that cinnamon flavourings are cytotoxic.<sup>41</sup>

Secondhand e-cigarette vapour can expose non-users to nicotine,<sup>77,127</sup> although exposure is some 10 times less than from cigarette smoke,<sup>127</sup> and to other toxicants, but at levels that are orders of magnitude lower than those found in secondhand smoke. There are no identified harms for bystanders from e-cigarette vapour.<sup>40</sup>

Nicotine from e-cigarettes vapour is deposited on surfaces, in very low amounts<sup>128</sup> and as such poses no detectable health risk to adults or children. One study found that the air in homes of vapers contained six times less nicotine than air in the home of smokers.<sup>129</sup> Non-smokers who were exposed to e-cigarette vapour had low levels of cotinine, a metabolite of nicotine, measured in their urine but at levels around 1000 times less than seen in smokers.

### ***I've heard that e-cigarettes can produce harmful chemicals?***

*Some studies have detected chemicals in e-cigarette vapour that are known to cause health problems. However, these chemicals have been found at very low levels that are unlikely to represent a serious risk to health. When e-cigarettes are used within normal operating levels (e.g. not overheated), there are far fewer harmful chemicals present in their vapour than in tobacco smoke. If the e-liquid is being overheated it tends to produce an acrid, unpleasant taste – you will know if this happens!*

E-cigarette studies have collected information on adverse events (AEs). None of the experimental<sup>66–70,72,73,77,81,82</sup> or prospective follow-up studies<sup>96,97</sup> have reported serious adverse events (SAEs). Any AEs were largely mild to moderate and included symptoms such as mouth and throat irritation and dry cough, similar to those reported in user surveys.<sup>30,31,34,60</sup>

There were no significant differences in the frequency of AEs between e-cigarette and control groups (non-nicotine e-cigarettes or nicotine patch) in the two randomised trials of e-cigarettes.<sup>98,99</sup> No AEs were rated as serious in one study<sup>99</sup> and in the other serious AEs did not differ between groups and were deemed unrelated to the study products.<sup>98</sup>

The most commonly reported symptoms by e-cigarette users in online forums are irritation of the mouth and throat. Among potentially more serious, although less common, AEs have been increased blood pressure.<sup>130</sup> The FDA Centre for Tobacco Products in the USA recorded three serious AEs related to e-cigarettes; two were second-degree facial burns caused by e-cigarettes exploding and an infant death caused by choking on an e-cigarette cartridge.<sup>131</sup>

Three case reports of serious adverse events associated with e-cigarette use have been published. Two were respiratory illnesses (lipoid pneumonia<sup>132</sup> and acute eosinophilic pneumonitis<sup>133</sup>) and the other acute asymptomatic atrial fibrillation;<sup>134</sup> in all three cases the problems resolved on cessation of e-cigarette use, but the causal relationship to e-cigarette use remains very uncertain. The case of lipoid pneumonia was attributed to glycerine-based oils in e-liquid,<sup>132</sup> but this is highly unlikely given that glycerine is an alcohol and not a lipid.<sup>135</sup>

### ***I get a bit of a cough when I use my e-cigarette***

*This isn't unusual and you may benefit from switching from an e-liquid with a high proportion of propylene glycol to one with more vegetable glycol, which can be more soothing.*

### ***Is secondhand vapour from e-cigarettes dangerous?***

*Some studies have found traces of toxicants in secondhand vapour, but at such low levels that they do not pose a health risk to bystanders. There is no evidence that secondhand vapour is dangerous to others; however, it helps to be respectful when using e-cigarettes around others, especially non-smokers.*

## **Are e-cigarettes renormalising smoking?**

There have been concerns that e-cigarettes might renormalise smoking, that is, make cigarette smoking appear to be a normal activity. Whilst this is a valid concern we do not have any data to show that this is occurring. Indeed, available data points in the opposite direction because cigarette smoking prevalence among both adults and young people has continued to fall in England as e-cigarette use has increased; the same has occurred in the USA.

***“Smokers should switch to vaping, and vapers should stop smoking completely.”***

*Martin Dockrell, Public Health England*

## Conclusion

The use of e-cigarettes among adults in Britain has increased substantially over the last five years and they have become the most popular stop smoking aid in England. Since their appearance on the market in 2006 e-cigarette technology has improved and some devices can deliver levels of nicotine that are similar to those achieved with smoking tobacco.

