Public Health England

Protecting and improving the nation's health

Evidence review of e-cigarettes and heated tobacco products 2018

A report commissioned by Public Health England

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Conflict of interest declaration

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Executive summary

1 Introduction

- In England, adult smoking prevalence in 2016 was 15.5% and while it has fallen considerably over the last few decades, smoking remains the leading preventable cause of illness and premature death and one of the largest causes of health inequalities.
- This report has been commissioned to summarise evidence to underpin policy and regulation of e-cigarettes/vaping devices.
- It is the fourth in a series of reports commissioned by Public Health England (PHE) on e-cigarettes. In particular, this report updates the 2015 PHE report on e-cigarettes.
- Since the previous report, heated tobacco products, so-called 'heat-not-burn' tobacco products, have come onto the market in the UK and the report will provide evidence on this new product type as well as on e-cigarettes.

2 Methods

- The methods and sources of data used in the remaining chapters of the report focus on evidence produced since the previous report in 2015.
- The evidence falls into three main categories: 1) peer-reviewed literature and 2) surveys and 3) other reports and database sourced by and made available to PHE, King's College London and other partner organisations since the publication of the 2015 report:

    1) Peer-reviewed literature
        - Searches of the published, peer reviewed literature on e-cigarette published between 1 January 2015 and 18 August 2017.
        - A separate literature search was conducted for heat-not-burn products. This was not included in the 2015 report so literature was searched from 1 January 2010 to 13 July 2017.
    2) The use of survey data
        - For youth, these included: ASH Smoke-free Great Britain – Youth survey; Wales Schools Health Research Network; Scottish Schools Adolescent Lifestyle and Substance Use Survey; Smoking, Drinking and Drugs Survey; Youth Tobacco Policy Survey.
        - For adults, these included: ASH Smoke-free Great Britain - Adult survey; Eurobarometer; International Tobacco Control Policy Evaluation Survey; Internet cohort Great Britain survey; Opinions and lifestyle survey; Smoking Toolkit Study.

3) Other reports and databases
    - Data from NHS Digital (derived from local authorities) were assessed for Stop Smoking Service information.
    - Publicly available data from the National Poison Information Service were used for information on poisonings.
    - UK Fire and Rescue Incident Recording System (as reported by the Home Office) data was used for information on fires due to e-cigarettes.
    - Freedom of information requests were also sent to the UK regional fire and rescue services for information on fires caused by e-cigarettes and mobile phones.
    - A freedom of information request was sent to burns units, but for many, the cost of accessing the data would have been excessive. No data was included in this report.
    - The Medicines and Healthcare products Regulatory Agency provided us with details for spontaneous suspected adverse reaction reports for e-cigarettes along with details of suspected adverse drug reactions for nicotine replacement therapy products.
    - The ECig Intelligence Global Database was used to explore average price of various categories of e-cigarette.

3 Policy

Key findings

- As with tobacco products, in most parts of the UK, there is a minimum age of sale of 18 for e-cigarettes and e-cigarettes cannot be purchased on behalf of someone under the age of 18.
- The revised European Union Tobacco Products Directive is now fully operational in England, transposed into UK law through the UK Tobacco and Related Products Regulations 2016, and covers e-cigarettes and nicotine-containing e-liquids that do not have a medicinal licence. These regulations include a notification process to the Medicines Healthcare products Regulatory Agency (MHRA), minimum standards for safety and quality of e-cigarette products, standards for information provision (including a nicotine health warning) and advertising restrictions and updated standards. The Advertising Standards Authority has carried out a consultation on health claims; the results are awaited. A system to report side-effects and safety concerns related to e-cigarettes has been implemented.
- Over 32,000 e-cigarette and nicotine containing e-liquid products have been notified which suggests a level of compliance with the regulations, and that the notification process is not too onerous.
- There are some signs that ways are being found to avoid the law, for example particularly on size of bottles, but evidence is limited.

- Alongside products regulated in line with the EU Tobacco Products Directive, manufacturers can also apply for medicinal licensing from the Medicines Healthcare products Regulatory Agency. However, no licensed e-cigarette has yet been marketed.
- Other e-cigarette related developments include consensus statements from a number of organisations and guidance on the use of e-cigarettes in public places and on their use in research.
- Non-nicotine e-cigarettes are governed by general product safety regulations (unlike combustible tobacco products).
- There is a separate notification process for heated tobacco products (to PHE) and results from a consultation on the tax treatment of these products are forthcoming. At the time of writing, two products had been notified.
- A new Tobacco Control Plan for England was published in July 2017.

Implications

Research

- There is a need for continued research on the impact of regulations on smoking rates and patterns, use of e-cigarettes by adults and young people, product design and quality, and adverse effects of e-cigarettes.
- Research should specifically assess the impact of the EU Tobacco Products Directive on production (with a specific focus on independent manufacturers who were the first to enter this field), innovation of products, and e-cigarette users and smokers.

Policy

- Regulations need to balance the risks of e-cigarettes with their potential benefits – and achieve key aims of reducing smoking and continuing to avoid uptake of e-cigarettes by non-smokers. This requires keeping them under regular review and evaluating their impact.
- Regulations for heated tobacco products should be made as least a stringent as for e-cigarettes.
- It remains a viable and important goal to facilitate regulation of some e-cigarettes as medicines via the Medicines Healthcare products Regulatory Agency. A review is needed of how to achieve this, possibly including more focus on post marketing surveillance and the provision of licences for short-term rather than extended use.
- Restrictions on communicating relative risks of e-cigarettes in comparison with combustible tobacco should be reconsidered. In any future review of the EU Tobacco Products Directive, consideration should be given to the wording of the health warning on nicotine *per se* given public misperceptions of its harmfulness.

- There appears to be no evidence justifying an urgent change regarding non-nicotine e-cigarettes or e-liquids which are currently outwith the scope of the EU Tobacco Products Directive.

4 Nicotine

Key findings

- The addictiveness of nicotine depends on the delivery system.
- It is possible that the addictiveness of tobacco cigarettes may be enhanced by compounds in the smoke other than nicotine.
- As e-cigarettes have evolved, their nicotine delivery has improved. This could mean that their addiction potential has increased, but this may also make them more attractive to smokers as a replacement for smoking. It is not yet clear how addictive e-cigarettes are, or could be, relative to tobacco cigarettes.
- While nicotine has effects on physiological systems that could theoretically lead to health harms, at systemic concentrations experienced by smokers and e-cigarette users, long-term use of nicotine by 'snus' (a low nitrosamine form of smokeless tobacco) users has not been found to increase the risk of serious health problems in adults, and use of nicotine replacement therapy by pregnant smokers has not been found to increase risk to the foetus.
- Adolescent nicotine use (separate from smoking) needs more research.
- The long-term impact of nicotine from e-cigarettes on lung tissue is not yet known and may be different from its impact systemically.

Implications

Research

- More research on nicotine in comparison to tobacco cigarette smoking is needed, and the popularity of e-cigarettes enables such research, albeit in the context of the other components in e-cigarette and e-cigarette aerosol.
- Further research is needed on the similarities and differences in addictiveness of e-cigarettes and tobacco cigarettes and the potential harms associated with *inhaled* nicotine.

Policy and practice

- Widespread misperceptions about the relative risks of nicotine and tobacco (see Chapter 10) need to be addressed and corrected.

- Clear messages, based on current evidence about nicotine, its relationship with harms, and its addictiveness, compared with smoking, are necessary and could have a marked impact on public health.
- Policies on tobacco and e-cigarettes should have at their core the recognition that nicotine use per se presents minimal risk of serious harm to physical health and that its addictiveness depends on how it is administered.

5 Use of e-cigarettes among young people

Key findings

- E-cigarettes cannot be legally sold to young people under the age of 18 in most parts of the UK. Purchasing does occur including from sources rarely used for tobacco, such as online suppliers.
- Despite some experimentation with these devices among never smokers, e-cigarettes are attracting very few young people who have never smoked into regular use.
- E-cigarettes do not appear to be undermining the long-term decline in cigarette smoking in the UK among young people.
- Never smokers in the UK who try e-cigarettes are more likely to have tried smoking subsequently than those who have not tried e-cigarettes. A causal link has not been established and neither has progression to regular smoking. The 'common liability' hypothesis seems a plausible explanation for the relationship between e-cigarettes and smoking implementation.

Implications

- Trends in e-cigarette use and smoking among youth should continue to be monitored using standardised definitions of use. This should include the use of nicotine in e-cigarettes and checks on the understanding of survey questions.
- Patterns of e-cigarette purchasing by young people should be closely monitored, particularly internet sales. Age of sale regulations are in place for e-cigarettes and cigarettes and should be strongly enforced.
- Research is needed on trajectories of use – not just from e-cigarette experimentation to smoking, but also from smoking to e-cigarette use among young people.

6 Use of e-cigarettes in adults

Key findings

Prevalence

- In GB, prevalence of e-cigarette use in adults has plateaued at approximately 6% of the adult population.
- E-cigarette use among never smokers in GB remains very rare at less than 1%, similar to the level of use of nicotine replacement therapy. Among never smokers who have ever used e-cigarettes, a minority have used nicotine-containing liquids and the vast majority not progressed to regular use.
- Prevalence of e-cigarette use and trial among smokers has plateaued while use and trial among ex-smokers continue to increase.
- Socioeconomic differences in e-cigarette use by smokers and recent ex-smokers have become smaller with no clear gradient in prevalence by occupational grade.
- Prevalence of dual use (use and smoking) is similar for e-cigarette users and users of nicotine replacement therapy.

Characteristics of use

- Most e-cigarette trial does not become regular use.
- Most current e-cigarette users use daily and have used e-cigarettes for more than six months.
- Models with refillable tanks for liquids are the most widely used type.
- Since May 2017, nicotine concentration in liquids has been limited to a maximum of 20mg/mL. In March 2017, around 6% of e-cigarette users reported using higher nicotine concentrations; substantial proportions had difficulties reporting these figures so more may have been affected by the limit.
- The most popular groups of flavours among current e-cigarette users are fruit (29%), tobacco (27%) and menthol/mint (25%).
- Specialist vape shops (physical premises rather than online) are the most popular place of purchase (>40%).
- The most common reason for e-cigarette use continues to be in order to stop smoking, and smokers who use e-cigarettes on average have higher motivation to stop smoking than other smokers.

International

- Data can be outdated by the time of publication.
- Prevalence of current use in GB is at the higher end for countries in the EU where the average is 2% for current e-cigarette use. Prevalence estimates for current e-cigarette use in the US are around 4% to 6%, which is similar to GB.
- Across international surveys, a consistently low prevalence (<1%) of e-cigarette use has been reported among never-smokers; one exception is one Spanish survey at 1.2%.
- Prevalence figures found for smokers and ex-smokers vary more widely across surveys in different countries (4% to 22% among smokers and 0.1% to 5% among ex-smokers).

Implications

Research

- As recommended in the 2015 PHE report, trends in e-cigarette use among adults should continue to be monitored using standardised definitions of use. Measures should include frequency and type of device used including different types of tank models.
- E-cigarette use among ex-smokers needs monitoring and further evidence to understand when and why they take up e-cigarette use and whether this is associated with an increase or decrease of relapse to smoking.
- More research is needed into different patterns of e-cigarette use while smoking and their effect on subsequent smoking behaviour to understand how best to move dual users to stop smoking.
- More research is needed on the impact of e-cigarettes on health and economic inequalities associated with smoking; in particular on use of e-cigarettes in disadvantaged groups with high smoking prevalence and smoking-related morbidity and mortality, such as those with mental health problems or offenders. Data that have been gathered from the Adult Psychiatric Morbidity Survey should be released for analysis.

Policy

- As recommended in 2015 and as per existing NICE guidance, all smokers should be supported to stop smoking completely, including ‘dual users’ who smoke and use e-cigarettes.
- Access to e-cigarettes should be improved for smokers in disadvantaged groups.

7 The effect of e-cigarette use on smoking cessation and reduction

Key findings

- In the first half of 2017, quit success rates in England were at their highest rates so far observed and for the first time, parity across different socioeconomic groups was observed. It is plausible that e-cigarettes have contributed to this.
- Recent estimates of additional quitters resulting annually from the availability of e-cigarettes, using the same dataset but two different methods, resulted in similar figures within the range of 16,000-22,000. Varying the assumptions, and updating these estimates for 2016, resulted in an upper bound estimate of around 57,000 additional quitters annually resulting from e-cigarettes (lower bound around 22,000). While caution is needed with these figures, the evidence suggests that e-cigarettes have contributed tens of thousands of additional quitters in England.
- E-cigarette use, alone or in combination with licensed medication and behavioural support from a Stop Smoking Service, appear to be helpful in the short term. However, fewer smokers use an e-cigarette as part of a quit attempt with a Stop Smoking Service compared with licensed medication.
- We identified 14 systematic reviews of e-cigarettes for smoking cessation and /or reduction published since our last report, seven of which included a meta-analysis. The authors of the systematic reviews arrived at the same conclusion that further randomised controlled trials of e-cigarettes are needed. However, the reviews that included a meta-analysis produced different results; two found a positive effect on cessation for e-cigarette use, four found an inconclusive effect for cessation and one found a negative effect.

Implications

Research

- An important focus of future research is longer-term relapse trajectories of people who use e-cigarettes for quitting compared with other stop smoking treatments and also assess whether the uptake of e-cigarettes after quitting can prevent relapse back to smoking.
- Funders should consider that although randomised controlled trials (RCTs) may yield higher internal validity this is at the cost of lower generalisability. Future robust observational studies and RCTs should consider allowing for user experimentation (eg trial and error of different types of e-cigarette products), as well as the inclusion of study outcomes that are relevant and meaningful for e-cigarette users.
- Funders should commission research about the effect of e-cigarettes on smoking cessation in vulnerable populations (eg people who smoke who have a mental illness, substance misuse disorder, homeless or prison populations).

Policy and practice

- Stop smoking practitioners and health professionals should provide behavioural support to smokers who want to use an e-cigarette to help them quit smoking.
- Stop smoking service practitioners and health professionals supporting smokers to quit should receive education and training in use of e-cigarettes in quit attempts.
- Local authorities should continue to fund and provide Stop Smoking Services in accordance with the evidence base.

8 Poisonings, fires and explosions

Key findings

Poisonings

- There are recorded cases of poisoning from e-liquid in the UK. These have predominantly involved accidental ingestion with fewer incidences of other routes (eg ocular or dermal) of exposure.
- Intentional poisoning using e-liquids has been reported in self-harm and suicide attempts.
- Toxic effects from e-cigarette poisoning are usually short in duration and of minimal severity; severe cases and fatalities, while very rare, have been recorded.
- E-cigarette poisonings reported to medical centres most commonly occur in children under five years old. Toxic effects for this age group are usually short in duration and non-severe. Fatalities, while very rare, have also been recorded in this age group.
- Incidents of poisoning in children are often preventable and have involved liquids stored non-securely, in unmarked containers or in containers without safety caps.

Fires

- E-cigarette fires are recorded at the discretion of individual fire rescue services in the UK. Information provided to us through a Freedom of Information request suggest that, where recorded, they occur in low numbers and are vastly outweighed by fires caused by smokers' materials. There were no fatalities from fires caused by e-cigarettes in the reporting period.
- E-cigarettes and/or their batteries are recorded as the cause of fires by UK fire rescue services. The root cause of e-cigarette fires is likely to be through a malfunctioning lithium-ion battery.

Explosions

- Exploding e-cigarettes can cause severe burns and injuries that require intensive and prolonged medical treatment especially when they explode in users' hands, pockets or mouths.
- Incidents are very rare. The cause is uncertain but appears to be related to malfunctioning lithium-ion batteries.

Implications

Research

- Research is required on the prevalence of e-liquid poisoning, fires and explosions caused by e-cigarettes in England. This will require some synthesis of existing datasets.
- Research on presence and effectiveness of safety features and instructions should be part of a future review of the EU Tobacco Products Directive.

