Public Health England

Protecting and improving the nation's health

E-cigarettes: an evidence update

A report commissioned by Public Health England

Authors:

McNeill A, Brose LS, Calder R, Hitchman SC
Institute of Psychiatry, Psychology & Neuroscience, National Addiction Centre, King's College London
UK Centre for Tobacco & Alcohol Studies

Hajek P, McRobbie H (Chapters 9 and 10)
Wolfson Institute of Preventive Medicine, Barts and The London School of Medicine and Dentistry Queen Mary, University of London
UK Centre for Tobacco & Alcohol Studies

UKCTAS UK Centre for Tobacco & Alcohol Studies

Queen Mary University of London

King's College London

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Public Health England
Wellington House
133-155 Waterloo Road
London SE1 8UG
Tel: 020 7654 8000
www.gov.uk/phe
Twitter: @PHE_uk
Facebook: www.facebook.com/PublicHealthEngland

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Foreword

The role and impact of electronic cigarettes has been one of the great debates in public health in recent years and we commissioned this independent review of the latest evidence to ensure that practitioners, policy makers and, most importantly of all, the public have the best evidence available.

Many people think the risks of e-cigarettes are the same as smoking tobacco and this report clarifies the truth of this.

In a nutshell, best estimates show e-cigarettes are 95% less harmful to your health than normal cigarettes, and when supported by a smoking cessation service, help most smokers to quit tobacco altogether.

We believe this review will prove a valuable resource, explaining the relative risks and benefits of e-cigarettes, in terms of harm reduction when compared with cigarettes and as an aid to quitting.

We will continue to monitor the position and will add to the evidence base and guidance going forward.





Duncan Selbie, Chief Executive, PHE

Key messages

1. Smokers who have tried other methods of quitting without success could be encouraged to try e-cigarettes (EC) to stop smoking and stop smoking services should support smokers using EC to quit by offering them behavioural support.

2. Encouraging smokers who cannot or do not want to stop smoking to switch to EC could help reduce smoking related disease, death and health inequalities.

3. There is no evidence that EC are undermining the long-term decline in cigarette smoking among adults and youth, and may in fact be contributing to it. Despite some experimentation with EC among never smokers, EC are attracting very few people who have never smoked into regular EC use.

4. Recent studies support the Cochrane Review findings that EC can help people to quit smoking and reduce their cigarette consumption. There is also evidence that EC can encourage quitting or cigarette consumption reduction even among those not intending to quit or rejecting other support. More research is needed in this area.

5. When used as intended, EC pose no risk of nicotine poisoning to users, but e-liquids should be in ‘childproof' packaging. The accuracy of nicotine content labelling currently raises no major concerns.

6. There has been an overall shift towards the inaccurate perception of EC being as harmful as cigarettes over the last year in contrast to the current expert estimate that using EC is around 95% safer than smoking.

7. Whilst protecting non-smoking children and ensuring the products on the market are as safe and effective as possible are clearly important goals, new regulations currently planned should also maximise the public health opportunities of EC.

8. Continued vigilance and research in this area are needed.

Executive summary

Following two previous reports produced for Public Health England (PHE) on e-cigarettes (EC) in 2014, this report updates and expands on the evidence of the implications of EC for public health. It covers the EC policy framework, the prevalence of EC use, knowledge and attitudes towards EC, impact of EC use on smoking behaviour, as well as examining recent safety issues and nicotine content, emissions and delivery. Two literature reviews were carried out to update the evidence base since the 2014 reports and recent survey data from England were assessed.

EC use battery power to heat an element to disperse a solution of propylene glycol or glycerine, water, flavouring and usually nicotine, resulting in an aerosol that can be inhaled by the user (commonly termed vapour). EC do not contain tobacco, do not create smoke and do not rely on combustion. There is substantial heterogeneity between different types of EC on the market (such as cigalikes and tank models). Acknowledging that the evidence base on overall and relative risks of EC in comparison with smoking was still developing, experts recently identified them as having around 4% of the relative harm of cigarettes overall (including social harm) and 5% of the harm to users.

In England, EC first appeared on the market within the last 10 years and around 5% of the population report currently using them, the vast majority of these smokers or recent ex-smokers. Whilst there is some experimentation among never smokers, regular use among never smokers is rare. *Cigarette* smoking among youth and adults has continued to decline and there is no current evidence in England that EC are renormalising smoking or increasing smoking uptake. Instead, the evidence reviewed in this report point in the direction of an association between greater uptake of EC and reduced smoking, with emerging evidence that EC can be effective cessation and reduction aids.

Regulations have changed little in England since the previous PHE reports with EC being currently governed by general product safety regulations which do not require products to be tested before being put on the market. However, advertising of EC is now governed by a voluntary agreement and measures are being introduced to protect children from accessing EC from retailers. Manufacturers can apply for a medicinal licence through the Medicines and Healthcare products Regulatory Agency (MHRA) and from 2016, any EC not licensed by the MHRA will be governed by the revised European Union Tobacco Products Directive (TPD).

A summary of the main findings and policy implications from the data chapters now follows.

Summary of Chapter 3: UK policy framework

The revised TPD will introduce new regulations for EC or refill containers which are not licensed by the MHRA. The cap on nicotine concentrations introduced by the TPD will take high nicotine EC and refill liquids off the market, potentially affecting heavier smokers seeking higher nicotine delivery products.

The fact that no licensed EC are yet on the market suggests that the licensing route to market is not commercially attractive. The absence of non-tobacco industry products going through the MHRA licensing process suggests that the process is inadvertently favouring larger manufacturers including the tobacco industry, which is likely to inhibit innovation in the prescription market.

Policy implications

- From May 2016, following the introduction of the revised TPD, ECs will be more strictly regulated. As detailed elsewhere in the report, the information we present does not indicate widespread problems as a result of EC. Hence, the current regulatory structure appears broadly to have worked well although protecting non-smoking children and ensuring the products on the market are as safe and effective as possible are clearly important goals. New regulations currently planned should be implemented to maximise the benefits of EC whilst minimising these risks.

- An assessment of the impact of the TPD regulations on the UK EC market will be integral to its implementation. This should include the degree to which the availability of safe and effective products might be restricted.

- Much of England's strategy of tobacco harm reduction is predicated on the availability of medicinally licensed products that smokers want to use. Licensed ECs are yet to appear. A review of the MHRA EC licensing process therefore seems appropriate, including manufacturers' costs, and potential impact. This could include a requirement for MHRA to adapt the processes and their costs to enable smaller manufacturers to apply, and to speed up the licensing process. The review could also assess potential demand for the EC prescription market and what types of products would be most appropriate to meet that demand.

Summary of Chapter 4: Prevalence of e-cigarette use in England/Great Britain

Adults: Around one in 20 adults in England (and Great Britain) use EC. Current EC users are almost exclusively smokers (~60%) or ex-smokers (~40%), that is smokers who now use EC and have stopped smoking altogether. EC use among long-term ex-smokers is considerably lower than among recent ex-smokers. Current EC use among

never smokers is very low, estimated to be 0.2%. The prevalence of EC use plateaued between 2013-14, but appeared to be increasing again in 2015.

Youth: Regular EC use among youth is rare with around 2% using at least monthly and 0.5% weekly. EC use among young people remains lower than among adults: a minority of British youth report having tried EC (~13%). Whilst there was some experimentation with EC among never smoking youth, prevalence of use (at least monthly) among never smokers is 0.3% or less.

Overall, the adult and youth data suggest that, despite some experimentation with EC among never smokers, EC are attracting few people who have never smoked into regular use.

Trends in EC use and smoking: Since EC were introduced to the market, cigarette smoking among adults and youth has declined. In adults, overall nicotine use has also declined (not assessed for youth). These findings, to date, suggest that the advent of EC is not undermining, and may even be contributing to, the long-term decline in cigarette smoking.

Policy implications

- Trends in EC use among youth and adults should continue to be monitored using standardised definitions of use.
- Given that around two-thirds of EC users also smoke, data are needed on the natural trajectory of ‘dual use’, ie whether dual use is more likely to lead to smoking cessation later or to sustain smoking (see also Chapter 6).
- As per existing NICE guidance, all smokers should be supported to stop smoking completely, including ‘dual users’ who smoke and use EC.

Summary of Chapter 5: Smoking, e-cigarettes and inequalities

Smoking is increasingly concentrated in disadvantaged groups who tend to be more dependent. EC potentially offer a wide reach, low-cost intervention to reduce smoking and improve health in disadvantaged groups.

Some health trusts and prisons have banned the use of EC which may disproportionately affect more disadvantaged smokers.

Policy implications

- Consideration could be given to a proactive strategy to encourage disadvantaged smokers to quit smoking as quickly as possible including the use of EC, where appropriate, to help reduce health inequalities caused by smoking.

- EC should not routinely be treated in the same way as smoking. It is not appropriate to prohibit EC use in health trusts and prisons as part of smokefree policies unless there is a strong rationale to do so.

Summary of Chapter 6: E-cigarettes and smoking behaviour

Recent studies support the Cochrane Review findings that EC can help people to quit smoking and reduce their cigarette consumption. There is also evidence that EC can encourage quitting or cigarette consumption reduction even among those not intending to quit or rejecting other support. It is not known whether current EC products are more or less effective than licensed stop smoking medications, but they are much more popular, thereby providing an opportunity to expand the number of smokers stopping successfully. Some English stop smoking services and practitioners support the use of EC in quit attempts and provide behavioural support for EC users trying to quit smoking; *self-reported* quit rates are at least comparable to other treatments. The evidence on EC used *alongside smoking* on subsequent quitting of smoking is mixed.

Policy implications

- Smokers who have tried other methods of quitting without success could be encouraged to try EC to stop smoking and stop smoking services should support smokers using EC to quit by offering them behavioural support.

- Research should be commissioned in this area including:
  - longitudinal research on the use of EC, including smokers who have not used EC at the beginning of the study
  - the effects of using EC while smoking (temporary abstinence, cutting down) on quitting, and the effects of EC use among ex-smokers on relapse
  - research to clarify the factors that i) help smokers using EC to quit smoking and ii) deter smokers using EC from quitting smoking, including different EC products/types and frequency of use and the addition of behavioural support, and how EC compare with other methods of quitting which have a strong evidence base

- It would be helpful if emerging evidence on EC (including different types of EC) and how to use EC safely and effectively could be communicated to users and health professionals to maximise chances of successfully quitting smoking.

Summary of Chapter 7: Reasons for use and discontinuation

A number of surveys in different populations provide evidence that reducing the harm from smoking (such as through cutting down on their cigarette consumption or helping with withdrawal during temporary abstinence) and the desire to quit smoking cigarettes are the most important reasons for using EC. Curiosity appears to play a major role in experimentation. Most trial of EC does not lead to regular use and while there is less evidence on why trial does not become regular use, it appears that trial due to curiosity is less likely to lead to regular use than trial for reasons such as stopping smoking or reducing harm. Dissatisfaction with products and safety concerns may deter continued EC use.

Policy implications

- Smokers frequently state that they are using EC to give up smoking. They should therefore be provided with advice and support to encourage them to quit smoking completely.

- Other reasons for use include reducing the harm from smoking and such efforts should be supported but with a long-term goal of stopping smoking completely.

Summary of Chapter 8: Harm perceptions

Although the majority of adults and youth still correctly perceive EC to be less harmful than tobacco cigarettes, there has been an overall shift towards the inaccurate perception of EC being at least as harmful as cigarettes over the last year, for both groups. Intriguingly, there is also some evidence that people believe EC to be less harmful than medicinal nicotine replacement therapy (NRT).

Policy implications

- Clear and accurate information on relative harm of nicotine, EC and tobacco cigarettes is needed urgently (see also Chapter 10).

- Research is needed to explore how health perceptions of EC are developed, in relation to tobacco cigarettes and NRT, and how they can be influenced.

Summary of Chapter 9: E-cigarettes, nicotine content and delivery

The accuracy of labelling of nicotine content currently raises no major concerns. Poorly labelled e-liquid and e-cartridges mostly contained less nicotine than declared. EC used

as intended pose no risk of nicotine poisoning to users. However, e-liquids should be in 'childproof' packaging.

Duration and frequency of puffs and mechanical characteristics of EC play a major role in determining nicotine content in vapour. Across the middle range of nicotine levels, in machine tests using a standard puffing schedule, nicotine content of e-liquid is related to nicotine content in vapour only weakly. EC use releases negligible levels of nicotine into ambient air with no identified health risks to bystanders. Use of a cigalike EC can increase blood nicotine levels by around 5 ng/ml within five minutes of use. This is comparable to delivery from oral NRT. Experienced EC users using the tank EC can achieve much higher blood nicotine levels over a longer duration, similar to those associated with smoking. The speed of nicotine absorption is generally slower than from cigarettes but faster than from NRT.

Policy implications

- General labelling of the strength of e-liquids, along the lines used for example indicating coffee strength, provides sufficient guidance to consumers.

- Regulatory interventions should ensure optimal product safety but make sure EC are not regulated more strictly than cigarettes and can continue to evolve and improve their competitiveness against cigarettes.

Summary of Chapter 10: Safety of e-cigarettes in light of new evidence

Two recent worldwide media headlines asserted that EC use is dangerous. These were based on misinterpreted research findings. A high level of formaldehyde was found when e-liquid was over-heated to levels unpalatable to EC users, but there is no indication that EC users are exposed to dangerous levels of aldehydes; stressed mice poisoned with very high levels of nicotine twice daily for two weeks were more likely to lose weight and die when exposed to bacteria and viruses, but this has no relevance for human EC users. The ongoing negative media campaigns are a plausible explanation for the change in the perception of EC safety (see Chapter 8).

None of the studies reviewed above alter the conclusion of Professor Britton's 2014 review for PHE. While vaping may not be 100% safe, most of the chemicals causing smoking-related disease are absent and the chemicals which are present pose limited danger. It has been previously estimated that EC are around 95% safer than smoking. This appears to remain a reasonable estimate.

Policy implications

- There is a need to publicise the current best estimate that using EC is around 95% safer than smoking.
- Encouraging smokers who cannot or do not want to stop smoking to switch to EC could be adopted as one of the key strategies to reduce smoking related disease and death.

Summary of Chapter 11: Other health and safety concerns

There is a risk of fire from the electrical elements of EC and a risk of poisoning from ingestion of e-liquids. These risks appear to be comparable to similar electrical goods and potentially poisonous household substances.

Policy implications

- The risks from fire or poisoning could be controlled through standard regulations for similar types of products, such as childproof containers (contained within the TPD but which are now emerging as an industry standard) and instructions about the importance of using the correct charger.
- Current products should comply with current British Standard operating standards.
- Records of EC incidents could be systematically recorded by fire services.

Summary of Chapter 12: International perspectives

Although EC use may be lower in countries with more restrictions, these restrictions have not prevented EC use. Overall, use is highest among current smokers, with low numbers of non-smokers reporting ever use. Current use of EC in other countries is associated with being a smoker or ex-smoker, similar to the findings in the UK. EC use is frequently misreported with experimentation presented as regular use. Increases in youth EC trial and use are associated with decreases in smoking prevalence in all countries, with the exception of one study from Poland.

Policy implications

- Future research should continue to monitor and evaluate whether different EC policies across countries are related to EC use and to smoking cessation and smoking prevalence.
- Consistent and agreed measures of trial, occasional and regular EC use among youth and adults are urgently needed to aid comparability.

1. Introduction

Despite the decline in smoking prevalence observed over the last few decades, there remain over eight million smokers in England. Most of these are from manual and more disadvantaged groups in society, including those with mental health problems, on low income, the unemployed and offenders. In some such population groups, the proportion who smoke is over two or three times higher than that in the general population, a level of smoking observed in the general population over 40 years ago. For those who continue to smoke regularly, much of their lives will be of lower quality and spent in poorer health than those who don't smoke, and they will have a one in two chance of dying prematurely, by an average of 10 years, as a direct result of their smoking. Smoking is therefore the largest single contributor to health inequalities as well as remaining the largest single cause of preventable mortality and morbidity in England.

Moving forward, it is therefore important to maintain and enhance England's comprehensive tobacco control strategy in order to motivate and support *all* smokers in society to stop smoking as quickly as possible, and prevent the recruitment of new smokers. Harm reduction guidance, published by the National Institute for Health and Care Excellence in England in 2013, recognised that some smokers struggled to quit abruptly and that cigarettes were a lethal delivery system for nicotine [1]; it is widely accepted that most smokers smoke for the nicotine but die from the other smoke constituents. Harm reduction has been identified as one of the more promising policy options to reduce smoking induced inequalities in health [2]. All experts agree that a well-resourced comprehensive strategy, involving cessation, prevention and harm reduction should make the goal of a smoke-free society in England quickly achievable.

However, the advent of electronic cigarettes (EC) over recent years has caused controversy. In 1991, Professor Michael Russell, a leading English smoking cessation expert from the Institute of Psychiatry, argued that *"it was not so much the efficacy of new nicotine delivery systems as temporary aids to cessation, but their potential as long-term alternatives to tobacco that makes the virtual elimination of tobacco a realistic future target",* and he recommended that "*tobacco should be rapidly replaced by cleaner, less harmful, sources of nicotine"* [3]. Professor Russell was one of the first to recognise the critical role that nicotine played in tobacco use and he identified that whilst there were good ethical and moral reasons not to promote nicotine addiction in society, the harm caused by nicotine was orders of magnitude lower than the harms caused by cigarette smoke. Professor Russell was also a pioneer of new treatments for smoking cessation, in particular, nicotine replacement therapies (NRT). Since then, the number of NRT products has proliferated such that there are now several different delivery routes and modes and countless different dosages and flavours. However, even with a relaxation of the licensing restrictions which increased their accessibility, NRT products have never become popular as an alternative to smoking.

In 2004, the first EC was marketed in China, and EC started to appear in England in 2006/7. The subsequent three years saw a rapid rise in their use. Whilst Professor Russell died in 2009, predating the arrival of these products in England, proponents of EC similarly recognised their potential to contribute towards making a smoke-free society more rapidly achievable [4]. Those against EC, however, believed that they were at best a distraction, at worst a means of undoing decades of progress in reducing smoking [5].

Any new tobacco control strategy for England must therefore incorporate a nicotine strategy, which should include recommendations and an appropriate regulatory framework for EC. This report attempts to inform that strategy by reviewing recent evidence and surveys relating to the **use** of EC and how they **impact smoking behaviour.** The focus is England, although we also draw on evidence from elsewhere in the UK and internationally.

Description of e-cigarettes

EC use battery power to heat an element to disperse a solution that usually contains nicotine. The dispersion of the solution leads to the creation of an aerosol that can be inhaled by the user. The heated solution typically contains propylene glycol or glycerine, water, nicotine, and flavourings. EC do not contain tobacco, do not create smoke and do not rely on combustion. Whilst EC 'smoke' is technically an aerosol, throughout this report we use the established terminology of vapour, vaping and vaper.

There is substantial heterogeneity between different types of EC and the speed with which they are evolving making them difficult to categorise. ECs available in England can be classified into three basic types: (1) EC that are either (a) disposable or (b) use pre-filled cartridges that need to be replaced once emptied. We will refer to these using their most common name, 'cigalikes'. Most cigalikes resemble cigarettes, although it is important to note that some do not; (2) EC that are designed to be refilled with liquid by the user. We will refer to these using their common name 'tank systems'. (3) Finally, some EC products, mostly tank systems that allow users to regulate the power delivery from the batteries to the atomizer. These we refer to as mods or 'variable power EC'.

In the UK, the most prominent brands of cigalikes are now owned by the tobacco industry. To the authors' knowledge only one tobacco company sells a tank model in the UK, with the rest of the market consisting of non-tobacco industry companies. Some products have also been introduced by the tobacco industry that could be referred to as 'hybrids' such that they use pre-filled nicotine cartridges but look like tank models. Additionally, a few EC that are similar to cigalikes in function are also sold that use cartridges that can be refilled, and some users will puncture holes/remove the ends of cigalike cartridges to refill them instead of buying new cartridges.

Studies have validated the ability of EC to deliver nicotine to the user. Blood plasma nicotine concentrations increase after inhalation of EC aerosol [6, 7], and cotinine, a biomarker for nicotine, has been detected in the saliva of EC users [8, 9]. Information about the overall and relative risks of EC in comparison with smoking has also been developing. Using a multi-criteria decision analysis (MCDA) model, the Independent Scientific Committee on Drugs selected experts from several different countries to compare a variety of nicotine products on variables of harm identified by the UK Advisory Council on the Misuse of Drugs [10]. EC were identified as having 4% of the relative harm of cigarettes overall (including social harm) and 5% of the harm to users, although it was acknowledged that there was a lack of hard evidence for the harms of most of the nicotine products on most of the criteria.

Structure of report

Following Chapter 2 on methodology, Chapter 3 assesses the current and future policy framework for EC. Chapters 4 and 5 assess trial and usage in England among adults and youth as well as different socioeconomic groups where evidence permits. Chapter 6 examines the evidence for the impact of EC on smoking behaviour including the use of EC in quit attempts as well as alongside smoking. Chapter 7 assesses reasons for trying and discontinuing EC and Chapter 8 perceptions of relative harms of EC and smoking. Chapter 9 discusses nicotine content and emissions of EC as well as nicotine uptake in users. Chapters 10 and 11 assess different aspects of safety drawing on recent published studies as well as national statistics. Chapter 12 examines international perspectives of EC policies and usage.

2. Methodology

For the present report we have included: (1) a synthesis of recent evidence (published since the two PHE 2014 EC reports) with the earlier evidence in the earlier PHE reports drawing on both national and international literature; and (2) *where feasible*, an analysis of any relevant national unpublished data available to PHE, KCL and partner organisations from England, Great Britain or the UK, including: i) Smoking Toolkit Study (UCL); ii) Action on Smoking and Health (ASH) Smokefree GB (adult and youth) surveys; iii) Internet Cohort GB survey; iv) Smokers' surveys 2014 commissioned by ASH from YouGov; and v) the International Tobacco Control (ITC) policy evaluation project.

For the evidence review (1) above, given the short timeframe for this report, a systematic review of the literature was not possible. However, we followed systematic review methods where possible and searched PubMed for studies from 2014 onwards using the following search terms: (("2014/01/01"[Date - Publication] : "3000"[Date - Publication])) AND (((((((e-cigarette) OR Electronic cigarettes) OR e-cig*) OR electronic cig*) OR ENDS) OR electronic nicotine delivery systems) OR electronic nicotine delivery system) OR ((Nicotine) AND Vap*)).

The term ENDS was used as some studies have referred to e-cigarettes as Electronic Nicotine Delivery Systems (ENDS). This search returned 3,452 records. The titles of all records were screened and 798 articles were identified as potentially relevant to the report. The full papers of abstracts considered relevant by two reviewers were retrieved and reviewed as identified in Appendix A.

We wanted to ensure we included the most up-to-date information on EC use and impact in England. In order to do this we used routine national data sources to retrieve measures of EC use prevalence, fires, poisoning and other adverse events. Specifically for (2) above, we assessed, in addition to published papers, unpublished national survey data relevant to this work, identifying where findings are peer reviewed/published. The methods of the surveys that we have accessed are as follows:

Smoking Toolkit Study (STS, University College London)

The STS consists of monthly **cross-sectional household interviews** of adults (aged 16 and over) in England that has been running since November 2006. Each month involves a **new nationally representative sample** of about 1,800 respondents. Since 2009, all respondents who smoked in the last year have been asked questions on EC; since November 2013 all respondents complete questions on EC. For more information, see www.smokinginengland.info

ASH Smokefree GB (adult and youth) surveys

Adult: ASH has conducted **cross-sectional internet surveys** of adults (aged 18 and over) in Great Britain (GB) since 2007. These surveys cover a wide range of tobacco control policies and smoking behaviour and are carried out on ~12,000 adults each year. Questions on EC were included first in 2010, with new EC questions added in each subsequent survey (2012, 2013, 2014, 2015).

Youth: ASH has conducted **cross-sectional surveys of British youth** (aged 11-18) three times to date (2013, 2014, 2015). **Younger** participants are recruited, **online,** through the adult YouGov participants with **older** participants contacted **directly**. It has been used to give a more contemporaneous and comprehensive snapshot of youth attitudes towards smoking and their behaviours (and includes a breakdown of trial and more prolonged use of EC) than UK Government national surveys have been able to.

Internet Cohort GB survey (King's College London, University College London)

A unique longitudinal internet survey of smokers and recent ex-smokers in GB (aged 16 and over) surveyed first in 2012 and then again in December 2013 and 2014. Of the 5,000 respondents in the initial sample, 1,031 respondents (20.7%) used EC at all at the time of the survey in 2012. The prevalence of past-year smoking in this baseline sample was similar to that identified through the STS (which, as stated above, recruited representative samples of the population in England), over a comparable period.

In 2013, 2,182 of the 5,000 were followed up and in 2014, 1,519 were followed up. EC use was 32.8% (n=717) in 2013 and 33.2% (n=505) in 2014. The study sample was recruited from an online panel managed by Ipsos MORI who were invited by email to participate in an online study and were screened for smoking status. The survey included questions on smoking and quitting behaviour and stress and general health as well as detailed questions on EC usage.

ASH GB Smokers' survey 2014

This is an online survey carried out by YouGov for ASH specifically to assess more detailed attitudinal measures concerning nicotine containing products. The 2014 survey involved 1,203 adult smokers and recent ex-smokers selected from the ASH Smokefree adult survey to have roughly equal numbers of smokers who had (n=510) and had not (n=470) tried EC and a smaller number of ex-smokers who had tried EC (n=223).

ITC Policy Evaluation project

A longitudinal cohort survey of smokers and recent ex-smokers (aged 18 and over), surveyed by telephone and internet. The ITC UK survey started in 2002 and surveys

have been conducted approximately annually since that time. Probability sampling methods are utilised through telephone surveys using random digit dialling, but in more recent survey waves participants could opt to complete surveys on the internet. The ITC UK study benefits from parallel cohort surveys in Australia, Canada and the United States, enabling comparisons across countries with different tobacco and EC policies. Each wave of the survey includes approximately 1,500 UK respondents. EC questions were added to the last three waves. Data from the last wave (in 2014) were not available for inclusion in this report, but published papers from earlier waves are included. More details of the methodology are available at www.itcproject.org

3. UK policy framework

E-cigarette regulations in England: current and proposed

Regulations have changed little in England since the previous PHE reports. Currently EC are governed by general product safety regulations (UK and EU) which do not require that the products be tested before being put on the market. However, manufacturers can apply for a medicinal licence through the Medicines and Healthcare products Regulatory Agency (MHRA) [11] and from next year any EC not licensed by the MHRA will be governed by the revised European Union Tobacco Products Directive (TPD)[12]. Both the MHRA licensing and the TPD regulatory routes are described below. The TPD regulations are extensive and will have a significant impact on the EC market.

One change from the previous PHE report, which was introduced by the Advertising Standards Authority in October 2014, is that until the TPD comes into force, advertising of EC is governed by a voluntary agreement. This agreement indicates, inter alia, that advertising must be socially responsible, not promote any design, imagery or logo that might be associated with a tobacco brand or show the use of a tobacco product in a positive light, make clear that the product is an EC and not a tobacco product, not undermine quit tobacco messaging, and must not contain health or medicinal claims unless the product is licensed. These guidelines will be reviewed in October 2015 and when more is known about the application of the TPD the role of the Code will be clarified.

A further recent change is the introduction of measures to protect children from EC: an age of sale lower limit of 18 years of age (in line with tobacco cigarettes) is being introduced and a ban on proxy purchasing of EC.

EU Tobacco Products Directive (TPD) route

The revised TPD will introduce new regulations for EC or refill containers (referred to below as products) which are not licensed by the MHRA. We have listed these in detail below because they are wide-ranging and will impose a significant step change for manufacturers, importers and Member State (MS) authorities:

- **notification**: Manufacturers must inform competent authorities of the MS six months before placing new products on the market. For those already on the market by 20 May 2016, the notification needs to be submitted within six months of this date. Each substantial modification of the product requires a new notification
- **reporting obligations** (for which manufacturers/importers might be charged) include:

    - details (including quantification) on all the ingredients contained in, and emissions resulting from the use of, the product, by brand name
    - toxicological data regarding ingredients and emissions, including when heated, with reference particularly to health of consumers when inhaled including any addictive effect
    - information on nicotine doses and uptake when consumed under normal or reasonably foreseeable conditions
    - description of the product components, including where appropriate opening and refill mechanisms of product or refill containers
    - description of the production process and declaration that it conforms with the TPD
    - declaration that manufacturer/importer bear full responsibility for the quality and safety of the product when placed on market and used under normal or reasonably foreseeable conditions
- **nicotine-containing liquid** restrictions:
    - EC must not contain more than 20 mg/ml of nicotine
    - nicotine-containing liquid must be in dedicated refill containers not exceeding 10ml volume, and cartridges or tanks do not exceed a volume of 2ml
    - additives are not prohibited but the nicotine-containing liquids cannot contain additives that are otherwise prohibited by the other Articles in the TPD
    - high purity ingredients must be used and substances other than those declared should only be present in trace quantities which are unavoidable during manufacture
    - ingredients must not pose a risk to health either when heated or not heated
    - nicotine doses must be delivered at consistent levels under normal conditions of use
- products are required to be child and tamper proof, protected against breakage and leakage and have a mechanism that ensures refilling without leakage
- products must include a **leaflet with information** on:
    - instructions for use and storage of the product, including a reference that the product is not recommended for use by young people and non-smokers
    - contra-indications
    - warnings for specific groups
    - possible adverse effects
    - addictiveness and toxicity
    - contact details of manufacturer/importer and a legal or natural contact person within the EU
- **outside packaging of products** must include:
    - list of all ingredients contained in the product in descending order of the weight
    - an indication of the nicotine content and delivery per dose
    - batch number
    - recommendation to keep the product out of reach of children

    - no promotional element or feature or such that suggests the product is harm reducing (or other features described in Article 13 of the Directive)
- **health warnings:**
    - One of the following must be shown:
        - 'This product contains nicotine which is a highly addictive substance. It is not recommended for use by non-smokers' or
        - 'This product contains nicotine which is a highly addictive substance'
    - Member States shall determine which health warning to use
    - health warnings must comply with regulations concerning specific provisions on position and size
- cross-border **advertising** and promotion, sponsorship etc of products will be prohibited (unless trade information)
- **cross-border sales** of products may be prohibited or subject to a registration scheme
- manufacturers/importers of products to submit an **annual submission** on their products to competent authorities in MS which should include:
    - comprehensive data on sales volumes, by brand name and product type
    - information on preferences of various consumer groups, including young people, non-smokers and the main types of current users
    - mode of sale of the products
    - executive summaries of any market surveys carried out in respect of the above, including an English translation thereof products
- MS shall monitor the market developments concerning products, including any evidence that their use is a gateway to nicotine addiction and ultimately traditional tobacco consumption among young people and non-smokers. This information to be made publicly available on a website although the need to protect trade secrets should be taken into account
- MS should on request, make all information relevant to this Article available to the Commission and other Member States who will respect confidential information
- MS shall require manufacturers, importers and distributors of products to establish and maintain a system for collecting information about all of the suspected adverse effects on human health
- **corrective action** should be taken immediately if economic operators consider or have reason to believe that products are not safe or of good quality or not conforming to the Directive, ensuring conformity or withdrawal or recall from the market. In such cases, operators are required to inform immediately market surveillance authorities of the MS giving details of risk to human health and safety, corrective action taken and results of such corrective action. MS may request additional information from the economic operators on safety and quality aspects or any adverse effect of products
- the Commission will submit a report to the European Parliament and the Council on potential risks to public health by 20 May 2016 and as appropriate thereafter

- where a competent authority believes specific products could pose a serious risk to human health it should take appropriate provisional measures, immediately inform Commission and competent authorities of other MS of measures taken and communicate any supporting data. The Commission will determine whether provisional measure is justified informing the MS concerned of its conclusions to enable appropriate follow-up measures to be taken
- the Commission can extend any prohibition to other MS if such an extension is justified and proportionate
- the Commission is empowered to adapt wording of health warnings and ensure factual
- the Commission will give a common format for notification and technical standard for the refill mechanism outlined above

The exact date of implementation in England is yet to be specified but full compliance is likely to be necessary by 2017. One UK company, Totally Wicked, has challenged the UK's intention to transpose the Directive into UK law. The case rests on whether the TPD was properly made and has been referred to the European Court of Justice for a preliminary ruling. This is expected in late 2015/early 2016.

During implementation, government will need to undertake an impact assessment for the UK market on the final proposals as set out in the Directive and this will be consulted upon. The TPD certainly raises the barrier for bringing EC products to market or continuing to market existing products, and will undoubtedly constrain the EC market. Understanding any unintended consequences of the EU TPD as well as intended ones will be important. For example, the cap on nicotine concentrations introduced by the TPD will take high nicotine EC and refill liquids off the market, potentially affecting heavier smokers seeking higher nicotine delivery products.

Medicines and Healthcare products Regulatory Agency (MHRA) licensing route

Following a consultation in 2010, the UK MHRA introduced a mechanism for the licensing of EC and other nicotine containing products as medicines requiring medicinal purity and delivery standards. Such a licence would be required for products to be prescribed on the NHS. As with other licensed nicotine containing products, advertising controls would be applied and VAT of 5% would be imposed.