E-cigarettes can alleviate symptoms of tobacco withdrawal and there is growing evidence that they can help people stop smoking. However, like other nicotine substitutes they are no 'magic cure'. Smokers take some time to get used to them and novice users are likely to benefit from support in how to use e-cigarettes to get the most out of them. As with users of NRT, e-cigarette users have the best chance of quitting with expert support from stop smoking services.

Whilst use of e-cigarettes is not without health risk, it is much less hazardous than smoking cigarettes. Current estimates put vaping somewhere in the vicinity of 95% less harmful than smoking tobacco, based on comparisons of the composition of carcinogens and toxicants in tobacco smoke and e-cigarette vapour.

Stop smoking services should be open to e-cigarette use in people keen to try them to help them quit. This is especially so in those who have tried and failed to quit using licensed stop smoking medicines.

## References

1. Public Health England. *E-cigarettes: an evidence update*. (Public Health England, 2015). at <https://www.gov.uk/government/publications/e-cigarettes-an-evidence-update>>
2. Public Health England. *E-cigarettes: a new foundation for evidence-based policy and practice*. (Public Health England, 2015). at <https://www.gov.uk/government/publications/e-cigarettes-an-evidence-update>
3. Hon, L. A *Flameless electronic atomizing cigarette*. (Best Partners Worldwide Limited (Beaufort House, P.O. Box 438, Road Town, Tortola, VG), 2004).
4. NCSCCT. *E-cigarette briefing*. (National Centre for Smoking Cessation and Training, 2014). at [www.ncsct.co.uk/publication\\_ecigarette\\_briefing.php](http://www.ncsct.co.uk/publication_ecigarette_briefing.php)
5. Health & Social Care Information Centre. Statistics on NHS Stop Smoking Services in England – April 2014 to March 2015. (2015). at [www.hscic.gov.uk/article/2021/Website-Search?productid=18388&q=stop+smoking&sort=Relevance&size=10&page=1&area=both#top](http://www.hscic.gov.uk/article/2021/Website-Search?productid=18388&q=stop+smoking&sort=Relevance&size=10&page=1&area=both#top)
6. Hajek, P., Corbin, L., Ladmore, D. & Spearing, E. Adding E-Cigarettes to Specialist Stop-Smoking Treatment: City of London Pilot Project. *J Addict Res Ther* **6**,
7. McEwen, A., Potts, J. & Bauld, L. (Editor). *Smoking Cessation: a briefing for midwifery staff*. (National Centre for Smoking Cessation and Training (NCSCCT), 2013). at [www.ncsct.co.uk/usr/pub/NCSCCT\\_midwifery\\_briefing.pdf](http://www.ncsct.co.uk/usr/pub/NCSCCT_midwifery_briefing.pdf)
8. Farsalinos, K. E. *et al.* Comparison of the cytotoxic potential of cigarette smoke and electronic cigarette vapour extract on cultured myocardial cells. *Int. J. Environ. Res. Public Health* **10**, 5146–5162 (2013).
9. Farsalinos, K. E., Romagna, G., Tsiapras, D., Kyzopoulos, S. & Voudris, V. Evaluating nicotine levels selection and patterns of electronic cigarette use in a group of ‘vapers’ who had achieved complete substitution of smoking. *Subst Abuse* **7**, 139–146 (2013).
10. European Parliament and Council of the European Union. *Directive 2014/40/EU of the European Parliament and of the Council of 3 April 2014 on the approximation of the laws, regulations and administrative provisions of the Member States concerning the manufacture, presentation and sale of tobacco and related products and repealing Directive 2001/37/EC*. (2014). at [http://ec.europa.eu/health/tobacco/docs/dir\\_201440\\_en.pdf](http://ec.europa.eu/health/tobacco/docs/dir_201440_en.pdf)
11. Adkison, S. E. *et al.* Electronic nicotine delivery systems: international tobacco control four-country survey. *Am. J. Prev. Med.* **44**, 207–15 (2013).
12. Dockrell, M., Morison, R., Bauld, L. & McNeill, A. E-Cigarettes: Prevalence and Attitudes in Great Britain. *Nicotine Tob. Res.* **15**, 1737–1744 (2013).
13. Action on Smoking and Health. *ASH fact sheet on the use of e-cigarettes in Great Britain*. (ASH, 2013).
14. West, R., Brown, J. & Beard, E. *Electronic cigarettes in England – latest trends*. (2015).
15. Douptcheva, N., Gmel, G., Studer, J., Deline, S. & Etter, J.-F. Use of electronic cigarettes among young Swiss men. *J. Epidemiol. Community Health* **67**, 1075–1076 (2013).
16. Kralikova E, Novak J, West O, Kmetova A & Hajek P. Do e-cigarettes have the potential to compete with conventional cigarettes?: a survey of conventional cigarette smokers’ experiences with e-cigarettes. *Chest* **144**, 1609–1614 (2013).