Policy and practice

- Monitoring of fires caused by e-cigarettes should be recorded by Fire Rescue Services in a mandatory way (similar to "cooking appliances", "smokers' materials" and "other electrical appliances") and should not continue to rely on free text entry.
- E-cigarettes can trigger fire/smoke detectors and therefore consumers should be advised to move away from detectors when using them.
- It is too early to assess the impact of the EU Tobacco Products Directive in reducing poisonings, fires or explosions, or whether further regulations are needed. Therefore, continued monitoring is required to assess effectiveness of EU Tobacco Product Directive regulations (such as childproof containers), in reducing accidental ingestion of e-liquid.
- Regulations should require that labelling on e-liquid bottles advises customers to store products away from similar looking medicines such as eye drops, ear drops and children's medicine.
- Regulations should require that labelling reinforces advice on the safe storage and transportation of batteries used by e-cigarettes. For example, advice should be given that e-cigarettes should not be carried in pockets with coins, keys or other metallic objects, and that the correct charger should always be used.

9 Health risks of e-cigarettes

Key findings

- One assessment of the published data on emissions from cigarettes and e-cigarettes calculated the lifetime cancer risks. It concluded that the cancer potencies of e-cigarettes were largely under 0.5% of the risk of smoking.
- Comparative risks of cardiovascular disease and lung disease have not been quantified but are likely to be also substantially below the risks of smoking. Among e-cigarette users, two studies of biomarker data for acrolein, a potent respiratory irritant, found levels consistent with non-smoking levels.
- There have been some studies with adolescents suggesting respiratory symptoms among e-cigarette experimenters. However, small scale or uncontrolled switching studies from smoking to vaping have demonstrated some respiratory improvements.
- E-cigarettes can release aldehydes if e-liquids are overheated, but the overheating generates an aversive taste.
- To date, there is no clear evidence that specific flavourings pose health risks but there are suggestions that inhalation of some could be a source of preventable risks.
- To date, the levels of metals identified in e-cigarette aerosol do not give rise to any significant safety concerns, but metal emissions, however small, are unnecessary.
- Biomarkers of exposure assessed to date are consistent with significant reductions in harmful constituents and for a few biomarkers assessed in this chapter, similar levels to smokers abstaining from smoking or non-smokers were observed.
- One study showed no reductions across a range of biomarkers for dual users (either for nicotine replacement therapy or e-cigarette dual users).
- To date, there have been no identified health risks of passive vaping to bystanders.
- Reporting of some academic studies has been misleading.

Implications

Research

- More research is needed with human users about biomarkers of exposure, risk and harm and health effects over time.
- More research with biomarkers across the range of different combinations of dual use is needed.
- Adverse effects of passive vaping should be monitored.

Policy

- Policy makers and regulators should ensure that e-cigarettes are manufactured in a way that minimises harm. An advantage of e-cigarettes is that particular constituents can be removed or minimised in a way that is not feasible with tobacco cigarettes.
- Regulations should therefore be flexible to ensure any emerging evidence of constituent harmfulness can be acted upon, such that products are modified to remove any components shown to pose avoidable risks.
- Consumers and health professionals should be encouraged to use the Yellow Card Scheme for reporting adverse reactions to e-cigarette use.
- Vaping poses only a small fraction of the risks of smoking and switching completely from smoking to vaping conveys substantial health benefits over continued smoking. Based on current knowledge, stating that vaping is at least 95% less harmful than smoking remains a good way to communicate the large difference in relative risk unambiguously so that more smokers are encouraged to make the switch from smoking to vaping. It should be noted that this does not mean e-cigarettes are safe.
- The lack of difference in biomarkers between dual users and smokers found so far underlines the need to encourage and support dual users to stop smoking altogether.

10 Perceptions of relative harms of nicotine, e-cigarettes and smoking

Key findings

- Perceived relative harm of e-cigarettes compared with cigarettes has continued to increase; less than half of adults in Great Britain think e-cigarettes are less harmful than smoking.
- Nicotine replacement therapy is subject to similar misperceptions and only just over half of adults in GB think that nicotine replacement therapy is any less harmful than smoking.
- Adult smokers are poorly informed about relative risks of different products.
  - Only half of smokers believe that e-cigarettes are less harmful than smoking and this decreases to one third among smokers who have never tried e-cigarettes.
  - In contrast to evidence to date, it appears that a majority of smokers and ex-smokers does not think that complete replacement of cigarettes with e-cigarettes would lead to major health benefits.
  - Only half of all adult smokers believe that nicotine replacement therapy is any less harmful than smoking.

- As the common factor for cigarettes, nicotine replacement therapy and (most) e-cigarettes is nicotine, these misperceptions may be linked to the perception of nicotine.
  - When adults in GB are asked what proportion of the health harms of smoking is due to nicotine, the accurate response (most health harms are not caused by nicotine) is the least common response consistently chosen by 8-9%. Smokers' knowledge around nicotine is similarly poor.
  - Four in ten smokers and ex-smokers incorrectly think nicotine in cigarettes is the cause of most of the smoking-related cancer.
  - Misperceptions around nicotine and cancer are greater in more disadvantaged groups.
- It is unclear to what extent the perception of addictiveness underpins the perception of harm.
- Among youth in GB, perceived harm of e-cigarettes relative to cigarettes has also increased over time and nicotine knowledge is similarly poor (7% correctly responded that none or a small portion of the harms of smoking is due to nicotine).
- Where available, international data show similar misperceptions around nicotine and relative harmfulness of e-cigarettes and smoking as in England. International data also support the trends of increased harm perception of e-cigarettes with the exception of one survey in youth in the US.

Implications

Research

- Future research should aim to assess causes and effects of misperceptions of the relative harmfulness of e-cigarettes and nicotine replacement therapy compared with cigarettes, including to what extent the perception of addictiveness contributes to these misperceptions.

Policy

- Misperceptions of nicotine and different nicotine-containing products need to be addressed. These have deteriorated further since the PHE report in 2015 which called for clear and accurate information on relative harms.
  - Misperceptions of the relative harms of nicotine replacement therapy and e-cigarettes compared with cigarettes need to be addressed, particularly among smokers who would benefit from switching to nicotine replacement therapy or e-cigarettes.
  - Knowledge about the role of nicotine in the development of cancers and other diseases caused by smoking needs improvement.

11 Pricing

Key findings

- Price varies considerably between products, and there appear to be differences between online and bricks and mortar shop prices, with closed system products tending to be cheaper online, and open system kits cheaper in bricks and mortar shops.
- Generally, average maximum and minimum prices seem to have remained relatively stable from August 2015 to July 2017 for all product categories.
- There appear to have been no major and consistent changes in price over the first year since implementation of the EU Tobacco Products Directive.

Implications

- Current available data provide minimum, maximum and average prices, but do not provide detail on nicotine levels, brands and flavours that would be helpful to our understanding of market developments.
- Currently e-cigarette products are available in a wide range of prices and therefore affordable to various types of e-cigarette users. Any changes in pricing need to ensure that e-cigarettes are affordable to smokers to avoid discouraging smokers from switching away from smoked tobacco which would be counter-productive in public health terms. There should therefore be a competitive advantage for the prices of e-cigarettes compared to combustible tobacco products.

12 Heated tobacco products

Key findings

- In mid 2017 heated tobacco products were commercially available in 27 countries and further country launches were planned. Three tobacco manufacturers were promoting heated tobacco products: ‘IQOS’ was promoted by Philip Morris International, ‘glo’ by British American Tobacco, and ‘Ploom TECH' by Japan Tobacco International.
- Out of 20 studies that were included in this review, 12 were funded by manufacturing companies so there is a lack of independent research.
- There is a variety of heated tobacco products, including some that deliver via both vapour and combustion.
- Most studies published at the time of the search for this review evaluated IQOS, none evaluated glo or Ploom TECH. An updated version of the review including later publications is in preparation to be published separately.

- In Great Britain, in 2017, awareness and ever use of heated tobacco products were very rare.
- Nicotine in mainstream aerosol from heated tobacco products reached 70%–84% of the nicotine detected in smoke from reference cigarettes.
- The tested heated tobacco products delivered more nicotine in aerosol than a cigalike e-cigarette and less nicotine than a tank style e-cigarette.
- Pharmacokinetics and delivery of nicotine after single use of a heated tobacco product were generally comparable with smoking a cigarette. However, studies that compared *ad libitum* use of heated tobacco products with smoking cigarettes consistently reported lower nicotine levels in heated tobacco product users compared with smokers.
  - Probably to compensate, smokers who were switched to using heated tobacco products adjusted their puffing behaviour.
- Heated tobacco product use reduced urges to smoke, but smokers consistently reported heated tobacco product use to be less rewarding compared with smoking a cigarette.
- Compared with cigarette smoke, heated tobacco products are likely to expose users and bystanders to lower levels of particulate matter and harmful and potentially harmful compounds. The extent of the reduction found varies between studies.
- The limited evidence on environmental emissions from use of heated tobacco products suggests that harmful exposure from heated tobacco products is higher than from e-cigarettes, but further evidence is needed to be able to compare products.
- Japan, where e-cigarettes are not available, has the most diverse heated tobacco product market with three tobacco manufacturers participating. Past 30 day use for the most frequently used product increased from 0.3% in 2015 to 3.7% in 2017, suggesting rapid penetration of heated tobacco products.

Implications

Research

- There is a need for more research that is independent of commercial interests.
- Different types of heated tobacco products will have different characteristics and effects, presenting a challenge for research.
- Research is needed on relative risks of heated tobacco products to users and those around them compared with cigarettes and e-cigarettes.
- Evidence is needed on appeal of heated tobacco products to smokers and non-smokers, particularly among youth.
- Effects on smoking need to be researched, this includes whether they replace or complement cigarettes. Due to co-branding of some products with cigarettes and the more similar sensory profile, findings may be different than for e-cigaretttes.

- Future studies, whether funded by manufacturers or independently, should ensure conduct of studies in line with established guidelines such as definitions of abstinence from smoking, using intention-to-treat analysis and registering trial protocols prior to the start of participant recruitment.
- The appropriateness of different methods for measuring emissions and their translation from cigarettes to heated tobacco products should be evaluated to be able to recommend a gold standard.
- Prevalence and market share should be monitored, particularly in markets targeted by manufacturers.
    - In line with recommendations for e-cigarette use, measures should go beyond lifetime use or past 30 day use to assess current use; uptake and use should be assessed by smoking status.
    - Monitoring should include transitions between smoking, e-cigarette use and heated tobacco product use.

Policy

- The available evidence suggests that heated tobacco products may be considerably less harmful than tobacco cigarettes and more harmful than e-cigarettes.
- With a diverse and mature e-cigarette market in the UK, it is currently not clear whether heated tobacco products provide any advantage as an additional potential harm reduction product.
- Depending on emerging evidence on their relative risk compared to combustible tobacco and e-cigarettes, regulatory levers such as taxation and accessibility restrictions should be applied to favour the least harmful options alongside continued efforts to encourage and support complete cessation of tobacco use.

1 Introduction

In England, smoking prevalence has fallen considerably over the last few decades, but smoking remains the leading preventable cause of illness and premature death and one of the largest causes of health inequalities. The decline has continued in the last few years: adult smoking prevalence in England declined from 19.9% in 2010 to 15.5% in 2016 (1). In 2017, the Department of Health and Social Care for England has published a new Tobacco Control Plan aiming to achieve a 'smokefree generation' with smoking prevalence eventually at 5% or below (2). Four ambitions were outlined, which highlighted the importance of reducing smoking in young people, in more disadvantaged groups including those with mental health problems and reducing smoking in pregnancy; the fourth ambition recognised the role that less harmful alternatives could play. The Tobacco Control Plan indicated that PHE would update their evidence report on e-cigarettes (EC) and other novel nicotine delivery systems annually until the end of Parliament in 2022. This report is the first of those updates.

EC comprise a battery-powered heating element that is designed to vaporise a solution made of propylene glycol and/or glycerine, water and frequently flavouring and nicotine. This vapour (or rather aerosol) is then inhaled. There are many different types of EC; they can be classified into three basic types: (1) one-time, disposable products (often referred to as cigalikes); (2) reusable, rechargeable kits that are designed to be refilled with liquid by the user (often referred to as tanks) and (3) reusable, rechargeable kits that allow users to customise their product such as by regulating the power delivery from the batteries to the heating element (sometimes these are included with other tank models). In contrast to EC, heated tobacco products in general apply heat to tobacco instead of liquids (although there are hybrid products). Typically, heated tobacco products are rechargeable and include a holder, and tobacco sticks, plugs or capsules to be heated with an electronically controlled heating element.

Objective of the report

This report has been commissioned to summarise evidence to underpin policy and regulation of EC and novel nicotine delivery systems. It is the fourth in a series of reports commissioned by PHE on EC (3, 4). In particular, this report updates the 2015 PHE report on EC (5). Since the previous report, heated tobacco products, so-called 'heat-not-burn' tobacco products have come onto the market in the UK and the report will summarise evidence on this new product type as well as on EC.

Structure of the report

Following this introduction, Chapter 2 describes the methods used for the chapters presenting the most recent evidence on EC and heated tobacco products. Chapter 3

provides a summary of the current regulations for EC and heated tobacco products in the UK and Chapter 4 summarises evidence on the role of nicotine in tobacco and EC use, its addictiveness and safety profile. Chapter 5 summarises evidence on use among young people and Chapter 6 summarises evidence on use among adults. Chapter 7 considers the evidence for EC in smoking cessation. Chapter 8 summarises the available evidence on the risks of fires, poisonings and explosions related to EC and Chapter 9 discusses health risks to users and bystanders. Chapter 10 provides evidence on the relative harm perceptions of different nicotine-containing products. Chapter 11 describes trends in indicative pricing of EC. Finally, Chapter 12 assesses the evidence on heated tobacco products. This report is focused on England, and draws on surveys from England, Great Britain and the United Kingdom. A brief overview is also given, where appropriate, of the international situation.

Acronyms and abbreviations used in this report

A&E = Accident and Emergency
ASA = Advertising Standards Authority
ASH = Action on Smoking and Health
ASH-A = ASH Smoke-free Great Britain-Adult survey
ASH-Y = ASH Smoke-free Great Britain-Youth survey
AOR = Adjusted Odds Ratio
BAT = British American Tobacco
CHTP = Carbon Heated Tobacco Product
CI = Confidence Interval
CO = Carbon Monoxide
CPD = Cigarettes Per Day
CVD = Cardiovascular Disease
EC = E-cigarette/E-cigarettes
ENDS = Electronic Nicotine Devices/Electronic Nicotine Delivery Systems
EU TPD = The Revised European Union Tobacco Products Directive
EU = European Union
FDA = Food and Drug Administration (US)
FOI = Freedom of Information
FOI-B = Freedom of information request made to UK burns treatment centres
FOI-F = Freedom of information request made to UK fire rescue services
GB = Great Britain
GBP = Pounds Sterling
GPs = General Practitioners
HCI = Health Canada Intense
HPHC = Harmful and Potentially Harmful Compounds
ICGBS = Internet cohort Great Britain survey
ISO = International Organization for Standardization
ITC = International Tobacco Control

IV = Intra Venous
KCL = King's College London
MHRA = Medicines and Healthcare products Regulatory Agency
NYTS = National Youth Tobacco Survey (US)
NHS = National Health Service (UK)
NICE= National Institute for Health and Care Excellence
NPIS = National Poisons Information Service
NRT = Nicotine Replacement Therapy
ONS = Office for National Statistics
OR = Odds Ratio
OTC = Over the Counter
PATH = Population Assessment of Tobacco and Health (US)
PG = Propylene Glycol
PHE = Public Health England
PMI = Philip Morris International
RCP = Royal College of Physicians
RCTs = Randomised Controlled Trials
SALSUS = Scottish Schools Adolescent Lifestyle and Substance Use Survey
SD = Standard Deviation
SDD = Smoking, Drinking and Drugs Survey
SHRN = Wales Schools Health Research Network survey
STS = Smoking Toolkit Study
WHO = World Health Organization
YTPS = Youth Tobacco Policy Survey

2 Methods

Introduction

This chapter describes the methods and sources of data used in the report and focuses on evidence produced since the previous report in 2015. The evidence falls into three main categories:

- peer-reviewed literature reviews: Searches of the published, peer reviewed literature on EC produced between 1 January 2015 and 18 August 2017. A separate literature search was conducted for heated tobacco products (often referred to as heat-not-burn). This was not included in the 2015 report so literature was searched from 1 January 2010 to 13 July 2017.
- survey data
- other reports and databases sourced by and made available to PHE, King's College London (KCL) and other partner organisations since the publication of the 2015 report

A summary of methods for each topic is given at the beginning of each chapter, but details of the literature reviews and sources of surveys and other data are given here.