The licensing process has been described by the MHRA [11]. This regulation was described initially as 'light touch' recognising a product that delivered nicotine could be effectively used for harm reduction or cessation purposes, thus implying a relatively speedy route to licensing. This was subsequently changed to 'right touch' as it was apparent that the process was more lengthy and costly than originally envisaged. We understand that the MHRA estimated costs for a one-off application of between £252K and £390K with an annually recurring cost of between £65K and £249K, for each

product. This does not include the costs of making manufacturing facilities and products MHRA compliant – estimated at several million pounds.

At the time of writing one non-EC nicotine inhaler product, Voke, developed by Kind Consumer, and to be marketed by British American Tobacco (BAT), had received a medicinal licence, although it is not yet being marketed in England. A further BAT product (an EC) is currently going through the application process. Other EC products are currently in the pipeline with the MHRA but it is not clear at what stage the applications are or what types of products, eg cigalikes or tank models, are involved.

The absence of a licensed product, five years after the MHRA's consultation took place, suggests that this route to market is not commercially attractive. The fact that the only product at the application stage is a BAT product suggests that the process is very resource intensive. As well as cost, other possible reasons include complexity, a lack of desire to engage with medicinal licensing or the MHRA, the entrepreneurial nature of the EC manufacturers and a possible lack of perceived benefits to acquiring a licence. This could be problematic when the EU TPD is implemented, which is likely to constrain the over-the-counter market. Additionally, having a diverse range of EC on prescription is likely to be beneficial (similar to nicotine replacement tobacco (NRT) products – when new products are introduced, evidence suggests that they do not cannibalise the existing NRT product market but instead expand the use of medications). This means that small manufacturers, particularly non-tobacco industry manufacturers, who may be producing a greater variety or more satisfying EC, will not compete with larger corporations such as the tobacco industry in the prescriptions market. There are several consequences of this which should be explored. These could include an inhibition of innovation and damage public health. Alternatively, given the demand for prescribed EC products is as yet unknown, particularly in the population groups where smoking prevalence is elevated, the medicinal route may not impact public health. The appeal of EC may rest in the fact that they are not medicines. A review of the MHRA licensing process for EC, and its likely impact, is recommended.

Summary of findings

The revised TPD will introduce new regulations for EC or refill containers which are not licensed by the MHRA. The cap on nicotine concentrations introduced by the TPD will take high nicotine EC and refill liquids off the market, potentially affecting heavier smokers seeking higher nicotine delivery products.

The fact that no licensed EC are yet on the market suggests that the licensing route to market is not commercially attractive. The absence of non-tobacco industry products going through the MHRA licensing process suggests that the process is inadvertently favouring larger manufacturers including the tobacco industry, which is likely to inhibit innovation in the prescription market.

Policy implications

- From May 2016, following the introduction of the revised TPD, ECs will be more strictly regulated. As detailed elsewhere in the report, the information we present does not indicate widespread problems as a result of EC. Hence, the current regulatory structure appears broadly to have worked well although protecting non-smoking children and ensuring the products on the market are as safe and effective as possible are clearly important goals. New regulations currently planned should be implemented to maximise the benefits of EC whilst minimising these risks.

- An assessment of the impact of the TPD regulations on the UK EC market will be integral to its implementation. This should include the degree to which the availability of safe and effective products might be restricted.

- Much of England's strategy of tobacco harm reduction is predicated on the availability of medicinally licensed products that smokers want to use. Licensed ECs are yet to appear. A review of the MHRA EC licensing process therefore seems appropriate, including manufacturers' costs, and potential impact. This could include a requirement for MHRA to adapt the processes and their costs to enable smaller manufacturers to apply, and to speed up the licensing process. The review could also assess potential demand for the EC prescription market and what types of products would be most appropriate to meet that demand.

4. Prevalence of e-cigarette use in England/Great Britain

This chapter assesses the use of EC by adults and young people in England by drawing on recent surveys carried out in England and Great Britain (GB). A later chapter discusses EC prevalence internationally.

Measures used

One of the main issues in measuring EC use is the lack of consistent and appropriate terminology, for example some studies equate ever having used EC with current use of EC which is clearly inappropriate. We recommend that definitions of usage categories should be standardised similar to those used in smoking surveys. Appendix B lists the different measures used in surveys focused on in this report, and gives definitions used in the other studies included in this review.

Use of e-cigarettes by adults

First, we assess e-cigarette use in the adult population in England. We summarise various data sources to provide an overview of EC use among the general population, and then specifically smokers, recent and long-term ex-smokers, and never-smokers. The two main surveys used in this chapter are the Smoking Toolkit Study (STS) and the ASH Smokefree GB surveys. However, in addition to these surveys, findings from the Office for National Statistics Opinions and Lifestyle Survey (ONS survey), a randomised probability sample omnibus survey in GB, have also been included in this section although the exact question used is not available [13]; preliminary released data from Q1 2014 are reported here in advance of the complete data due for publication later in 2015.

Population use of e-cigarettes

Of the available datasets, just two – the Smoking Toolkit Study (STS, England) and the ASH Smokefree GB adult surveys – provide information on population prevalence (Table 1). Using the STS, it is estimated that 5.5% of the adult population of England used EC in the first quarter of 2015 indicating a marked rise from 0.5% in 2011. The measure of use in the STS is compiled from four survey questions and assesses *current use for any reason* (Appendix B). A very similar estimate is obtained for GB using the 2015 ASH survey, with 5.4% of the population estimated to be current (defined as *tried EC and still use* them, see Appendix B) EC users. This translates to about 2.6 million EC users in GB in 2015 [14](for comparison there are about nine million tobacco

smokers in GB and as discussed later, most EC users are smokers or ex-smokers). The ASH survey also assessed trial and about 17% of the adult GB population was estimated to have tried EC.

Table 1: Adult EC current use[1]

Source (date of data collection)	Population Prevalence	Never smokers	Ex-smokers	Smokers ('Dual users')
ASH Smokefree GB adult survey *(2015 - March)*	5.4%	0.2%	6.7%	17.6%
Office for National Statistics *(2014 - Q1)*	N/A	0.1%	4.8%	11.8%
Smoking Toolkit Study *(2015 – Q1)*	5.5%	0.2%[2]	3.3%[2]	21.2%

[1]For definitions of current use please see Appendix B. The ONS question is unavailable.
[2]Figures for never and long-term ex-smokers are derived from n=22489 never and long-term ex-smokers surveyed between November 2013 and March 2015

Never smokers and long-term ex-smokers

All three surveys estimate *current* EC use among adult *never* smokers to be very rare at 0.2% or less, and between 3% and 7% among *ex*-smokers – the latter estimates may vary because in the STS recent ex-smokers (last-year) are not included in this category (Table 1). Prevalence of current EC use among recent ex-smokers in the STS was around 40% in the first quarter of 2015 [15].

The ASH survey estimated that around 1.5% of *never* smokers and 16% of *ex*-smokers had *ever tried* EC.

Smokers

Recent surveys estimate that *current* EC use among smokers, sometimes referred to as 'dual users' of cigarettes and e-cigarettes, is between 12 and 21% (Table 1). The prevalence of EC use among last-year smokers (defined as smokers and recent ex-smokers) using the STS in England is estimated at 22.9% for *any* use of EC and 14.9% for *daily* EC use. The ASH 2015 survey indicated that 17.6% of current smokers use EC currently (18% of occasional and 17% of daily smokers); the same survey indicated that a small majority of smokers (59%) have now tried EC.

The Q1 2014 ONS Survey data estimates for current use are considerably lower, suggesting that just under 12% of current smokers used EC in early 2014. The survey question/s used to determine this is/are not available to assess whether different ways of assessing use may be a reason for this discrepancy in findings.

The ASH survey indicates that about 60% of current EC users are current smokers, and about 40% are ex-smokers. The proportion of EC users among never smokers remains negligible.

Summary

Around one in 20 of the general adult population in England (and GB) use EC. Current EC users are almost exclusively smokers or ex-smokers. EC use among long-term ex-smokers is considerably lower than among recent ex-smokers.

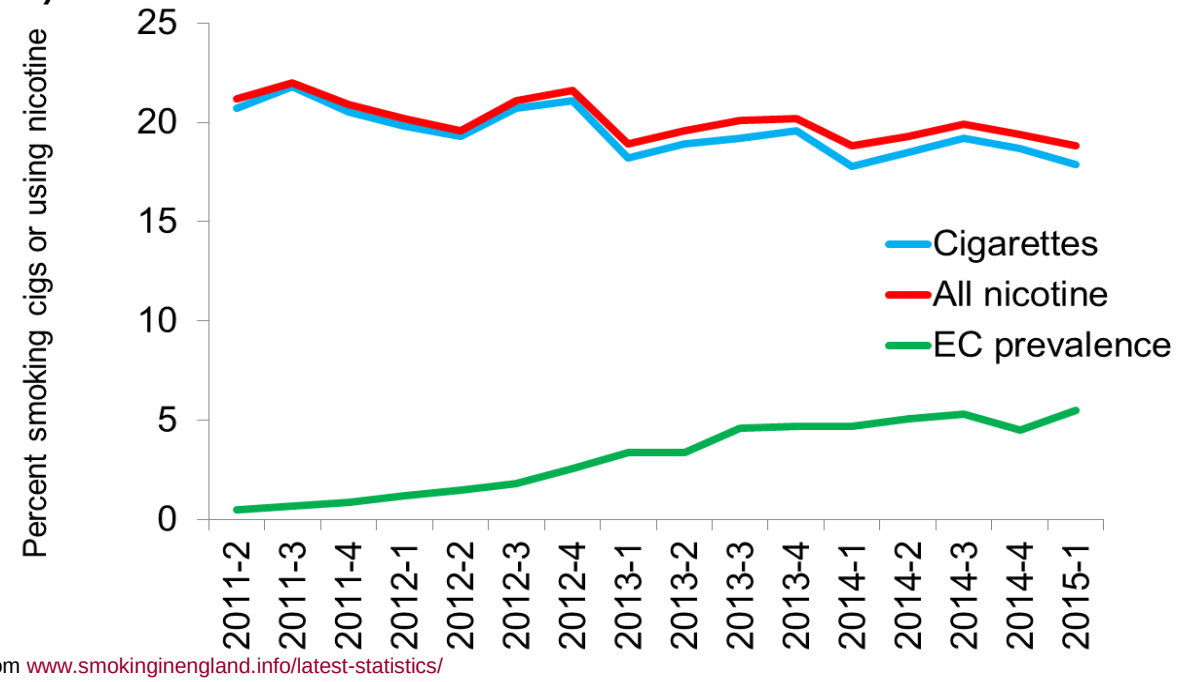
Trends in e-cigarette use among adults

Both the STS and ASH surveys demonstrate that there was a steady increase in EC use in the population from 2011 to 2013.

Smoking Toolkit Study (STS) data

The STS data indicate that this increase slowed down, even declining at the end of 2014 from 5.3% in Q3 to 4.5% in Q4 (Figure 1). However, as Q1 data from 2015 show a recent upswing to 5.5%, this decline may have been temporary. The STS data show that alongside the increase in EC use, smoking of tobacco cigarettes declined. Overall nicotine use, ie any consumption via cigarette smoking, NRT use or EC use, has also declined.

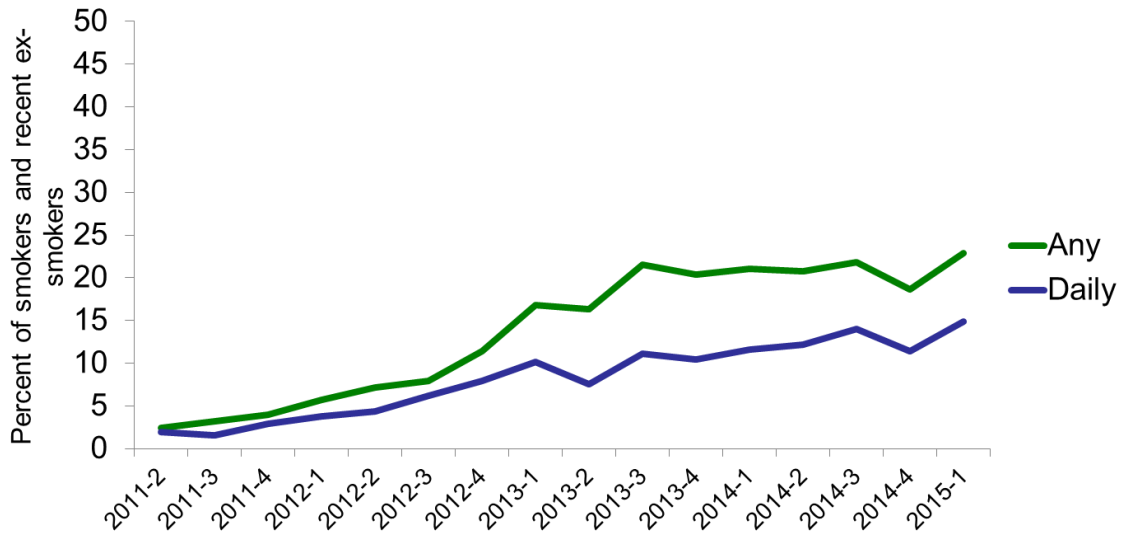
Figure 1: Prevalence of smoking and e-cigarette use among the adult English population (STS)



From www.smokinginengland.info/latest-statistics/

The overall pattern of EC use in the population is mirrored among last year smokers for whom EC prevalence increased from 2011, but declined from 22% for *any* use and 14% for *daily* use in Q3 2014, to 19% and 11% respectively in Q4 2014; however, any and daily use increased again to 23% and 15% respectively in Q1 2015 (Figure 2).

Figure 2: Prevalence of e-cigarette use among last year smokers (STS)



From www.smokinginengland.info/latest-statistics/

ASH Smokefree GB adult survey

The ASH surveys indicated a slowing down in the increase of EC use in the population between 2014 and 2015 and use among current smokers in 2015 remained at the 2014 level (17.6% of smokers in 2014 and 2015). Use among ex-smokers increased from 1.1% in 2012, to 4.5% in 2014 and 6.7% in 2015, whereas no increase in use was observed among never smokers over the last few years, remaining at 0.2% since 2013. **This means that the increase in EC use observed overall was accounted for by an increase in use by ex-smokers.** It is not clear to what extent this is due to smokers stopping smoking using EC or ex-smokers taking up ECs.

Summary

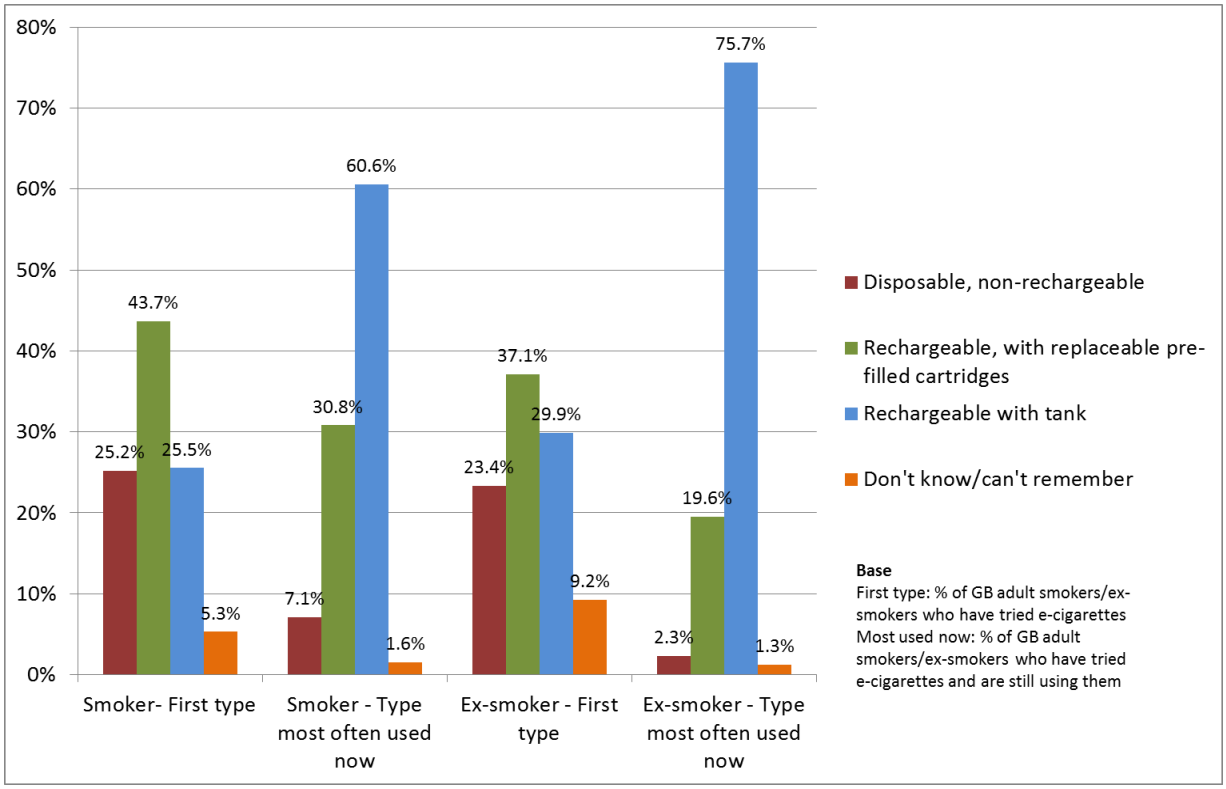
The prevalence of EC use among adults has plateaued. Most of the recent increase in use appears to be among ex-smokers. Cigarette smoking has declined over the period when EC use increased and overall nicotine use has also declined. These findings suggest that the advent of EC is not undermining and may be contributing to the long-term decline in cigarette smoking.

Types and flavours of e-cigarettes used among adults

When those who had tried EC in the 2015 ASH survey were asked about which EC *they used first*, 24% reported a disposable, 41% a rechargeable with replaceable pre-filled cartridges and 28% rechargeable with tank/reservoir filled with liquids (7% didn't know/couldn't remember). The different types were in the same order of popularity for first use regardless of smoking status (Figure 3).

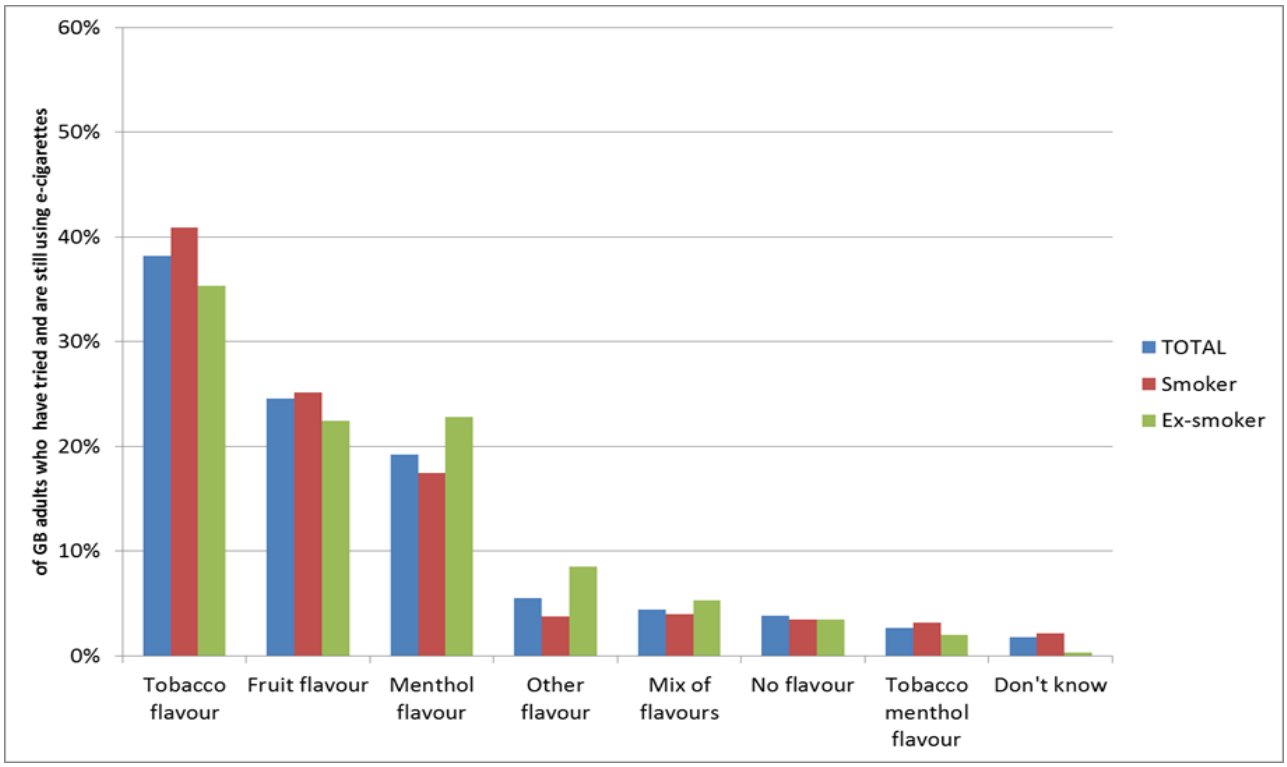
For those *still using EC* from the same survey, only 5% were *now mostly* using a disposable, 26% a rechargeable with replaceable pre-filled cartridges and 66% rechargeable with tank/reservoir filled with liquids (2% didn't know/couldn't remember). **This suggests that a considerable proportion of those who continue to use EC over time switch to the tank models.** Among EC users, ex-smokers were particularly likely to use tank models mostly and very few ex-smokers were using disposables (Figure 3). This is in agreement with findings reported in Chapter 6 of this report, where tank models were found to be associated with having quit smoking [16].

Figure 3: Type of e-cigarettes first used and currently used (ASH Smokefree GB data 2015)



The ASH Smokefree GB 2015 adult survey also shows that the most popular flavour was tobacco flavour, followed by fruit and menthol flavours (Figure 4).

Figure 4: Use of different flavoured e-cigarettes (ASH Smokefree GB data 2015)



Use of e-cigarettes among young people

The main source for estimating *smoking* prevalence in England among youth is the '*Smoking, drinking and drug use among young people'* surveys [17], however, EC use was first assessed in 2014 and these data are not yet available. This section therefore draws on the ASH Smokefree GB youth surveys to assess EC usage in young people, supplemented by a study in the North West of England, two cross-sectional national surveys in Wales and one national survey in Scotland. The measures used are detailed in Appendix B.

In 2015, the ASH survey found that 12.7% of 11 to 18-year olds reported *having tried EC;* of these, 80.9% had only used one once or twice (10.2% of all respondents). Current EC use was considerably lower: 0.7% had used an EC sometimes but not more than once a month; 1.2% more than once a month but not weekly; and 0.5% weekly (Table 2). **The prevalence of EC use (2.4% overall)** among people aged between 11 and 18 was therefore lower than among the general population. In comparison, 21% of all 11 to 18-year olds reported having tried cigarettes, of whom 54% only tried once (11.4% of all respondents). Current smoking was reported by a total of 6.7%; 2.7% smoked less than weekly and 4% at least weekly.

Experimentation increased with age: 2.9% of 11-year olds and 20.2% of 18-year olds had tried EC. In comparison, among 11-year olds, 3.9% had tried cigarettes (0.7% current smokers), whereas 40.9% of 18-year olds had tried cigarettes (14.3% current smokers).

Use of EC was very closely linked with smoking status. Among never smokers, 0.3% used EC monthly or more often, compared with 10.0% of ever smokers and 19.1% of current smokers. The majority of EC users had tried tobacco cigarettes first (Table 2).

Table 2: E-cigarette use among young people

Source	Ever tried	Use more than /at least once a month	Use more than once a week	Use (at least monthly) in *never* smokers	Those using e-cigarettes who had tried tobacco first
ASH Smokefree GB youth survey (11-18 years) [1] *(2015 – March)*	12.7%	1.9%	0.5%	0.1%	63.7%
Health Behaviour in School-aged Children, Wales (11-16 years) *(Nov 2013 – Feb 2014)* **[18]** [2]	12.3%	1.5%	Not reported	0.3%	Not reported
CHETS Wales survey (10—11 year olds)[19] 2014	5.8%	Not reported	Not reported	Not reported	Not reported
SALSUS Scotland survey (15 and 13 year olds)[20] 2013/2014	12%	0.4%	0%	0%	Not reported

[1]For question on e-cigarette categories please see Appendix B. Use more than/ at least once a month excludes those using more than once a week who are reported separately
[2] N=9055, use defined as at least monthly

Similar findings have been observed in Scotland. A national survey carried out in 283 schools across Scotland in late 2013/early 2014 involved more than 33,000 schoolchildren aged 13 and 15 years old [20]. Seven per cent of 13-year olds, and 17% of 15-year olds, had ever used an EC. Trial was associated with smoking status – 4% of never smokers had tried EC (3% trying them once and 1% having tried a few times) compared with 24% of ever smokers, 39% of ex-smokers, 46% of occasional smokers and 66% of regular smokers. Eleven per cent of regular smokers and 6% of occasional smokers reported using e-cigarettes at least monthly.

Very similar findings have been reported from a survey in Wales (Table 2). A survey of secondary schoolchildren was carried out under the auspices of the Health Behaviour of

School Children (HBSC) study and more than 9,000 participants aged 11–16 from 82 schools were included [18]. Overall, 12.3% had tried EC, 1.5% were monthly users, compared with 12.1% reporting ever having smoked and 5.4% current smokers (reported smoking less than once a week or more frequently). Whilst many *experimental* EC users had never smoked, most *regular* EC users had also smoked tobacco. The authors commented that *"the very low prevalence of regular use…suggests that e-cigarettes are unlikely to be making a significant direct contribution to adolescent nicotine addiction".*

Additionally, around 1,500 **10 to 11-year olds** were surveyed in Wales, from 75 schools in the CHETS Wales study [18, 19] (Table 2). Overall, 5.8% (n=87) had ever used an EC; most reported only using once (3.7%, n=55 overall) and only 2.1% (n=32) reported using them more than once. Again, EC use was associated with smoking. Just under half (47.6%) of those who reported having used tobacco had ever used an EC compared with 5.3% of never smokers. Controlling for other variables associated with EC use, parental use of EC and peer smoking remained significantly associated with having ever used an EC. Having ever used an EC was associated with weaker anti-smoking intentions. **Parental EC use was not associated with weakened anti-smoking intentions whereas parental smoking was [19].** This study, published prior to the one above, concluded that EC represented a new form of experimentation with nicotine that was more common than tobacco usage. It also commented that the findings added *"some tentative support for the hypothesis that use of e-cigarettes may increase children's susceptibility to smoking"*. However, as this was a cross-sectional survey, causal connections cannot be inferred. It is possible that children who had used EC would have smoked cigarettes in their absence and this could explain the relationship between intentions and EC usage (see below).

An additional survey of schoolchildren has been carried out in England. Trading Standards in the North West of England have been running biennial surveys of schoolchildren since 2005. The 2013 findings on EC, smoking and alcohol were published [21]. The survey was not designed to be representative (no compliance or completion rates were collected) but instead *"to provide a broad sample of students from a range of community types".* More than 100 schools participated and more than 16,000 participants aged 14–17 years of age were included in the analyses. It is important to acknowledge that the question about EC was "*Have you ever bought or tried electronic cigarettes?*", and this study cannot therefore add to knowledge on current usage. Around one in five of the sample had accessed EC, with access being higher in those who had experience of smoking. Around 5% of those who had *never* smoked cigarettes reported accessing EC; around half of *ex-smokers* and over two thirds of *regular smokers* had accessed them. Parental smoking and alcohol use were also associated with EC access.

Summary

Regular use of EC among youth is rare with around 2% using at least monthly and 0.5% weekly. A minority of British youth report having tried EC (national estimates suggest around 12%). Whilst there was some experimentation with EC among never smokers, **nearly all those using EC regularly were cigarette smokers.**

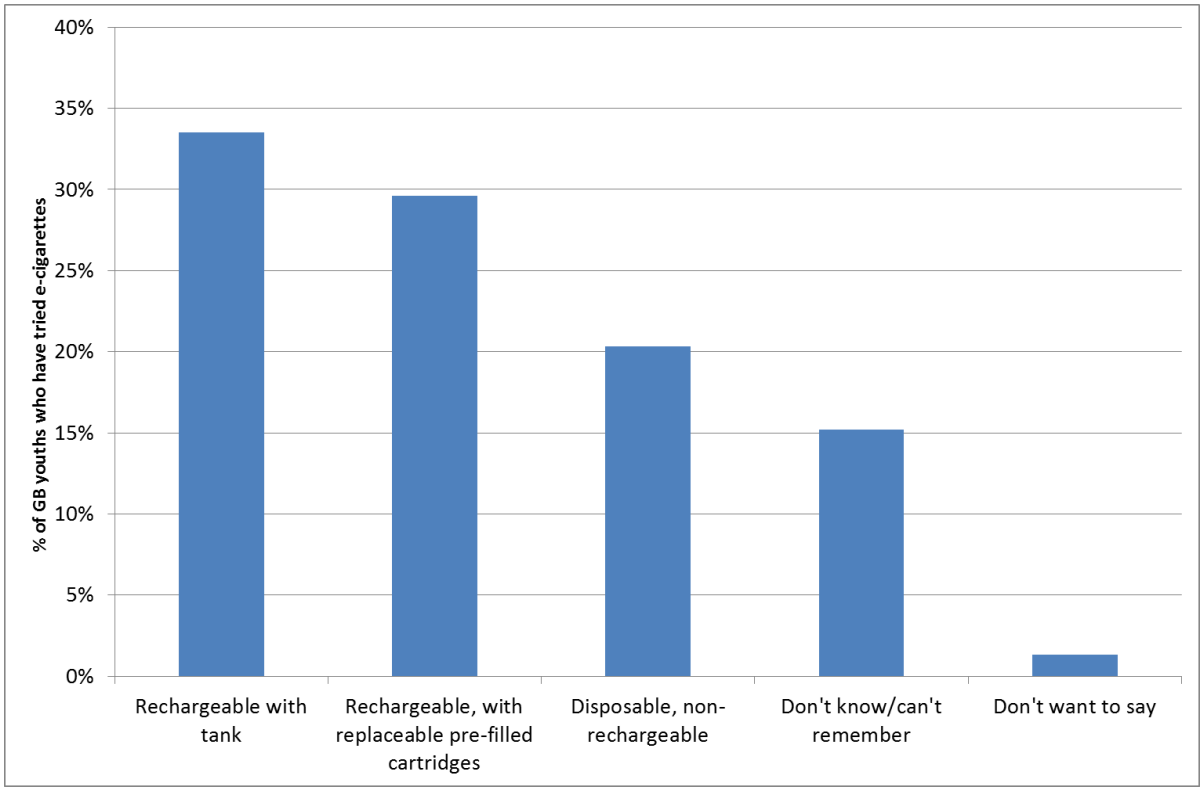
Trends in e-cigarette use among young people (ASH Smokefree GB youth)

The ASH Smokefree GB youth surveys indicate that awareness of EC has increased markedly, with the proportion of individuals who had *never heard* of EC falling from 33.1% in 2013 to 7.0% in 2015*. Ever having tried* EC also increased, from 4.5% in 2013, to 8.1% in 2014, and to 12.7% in 2015. However, the proportion using an EC monthly or more frequently remained virtually unchanged from 2014 (1.6%) to 2015 (1.7%). Over the same period, the proportion of regular smokers (at least weekly) remained at around 4% (2013: 4%, 2014: 3.6%, 2015: 4%).

Type and flavour among youth

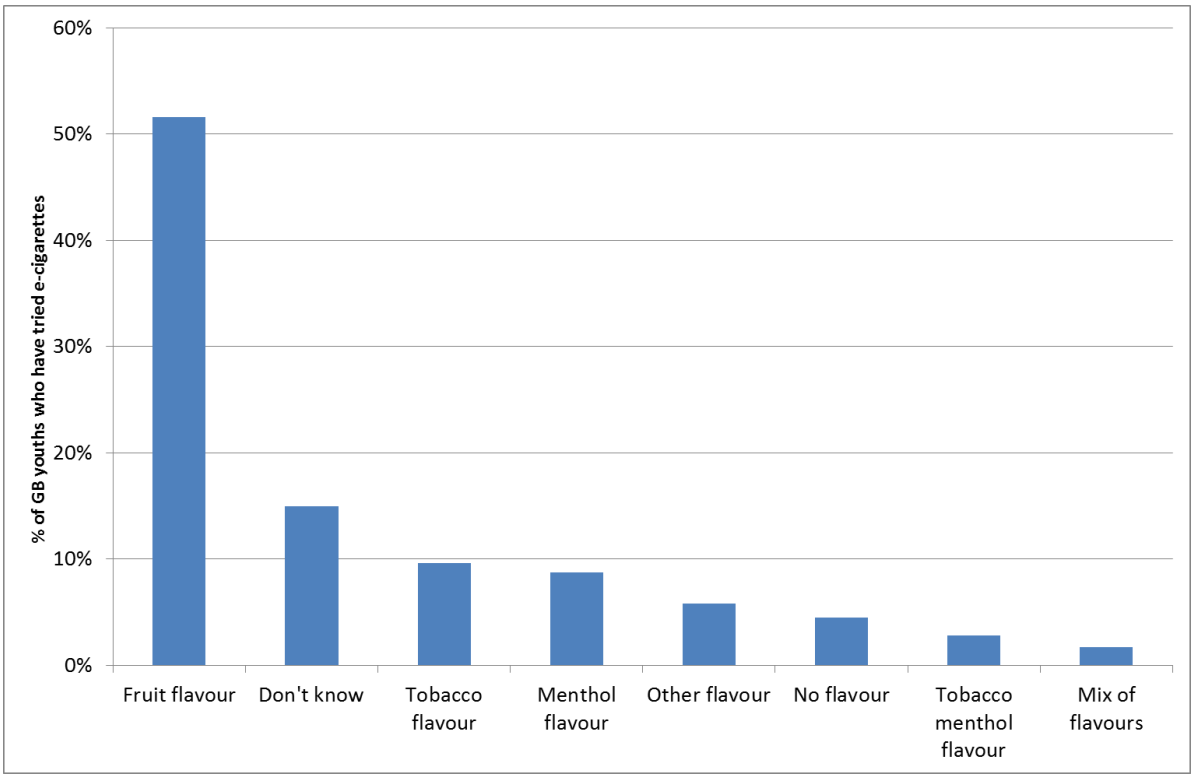
The proportion of youth reporting current use was too small to assess the most frequently used types or flavours in current users, so Figures 5 and 6 include everyone *who had tried* an EC. One third had first used a tank model and the most popular flavours among triers by far were fruit flavours. The responses for adults and youth are not directly comparable given flavours were assessed for adult current EC users, but in the latter group, fruit flavours were less popular than tobacco flavours.