17. Zhu, S.-H. *et al.* The Use and Perception of Electronic Cigarettes and Snus among the U.S. Population. *PLoS One* **8**, e79332 (2013).
18. Amato, M. S., Boyle, R. G. & Levy, D. How to define e-cigarette prevalence? Finding clues in the use frequency distribution. *Tob. Control* (2015). doi:10.1136/tobaccocontrol-2015-052236
19. Action on Smoking and Health. *ASH Fact Sheet on the use of electronic cigarettes among adults in Great Britain*. (ASH UK, 2015). at <http://www.ash.org.uk/information/facts-and-stats/fact-sheets>
20. McMillen, R., Maduka, J. & Winickoff, J. Use of emerging tobacco products in the United States. *J. Environ. Public Health* **2012**, 989474 (2012).
21. Li J, Bullen C, Newcombe R, Walker N & Walton D. The use and acceptability of electronic cigarettes among New Zealand smokers. *N. Z. Med. J.* **126**, 48–57 (2013).
22. Choi, K. & Forster, J. Characteristics associated with awareness, perceptions, and use of electronic nicotine delivery systems among young US Midwestern adults. *Am. J. Public Health* **103**, 556–61 (2013).
23. Action on Smoking and Health. *Use of e-cigarettes among children and adults in Great Britain*. (2013).
24. Action on Smoking and Health. *Use of electronic cigarettes among children in Great Britain*. (ASH UK, 2015). at [www.ash.org.uk/information/facts-and-stats/fact-sheets](http://www.ash.org.uk/information/facts-and-stats/fact-sheets)
25. ISD Scotland. *Scottish Schools Adolescent Lifestyle and Substance Use Survey (SALSUS)*. (2014). at [www.isdscotland.org/Health-Topics/Public-Health/SALSUS/](http://www.isdscotland.org/Health-Topics/Public-Health/SALSUS/)
26. Moore, G. *et al.* Electronic-cigarette use among young people in Wales: evidence from two cross-sectional surveys. *BMJ Open* **5**, e007072 (2015).
27. Choi K, Fabian L, Mottey N, Corbett A & Forster J. Young adults' favorable perceptions of snus, dissolvable tobacco products, and electronic cigarettes: findings from a focus group study. *Am. J. Public Health* **102**, 2088–2093 (2012).
28. Pepper, J. K. *et al.* Adolescent males' awareness of and willingness to try electronic cigarettes. *J. Adolesc. Health Off. Publ. Soc. Adolesc. Med.* **52**, 144–50 (2013).
29. Dutra, L. M. & Glantz, S. A. Electronic cigarettes and conventional cigarette use among U.S. adolescents: a cross-sectional study. *JAMA Pediatr.* **168**, 610–617 (2014).
30. Etter, J.-F. & Bullen, C. Electronic cigarette: users profile, utilization, satisfaction and perceived efficacy. *Addiction* **106**, 2017–28 (2011).
31. Goniewicz, M. L., Lingas, E. O. & Hajek, P. Patterns of electronic cigarette use and user beliefs about their safety and benefits: An Internet survey. *Drug Alcohol Rev.* **32**, 133–140 (2013).
32. Pepper, J. K., Ribisl, K. M., Emery, S. L. & Brewer, N. T. Reasons for starting and stopping electronic cigarette use. *Int. J. Environ. Res. Public Health* **11**, 10345–10361 (2014).
33. Kong, G., Morean, M. E., Cavallo, D. A., Camenga, D. R. & Krishnan-Sarin, S. Reasons for Electronic Cigarette Experimentation and Discontinuation among Adolescents and Young Adults. *Nicotine Tob. Res. Off. J. Soc. Res. Nicotine Tob.* (2014). doi:10.1093/ntr/ntu257
34. Dawkins, L., Turner, J., Roberts, A. & Soar, K. 'Vaping' profiles and preferences: an online survey of electronic cigarette users. *Addiction* **108**, 1115–25 (2013).