Literature reviews

A full systematic review was not possible given the timeframe within which the report was commissioned and needed to be delivered, and the wide scope of the topics covered. However, a systematic review was carried out for heated tobacco products – see below for the search strategies and methods used, and chapter 12. For the remainder of the report topics covering EC, we carried out one literature search using systematic review methods, and we included key material on EC relevant to the topics studied, such as new syntheses of evidence, new evidence or data from research studies or detailed case studies. In addition, studies published since the search were included where they were pertinent to the topics we were studying and provided new relevant information.

EC literature

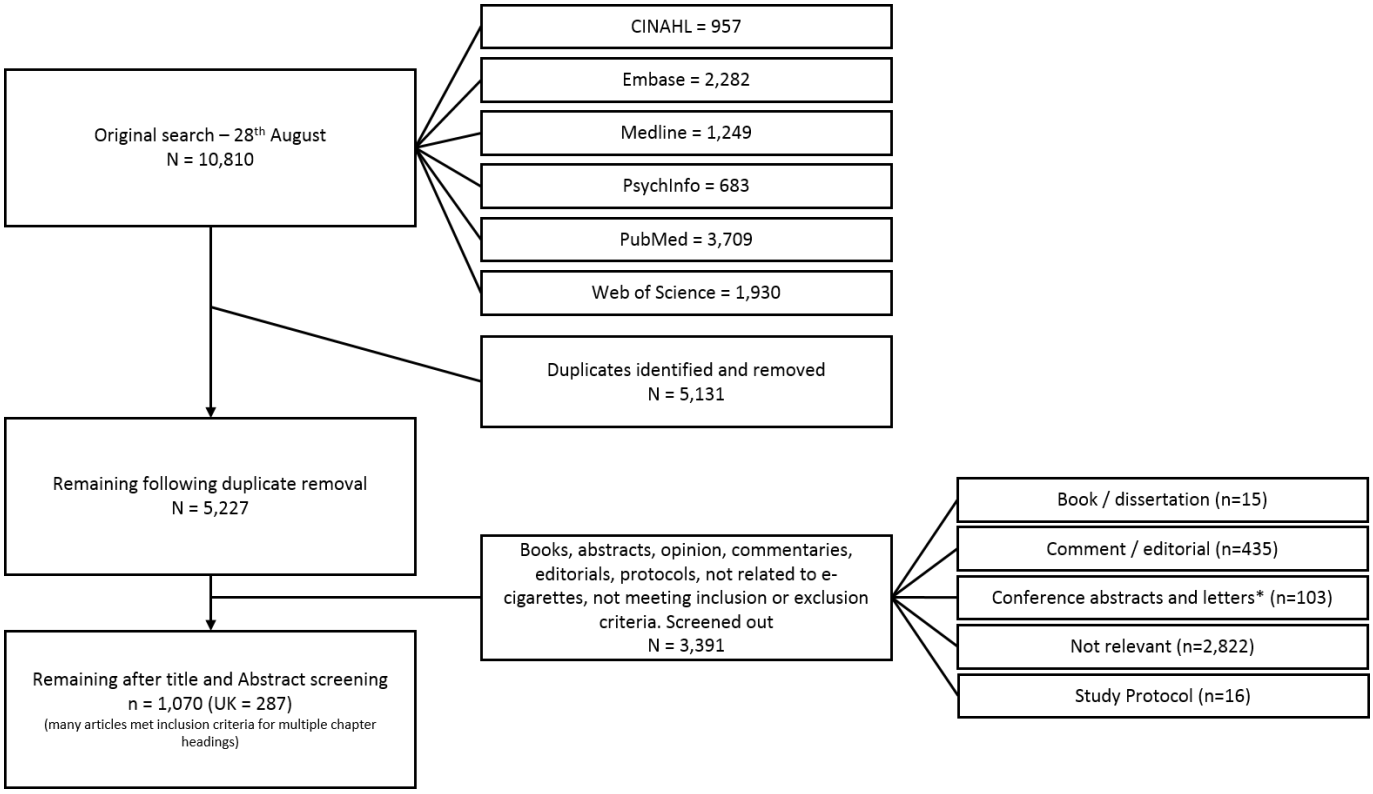
The literature search was based on the search developed and used in the 2015 PHE report (5) to ensure consistency between the two reports. However two terms within the search were updated. The terms "ENDS" and "Vap*" were both combined with the term "nicotine" because of their use in non-nicotine fields. The final search term was:

(("2015/01/01"[Date - Publication]: "3000"[Date -Publication])) AND (((((((e-cigarette) OR Electronic cigarettes) OR e-cig) OR electronic cig*) OR (ENDS AND Nicotine)) OR electronic nicotine delivery systems) OR electronic nicotine delivery system) OR ((Nicotine) AND (Vaping* OR Vape* OR Vaporiz* OR Vaporis* OR Vapouris*)).* The term *"(2015/01/01"[Date - Publication]: "3000"[Date -Publication])"* limits the search to all literature published after 1 January 2015 to the day of the search.

The final search was completed on 18 August 2017 and covered the following databases: Pubmed, Embase, PsychInfo, MEDLINE, Web of Science and CINAHL. This search yielded 10,810 results which were screened initially by title and abstract and then by full text. The full screening process is shown in Figure 1. Literature was included where it reported on EC, published new evidence or data from research studies, presented a new synthesis of existing evidence, detailed case studies relevant to EC, analysed policy and was published in English. Literature was excluded where they did not present new data, were editorial or opinion based in nature (ie did not contain new data), syntheses or research findings, were not peer-reviewed or were published before 1 January 2015. Additional literature known to the authors was included where it was able to provide context.

In addition to literature identified by this screening process, high profile studies that were published since the search were included where they provided new relevant information or generated particular media interest. Some studies published before 2015 were also included where they provided relevant background or context.

Figure 1: PRISMA Flowchart of the EC literature search



Heated tobacco products literature review

A separate literature search was conducted for evidence on heated tobacco products.

Search strategy and selection of studies

MEDLINE, EMBASE, PsychInfo, ProQuest, Scopus, and Web of Science databases were searched on 13 July 2017. The search included terms relating to general heated tobacco product names ('heat not burn', 'tobacco heating system') and brand names ('IQOS', 'Ploom', 'Heets'), and were limited to studies published from 2010. Endnote X7 was used to record publications at all stages of the review.

The final search term was as follows:

(("2010/01/01"[Date - Publication]: "3000"[Date -Publication])) AND ((Heat not burn) OR (tobacco heating system) OR (heat adj3 tobacco) OR (IQOS) OR (Ploom) OR (Heets))*

One reviewer (ES) screened all titles and abstracts of initially included studies, and two reviewers (ES and LBr) independently screened full text papers; Cohen's *kappa* was calculated as a measure of agreement. Articles were screened in if they were studies of

heated tobacco products, studies of emissions or human studies, studies that presented new data or evidence and were research papers. Articles were excluded if the subject was not heated tobacco, not peer reviewed (eg conference abstracts, commentaries, editorials), published before 1 January 2010, were animal or in vitro studies, if focused on products that are no longer available such as Premier or Eclipse. The full screening process is shown in Chapter 12.

Data extraction

Data was extracted to a pre-defined table by one reviewer (ES) and checked by a second reviewer (LBr).

Data synthesis

Data from studies on heated tobacco product emissions and on use of heated tobacco products by humans were synthesised separately. Key findings were summarised in a narrative synthesis, and quantitative results were compared between studies where comparison was possible.

Surveys

In the introduction of each chapter in this report we detail the specific datasets used in that chapter. Data from several surveys were used, their details are listed in Table 1. Where possible, references are made to peer-reviewed publications that have used the data.

Table 1: Surveys used in this report

Name and acronym	Commissioned & conducted by	Geographic coverage, sample	Representativeness	Design	Time-frame included	Example publications
Youth surveys						
ASH Smoke-free Great Britain-Youth survey (ASH-Y)	ASH, YouGov plc	GB, aged 11-18, annual n>2,000	Recruited via a panel, weighted to be representative of all GB 11-18 year olds	Online, repeated cross-sectional	2016 and 2017	(6, 7) (8)
Wales Schools Health Research Network survey (SHRN)	Partnership led by Cardiff University; with Welsh Government, Public Health Wales, Cancer Research UK and 113 secondary schools	Wales secondary school pupils, n=32,479	Network schools represent about half of all secondary schools, representation in all local authority areas. 87 participating schools; where full participation was not possible two randomly selected mixed ability classes	Online, school-based, repeated cross-sectional	2015	(6) (9) (10)
Scottish Schools Adolescent Lifestyle and Substance Use Survey (SALSUS)	Scottish Government, Ipsos MORI Scotland	Scotland, second-year (n=13,607) and fourth-year (n=11,697) secondary school pupils	Sample weighted to be in line with the pupil census at national level	School-based, online and on paper in exam conditions, repeated cross-sectional	2015/16	(6) (10)
Smoking, Drinking and Drugs Survey (SDD)	NHS Digital, Ipsos MORI	England, school pupils aged 11-15, 2016 n=12,051	Sample weighted to be in line with the pupil census at national level	Completed on paper in exam conditions, repeated cross-sectional	2016	(11)
Youth Tobacco Policy Survey (YTPS)	Stirling University, FACTS International (Ashford, UK),	UK, aged 11-16, n=1,213	Random location sampling in 92 electoral wards, stratified to cover geographic areas and socio-demographic backgrounds	Face-to-face household interviews, repeated cross-sectional	2016	(6)

Name and acronym	Commissioned & conducted by	Geographic coverage, sample	Representativeness	Design	Time-frame included	Example publications
Adult surveys						
ASH Smoke-free Great Britain-Adult survey (ASH-A)	ASH, YouGov plc	GB, aged 18+, annual n>12,000	Recruited from a panel according to quotas; responses weighted to be representative	Online, repeated cross-sectional	Annually 2010 to 2017	(12-14)
Eurobarometer	European Commission, TNS	EU, aged 15+, n=27,901	Multi-stage random probability sampling in each country, responses weighted	Face-to-face interviews, repeated cross-sectional	2017	(15)
ITC Policy Evaluation Survey (ITC)	A variety of funders, see http://www.itcproject.org/sponsors	29 country cohorts typically smokers and ex-smokers aged 18 years and over. N~ 2000 per country per survey.	Typically random sampling within stratified population quota. Weighted data	Telephone, online, longitudinal	Surveys 2002-2016	(16) For more detail about the methods of this survey see http://www.itcproject.org/methods
Internet cohort Great Britain survey (ICGBS)	KCL, Ipsos MORI	GB, smokers and ex-smokers, aged 18+, 2012: N=5,000, 2013: N=2,182, 2014: N=1,519, 2016: N=3,431 (incl n=2,403 new recruits)	Recruited from a panel using quotas on age, sex and region	Online, longitudinal	2012, 2013, 2014, 2016	(17-21)

Name and acronym	Commissioned & conducted by	Geographic coverage, sample	Representativeness	Design	Time-frame included	Example publications
Opinion and lifestyle survey (ONS)	ONS	GB, aged 16+, n=7,713	Two stage, stratified random probability sample, responses weighted	Household face-to-face interviews, repeated cross-sectional	2016	(22) For more detail about the methods of this survey see https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/healthandlifeexpectancies/bulletins/adultsmokinghabitsingreatbritain/2016,
Smoking Toolkit Study (STS)	University College London, Ipsos MORI	England, aged 16+, n~1800 per month	Recruited to be nationally representative to the population of England according to census data	Household face-to-face interviews, repeated cross-sectional	Monthly 2011-2017	(23)

Other reports and databases

The following section details sources of data used in the present report. These include data sources that were available, or otherwise sought by PHE, KCL and other partners. The methods used to create each individual dataset are summarised here as well as methods used to source the data where relevant.

NHS Digital; formerly Health and Social Care Information Centre (HSCIC)

PHE monitors the delivery of Stop Smoking Services in England. Data are collected from local authorities by NHS Digital (formerly the HSCIC), an internal NHS Information technology provider. The data include information on the number of patients setting a quit date; the number who successfully quit and key measures of the service including intervention type, intervention setting and type of pharmacotherapy received. Since 2014, Stop Smoking Services have been asked to record if an EC was used in a quit attempt. A successful quitter is defined as a person who reports they have not smoked in the past two weeks, when assessed 4 weeks after their designated quit date. Clients who self-report as having quit at the 4-week follow up are required to have their CO levels monitored as a validation of their quit attempt; self-reported quit rates and CO validated rates are reported separately by NHS Digital. We report data from April 2015 to March 2017.

National Poisons Information Service (NPIS)

Data from publicly available reports by NPIS were used. The NPIS advises hospitals, emergency services and members of the public on the treatment of poisoned patients by providing up-to-date advice and information by telephone and online. NPIS records the numbers of enquiries, treatments and outcomes for different types of poisoning and publishes annual activity reports. Activity between 2015 and 2017 were used here.

For more detail about the methods of this survey see (24)

Fire Service data

Fire statistics are published by the UK government Home Office (25) using data collected from the UK Fire and Rescue Incident Recording System. An entry on to the system is made after each incident attended and covers the causes of fires (or other incidents), contributing factors, injuries and fatalities, locations and outcomes. The Incident Recording System uses pre-determined categories which includes the category “smokers’ materials” but does not specify EC materials. There is however a free text box in which extra data can be entered where the cause of fire is not adequately represented by existing categories. Data from April 2015 to March 2017 was used here.

Freedom of Information data – Fire services (FOI-F)

Fifty-two regional UK fire services were identified and a Freedom of Information (FOI) request was sent to each asking for data on fires caused by EC (including their batteries and chargers) as well as fires caused by mobile phones (including their batteries and chargers) for context. It was not possible to send an FOI to one service because their regulations specified that you must be a local resident to do so. The data was requested for each year from 2015 to 2017. Data for 2017 were requested during August 2017 and the data available up to that point were provided, accordingly the cut off dates for 2017 data varied between services. Data was collected and analysed specifically for the current report. Responses came from fire services who were able to search the free text box in the incident recording system described above (see “Fire Service Data”).

All Fire and Rescue Services were asked for the following information:

The number of recorded fires and false alarms related to ECs and mobile phones for 2015, 2016 and 2017. (False Alarms are incidents where the Fire Rescue Service attends a location believing there to be an incident, but on arrival, discovers that no such incident exists or existed.)

The number of injuries and fatalities related fires caused by EC or mobile phones for 2015, 2016 and 2017.

FOI Burns units (FOI-B)

Twenty-five adult, and four children’s UK burns services were identified and a FOI request was sent to each asking for data on burns caused by EC as well as burns caused by mobile phones for each year from 2015 to 2017. Data was collected and analysed specifically for the current report. For many burns services the data was only recorded in case notes and therefore the cost of accessing these data exceeded the limit set by the FOI Act.

MHRA Yellow Card Scheme

The Yellow Card Scheme, run by the MHRA, is the system for recording suspected adverse reactions to medicines and medical devices in the UK. On 20 May 2016 the Yellow Card Scheme launched an online reporting form tailored to collecting cases of suspected adverse reactions and physical safety concerns associated with EC. The Yellow Card Scheme was established in 1964 and is an important way in which the MHRA collects information to monitor the safety of medicines in the UK; medicines safety information from other UK and international data sources supplements data

collected by the Yellow Card Scheme. Any suspected adverse drug reaction to a medicine can be reported by a health professional, or member of the public and manufacturers have a legal obligation to report reactions. Inclusion of a report in the Yellow Card Scheme database does not necessarily mean that the reactions reported were caused by a medicine or an EC, only that the person reporting the event had a suspicion it may have, or it had a close temporal relationship to the administration of the medicine or EC. The MHRA provided us with anonymised details for spontaneous suspected adverse reaction reports for EC along with details of suspected adverse drug reactions for NRT products. We report spontaneous adverse drug reactions for the period 1 January 2015 to 20 October 2017.