Figure 5: First type of e-cigarette tried by youth, ASH Smokefree GB youth survey, 2015



Note: The proportion of youth reporting current use was too small to assess the most frequently used types.

Figure 6: Last flavour tried by youth, ASH Smokefree GB youth survey, 2015



Note: The proportion of youth reporting current use was too small to assess flavours in current users.

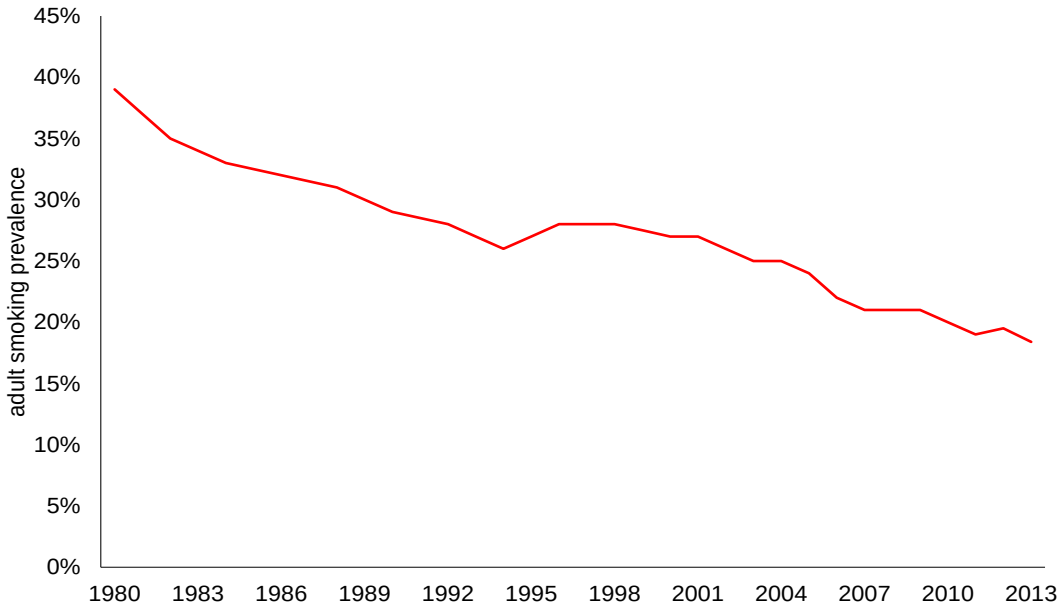
Concerns about impact of e-cigarette use on smoking

Three main concerns raised about EC use are that they might 1) renormalise smoking 2) reduce quitting and 3) act as a 'gateway' to smoking or nicotine uptake. An ultimate test for the first concern, and to some extent all three concerns, is the impact of EC use on smoking prevalence nationally which is explored first below. Evidence for effectiveness of EC on quitting smoking is explored in more detail in Chapter 6. Whilst other concerns have been raised such as renormalising the tobacco industry, we are only able to comment on issues pertaining to the objectives of our report.

Recent trends in smoking prevalence

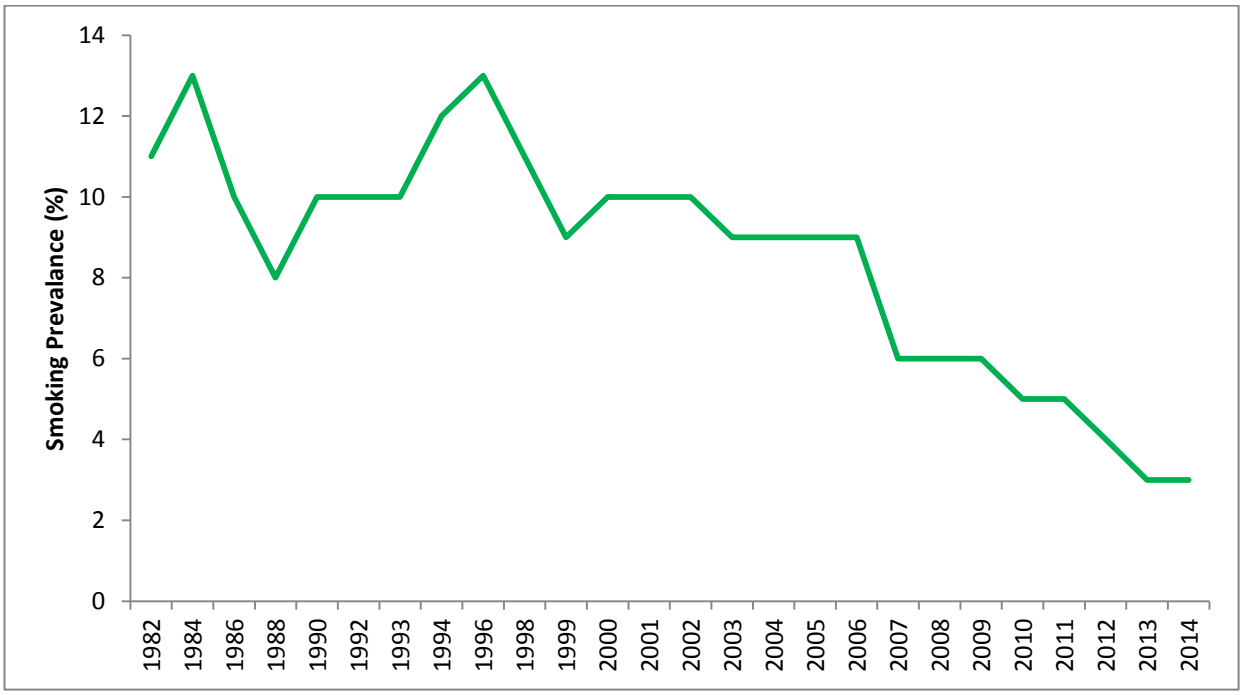
Since EC arrived on the market in England, smoking prevalence has continued to decline among both adults and youth (Figures 1, 7 and 8). Evidence to date therefore conflicts with any suggestion that EC are renormalising smoking. Whilst other factors may be contributing to the decline in smoking, it is feasible that EC may be contributing to reductions in smoking over and above any underlying decline.

Figure 7: Adult smoking prevalence in England 1980–2013[1]



[1] General Lifestyle Survey aged 16+(1980-2010); Integrated Household Survey aged 18+ (2011). Diagram courtesy of ASH.

Figure 8: Prevalence of regular smoking among 11–15 year olds in England 1980–2014[2]



Please note: decimal places were not used in the published data.

Gateway

The gateway theory or hypothesis is commonly invoked in addiction discourse, broadly to suggest that the use of one drug (sometimes a legal one such as tobacco or alcohol) leads to the use of another drug (sometimes an illegal one) but its definition is contested. No clear provenance exists and its origin appears to derive from lay, academic and political models [22]. It is apparent that discussions about the natural progression of drug use observed in longitudinal studies of young people appear to have morphed into implicit conclusions on causality without any evidential backing. Some have argued that the effect could be causal if the use of one drug, biochemically or pharmacologically, sensitises the brains of users to the rewarding effects of other drugs [23] making the dependent use of these other drugs more likely. However, there are many plausible competing hypotheses for such a progression [24] including i) shared networks and opportunities to purchase the drugs; and ii) individual characteristics such as genetic predispositions or shared problematic environment. Academic experts have stated that the gateway concept "*has been one of the most controversial hypotheses…in part because proponents and opponents of the hypothesis have not always been clear about what the hypothesis means and what policies it entails*" [24]. Indeed, a recent analysis of gateway concluded *"Although the concept of*

[2] Smoking drinking and drug use among young people in England surveys. Health and Social Care Information Centre, 2014.

the gateway theory is often treated as a straightforward scientific theory, its emergence is rather more complicated. In effect, it is a hybrid of popular, academic and media accounts – a construct retroactively assembled rather than one initially articulated as a coherent theory" [22].

Despite these serious and fatal flaws in the arguments, the use of the term 'gateway' is commonplace both in the academic literature and the lay press, particularly in relation to EC use and whether EC are a gateway to smoking. Some have suggested that if EC use increases at the same time as smoking increases then EC are acting as a gateway to smoking. Similarly, it's been argued that if someone uses an EC first and then initiates smoking, EC are a gateway. These arguments are clearly erroneous. To give one example of the misuse of the gateway concept, a BMJ news item on the Moore et al., 2014 [18] *cross-sectional* study discussed above commented that "[EC} *could be a gateway into smoking*" [25].

Kandel recently argued that evidence from mice offers a biological basis for the sequence of nicotine to cocaine use in people [26], but there is limited evidence for this. In reality, the gateway theory is extremely difficult to test in humans. For example, a clean test of the gateway hypothesis in relation to EC and smoking would require randomising people to an environment with EC and one without, and then following them up over a number of years to assess uptake of EC and smoking.

We strongly suggest that use of the gateway terminology be abandoned until it is clear how the theory can be tested in this field. Nevertheless, the use of EC and smoking requires careful surveillance in young people. The preferred option is that young people do not use EC but it would be preferable for a young person to use an EC instead of smoking, given the known relative risks of the EC and smoking cigarettes [10].

Summary

Since EC were introduced to the market, smoking prevalence among adults and youth has declined. Hence there is no evidence to date that EC are renormalising smoking, instead it's possible that their presence has contributed to further declines in smoking, or denormalisation of smoking. The gateway theory is ill defined and we suggest its use be abandoned until it is clear how it can be tested in this field. Whilst never smokers are experimenting with EC, the vast majority of youth who regularly use EC are smokers. Regular EC use in youth is rare.

Summary of findings

Adults: Around one in 20 adults in England (and Great Britain) use EC. Current EC users are almost exclusively smokers (~60%) or ex-smokers (~40%), that is smokers

who now use EC and have stopped smoking altogether. EC use among long-term ex-smokers is considerably lower than among recent ex-smokers. Current EC use among never smokers is very low, estimated to be 0.2%. The prevalence of EC use plateaued between 2013-14, but appeared to be increasing again in 2015.

Youth: Regular EC use among youth is rare with around 2% using at least monthly and 0.5% weekly. EC use among young people remains lower than among adults: a minority of British youth report having tried EC (~13%). Whilst there was some experimentation with EC among never smoking youth, prevalence of use (at least monthly) among never smokers is 0.3% or less.

Overall, the adult and youth data suggest that, despite some experimentation with EC among never smokers, EC are attracting few people who have never smoked into regular use.

Trends in EC use and smoking: Since EC were introduced to the market, cigarette smoking among adults and youth has declined. In adults, overall nicotine use has also declined (not assessed for youth). These findings, to date, suggest that the advent of EC is not undermining, and may even be contributing to, the long-term decline in cigarette smoking.

Policy implications

- Trends in EC use among youth and adults should continue to be monitored using standardised definitions of use.
- Given that around two-thirds of EC users also smoke, data are needed on the natural trajectory of ‘dual use’, ie whether dual use is more likely to lead to smoking cessation later or to sustain smoking (see also Chapter 6).
- As per existing NICE guidance, all smokers should be supported to stop smoking completely, including ‘dual users’ who smoke and use EC.

5. Smoking, e-cigarettes and inequalities

Smoking and inequalities

Whilst smoking prevalence overall has been declining over the past 50 years, smoking has become increasingly concentrated in more disadvantaged groups in society. Over the last decade, the gap between smoking in the different social groups has not narrowed (Figure 9) and some of the most disadvantaged groups in society (such as people with serious mental illness or prisoners) have shown no change in smoking prevalence over time (e.g. Figure 10). Furthermore, among smokers, the level of nicotine dependence increases systematically as deprivation increases [2]. A key challenge in tobacco control is therefore how to encourage smokers from disadvantaged groups to stop smoking.

Whilst quitting cigarettes and all nicotine use should remain the main goal across all social groups, EC are of interest because, as with other cleaner nicotine delivery systems, they potentially offer a wide reach, low-cost, intervention to reduce smoking and improve health in these more deprived groups in society where smoking is elevated [2]. It is therefore important to examine the potential impact of EC on inequalities.

Figure 9: Smoking trends by socioeconomic group status (GHS data)

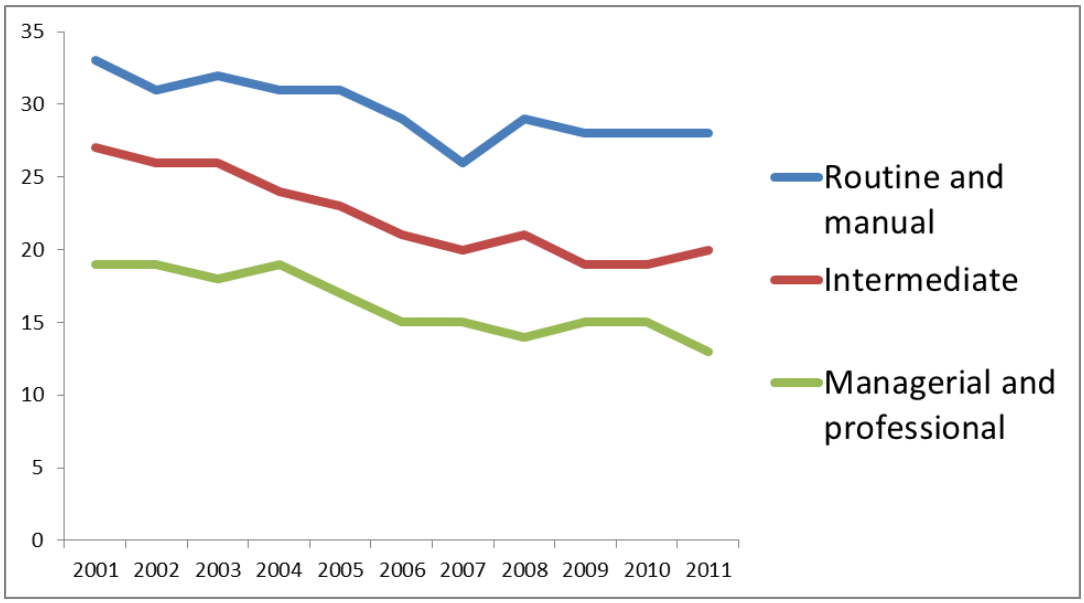
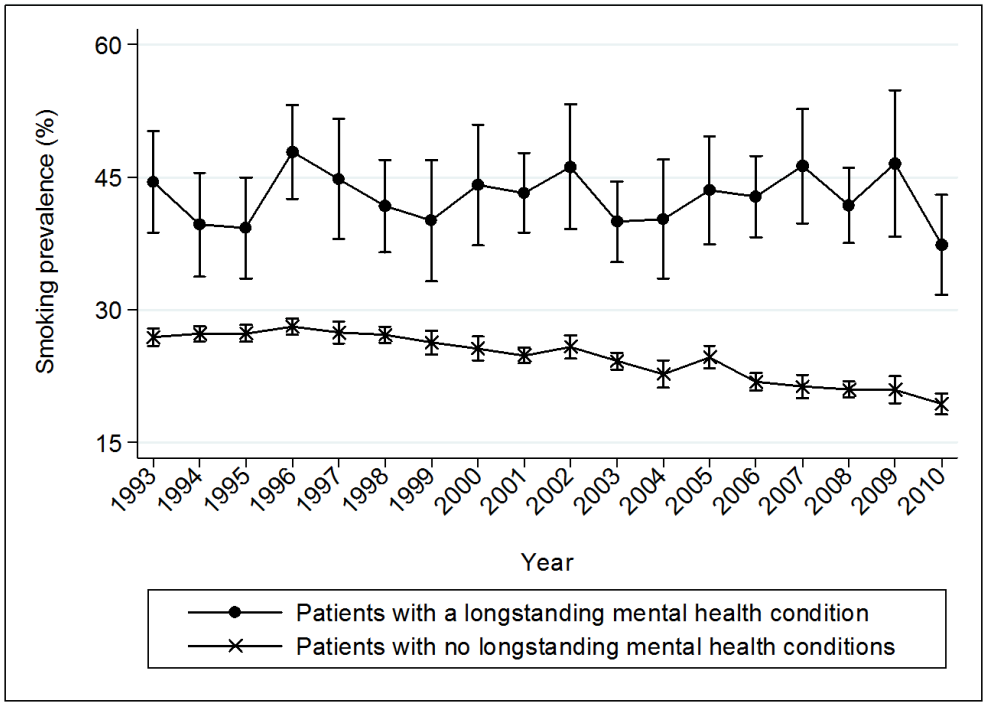


Figure 10: Smoking trends and mental health [27]

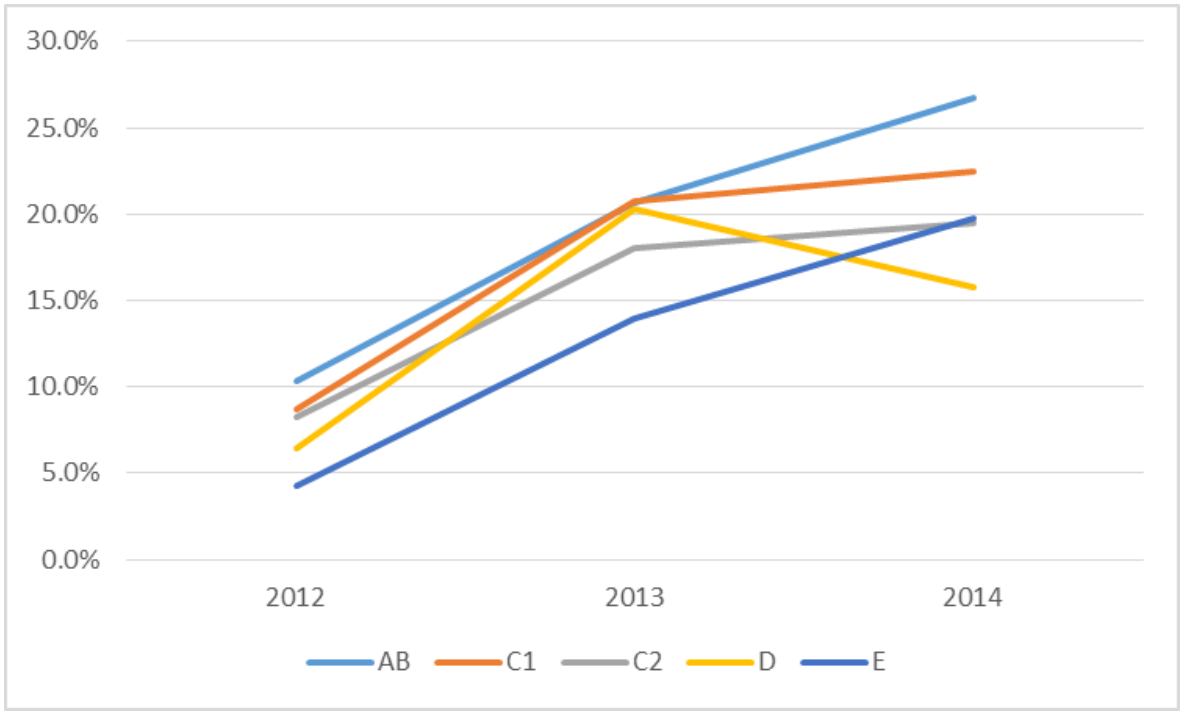


E-cigarette use and different social groups

Earlier surveys in GB and internationally suggested a social gradient in the use of EC, with smokers of higher income and education being more likely to have used and tried [28, 29]. However, the 2015 ASH Smokefree GB adult 2015 survey indicated only small differences across groups, with lower socioeconomic groups slightly more likely to have tried and be using EC. At the population level, 14.4% of ABC1 groups ('non-manual' occupational groups) had tried EC compared with 19.4% in C2DE groups ('manual' occupational groups); 4.6% of ABC1 were still using EC compared with 6.3% of C2DE groups. Nevertheless, given the higher prevalence of smoking in C2DE groups, when examined within the smoker population by social class, 20.0% of ABC1 smokers compared with 16.0% of C2DE smokers were EC current users.

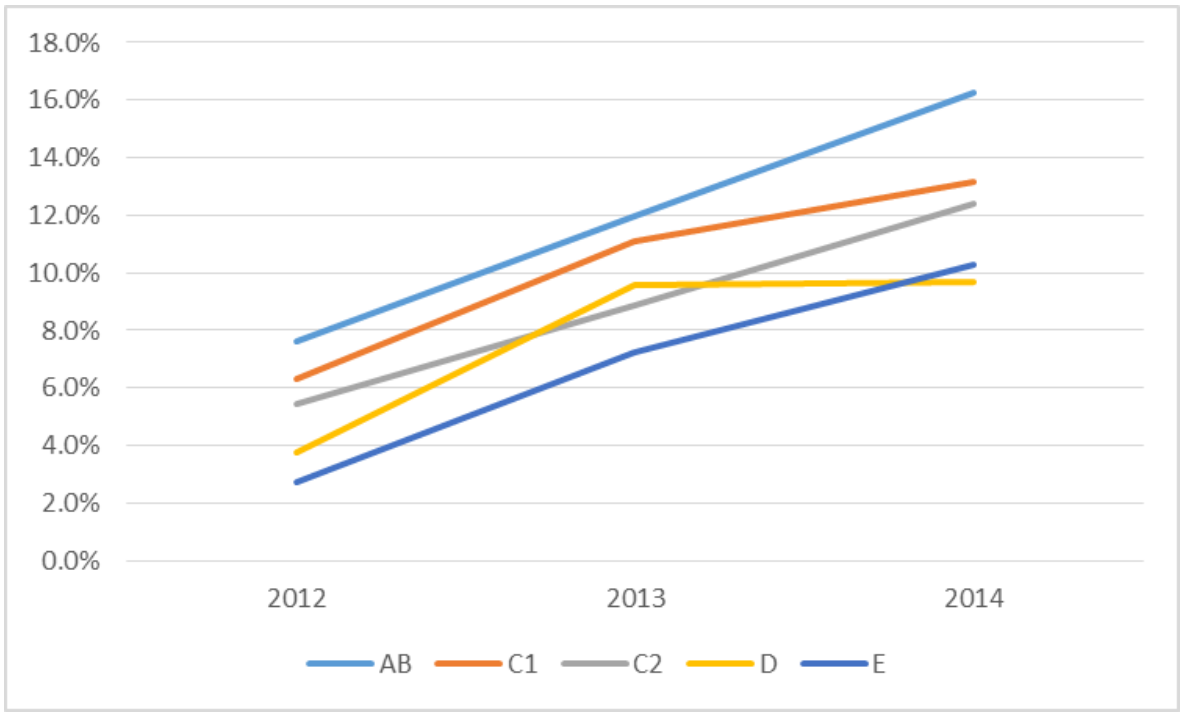
The STS data surveys show an increase in EC use in all social groups between 2012 and 2014 (Figures 11 and 12) but at a relatively similar rate such that socioeconomic differences are still apparent both for current and daily use of EC.

Figure 11: *Current* use of e-cigarettes by social class among last year smokers (STS data)



From www.smokinginengland.info/latest-statistics/

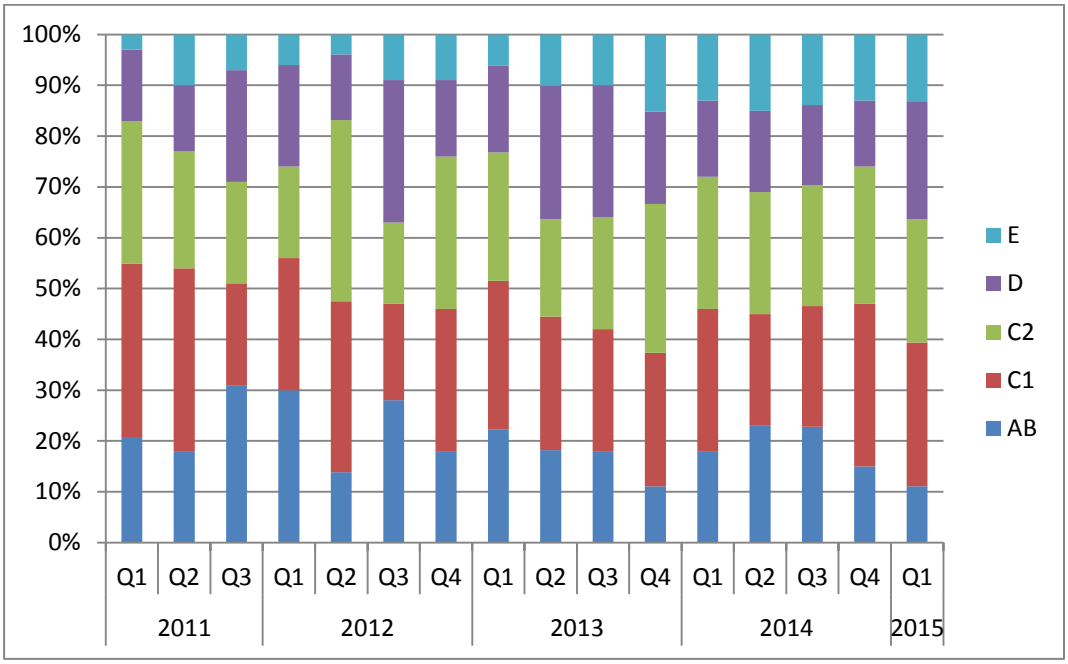
Figure 12: *Daily* use of e-cigarettes by social class among last year smokers (STS data)



From www.smokinginengland.info/latest-statistics/

Nevertheless, EC are penetrating the lower socioeconomic groups. Figure 13 shows the social class breakdown of EC users by quarter over time, also derived from STS data.

Figure 13: E-cigarette use by social class over time (STS data)



From www.smokinginengland.info/latest-statistics/

E-cigarette use in other disadvantaged groups

There are no GB data, to our knowledge, on EC use among groups where smoking prevalence is known to be very high, such as offenders and people with serious mental illness. There is emerging evidence on the effectiveness of EC in people with mental illness (see Chapter 6). However, to some extent, usage among these groups will be dependent on EC policies being introduced in prisons and mental health settings.

Recent NICE guidance on smoking cessation in secondary care settings [30] recommended the implementation of smokefree policies in these settings, alongside advice to stop smoking and nicotine dependence treatment. Trusts are now implementing this guidance but many prohibit EC usage as well as cigarettes. The rationale for such prohibition is unclear.

The South London and Maudsley NHS Foundation Trust (SLaM) was the second NHS mental health trust to go comprehensively smoke free in England. It has developed an EC policy alongside the smokefree policy which allows EC to be used in private spaces or grounds, although EC are not to be offered as first line treatment or replace tobacco cigarette smoking and can only be used as part of a care treatment pathway [31]. Currently, the use of disposable products or rechargeable models with cartridges is allowed (the latter only under supervision), but tanks are prohibited because of fears

that they might be used for new psychoactive substances (sometimes also known as ‘legal highs’). The basis for this fear is being assessed and the use of tank models may be assessed in a restricted pilot shortly. During the first six months of the policy, the EC policy has been implemented smoothly.

A more general concern has been raised that EC can be used as a vehicle for other drugs. This concern needs exploring and is not something that should be promoted. Nevertheless, if true, EC are likely to offer a less harmful delivery route for the drugs than smoking which could be the subject of research.

Prisons are likely to introduce comprehensive smokefree policies over the next few years [32]. Similar to mental health trusts, it would seem inappropriate to prohibit EC and disposable EC are currently being piloted in at least three prisons [33]. Consideration should also be given to the use of other models of EC in pilots. The use of EC in prisons has been considered in other jurisdictions which should also be informative [34].

Summary of findings

Smoking is increasingly concentrated in disadvantaged groups who tend to be more dependent. EC potentially offer a wide reach, low-cost, intervention to reduce smoking and improve health in disadvantaged groups.

Some health trusts and prisons have banned the use of EC which may disproportionately affect more disadvantaged smokers.

Policy implications

- Consideration could be given to a proactive strategy to encourage disadvantaged smokers to quit smoking as quickly as possible including the use of EC, where appropriate, to help reduce health inequalities caused by smoking.

- EC should not routinely be treated in the same way as smoking. It is not appropriate to prohibit EC use in health trusts and prisons as part of smokefree policies unless there is a strong rationale to do so.

6. E-cigarettes and smoking behaviour

Introduction

Studies examining the relationship between EC use and smoking behaviour have focused on two main questions to date: (1) do EC help people to quit when used on a quit attempt, and, (2) what is the effect of using EC while smoking, on reductions in smoke intake, cigarettes per day, quit attempts, and stopping smoking? Because EC use is a relatively new phenomenon and the products are constantly changing with technological innovation, the studies examining these questions to date are heterogeneous. As mentioned earlier, studies vary in their definitions of EC use, including ever use, which could include one puff, to studies that discriminate between daily and non-daily use. Additionally, it is evident that many of the studies were not originally designed to study the effects of EC use on smoking behaviour due to the absence of rigour and omitted/unmeasured variables.

Current recommendations for use of e-cigarettes to quit

The National Centre for Smoking Cessation and Training (NCSCT) has published current recommendations for practice regarding the use of EC for stopping smoking [35]. The NCSCT recommends that practitioners be open to EC use among smokers trying to quit, particularly if they have tried other methods of quitting and failed. The NCSCT also provides more detailed guidelines for smokers wanting to use EC to quit, including differences in puffing on EC versus regular cigarettes, the need to try different types of EC to find one that works for them, and that multi-sessional behavioural support is likely to improve their success of quitting. Some services have welcomed smokers who wish to stop with the help of EC [36].

The NICE guidelines for tobacco harm reduction cover recommendations for the use of *licensed* EC for quitting, cutting down (reduction in cigarettes per day), and temporary abstinence [1], similar to NRT. Use for both cutting down and temporary abstinence have been shown to be precursors to quitting among smokers using NRT. As discussed in Chapter 3, no licensed EC are currently available.

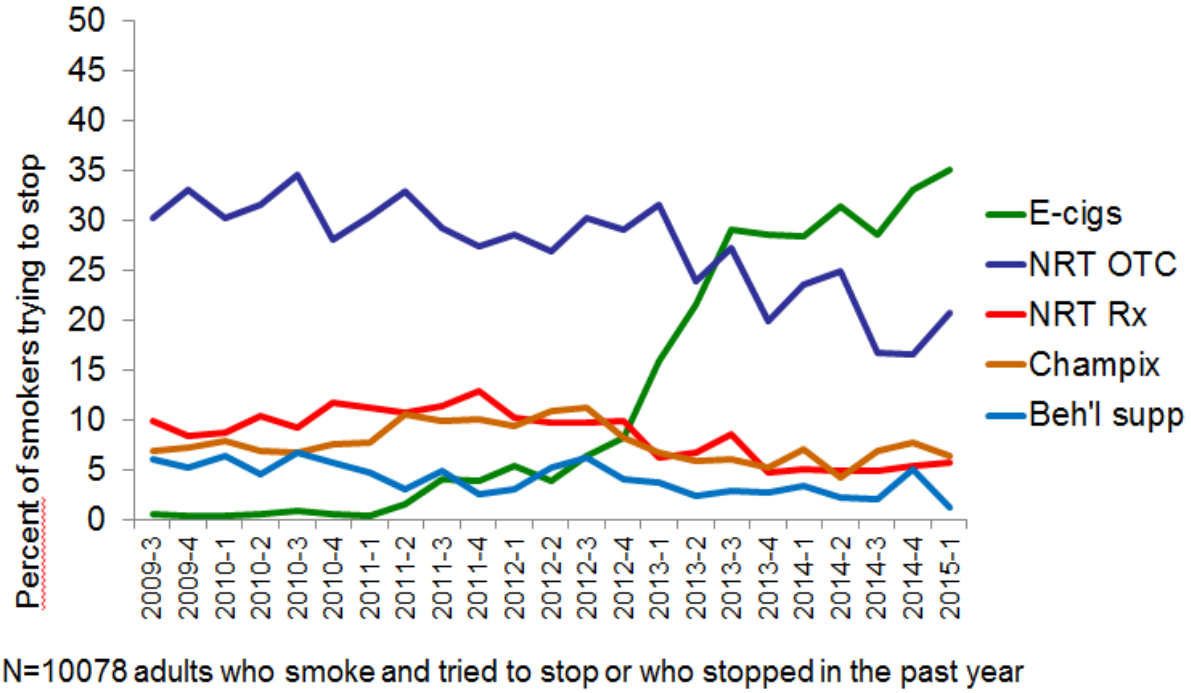
Use of e-cigarettes for stopping smoking

STS data have shown that EC have quickly become the most common aid that smokers in England use to help them stop smoking (Figure 14). The rise in the use of EC as a stop smoking aid is occurring despite the fact that no licensed EC are available. Although the most effective way for stopping smoking, currently supported by the research literature [37, 38] is a combination of behavioural support (NHS in Figure 14)

and medication (NRT on prescription or Champix), the problem is that few smokers access these services, limiting their impact on population health.