35. Goniewicz, M. L., Hajek, P. & McRobbie, H. Nicotine content of electronic cigarettes, its release in vapour and its consistency across batches: regulatory implications. *Addiction* **109**, 500–507 (2014).
36. Djordjevic, M. V., Stellman, S. D. & Zang, E. Doses of nicotine and lung carcinogens delivered to cigarette smokers. *J. Natl. Cancer Inst.* **92**, 106–111 (2000).
37. Farsalinos, K. E. *et al.* Impact of flavour variability on electronic cigarette use experience: an internet survey. *Int. J. Environ. Res. Public Health* **10**, 7272–82 (2013).
38. Westenberger, B. J. *Evaluation of e-Cigarettes*. (Department of Health and Human Services, Food and Drug Administration, Center for Drug valuation and Research, Division of Pharmaceutical Analysis, 2009).
39. Etter, J. F., Zather, E. & Svensson, S. Analysis of refill liquids for electronic cigarettes. *Addiction* **108**, 1671–1679 (2013).
40. 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* **14**, 18 (2014).
41. Bahl, V. *et al.* Comparison of electronic cigarette refill fluid cytotoxicity using embryonic and adult models. *Reprod. Toxicol.* **34**, 529–537 (2012).
42. Cheng, T. Chemical evaluation of electronic cigarettes. *Tob. Control* **23**, ii11–7 (2014).
43. Geiss, O., Bianchi, I., Barahona, F. & Barrero-Moreno, J. Characterisation of mainstream and passive vapours emitted by selected electronic cigarettes. *Int. J. Hyg. Environ. Health* **218**, 169–180 (2015).
44. Goniewicz, M. L. *et al.* Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. *Tob. Control* **23**, 133–9 (2014).
45. Hutzler C *et al.* Chemical hazards present in liquids and vapors of electronic cigarettes. *Arch. Toxicol.* **88**, 1295–1308 (2014).
46. Kim, H. J. & Shin, H. S. Determination of tobacco-specific nitrosamines in replacement liquids of electronic cigarettes by liquid chromatography-tandem mass spectrometry. *J. Chromatogr. A* **1291**, 48–55 (2013).
47. Kosmider, L. *et al.* Carbonyl Compounds in Electronic Cigarette Vapors-Effects of Nicotine Solvent and Battery Output Voltage. *Nicotine Tob. Res.* **16**, 1319–1326 (2014).
48. Lerner, C. A. *et al.* Environmental health hazards of e-cigarettes and their components: Oxidants and copper in e-cigarette aerosols. *Environ. Pollut. Barking Essex 1987* **198C**, 100–107 (2015).
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.* **24**, 850–857 (2012).
50. Misra, M., Leverette, R. D., Cooper, B. T., Bennett, M. B. & Brown, S. E. Comparative in vitro toxicity profile of electronic and tobacco cigarettes, smokeless tobacco and nicotine replacement therapy products: e-liquids, extracts and collected aerosols. *Int. J. Environ. Res. Public Health* **11**, 11325–11347 (2014).
51. Saffari, A. *et al.* Particulate metals and organic compounds from electronic and tobacco-containing cigarettes: comparison of emission rates and secondhand exposure. *Environ. Sci. Process. Impacts* (2014). doi:10.1039/c4em00415a
52. Wieslander, G., Norbäck, D. & Lindgren, T. Experimental exposure to propylene glycol mist in aviation emergency training: acute ocular and respiratory effects. *Occup. Environ. Med.* **58**, 649–655 (2001).