ECigIntelligence data

ECigIntelligence is an independent resource that tracks market intelligence for the EC sector. The available data from the ECigIntelligence Global Database from August 2015 to July 2017 describe average prices of various categories of EC. Since the number of products available is substantial, ECigIntelligence data typically present average lowest prices, thus reflecting the floor price of the products involved though towards the end of study period offers prices for some of the most expensive clearomiser/tank. The categories are:

- Closed system products: EC with pre-filled clearomisers or cartomisers
  - Cheapest closed system kit- products with varying content but include at least one of the following- a USB charger, one cartomiser/capsule/ clearomiser (prefilled and containing nicotine) or one battery (non-reusable kit);
  - Cheapest pre-filled clearomiser- the refillables of the closed system kit are pre-filled cartridges, capsules or clearomisers;
  - Cheapest disposable EC - must contain nicotine, generally come in a cigalike form
- Open system products: EC that allows a user to choose their preferred e-liquid to refill their hardware device
  - Cheapest basic open system kit- products with varying content but include at least one of the following- a USB charger, one cartomiser/capsule/ clearomiser (prefilled and containing nicotine) or one battery. This kit should allow user to use any e-liquid without any modifications.
  - Cheapest clearomiser- the clearomiser is ready to use and include outer casing, an atomiser and a mouthpiece.
  - Cheapest e-liquid- lowest prices e-liquid bottle containing at least 10mL, and the price per mL is calculated
  - Variable wattage/ voltage kits
  - Most expensive clearomiser

Price data was provided in US dollars and converted to British pounds using monthly exchange rates obtained from Bank of England website (26). For most categories, the majority of data was derived from online sales, though towards the end of the study period data from retailers such as vape shops were included in the analysis. Average, minimum, maximum and median prices were provided; we used average price to explore the trends and maximum and minimum values to illustrate the price range.

3 Policy

Introduction

Since the 2015 PHE report (5), several new regulations for EC have been implemented. These include age of sale regulations and the Revised European Union Tobacco Products Directive (EU TPD) (27) translated into UK law through the UK Tobacco and Related Products Regulations 2016 (see below). The national competent authority for these regulations is the MHRA acting for the Secretary of State for Health. The MHRA has implemented a notification scheme for EC and e-liquids (EC refill containers) and a system for notification of side-effects and safety concerns from EC under the TPD. Other TPD regulations cover minimum standards for safety and quality, advertising, labelling and packaging. E-liquid products that do not contain nicotine when sold (eg disposable EC and 0% nicotine e-liquids) are not deemed to fall within the scope of the TPD in the UK regulations and therefore do not have to meet its requirements, but are regulated under General Product Safety Regulations (28). The General Product Safety Regulations impose requirements concerning the safety of products intended for consumer use, and require producers only to place safe products on the market (it is worth noting that combustible tobacco products are exempt from this). Another regulatory option for EC is for manufacturers to apply for a medicines licence through the MHRA. Additionally, the Department of Health and Social Care in England has published a new Tobacco Control for England plan (2) and heated tobacco products (a new type of product often called heat-not-burn) have appeared on the market. Although we heralded some of these in our previous report, we describe relevant new regulations in detail in this chapter, roughly in order of date of implementation.

Age of sale of EC

New legislation came into force in England and Wales on 1 October 2015 and in Scotland on 1 April 2017 (29), introducing a minimum age of sale of 18 for EC and prohibiting the purchase of these products on behalf of someone under the age of 18. This mirrors the law for the age of sale for tobacco cigarettes.

The data in Chapter 5 suggest that among those who use these products, similar proportions (approximately one third) of 11-15 year olds purchase EC as do purchase cigarettes. A smaller proportion of young people purchase EC than purchase cigarettes, from newsagents, but this may reflect the lower prevalence of EC available for purchase in newsagents. Around a quarter of 11-15 year olds reported buying EC from EC shops, and large proportions reported being given or buying their EC or

cigarettes from other people. Clearly there is scope to improve enforcement of age of sale laws for EC and cigarettes.

European Union Tobacco Products Directive (EU TPD)

Article 20 of the revised EU TPD (27) introduced new regulations for nicotine-containing EC. The EU TPD was adopted in 2014 and translated into UK law through the UK Tobacco and Related Products Regulations 2016 (30) (Parts 6 and 7) which came into force on 20 May 2016, although some provisions were phased in during the period leading up to 20 May 2017[1]. The advertising component of the EU TPD was implemented in May 2016 and superseded the previous voluntary agreement on advertising which was revised and a further consultation closed in October 2017 (see below).

Under the TPD, the Secretary of State can require EC producers to withdraw their products from the market if they believe that they could present a serious risk to human health. The Secretary of State is obliged to review the regulations and publish a report within five years of coming into force and within every five years afterwards.

In our last report we described the challenge by Totally Wicked, a privately-owned business selling EC devices and e-liquids, against one Article of the EU TPD, on the basis that it represented disproportionate and inappropriate regulation. The challenge was supported by nearly 100,000 EC users from across the European Union (EU) who signed a petition that was delivered to the Department of Health and Social Care in England. On 4 May 2016 the European Court (31) rejected the challenge ruling in agreement with the European Commission and upholding the EU TPD.

Notification process

Producers of EC and nicotine containing e-liquids are required to notify the MHRA and submit relevant information (a producer is defined as anyone who manufactures or imports these products or who re-brands any product as their own). Producers of all EC and e-liquids that were on the market before 20 May 2016 had until 20 November 2016 to submit a notification to the MHRA. Producers of new EC and/or e-liquid products must submit a notification six months before they intend to put their product on the UK market. Submissions must be updated when products are modified or withdrawn. Relevant information required must be submitted electronically (by type of submission required); Table 2 summarises the key components.

[1] For an overview of consumer product regulations for EC please see https://www.gov.uk/guidance/e-cigarettes-regulations-for-consumer-products ,updated 29 November 2017

Table 2: Details of notification requirements for EC

Information required	Guidance and notes
Name and contact details of manufacturer, importer or a responsible person within an EU Member State	
Product type	EC guidance Chapter 2 (32)
A list of all ingredients contained in, and emissions resulting from the use of the product by brand and variant name including quantities	EC guidance Chapter 3 for emissions (33) EC guidance Chapter 6 for ingredients (34)
Toxicological data regarding the product's ingredients (including in heated form) and emissions, referring in particular to their effects on the health of consumers when inhaled and taking into account, among other things, any addictive effect (see also prohibited additives below)	EC guidance Chapter 6 for ingredients (34)
Nicotine dose and consistency of dose uptake	EC guidance Chapter 4 (35)
Uptake when consumed under normal or reasonably foreseeable conditions	
A description of the components of the product including, where applicable, the opening and refill mechanism of the EC or refill container	
A description of the production process and a declaration that the production process ensures conformity with the requirements	
A declaration that the producer bears full responsibility for the quality and safety of the product when supplied and used under normal or reasonable foreseeable conditions	
Annual submissions (on or before 20 May) including sales volume by brand/type in the UK, preferences of consumer groups (published or unpublished data), mode of sale of products, executive summaries of market surveys	EC guidance chapter 1 (36) Annual reporting guide (37) The Secretary of State is required to monitor this information particularly in relation to their use acting as a "gateway to nicotine addiction and ultimately traditional tobacco consumption among young people and non-smokers"

The fee (38) for notifying each product is £150. A fee of £60 is also payable on 1 April annually for each product remaining on the market. These fees are to cover the MHRA's costs of administering the notification scheme and also the requirement to oversee the publication of the notification information on a website (although trade secrets are treated in a confidential manner). The MHRA has given a commitment to review the level of fees in the light of the number of notifications received in the first year, so it is likely these will be reduced.

Notifications registered with the MHRA

As of 31/10/2017, almost 400 different producers had submitted information about 32,407 different e-liquids (90% of notifications) or devices (10% of notifications). A recent rise in the number of nicotine shots notified has been observed (39). Nicotine shots are 10mL bottles of high strength nicotine e-liquid which are flavourless, and which comply with the EU TPD regulations. Nicotine shots can then be added to much larger bottles of flavoured nicotine free e-liquids (which are not covered by the EU TPD, but would be prohibited if they contained nicotine) to make the desired nicotine content. These larger bottles are deliberately made to leave space for the nicotine shots to be added (referred to as “short-fills”). This practice is sometimes referred to as ‘Shake and Vape’. A survey carried out by ECigIntelligence of industry associations and New Nicotine Alliance members estimated that approximately 20% of the total EC product market was outside of the EU TPD and notification process (the percentage of EC user respondents claiming to use non-EU TPD products was multiplied by the percentage of the market estimated to be represented by enthusiast advanced tank users; ECigIntelligence consumer survey 2017 (39) and personal correspondence). This survey also estimated that the reduction in price between a 10mL EU compliant bottle and a 60mL short fill and 10mL shot was on average 30% (ECigIntelligence consumer survey 2017 (39)).

Minimum standards for safety and quality

Minimum standards for the safety and quality of all nicotine containing EC and e-liquids came into effect 20 May 2016, with a transition period until 20 May 2017. These included:

- child-resistant and tamper evident packaging
- protection against breakage and leakage
- a mechanism for ensuring re-filling without leakage
- prohibition of certain additives such as colourings, caffeine and taurine (these are listed under Article 16 of the Tobacco and Related Products Regulations, 2016 and pertain to tobacco products but are extended to EC)

Additional restrictions have been placed on the size of the tank and strength of nicotine in e-liquid, summarised in Table 3.

Table 3: Restrictions on tanks and nicotine strength

Component	Maximum allowed
Tank capacity	2mL
E-liquid refill container capacity	10mL
Nicotine strength of e-liquid	20mg/mL

Information provision

From 20 May 2017, all EC/liquids had to comply with requirements to have a health warning and provision of other information on the pack or on the device/bottle if there was no outer packaging (40, 41).

Health warning

This must be prominent in black text on a white background covering 30% of the area on the front and back of the unit packet and any container pack:

"*This product contains nicotine which is a highly addictive substance"*

Other labelling requirements

On the pack:

- list of ingredients in liquid where they are used in quantities of 0.1% or more
- nicotine content and delivery per dose
- batch number
- recommendation to keep the product out of reach of children

Unless included on the pack, the following information was required on an accompanying leaflet:

- instructions for use and storage, including instructions for refilling where appropriate and the MHRA advise the information should include appropriate advice on product storage, particularly on how to ensure the battery does not malfunction
- contra-indications, warnings for specific risk groups and possible adverse effects, addictiveness and toxicity
- contact details of producer including a contact within the EU

There are requirements on product presentation such as not to encourage consumption. Offers and discounts and product safety/health claims are prohibited (see below).

Advertising

The EU TPD prohibited cross-border advertising of nicotine-containing EC which covered broadcast television and radio, newspapers, magazines, periodicals, online media and some other forms of electronic media. This superseded a voluntary code which had been in place prior to EU TPD implementation. In 2017, the Committee of Advertising Practice (CAP) introduced a new rule in its Code, to reflect the prohibitions in the revised EU TPD and Tobacco and Related Products Regulations 2016. These outlined the channels that are and are not allowed,Table 4 (42). The guidance indicates that indirect effects are also prohibited (such as non-nicotine EC should not have the indirect effect of cross-promoting a nicotine-containing EC).

Table 4: Advertising regulations (other than broadcast media which is all prohibited)

Prohibited	Allowed*
Newspapers	Outdoor advertising, including digital outdoor advertising
Magazines	Posters on public transport (not leaving the UK)
Periodicals	Cinema
Commercial email	Direct copy hard mail
Commercial text messaging (for this and the prior item, unless specifically opted in, should be given to opt-out with every communication)	Leaflets
Marketers online activities eg website/social media (except factual information, see guidance as this is a complex area)	Private, bespoke correspondence between a marketer and a consumer
Online (display) ads in paid-for space	Media which are targeted exclusively to the trade
Paid-for search listings; preferential listings on price comparison sites; viral advertisements	Advertisements for businesses in non-broadcast media
Paid social media placements, advertisement features and contextually targeted branded content	Sponsorship of events which isn't across borders
In-game advertisements	
Commercial classified ads	
Advertisements which are pushed electronically to devices	
Advertisements distributed through web widgets	
Promotional marketing online	
Affiliate links	
In-app advertising	
Product placement	

** must still comply with relevant CAP rules about content and placement*

A further CAP Code 22 (43) indicates restrictions to protect those under 18 from EC, such as ensuring marketing communications for EC are socially responsible, clear they are for EC rather than tobacco cigarettes, etc.

In autumn 2017, CAP and BCAP (the UK Code of Broadcast Advertising) carried out a consultation on changes to their Codes to remove the current prohibition on health claims being made for EC and to guide advertisements for health campaigns which refer to EC (44). The outcome might mean that advertisers could make claims about the health benefits of EC in comparison to tobacco, although the likelihood is that such claims would need to be linked to evidence for the exact product under consideration, rather than to the generic category (eg EC).

Retailers

Retailers of EC had until 20 May 2017 to sell existing stock of products that did not comply with EU TPD labelling and product composition requirements. Guidance for retailers on EC is available (45). The Independent British Vape Trade Association (IBVTA)(46) reported that there were around 2,000 independent vape stores on the high streets in the UK, compared with over 50,000 convenience stores and around 10,000 supermarkets in the UK, the vast majority of which are likely to sell tobacco. While tobacco outlets may also sell EC, it's likely that the independent vape stores sell a greater variety of EC models (including those thought to be more effective, the tank models) than the tobacco outlets.

Reporting of side-effects and safety concerns

In May 2016, the MHRA extended its Yellow Card reporting system to include reporting on EC and e-liquids. Consumers and healthcare professionals can report both side-effects and product safety concerns to the MHRA. Report received are summarised in Chapter 9. Alternatively, issues about defective/non-compliant EC can be raised with local Trading Standards offices. However, a recent report from the National Audit Office (47) indicated concern about capacity of local Trading Standard offices which had lost 56% of full time equivalent staff since 2009, with 20% of services having had reduced funding by over 60% since 2011 (47). Trading Standards therefore may not have the capacity to deal with EC issues, or enforce relevant regulations.

Medicines licensing process through the MHRA

As indicated above, EC producers can also apply for a medicines licence for their products from the MHRA (48). Nicotine–containing products that make claims for cutting down, quitting or reducing the harms of smoking are considered to be medicinal products and regulated by the MHRA. Licences can be for the General Sales List, Pharmacy Medicines or Prescription Only Medicines. Licensed EC are exempt from the

EU TPD and Classification, Labelling and Packaging regulations, and subject to the requirements of medicinal regulation instead. Licensing is important as this may allow health professionals to prescribe EC which could make them more accessible to more disadvantaged smokers, and also enable them to be supplied with advice and support about their use (see Chapter 7).

In the 2015 PHE report (5), we described how Voke (a non-EC nicotine inhaler product) had been granted a medicines licence and that a British American Tobacco (BAT) electronic product (e-Voke) was going through the medical licensing process. In November 2015, general sales list marketing authorisations were indeed given for 10mg and 15mg e-Voke to Nicovations (formerly Nicoventures, both fully-owned BAT subsidiaries) for marketing as an aid to help people to stop smoking (49). E-Voke uses cartridges containing pharmaceutical grade nicotine. Medicines licensing meant that the product could be prescribed by medical practitioners. However, neither Voke nor e-Voke have been brought to market so far. In January 2017, BAT and the original developer of Voke, Kind Consumer Ltd, announced a new approach to its commercialisation, with Kind Consumer taking back ownership. There is no EC product that has received a medical licence currently available on the market or on prescription.

In February 2017 the MHRA updated its guidance on the licensing process. This indicated that manufacturers would be expected to comply with relevant standards. The British Standards Institute had published a British Standards Institute-endorsed Publicly Available Specification (PAS) (50) for EC produced by key stakeholders. The standard covers, inter alia: purity of e-liquid ingredients, potential contaminants from device materials and potential emissions from device operation; a test solution-liquid, and an outline for the toxicological and chemical analysis of emissions; safety of batteries and chargers. The French national standards authority AFNOR has also produced a standard (51). European and international standards are in the process of being developed by the European Committee for Standardisation (CEN) and the International Organization for Standardization (ISO) respectively. For medicinal EC and nicotine containing products, the MHRA stated that additional requirements, additional to published standards, might also be needed to meet safety, quality and efficacy criteria under medicines regulations. It is likely that efficacy standards are clear, as manufacturers need to be able to demonstrate that nicotine delivery is comparable with licensed nicotine replacement therapies. However, demonstrating long-term safety may be more difficult for newer products. This might suggest that, in the first instance, licences could be granted for short-term use as was the case with NRT licences initially, before the harm reduction licence was added in 2010 (52).

Other policy-related developments

General product safety regulations

These regulations exist for all consumer products and non-nicotine EC are required to comply with these regulations (28). As noted above, combustible tobacco products are exempt from these regulations.