This section reviews the evidence regarding the use of EC for stopping smoking that has been published since the Cochrane Review [39] on the use of EC for smoking cessation and reduction (cutting down). The Cochrane Review is briefly summarised below.

Figure 14: Support used in quit attempts



From: smokinginengland.info/latest-statistics

Randomised controlled trials

To date, two randomised controlled trials (RCTs) have tested the efficacy of EC for stopping smoking, one among smokers wanting to stop and the other among smokers not intending to quit within the next month [40, 41]. Both were among highly dependent smokers. A recent Cochrane Review of these RCTs [39] concluded that they demonstrated that EC with nicotine help smokers reduce their cigarette consumption and stop smoking compared with no nicotine EC (placebo). However, the authors cautioned that there was uncertainty in the findings, and gave their findings a 'low' confidence rating using GRADE standards. The Cochrane Review also considered observational studies of EC use and cessation. They concluded that these observational studies were generally consistent with the findings of RCTs. Since the Cochrane Review, one RCT[41], and a secondary analysis of one of the RCTs in the Cochrane Review[42] have been published and are discussed below.

O'Brien et al., 2015 [42] conducted a secondary analysis of the RCT data from Bullen et al., 2013 [43] to examine the effectiveness of EC with and without nicotine compared to the nicotine patch among individuals with mental illness (MI). They identified 86 participants among the original 657 participants (all motivated to quit) using secondary data from the trial on reported use of any medications associated with MI. Overall, when compared to participants without MI, there were no significant differences for those with MI on the primary outcomes of smoking reduction and smoking cessation. One exception was that the six-month quit rate was higher among participants with MI in the patch condition compared to those without MI. Although not a primary outcome, there was evidence of a greater rate of relapse among participants with MI. In the analysis that only included participants with MI, there were no significant differences in quit rates across the three conditions, however participants allocated to 16mg EC showed greater smoking reduction than those allocated to patch. **The authors concluded that EC appear to be equally effective for smoking cessation among individuals with and without MI**, building on other promising research involving EC and people with MI.

Adriaens et al., 2014 [41] conducted an eight-week RCT in Belgium with control where they randomised 48 smokers **who did not want to quit** to one of two conditions: (1) use of tank model EC, and training on how to use, with no encouragement to quit, and (2) no use of EC. Both groups attended similar periodic lab sessions over an eight-week period where measurements of craving, withdrawal, saliva cotinine, and expired-air CO levels were taken. Adriaens found that after eight weeks of use 34% of those given EC had quit smoking compared to 0% of those not given EC, the EC group also showed substantially greater cigarette reduction. After eight weeks, the group which did not receive EC at baseline was given EC, but no training on how to use the products. At the final eight-month follow-up, 19% of the original EC group and 25% of the control group (given EC at week eight) had quit smoking. Significant reductions in cigarette consumption were also found.

Population studies

One problem with RCTs is that because of the time taken to set up and implement trials, the EC used in the trials are often no longer available for sale by the time the research is published. This is problematic because many new EC enter onto the market and it is possible they may be more effective at delivering nicotine than the products used in the trial, and possibly more effective for smoking cessation. Additionally, the controlled environment of RCTs is unable to provide evidence of the effectiveness of EC in the real world where use is much more subject to external forces, such as availability, price and social norms around use. RCTs also reveal little about the attractiveness of the products and thus likely uptake of the products used and what happens after a successful or failed attempt to stop smoking with an EC in the long-term.

Observational and natural history studies are therefore important. Only one population-based survey has examined the effectiveness of EC used during quit attempts. A large cross-sectional study of 5,863 English smokers who attempted to quit in the past year without using professional support [29] found that those who used EC on their last quit attempt were more likely to quit than those who used over the counter NRT – (the most common help sought by smokers after EC, see Figure 14), or no quit aid, controlling for factors related to quitting. This study was, however, unable to explore prospective predictors of quitting, including pre-quit nicotine dependence. Still, this study offers some of the best evidence to date on the effectiveness of EC for use in quit attempts.

Other recent population studies [16, 44, 45] have also examined the association between EC use and quitting. However, because these studies (1) included smokers who were already using EC at baseline, and (2) did not examine the use of EC during a specific quit attempt, we discuss them below in the section on use of EC while smoking.

Pilot studies

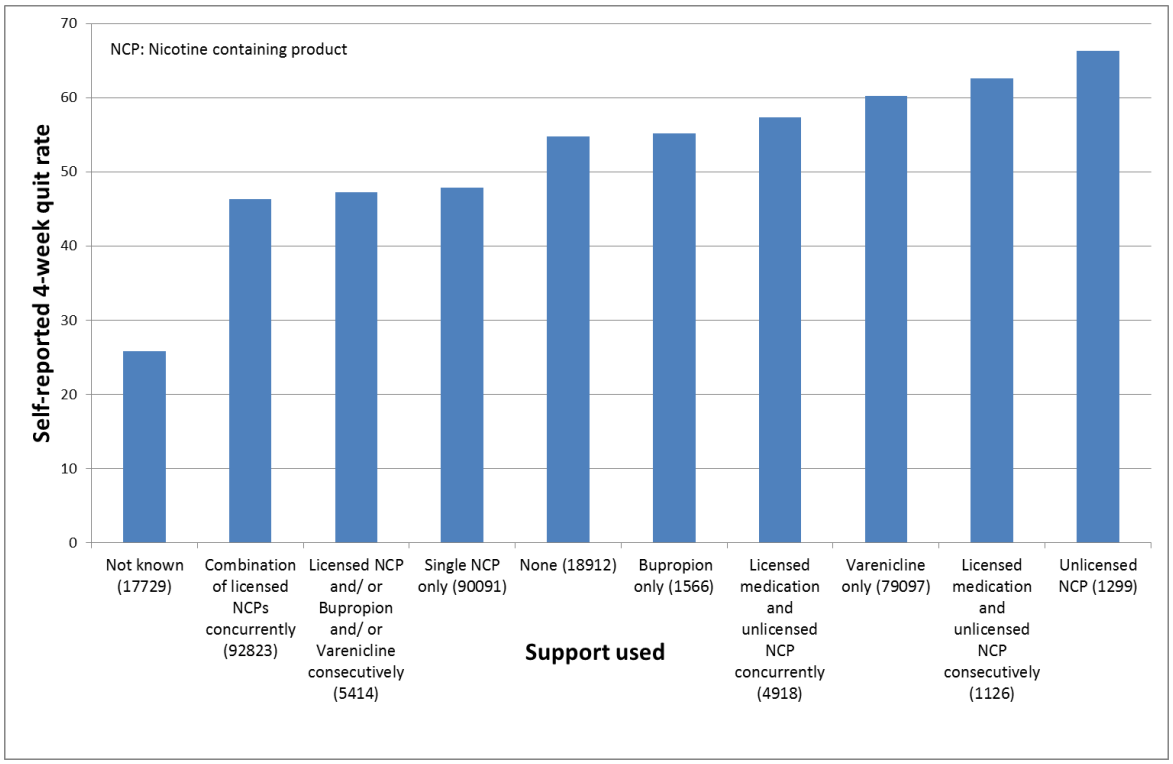
Polosa et al., 2014 [46] conducted a six-month pilot study of tank-type EC users with no control group among 72 smokers **who did not want to quit (smokers were enrolled after rejecting participation in smoking cessation program at a hospital)**. At six months, they found significant 50% and 80% reductions in cigarette consumption, and a quit rate of 36% [46]. Another study by Polosa et al., 2014 [47] followed 71 vape shop customers (seven different shops) after their first visit to the shop. The first visit included instructions on how to use EC and encouragement to use their EC of choice to reduce their smoking, along with a telephone number they could call for help. At six and twelve months after their initial visit they found that the smokers reported significant 50% and 80% reductions in cigarettes per day at six and twelve months, and that at six and twelve months, 42.2% and 40.8% had quit smoking.

E-cigarettes and stop smoking services

Some English stop smoking services and practitioners support the use of EC in quit attempts [48], and provide behavioural support for EC users trying to quit smoking. The most recent monitoring data from the stop smoking services show the self-reported success rates for different medications and nicotine-containing products used (Figure 15). Data are not given by validated success rates but overall, 69% of those who self-report stopping smoking are carbon-monoxide validated [49]. Hence, there are limitations with these data as they are self-reported success rates and it is possible that they may vary by treatment used. Additionally, the data are not adjusted for other factors, such as dependence, known to influence success rates, and it is likely that they emanate from a limited number of services who record unlicensed nicotine-containing products and who might therefore be more supportive of their use. Nevertheless, the

evidence is consistent with evidence from trials and other observational data that e-cigarettes are likely to support successful quitting.

Figure 15: Support used and stop smoking service self-reported quit rates[3]



Note: Figures in brackets represent the number of quit attempts in which each type of support was used. The number of clients with recorded e-cigarette use is very small in comparison to those recorded to have used other types of support.

Use of e-cigarettes while smoking

Population studies

Two studies using data drawn from a longitudinal population sample of more than 1,500 smokers in GB recently examined the impact of EC use on quitting, considering the effects of frequency of EC used and type of EC. Brose et al., 2015 [45] found that respondents who used EC daily at baseline were more likely to make a quit attempt one year later, but were no more or less likely to quit than those who did not use EC. Daily EC use at follow-up was found to be associated with reduced cigarette consumption since baseline. No effects of non-daily EC use on quit attempts, quitting, or reduction in consumption were found. Using data from the same Internet Cohort GB study, Hitchman et al., 2015 [16] found differences in quitting between baseline and follow-up

[3] Taken from Health and Social Care Information Centre. Statistics on NHS Stop Smoking Services in England - April 2014 to December 2014.Publication date: April 23, 2015 Source: Ref 47. http://www.hscic.gov.uk/catalogue/PUB17302

depending on the type and frequency of EC used at follow-up: compared to no EC use, non-daily cigalike users were less likely to have quit smoking since baseline, daily cigalike or non-daily tank users were no more or less likely to have quit, and daily tank users were more likely to have quit. Overall, the two studies showed that daily use of EC does not lead to lower cessation, and is associated with making quit attempts, cigarette reduction, and if tank-type EC is used, is associated with smoking cessation. Non-daily use of EC is not associated with quit-related outcomes, and may, if cigalike-type EC are used, be associated with lower cessation.

Supporting these findings, using data from a longitudinal population study of smokers in two metropolitan areas in the US, Biener et al., 2015 [44] measured use and intensity of EC use at *follow-up* in a longitudinal sample of smokers at baseline from two US cities. Biener also found that it was only intensive EC users (used daily for at least one month) that were more likely to quit, less intensive EC users were no more likely to quit than those not using EC.

There are limitations with these studies. For example, an unavoidable methodological problem is that only people who currently smoke are included in these studies meaning that smokers who switched completely to EC and stopped smoking are excluded. The efficacy of EC is thus invariably underestimated.

A longitudinal telephone survey reported by Al-Delaimy et al., 2015 [50] among a sample of 368 current smokers from California at baseline (2011) investigated the relation between '*ever have used*' versus *'never will use'* EC, and making a quit attempt, a 20% reduction in cigarettes per month, and quitting for more than one month at follow-up (2012). Al-Delaimy included smokers at baseline who at both baseline and follow-up reported the same EC status: never will use EC at both baseline and follow-up OR ever have used EC at both baseline and follow-up, excluding anyone who gave different responses. Also excluded were respondents who said they might use EC in the future at baseline or follow-up, and respondents who had never heard of EC, reducing sample size from n=980 to n=368. Al-Delaimy concluded that compared to smokers who reported they never will use EC, respondents who had ever used EC were significantly less likely to have reduced their cigarette consumption and quit at follow-up, with no differences reported of quit attempts at follow-up. This study has serious methodological problems that make its conclusions uninterpretable, first, the measure of EC use is 'ever use', which could include even a puff on an EC and second, they applied several exclusion criteria that are not clearly justified.

Studies of smokers enrolled in smoking cessation programs

Two recent studies have examined the use of EC among smokers enrolled in smoking cessation programmes in longitudinal studies [51, 52]. Pearson et al., 2015 [51] examined the relation between reporting using an EC for quitting at follow-up and

smoking cessation (30-day abstinence) in a sample of smokers enrolled in a web-based cessation programme in the US with three-month follow-up. Pearson illustrated how the relation between using EC to quit and successful smoking cessation depended on the factors that were adjusted for and how the data were analysed, finding that under some conditions EC use was related to being less likely to quit and in others there was no relationship. The authors concluded that caution needs to be exerted when interpreting observational studies of the effects of EC use on smoking cessation.

Borderud et al., 2014 [52] examined whether any use of EC in the past 30 days was related to smoking cessation outcomes in a group of cancer patients enrolled in a smoking cessation programme in the US. When treating all smokers who dropped out of the study as smoking cessation failures, the authors found that any use of EC in the last 30 days was related to being less likely to quit; however, this treatment of the data may have been problematic because more EC users than non-users dropped out of the study. No relationship between EC use in the last 30 days and smoking cessation was observed when drop-outs were excluded from the analyses. One potential problem with this study is the measure of any EC use in the last 30 days, as this could range from using an EC once in the last 30 days to using an EC daily for the past 30 days. As illustrated [16, 44, 45] and discussed in previous studies [51], measurements of EC use that do not fully capture frequency of use may influence the relation between EC use and smoking cessation. As with studies in the previous section, the Borderud study started with smokers who had tried EC but did not stop smoking. This, of course, seriously reduces the chance of detecting a positive effect.

Summary of findings

Recent studies support the Cochrane Review findings that EC can help people to quit smoking and reduce their cigarette consumption. There is also evidence that EC can encourage quitting or cigarette consumption reduction even among those not intending to quit or rejecting other support. It is not known whether current EC products are more or less effective than licensed stop-smoking medications, but they are much more popular, thereby providing an opportunity to expand the number of smokers stopping successfully. Some English stop smoking services and practitioners support the use of EC in quit attempts and provide behavioural support for EC users trying to quit smoking; *self-reported* quit rates are at least comparable to other treatments. The evidence on EC used *alongside smoking* on subsequent quitting of smoking is mixed.

Policy implications

- Smokers who have tried other methods of quitting without success could be encouraged to try EC to stop smoking and stop smoking services should support smokers using EC to quit by offering them behavioural support.

- Research should be commissioned in this area including:
  - longitudinal research on the use of EC, including smokers who have not used EC at the beginning of the study
  - the effects of using EC while smoking (temporary abstinence, cutting down) on quitting, and the effects of EC use among ex-smokers on relapse
  - research to clarify the factors that i) help smokers using EC to quit smoking and ii) deter smokers using EC from quitting smoking, including different EC products/types and frequency of use and the addition of behavioural support, and how EC compare with other methods of quitting which have a strong evidence base

- It would be helpful if emerging evidence on EC (including different types of EC) and how to use EC safely and effectively could be communicated to users and health professionals to maximise chances of successfully quitting smoking.

7. Reasons for use and discontinuation

Reasons for using e-cigarettes

Reasons for using EC have been assessed for adult smokers and ex-smokers in a number of different ways. Across different populations, help to quit smoking and harm reduction were the top reasons endorsed for using EC [44, 53-57].

In the Internet Cohort GB survey, the list of possible reasons for using EC was extended after the first year (the survey was carried out in 2012, 2013 and 2014). Nevertheless, the most frequently endorsed reasons were health, to cut down and to quit smoking. These were endorsed by approximately 80% of current users at all three time points. The biggest change over time was recorded for '*they are cheaper'* which appeared to be more popular in 2014 than 2013 (Table 3). Because of the way the question is phrased, a user endorsing a reason does not indicate that current use is for this particular reason, for example, 80% of current users agree that e-cigarettes may help you quit, but this does not mean that 80% of all users were using them in a quit attempt.

Table 3: Internet cohort GB survey, reasons for using e-cigarettes (in order of frequency of endorsement in 2014)

Which of the following were reasons for your using electronic cigarettes? (multiple responses possible)	2012 (n=1031)	2013 (n=717)	2014 (n=505)
They may make it easier for you to cut down the number of cigarettes you smoke	81.0	78.1	79.4
They may not be as bad for your health	81.7	79.8	79.2
They might help you quit	81.8	79.9	79.0
No tobacco smoke	not asked	70.9	71.3
They are cheaper	not asked	36.1	65.5
The smell or cleanliness	not asked	65.4	65
So you can use them in places where smoking regular cigarettes is banned	67.2	66.5	61
They may be more socially acceptable	not asked	55.8	54.3
Because I enjoy it	not asked	38.6	48.7
They taste better	28.5	26.1	34.1
Friends or family use them	not asked	37.0	33.3
The technology	not asked	34.2	30.3
A health professional advised you to do so	not asked	16.7	16.4

The ASH Smokefree GB survey similarly found that EC users who were ex-smokers most frequently endorsed that they used or had used EC to help them stop smoking entirely (Table 4). Among smokers, this was the second most frequently endorsed reason, with curiosity being the most frequent reason. Smokers also often reported use to help them cut down on smoked tobacco, which was rarely reported by ex-smokers.

Table 4: Reasons for use, ASH Smokefree GB adult survey, 2015 (weighted)

I use/used electronic cigarettes…	Smokers	Ex-smokers
Just to give it a try	35%	29%
To help me stop smoking tobacco entirely	30%	44%
To help me reduce the amount of tobacco I smoke, but not stop completely	29%	9%
Because I had made an attempt to quit smoking already and I wanted an aid to help me keep off tobacco	27%	35%
To save money compared with smoking tobacco	24%	22%
Because I felt I was addicted to smoking tobacco and could not stop using it even though I wanted to	16%	17%
Because I want to continue to smoke tobacco and I needed something to help deal with situations where I cannot smoke (e.g. workplaces, bars or restaurants)	15%	8%
To avoid putting those around me at risk due to second-hand tobacco smoke	12%	13%
Other	1%	3%

A smaller number of surveys specifically assessed reasons for trial and gave the option of selecting curiosity, which was frequently endorsed as an important reason for experimentation in US adults from the general population as well as in a sample of opioid-dependent smokers [58-60].

In youth, reasons for use has rarely been surveyed; one survey on reasons for experimentation among 1,175 students (middle school, high school and college) who had ever tried EC reported that the top three reasons for e-cigarette experimentation were curiosity (54.4%), the availability of appealing flavours (43.8%) and friends' influence (31.6%). Compared with never smokers, however, ever cigarette smokers (OR=37.5, 95% CI: 5.0 to 283.3) and current cigarette smokers (OR=102.2, 95% CI: 13.8 to 755.9) were many times more likely to say they tried EC to stop smoking [61].

A national survey in New Zealand of 3,127 year 10 students (mostly aged 14 to 15) also showed that the most frequently given reason for first trying EC was curiosity, irrespective of smoking status (64.5% overall) [62].

Reasons *not* to use EC are rarely assessed. The ASH Smokers' survey 2014 asked current and ex-smokers about advantages and disadvantages of EC. Among those who had never used EC, the three most important disadvantages were "*They might be too expensive*" (46%), "*They might not be safe enough as a product*" (39%) and "*They might not satisfy my desire to smoke enough*" (31%).

Reasons why trial does not become use

The rates of ever having tried an EC in the ASH GB Smokefree adult survey are more than three times those of current use; in the ASH GB Smokefree youth survey, about five times as many respondents had tried an EC as were currently using an EC, indicating that **most of those who try EC do not progress to current use**. A small number of surveys assessed why respondents who had tried an EC did not continue use.

In a national sample of 3,878 US adults who reported ever trying EC, two-thirds did not continue to use them and this was linked to the main reason for trying them. Trial turned into continued use for only a minority (19%) of those who did not know their main reason for trying them or whose main reasons were curiosity, friends or family members or advertising. Continued use was more common for those whose main reasons for trial included help to quit smoking or reduce harm. Those who did not continue use were asked for their reasons for stopping. The reason most often given was that they were just experimenting (49%) [58].

In the survey by Kong et al., reported previously, it appears that 98.5% of experimenting students did not continue use. Reasons for discontinuation were assessed but unfortunately the most commonly chosen response was 'other' (23.6%, open-ended responses included "I don't like it", "I just tried once") followed by "uncool" (16.3%) and health risks (12.1%) [61].

Some surveys can be used to assess why smokers may not continue to use EC. The ASH Smokers' survey in 2014 indicates that disappointment with the help EC provide in reducing smoking urges may be an important reason. Among smokers who had tried EC but did not continue using them, 44% said that a disadvantage of the products was that "*They might not satisfy my desire to smoke enough*". No other reason got a higher rate of agreement in this group. A high proportion of smokers who were currently using EC also stated this reason (37%), but the proportion was significantly ($p<0.05$) lower in ex-smokers who had used (32%) or were currently using EC (7%), suggesting that satisfaction with the device/s may be a correlate of stopping smoking.

Of concern is that data suggest that some smokers may not continue to use EC instead of smoking because of a misguided belief that EC would be harmful to their health. In the ASH Smokers' survey 2014, the second most frequently endorsed disadvantage was "*They might not be safe enough as a product*" (35%) among smokers who had tried an EC but were not using one anymore. Similarly, in a survey of US respondents, among 227 respondents who had tried EC in the past, were no longer using them but were still smoking cigarettes [44], the most frequently endorsed reason was that EC didn't feel enough like smoking cigarettes, followed by dislike of the taste and that they were bad for health. It would appear therefore that these respondents stopped EC use in favour of continuing to smoke more deadly cigarettes.

Summary of findings

A number of surveys in different populations provide evidence that reducing the harm from smoking (such as through cutting down on their cigarette consumption or helping with withdrawal during temporary abstinence) and the desire to quit smoking cigarettes are the most important reasons for using EC. Curiosity appears to play a major role in experimentation. Most trial of EC does not lead to regular use and while there is less evidence on why trial does not become regular use, it appears that trial due to curiosity is less likely to lead to regular use than trial for reasons such as stopping smoking or reducing harm. Dissatisfaction with products and safety concerns may deter continued EC use.

Policy implications

- Smokers frequently state that they are using EC to give up smoking. They should therefore be provided with advice and support to encourage them to quit smoking completely.

- Other reasons for use include reducing the harm from smoking and such efforts should be supported but with a long-term goal of stopping smoking completely.

8. Harm perceptions

Perceptions of the harmfulness of EC are frequently assessed in surveys, most commonly relative to conventional tobacco cigarettes. However, a recent Eurobarometer survey [63] asked smokers in absolute terms whether EC were harmful to the health of those using them. Overall in Europe, 40.6% perceived EC as not harmful (UK: 48.6%), 28.5% as harmful (UK: 14.6%) and 30.9% did not know if they were or were not harmful (UK: 36.8%).

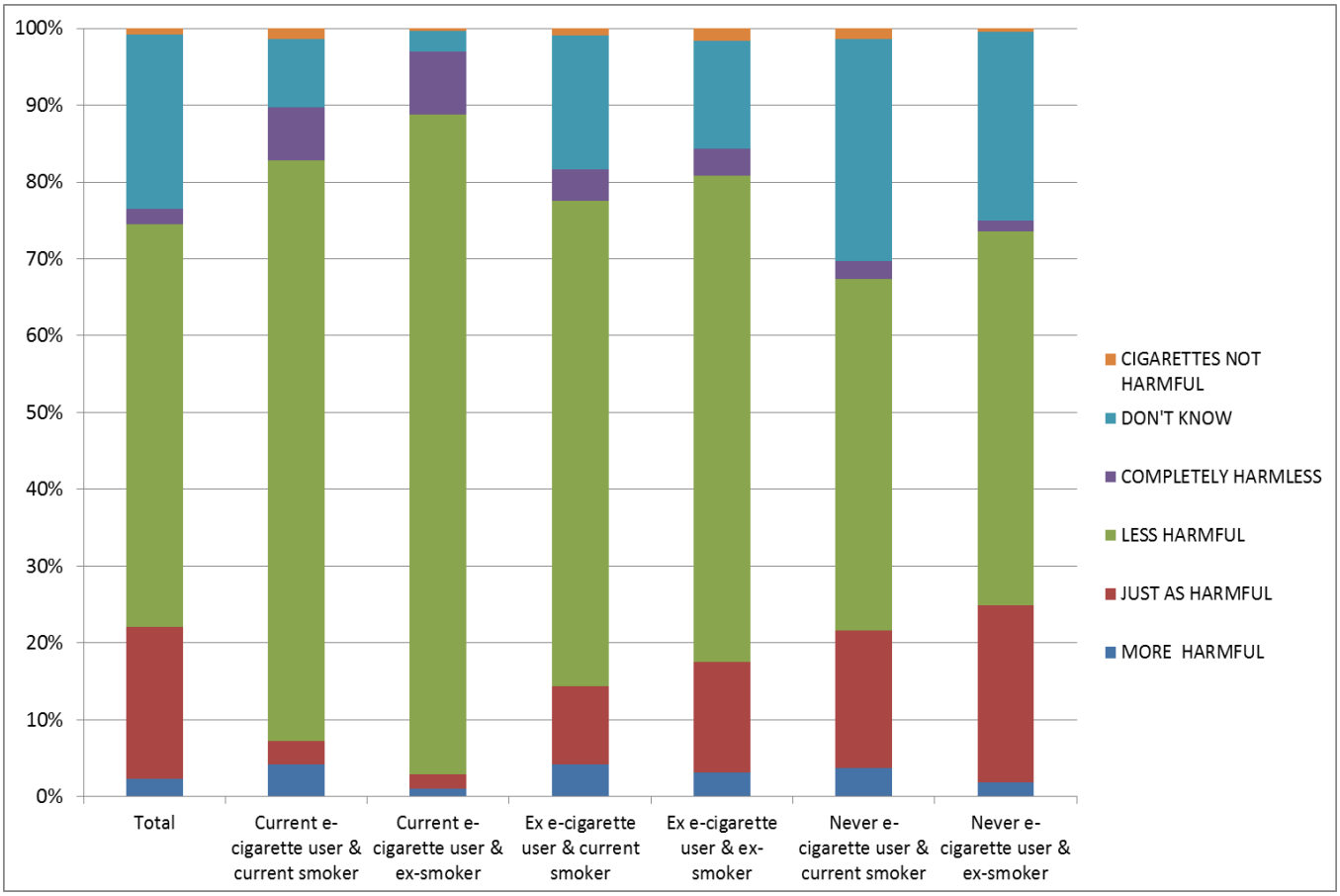
Harm perception relative to cigarettes

In GB, the ASH surveys and the Internet Cohort survey have included questions on the perceived relative harm of EC. These surveys consistently show that compared with conventional tobacco products, EC were perceived as less harmful by a small majority of respondents, **but with a sizeable minority inaccurately judging them to be more harmful, about as harmful or being unsure about their relative risks**. For example, in the 2015 ASH Smokefree GB adult survey, 2% thought that EC were more harmful than cigarettes, 20% equally harmful, 52% less harmful, 2% completely harmless and 23% did not know.

Harm perception differed by smoking status ($\chi 2=104.05$, $p<0.001$) and by EC use status ($\chi^2=453.4$, $p<0.001$) (Figure 15). Overall, smokers were more likely to judge EC to be less harmful compared with cigarettes (63.7%, including 'completely harmless') than ex-smokers (55.6%), whereas never-smokers were least likely to judge EC as less harmful (51.2%, all $p<0.05$). A higher proportion of current EC users (87.4%) thought that they were less harmful compared with cigarettes than those who had tried but were not using (68.8%) or never-users (50.4%), among whom the proportion was lowest (all differences $p<0.05$). Perceptions among youth were similar to adults. For example, in the 2015 ASH Smokefree GB youth survey, 2% thought that EC were more harmful than cigarettes, 21% equally harmful, 67% less harmful and 10% did not know.

In the STS, the proportion believing EC to be less harmful appears to be even lower. Only 44.1% of current smokers in England between November 2014 and March 2015 believed that EC were less harmful than cigarettes [15].

Figure 15: Perceptions of relative harmfulness of e-cigarettes in comparison with tobacco cigarettes by e-cigarette use and smoking status. ASH Smokefree GB adult surveys (weighted)



Trends in harm perceptions relative to cigarettes over time

Since 2013, perceptions of the relative harmfulness of EC have become less accurate. Significantly larger proportions perceived EC to be at least as harmful as cigarettes in 2014 than in 2013 both in the Internet Cohort GB surveys (Figure 16) and in the ASH youth surveys (Figure 17 [64]). In the Internet Cohort GB survey, there was no significant change from 2012 to 2013, but from 2013 to 2014 the proportion thinking that EC were less harmful decreased in favour of equally or more harmful ($p<0.001$). For youth, between 2013 and 2014, the decrease in the proportion endorsing 'less harmful' and the increase in the proportion endorsing 'equally harmful' were significant ($p<0.01$). There were no significant changes in the proportion endorsing 'more harmful' or 'don't know'.

In the ASH adult surveys, data on harm perception are available for 2013 to 2015 (Figure 17). In line with the other GB surveys, this survey found a steep increase in the proportion perceiving EC to be equally harmful as cigarettes ($p<0.001$).