53. Williams, M., Villarreal, A., Bozhilov, K., Lin, S. & Talbot, P. Metal and silicate particles including nanoparticles are present in electronic cigarette cartomizer fluid and aerosol. *PLoS One* **8**, e57987 (2013).
54. Zhang Y, Sumner W & Chen DR. In vitro particle size distributions in electronic and conventional cigarette aerosols suggest comparable deposition patterns. *Nicotine Tob. Res.* **15**, 501–508 (2013).
55. Centers for Disease Control and Prevention (US), National Center for Chronic Disease Prevention and Health Promotion (US) & Office on Smoking and Health (US). *How Tobacco Smoke Causes Disease: The Biology and Behavioral Basis for Smoking-Attributable Disease: A Report of the Surgeon General*. (Centers for Disease Control and Prevention (US), 2010). at [www.ncbi.nlm.nih.gov/books/NBK53017/](http://www.ncbi.nlm.nih.gov/books/NBK53017/)
56. Jensen, R. P., Luo, W., Pankow, J. F., Strongin, R. M. & Peyton, D. H. Hidden formaldehyde in e-cigarette aerosols. *N. Engl. J. Med.* **372**, 392–394 (2015).
57. Farsalinos, K. E., Voudris, V. & Poulas, K. E-cigarettes generate high levels of aldehydes only in 'dry puff' conditions. *Addiction* **110**, 1352–1356 (2015).
58. Nitzkin, J. L., Farsalinos, K. & Siegel, M. More on hidden formaldehyde in e-cigarette aerosols. *N. Engl. J. Med.* **372**, 1575 (2015).
59. McRobbie, H. et al. Effects of Switching to Electronic Cigarettes with and without Concurrent Smoking on Exposure to Nicotine, Carbon Monoxide, and Acrolein. *Cancer Prev. Res. Phila. Pa* **8**, 873–878 (2015).
60. Etter, J.-F. Electronic cigarettes: a survey of users. *BMC Public Health* **10**, 231 (2010).
61. Trtchounian A & Talbot P. Electronic nicotine delivery systems: is there a need for regulation? *Tob. Control* **20**, 47–52 (2011).
62. Hadwiger, M. E. et al. Identification of amino-tadalafil and rimonabant in electronic cigarette products using high pressure liquid chromatography with diode array and tandem mass spectrometric detection. *J. Chromatogr. A* **1217**, 7547–55 (2010).
63. Goniewicz, M. L., Kuma, T., Gawron, M., Knysak, J. & Kosmider, L. Nicotine Levels in Electronic Cigarettes. *Nicotine Tob. Res. Off. J. Soc. Res. Nicotine Tob.* **15**, 158–166 (2013).
64. Trtchounian A, Williams M & Talbot P. Conventional and electronic cigarettes (e-cigarettes) have different smoking characteristics. *Nicotine Tob. Res.* **12**, 905–912 (2010).
65. Hua, M., Yip, H. & Talbot, P. Mining data on usage of electronic nicotine delivery systems (ENDS) from YouTube videos. *Tob. Control* **22**, 103–106 (2013).
66. Bullen C et al. Effect of an electronic nicotine delivery device (e cigarette) on desire to smoke and withdrawal, user preferences and nicotine delivery: randomised cross-over trial. *Tob. Control* **19**, 98–103 (2010).
67. Eissenberg T. Electronic nicotine delivery devices: ineffective nicotine delivery and craving suppression after acute administration. *Tob. Control* **19**, 87–88 (2010).
68. Vansickel AR, Cobb CO, Weaver MF & Eissenberg TE. A clinical laboratory model for evaluating the acute effects of electronic 'cigarettes': nicotine delivery profile and cardiovascular and subjective effects. *Cancer Epidemiol. Biomarkers Prev.* **19**, 1945–1953 (2010).
69. Nides MA, Leischow SJ, Bhatler M & Simmons M. Nicotine blood levels and short-term smoking reduction with an electronic nicotine delivery system. *Am. J. Health Behav.* **38**, 265–274 (2014).