Classification, labelling and packaging regulations

EC must comply with the EU TPD but also with classification, labelling and packaging regulations (53) which are European regulations based on a United Nations system. Classification, labelling and packaging regulations apply to chemicals in EC as it does to other chemicals placed on the market, irrespective of whether they contain nicotine or not. Labelling and packaging requirements therefore pertain to any chemicals in EC.

Consensus statements

Following the publication of the 2015 PHE report, an emerging public health consensus was published on EC between PHE and 12 other organisations (54). This consensus statement emphasized the opportunity that EC provide by helping smokers to quit, but that combining EC (the most popular method) with most effective (stop smoking services) would optimise that opportunity. A recent publication by the British Medical Association on EC (55) is in line with this consensus.

In September 2017, NHS Scotland published a consensus statement on EC (56) created in collaboration with, NHS and public health bodies, Royal Colleges, charities and universities. One of its two key messages addressed smokers, urging them to try stopping smoking whether or not they use EC and advising them of the help available. The other key message urged health professionals to advise smokers about the different ways they can quit and the evidence base and not to turn anyone away because they choose to use EC.

Guidance on the use of EC in public places

In 2015, Action on Smoking and Health (ASH) and the Chartered Institute of Environmental Health published a briefing on ‘five questions’ concerning the implementation of controls on vaping in work and public places (57). Following on from this, PHE carried out a consultation and survey on five principles for policy and practice (58). In July 2016, PHE published advice for organisations to support policy making in relation to the use of EC in public places and workplaces (59). The advice is based around the five principles, covering the need to make a clear distinction between

vaping and tobacco cigarette smoking, ensuring policies are informed by the evidence on risks to bystanders, identifying and managing risks of uptake by children and young people, supporting smokers to stop smoking and stay stopped, and supporting compliance with the smokefree law and policies. The advice, published together with a brief five-point guide, is non-prescriptive in recognition of the fact that settings differ and there is no 'one-size-fits-all solution'.

MHRA guidance on EC in research

The MHRA has produced an algorithm, guidance and examples on the use of EC in clinical trials (60). As EC are not medicinal they are not considered as investigational medicinal product (IMP) in health or clinical research. A clinical trial authorisation (CTA) would only be required in most circumstances if the research uses a licensed nicotine product as a comparator. Accessing this guidance should be made easier for researchers.

Heated tobacco product (heat-not-burn) regulations

In heated tobacco products, processed tobacco is heated instead of being combusted. Part 4 and Part 5 of the UK Tobacco and Related Products Regulations 2016 detail the notification process for novel tobacco products such as heated tobacco products (30). Notification must be done electronically to PHE which is an executive agency sponsored by the Department of Health and Social Care and the UK's competent authority for overseeing and publishing the notifications for tobacco products as well as herbal products for smoking. Notification of novel tobacco products must be done at least six months before the producer intends to supply the product. Fees apply for the notification process, for the annual reports and testing, and for any modifications.

Notification should include the following information:

a) detailed description (including components, mechanisms by which any emission/vapour is generated, and means by which nicotine is absorbed by the consumer)
b) instructions for use
c) ingredients (by weight and quantity and including reasons for inclusion, status of each ingredient, classification, any available toxicological data in burnt or unburnt form as appropriate, referring in particular to the effect of the ingredient on health including addictive effects)
d) emissions (including information about the product's tar, nicotine and CO and other emissions by brand and variant name)
e) available studies on the toxicity, addictiveness and attractiveness of the product in particular with regard to ingredients and emissions

f) any available studies, executive summaries or market research, in relation to the product on the preferences of consumer groups, including young people and current smokers
g) any other available information (including risks and benefits, expected effects on cessation of tobacco consumption, expected effects on tobacco consumption initiation, and the predicted perception of the product by consumers and potential consumers).

A recent HM Treasury consultation (61) on the tax treatment of heated tobacco products in the UK classified heated tobacco products into three main types:

- Type 1 - processed tobacco heated directly to produce vapour
- Type 2 - tobacco designed to be heated in a vaporiser
- Type 3 - devices that produce vapour from non-tobacco sources, where the vapour is then passed over processed tobacco in order to flavour the vapour

Type 2 products include vaporisers often used for cannabis which have been sold for some time in the UK but we are not aware of any such products being marketed by the tobacco industry in the UK or elsewhere. The Treasury are currently analysing the responses to their consultation.

It should be noted that the Treasury made clear that this category of tobacco product did not include EC, stating that EC do not contain tobacco and are therefore not liable for tobacco duty.

Two products have been notified to PHE, one Type 1 (IQOS, produced by Philip Morris International) and one Type 3 product (iFuse, produced by British American Tobacco) and are currently available on the market in the UK (see Chapter 12).

Towards a Smokefree Generation. A Tobacco Control Plan for England

The new Tobacco Control Plan for England (2) sets out the commitments of the Department of Health and Social Care, PHE and MHRA (Table 5) to support smokers to quit and adopt the use of less harmful nicotine products.

Over the next five years the ambition is to:

- reduce the prevalence in:
  - 15 year olds who regularly smoke to 3% or less
  - adults in England from 15.5% to 12% or less
  - pregnancy to 6% or less
- reduce the inequality gap in smoking prevalence between those in routine and manual occupations and the general population

- improve data collected on smoking and mental health to help support people with mental health conditions to quit smoking and make all mental health inpatient services sites smokefree by 2018
- help people to quit smoking by permitting innovative technologies that minimise the risk of harm and maximise the availability of safer alternatives to smoking

Table 5: Organisational commitment to support smokers to quit and adopt the use of less harmful nicotine products

Organisation	Commitment
PHE	• Update their evidence report on EC and other novel nicotine delivery systems annually until the end of the Parliament in 2022. • Include within quit smoking campaigns messages about the relative safety of EC. • Continue to provide smokers and the public with evidence based information on the relative harm of nicotine, EC, other nicotine delivery systems and smoked tobacco, to enable informed decision-making. This will include the publication of an assessment of the risks of nicotine addiction. • Provide evidence based guidance for health professionals to support them in advising smokers who want to use EC or other nicotine delivery systems to quit.
Department of Health and Social Care	• Monitor the impact of regulation and policy on EC and novel tobacco products in England, including evidence on safety, uptake, health impact and effectiveness of these products as smoking cessation aids to inform our actions on regulating their use. • Based on the evidence reviews undertaken by PHE, review policy and regulation of nicotine delivery systems to provide an environment that facilitates smokers taking action to improve their health and the health of those around them, while minimising any risk of new nicotine addiction in children.
The MHRA	• Ensure that the route to medicinal regulation for EC products is fit for purpose so that a range of safe and effective products can potentially be made available for NHS prescription.

International policy overview

World Health Organization position statement

In August 2016, a report was published by the World Health Organization (WHO) on Electronic Nicotine Devices and electronic non-nicotine delivery systems (ENDS) for discussion at the November 2016 Conference of the Parties to the WHO Framework Convention on Tobacco Control (62). The paper concluded with a list of regulatory options that Parties might consider to: 1) prevent initiation by non-smoker and youth; 2) minimise potential health risks to users and protect non-users from exposure to emissions; 3) prevent unproven health claims being made about the products; and 4) protect tobacco control activities from all commercial and other vested interests relating to the products including interests of the tobacco industry. The vast majority of these options have been implemented in England.

Global situation

At the time of writing, 27 countries ban sales of all types of EC, nine countries prohibit the sale of nicotine-containing EC (63).

Within the EU, there were some changes due to the EU TPD with some European countries now having fewer restrictions (eg Croatia, Sweden, Switzerland) but others, like the UK having greater restrictions (eg Netherlands, Cyprus, France).

Conclusions

Key findings

- As with tobacco products, in most parts of the UK, there is a minimum age of sale of 18 for EC and EC must not be purchased on behalf of someone under the age of 18.
- The revised European Union Tobacco Products Directive is now fully operational in England, transposed into UK law through the UK Tobacco and Related Products Regulations 2016, and covers e-cigarettes and nicotine-containing e-liquids that do not have a medicinal licence. These regulations include a notification process (to the MHRA), minimum standards for safety and quality of EC products, standards for information provision (including a nicotine health warning) and advertising restrictions and updated standards. The Advertising Standards Authority (ASA) has carried out a consultation on health claims; the results are awaited. A system to report side-effects and safety concerns related to EC has been implemented.
- Over 32,000 EC products have been notified which suggests a level of compliance with the regulations and that the notification process is not too onerous.

- There are some signs that ways are being found to avoid the law, for example particularly on size of bottles, but evidence is limited.
- Alongside products regulated in line with the EU TPD, manufacturers can also apply for medicinal licensing from the MHRA. However, no licensed EC has yet been marketed.
- Other EC-related developments include consensus statements from a number of organisations and guidance on the use of EC in public places and on their use in research.
- Non-nicotine EC are governed by general product safety regulations (unlike combustible tobacco products).
- There is a separate notification process for heated tobacco products (to PHE) and results from a consultation on the tax treatment of these products are forthcoming. At the time of writing, two products had been notified.
- A new Tobacco Control Plan for England was published in July 2017.

Implications

Research

- There is a need for continued research on the impact of regulations on smoking rates and patterns, use of EC by adults and young people, product design and quality and adverse effects of EC.
- Research should specifically assess the impact of the EU TPD on production (with a specific focus on independent manufacturers who were the first to enter this field), innovation of products, and EC users and smokers.

Policy and practice

- Regulations need to balance the risks of EC with their potential benefits – and achieve key aims of reducing smoking and continuing to avoid uptake of EC by non-smokers. This requires keeping them under regular review and evaluating their impact.
- Regulations for heated tobacco products should be made as least as stringent as for EC.
- It remains a viable and important goal to facilitate regulation of some EC as medicines via the MHRA. A review is needed of how to achieve this, possibly including more focus on post marketing surveillance and the provision of licences for short-term rather than extended use.
- Restrictions on communicating relative risks of EC in comparison with combustible tobacco should be reconsidered. In any future review of the EU TPD, consideration should be given to the wording of the health warning on nicotine *per se* given the public misperceptions of its harmfulness (Chapters 4 and 10).
- There appears to be no evidence justifying an urgent change regarding non-nicotine EC or e-liquids which are currently outwith the scope of the EU TPD.

4 Nicotine

Introduction

Professor Michael Russell was one of the pioneers of nicotine research (64). In 1971 Professor Russell (65) explained that over recent centuries '*no population has dispensed with one form of tobacco use without replacing it by another*' and *'once experienced, nicotine use has continued in populations as it does in individuals.*' He subsequently commented that '*people smoke for the nicotine, but die from the tar* '(66), and in a later paper (67) discussed the potential for recreational use of cleaner nicotine delivery devices to be a solution to the tobacco epidemic. NRTs, while cleaner forms of nicotine delivery, have simply not been taken up by significant proportions of the smoking population in the way that EC have. In the light of the advent of EC, therefore, Russell's prophecy has now become a realistic possibility, but their widespread use will depend on their relative safety and addictiveness compared to smoking tobacco cigarettes.

A systematic review of nicotine was not carried out for this report because it was agreed by the commissioners that nicotine would have a stronger focus in a forthcoming PHE review. This chapter, therefore, briefly summarises and updates evidence in the Royal College of Physicians (RCP) report (68), focusing on nicotine addictiveness, nicotine delivery in relation to EC, and any recent evidence which suggested nicotine use could cause significant harm. Chapters 8 and 9 discuss safety and health risks pertaining to EC.

By acknowledging the centrality of nicotine to smoking and other tobacco use, we do not wish to diminish the role of other social and environmental factors (69). However, because most EC use in England involves nicotine (see Chapter 5 and 6), studying nicotine itself is an important focus in improving our understanding of EC use.

Nicotine addictiveness

It is well established that nicotine is the primary addictive component of tobacco smoke (70). In this section we explore the addictiveness of nicotine, as well as the extent to which it varies across different forms of nicotine delivery.

Nicotine delivery and dose

The dose and rate at which a drug reaches the brain influences its addictive potential. In one of the earliest studies to assess nicotine delivery, Russell and Feyerabend (71) concluded that, for smokers, it was the puff-by-puff high-nicotine bolus, which reached

the brain within seconds of inhalation, that made cigarette smoking so addictive. Nicotine is inhaled into the lungs in the form of tobacco smoke reaching the brain within 15-20 seconds; the rate of increase in arterial nicotine concentrations is much faster than those achieved by intravenous (IV) injection (68, 72).

All forms of NRT deliver nicotine much more slowly and at lower doses than smoking, but the speed and amount vary according to the delivery system (oral, dermal or nasal) and the dose. The faster acting NRT products (nasal and mouth spray) deliver peak plasma nicotine levels within about 10 minutes. Use of NRT therefore results in much slower nicotine delivery than smoking. Absorption of nicotine is also affected by other factors such as pH. Overall, the addictiveness of NRT is much lower than that of cigarettes, with only a very small proportion of those who use these products persevering with use for a year or longer. Around 10% of nasal nicotine spray users will use for a year or longer, 5% of those using oral nicotine products, and fewer for the patch (68).

It is useful to compare the dependence potential of smokeless tobacco with smoking and NRT. Smokeless tobacco covers a heterogeneous array of very different products. One product, snus, which is a low nitrosamine smokeless tobacco product with a long history of use in Sweden, has been studied as a proxy for the long-term health effects of nicotine (see below). We will therefore discuss snus in relation to dependence here. Similar to oral nicotine products, nicotine absorption with snus also occurs through the buccal route, aided by the alkaline pH of snus. As such, nicotine absorption is slower when using snus, than from cigarette smoking, as there are no arterial boli of nicotine delivered to the brain. Nevertheless, nicotine exposure overall can be very similar between snus users and cigarette smokers. There is strong evidence that using snus induces dependence, since snus users exhibit a withdrawal syndrome when attempting to quit, with some similarity to that observed in cigarette smokers abstaining. This indicates that factors other than speed of delivery are important in the dependence potential of nicotine delivery products. It is possible that the higher addictiveness of snus relates to the tobacco and other factors such as the pH, compared with oral nicotine products. This may be relevant to heated tobacco products (see Chapter 12).

We discussed nicotine delivery of EC in our last report, commenting that no studies had allowed an appraisal of the comparison between EC and cigarettes in terms of giving a rapid increase in arterial blood nicotine levels after puffing, but that it was likely some EC products were providing a degree of lung absorption. Since our last report, nicotine delivery has been shown to vary considerably across the variety of EC products, (eg(73, 74)). However, experienced users can achieve greater increases in blood nicotine levels than naïve users under the same puffing regime, albeit slower than from cigarette smoking (75-77). Studies with experienced users found comparable or, in some cases, higher venous blood nicotine levels than with cigarette smokers. A study with 16 experienced users and high nicotine concentrations (36mg/mL) found a higher

pre-post nicotine boost following a standardised puffing regimen than that typically seen with tobacco cigarettes (78).A further study (77) with 30 participants (10 smokers and 20 experienced EC users) found similar doses and speed of nicotine delivery to tobacco cigarettes among those using third generation devices (mods). An additional study, with 13 experienced users again during a standardised puffing session demonstrated that venous nicotine blood levels of experienced EC users from later generation devices were comparable to, and in some cases higher than those of smokers (79). Most of the participants had peak nicotine levels within two to five minutes after puffing an EC, suggestive of pulmonary delivery and likely to lead to dependence, although not all the nicotine retained was absorbed through the lungs (79). The same study also included a subsequent ad libitum phase (80). Here the authors found that vaping behaviour differed from smoking behaviour in that EC users took longer puffs and grouped their puffs in shorter clusters (two to five puffs). The intermittent puffing patterns led to a more gradual rise in plasma nicotine levels across the session, in contrast to the bolus dosing from cigarette smoking. Nicotine intake was related to puff topography only for the tank users but not across the whole sample (which included cigalikes and other devices).

In summary, nicotine dose and rate of delivery are important factors in the dependence potential of nicotine delivery devices, but other factors such as pH and what comes along with the nicotine (also see below) are involved. Experienced EC users can have nicotine levels similar to those of cigarette smokers, although the speed of delivery is slower. Nicotine delivery varies across the different designed EC products. As yet, it is unclear how addictive EC are, or could be, compared to tobacco cigarettes.

Self-reported dependence

Several studies have found that self-reported dependence is lower in daily vaping ex-smokers compared with daily smokers (eg (81, 82). In a comparison between EC dependence and dependence on nicotine gum, Etter and Eissenberg (83) reported that EC were either as addictive or less addictive than the nicotine gum, but more likely to be reported as being used to avoid relapse to smoking. Liu and colleagues (82) found that self-reported dependence in EC users was lower than among smokers but reported that over three-quarters considered themselves addicted to EC.