Figure 16: Perceptions of relative harmfulness of e-cigarettes in comparison with tobacco cigarettes. Internet Cohort GB surveys (N=1,209 respondents with data at all three time points)

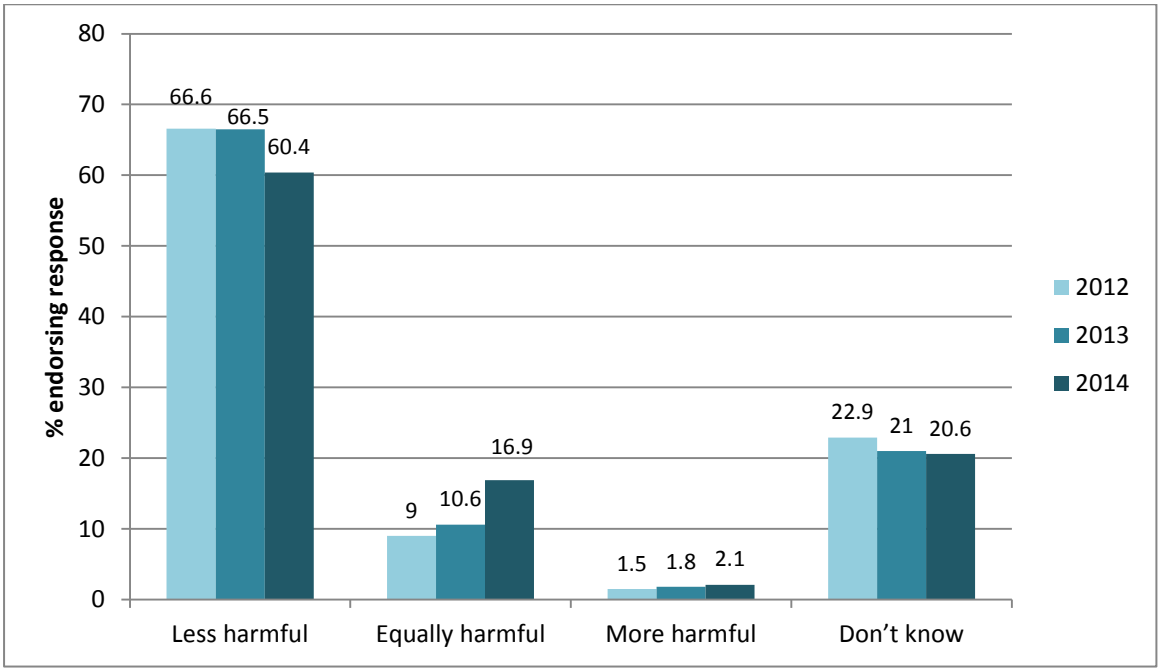
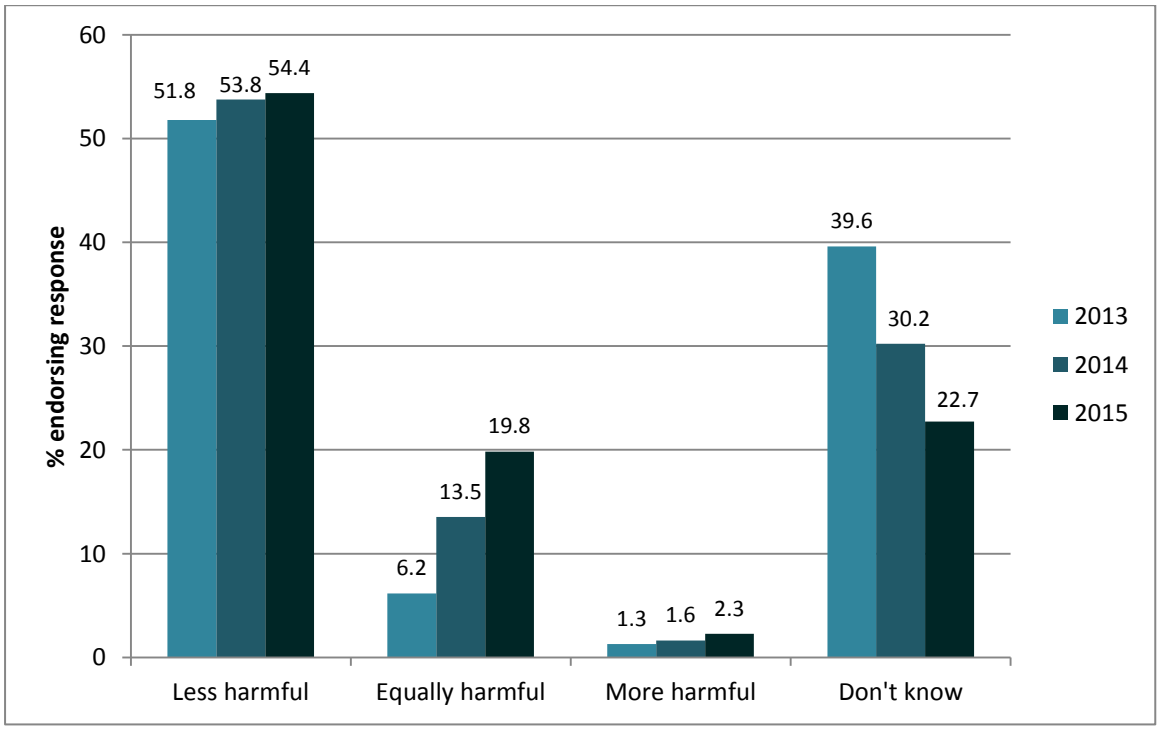
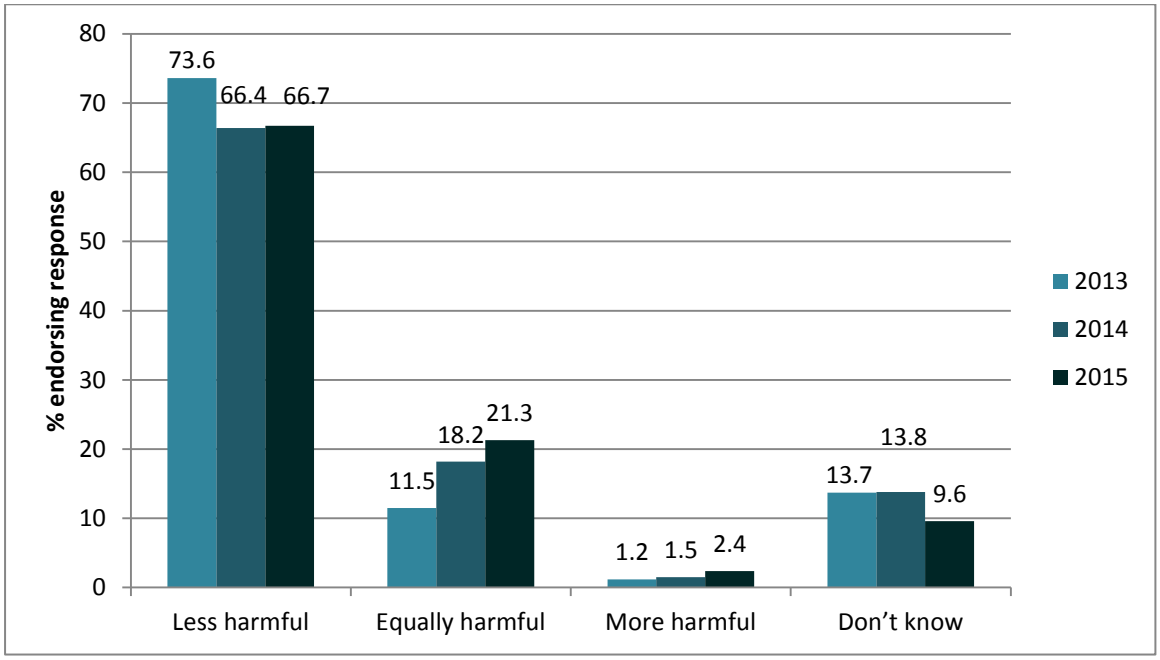


Figure 17: Perceptions of relative harmfulness of e-cigarettes in comparison with tobacco cigarettes. ASH Smokefree GB adult surveys (weighted)



Notes: "Less harmful" includes those saying "Electronic cigarettes are completely harmless". "Not applicable – I do not think regular cigarettes are harmful" not shown (2013: 1.2%, 2014: 0.9%, 2015: 0.8%)

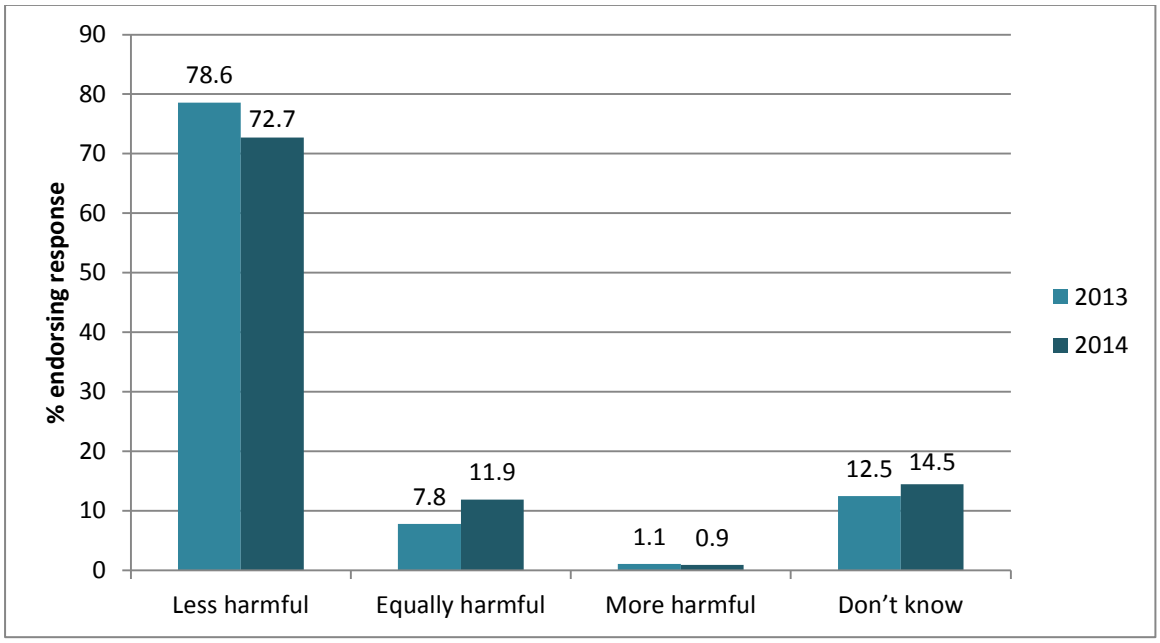
Figure 18: Perceptions of relative harmfulness of e-cigarettes in comparison with tobacco cigarettes. ASH Smokefree GB youth surveys (2013 and 2014) taken from Eastwood et al., in press[64].



Surveys from the US also suggest that from 2010 to 2013, the proportion of current smokers aware of EC who believed that EC were less harmful than smoking cigarettes declined considerably [65]. Youth in the US appear to have a less realistic perception of the relative harm of EC compared with cigarettes than UK youth. In the 2012 National Youth Tobacco Survey, of those who were aware of EC, around one-third perceived them to be less harmful than cigarettes and around half were unsure [66, 67].

The ASH Smokefree GB youth survey in 2013 and 2014 further included a question on the harm of EC to persons around a user. Again, the proportion who thought them less harmful than traditional cigarettes decreased from 2013 to 2014 ($p<0.05$), and the proportion who thought they caused similar levels of harm increased ($p<0.01$) (Figure 19).

Figure 19: Perceptions of relative harmfulness of e-cigarettes to people around the user. ASH Smokefree GB youth surveys



Harm perception relative to nicotine replacement therapy (NRT)

The ASH Smokers' survey in 2014 asked respondents about their perception of EC compared with NRT (Table 20). The largest group of respondents thought EC were about as safe. Notably, a higher proportion thought that EC were safer than NRT than believed that NRT was safer than EC. This was particularly pronounced in current EC users.

Table 5: Relative harm perception by e-cigarette use status ASH Smokers' survey 2014

	E-cigarette use status			
	Never	**Current**	**Ex**	**Total**
	39.10%	**21.30%**	**39.70%**	
	(n=470)	**(n=256)**	**(n=477)**	**(n=1203)**
Compared to NRT				
Safer	14 (66)	28.1 (72)	22 (105)	**20.2 (243)**
About as safe	28.1 (132)	44.1 (113)	35.6 (170)	**34.5 (415)**
Less safe	16.2 (76)	6.3 (16)	13 (62)	**12.8 (154)**
Don't know	41.7 (196)	21.5 (55)	29.4 (140)	**32.5 (391)**

One US survey of 1,400 current and former smokers also assessed expected outcomes of using EC compared with NRT [68]. EC were perceived to be less risky, cost less, cause fewer negative physical feelings, taste better, provide more satisfaction, and be better at reducing craving, negative affect, and stress.

Summary of findings

Although the majority of adults and youth still correctly perceive EC to be less harmful than tobacco cigarettes, there has been an overall shift towards the inaccurate perception of EC being at least as harmful as cigarettes over the last year, for both groups. Intriguingly, there is also some evidence that people believe EC to be less harmful than medicinal nicotine replacement therapy (NRT).

Policy implications

- Clear and accurate information on relative harm of nicotine, EC and tobacco cigarettes is needed urgently (see also Chapter 10).
- Research is needed to explore how health perceptions of EC are developed, in relation to tobacco cigarettes and NRT, and how they can be influenced.

9. E-cigarettes, nicotine content and delivery

Background

We have undertaken a review of available evidence concerning nicotine released by EC. The review is divided into four parts, covering nicotine that EC use (vaping) releases into ambient air, nicotine content of e-liquid, nicotine content in e-vapour, and nicotine delivery to EC users (vapers). The main concern with nicotine in EC relates to the question of whether EC use exposes users or bystanders to the risk of nicotine poisoning. For this reason, we start with a short introductory review of this topic.

Toxicity of nicotine

Nicotine in the form of tobacco and more recently NRT has been available to thousands of millions of people and large numbers of them, including small children, have ingested considerable doses of nicotine. Fatal nicotine poisoning, however, is extremely rare. This fact strongly contradicts the often-repeated claim that an ingestion of 30-60mg of nicotine is fatal. The source of this claim proved difficult to locate – textbooks just cite older textbooks. Eventually, the assertion was found to be based on dubious self-experiments conducted in the 1890s [69].

We are aware of one unconfirmed newspaper report of a fatal poisoning of a two-year old child [70] and of three published case studies of small children who drank e-liquid. A two-year old was admitted to hospital with vomiting, ataxia, and lethargy, and was discharged after 24 hours of observation [71]. In the second report, an 18-month old girl drank 24mg nicotine in e-liquid, vomited and was irritable, and recovered fully within an hour or so [72]. The third article presented a case of a 30-month old child suspected to have ingested e-liquid. The quantity of e-liquid was uncertain and the child was asymptomatic with all clinical observations reported to be normal [73].

With the increase in EC use, there has been an increase in calls to poison centres following accidental exposures but these remain lower than calls following such exposure from tobacco and none resulted in any serious harm [74] (see next chapter for UK data). Serious nicotine poisoning seems normally prevented by the fact that relatively low doses of nicotine cause nausea and vomiting, which stops users from further intake.

Apart from accidental poisoning, nicotine has also been used in suicide attempts. Suicide attempts with large amounts of pesticides containing nicotine sulphate often succeed [75] but completed suicides using e-liquids are extremely rare. Where adults

drank up to 1,500mg of nicotine in e-liquid, the result was vomiting and recovery within a few hours [76]. One fatal outcome was recorded with 3,950mg of nicotine found in gastric content. The victim seems to have drunk three vials of e-liquid totalling over 10,000mg of nicotine[76]. An intravenous injection of unknown quantity of e-liquid also resulted in death [77].

E-liquid normally comes in 10ml bottles containing up to 360mg of nicotine (see below). This poses no risk to vapers if used as intended. The liquid however should be in 'childproof' packaging to prevent small children, who may find the flavouring appealing, from drinking it. This seems to have been widely accepted by the EC industry. All e-liquids we have seen so far in the UK and globally were sold in child-resistant packaging.

Review methods

We searched the US National Library of Medicine (Pubmed) using the following search terms: ((cotinine OR nicotine) AND (blood OR plasma OR urine OR saliva OR liquid OR aerosol OR pharmacokinetic$)) AND (electronic cigarette$ OR e-cig$ OR ENDS). This search returned 161 records. The abstracts of all records were screened.

Papers were included if they were peer-reviewed and presented data regarding nicotine in e-liquid, aerosol, or body fluids (blood, saliva or urine). Studies that reported data on blood, salivary, or urine cotinine were also included.

A total of 112 records were excluded as they did not contain any relevant information, leaving 49 records. The full papers of these records were retrieved and reviewed.

From the full text review, 25 studies provided data regarding nicotine content of ambient air, e-liquid and vapour, and 16 provided data on nicotine delivery to users. The remaining eight papers did not contain any relevant information. Three further relevant papers were published during the writing of this report and were also included.

Nicotine in ambient air, e-liquid and e-vapour

We identified five studies of nicotine in ambient air, 14 studies of nicotine in e-liquid and nine studies of nicotine vapour. The results are summarised below. We tabulate the results where appropriate and provide a narrative summary where there are only a few studies available. Each section is concluded with a brief summary.

Passive vaping: Nicotine from e-cigarette use in ambient air

Four studies examined nicotine exposure from passive vaping. Long et al., 2014 measured nicotine content of EC exhalations. EC exhalations contained eight times less

nicotine than cigarette exhalations [78]. Estimating environmental nicotine exposure, however, has to take into account the fact that side-stream smoke (ie the smoke from the lighted end of the cigarette, which is produced regardless of whether the smoker is puffing or not) accounts for some 85% of passive smoking and there is no side-stream EC vapour. A study measuring nicotine residue on surfaces in houses of smokers and vapers reported only negligible levels from vaping, 169 times lower than from smoking [79].

Colard et al., 2015 describe a model for estimating environmental workplace exposure [80]. The model predicts much lower nicotine exposure from vaping than from smoking, at levels negligible in health terms.

Goniewicz and Lee 2014 found that nicotine from EC vapour gets deposited on surfaces, but at very low levels [81]. This poses no concerns regarding exposure to bystanders. At the highest concentration recorded (550 µg/m^2), an infant would need to lick over 30 square metres of exposed surface to obtain 1mg of nicotine.

Ballbe et al., 2014 provide the most informative data collected to date as this study measured the actual levels of airborne nicotine in homes of ex-smokers who live either with smokers (N=25) or with vapers (N=5) and also in 24 control homes [82]. The study also measured salivary and urinary cotinine in partners of smokers and vapers. As expected, there was little nicotine in non-smokers' homes. The air in the homes of vapers contained six times less nicotine than the air in the homes of smokers. There was less of a difference between cotinine levels of partners of vapers and smokers (1.4 to 2 fold difference), most likely due to some 'ex-smokers' still occasionally smoking, but even with this possible contamination, the nicotine levels absorbed via passive vaping were negligible. Partners of vapers had mean cotinine concentrations of 0.19 ng/ml in saliva and 1.75 ng/ml in urine, which is about 1,000 times less than the concentrations seen in smokers and similar to levels generated by eating a tomato [83].

Summary

EC release negligible levels of nicotine into ambient air with no identified health risks to bystanders.

Nicotine in e-liquids

Fourteen studies tested more than 400 different e-liquids, mainly to check the accuracy of product labelling. Their results are summarised in Table 6, updated from an earlier review by Cheng et al., 2014 [84].

Table 6: Nicotine in refill solutions, cartridges and aerosols of e-cigarette products
(Adjusted from Cheng et al. 2014)

Study	Matrix	Units	Nicotine level	Maximum deviation from label*
Westenberger [85]	Cartridge	mg/cartridge	0.00 to 6.76	N.A.
	Aerosol	µg/100mLpuff	0.35 to 43.2	N.A.
	Refill solution	µg/mL	N.D. to 25.6	N.A.
	Cartridge	mg/cartridge	0.00 to 6.76	N.A.
Cobb *et al* [86]	Cartridge	mg/cartridge	3.23±0.5 to 4.07±0.54	–80 to –77%†
	Aerosol	µg/35 mL puff	0.3 for puffs 11 to 50 to 1 for puffs 1 to 10	N.A.
Trehy *et al* [87]	Refill solutions	mg/mL	0 to 25.6	–100 to 100%†
	Cartridge	mg/cartridge	0 to 21.8	–100 to 100%†
	Aerosol	µg/100 mL puff	0 to 43.2	N.A.
Cheah *et al* [88]	Cartridge	mg/cartridge	0.00 to 15.3	–89 to 105%†
Pellegrino *et al* [89]	Cartridge	% W/W	<0.001 to 0.25	N.A.
	Aerosol	mg/m^3	<0.01 to 6.21	N.A.
McAuley *et al* [90]	Indoor air	ng/L	538 to 8770	N.A.
Goniewicz *et al* [91]	Refill solution	mg	0±0.0 to 25±1.1	–75 to 28%
	Cartridge	mg	0±0.0 to 19±0.5	–89 to 25%
	Aerosol	mg/150 puffs	0.3±0.2 to 8.7±1.0	N.A.
Etter *et al* [92]	Refill solution	mg/mL	N.D. to 29.0	–15 to 21%†
Kirschner *et al* [93]	Refill solution	mg/mL	14.8±0.2 to 87.2±2.7	–50 to 40%†
Cameron *et al* [94]	Refill solution	mg/mL	8.5±0.16 to 22.2±0.62	–66 to 42%†
Goniewicz *et al* [95]	Liquids	mg/mL	N.D. to 36.6 (150.3 'pure nicotine')	-92 to 104%
Geiss *et al* [96]	Liquids	mg/mL	N.D. to 20.8	-0 to 16%
Kavvalakis *et al* [97]	Liquids	%w/v	1.01 to 1.62	-17 to +6%
Farsalinos *et al* [98]	Liquids	mg/ml	Labelled 12-18	-21 to +22%

*Deviation from label = (measured value – labelled value) * 100/labelled value.

†Calculation performed by this analysis based on reported data in each study.

N.A. = not available; N.D. = none detected.

A range of analytical methods was used, which may have contributed some variation. There is no established standard and different studies use different approaches. Cheah et al., used gas chromatography coupled with flame ionization detector [88]; Etter et al., gas chromatography coupled with mass spectrometry and ultra high-performance liquid chromatography coupled with diode array detector [92]; McAuley et al., gas chromatography coupled with nitrogen-phosphorus detector [90]; Goniewicz et al., gas chromatography coupled with thermionic specific detector [95]; Trehy et al., high-performance liquid chromatography coupled with diode array detector [87]; Westenberger high-performance liquid chromatography coupled with ultraviolet/ visible spectroscopic detector [85]; Kubica et al., liquid chromatography coupled with tandem mass spectrometry [99]; and Kirschner et al., liquid chromatography coupled with time-of-flight mass spectrometry [93].

The data generated so far provide answers to three questions:

Do e-liquids pose a poisoning hazard?

The vast majority of vapers use ‘ready-made’ liquids in 10ml bottles, but some aficionados, primarily in the US, buy high concentration nicotine solutions in larger quantities for DIY dilution. An e-liquid was identified labelled as containing 210mg/ml which in fact contained only 150mg/ml [95] but even this may pose risk if ingested in larger volume. DIY liquids are rarely used in Europe, but for spurious reasons, Europe is poised to prohibit sales of products with nicotine concentrations above 20mg/ml. When this happens, the popularity of DIY e-liquids among dependent vapers, who now cannot access the products they need but can mix them themselves at home at low cost, may increase.

‘Ready-made’ e-liquids come in strengths of up to 36mg/ml nicotine, with the highest concentration recorded of 36.6mg/ml. This poses no risk of nicotine poisoning if used as intended. An overenthusiastic vaper, like someone who is over-smoking, receives a reliable warning via nausea. If the 10ml bottle of e-liquid was drunk, it would cause nausea and vomiting but would be unlikely to inflict serious harm. To protect young children from accidental exposure though, e-liquids should be in ‘childproof’ packaging.

How accurate is product labelling?

The real content exceeded markedly the labelled concentration only in samples where the declared content was very low (6mg/ml) and the real concentrations ranged up to 12mg/ml (ie still low levels). The most striking examples of inaccurate labelling concerned much lower nicotine levels than those declared in e-liquids confiscated in Singapore where EC are banned, for example, a liquid labelled as containing 24mg of nicotine contained only 3mg [88]. This however was most likely due to samples being several years old. Market competition seems to have led to improved standards as

poorly labelled products are now less common and overall the labelling accuracy has improved. For instance in the latest study which sampled 263 liquids from 13 manufacturers, the correlation between the declared and measured concentrations was r=0.94 with the samples ranging from -17% to +6% of the declared value [85]. In another study testing the five most popular EC brands, the consistency of nicotine content across different batches of nicotine cartridges of the same products was found to be within the accuracy required from medicinal nebulisers [100]. Given the generally adequate labelling accuracy and the fact that the actual nicotine intake by vapers is dictated by a host of other factors discussed below, the accuracy of labelling of common e-liquids poses no major concerns.

Is there is a risk from e-liquids inaccurately labelled as containing 0 nicotine?

All samples labelled as containing 0 nicotine were nicotine free in the newer studies, but three early studies found nicotine in some samples of '0 nicotine' e-liquids. One sample reported in 2011 was clearly mislabelled [87] but in all other cases, only trace contamination was detected (below 1mg/ml). This would have no central effect on users.

Summary

Poorly labelled e-liquid and e-cartridges mostly contained less nicotine than declared and so posed no risk to users. The accuracy of product labelling currently raises no major concerns.

Nicotine in e-vapour

A number of studies evaluated nicotine in EC vapour generated by puffing machines. A recent experiment [101] has shown that parameters of puffing topography, especially puff duration and puff frequency, have a major influence on nicotine delivery. This poses a serious problem in interpreting the existing studies. The key parameters used by puffing machines differ widely across studies, and may not correspond well or at all with vapers' behaviour generally and especially with the way individual EC products are used. To illustrate the point, Table 7 below, from Cheng et al. 2014 [84], shows the wide range of settings used in different studies. (Table 7 includes some unpublished studies).

Table 7. Settings of EC puffing parameters. From Cheng et al 2014 [84].

Study	Puff volume (mL)	Puff interval (s)	Puff duration (s)	Puffs/session	Smoking machine
Goniewicz *et al [100]*	70	10	1.8	15	Palaczbot*
Pellegrino *et al [89]*	498	8	3	16	Aspiration

Ingebrethsen [102]	55	30	2 to 4	10	Lab-built device
McAuley *et al [90]*	50	30	4	50	SCSM
Trehy *et al [87]*	100	60	2	30	Lab-built device
Williams & Talbot [103]	N.A.	60	2.2	10/11	Lab-built device
Cobb *et al[86]*	35	60	2	≥50	Machine ISO
Trtchounian *et al [104]*	N.A.	60	2.2	10	Lab-built Puff box
Uchiyama *et al [105]*	N.A.	N.A.	N.A.	N.A.	Premium Smoker
Westenberger [85]	100	60	N.A.	N.A.	Lab-built device
Laugesen [106]	38, 58	N.A.	N.A.	N.A.	Syringe

N.A., not available.

For instance, the average puff duration in experienced vapers is 2.8 seconds [101], but some studies used puffs lasting for up to 4 seconds. This can overheat the e-liquid and provide unrealistically high readings (see Chapter 11).

Although it would be feasible to establish some empirical standards, eg of puff duration and frequency, by observing vapers, any general standard would have to average values across different products. As different products, and especially products from different ‘generations’, are used differently, such a blanket regimen would still provide inaccurate and potentially misleading information.

A recent study discovered another serious problem with trying to make sense of nicotine content in e-vapour. Across five common e-liquids with middle ranges of strength, the actual nicotine concentration in the e-liquid had almost no relationship with the nicotine content in vapour when the devices were puffed on by a machine at a standard rate [100]. The e-liquid of course had to contain a certain minimal level of nicotine as with little or no nicotine in e-liquid, there would be little or no nicotine in vapour. This finding concerning machine testing also does not mean that nicotine levels in e-liquids are irrelevant for EC users. Although EC technology is developing to maximise nicotine delivery, a vaper seeking high blood nicotine levels is likely to struggle to achieve them with a weak e-liquid. The reason for the low correlation between nicotine in e-liquid and in e-vapour is that the battery output, type of wicks, ventilation holes and other mechanical characteristics of each individual EC product determine how much vapour and nicotine is released – before the individual puffing style and preferences generate yet another key determinant of nicotine delivery to users.

These findings have an important implication. Above the necessary minimum level of nicotine, nicotine concentrations in e-liquid and even the concentrations in vapour, if measured by standard puffing schedules, are of limited relevance. For light smokers, 18mg/ml ‘mild’ e-liquid may be sufficient, but they may also prefer a stronger liquid and take shorter and less frequent puffs. A heavy smoker who would be expected to prefer a 28mg/ml ‘strong’ liquid may in fact chose a ‘moderate’ strength if they favour long and frequent puffs.

In real-life use, vapers have no way of knowing in advance what liquid strength and product characteristics they will prefer. As with other consumer products of this type, such as cigarettes, coffee and soft drinks, vapers have to try several EC models and different e-liquids before settling on a preferred product that matches their preferences.

For practical purposes, general labelling of the strength of e-liquid, along the lines used for indicating coffee strength, may provide sufficient information for consumers. The current vapers’ preferences suggest as a rough rule of thumb that ‘mild’ equates to 16–20mg/ml, ‘medium’ to 21–26mg/ml and ‘strong’ to 27–36mg/ml.

Translating these findings into regulatory recommendations, it would seem that regulation to enforce standard nicotine delivery may not be needed because nicotine delivery is influenced by a host of factors, including user puffing preferences, and because consumer preferences differ. EC products will hopefully continue to evolve guided by differential market success, with the result that more smokers find EC helpful and switch to them.

Summary

Across the middle range of nicotine levels, nicotine delivery to vapour is determined primarily by mechanical and electrical characteristics of EC products and by the duration and frequency of puffs. General labelling of the strength of e-liquids, along the lines used for indicating coffee strength (eg mild, medium and strong), is likely to provide sufficient information for consumers.

Nicotine delivery to e-cigarette users

To assess nicotine intake from EC, a number of studies took blood samples from smokers during and after vaping. Table 8 summarises data from 17 studies that investigated nicotine delivery from EC in humans. The narrative description of the studies and additional details concerning their findings are presented in Appendix C.

The two key questions in this field are:

a) How much nicotine EC deliver compared to cigarettes, and
b) How fast EC deliver nicotine compared to cigarettes.

As in every new field, methodological problems limit the usefulness of some of the data collected so far. Two problems in particular are prominent.

1) Almost all studies used prescribed puffing regimes, sometimes derived from observations of smokers rather than vapers. We described above the evidence that puffing schedules have a major influence on nicotine delivery to vapour. Puffing schedules that do not correspond with vapers' behaviour are thus unlikely to provide realistic nicotine delivery data. Only three studies allowed vapers to puff ad-lib on first use.

2) Regarding the question of the speed of nicotine delivery, all existing studies started blood sampling only after five minutes of vaping. Cigarettes provide peak nicotine plasma levels very quickly (eg peak arterial nicotine concentrations of around 20ng/ml nicotine are reached within 20 seconds of starting to puff on an cigarette [107]). Data collected so far do not allow an appraisal of whether EC are approaching cigarettes in this key parameter.

Despite these limitations, the studies above have generated several strands of useful information on how much nicotine vapers obtain over time and how this compares with nicotine intake from cigarettes.

Cotinine is a metabolite of nicotine with a long half-life which shows nicotine exposure over time. Cotinine data are thus not influenced by the laboratory puffing schedules. Some studies suggest that experienced vapers can, over time, reach nicotine levels comparable to those obtained from smoking [108-110], although others have found plasma or salivary cotinine levels that are still lower than those observed in daily smokers [111-113].

Cigalike EC deliver lower levels of nicotine than cigarettes [114-116], especially to novice users [117-119]. Vapers obtain slightly more nicotine from them with practice, but nicotine delivery is comparatively low and slow [115]. Experienced users can obtain a rise in blood nicotine concentration of between 8 and 16ng/ml [120, 121]. Tank systems deliver nicotine more efficiently than cigalikes and somewhat faster [120, 122, 123].

Overall, the data indicate that within five minutes of use of a cigalike EC, blood nicotine levels can rise by approximately 5ng/ml. For comparison, after chewing a piece of 2mg nicotine chewing gum, peak plasma concentrations of 3–5ng/ml are observed within approximately 30 minutes [124, 125]. For experienced users of tank systems the increase in blood nicotine concentration within five minutes of use can be 3–4 times higher.

Speed of nicotine delivery seems important for smokers' satisfaction. Cigarettes deliver nicotine very fast via the lungs. It is likely that to out-compete cigarettes, EC will need to provide nicotine via the lungs as well. Although some EC products may already provide a degree of lung absorption, most nicotine is probably delivered via a much slower route through buccal mucosa and upper airways, in a way that is closer to the delivery from nicotine replacement medications than to the delivery from cigarettes.

This tallies with two other observations. Vapers feel they are less dependent on EC than they were on cigarettes [126]; and non-smokers experimenting with EC do not find them attractive and almost none progress to daily vaping [127]. This contrasts with the fact that about half of adolescents who experiment with cigarettes progress to daily smoking [128].

In addition to mechanical characteristics of EC and user puffing behaviour discussed in previous sections, the composition of the chemicals used to produce the vapour, typically vegetable glycerol and/or propylene glycol (PG), may also influence nicotine delivery. E-liquid with a mix of vegetable glycerol/PG was associated with better nicotine delivery than a vegetable glycerol-only e-liquid with the same concentration of nicotine [129]. The presumed effect is that PG vaporises at a faster rate than vegetable glycerol when heated in the EC and so is able to carry more nicotine to the user.

If EC continue to improve in the speed of nicotine delivery, they are likely to appeal to more smokers, making the switch from smoking to vaping easier. It may be important in this context to note that if the smoking-associated risk is removed, nicotine use by itself, outside pregnancy, carries little health risk and in fact conveys some benefits.