70. Vansickel AR, Weaver MF & Eissenberg T. Clinical laboratory assessment of the abuse liability of an electronic cigarette. *Addiction* **107**, 1493–1500 (2012).
71. St Helen, G., Havel, C., Dempsey, D., Jacob, P. & Benowitz, N. L. Nicotine delivery, retention, and pharmacokinetics from various electronic cigarettes. *Addiction* (2015). doi:10.1111/add.13183
72. Vansickel, A. R. & Eissenberg, T. Electronic Cigarettes: Effective Nicotine Delivery After Acute Administration. *Nicotine Tob. Res.* **15**, 267–70 (2012).
73. Dawkins, L. & Corcoran, O. Acute electronic cigarette use: Nicotine delivery and subjective effects in regular users. *Psychopharmacol. Berl* **231**, 401–7 (2014).
74. Benowitz, N. L., Jacob, P., 3rd & Herrera, B. Nicotine intake and dose response when smoking reduced-nicotine content cigarettes. *Clin. Pharmacol. Ther.* **80**, 703–714 (2006).
75. Etter, J. F. Levels of saliva cotinine in electronic cigarette users. *Addiction* **109**, 825–9 (2014).
76. Etter JF & Bullen C. Saliva cotinine levels in users of electronic cigarettes. *Eur. Respir. J.* **38**, 1219–1220 (2011).
77. Flouris AD *et al.* Acute impact of active and passive electronic cigarette smoking on serum cotinine and lung function. *Inhal. Toxicol.* **25**, 91–101 (2013).
78. Hajek, P. *et al.* Nicotine intake from electronic cigarettes on initial use and after 4 weeks of regular use. *Nicotine Tob. Res. Off. J. Soc. Res. Nicotine Tob.* **17**, 175–179 (2015).
79. Yan, X. S. & D’Ruiz, C. Effects of using electronic cigarettes on nicotine delivery and cardiovascular function in comparison with regular cigarettes. *Regul. Toxicol. Pharmacol. RTP* (2014). doi:10.1016/j.yrtph.2014.11.004
80. Farsalinos, K. E. *et al.* Nicotine absorption from electronic cigarette use: comparison between first and new-generation devices. *Sci Rep* **4**, 4133 (2014).
81. Dawkins, L., Turner, J., Hasna, S. & Soar, K. The electronic-cigarette: effects on desire to smoke, withdrawal symptoms and cognition. *Addict. Behav.* **37**, 970–3 (2012).
82. Dawkins, L., Turner, J. & Crowe, E. Nicotine derived from the electronic cigarette improves time-based prospective memory in abstinent smokers. *Psychopharmacol. Berl* **227**, 377–84 (2013).
83. Lechner, W. V. *et al.* The comparative efficacy of first- versus second-generation electronic cigarettes in reducing symptoms of nicotine withdrawal. *Addict. Abingdon Engl.* **110**, 862–867 (2015).
84. Dawkins, L., Kimber, C., Puwanesarasa, Y. & Soar, K. First- versus second-generation electronic cigarettes: predictors of choice and effects on urge to smoke and withdrawal symptoms. *Addict. Abingdon Engl.* **110**, 669–677 (2015).
85. Nelson, V. A. *et al.* Comparison of the characteristics of long-term users of electronic cigarettes versus nicotine replacement therapy: A cross-sectional survey of English ex-smokers and current smokers. *Drug Alcohol Depend.* (2015). doi:10.1016/j.drugalcdep.2015.05.005
86. Siegel MB, Tanwar KL & Wood KS. Electronic cigarettes as a smoking-cessation: tool results from an online survey. *Am. J. Prev. Med.* **40**, 472–475 (2011).

87. Etter JF & Bullen C. A longitudinal study of electronic cigarette users. *Addict. Behav.* **39**, 491–494 (2014).
88. Brown, J., Beard, E., Kotz, D., Michie, S. & West, R. Real-world effectiveness of e-cigarettes when used to aid smoking cessation: a cross-sectional population study. *Addiction* **109**, 1531–40 (2014).
89. Brose, L. S., Hitchman, S. C., Brown, J., West, R. & McNeill, A. Is the use of electronic cigarettes while smoking associated with smoking cessation attempts, cessation and reduced cigarette consumption? A survey with a 1-year follow-up. *Addiction* (2015). doi:10.1111/add.12917
90. Hitchman, S. C., Brose, L. S., 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. Off. J. Soc. Res. Nicotine Tob.* **17**, 1187–1194 (2015).
91. Biener, L. & Hargraves, J. L. 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. Off. J. Soc. Res. Nicotine Tob.* **17**, 127–133 (2015).
92. Vickerman, K. A., Carpenter, K. M., Altman, T., Nash, C. M. & Zbikowski, S. M. Use of Electronic Cigarettes Among State Tobacco Cessation Quitline Callers. *Nicotine Tob. Res.* **15**, 1787–1791 (2013).
93. Al-Delaimy, W. K., Myers, M. G. & Strong, D. R. E-cigarettes are losing ground among smokers and non-smokers. *Am. J. Public Health* **105**, e1–2 (2015).
94. Borderud, S. P., Li, Y., Burkhalter, J. E., Sheffer, C. E. & Ostroff, J. S. Electronic cigarette use among patients with cancer: characteristics of electronic cigarette users and their smoking cessation outcomes. *Cancer* **120**, 3527–3535 (2014).
95. Polosa, R. *et al.* Effect of an electronic nicotine delivery device (e-Cigarette) on smoking reduction and cessation: a prospective 6-month pilot study. *BMC Public Health* **11**, 786 (2011).
96. Polosa, R. *et al.* Effectiveness and tolerability of electronic cigarette in real-life: a 24-month prospective observational study. *Intern Emerg Med* [Epub ahead of print] (2013). doi:10.1007/s11739-013-0977-z
97. Caponnetto, P., Auditore, R., Russo, C., Cappello, G. C. & Polosa, R. Impact of an electronic cigarette on smoking reduction and cessation in schizophrenic smokers: a prospective 12-month pilot study. *Int. J. Environ. Res. Public Health* **10**, 446–61 (2013).
98. Bullen, C. *et al.* Electronic cigarettes for smoking cessation: a randomised controlled trial. *Lancet* **382**, 1629–37 (2013).
99. Caponnetto, P. *et al.* Efficiency and Safety of an Electronic Cigarette (ECLAT) as Tobacco Cigarettes Substitute: A Prospective 12-Month Randomized Control Design Study. *PLoS One* **8**, e66317 (2013).
100. Adriaens, K., Van Gucht, D., Declerck, P. & Baeyens, F. Effectiveness of the Electronic Cigarette: An Eight-Week Flemish Study with Six-Month Follow-up on Smoking Reduction, Craving and Experienced Benefits and Complaints. *Int. J. Environ. Res. Public Health* **11**, 11220–11248 (2014).
101. McRobbie, H., Bullen, C., Hartmann-Boyce, J. & Hajek, P. Electronic cigarettes for smoking cessation and reduction. *Cochrane Database Syst. Rev.* **12**, CD010216 (2014).
102. West, R. *et al.* Health-care interventions to promote and assist tobacco cessation: a review of efficacy, effectiveness and affordability for use in national guideline development. *Addiction* **110**, 1388–1403 (2015).
103. Lee, P. N. Epidemiological evidence relating snus to health—an updated review based on recent publications. *Harm. Reduct. J.* **10**, 36 (2013).