A recent analysis of US tobacco and nicotine (EC) users, (84) included an instrument to assess tobacco dependence across different tobacco and nicotine group users. Using this measure, cigarette smokers had the highest mean level of tobacco dependence, with similar levels among multiple products users, and slightly lower mean levels in smokeless tobacco users; EC only users were among the lowest levels (with cigar only users and waterpipe only users).

The findings of these studies need to be viewed with caution pending validation of the measures.

Uptake among non-smokers

Concerns have also been raised about the propensity for adolescent non-smokers to become dependent on cleaner nicotine products. This propensity is likely to be affected by addictiveness (alongside other variables such as marketing and accessibility). Consistent with the above, the RCP report concluded that there was no substantial evidence of non-smokers becoming dependent on NRT (68). In comparison, the dependence of tobacco smoking is much greater with a recent meta-analysis finding that around two-thirds of non–smokers who experiment with smoking becoming regular daily smokers (85). As we will see later, there is evidence of EC experimentation among non-smokers, but little regular use, consistent with these observations for NRT (Chapters 5 and 6).

Nicotine effects

Although the metabolism of nicotine varies considerably between individuals, nicotine has a short-half life, approximately two hours which, together with the repeat high boli of nicotine resulting from puffing on tobacco cigarettes, enables users to self-titrate. Self-titration is also seen in EC users (86). The speed at which nicotine is metabolised is affected by a number of factors, and plays a role over and above the rate at which it is absorbed and delivered to the brain and the dose received.

At low doses, nicotine is a stimulant. However, tolerance develops quickly and chronic exposure results in neuroadaptations, causing withdrawal effects. Addictiveness may be related to the severity of these negative withdrawal symptoms. Nicotine has complex effects, caused by its binding to and desensitizing nicotine acetylcholine receptors, and facilitating the release of a variety of neurotransmitters, including dopamine. Dopamine acts as a positive reinforcer, is involved in other addictive drug use, and is likely to underpin the pleasure that smokers report from smoking. Addictiveness and pleasure are likely to be intertwined. Pleasure is rarely reported from NRT users, but has been reported by EC users (87). It can be hard, however, to distinguish positive reward and relief from incipient withdrawal.

Other influences on addictiveness of nicotine products

Other aspects of nicotine products may potentiate addictiveness (68). These include the monoamine oxidase (MAO) inhibitors in tobacco smoke, substances added to tobacco such as sugars and polysaccharides, flavourings such as menthol or alkaline additives, as well as design characteristics. Secondary reinforcers, such as the

behavioural aspects, smell or taste, may also be acting to enhance the addictiveness of cigarette smoking.

The PHE and the RCP reports detailed how nicotine concentration and other constituents of e-liquid, such as the presence of propylene glycol (PG) (probably due to its lower boiling point than glycerine), and vaping topography affect nicotine delivery (5, 68). Thus, similar to tobacco cigarettes, various factors influence the nicotine delivery of EC. One study (77) suggested that a floor level of nicotine, rather than a ceiling (as in the EU, see Chapter 3) would prevent excessive puffing of EC in order to achieve desired nicotine levels. Flavours may also affect the rate of nicotine absorption and affect satisfaction from EC (88).

Typologies of nicotine users

Russell (89) also argued that there were three types of smokers: non-inhalers, peak-seekers (~ one cigarette per hour gives a blood nicotine profile of repeated high blood nicotine peaks), who smoke predominantly for positive pleasure, and trough-maintainers (~ one cigarette every 30 minutes), motivated by the need to maintain a high blood nicotine level to avoid unpleasant withdrawal effects. A recent study (90) identified three different accounts of vaping: '*Vaping as pleasure*' in which ex-smoking EC users reported vaping as enjoyable and likely to be sustained over time, held a strong vaping identity and rejected a medical model of vaping; '*Vaping as medical treatment*' in which ex-smoking EC users reported vaping as a pragmatic choice to medicate one's smoking addiction, with the aim of treating and reducing their nicotine dependence; and '*Ambivalent e-cigarette us*e' in which dual users reported fewer benefits and more negative beliefs about EC, rejecting an EC user (or vaper) identity. While these typologies have not been shown to be related to duration of use of either tobacco cigarettes or EC, they are included to illustrate the heterogeneity of nicotine users.

Summary

In summary, nicotine addictiveness depends on a number of factors including presence of other chemicals, speed of delivery, pH, rate of absorption, the dose, and other aspects of the nicotine delivery system, environment and behaviour. Tobacco smoking with rapid delivery of nicotine to the lungs and absorption, has been demonstrated to be highly addictive, compared with the NRT patch, for example, which has much lower dependence potential and long term use. Addictiveness is related to pleasure as well as severity of withdrawal discomfort, which are hard to tease apart. The addictive potential of other nicotine products is likely to be within the two extremes set by the cigarette and NRT patch, with some products, eg snus, also being addictive. It is thus inaccurate to say that nicotine per se is highly addictive, such statements need to be more nuanced, as addictiveness is dependent on the delivery system.

Nicotine safety

Nicotine toxicity

As we detailed in our last report, the source of the oft-repeated claim about ingestion of 30-60mg of nicotine being fatal, was hard to locate. A recent study (91) concluded that the lower dose limit for fatal nicotine is thought to be considerably higher, in the region of 500-1,000 mg ingested nicotine.

Health effects of nicotine use

The health effects of cleaner nicotine products per se is important, but the key comparison should be with smoking as, to our knowledge, no-one in public health is recommending nicotine to never smokers. For smokers, cleaner nicotine delivery systems will be orders of magnitude safer. Risk benefit assessments are carried out for medications routinely and many medications used to treat serious diseases bear some risks (92).

The RCP report indicated that short-term nicotine use does not result in '*clinically significant harm'* and concluded that there was no evidence of any increase in the risk of heart attack, stroke or death from use of NRT in quit attempts. The best study of long-term NRT use, dates from 2009, the Lung Health study (93), a randomised controlled trial of five years duration, in which all subjects were offered NRT and subjects were followed up for up to seven and a half years. There was no evidence of a relationship between NRT and cancers, whereas continued smoking was associated with developing cancer.

For harms of longer term use of nicotine, the best evidence stems from snus, described earlier. The Global Burden of Disease Study (94), did not find sufficient evidence of a detrimental effect of snus on any outcome. This includes oral and pharyngeal cancer which had both been linked with smokeless tobacco use in general, and the latter with snus.

These studies suggest that, for smokers, the risks of nicotine use are likely to be very low or negligible. The risks of long-term inhaled nicotine separate from inhaling smoke have not been studied in humans, and it is possible that inhaled nicotine could have adverse effects that nicotine taken in through other routes does not have.

The health risks of EC are discussed in more detail in Chapter 9 and below we highlight recent studies reported as finding risks of nicotine use which were of concern.

Recent studies assessing nicotine safety

A recent animal study suggested that nicotine can have adverse effects on the lung (95). The study used very large doses of nicotine administered intermittently for four months. The organ damage could have been due to systemic poisoning and may not be relevant to exposure in smokers and EC users (96). Nevertheless, the effects of inhaled nicotine on lung function in humans require further investigation.

A reference made at a conference to a research letter (97) reported that nicotine in EC causes transient stiffening of arteries and the author claimed in a media release that this shows risks of vaping and that he would '*not encourage the use of the devices*'. This generated several headlines, such as the front page headline '*Vaping as bad as fags: E-cigs seriously damage heart*' (McDermott, the Sun 2016, available at: https://www.thesun.co.uk/living/1693653/e-cigs-are-just-as-bad-for-your-heart-as-smoking-fags-as-they-damage-key-blood-vessels-say-experts/) and other similar headlines '*E-cigarettes are as bad for the heart as tobacco: Nicotine vapour damages blood vessels and raises risk of disease*'; and '*Vaping as bad for your heart as smoking cigarettes*' (http://www.telegraph.co.uk/news/2016/08/29/vaping-as-bad-for-your-heart-as-smoking-cigarettes-study-finds/). It seems likely that this effect is due to the acute sympathetic activation induced by nicotine through the release of norepinephrine. However, the same author (98) had previously found that the same effect, but stronger and longer lasting, follows drinking coffee, and also after chronic consumption (99). Similar effects have also been observed among students who are sitting an exam or engage in other common activities that can result in mental stress (100).

A study using the UK Clinical Practice Research Datalink detected a shorter survival time in patients with pre-existing CVD who were prescribed NRT compared to those receiving stop-smoking advice only (16). The raw data, however, did not control for potential selection biases: for example, General Practitioners (GPs) may have a greater propensity to prescribe NRT to heavier smokers about whom they are concerned; similarly, smokers with more severe symptoms may be more willing to accept the prescription. The study also did not control for or assess the duration of NRT use – any past use was sufficient to categorise the patient as an NRT user. Further studies controlling for relevant covariates would be useful to clarify the above issues.

A new review of possible effects of nicotine in EC on cardiovascular function concluded that short-term use of EC appeared to pose low cardiovascular risk in healthy users (72). The authors commented that some adverse effects may exist in people with pre-existing CVD, though these would be lower than risks of smoking. The concern is based on a finding that although snus use does not increase CVD risks, among people who suffer a myocardial infarction, those who continue using snus have lower survival rates compared to those who quit snus. This could be due to post-myocardial infarction nicotine use. However, it is also possible that people unable to stop tobacco use

despite suffering a myocardial infarction are typically highly dependent and this is associated with lower socioeconomic status, less access to health care and a possibility that they seek help later than non-tobacco users, have higher levels of stress, and a range of lifestyle behaviours detrimental to health. Studies controlling for such factors are needed to clarify this issue.

Foetal nicotine exposure

There has been much concern about the use of EC by pregnant women and the role that nicotine may play in harming foetal development. Animal research has suggested foetal exposure to very high doses of nicotine has adverse consequences which are maintained through to adolescence, but the relevance for humans is unclear (101, 102).

In humans, it has been difficult to separate the impact of nicotine from smoking in pregnancy, given the low use of cleaner nicotine products among pregnant women. Thus assumptions about harms from nicotine in human pregnancies, have until recently, emerged either as a result of studies of tobacco use in pregnancy or are extrapolated from animal research. More recently, however, it has been reported that infants born to pregnant smokers, who used NRT for smoking cessation during pregnancy, were less likely to have developmental impairments compared with those who used placebo two years after birth (103). The reason for this requires more research but the authors argued it could be due to reduced smoking early in pregnancy as a consequence of NRT use. The licence for prescribing NRT was extended in the UK in 2005 to include use in pregnancy and NRT is currently widely prescribed in the UK to pregnant women who smoke (104).

Limited research has been conducted with pregnant smokers or ex-smokers who use EC (105). Further research is needed and a large trial of EC for smoking cessation in pregnant women is now underway in the UK (https://www.journalslibrary.nihr.ac.uk/programmes/hta/155785/#/).

Adolescent nicotine exposure

As discussed in the RCP report, smoking in adolescence has been associated with cognitive and attentional deficits and suggested to impact mental health, although confounding factors (such as self-selection) have not been taken into account thus far. The recent US Surgeon General's report (106) gave a comprehensive review of the potential impact of nicotine on adolescent brains using human studies with smokers and animal studies. It concluded that the use EC by youth should be avoided and actively discouraged. We concur with that recommendation. However, we do not see this as a major issue when discussing adolescent smokers, who are already getting nicotine from tobacco cigarette smoking; and providing smoking and nicotine use

among adolescents overall continues to decline (Chapter 5). Nevertheless, careful monitoring of these trends is needed and more research of the impact of nicotine, as opposed to cigarette smoke, on cognitive functioning and attention would be welcomed.

Summary

Overall, there is evidence that nicotine plays a very minor role in the harmfulness of tobacco smoking. The risk profile may be different with inhaled nicotine but this would appear unlikely. As we will see in Chapter 10, this evidence is at odds with public perceptions of the harm caused by nicotine in tobacco smoking, and these perceptions need addressing.

International developments

One of the most recent developments internationally, has been the re-emergence of policy discussions and initiatives on the role of nicotine-reduced cigarettes for tobacco product regulation. In the US, the US Food and Drug Administration (FDA) (107) has commissioned research into nicotine reduced cigarettes and released a consultation on this. Recently, the need for, and role of, less harmful nicotine delivery devices, alongside such a strategy has been given more prominence. Similarly, the WHO has discussed the role of nicotine-reduced cigarettes for tobacco product regulation, producing an advisory note (108). There is currently no appetite for a nicotine reduction strategy in cigarettes in England. Greater discussion of this will follow in a subsequent report.

Niaura (109) and Abrams (110) on behalf of the Truth Initiative and Schroeder Institute for Tobacco Research and Policy Studies in the US, re-examined the role nicotine plays in society and presents a view that nicotine products may contribute to an overall tobacco harm reduction and control strategy. In line with the thrust of this chapter, Niaura and Abrams assert that most of the physiological harm attributable to cigarette smoking derives from the toxicants in tobacco and combustion and that, separated from combustion or other toxic modes of delivery, nicotine, by itself, is much less harmful.

Conclusions

Key findings

- The addictiveness of nicotine depends on the delivery system.
- It is possible that the addictiveness of tobacco cigarettes may be enhanced by compounds in the smoke other than nicotine.
- As EC have evolved, their nicotine delivery has improved. This could mean that their addiction potential has increased, but this may also make them more attractive to smokers as a replacement for smoking. It is not yet clear how addictive EC are, or could be, relative to tobacco cigarettes.
- While nicotine has effects on physiological systems that could theoretically lead to health harms, at systemic concentrations experienced by smokers and EC users, long-term use of nicotine by 'snus' (a low nitrosamine smokeless tobacco) users has not been found to increase the risk of serious health problems in adults, and use of NRT by pregnant smokers has not been found to increase risk to the foetus.
- Adolescent nicotine use (separate from smoking) needs more research.
- The long-term impact of nicotine from EC on lung tissue is not yet known and may be different from its impact systemically.

Implications

Research

- More research on nicotine, compared to tobacco cigarette smoking is needed, and the popularity of EC enables such research, albeit in the context of the other components in EC and EC aerosol.
- Further research is needed on the similarities and differences in addictiveness of EC and tobacco cigarettes and the potential harms associated with *inhaled* nicotine.

Policy and practice

- Widespread misperceptions about relative risks of nicotine and tobacco (see Chapter 10) need to be addressed and corrected.
- Clear messages, based on current evidence about nicotine, its relationship with harms, and its addictiveness, compared with smoking, are necessary and could have a marked impact on public health.
- Policies on tobacco and EC should have at their core the recognition that nicotine use per se represents minimal risk of serious harm to physical health and that its addictiveness depends on how it is administered.

5 Use of EC among young people

Introduction

Our literature search identified studies examining EC use by children and young people described in articles published between 1 January 2015 and 18 August 2017, updating searches conducted for the 2015 PHE report (5). Twenty-four articles from the UK that included data from adolescents were identified and an additional 223 articles were identified that included data from countries other than the UK.

The focus of this section is on current patterns of EC use by young people in the UK. In this section, therefore, we focus on the existing literature that examines the prevalence of EC use in young people rather than the wider literature from the UK which includes studies of issues such as EC marketing and young people, qualitative accounts of young people's perceptions of EC, studies reporting on intentions to use EC, or perceptions of product characteristics, for example. In addition, the extensive international literature identified could not be thoroughly reviewed because of time and resource limitations but key points are highlighted below, to put the UK data in context.

The literature on EC marketing in particular is now well-developed, but has recently been reviewed in a report for Cancer Research UK (111). This literature largely relates to the impact of EC marketing on young people in countries other than the UK. Since May 2016, cross-border advertising of EC was prohibited in the UK as discussed in Chapter 3.. Thus with the exception of billboard and point of sale promotion, almost all forms of EC marketing are no longer permitted in the UK, measures largely designed to protect non-smokers and children from marketing. These new changes limit the relevance of the available marketing literature on EC to the UK context.

Since the literature search was conducted, the authors of this report, along with other colleagues, have published a detailed analysis of the most up to date survey data on smoking and vaping among young people in the UK. This paper was in press at the time of the cut off for the literature search and published just ten days later. Its findings are outlined in detail here, supplemented by more recent data as appropriate.