Table 8: Studies examining nicotine intake in vapers

Study	Participants	EC Device	Methods	Results
Vansickel et al 2012 [119]	20 smokers naïve to EC	Vapor King (cigalike), 18mg/ml nicotine	Overnight abstinence, baseline blood sample, after 5 mins 10 puffs, 30 sec inter-puff interval, 5 mins after last puff blood sample. Repeated 5x, 30 mins in between	At end of last puffing bout plasma nicotine increased from 2.2 ng/ml at baseline to 7.4 ng/ml.
Vansickel & Eissenberg 2012 [121]	8 vapers using EC for average of 12 months	Own EC 1 used 9 mg/ml 6 used 18 mg/ml 1 used 24 mg/ml	Overnight abstinence, Baseline blood, after 5 mins 10 EC puffs at 30 sec intervals, 5 and 15 mins after first puff blood sample, 60 min ad-lib vaping	Increase in plasma nicotine from 2.0 ng/ml to 10.3 ng/ml in 5 mins. Cmax = 16.3 ng/ml at end of ad lib period
Yan & D'Ruiz 2014 [129]	23 smokers	4 types of Blu (cigalike) EC (1.6% to 2.4%) Marlboro cigarette	Randomised 6 sessions 7-days get used to EC, 36 h abstinence. EC = 50x5 sec puffs, 30 sec	During controlled puffing Cmax (ng/ml): EC 10.3 to 18.9; cig 15.8

Study	Participants	EC Device	Methods	Results
		(cig)	intervals. Cig ad lib puff duration at 30 sec intervals. Then ad lib use for 60 mins. Blood: 10 mins pre, 5, 10, 15, 20, 25, 30, 45, 60, 75, 90 mins post start of controlled puffing.	Tmax: 30mins for EC and 5 mins for cig During ad lib use -Cmax (ng/ml): EC 13.7 to 22.42; cig 29.3
Vansickel et al 2010 [118]	32 smokers)	Own brand cig NJOY EC (18mg) Crown 7 EC (16mg) Sham (unlit cig) EC were cigalike	Randomised crossover, overnight abstinence. Baseline blood, EC – 10 puffs at 30 sec intervals, blood at 5, 15, 30, 45, 60 mins	Only cig produced significant rise in nicotine (18.8 ng/ml at 5 mins)
Van Staden et al 2013 [113]	13 smokers	Twisp eGo (18mg/ml nicotine)	Provided with EC and asked to use this and stop smoking for two weeks	Cotinine ng/ml Baseline: 287, at 2 weeks 97 (p=0.0011)
Spindle et al 2015 [120]	13 vapers > 3 months, e-liquid ≥12mg/ml	Own EC (all tank systems) 1 x 12 mg/ml 3 x 18 mg/ml 9 x 24 mg/ml	Overnight abstinence, two sessions. Baseline blood, EC – 10 puffs at 30 sec interval. Blood at 5 and 15 min.	Plasma nicotine at Baseline: 2.4 ng/ml 5 mins: 19.2 ng/ml 10 mins: 10.2 ng/ml
Bullen et al 2010 [117]	8 smokers	Ruyan V8 (cigalike) 16mg/ml (puff for 5 mins) Inhalator 10mg (puff for 20 mins) Own brand cig (puff for 5 mins)	Randomised crossover, overnight abstinence. Baseline blood, product use, blood at 5, 10, 15, 30, and 60 mins.	Cmax (ng/nl): EC=1.3; Inh=2.1; Cig=13.4 Tmax (mins): EC=19.6; Inh=32.0; Cig=14.3
Flouris et al 2013 [130]	15 smokers	Giant (cigalike) 11mg/ml	Smoked 2 cigs, puffed EC to match smoking. Cotinine immediately and 1 h after puffing	No difference between products
Capon-netto et al 2013 [40]	Sample size not stated	Categoria (cigalike) 7.2mg for 12 weeks 7.2mg/5.4mg for 12 weeks	RCT – 12 weeks of EC use	Salivary cotinine 6 weeks: 42 ng/ml; 12 weeks: 91 ng/ml 6 weeks: 68 ng/ml; 12 weeks: 70 ng/ml
Etter & Bullen 2011 [110]	30 vapers Mean EC use 94 days	Own brand EC Mean nicotine content 18mg/ml	Ad libitum use	Salivary cotinine 322 ng/ml
Dawkins & Corcoran 2014 [114]	14 vapers, 7 dual users,	Skycig (cigalike) 18mg/ml	10 puffs in 5 mins, then 1 hour ad lib	After 10 mins: 0.74 – 6.77 ng/ml After ad lib: 4.35-25.6 ng/ml

Study	Participants	EC Device	Methods	Results
	Used EC for 4.7 months			
Nides et al 2014 [116]	29 smokers, 55% used EC in past	NJOY®King Bold (cigalike) 26mg	EC ad lib 1 week, 12 h abstinence. 2x10 puffs (30 sec inter-puff interval) 60 mins apart Blood before and 5, 10, 15, 30 minutes after	N=16 had no baseline plasma nicotine Rise 5 min after first puffs: 3.5 ng/ml; after second puffs: 5.1 ng/ml
Norton et al 2014 [112]	16 smokers	Smoke 51 TRIO (cigalike) 11 mg/ml	Day 1: own brand, saliva sample Given EC and stopped smoking. Saliva at day 5. Analysis of 16 who abstained from smoking for 72 hours	Significant decrease in saliva cotinine between baseline (338.0 ng/ml) and day 5 (178.4 ng/ml), p<0.001
Hecht et al 2014 [111]	28 vapers (median 9 months), 96% daily users	Average nicotine 12.5 +/- 7.0 mg/ml All tank system EC	Measured toxicants, carcinogens, nicotine and cotinine in urine	Nicotine: 869 ng/ml Cotinine: 1880 Smokers normally Nicotine: 1380 ng/ml, cotinine: 3930 ng/ml
Hajek et al 2014 [115]	40 smokers,	Greensmoke (cigalike) EC (2.4% nicotine)	Overnight abstinence Baseline blood, first EC use ad-lib 5 mins, blood at 5, 10, 15, 20, 30 and 60 mins. Repeated after 4-weeks of ad lib use	***Baseline:*** Cmax: 4.6, Tmax: 5, AUC: 96 ***4-weeks:*** Cmax: 5.7, Tmax: 5, AUC: 142
Farsalinos et al 2014 [122]	N=23 vapers (19 months use)	A: V2 (cigalike) B: Tank system EVIC at 9 watts, EVOD Same 18mg/ml liquid	Abstained for 8 hrs Blood baseline and after 10 puffs over 5 mins, 1 h ad lib, blood every 15 mins	A:5 mins: 4.9 ng/ml 1h: 15.8 ng/ml B: 5 mins: 6.6 ng/ml 1h: 23.5 ng/ml
Oncken et al 2015 [123]	N=20 smokers given EC for 2 weeks	Menthol or non-menthol tank system with 18mg/ml liquid	Blood baseline, 5 min ad lib vaping, blood at 5,10,15,20,30 min	At 5 min nicotine increased by 4-5 ng/ml

Summary of findings

The accuracy of labelling of nicotine content currently raises no major concerns. Poorly labelled e-liquid and e-cartridges mostly contained less nicotine than declared. EC used as intended poses no risk of nicotine poisoning to users. However, e-liquids should be in ‘childproof’ packaging.

Duration and frequency of puffs and mechanical characteristics of EC play a major role in determining nicotine content in vapour. Across the middle range of nicotine levels, in machine tests using a standard puffing schedule, nicotine content of e-liquid is related to nicotine content in vapour only weakly. EC use releases negligible levels of nicotine into ambient air with no identified health risks to bystanders. Use of a cigalike EC can increase blood nicotine levels by around 5ng/ml within five minutes of use. This is comparable to delivery from oral NRT. Experienced EC users using the tank EC can achieve much higher blood nicotine levels over a longer duration, similar to those associated with smoking. The speed of nicotine absorption is generally slower than from cigarettes but faster than from NRT.

Policy implications

- General labelling of the strength of e-liquids, along the lines used for example indicating coffee strength, provides sufficient guidance to consumers.

- Regulatory interventions should ensure optimal product safety but make sure EC are not regulated more strictly than cigarettes and can continue to evolve and improve their competitiveness against cigarettes.

10. Safety of e-cigarettes in the light of new evidence

Introduction

PHE commissioned a review of EC in 2014, which covered EC safety [131]. The review found that the hazard associated with use of EC products currently on the market "is likely to be extremely low, and certainly much lower than smoking" and "the health risks of passive exposure to electronic cigarette vapour are likely to be extremely low".

These conclusions tally with a review by an international team of experts, which estimated the risks of vaping at less than 5% of the risks of smoking [10] and a comprehensive review of relevant literature by another international team which concluded that "EC aerosol can contain some of the toxicants present in tobacco smoke, but at levels which are much lower. Long-term health effects of EC use are unknown but compared with cigarettes, EC are likely to be much less, if at all, harmful to users or bystanders" [132].

Over the past few months, however, several reports have suggested that EC may pose more risks than previously thought [133-137].

We were asked to review these studies to see if in the light of this new evidence, the conclusions of the PHE 2014 review need to be adjusted. We present below the details of these studies together with any additional data that may assist with their interpretation.

Aldehydes in vapour from e-cigarettes

Two recent reports raised a possibility that under certain conditions, EC may release high levels of aldehydes. Aldehydes, including formaldehyde, acrolein and acetaldehyde, are released in tobacco smoke and contribute to its toxicity. Aldehydes are also released with thermal degradation of propylene glycol and glycerol in e-liquids. Previous studies detected the presence of aldehydes, especially formaldehyde, in the vapour from some EC, but at levels much lower than in cigarette smoke [138]. Across brands, EC released 1/50th of the level of formaldehyde released by cigarettes. The highest level detected was six times lower than the level in cigarette smoke [138].

In November 2014, following a press release from Japan [136], major media around the world reported variations of a headline: "E-cigarettes contain 10 times the carcinogens of regular tobacco". This was based on a Japanese researcher reporting at a press conference that during tests on a number of EC brands, one product was identified

which released 10 times more formaldehyde than cigarettes. The press release states that the formaldehyde was released when the e-liquid was over-heated. The study has not been published yet and so no further details are available, but the two experiments described below provide the explanation for this finding.

In January 2015, a similar report was published as a research letter to the *New England Journal of Medicine* (NEJM) [133]. In this study, negligible levels of formaldehyde were released at lower EC settings, but when a third generation EC (EC with variable power settings) was set to the maximum power and the apparatus was set to take puffs lasting 3–4 seconds, this generated levels of formaldehyde that, if inhaled in this way throughout the day, would exceed formaldehyde levels in cigarette smoke between five and 15 times.

The EC was puffed by the puffing machine at a higher power and longer puff duration than vapers normally use. It is therefore possible that the e-liquid was overheated to the extent that it was releasing novel thermal degradation chemicals. Such overheating can happen during vaping when the e-liquid level is low or the power too high for a given EC coil or puff duration. Vapers call this phenomenon ‘dry puff’ and it is instantly detected due to a distinctive harsh and acrid taste (it is detected by vapers, but not by puffing machines) [139]. This poses no danger to either experienced or novice vapers, because dry puffs are aversive and are avoided rather than inhaled.

A study has just been published testing the hypothesis that the NEJM report used dry puffs [140]. An equivalent EC product was set to the same or normal settings and used by seven vapers. The vapers found it usable at normal settings, but all received dry puffs and could not use the device at the settings used in the NEJM report [133]. The product was then machine tested. At the dry puff setting, formaldehyde was released at levels reported in the NEJM letter and the Japanese press release. At normal settings, there was no or negligible formaldehyde release.

We are aware of two studies that examined aldehyde levels in vapers. In a cross-sectional study, vapers had much lower levels of acrolein and crotonaldehyde in urine than smokers [111]. The other study, funded by the Medicines and Healthcare products Regulatory Agency (MHRA), examined changes in acrolein levels in smokers who switched to exclusive EC use and in those who continued to smoke while also using EC. As both EC and cigarettes release acrolein, there was a concern that ‘dual users’ may increase their acrolein intake compared to smoking only. The results showed a substantial decrease in acrolein intake in smokers who switched to EC, but it also found a significant decrease in acrolein intake in dual users (ie people that were both smoking and vaping). This was because they reduced their smoke intake as indexed by exhaled CO levels. Normal vaping generated negligible aldehyde levels [141].

Although e-liquid can be heated to a temperature which leads to a release of aldehydes, the resulting aerosol is aversive to vapers and so poses no health risk.

Summary

There is no indication that EC users are exposed to dangerous levels of aldehydes.

Effects of e-cigarette vapour on mice lungs

A paper published in February 2015 [135] generated worldwide media coverage with claims that it linked EC to lung inflammation, lung infection, and even lung cancer.

Groups of mice were put in a small container exposing them to vapour from six EC ('Menthol Bold' 1.8% nicotine) puffed on a rotating wheel at six puffs per minute for 1.5 hours, twice daily, over two weeks. The control mice were not exposed to this treatment.

Animals were infected with either streptococcus pneumonia via intranasal instillation and killed 24 hours later, or with tissue culture influenza virus and monitored for weight loss, mortality, and lung and airways inflammation. Compared to the control group, the experimental animals had an increase in pro-inflammatory cytokines, diminished lung glutathione levels, higher viral titre, and were more likely to lose weight and die. The study identified free radicals in EC vapour as the potential culprit.

There are several problems with the study and with the way its results have been interpreted.

EC vapour is inhaled as a replacement for tobacco smoke, but the study attempted no comparison of the effects on the lungs from smoke and vapour exposures. This makes a meaningful interpretation of the results difficult. A comparison was made, however, of the levels of free radicals. Even at the very high vapour density generated by the study procedure, the level of free radicals identified in vapour was "several orders of magnitude lower than in cigarette smoke".

In addition to this, the mice in the experimental group were exposed to a much higher level of stress than the control group, and stress affects bacterial and viral response. Long and repeated containment in the small and crowded smoke chamber emitting an overpowering smell is a stressor in itself, but the animals also suffered repeated nicotine poisoning. The mice showed an average cotinine concentration of 267ng/ml. Cotinine is the primary metabolite of nicotine and in humans the amount of nicotine needed to give similar cotinine levels are tolerated by heavy smokers, but highly aversive to non-smokers, who would be expected to feel sick and vomit at this level of exposure. Mice are much more sensitive to nicotine than humans (LD50 in mice is 3mg/kg, in humans

6.5–13mg/kg [69]). Accelerated weight loss, reduced immunity and early death in the experimental group were much more likely the result of protracted stress and nicotine poisoning than the result of exposure to free radicals (which were in any case 1,000 times lower than from cigarettes).

A similar study from 2015 [134] reported oxidant reactivity (which is linked to free radicals) of e-liquid and cytokine release in exposed lung tissue and in mice exposed to EC vapour. Again, no comparison with exposure to smoke was reported.

Human studies do not corroborate any of the findings reported here. A case study of lipoid pneumonia, which could have been caused by EC flavouring, received worldwide attention in 2012 [142] but despite extensive interest in the phenomenon, no further cases were published. Adverse effects of vaping are primarily local irritation and dry mouth [132]. A study that monitored asthma patients who switched from smoking to vaping found significant improvements in symptoms and in respiratory function [143]. The recent Cochrane Review found no significant adverse effects associated with EC use for up to 1.5 years [39].

Summary

The mice model has little relevance for estimating human risk and it does not raise any new safety concerns.

Particles in e-cigarette vapour

For completeness we are including information on another recent report which was interpreted as showing that EC may be dangerous to bystanders. At an EC Summit conference in London in November 2014, Harrison and McFiggans reported on particles present in EC vapour. Their presentation was reported in the British Medical Journal under the title “E-cigarette vapour could damage health of non-smokers” [137]. McFiggans and Harrison requested a retraction of the piece because their findings did not concern any health risks. It is the content of the particles rather than their presence or size which has health implications [144].

Impact of media reports that e-cigarettes are dangerous

Together with previous health scares, the articles reviewed here may be having a significant impact on public perception of EC safety. In the US, 82% of responders believed that vaping is safer than smoking in 2010, but the figure has shrunk to 51% in 2014 [65]. A perception that EC pose as much risk as smoking is the most likely explanation of the recent decline in adoption of EC by smokers [145].

Summary of findings

Two recent worldwide media headlines asserted that EC use is dangerous. These were based on misinterpreted research findings. A high level of formaldehyde was found when e-liquid was over-heated to levels unpalatable to EC users, but there is no indication that EC users are exposed to dangerous levels of aldehydes; stressed mice poisoned with very high levels of nicotine twice daily for two weeks were more likely to lose weight and die when exposed to bacteria and viruses, but this has no relevance for human EC users. The ongoing negative media campaigns are a plausible explanation for the change in the perception of EC safety (see Chapter 8).

None of the studies reviewed above alter the conclusion of Professor Britton's 2014 review for PHE. While vaping may not be 100% safe, most of the chemicals causing smoking-related disease are absent and the chemicals that are present pose limited danger. It had previously been estimated that EC are around 95% safer than smoking [10, 146]. This appears to remain a reasonable estimate.

Policy implications

- There is a need to publicise the current best estimate that using EC is around 95% safer than smoking.

- Encouraging smokers who cannot or do not want to stop smoking to switch to EC could be adopted as one of the key strategies to reduce smoking related disease and death.

11. Other health and safety concerns

There have been a number of newspaper reports about the hazards of EC use including e-liquid ingestion/poisonings, fires, battery explosions etc [147-149]. In this chapter we review available national data on these issues to endeavour to quantify the risk.

Poison reports

Data on e-liquid exposures in the UK are available from the National Poisons Information Service (NPIS)[150]. The NPIS provides information about poisoning to NHS staff and publishes data based on enquiries made by phone, using their online database TOXBASE, and by consultant referrals. The NPIS report for 2013/14 [150] details 204 enquiries related to the liquid content of EC and their refills, most of which reported accidental exposure, however 21 enquiries were related to intentional overdoses using e-liquids. Most incidences concerned ingestion of the liquid in EC or their refills (n=182) although small numbers of inhalation (n=17), eye contact (n=13) and skin contact (n=12) enquiries were also reported. The NPIS further reported that the number of enquiries about e-liquids has increased since 2007 (Figure 20) broadly reflecting the increasing popularity of EC.

A large proportion of exposures to e-liquids were in children under five years old (Figure 21), a finding that is replicated in a US study on calls to poison centres [151]. However, the concentration of events concerning children is not unique to e-liquids. Children under five years old appear to be more vulnerable than adults to accidental poisoning in general (Figure 22).

Figure 20: Number of telephone enquiries to National Poisons Information Service (NPIS) about e-cigarettes over time

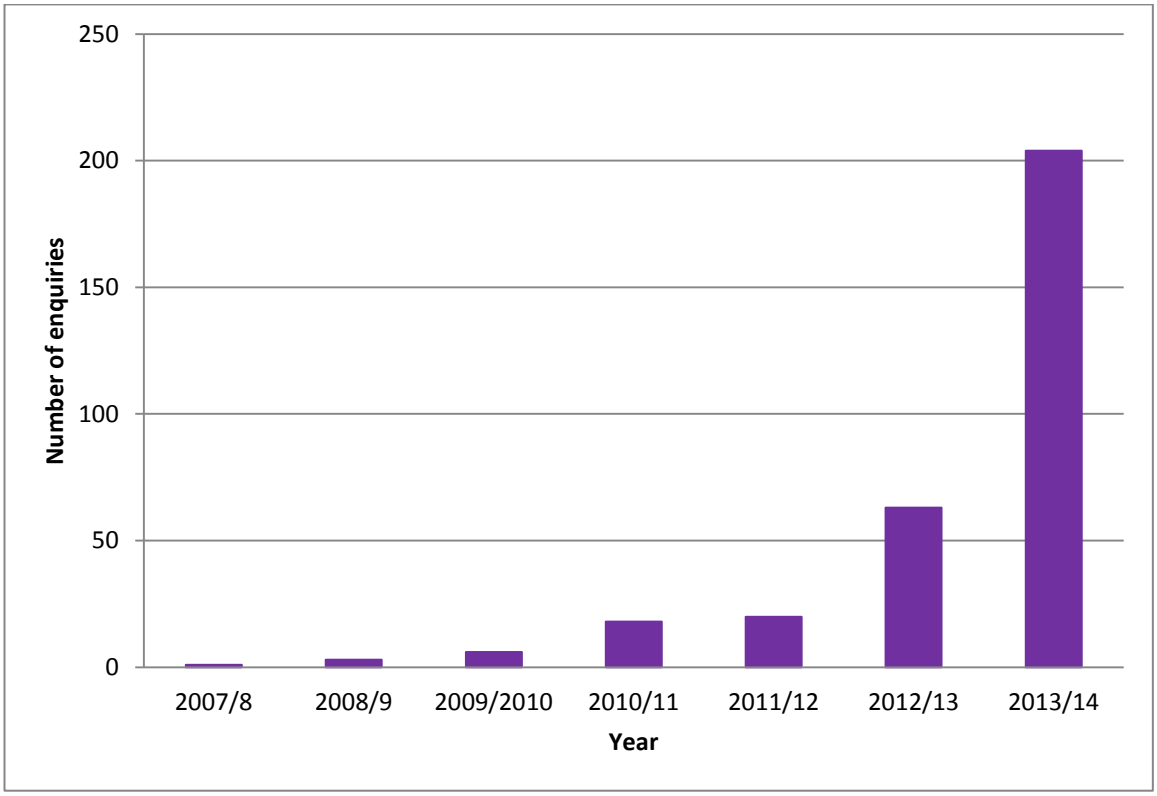


Figure 21: Number of enquiries about e-cigarettes to NPIS by age

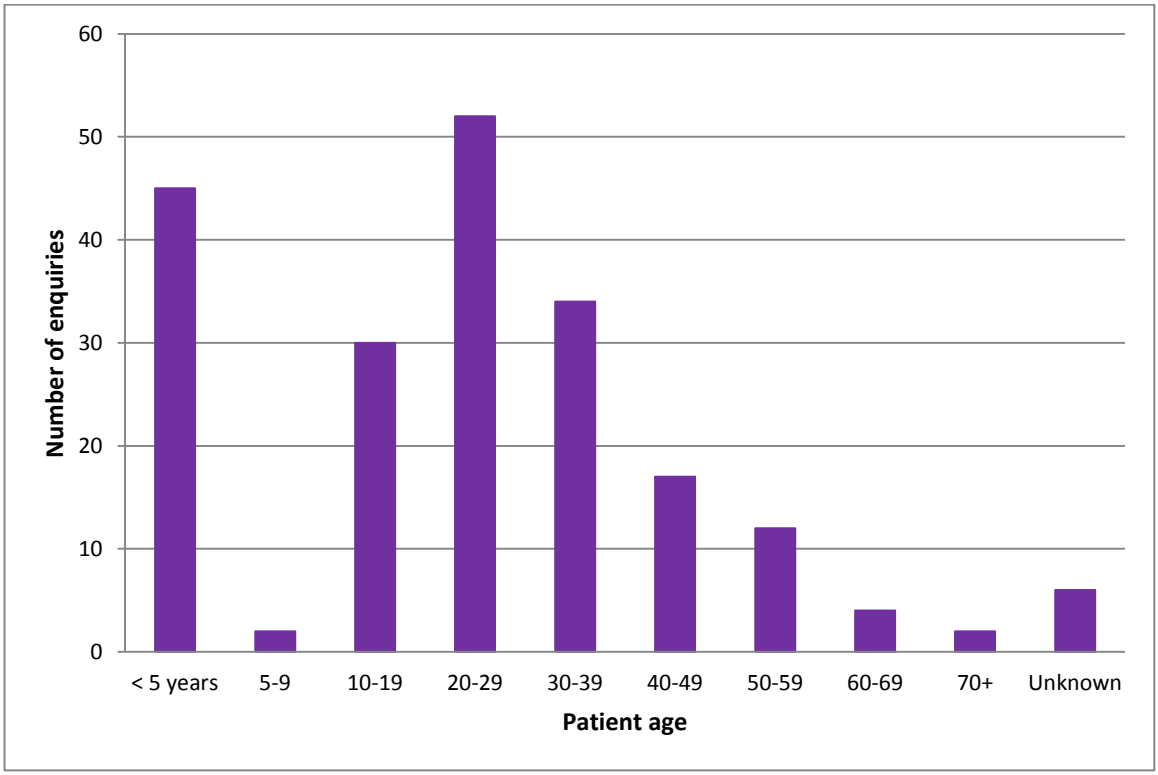
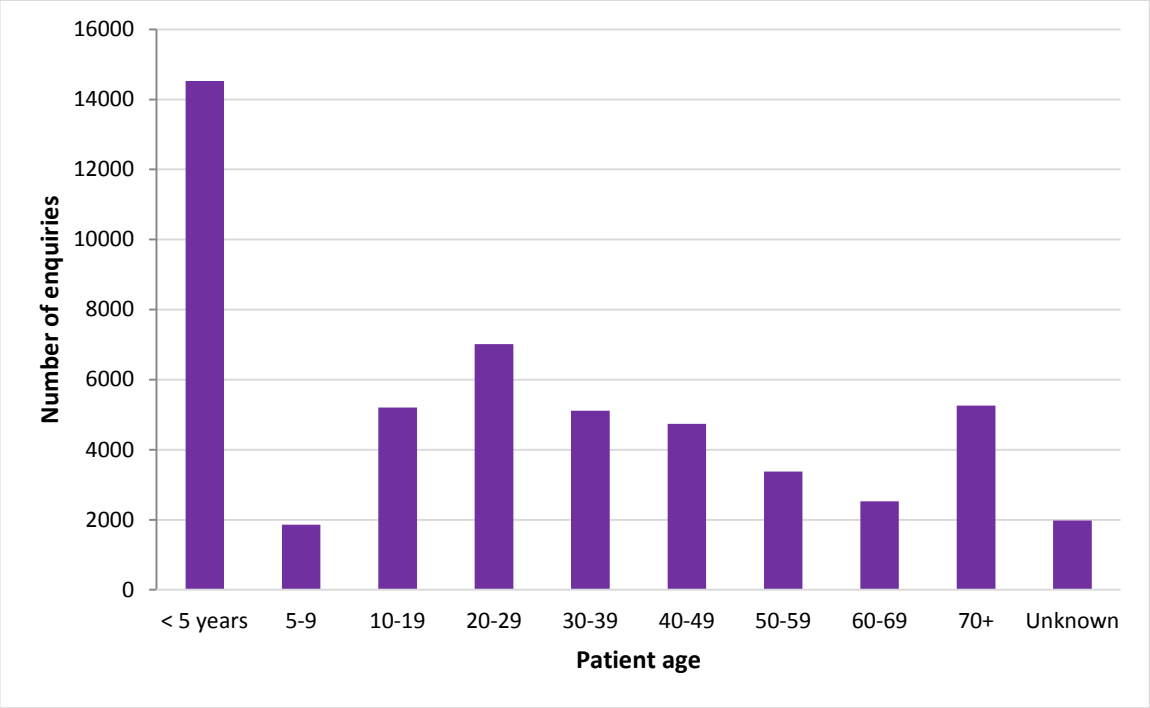


Figure 22: Age of poisoned patients overall reported in telephone enquiries to NPIS 2013/4



Exposures to poisonous liquid among children are of concern; however they should be taken in context. The same report from the NPIS recorded 208 exposures to liquid in reed diffusers, 1,168 exposures to pesticides and more than 600 to paracetamol. E-liquids seem to contribute towards domestic poisoning incidents but regulations, such as child safety caps, could limit this risk.

The clinical outcomes of exposures to e-liquids, as detailed in the NPIS report, were predominantly either ‘no toxicity’ or ‘mild toxicity’. There were two reported cases of ‘moderate toxicity’ and one ‘severe’ case that required treatment in an intensive care unit. Toxicity symptoms included conjunctivitis, irritation of the oral cavity, anxiety, vomiting, hyperventilation and changes in heart rate.

Fire

A number of news articles report the risk of fire and explosions from EC [147, 149, 152]. These reports suggest that faulty or incompatible chargers are the main causes of EC related fires along with faults relating to lithium batteries [152]. In order to assess the risks of fire we used the two data sources below:

1) In 2014, the BBC made Freedom of Information requests to UK fire services [153] and reported that there were 43 recorded call outs for fires related to EC in 2013 and 62 between 1 January 2014 and 15 November 2014. They added that call outs to EC related fires were rising in frequency. This report was based on responses from 43 out of 46 fire services in the UK [153, 154]

2) The official reporting statistics for the UK [155] do not specifically report EC as a cause of fire. There were 2,360 accidental fires between April 2013 and March 2014 where the source of ignition was “smokers’ materials” causing 80 fatalities and 673 non-fatal casualties. Additionally, there were 3,700 fires from faulty appliances and electrical leads causing 19 fatalities and 820 non-fatal casualties. It is not clear what proportion of these were caused by EC.

Regulations covering chargers and quality standards of production could help reduce the risk of fire and explosion in EC. An unpublished Department for Business, Innovation and Skills (BIS) funded market surveillance exercise in 2013/14 found that six out of 17 EC had no instructions for charging, and that eight out of 17 EC did not have a charging cut-off device and therefore did not meet the requirements of BS EN 62133:2013 'Safety requirements for portable sealed secondary cells and batteries for use in portable devices'[4]. It seems likely that the risk of fire and electrical fault is similar to other domestic electrical products, indicating that EC should be subject to the same guidelines and safety mechanisms.

Summary of findings

There is a risk of fire from the electrical elements of EC and a risk of poisoning from ingestion of e-liquids. These risks appear to be comparable to similar electrical goods and potentially poisonous household substances.

Policy implications

- The risks from fire or poisoning could be controlled through standard regulations for similar types of products, such as childproof containers (contained within the TPD but which are now emerging as an industry standard) and instructions about the importance of using the correct charger.
- Current products should comply with current British Standard operating standards.
- Records of EC incidents could be systematically recorded by fire services.

[4] BIS Funded Market Surveillance Exercise 2013/14. The Electrical Safety of Electronic Cigarettes and the Labelling of E-liquids. Lancashire County Council. Unpublished report.

12. International perspectives

Overview

Internationally, countries have taken a wide variety of approaches to regulating EC [156]. Current approaches range from complete bans on the sale of any EC, to applying existing laws on other products to EC (poison, nicotine, and/or tobacco laws), to allowing EC to be sold under general consumer product regulations. Similarly, within countries, different laws have also been applied at the state/provincial level, along with municipal by-laws, extending into areas including taxes on EC, and bans on use in places where smoking is banned. Furthermore, several nuances in laws exist, making it difficult to make broad statements about the regulations in a given country. This section focuses on presenting (1) studies that have compared the use of EC internationally across countries using representative samples and comparable methods, (2) a brief review of adolescent surveys internationally, and (3) the cases of Australia and Canada, two countries that have very similar tobacco control policies to the UK but very different policies relating to EC.

Use of e-cigarettes among adults internationally

Three studies have compared the use of EC internationally: (1) International Tobacco Control Project (described in the Methodology section), (2) Eurobarometer study and (3) Global Adult Tobacco Survey.

The International Tobacco Control Project compared EC use (use defined as less than monthly or more often) among smokers and ex-smokers across 10 countries [157]. Gravely et al., 2014 found significant variability in use across countries, but data were gathered across different years. Gravely et al., 2014 concluded that the study provided evidence of the rapid progression of EC use globally, and that variability was due partly to the year the survey was conducted, but also market factors, including different regulations on EC. Notably, EC use was highest in Malaysia at 14%, where a ban on EC was in place.

Two studies using secondary data from the 2012 Eurobarometer 385 survey have examined EC use. Vardavas, et al., 2014 [158] examined ever use (tried once or twice) of EC among smokers, ex-smokers and never smokers aged 15 years and over across 27 EU countries. The study found wide variation in ever EC use among smokers and non-smokers, with ever use varying from 20.3% among smokers, 4.4% among ex-smokers, and 1.1% among never smokers. Of those who had tried, 69.9% reported using EC once or twice, and 21.1% and 9% reported ever using or currently using occasionally or regularly (use or used regularly or occasionally). It is important to note that the question asked about ever using or currently using occasionally or regularly,

and thus would overestimate actual current use. Overall, being a smoker was the strongest predictor of ever using an EC, younger age was also predictive. Respondents who were uncertain about the harmfulness of EC were less likely to have tried an EC. Among current smokers, those who had a made a quit attempt in the past year were most likely to have ever used EC, along with heavier smokers. With regards to use as a smoking cessation aid, 7.1% of smokers who had ever made a quit attempt reported having used EC, compared to 65.7% who used no help, 22.5% who used nicotine replacement therapy, and 7.3% who received behavioural counselling. Geographical differences in EC use noted by the authors included higher ever use in Northern and Eastern Europe compared to Western Europe. The study did not go into detail on occasional or regular users of EC because the numbers were too low for any detailed analyses.

A 2012 study using the same Eurobarometer 385 survey data gave further detail on ever having used or currently using EC occasionally or regularly among smokers and non-smokers [63]. The study found that regular/occasional use was highest in Denmark at 4.2% and lowest in Lithuania and Portugal at 0.6%, and 2.5% in the UK [63].

The Global Adult Tobacco Survey [159] published findings on EC use in Indonesia (2011), Malaysia (2011), Qatar (2013) and Greece (2013) among smokers and non-smokers, the first countries with available data. Of those respondents who were aware of EC, they asked, “Do you currently use e-cigarettes on a daily basis, less than daily, or not at all?” and considered those who said they used ‘less than daily’ or ‘daily’ to be current EC users.

Overall, awareness of EC was highest in Greece (88.5%), followed by Qatar (49%), Malaysia (21%), and Indonesia (10.9%). Use of EC among smokers was highest in Malaysia (10.4%), followed by Qatar (7.6%), Indonesia (4.2%) and Greece (3.4%). Use of EC among non-smokers was highest in Greece (1.3%), followed by the other three countries, Malaysia (0.4%), Indonesia (0.4%) and Qatar (0.4%). Similar to findings from the ITC Project, these numbers are likely influenced by timing of the survey, due to the rapid progression of use of EC globally, and other market factors. Together with the findings from Gravely et al., 2014 [157] they show the rapid global progression of EC use across both high income and lower middle income countries.

Use of e-cigarettes among youth internationally

Whilst there are very few international or European studies which use consistent methodology, there is a rapidly growing body of research on the prevalence of EC use in young people at the country level, as well as reviews in this area [eg [160]]. However, much of this literature on EC use among adolescents is incomparable because of inconsistent measurements of use (confusing ever use, trial, current use), and different age ranges involved. In addition, many of the studies have been poorly reported. For

example, much has been made of the increase in EC observed in the US using the cross-sectional Centers for Disease Control & Prevention (CDC) National Youth Tobacco Surveys [161-163].These reports and press coverage have been heavily criticised [164-166]. The most important feature of the NYTS data was the fall in smoking prevalence over the same period (as observed in the UK, France [167] and elsewhere).

The CDC findings indicated that past 30-day use of EC increased among middle and high school students. For example, the 2014 data indicated that among high school students use increased from 4.5% to 13.4% between 2013 and 2014. Among middle school students, current EC use increased from 1.1% in 2013 to 3.9% in 2014. However, cigarette smoking had continued to decline during this period (high school students: 15.8% to 9.2%; middle school students: 4.7 % to 2.5%) such that smoking was at a 22-year low in the US. These findings strongly suggest that EC use is not encouraging uptake of cigarette smoking.