104. Le Houezec, J., McNeill, A. & Britton, J. Tobacco, nicotine and harm reduction. *Drug Alcohol Rev.* **30**, 119–123 (2011).
105. Bruin, J. E., Gerstein, H. C. & Holloway, A. C. Long-term consequences of fetal and neonatal nicotine exposure: a critical review. *Toxicol. Sci. Off. J. Soc. Toxicol.* **116**, 364–374 (2010).
106. Shaw, L. & Nelson, L. S. Smoking cessation can be toxic to your health. *Emerg. Med.* **45**, 7–9 (2013).
107. Gill, N., Sangha, G., Poonai, N. & Lim, R. E-Cigarette Liquid Nicotine Ingestion in a Child: Case Report and Discussion. *CJEM* 1–5 (2015). doi:10.1017/cem.2015.10
108. Gupta, S., Gandhi, A. & Manikonda, R. Accidental nicotine liquid ingestion: emerging paediatric problem. *Arch. Dis. Child.* **99**, 1149 (2014).
109. Christensen, L. B., van't Veen, T. & Bang, J. Three cases of attempted suicide by ingestion of nicotine liquid used in e-cigarettes. *Clin. Toxicol.* **51**, 290 (2013).
110. Bartschat, S., Mercer-Chalmers-Bender, K., Beike, J., Rothschild, M. A. & Jübner, M. Not only smoking is deadly: fatal ingestion of e-juice—a case report. *Int. J. Legal Med.* (2014). doi:10.1007/s00414-014-1086-x
111. Mogalian, E. & Myrdal, P. B. in *Solvent Systems and Their Selection in Pharmaceuticals and Biopharmaceuticals* (eds. Augustijns, P. & Brewster, M.) **VI**, 427–441 (Springer New York, 2007).
112. Shen, X., Hindle, M. & Byron, P. R. Effect of energy on propylene glycol aerosols using the capillary aerosol generator. *Int. J. Pharm.* **275**, 249–258 (2004).
113. Werley, M. S. *et al.* Non-clinical safety and pharmacokinetic evaluations of propylene glycol aerosol in Sprague-Dawley rats and Beagle dogs. *Toxicology* **287**, 76–90 (2011).
114. Robertson, O. H. & Loosli, C. G. Tests for the chronic toxicity of propylene glycol and triethylene glycol on monkeys and rats by vapor inhalation and oral administration. *J. Pharmacol. Exp. Ther.* **91**, 52–76 (1947).
115. Miura, K. *et al.* Safety Assessment of Electronic Cigarettes in Smokers. *Seikatsu Eisei* **55**, 59–64 (2011).
116. Czogala, J., Cholewinski, M., Kutek, A. & Zielinska-Danch, W. [Evaluation of changes in hemodynamic parameters after the use of electronic nicotine delivery systems among regular cigarette smokers]. [Polish]. *Przegl. Lek.* **69**, 841–845 (2012).
117. Flouris AD *et al.* Acute effects of electronic and tobacco cigarette smoking on complete blood count. *Food Chem. Toxicol.* **50**, 3600–3603 (2012).
118. Farsalinos, K. *et al.* Acute effects of using an electronic nicotine-delivery device (e-cigarette) on myocardial function: comparison with the effects of regular cigarettes. *Eur. Heart J.* **33**, 203 (2012).
119. Benowitz, N. L., Kuyt, F. & Jacob, P. Influence of nicotine on cardiovascular and hormonal effects of cigarette smoking. *Clin. Pharmacol. Ther.* **36**, 74–81 (1984).
120. Vardavas CI *et al.* Short-term pulmonary effects of using an electronic cigarette: impact on respiratory flow resistance, impedance, and exhaled nitric oxide. *Chest* **141**, 1400–1406 (2012).
121. Polosa, R. *et al.* Effect of Smoking Abstinence and Reduction in Asthmatic Smokers Switching to Electronic Cigarettes: Evidence for Harm Reversal. *Int. J. Environ. Res. Public Health* **11**, 4965–4977 (2014).