This section of the report outlines existing data on four key themes:

- use of EC among young people
- trajectories of smoking and EC use
- where young people obtain EC
- the international context

Use of EC among 11 to 16 year olds

Each of the four countries that make up the UK conduct representative surveys of young people which now include questions on EC use. Some of these are not conducted annually and thus availability of the most recent data varies by year. In the 2015 PHE report, findings from one survey that covers all of Great Britain, a regional survey in the North West of England, two surveys in Wales and one in Scotland were included.

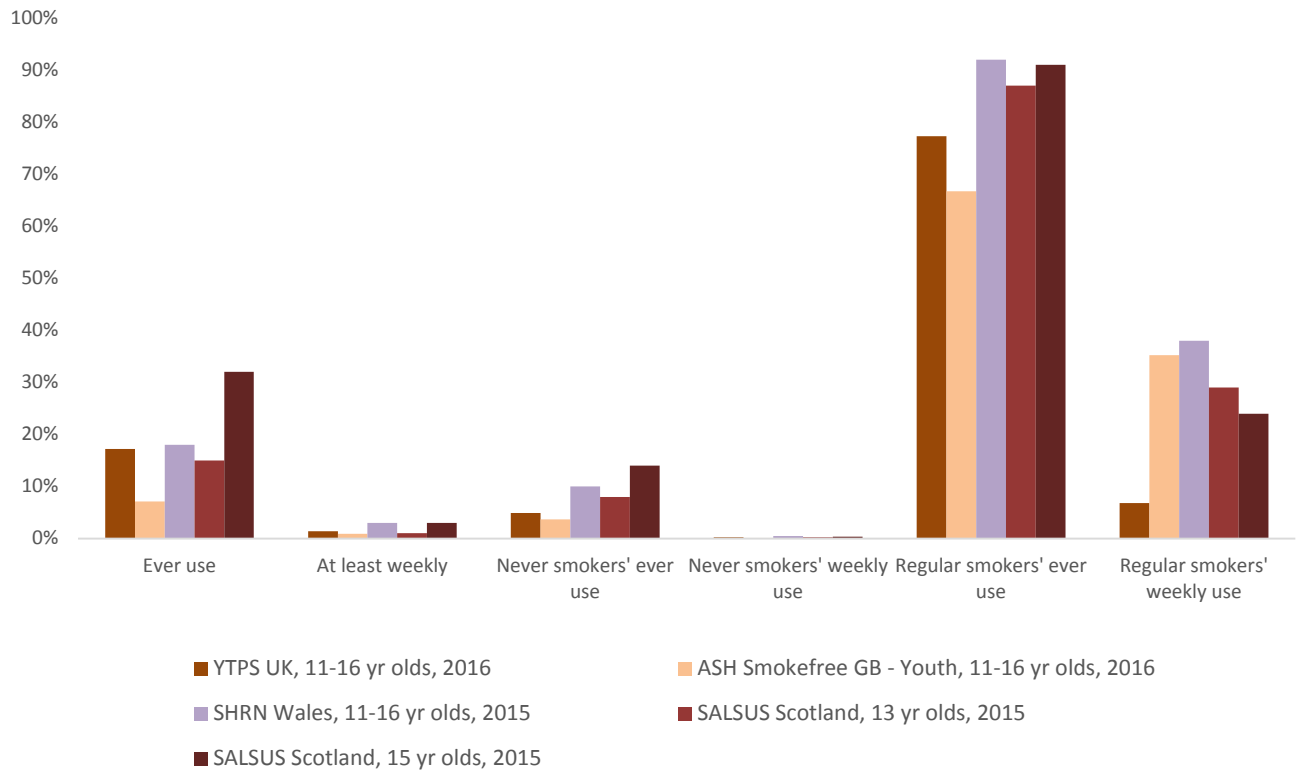
The most recent data are from surveys conducted between 2015 and 2017, recently published in an article outlining finding from these surveys that include just over 60,000 11 to 16 year olds from across all of the UK (6).

Five surveys are available for this latest period (also see Chapter 2 for details). These include:

- The Youth Tobacco Policy Survey (YTPS) which includes a representative sample of young people from the UK including Wales, Scotland, England and Northern Ireland (n=1,213 11-16 year olds)
- The ASH Smokefree Great Britain (GB) -Youth (two surveys) (ASH-Y). This includes a sample of 1,205 11-16 year olds in 2016 and 1,361 in 2017
- The Schools Health Research Network (SHRN) Wales which includes 32,479 young people aged 11-16
- The Scottish Schools Adolescent Lifestyle and Substance Use Survey (SALSUS) which surveys a representative sample of pupils in their second year of secondary school in Scotland (average age 13, n=13,607) and a representative sample of pupils in the fourth year of secondary school in Scotland (average age 15, n=11,697).

Questions about EC use were comparable in each survey but employed slightly different wording to describe the products. Details on question wording and the data collection methods are outlined in the original article (6). Results from these surveys for 2015 to 2016 are included in Figure 2.

Figure 2: Prevalence of EC use in teenagers by smoking status, UK surveys 2015/16



Notes: YTPS, N=1,213 (2016); ASH-Y, N=1,205 (2016); SHRN, N=32,479 (11 to 16 year olds in 2015); SALSUS, N=13,607 (13 year olds in 2015), N=11,697 (15 year olds in 2015). Base for regular smokers in YTPS and ASH-Y is less than 50.

As Figure 2 illustrates, data was available on: ever use of EC among all respondents; regular (defined as at least weekly) use of EC among all respondents; never smokers' use of EC (ever and regular use); and regular smokers' use of EC (ever and regular use).

For 11-16 year olds overall, ever use of an EC ranged from 7-18% among the surveys that included this age range. In the SALSUS survey, ever use was 15% among 13 year olds and 32% among 15 year olds. This rate of ever use represents an increase compared with surveys from previous years. For example, in the single survey that covers the UK as a whole, the YTPS, the rate of ever use for 11-16 year olds was 12% in 2014 compared with 17% in 2016 (112).

Rates of regular (at least weekly) use among all 11-16 year olds are much lower, ranging from 1-3% in all the surveys, including among the sample of 15 year olds in Scotland. Rates of regular use have not increased in recent years in the surveys where comparisons are possible - for example between the YTPS in 2014 and 2016.

Among young people who have never smoked, some experimentation – or 'ever use' – of EC is occurring in the UK. This ranges from 4-10% among 11-16 year olds, and up

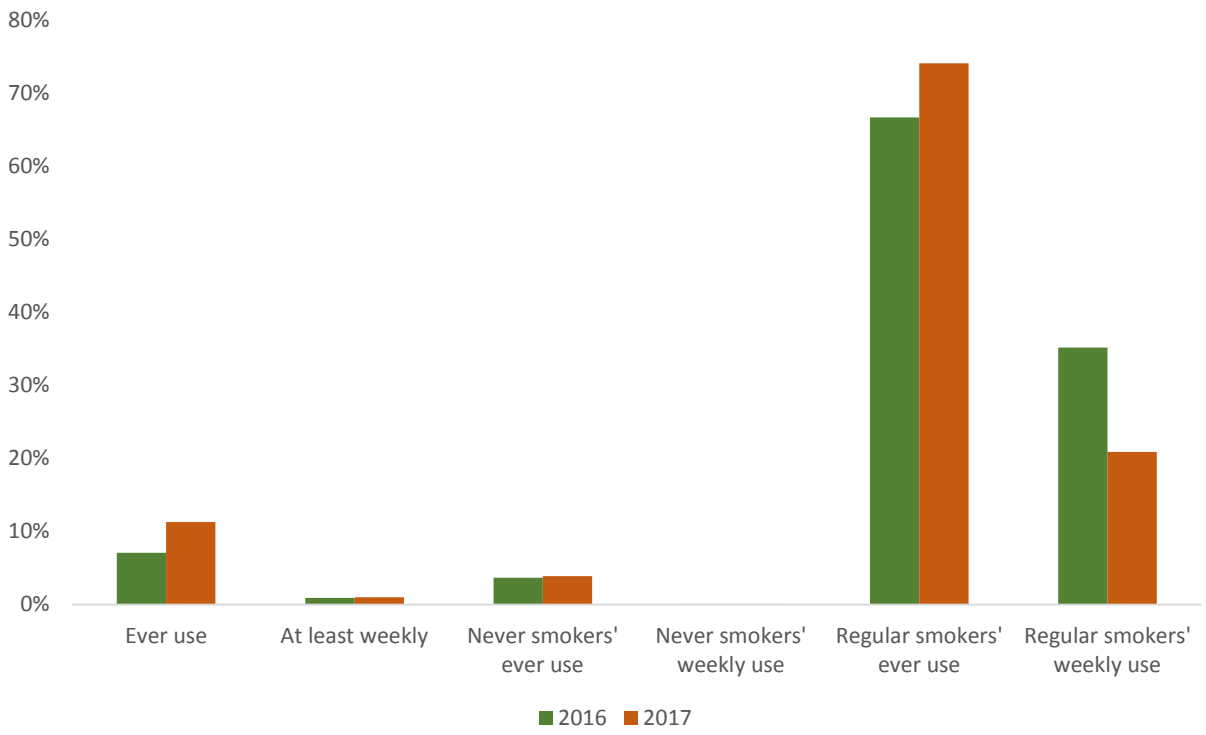
to 14% among 15 year olds in the SALSUS survey in Scotland. Never smokers' ever use has increased slightly compared with previous years - for example from 3% in 2014 in the UK wide survey (YTPS) to 5% in 2016.

However, rates of regular use of EC in young people who have never smoked remain very low in all surveys, ranging from 0.1% to 0.5%.

EC use is concentrated in young people who already smoke. As Figure 2 shows, up to 91% of regular smoking youth in UK surveys have tried an EC and up to 38% of them use an EC at least weekly.

The ASH-Y survey is also available for 2017, representing the most recent data available. Figure 3 provides data comparing 2016 with 2017 for 11-16 year olds in this particular survey. Ever use increased between the two years when all young people were included (from 7% in 2016 to 11% in 2017) but this is largely accounted for by a rise in use among young people who are regular smokers. Both ever and regular use among never smokers did not increase between the two years.

Figure 3: Prevalence of EC use in 11-16 year olds 2016-2017, ASH-Y



Notes: ASH-Y N=1,205 (2016), N=1,361 (2017). Base for regular smokers in 2016 survey is only 14 and for 2017 is only 28.

The ASH-Y survey is also the only UK survey that asked whether EC used by young people contain nicotine. Among 11 to 16 year olds who had used EC in the past or were currently using (those who had tried EC once or twice were not asked), 22% said that the device had always contained nicotine, 39% that it had sometimes contained

nicotine, 27% that it had never contained nicotine, and 12% didn't know. However, it is unclear how accurate recall or understanding of this issue is among participants in youth surveys. Future research should examine this in more detail.

Use of EC among 17 to 18 year olds

Comparable data to the above for 17 to 18 year olds are only available from the ASH-Y surveys and these are presented here (Table 6).

Table 6: EC use among all 17 to 18 year olds in Great Britain, and by smoking status

	2015 *(n=728)*	**2016** *(n=814)*	**2017** *(n=790)*
All: Ever Use	22.2%	25.2%	28.0%
All: At least weekly	1.0%	1.3%	1.8%
Never smokers: Ever use	5.7%	8.8%	8.5%
Never smokers: Weekly use	0.3%	0.0%	0.0%
Regular Smokers: Ever use	81.8%	74.2%	75.8%
Regular Smoker: Weekly use	3.9%	9.6%	8.2%

Notes: Source ASH-Y

These data are consistent with the data for 11 to 16 year olds, with never-smokers' weekly EC use being negligible and never smokers' EC experimentation being around 9% since 2016.

Trajectories of smoking and EC use

A key question for policy-makers and others is whether EC use contributes to the uptake of tobacco smoking in young people. In the period covered by our review, two new UK studies were published that provide relevant data. Both were longitudinal studies originally designed to focus on other tobacco control topics, with questions on EC use added after the studies commenced.

The first study added questions on EC to a project designed to assess the impact of the point of sale tobacco display ban in Scotland (113). This particular project has produced other papers on EC identified in our review from cross-sectional survey results. However, the 2017 paper was distinctive in that it included both baseline and follow up data collected from 11-18 year old never smokers who were originally surveyed in 2015 and followed up one year later in 2016.

At baseline, 8.6% of never smokers who completed the initial survey and follow-up had tried an EC. Of those that had tried EC at baseline, 40.4% had tried smoking by the

follow-up stage. This compares to 12.8% of baseline never EC users who had tried smoking at follow-up. A total of 22.9% of those that tried cigarettes at follow up had previously tried an EC, compared to 77.1% who had never used an EC at baseline. The fully adjusted model showed that having tried an EC at baseline was significantly associated with trying cigarettes in the following year (OR = 6.64, 95% CI: 3.60-12.26).

The second study took place in England with 13-14 year olds who were originally surveyed towards the end of 2014 and followed up one year later[2]. At baseline, 61.5% of these school pupils hadn't tried either EC or cigarettes, 16.0% had tried EC but not cigarettes, 4.4% had tried cigarettes but not EC, and 18.2% had tried both. After controlling for covariates, having tried EC at baseline was significantly associated with having tried smoking at follow up (OR = 4.06, 95% CI: 2.94-5.60). In those that had tried smoking at baseline, there was no significant relationship between having tried EC at baseline and subsequent increased smoking (OR = 1.89, 95% CI: 0.82-4.33).

Both these studies conducted statistical modelling which attempted to account for other factors that might explain the fact that young never smokers who had tried an EC had gone on to try smoking by follow up. This included factors such as having friends or family who smoked or other measures of susceptibility to smoking. However even after controlling for these, EC use emerged as a predictor of subsequent tobacco use. These findings are similar to those identified in a number of longitudinal studies in the US whose results have been summarised in a recent systematic review identified in our literature search (114). They are also similar to a recent study from Canada published after the systematic review but employing similar methods. This was a longitudinal cohort study of secondary school pupils (115). It identified an association between recent (past 30 day) EC use among never smokers at baseline and both ever smoking and daily smoking at follow up.

These studies suggest that EC use is associated with subsequent smoking in young people. However, all of them face similar limitations which need to be understood before assuming that this relationship is causal. One of the most significant relates to the measurement of both vaping and smoking. In both the UK studies, for example, EC use was classified as ever use meaning that many of the young people included could have tried a device just once or twice. Likewise the measure of tobacco use at follow up was ever use, which includes experimentation. Some of the American studies and also the Canadian study assessed recent use of EC (past 30 day) but not regular use of EC. This does not mean that the findings of the US or Canadian studies are incorrect, just that the measures are different from those in the UK.

[2] Conner M, Grogan S, Simms-Ellis R, et al. Do electronic cigarettes increase cigarette smoking in UK adolescents? Evidence from a 12-month prospective study. Tobacco Control published online first: 17 August 2017.

Secondly, smoking uptake is determined by a wide range of factors. Despite the statistical analysis techniques employed, the studies can't control for all relevant confounders. There may well be other factors not measured in the studies (such as sensation seeking, curiosity, expectancies, genetic vulnerabilities) that explain why some young people had tried smoking by follow up. It is also possible that there are groups of teenagers who are more susceptible to trying new things in general, or participating in risk-taking behaviour, and this is the group that may try both vaping and smoking.