Whilst most of the recent studies examining youth EC use emanated from North America, the common pattern emerging worldwide is of a very high awareness of EC and an increase in trial of these products among young people [168-178]. Nevertheless, estimates of prevalence of current use of EC vary widely with the highest being reported in Poland at around 30% [174] and Hawaii (29% tried, 18% current) [178]. Most other estimates indicate that a very small minority of youth, less than 3%, currently or recently used EC. Whilst EC experimentation is increasing, regular or current use of EC appears to be largely concentrated in those already smoking conventional cigarettes. The most recent Europe-wide data indicated that 1.1% of never-smokers aged 15 and above had ever tried an EC [158]. Yet little research has focused on how EC are being used among young people, with limited qualitative research studies in this area [179, 180]. Other findings relate to the influence of parents who smoke on EC experimentation in youth [eg [170] and associations between EC experimentation and other substance use [eg [170, 181]. Several studies have also found an association between EC use and openness to cigarette smoking [eg [182] or intentions to smoke cigarettes [eg [168].

The cases of Australia and Canada

Australia has applied existing laws on poisons, therapeutic goods, and tobacco products to EC. Very broadly speaking, the current laws in Australia have resulted in a ban on the sale and importation of EC with nicotine (although there is a mechanism for legal import as an unapproved medicine with a doctor’s prescription). There are no national level prevalence data on EC use in Australia available at this time. One study comparing trends in awareness, trial, and use of EC among nationally representative samples of smokers and ex-smokers (use defined as less than monthly or more often) in Australia and the UK in 2010 and 2013 found reported EC use in Australia in 2013 at 6.6% and use in the UK at 18.8% [183]. Although the use of EC was found to be

significantly lower in Australia than in the UK in 2013, the use of EC increased at the same rate in Australia and the UK between 2010 and 2013 [183].

Canada took a similar approach to regulating EC as Australia by prohibiting the sale of EC with nicotine through existing laws. However, a recent House of Commons report stated that the current regulatory approach was not working to restrict access to EC with nicotine [184]. Canada has now put forward recommendations to develop a new legislative framework for EC that would most likely allow the sale of EC with nicotine [184]. There has been only one population-level survey of EC use in Canada. The 2013 Canadian Tobacco, Alcohol and Drugs Survey (CTADS) of Canadians 15 years and older found that 9% had ever tried an EC, with trial being higher among young people aged 15–19 years at 20% [185]. Use in the past 30 days was lower at 2%, with past 30 day use being higher among young people aged 15–19 years at 3%. Of those who tried an EC, 55% stated the EC did not contain nicotine, while 26% reported it did contain nicotine, with 19% reporting uncertainty. Whether the EC they tried contained nicotine is uncertain given (1) the ban on the sale of EC with nicotine, and (2) reports that many EC sold and bought in Canada are labelled as not containing nicotine but actually contain nicotine [184]. Although it is difficult to make comparisons due to different survey methods and questions, the percentage of young people (15–19 years) who have tried EC in Canada (20%) is roughly similar to the percentage who have tried EC in GB in 2014 (reported at 8%, 15%, 18%, and 19%, for ages 15 to 18, respectively).

Summary of findings

Although EC use may be lower in countries with more restrictions, these restrictions have not prevented EC use. Overall, use is highest among current smokers, with low numbers of non-smokers reporting ever use. Current use of EC in other countries is associated with being a smoker or ex-smoker, similar to the findings in the UK. EC use is frequently misreported, with experimentation presented as regular use. Increases in youth EC trial and use are associated with decreases in smoking prevalence in all countries, with the exception of one study from Poland.

Policy implications

- Future research should continue to monitor and evaluate whether different EC policies across countries are related to EC use and to smoking cessation and smoking prevalence.

- Consistent and agreed measures of trial, occasional and regular EC use among youth and adults are urgently needed to aid comparability.

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Declaration of interests

Professor Ann McNeill leads the Nicotine Research Group at the Institute of Psychiatry, Psychology & Neuroscience (IoPPN), King's College London (KCL). She is a Deputy Director of the UK Centre for Tobacco and Alcohol Studies (UKCTAS), President-Elect of the Society for Research on Nicotine and Tobacco European Chapter and a member of the Royal College of Physicians tobacco advisory group. She is a trustee of the Society for the Study of Addiction, a Member of the Board of Tobacco Free Futures and of the Advisory Council of Action on Smoking and Health, and Senior Editor for the journal Addiction. She has no financial or other conflicts of interest and no links with any tobacco or e-cigarette manufacturers.

Dr Leonie Brose is a Lecturer in Addictions in the Nicotine Research Group, IoPPN, KCL and a member of the UKCTAS. She is an Assistant Editor for the journal Addiction. She has no financial or other conflicts of interest and no links with any tobacco or e-cigarette manufacturers.

Robert Calder is a research assistant and PhD student at the IoPPN, KCL, and has no financial or other conflicts of interest and no links with any tobacco or e-cigarette manufacturers.

Dr Sara Hitchman is a Lecturer in Addictions in the Nicotine Research Group, IoPPN, KCL and a member of the UKCTAS. She has no financial or other conflicts of interest and no links with any tobacco or e-cigarette manufacturers.

Professor Peter Hajek is director of Health and Lifestyle Research Unit at Wolfson Institute of Preventive Medicine, Queen Mary University of London (QMUL). He provided consultancy to and received research funding from manufacturers of stop-smoking medications including Pfizer, GSK and Johnston and Johnston. His research into safety and effects of e-cigarettes was funded by MHRA and NIHR. He has no links with any tobacco or e-cigarette manufacturers.

Dr Hayden McRobbie is a researcher at QMUL and Director of the Dragon Institute for Innovation (New Zealand), which has no links with any tobacco or e-cigarette manufacturers. He contributed to educational sessions sponsored by Pfizer and Johnson & Johnson, manufacturers of stop-smoking medications, and received investigator-led research funding from Pfizer. He was an investigator on a study of e-cigarettes (EC) produced by Ruyan Group, Beijing and Hong Kong. Ruyan sponsored Health New Zealand Ltd. who provided funding to the University of Auckland to conduct the trial, independently of Ruyan. He was also an investigator on an EC trial funded by the Health Research Council of New Zealand that used EC supplied at no charge by PGM international, a retailer of EC.

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References

1. National Institute for Health Care and Excellence. *Tobacco: harm-reduction approaches to smoking*. 2013; Available from: https://www.nice.org.uk/guidance/ph45/resources/guidance-tobacco-harmreduction-approaches-to-smoking-pdf.
2. Jarvis, M.J. and J. Wardle, *Social patterning of individual health behaviours: the case of cigarette smoking.* Social determinants of health, 1999. **2**: p. 224-37.
3. Russel, M.A.H., *The future of nicotine replacement.* British Journal of Addiction, 1991. **86**(5): p. 653-658.
4. Gray, N.J., *Nicotine yesterday, today, and tomorrow: A global review.* Nicotine & Tobacco Research, 2013: p. ntt171.
5. Chapman, S., *E-cigarettes: the best and the worst case scenarios for public health—an essay by Simon Chapman.* BMJ, 2014. **349**: p. g5512.
6. Dawkins, L. and O. Corcoran, *Acute electronic cigarette use: nicotine delivery and subjective effects in regular users.* Psychopharmacology (Berl), 2014. **231**(2): p. 401-7.
7. Vansickel, A.R. and T. Eissenberg, *Electronic cigarettes: effective nicotine delivery after acute administration.* Nicotine Tob Res, 2013. **15**(1): p. 267-70.
8. Etter, J.F., *Levels of saliva cotinine in electronic cigarette users.* Addiction, 2014. **109**(5): p. 825-9.
9. Etter, J.F. and C. Bullen, *Saliva cotinine levels in users of electronic cigarettes.* Eur Respir J, 2011. **38**(5): p. 1219-20.
10. Nutt, D.J., et al., *Estimating the harms of nicotine-containing products using the MCDA approach.* European addiction research, 2014. **20**(5): p. 218-225.
11. Medicines & Healthcare Products Regulatory Agency. *Licensing Procedure for Electronic Cigarettes and Other Nicotine Containing Products (NCPs) as Medicines*, MHRA, Editor.
12. EU Tobacco Directive. *Revision of the Tobacco Products Directive*. 2014 15 April 2015]; Available from: http://ec.europa.eu/health/tobacco/products/revision/index_en.htm.
13. Office of National Statistics. *Adult Smoking Habits in Great Britain, 2013*. 2014 23 July 2015]; Available from: http://www.ons.gov.uk/ons/rel/ghs/opinions-and-lifestyle-survey/adult-smoking-habits-in-great-britain--2013/stb-opn-smoking-2013.html#tab-background-notes).
14. Action on Smoking and Health. *Use of electronic cigarettes (vapourisers) among adults in Great Britain*. 2015 23 July 2015]; Available from: http://www.ash.org.uk/files/documents/ASH_891.pdf.
15. Brown, J., R. West, and E. Beard, *Smoking Toolkit Study. Trends in electronic cigarette use in England.* http://www.smokinginengland.info/latest-statistics/, 2014. **23 April 2014**.
16. Hitchman, S.C., et al., *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. HSCIC. *Smoking, Drinking and Drug Use among Young people in England*. 2014 18 May 2015]; Available from: http://www.hscic.gov.uk/article/3743/Smoking-Drinking-and-Drug-Use-among-Young-People-in-England.
18. Moore, G., et al., *Electronic-cigarette use among young people in Wales: evidence from two cross-sectional surveys.* BMJ Open, 2015. **5**(4): p. e007072.
19. Moore, G.F., et al., *E-cigarette use and intentions to smoke among 10-11-year-old never-smokers in Wales.* Tob Control, 2014: p. tobaccocontrol-2014-052011.
20. ISD Scotland. *Scottish School's Adolescent Lifestyle and Substance Use Survey (SALSUS)*. 2014 18 May 2015]; Available from: http://www.isdscotland.org/Health-Topics/Public-Health/SALSUS/.
21. Hughes, K., et al., *Associations between e-cigarette access and smoking and drinking behaviours in teenagers.* BMC Public Health, 2015. **15**(1): p. 244.
22. Bell, K. and H. Keane, *All gates lead to smoking: The 'gateway theory', e-cigarettes and the remaking of nicotine.* Social Science & Medicine, 2014. **119**: p. 45-52.
23. Kandel, E.R. and D.B. Kandel, *A molecular basis for nicotine as a gateway drug.* New England Journal of Medicine, 2014. **371**(10): p. 932-943.

24. Hall, W.D. and M. Lynskey, *Is cannabis a gateway drug? Testing hypotheses about the relationship between cannabis use and the use of other illicit drugs.* Drug and alcohol review, 2005. **24**(1): p. 39-48.
25. Wise, J., *Children are three times as likely to try e-cigarettes as tobacco products, study finds.* BMJ, 2014. **349**: p. g7508.
26. Kandel, D. and E. Kandel, *The Gateway Hypothesis of substance abuse: developmental, biological and societal perspectives.* Acta Paediatrica, 2014.
27. Szatkowski, L. and A. McNeill, *Diverging Trends in Smoking Behaviors According to Mental Health Status.* Nicotine & Tobacco Research, 2014: p. ntu173.
28. Adkison, S.E., et al., *Electronic nicotine delivery systems: international tobacco control four-country survey.* Am J Prev Med, 2013. **44**(3): p. 207-215.
29. Brown, J., et al., *Real-world effectiveness of e-cigarettes when used to aid smoking cessation: a cross-sectional population study.* Addiction, 2014. **109**(9): p. 1531-40.
30. National Institute for Health Care and Excellence. *Smoking cessation in secondary care: acute, maternity and mental health services. [PH48]*. 2013; Available from: https://www.nice.org.uk/guidance/ph48.
31. South London and Maudsley NHS Foundation Trust. *Smokefree Policy*. 2015 18 May 2015]; Available from: http://www.slam.nhs.uk/our-services/smokefree.
32. Barbry, C., S. Hartwell-Naguib, and S. Barber. *Smoking in public places*. 2015 15 April 2015]; Available from: www.parliament.uk/briefing-papers/sn04414.pdf.
33. BBC News., *E-cigarettes being sold in prison shops in smoking ban pilot*, in *BBC News*. 2014. Available from: http://www.bbc.co.uk/news/uk-30596976.
34. Curry, L., Y.O. Lee, and T. Rogers, *E-cigarettes made especially for inmates.* Tob Control, 2014. **23**(e2): p. e87-e88.
35. McRobbie, H. *NCSCT: Electronic Cigarettes*. 2014; Available from: http://www.ncsct.co.uk/usr/pub/e-cigarette_briefing.pdf.
36. Leicester Stop Smoking Service. *Stop Smoking Service* 2015 1 May 2015]; Available from: http://www.stopsmokingleic.co.uk/.
37. Stead, L.F. and T. Lancaster, *Behavioural interventions as adjuncts to pharmacotherapy for smoking cessation.* The Cochrane Library, 2012.
38. Kotz, D., J. Brown, and R. West. *Prospective cohort study of the effectiveness of smoking cessation treatments used in the "real world"*. in *Mayo Clinic Proceedings*. 2014. Elsevier.
39. McRobbie, H., et al., *Electronic cigarettes for smoking cessation and reduction.* Cochrane Database Syst Rev, 2014. **12**: p. CD010216.
40. 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, 2013. **8**(6): p. e66317.
41. Adriaens, K., et al., *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, 2014. **11**(11): p. 11220-48.
42. O'Brien, B., et al., *E-cigarettes versus NRT for smoking reduction or cessation in people with mental illness: secondary analysis of data from the ASCEND trial.* Tob Induc Dis, 2015. **13**(1): p. 5.
43. Bullen, C., et al., *Electronic cigarettes for smoking cessation: a randomised controlled trial.* Lancet, 2013. **382**(9905): p. 1629-37.
44. Biener, L. and J.L. Hargraves, *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, 2015. **17**(2): p. 127-33.
45. Brose, L.S., et al., *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.
46. Polosa, R., et al., *Success rates with nicotine personal vaporizers: a prospective 6-month pilot study of smokers not intending to quit.* BMC Public Health, 2014. **14**: p. 1159.
47. Polosa, R., et al., *Quit and smoking reduction rates in vape shop consumers: a prospective 12-month survey.* Int J Environ Res Public Health, 2015. **12**(4): p. 3428-38.

48. Beard, E., et al., *How are the English Stop Smoking Services responding to growth in use of electronic cigarettes?* Patient education and counseling, 2014. **94**(2): p. 276-281.
49. HSCIC. *NHS Stop Smoking Services Collection*. 2015 18 May 2015]; Available from: http://www.hscic.gov.uk/stopsmoking.
50. Al-Delaimy, W.K., et al., *E-cigarette use in the past and quitting behaviour in the future: a population-based study.* Am J Public Health, 2015.
51. Pearson, J.L., et 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.
52. Borderud, S.P., et al., *Electronic cigarette use among patients with cancer: characteristics of electronic cigarette users and their smoking cessation outcomes.* Cancer, 2014. **120**(22): p. 3527-35.
53. Berg, C.J., et al., *Cigarette Users' Interest in Using or Switching to Electronic Nicotine Delivery Systems for Smokeless Tobacco for Harm Reduction, Cessation, or Novelty: A Cross-Sectional Survey of US Adults.* Nicotine Tob Res, 2015. **17**(2): p. 245-55.
54. Farsalinos, K.E., et al., *Characteristics, perceived side effects and benefits of electronic cigarette use: a worldwide survey of more than 19,000 consumers.* Int J Environ Res Public Health, 2014. **11**(4): p. 4356-73.
55. Hummel, K., 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.
56. Richardson, A., et al., *Prevalence, harm perceptions, and reasons for using noncombustible tobacco products among current and former smokers.* Am J Public Health, 2014. **104**(8): p. 1437-44.
57. Rutten, L.J., et al., *Use of e-Cigarettes among Current Smokers: Associations among Reasons for Use, Quit Intentions, and Current Tobacco Use.* Nicotine Tob Res, 2015.
58. Pepper, J.K., et al., *Reasons for starting and stopping electronic cigarette use.* Int J Environ Res Public Health, 2014. **11**(10): p. 10345-61.
59. Schmidt, L., et al., *Prevalence and reasons for initiating use of electronic cigarettes among adults in Montana, 2013.* Prev Chronic Dis, 2014. **11**: p. E204.
60. Stein, M.D., et al., *E-cigarette knowledge, attitudes, and use in opioid dependent smokers.* J Subst Abuse Treat, 2014.
61. Kong, G., et al., *Reasons for Electronic Cigarette Experimentation and Discontinuation Among Adolescents and Young Adults.* Nicotine & Tobacco Research, 2014: p. ntu257.
62. White, J., et al., *Tripling Use of Electronic Cigarettes Among New Zealand Adolescents Between 2012 and 2014.* Journal of Adolescent Health, 2015. **56**(5): p. 522-528.
63. Agaku, I.T., et al., *Poly-tobacco use among adults in 44 countries during 2008-2012: evidence for an integrative and comprehensive approach in tobacco control.* Drug Alcohol Depend, 2014. **139**: p. 60-70.
64. Eastwood, B., et al., *Trends in electronic cigarette use in young people in Great Britain 2013-2014.* (in press).
65. Tan, A.S. and C.A. Bigman, *E-cigarette awareness and perceived harmfulness: prevalence and associations with smoking-cessation outcomes.* Am J Prev Med, 2014. **47**(2): p. 141-9.
66. Ambrose, B.K., et al., *Perceptions of the relative harm of cigarettes and e-cigarettes among U.S. youth.* Am J Prev Med, 2014. **47**(2 Suppl 1): p. S53-60.
67. Amrock, S.M., et al., *Perception of e-cigarette harm and its correlation with use among u.s. Adolescents.* Nicotine Tob Res, 2015. **17**(3): p. 330-6.
68. Harrell, P.T., et al., *Expectancies for Cigarettes, E-Cigarettes, and Nicotine Replacement Therapies Among E-Cigarette Users (aka Vapers).* Nicotine Tob Res, 2015. **17**(2): p. 193-200.
69. Mayer, B., *How much nicotine kills a human? Tracing back the generally accepted lethal dose to dubious self-experiments in the nineteenth century.* Archives of toxicology, 2014. **88**(1): p. 5-7.
70. Kloosterman, K., *Electronic cigarette kills toddler in Israel.* Green Prophet, 2013. **29**.
71. Shawn, L. and L.S. Nelson, *Smoking cessation can be toxic to your health.* EMErGEnCy MEDICInE, 2013.
72. Gill, N., et al., *E-Cigarette Liquid Nicotine Ingestion in a Child: Case Report and Discussion.* CJEM, 2015: p. 1-5.
73. Gupta, S., A. Gandhi, and R. Manikonda, *Accidental nicotine liquid ingestion: emerging paediatric problem.* Arch Dis Child, 2014. **99**(12): p. 1149.

74. Chatham-Stephens, K., et al., *Notes from the field: calls to poison centers for exposures to electronic cigarettes--United States, September 2010-February 2014.* MMWR Morb Mortal Wkly Rep, 2014. **63**(13): p. 292-293.
75. Bartschat, S., et al., *Not only smoking is deadly: fatal ingestion of e-juice-a case report.* Int J Legal Med, 2014.
76. Christensen, L.B., T. van't Veen, and J. Bang. *Three cases of attempted suicide by ingestion of nicotine liquid used in e-cigarettes*. in *Clinical Toxicology*. 2013. INFORMA HEALTHCARE 52 VANDERBILT AVE, NEW YORK, NY 10017 USA.
77. Thornton, S.L., L. Oller, and T. Sawyer, *Fatal intravenous injection of electronic nicotine delivery system refilling solution.* J Med Toxicol, 2014. **10**(2): p. 202-4.
78. Long, G.A., *Comparison of Select Analytes in Exhaled Aerosol from E-Cigarettes with Exhaled Smoke from a Conventional Cigarette and Exhaled Breaths.* Int J Environ Res Public Health, 2014. **11**(11): p. 11177-11191.
79. Bush, D. and M.L. Goniewicz, *A pilot study on nicotine residues in houses of electronic cigarette users, tobacco smokers, and non-users of nicotine-containing products.* International Journal of Drug Policy, 2015.
80. Colard, S., et al., *Electronic Cigarettes and Indoor Air Quality: A Simple Approach to Modeling Potential Bystander Exposures to Nicotine.* Int J Environ Res Public Health, 2014. **12**(1): p. 282-299.
81. Goniewicz, M.L. and L. Lee, *Electronic cigarettes are a source of thirdhand exposure to nicotine.* Nicotine & Tobacco Research, 2014: p. ntu152.
82. Ballbè, M., et al., *Cigarettes vs. e-cigarettes: Passive exposure at home measured by means of airborne marker and biomarkers.* Environmental research, 2014. **135**: p. 76-80.
83. Domino, E.F., E. Hornbach, and T. Demana, *The nicotine content of common vegetables.* New England Journal of Medicine, 1993. **329**(6): p. 437-437.
84. Cheng, T., *Chemical evaluation of electronic cigarettes.* Tob Control, 2014. **23**(suppl 2): p. ii11-ii17.
85. Westenberger, B., *Evaluation of e-Cigarettes. St Louis, MO: Department of Health and Human Services.* Food and Drug Administration, Center for Drug Evaluation and Research, Division of Pharmaceutical Analysis, http://truthaboutecigs. com/science/2. pdf, accessed, 2010. **16**.
86. Cobb, N.K., et al., *Novel nicotine delivery systems and public health: the rise of the "e-cigarette".* Am J Public Health, 2010. **100**(12): p. 2340-2342.
87. Trehy, M.L., et al., *Analysis of electronic cigarette cartridges, refill solutions, and smoke for nicotine and nicotine related impurities.* Journal of Liquid Chromatography & Related Technologies, 2011. **34**(14): p. 1442-1458.
88. Cheah, N.P., et al., *Electronic nicotine delivery systems: regulatory and safety challenges: Singapore perspective.* Tob Control, 2012: p. tobaccocontrol-2012-050483.
89. Pellegrino, R., et al., *Electronic cigarettes: an evaluation of exposure to chemicals and fine particulate matter (PM).* Ann Ig, 2012. **24**(4): p. 279-288.
90. McAuley, T.R., et al., *Comparison of the effects of e-cigarette vapor and cigarette smoke on indoor air quality.* Inhalation toxicology, 2012. **24**(12): p. 850-857.
91. Goniewicz, M.L., et al., *Nicotine levels in electronic cigarettes.* Nicotine & Tobacco Research, 2013: p. nts103.
92. Etter, J.F., E. Zäther, and S. Svensson, *Analysis of refill liquids for electronic cigarettes.* Addiction, 2013. **108**(9): p. 1671-1679.
93. Kirschner, R.I., R. Gerona, and K.L. Jacobitz. *Nicotine content of liquid for electronic cigarettes*. in *CLINICAL TOXICOLOGY*. 2013. INFORMA HEALTHCARE 52 VANDERBILT AVE, NEW YORK, NY 10017 USA.
94. Cameron, J.M., et al., *Variable and potentially fatal amounts of nicotine in e-cigarette nicotine solutions.* Tob Control, 2014. **23**(1): p. 77-78.
95. Goniewicz, M.L., et al., *Nicotine levels in electronic cigarette refill solutions: A comparative analysis of products from the US, Korea, and Poland.* International Journal of Drug Policy, 2015.
96. Geiss, O., et al., *Characterisation of mainstream and passive vapours emitted by selected electronic cigarettes.* International journal of hygiene and environmental health, 2015. **218**(1): p. 169-180.

97. Kavvalakis, M.P., et al., *Multicomponent Analysis of Replacement Liquids of Electronic Cigarettes Using Chromatographic Techniques.* Journal of analytical toxicology, 2015: p. bkv002.
98. Farsalinos, K.E., 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**(4): p. 3439-3452.
99. Kubica, P., et al., *"Dilute & shoot" approach for rapid determination of trace amounts of nicotine in zero-level e-liquids by reversed phase liquid chromatography and hydrophilic interactions liquid chromatography coupled with tandem mass spectrometry-electrospray ionization.* Journal of Chromatography A, 2013. **1289**: p. 13-18.
100. Goniewicz, M.L., P. Hajek, and H. McRobbie, *Nicotine content of electronic cigarettes, its release in vapour and its consistency across batches: regulatory implications.* Addiction, 2014. **109**(3): p. 500-507.
101. Kosmider, L., et al., *Influence of Electronic Cigarettes Puffing.* 2015.
102. Ingebrethsen, B.J., S.K. Cole, and S.L. Alderman, *Electronic cigarette aerosol particle size distribution measurements.* Inhalation toxicology, 2012. **24**(14): p. 976-984.
103. Williams, M. and P. Talbot, *Variability among electronic cigarettes in the pressure drop, airflow rate, and aerosol production.* Nicotine & Tobacco Research, 2011. **13**(12): p. 1276-1283.
104. Trtchounian, A., M. Williams, and P. Talbot, *Conventional and electronic cigarettes (e-cigarettes) have different smoking characteristics.* Nicotine & Tobacco Research, 2010. **12**(9): p. 905-912.
105. Uchiyama, S., et al., *Determination of carbonyl compounds generated from the E-cigarette using coupled silica cartridges impregnated with hydroquinone and 2, 4-dinitrophenylhydrazine, followed by high-performance liquid chromatography.* Analytical Sciences, 2013. **29**(12): p. 1219-1222.
106. Laugesen, M., *Safety report on the Ruyan® e-cigarette and cartridge.* 2008: Health New Zealand Ltd.
107. Rose, J.E., et al., *Arterial nicotine kinetics during cigarette smoking and intravenous nicotine administration: implications for addiction.* Drug Alcohol Depend, 1999. **56**(2): p. 99-107.
108. Adriaens, K., et al., *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, 2014. **11**(11): p. 11220-11248.
109. Etter, J.F., *Levels of saliva cotinine in electronic cigarette users.* Addiction, 2014. **109**(5): p. 825-829.
110. Etter, J.-F. and C. Bullen, *Saliva cotinine levels in users of electronic cigarettes.* European Respiratory Journal, 2011. **38**(5): p. 1219-1220.
111. Hecht, S.S., et al., *Evaluation of toxicant and carcinogen metabolites in the urine of e-cigarette users versus cigarette smokers.* Nicotine & Tobacco Research, 2014: p. ntu218.
112. Norton, K.J., K.M. June, and R.J. O'Connor, *Initial puffing behaviors and subjective responses differ between an electronic nicotine delivery system and traditional cigarettes.* Tob Induc Dis, 2014. **12**(1): p. 17.
113. van Staden, S.R., et al., *Carboxyhaemoglobin levels, health and lifestyle perceptions in smokers converting from tobacco cigarettes to electronic cigarettes.* SAMJ: South African Medical Journal, 2013. **103**(11): p. 865-868.
114. Dawkins, L. and O. Corcoran, *Acute electronic cigarette use: nicotine delivery and subjective effects in regular users.* Psychopharmacology (Berl), 2014. **231**(2): p. 401-407.
115. Hajek, P., et al., *Nicotine intake from electronic cigarettes on initial use and after 4 weeks of regular use.* Nicotine & Tobacco Research, 2015. **17**(2): p. 175-179.
116. Nides, M.A., et al., *Nicotine blood levels and short-term smoking reduction with an electronic nicotine delivery system.* American journal of health behavior, 2014. **38**(2): p. 265-274.
117. 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, 2010. **19**(2): p. 98-103.
118. Vansickel, A.R., et al., *A clinical laboratory model for evaluating the acute effects of electronic "cigarettes": nicotine delivery profile and cardiovascular and subjective effects.* Cancer Epidemiology Biomarkers & Prevention, 2010. **19**(8): p. 1945-1953.
119. Vansickel, A.R., M.F. Weaver, and T. Eissenberg, *Clinical laboratory assessment of the abuse liability of an electronic cigarette.* Addiction, 2012. **107**(8): p. 1493-1500.

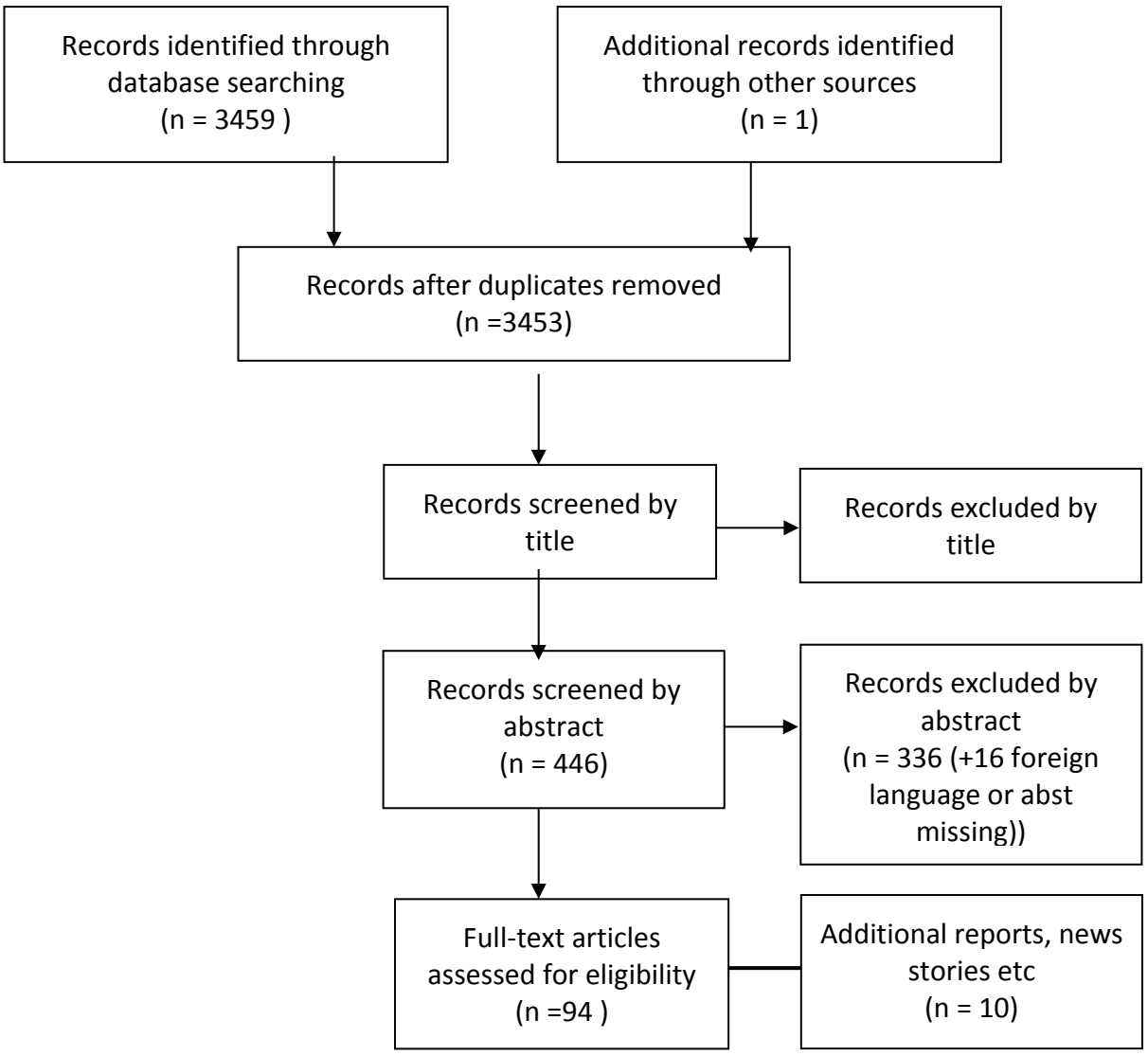
120. Spindle, T.R., et al., *Preliminary results of an examination of electronic cigarette user puff topography: the effect of a mouthpiece-based topography measurement device on plasma nicotine and subjective effects.* Nicotine & Tobacco Research, 2014: p. ntu186.
121. Vansickel, A.R. and T. Eissenberg, *Electronic cigarettes: effective nicotine delivery after acute administration.* Nicotine & Tobacco Research, 2013. **15**(1): p. 267-270.
122. Farsalinos, K.E., et al., *Nicotine absorption from electronic cigarette use: comparison between first and new-generation devices.* Scientific reports, 2014. **4**.
123. Oncken, C.A., et al., *Nicotine Concentrations With Electronic Cigarette Use: Effects of Sex and Flavor.* Nicotine & Tobacco Research, 2015. **17**(4): p. 473-478.
124. Choi, J.H., et al., *Pharmacokinetics of a nicotine polacrilex lozenge.* Nicotine & Tobacco Research, 2003. **5**(5): p. 635-644.
125. Dautzenberg, B., et al., *Pharmacokinetics, safety and efficacy from randomized controlled trials of 1 and 2 mg nicotine bitartrate lozenges (Nicotinell®).* BMC Pharmacology and Toxicology, 2007. **7**(1): p. 11.
126. Farsalinos, K.E., et al., *Evaluating nicotine levels selection and patterns of electronic cigarette use in a group of "vapers" who had achieved complete substitution of smoking.* Substance abuse: research and treatment, 2013. **7**: p. 139.
127. Douptcheva, N., et al., *Use of electronic cigarettes among young Swiss men.* Journal of epidemiology and community health, 2013: p. jech-2013-203152.
128. Johnston, L.D., et al., *Monitoring the Future National Survey Results on Drug Use, 1975-2010. Volume I, Secondary School Students.* Institute for Social Research, 2011.
129. Yan, X.S. and C. D'Ruiz, *Effects of using electronic cigarettes on nicotine delivery and cardiovascular function in comparison with regular cigarettes.* Regulatory Toxicology and Pharmacology, 2015. **71**(1): p. 24-34.
130. Flouris, A.D., et al., *Acute impact of active and passive electronic cigarette smoking on serum cotinine and lung function.* Inhalation toxicology, 2013. **25**(2): p. 91-101.
131. Britton, J. and I. Bogdanovica, *Electronic cigarettes: A report commissioned by Public Health England.* London: Public Health England, 2014.
132. Hajek, P., et al., *Electronic cigarettes: review of use, content, safety, effects on smokers and potential for harm and benefit.* Addiction, 2014. **109**(11): p. 1801-1810.
133. Jensen, R.P., et al., *Hidden Formaldehyde in E-Cigarette Aerosols.* New England Journal of Medicine, 2015. **372**(4): p. 392-394.
134. Lerner, C.A., et al., *Vapors produced by electronic cigarettes and e-juices with flavorings induce toxicity, oxidative stress, and inflammatory response in lung epithelial cells and in mouse lung.* PLoS One, 2015. **10**: p. e0116732.
135. Sussan, T.E., et al., *Exposure to Electronic Cigarettes Impairs Pulmonary Anti-Bacterial and Anti-Viral Defenses in a Mouse Model.* PLoS One, 2015. **10**(2): p. e0116861.
136. The Japan Times. *E-cigs pose much higher cancer risk than thought: Japanese study.* 28 November 2014 01/05/15]; Available from: http://www.japantimes.co.jp/news/2014/11/28/national/science-health/e-cigarettes-contain-10-times-carcinogens-regular-tobacco-japan-research/#.VOOJbiyMjdU.
137. Torjesen, I., *E-cigarette vapour could damage health of non-smokers.* BMJ, 2014. **349**: p. g6882.
138. Farsalinos, K. *Electronic cigarette aerosol contains 6 times LESS formaldehyde than tobacco cigarette smoke*. 27 November 2014 01/05/15]; Available from: http://www.ecigarette-research.com/web/index.php/2013-04-07-09-50-07/2014/188-frm-jp.
139. Farsalinos, K.E., et al., *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**(6): p. 2500-2514.
140. Farsalinos, C., *E-cigarette aerosols generates high levels of formaldehyde only in 'dry puff' conditions.* Addiction, (in press).
141. McRobbie, H., et al., *Effects of the use of electronic cigarettes with and without concurrent smoking on acrolein delivery.* 2014: London.
142. McCauley, L., C. Markin, and D. Hosmer, *An unexpected consequence of electronic cigarette use.* CHEST Journal, 2012. **141**(4): p. 1110-1113.