122. Sussan, T. E. *et al.* Exposure to electronic cigarettes impairs pulmonary anti-bacterial and anti-viral defenses in a mouse model. *PLoS One* **10**, e0116861 (2015).
123. Public Health England. *E-cigarettes: an evidence update – Authors’ note on evidence for ‘around 95%’ safer estimate.* (Public Health England, 2015). at <https://www.gov.uk/government/publications/e-cigarettes-an-evidence-update>
124. Britton, J. E-cigarettes, Public Health England, and common sense. *Lancet Lond. Engl.* (2015). doi:10.1016/S0140-6736(15)00145-2
125. Tierney, P. A., Karpinski, C. D., Brown, J. E., Luo, W. & Pankow, J. F. Flavour chemicals in electronic cigarette fluids. *Tob. Control* (2015). doi:10.1136/tobaccocontrol-2014-052175
126. Kreiss, K. *et al.* Clinical bronchiolitis obliterans in workers at a microwave-popcorn plant. *N. Engl. J. Med.* **347**, 330–338 (2002).
127. Czogala, J. *et al.* Secondhand Exposure to Vapors From Electronic Cigarettes. *Nicotine Tob. Res.* **16**, 655–662 (2013).
128. Goniewicz, M. L. & Lee, L. Electronic Cigarettes Are a Source of Thirdhand Exposure to Nicotine. *Nicotine Tob. Res. Off. J. Soc. Res. Nicotine Tob.* (2014). doi:10.1093/ntr/ntu152
129. Ballbè, M. *et al.* Cigarettes vs. e-cigarettes: Passive exposure at home measured by means of airborne marker and biomarkers. *Environ. Res.* **135C**, 76–80 (2014).
130. Hua M, Alfi M & Talbot P. Health-related effects reported by electronic cigarette users in online forums. *J. Med. Internet Res.* **15**, e59 (2013).
131. Chen, I. L. FDA summary of adverse events on electronic cigarettes. *Nicotine Tob. Res.* **15**, 615–6 (2013).
132. McCauley L, Markin C & Hosmer D. An unexpected consequence of electronic cigarette use. *Chest* **141**, 1110–1113 (2012).
133. Thota D & Latham E. Case Report of Electronic Cigarettes Possibly Associated with Eosinophilic Pneumonitis in a Previously Healthy Active-duty Sailor. *J. Emerg. Med.* **47**, 15–17 (2014).
134. Monroy AE, Hommel E, Smith ST & Raji M. Paroxysmal atrial fibrillation following electronic cigarette use in an elderly woman. *Clin. Geriatr.* **20**, 28–32 (2012).
135. Farsalinos, K. E. Doctors, open your textbooks: glycerol CANNOT cause lipoid pneumonia (but other things can). (2014). at [www.ecigarette-research.com/web/index.php/2013-04-07-09-50-07/2014/157-glycerol](http://www.ecigarette-research.com/web/index.php/2013-04-07-09-50-07/2014/157-glycerol) Archived at: [www.webcitation.org/6arGjksNT](http://www.webcitation.org/6arGjksNT)