143. 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, 2014. **11**(5): p. 4965-4977.
144. McFiggans, G. and R. Harrison. *Re: E-cigarette vapour could damage health of non-smokers*. 2014 5 Jun 2015]; Available from: http://www.bmj.com/content/349/bmj.g6882/rr/780389.
145. West, R., J. Brown, and E. Beard, *Trends in electronic cigarette use in England.* University College London, Smoking Toolkit Study, 2014. **21**.
146. West, R., et al., *Electronic cigarettes: what we know so far. Briefing report to UK All-Party Parliamentary Group on Pharmacy.* 2014.
147. BBC News. *Man Killed as E-Cigarette 'Explodes' Merseyside Fire Service Says*. 2014 8th August 2014 [cited 2015 20th March]; Available from: http://www.bbc.co.uk/news/uk-england-merseyside-28701515.
148. Meikle, J. *E-cigarette Poisoning Figures Soar as Vaping Habit Spreads Across UK*. The Guardian. 14th April 2014 [cited 2015 20th March]; Available from: http://www.theguardian.com/society/2014/apr/14/e-cigarette-poisoning-figures-soar-adults-children.
149. BBC News. *Poole Parkstone Road Flats Evacuated After E-Cigarette Fire*. 2015 [cited 2015 20th March]; Available from: http://www.bbc.co.uk/news/uk-england-dorset-26262633.
150. *National Poisons Information Service: Report 2013/14*. 2014: Public Health England.
151. Ordonez, J.E., K.C. Kleinschmidt, and M.B. Forrester, *Electronic cigarette exposures reported to Texas poison centers.* Nicotine Tob Res, 2015. **17**(2): p. 209-11.
152. Lavigueur, N. *Fire Warning After E-Cigarette Explodes While Being Charged*. 2013 21st December 2013 [cited 2015 1st May]; Available from: http://www.mirror.co.uk/news/uk-news/e-cigarette-dangers-fire-chiefs-warning-2949094.
153. BBC News. *Call for E-Cigarette Safety Warnings*. 2014 15th November 2014 [cited 2015 1st May]; Available from: http://www.bbc.co.uk/news/uk-30064154.
154. *Fire and Rescue: Operational Statistics Bulletin for England 2013-2014*. 2014: Department for Communities and Local Government.
155. *Fire Statistics: Great Britain April 2013 to March 2014*. 2015: Department for Communities and Local Government.
156. Institute for Global Tobacco Control. *Country Laws Regulating E-cigarettes: A Policy Scan*. 2015, MD: Johns Hopkins Bloomberg School of Public Health.
157. Gravely, S., et al., *Awareness, trial, and current use of electronic cigarettes in 10 countries: Findings from the ITC project.* Int J Environ Res Public Health, 2014. **11**(11): p. 11691-704.
158. Vardavas, C.I., F.T. Filippidis, and I.T. Agaku, *Determinants and prevalence of e-cigarette use throughout the European Union: a secondary analysis of 26 566 youth and adults from 27 Countries.* Tob Control, 2014.
159. Palipudi, K.M., et al., *Awareness and Current Use of Electronic Cigarettes in Indonesia, Malaysia, Qatar, and Greece: Findings from 2011-2013 Global Adult Tobacco Surveys.* Nicotine & Tobacco Research, 2015: p. ntv081.
160. Collaco, J.M., M.B. Drummond, and S.A. McGrath-Morrow, *Electronic Cigarette Use and Exposure in the Pediatric Population.* JAMA pediatrics, 2014.
161. Arrazola, R.A., et al., *Tobacco use among middle and high school students—United States, 2011-2014.* MMWR Morb Mortal Wkly Rep, 2015. **64**: p. 381-5.
162. Dutra, L.M. and S.A. Glantz, *Electronic cigarettes and conventional cigarette use among US adolescents: a cross-sectional study.* JAMA pediatrics, 2014. **168**(7): p. 610-617.
163. Centre for Disease Control and Prevention. *E-cigarette use triples among middle and high school students in just one year.* 2015 15 April 2015]; Available from: http://www.cdc.gov/media/releases/2015/p0416-e-cigarette-use.html.
164. Farsalinos, K. and R. Polosa, *Youth tobacco use and electronic cigarettes.* JAMA pediatrics, 2014. **168**(8): p. 775.
165. McNeill, A., et al., *A critique of a World Health Organization-commissioned report and associated paper on electronic cigarettes.* Addiction, 2014. **109**(12): p. 2128-2134.
166. Niaura, R.S., T.J. Glynn, and D.B. Abrams, *Youth experimentation with e-cigarettes: another interpretation of the data.* JAMA, 2014. **312**(6): p. 641-642.

167. Houezec, J., *According to a new survey, youth smoking decreased during the last 4 years while e-cig used increased.* 2014.
168. Bunnell, R.E., et al., *Intentions to smoke cigarettes among never-smoking US middle and high school electronic cigarette users, National Youth Tobacco Survey, 2011-2013.* Nicotine & Tobacco Research, 2014: p. ntu166.
169. Camenga, D.R., et al., *Trends in use of electronic nicotine delivery systems by adolescents.* Addictive behaviors, 2014. **39**(1): p. 338-340.
170. Camenga, D.R., et al., *Alternate tobacco product and drug use among adolescents who use electronic cigarettes, cigarettes only, and never smokers.* Journal of Adolescent Health, 2014. **55**(4): p. 588-591.
171. Czoli, C.D., D. Hammond, and C.M. White, *Electronic cigarettes in Canada: Prevalence of use and perceptions among youth and young adults.* Can J Public Health, 2014. **105**(2): p. e97-e102.
172. Dautzenberg, B., et al., *E-Cigarette: a new tobacco product for schoolchildren in Paris.* Open Journal of Respiratory Diseases, 2013. **3**(01): p. 21.
173. Goniewicz, M.L., et al., *Rise in electronic cigarette use among adolescents in Poland.* Journal of Adolescent Health, 2014. **55**(5): p. 713-715.
174. Hamilton, H.A., et al., *Ever use of nicotine and non-nicotine electronic cigarettes among high school students in Ontario, Canada.* Nicotine & Tobacco Research, 2014: p. ntu234.
175. Krishnan-Sarin, S., et al., *E-cigarette Use among High School and Middle School Adolescents in Connecticut.* Nicotine & Tobacco Research, 2014: p. ntu243.
176. Lee, S., R.A. Grana, and S.A. Glantz, *Electronic cigarette use among Korean adolescents: a cross-sectional study of market penetration, dual use, and relationship to quit attempts and former smoking.* J Adolesc Health, 2014. **54**(6): p. 684-90.
177. Ramo, D.E., K.C. Young-Wolff, and J.J. Prochaska, *Prevalence and correlates of electronic-cigarette use in young adults: Findings from three studies over five years.* Addictive behaviors, 2015. **41**: p. 142-147.
178. Wills, T.A., et al., *Risk factors for exclusive e-cigarette use and dual e-cigarette use and tobacco use in adolescents.* Pediatrics, 2015. **135**(1): p. e43-e51.
179. Camenga, D.R., et al., *Adolescents' and young adults' perceptions of electronic cigarettes for smoking cessation: A focus group study.* Nicotine & Tobacco Research, 2015: p. ntv020.
180. Lippert, A.M., *Do Adolescent Smokers Use E-Cigarettes to Help Them Quit? The Sociodemographic Correlates and Cessation Motivations of US Adolescent E-Cigarette Use.* American Journal of Health Promotion, 2014.
181. Meier, E.M., et al., *Which Nicotine Products Are Gateways to Regular Use?: First-Tried Tobacco and Current Use in College Students.* Am J Prev Med, 2015. **48**(1): p. S86-S93.
182. Coleman, B.N., et al., *Association between electronic cigarette use and openness to cigarette smoking among US young adults.* Nicotine & Tobacco Research, 2014: p. ntu211.
183. Yong, H.H., et al., *Trends in E-Cigarette Awareness, Trial, and Use Under the Different Regulatory Environments of Australia and the United Kingdom.* Nicotine Tob Res, 2014.
184. Lobb, B., *Vaping: Towards a regulatory framework for e-cigarettes: Report of the standing committee on health*. 2015.
185. Government of Canada. *Canadian Tobacco, Alcohol and Drugs Survey (CTADS): Summary of results for 2013*. 2015 5 Jun 2015]; Available from: http://healthycanadians.gc.ca/science-research-sciences-recherches/data-donnees/ctads-ectad/summary-sommaire-2013-eng.php.

Appendices

APPENDIX A: PRISM Flow Diagram[5]



[5] Please note that we did not carry out a full systematic review for this report but followed systematic review methods. We assessed 94 papers and 9 additional reports included those that were relevant to our objective of describing the **use** of e-cigarettes and how they **impact smoking behaviour,** with a particular focus on the UK.

APPENDIX B: Measures of e-cigarette use

Measures of EC use in studies referenced, in most cases respondents were only asked about EC use if they first answered yes to ever trying an EC/had heard of EC.

Surveys

These questions in all surveys below may have been slightly altered from year to year as the EC market evolved and awareness grew.

Smoking Toolkit Study (STS)

The following four questions are used to assess current use of e-cigarettes: (if already responded they are cutting down)

Q632e37. Which, if any, of the following are you currently using to help you cut down the amount you smoke?
Nicotine gum
Nicotine replacement lozenges\tablets
Nicotine replacement inhaler
Nicotine replacement nasal spray
Nicotine patch
Electronic cigarette
Nicotine mouthspray
Other (specify)

Q632e1. Do you regularly use any of the following in situations when you are not allowed to smoke?
Nicotine gum
Nicotine lozenge
Nicotine patch
Nicotine inhaler\inhalator
Another nicotine product
Electronic cigarette
Nicotine mouthspray
Other (specify)

NEWW53a. Can I check, are you using any of the following either to help you stop smoking, to help you cut down or for any other reason at all?

Nicotine gum
Nicotine lozenge

Nicotine patch
Nicotine inhaler\inhalator
Another nicotine product
Electronic cigarette
Nicotine mouthspray
Other (specify)

QIMW86_1. Can I check, are you using any of the following?
PROBE FULLY: Which others? PROBE UNTIL RESPONDENT SAYS 'NO OTHERS'
PLEASE TYPE IN OTHER ANSWERS CAREFULLY AND USE CAPITAL LETTERS
Nicotine gum
Nicotine lozenge
Nicotine patch
Nicotine inhaler\inhalator
Another nicotine product
Electronic cigarette
Nicotine mouthspray
Other (specify)

ASH Smokefree GB adult survey

Which of the following statements BEST applies to you?

- I have heard of e-cigarettes and have never tried them
- I have heard of e-cigarettes but have never tried them
- I have tried e-cigarettes but do not use them (anymore)
- I have tried e-cigarettes and still use them
- Don't know

The fourth option constitutes 'current use'

ASH Smokefree GB youth survey

An e-cigarette is a tube that looks like a normal cigarette, has a glowing tip and puffs a vaour that looks like smoke but unlike normal cigarettes, they don't burn tobacco.
Have you ever heard of e-cigarettes?

- Yes, I have
- No, I haven't

All those who have heard of e-cigarettes: Which one of the following is closest to describing your experience of e-cigarettes?

- I have never used them
- I have tried them once or twice
- I use them sometimes (more than once a month)

- I use them often (more than once a week)
- Don't want to say

Internet cohort survey

Have you ever heard of electronic cigarettes or e-cigarettes? These are electronic devices that contain nicotine in a vapour and are designed to look like cigarettes, but contain no tobacco.
Yes/No/Don't know

If Yes, Have you ever tried an electronic cigarettes?
Yes/No/Don't know

If Yes, How often if at all, do you currently use an electronic cigarette? (PLEASE SELECT ONE OPTION)

1. Daily
2. Less than daily, but at least once a week
3. Less than weekly, but at least once a month
4. Less than monthly
5. Not at all
6. Don't know

Other studies

Amrock et al., 2015 (US)

Which of the following tobacco products have you ever tried, even just one time?" to which they could select, "electronic cigarettes or e-cigarettes, such as Ruyan or NJOY" alongside other tobacco products. A related question asked if students used e-cigarettes on at least one of the past 30 days.

Biener & Hargraves, 2014 (US)

At baseline, three questions were asked about e-cigarettes: whether the respondent had "ever heard of electronic cigarettes, also known as e-cigarettes"; if so, whether he/she had ever used an e-cigarette even one time, and if so, on how many of the past 30 days the respondent had used an e-cigarette. To assess how intensively and for how long the respondent had used e-cigarettes during the period between interviews, the follow-up interviews included questions to describe e-cigarette usage. Those who were not aware of e-cigarettes at baseline were asked if they had heard of them at follow-up. Those who had not tried e-cigarettes at baseline were asked if they had done so by follow-up. All respondents who reported ever trying them by follow-up were asked

whether they currently used e-cigarettes every day, some days or not at all. If not at all, they were asked if they ever used e-cigarettes “fairly regularly.” If not, whether they had used only once or twice or more often than that. All who had used more than once or twice, were asked a series of questions about their patterns of use: for how long they had used e-cigarettes (less than a month, 1–6 months, more than 6 months); whether they had ever used e-cigarettes daily for at least one week; if so for how long they had used e-cigarettes daily. From these variables, a 3-level measure of intensity of e-cigarette usage was computed: 3 = intensive (used daily for at least 1 month); 2 = intermittent (more than once or twice but not daily for a month or more); 1 = non-use or at most once or twice.

Borderud et al., 2014 (US)

Patients were asked if they had used E-cigarettes within the past 30 days, with the response options being yes or no.

Brose et al, 2015 and Hitchman et al., 2015 (GB)

How often, if at all, do you currently use an electronic cigarette? [Asked of respondents who had ever heard of e-cigarettes and had ever tried one.]

1. Daily
2. Less than daily, but at least once a week
3. Less than weekly, but at least once a month
4. Less than monthly
5. Not at all
6. Don't know

What electronic cigarette equipment do you currently use the most?

1. A disposable electronic cigarette (non-rechargeable)
2. A commercial electronic cigarette kit which is refillable with pre-filled cartridges
3. A commercial electronic cigarette kit which is refillable with liquids
4. A modular system (I use my own combination of separate devices: batteries, atomizers, etc.)
5. Don’t know

Brown et al., 2014 (England)

Which, if any, of the following did you try to help you stop smoking during the most recent serious quit attempt?

1. E-cigarettes
2. NRT bought over-the-counter
3. No aid

Canadian Tobacco, Alcohol and Drugs Survey 2013 (CTADS)

Trial

Have you ever tried an electronic cigarette, also known as an e-cigarette?

1. Yes
2. No
3. Refused
4. Don't know

Last 30 day use

In the past 30 days did you use an electronic cigarette, also known as an e-cigarette?

1. Yes
2. No
3. Refused
4. Don't know

CDC/NYTS and Dutra and Glantz

During the past 30 days, on how many days did you use electronic cigarettes or e-cigarettes such as Blu, 21st Century Smoke, or NJOY?

Gravely et al., 2014 (Republic of Korea, US, UK, Canada, Australia, and Malaysia); Yong et al., 2014 (UK and Australia)

How often, if at all, do you currently use an electronic cigarette? (dichotomised into current use and non-current by combining any use responses vs. not at all)

1. Daily, Less than daily but at least once a week
2. Less than weekly but at least once a month
3. Less than monthly
4. Not at all

Gravely et al., 2014 (Netherlands)

How often do you currently use an electronic cigarette? (dichotomised into current use and non-current by combining any use responses vs. have you stopped altogether)

1. Daily
2. Less than daily, but at least once a week
3. Less than weekly, but at least once a month
4. Less than monthly versus, or
5. Have you stopped altogether?

Gravely et al., 2014 (China)

Are you currently using an electronic cigarette at least weekly? (Yes vs. No)

1. Yes
2. No

Hughes et al., 2014 (Trading Standards NW Study)

"Have you ever bought or tried electronic cigarettes?"

Hummel et al., 2014 (Netherlands)

Respondents who had ever tried e-cigarettes were asked how often they currently used an e-cigarette (daily, at least once a week, at least once a month, less than monthly, or stopped altogether

Lee et al., 2014 (US)

E-cigarette use questions were:

Have you ever used e-cigarettes?

1. yes
2. no

Have you used e-cigarettes in the past 30 days?

1. yes
2. no

Moore et al., 2014 (Welsh study 10-11 year olds)

"Have you heard of e-cigarettes before this survey?"
'Have you ever used an e-cigarette? with response options of 'no', 'yes, once' or' yes, more than once'

Moore et al., 2015 (Welsh study HBSC)

Asked whether they had ever used an e-cigarette with response options of:

- I have never used or tried e-cigarettes
- I have used e-cigarettes on a few occasions (1-5 times);
- I regularly use e-cigarettes (at least once a month)'.

Palipudi et al., 2015 (Global Adult Tobacco Survey)

“Do you currently use e-cigarettes on a
1. Daily basis,
2. Less than daily,
3. Or, not at all?”

Pearson et al., 2014 (US)

Participants were asked which methods they had used to quit in the past 3 months and were presented a list of common quit methods. Participants were considered e-cigarette users if they selected “e-cigarettes” in response to this question or if they entered terms like “vapors,” “vaping,” “vape,” or “ecigs” in the “other quit methods” open-ended response option.

Pepper et al., 2014 (US)

Have you ever used an e-cigarette, even one puff?
Do you now use e-cigarettes every day, some days, or not at all?

Richardson et al., 2014 (US)

Please indicate whether you have ever heard of these products, if you have ever tried them and if you have ever purchased them. Products included ENDS; dissolvables; chew, dip, or snuff (assessed in 1 question); and snus, each presented with brand names to increase validity of responses. Respondents could choose multiple options from the following choices: (1) heard of; (2) tried; (3) purchased; (4) never heard of, tried, or purchased (for those to whom options 1, 2, and 3 were not applicable); (5) refused; and (6) don’t know.

Rutten et al., 2014 (US)

Do you now use e-cigarettes (eg BluCig, NJoy, V2, Red Dragon, etc)? [Picture of three different e-cigarettes included]
1. Every day
2. Some days
3. Not at all

Schmidt et al., 2014 (US)

Have you ever used an electronic cigarette, even just one time in your entire life?
Do you now use electronic cigarettes every day, some days, rarely, or not at all?

Vardavas et al., 2014 (Eurobarometer 27 countries), dichotomised into regularly, occasionally, tried once or twice vs. otherwise; Agaku et al., 2014 (Eurobarometer, 25 countries), dichotomised into regularly or occasionally vs. otherwise;

Have you ever tried any of the following products? (Electronic cigarettes)

1. Yes, you use or used it regularly.
2. Yes, you use or used it occasionally.
3. Yes, you tried it once or twice.
4. No.
5. Don’t Know.

White et al., 2015, New Zealand national youth tobacco use survey in 2012 and 2014

Ever use: Have you ever tried electronic cigarettes?

Appendix C: Narrative summary of studies on nicotine delivery from e-cigarettes

Early studies

Two studies, both published in 2010, examined nicotine delivery from cigalike EC.

Bullen et al., 2010 used a cross-over design to compare nicotine delivery of a 16mg/ml Ruyan V8 EC with a 0mg/ml EC, a nicotine inhalator (10mg) and a conventional cigarette among 8 smokers who abstained from smoking overnight [43]. Participants puffed on their cigarettes and EC ad libitum over 5 minutes, and on the inhalator over 20 minutes. The nicotine containing EC had similar pharmacokinetic parameters to the inhalator (Cmax: 1.3 vs. 2.1 ng/ml; Tmax: 19.6 vs. 32.0 mins), and both were out-performed by a conventional cigarette (Cmax 13.4 ng/ml; Tmax 14.3 mins).

Vansickel et al., 2010 also used a cross-over design and tested nicotine delivery of two EC (NJOY EC (18mg) and Crown 7 EC (16mg) and participants own brand cigarette[118]. Participants abstained overnight and then took 10 puffs on the EC with a 30 sec inter-puff interval. Only the conventional cigarette produced a significant rise in plasma nicotine, from baseline 2.1 ng/ml (SD 0.32) to a peak at 5 minutes 18.8 ng/ml (SD 11.8).

The poor nicotine delivery of these EC was likely to be due to several factors. The EC tested were some of the first to market. The EC used in the Bullen 2010 study were noted to leak and the vaporising component did not always function. Both of these early studies recruited EC naïve smokers, without opportunity to practice using the EC prior to experimentation.

There are other factors that are associated with nicotine delivery, which we have summarised below.

1) More intensive vaping regimens
Vansickel et al., examined nicotine delivery associated with the use of Vapor King (cigalike EC with 18mg/ml nicotine) in 20 smokers naïve to EC [119]. After overnight abstinence, participants used the EC for 5 minutes on a total of six occasions (10 puffs, 30 sec inter-puff interval) 30 minutes apart. A significant increase in plasma nicotine was observed after the fourth bout of puffing, and mean blood nicotine levels had increased from 2.2 ng/ml (SD 0.78) at baseline to 7.4 ng/ml (SD 5.1) at the end of the last bout of puffing.

2) Experience with EC
Vansickel & Eissenberg (2012) report nicotine pharmacokinetics in eight vapers who had been using EC for average of 11.5 (SD 5.2) months [7]. They used their own EC and e-liquid (the majority used an e-liquid with a concentration of 18 mg/ml).

Participants attended the laboratory after overnight abstinence and used their EC under a standardised vaping regimen (10 puffs with a 30 second inter-puff interval) and then a 60 minutes period of *ad lib* vaping. The PK analyses showed a significant increase in plasma nicotine from baseline 2.0 ng/ml to 0.3 ng/ml within five minutes of the first puff. At the end of the ad-lib vaping period the maximum plasma nicotine concentration was 16.3 ng/ml.

Dawkins and Corcoran (2014) examined nicotine delivery associated with the used of the Skycig 18 mg Crown tobacco bold cartridges in 14 vapers, who had been vaping for almost 5 months on average[6]. Using a similar methodology to Vansickel & Eissenberg (2012), the analysis of plasma nicotine from the seven participants that provided a full blood set, showed that levels had increased from 0.74 to 6.77 ng/ml in 10 minutes. However there was individual variation (2.5 ng/ml to 13.4 ng/ml). After an hour of *ad lib* use the maximum nicotine concentration reached was 13.91 ng/ml, again with a wide range of levels observed between individuals (4.35-25.6 ng/ml).

Spindle et al., 2015 studied 13 experienced EC users (> 3 months, with the majority 9/13 using e-liquid strength of 24mg/ml and all using tank systems)[120]. Taking 10 puffs over 5 minutes resulted in an increase in mean blood nicotine levels from 2.4 ng/ml baseline to 19.2 ng/ml at 5 minutes.

Practice in EC use also results in a modest increase in blood nicotine levels. Hajek et al., 2014 tested Greensmoke EC (a cigalike EC with 2.4% nicotine) in 40 smokers, naïve to EC[115]. Participants abstained from any nicotine use overnight and after a baseline blood sample was collected used the EC, *ad lib*, for 5 minutes. This procedure was undertaken twice, on first use and then again after 4 weeks of use. The maximum plasma concentrations increased from 4.6 ng/ml (range 0.9-9.0) to 5.7 ng/ml (range 1.9-11.0), although this increase was not significant. The area under the curve (AUC), however, did show a significant increase, from 96 (range 12-198) to 142 (range 56-234). The time to maximum plasma concentration (5 minutes) did not change.

Nides et al., 2014 provided EC to participants (29 smokers, mean cigarette consumption of 20 cpd, and of 55% of whom had used EC in past) but also allowed them to practice using the EC (NJOY®King Bold, a cigalike EC, with 26mg nicotine) for a week prior to undertaking a PK analysis [116]. Participants (who abstained from all nicotine products for at least 12 hours) then were asked to use EC (10 puffs with a 30 second inter-puff interval) on two occasions 60 minutes apart. Pharmacokinetic (PK) analyses were undertaken in 16 participants who had no detectable plasma nicotine at baseline. The mean rise in blood nicotine was 3.5 ng/ml (range 0.8-8.5 ng/ml) at 5 minutes after the first round of puffing and 5.1 ng/ml (range 1.1 – 7.1 ng/ml) at 10 minutes after the second.

3) Nicotine concentration and chemical composition of e-liquid

Yan & D'Ruiz (2014) examined nicotine delivery from Blu cigalike EC with differing levels of nicotine (2.4% and 1.6%), glycerin/propylene glycol (75% glycerin and 50% glycerin/20% propylene glycol), and flavours (classic tobacco and menthol)[129]. Participants (23 smokers) were randomized to 5 different EC conditions and smoking a regular cigarette in a cross over design. They were given 7 days to familiarize with EC use, and then abstain from all nicotine products for 36 hours prior to test days. On test days participants were asked to take 50 x 5 second puffs on EC at 30 sec intervals (in the cigarette arm they smoked 1 cigarette with usual puff duration at 30 sec intervals). After the controlled puffing testing ppts were allowed 60 minutes of *ad lib* use.

Peak plasma nicotine concentrations were reached sooner for cigarettes (5 minutes) than for EC (30 minutes). During the 30 minutes controlled puffing phase, within EC conditions the highest Cmax was seen with the 2.4% nicotine, 50% glycerin/20% PG (18.09 ng/ml, SD=6.47 ng/ml). The lowest Cmax was observed in the 1.6% nicotine, 75% glycerine (10.34 ng/ml SD=3.70 ng/ml). The Cmax associated with smoking one conventional cigarette was 15.84 ng/ml (SD = 8.64 ng/ml). At the end of the *ad lib* period, the highest Cmax was seen with the conventional cigarette (29.23 ng/ml SD = 10.86 ng/ml), followed by the 2.4% nicotine, 50% glycerin/20% PG EC (22.42 ng/ml; SD = 7.65ng/ml). The glycerine/PG mix resulted in better nicotine delivery than the 75% glycerine solution, which was confirmed in the bench top tests that measured nicotine content in vapour using the Canadian Intense regimen. The high nicotine content in vapour is a likely consequence of the lower boiling point of PG (187.6 degrees Celsius) compared with glycerine (290 degrees Celsius).

4) Type of EC device

Although many vapers start off with using a cigalike EC experienced vapers are more likely to be using tank systems or variable power EC. One of the reasons for this observation is that the tank systems and variable power ECs deliver nicotine more nicotine to the user.

Farsalinos et al., (2014) examined plasma nicotine levels in experienced vapers (n=23) who used a cigalike (V2 with cartomiser) and a new generation (EVIC set at 9 watts with EVOD atomizer) EC with standardized flavour and nicotine concentration (18mg/ml) in a cross-over design[129]. Participants' abstained from EC use for at least 8 hours before completing a bout of 10 puffs over 5 minutes followed by one hour of *ad lib* use. Use of the cigalike EC was associated with an increase in blood nicotine from 2.80 ng/ml at baseline, to 4.87 ng/ml at 5 minutes and 15.75 ng/ml at the end of ad lib use. Significantly greater increases were observed with use of the new generation EC from 2.46 ng/ml to 6.59 ng/ml to 23.47 ng/ml at baseline, 5 minutes and at the end of the *ad lib* period.

Oncken et al., (2015) also examined nicotine delivery in a tank system EC (Joye eGo-C with 18 mg/ml nicotine e-liquid) in 20 smokers who were asked to use an EC for two weeks[123]. Participants were asked to use the EC for 5 minutes ad lib in two laboratory sessions where blood samples were taken for PK analysis. Blood nicotine concentrations increased, significantly, by 4 ng/ml (Cmax 8.2 ng/ml) at the first session and 5.1 ng/ml (Cmax 9.3 ng/ml) at the second session. These levels were reached at five minutes.

Studies that examine cotinine as a measure of nicotine replacement in vapers

We found eight studies that reported on cotinine in urine, blood or saliva as a marker of nicotine exposure in people using EC.

In an RCT of nicotine containing EC versus placebo Caponnetto and colleagues (2013) measured salivary cotinine in participants who had stopped smoking cigarettes, but were still vaping EC (Categoria 7.5mg/ml)[40]. After 12 weeks of use the mean salivary cotinine concentration was 67.8 ng/ml, which is at the lower end of what is typically observed in smokers (eg 66.9-283.7 ng/ml).

In a study that randomised 48 smokers unwilling to quit to one of two tank system EC (18mg/ml nicotine) or to continue to smoke found that at 8 month follow-up mean salivary cotinine did not significantly differ between those who had stopped smoking but were vaping (428.27 ng/ml), achieved a ≥50% reduction in cigarette consumption (356.49 ng/ml) and those who continued to smoke (545.23 ng/ml, SD = 46.32)[41].

Van Staden et al., (2013) examined the change in serum cotinine in 13 smokers who were asked to stop smoking and instead use a Twisp eGo (18mg/ml nicotine) tank system EC for two weeks[113]. There was a significant decrease in cotinine from baseline 287.25 ± 136.05 to two weeks 97.01 ± 80.91 ng/ml suggesting that the EC used did not provide as much nicotine as participants usual cigarettes.

Norton et al., (2014) observed a similar result in 16 abstinent smokers who used a cigalike EC (11 mg/ml) for five days, finding a significant decrease in saliva cotinine between baseline (338.0 ng/ml) and day five (178.4 ng/ml)[112].

Flouris et al., (2013) measured serum cotinine in 15 smokers, who had abstained overnight, after smoking two of their usual cigarettes over 30 minutes and after 30 minutes of vaping a cigalike EC (Giant, 11mg/ml)[130]. EC and cigarettes produced similar effects on serum cotinine levels (60.6 ± 34.3 versus 61.3 ± 36.6 ng/ml). However measurement of cotinine would not give an accurate indicator of exposure in an acute study such as this.

Experienced vapers, using their own devices, however obtain much better nicotine substitution. Etter and Bullen (2011) measured salivary cotinine concentrations in 30 vapers who had been using EC for approximately 3 months on average and no longer smoking[9]. The mean nicotine content of e-liquid was 18mg/ml. Mean salivary cotinine was found to be 322 ng/ml indicating a high level of nicotine replacement via EC.

Similarly Etter (2014) found mean cotinine levels of 374 ng/ml (95% CI: 318-429) in 62 vapers who had not used any other nicotine containing products in the last 5 days [8].

Hecht et al., 2014 measured nicotine and cotinine in urine of 28 EC users (median use of 9 months, using tank system EC with e-liquid containing, on average 12.5 ± 7.0 mg/ml)[111]. Nicotine and cotinine levels in urine were 869 ng/ml (95% CI: 604-1250) and 1880 ng/ml (95% CI: 1420-2480) respectively, although these levels are lower than what are typically observed in smokers (eg nicotine 1380 ng/ml 95% CI: 1190-1600 and cotinine 3930 ng/ml; 95% CI: 3500-4400).