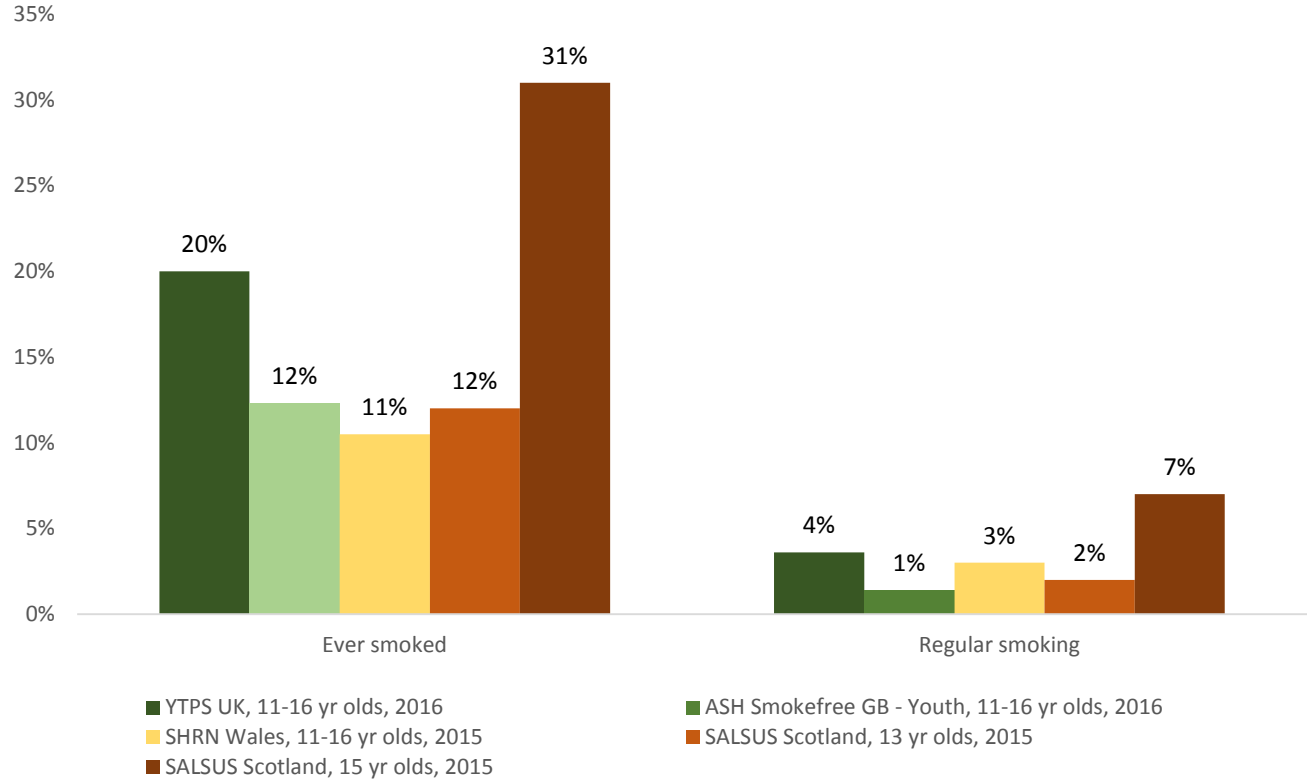
Some support for this explanation, known as a 'common liability' theory, comes from a study in the UK (and one in the US see below). This study used a cohort of over 1,000 11-18 year olds surveyed in April 2016 and followed up four-six months later. The study used logistic regression models and causal mediation analysis to assess the relationships between 1) ever EC use and escalation among baseline never smokers and its association with smoking initiation at follow up and 2) ever smoking and escalation among baseline never EC users and EC initiation at follow up. As well as finding support for relationship 1) between ever EC use and smoking initiation (as found in the other studies above), this study also found support for the opposite relationship identified in 2) ie that ever smokers at baseline were more likely to initiate EC use at follow up[3].

However, the main factor which challenges the 'vaping leads to smoking' hypothesis is what is happening with rates of youth tobacco cigarette use in the UK (and indeed in North America where the other studies were conducted). During the period when surveys show that young people are experimenting with EC, including some non-smokers, tobacco cigarette smoking rates have continued to decline.

To expand on this, we include the latest data on the prevalence of smoking in teenagers from UK surveys conducted between 2015 and 2017. As Figure 4 shows, rates of ever having tried a tobacco cigarette range from 11-20% in surveys of 11-16 year olds overall, but were higher (31%) in the sample of 15 year olds in the SALSUS survey in Scotland. Rates of regular smoking are much lower - between 1-4% for 11-16 year olds as a whole and 7% for 15 year olds in Scotland.

[3] East K, Hitchman SC, Bakolis I, Williams S, Cheeseman H, Arnott D, McNeill A. The association between smoking and electronic cigarette use in a cohort of young people. Journal of Adolescent Health, in press.

Figure 4: Prevalence of smoking in teenagers, UK Surveys 2015/16



Notes: YTPS, N=1,213 (2016); ASH-Y, N=1,205 (2016); SHRN, N=32,479 (11 to 16 year olds in 2015); SALSUS, N=13,607 (13 year olds in 2015), N=11,697 (15 year olds in 2015)

These smoking prevalence figures represent much lower rates than in the past. For example in Scotland, regular smoking has dropped from 30% in 15 year olds and 10% in 13 year olds at the turn of the century to these current low rates of 7% (15 year olds) and 2% (13 year olds) in 2015 (117). In England, 10% of 11-15 year olds were weekly smokers in 2002, but by 2014 this had dropped to 3% (118). In fact this same survey in England found that 18% of youth in 2014 reported ever trying smoking at all, even once, which was the lowest level identified since the survey began in 1982 (118).

The ASH-Y survey also gives smoking prevalence among 17-18 year olds which are also consistent with the above trends in younger age groups (
Table 7).

Table 7: Smoking prevalence in Great Britain among 17 to 18 year olds

	2015 *(n=728)*	**2016** *(n=814)*	**2017** *(n=790)*
Smoking prevalence (ever)	40.3%	38.4%	45.2%
Smoking prevalence (regular)	8.7%	6.5%	7.1%

Notes: Source ASH-Y

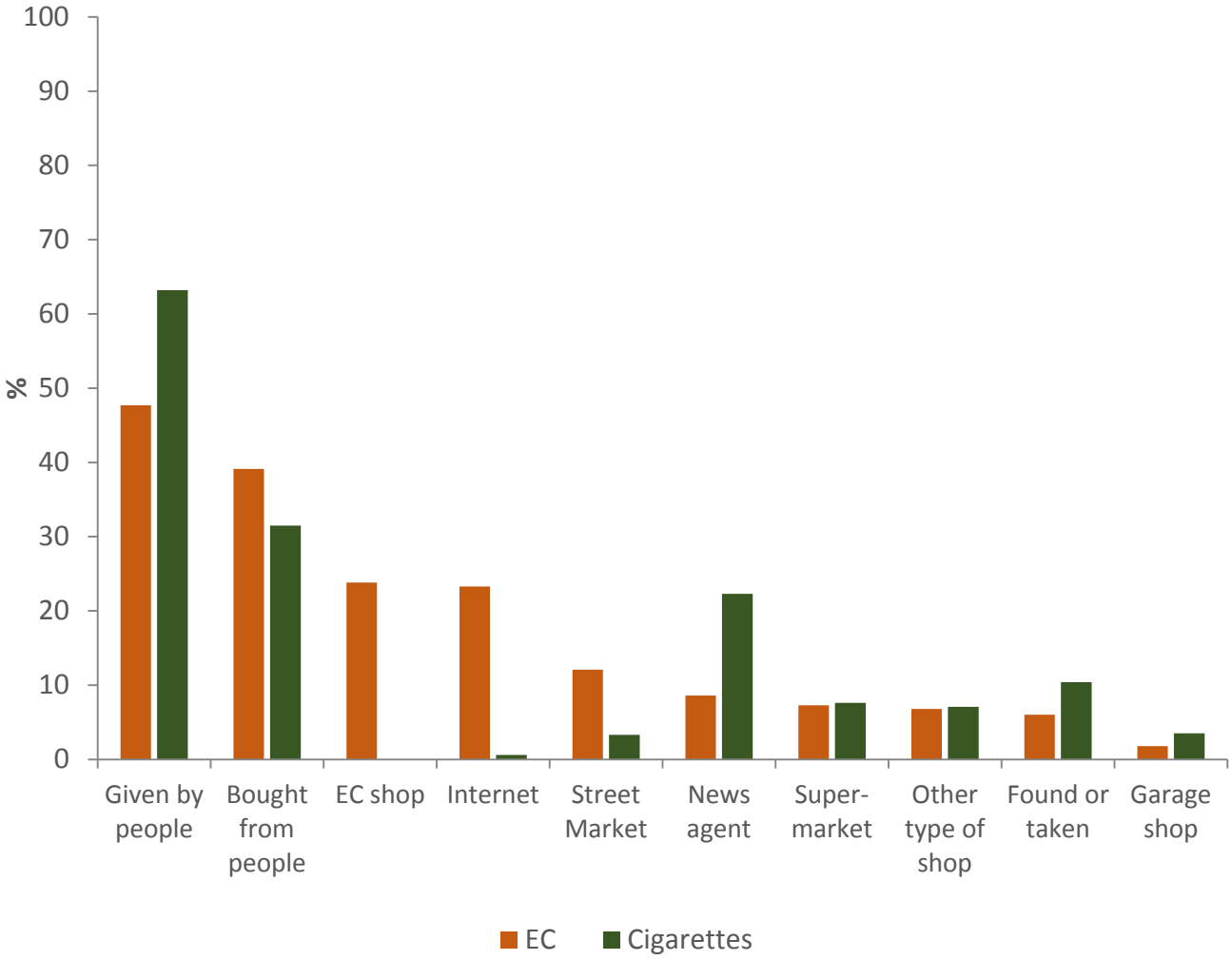
Since the Bauld and colleagues article (6) was released, a further official survey of Smoking Drinking and Drug Use (SDD) in young people (aged 11-15 years) in England has been published. Consistent with the trends above, it also identified a continued decline in youth smoking in England. For example, in 2006, 20% of 15 year olds in England were regular cigarette smokers but in the latest results, for 2016, this had dropped to 7% (11). Similar declines have been noted in the US including during the period when US studies (such as those outlined in Soneji and colleagues, 2017 (114)) were reporting a relationship between EC and tobacco experimentation (119, 120).

If EC use was causing smoking at the population level, these reductions in youth cigarette smoking would have significantly slowed or indeed reversed in the UK. This is not happening, and suggests that EC are not currently undermining what decades of efforts to prevent youth smoking uptake have achieved.

Where young people obtain EC

The SDD survey also included questions on how young people obtain EC, with data from 2016 in England (11). Respondents could give more than one answer (Figure 5). The most common source was being given them by other people (48%). This compares to 63% of current smokers in the same survey who reported being given cigarettes by other people. Thirty-nine per cent of regular EC users reported buying (rather than being given) EC from other people (mostly friends or relatives) compared to 32% of current smokers. Thirty-seven per cent of EC users reported buying an EC from a shop compared to 33% of current smokers.

Figure 5: Young People's sources of EC and cigarettes, England 2016



Notes: Smoking, Drinking and Drug Use Survey 2016. EC n=311; cigarettes n=290

The most popular place to purchase EC among regular users was a vape shop with 24% reporting purchasing from these specialist stores. Slightly fewer (23%) reported buying online, making the two most common purchase points for EC different ones than for tobacco – with no sales of tobacco reported from vape shops, and just 0.6% of smokers buying online. Newsagents were the most popular place to purchase cigarettes by young smokers, accounting for 22% of purchases, whereas just 9% of EC purchases by young people were from newsagents.

Fifty-six percent of regular EC users reported asking someone else to buy a device or refills from a shop compared to 79% of current smokers. Seventy-two percent of those who asked someone else to purchase an EC on their behalf reported success compared to 85% of those asking someone else to purchase cigarettes.

These findings have a number of implications. First, it is concerning that young people can continue to access tobacco cigarettes, including purchasing them from newsagents despite age of sale laws that have been in place for many years in England and throughout the UK. Similar age of sale laws (age 18) now exist for EC in England (and also in Wales and Scotland – age of sale is not yet in place in Northern Ireland but should be enacted soon) but this legislation does not appear to be deterring around one third of young EC users in England from purchasing them in retail outlets. In addition, almost one in four young people in England who use EC are purchasing them online – while online purchase of tobacco by young people is negligible. Online purchases of EC by young people should be monitored.

That said, the most common source of young people obtaining either EC or tobacco was from friends and relatives and this proxy purchasing needs further attention. This is particularly concerning for the much more harmful product - cigarettes - and provides the basis for Scotland's legislation which includes powers to fine adults convicted of proxy sales of tobacco – legislation not in place in other parts of the UK.

The international context

An additional issue of interest is how EC use by young people in the UK compares to that in other countries. Direct comparisons are challenging for at least three reasons:

- the ages of adolescents included in surveys varies between jurisdictions
- many surveys are not representative of young people in the relevant jurisdictions but instead include convenience samples or those from particular schools or communities
- surveys do not use identical or even similar questions to assess use of EC

The issue of survey questions is particularly challenging. In the UK, a clear distinction is made between ever or occasional use and regular (at least weekly) use. This is rarely attempted in other countries where the vast majority of surveys include (or only report) measures of ever or recent use, with recent use defined as in the past 30 days, a measure not used in the UK.

However, it is possible to describe general trends in countries that report data from youth surveys. These are almost all high income countries where EC are available for sale. Our literature search identified one systematic review of the international literature on youth use of EC (121). This included 22 relevant studies on EC awareness and use in under 18s from January 2014 to January 2016. Seventeen of these reported prevalence figures on: ever use; recent use (past 30 days); and, in three articles, regular use. Given the review was conducted to include articles published up to 2016 many of these data are now some years old. For example, articles published in 2016 commonly included data from 2013/14, meaning that this overview may now be five

years out of date. In addition, as the authors point out, the surveys vary in terms of the age groups involved.

Despite these considerable limitations, Greenhill and colleagues' paper (14) provides a snap shot of youth prevalence figures from a few years ago. Ever use, for example, varied from 4.4% in Germany to 38.5% in Romania.

Recent (past 30 day) use of EC in the various youth surveys identified in the systematic review (121) ranged between 2 and 14% in the US, 7.2% in Canada and 1.1% in Hong Kong. Regular use in the review was defined as at least once per month and only reported in one study from the UK (again 2014 figures, at 1.5%), 3.2% in Ireland and 0.5% in Greece.

These international comparisons paint a rather confusing picture, and as Greenhill and colleagues point out, the measurement challenges we identify above make direct comparisons very difficult if not impossible.

However, considerable attention has been paid to comparisons between the UK and North America and here it may be instructive to look at more recent surveys in an attempt to describe whether what is observed in the UK is unusual or not.

One recent large, nationally representative survey of young people in grades 6-12 (aged 11 to 18) in Canada has recently been published (122). This includes data from the Canadian Student Tobacco, Alcohol and Drugs Survey across 336 schools, capturing results from 42,094 students between October 2014 and May 2015. The Canadian findings for ever use are broadly similar with those in the UK from the subsequent year, as outlined above. They found that 17.7% of young people reported ever using EC. Overall 5.7% reported use in the past 30 days, but this rate was just 1.8% in never smokers - illustrating, like UK data, that these products are used primarily by young people who also smoke tobacco cigarettes.

Likewise in the US, an analysis of the 2015 National Youth Tobacco Survey (NYTS) has recently been published (123). As with the Canadian survey and our UK data, this is a representative survey of young people across the US and included 17,711 young people in middle school (aged 11-14) and high school (aged 14-19). This is a slightly broader age group than in the UK datasets above. The NYTS focuses on 'current use' of tobacco products and EC which is use in the past 30 days. Overall 11.3% of all young people in the survey reported current EC use (124).

Collins and colleague examined the NYTS data in more detail and identified similar patterns to an earlier study of the 2014 data from the same survey (125). They found that almost all EC users were either currently using another tobacco products (such as cigarettes) or had used tobacco at some point in the past. Only 1.6% of never tobacco

users ('tobacco naïve' youth) were current EC users. Although 'frequent' use is not reported in the NTYS reports, Collins and colleagues analysed the raw data and found that less than 0.1% of tobacco naïve youth reported using EC on 10 days or more in the past month.

At least one survey in the US asked questions about whether youth had vaped nicotine and found that the vast majority of youth (65-66%) who report trying or currently using an EC used one that did not contain nicotine (126).

Although these surveys in Canada and the US cannot be directly compared with data from the UK, they suggest similar patterns. First, that ever or recently using an EC is not unusual among young people overall. However, both ever and recent use is far more common among young people who smoke than young people who have never smoked. The very recent analysis by Collins and colleagues also shows that regular use of EC is extremely rare among never smoking young people in the US, as the UK data also shows. A future priority for research should be to harmonise measures and questions across youth surveys to allow reliable and accurate international comparisons to be made.

As mentioned above, a recent systematic review of studies on trajectories of use (114) has identified in the international literature a link between EC ever use at baseline and smoking initiation at follow up. In addition, one of these studies (127) also found a relationship between smoking at baseline and recent use of EC at follow up, similar to the UK study identified above.

Conclusions

Key findings

- E-cigarettes cannot be legally sold to young people under the age of 18 in most parts of the UK with the exception of Northern Ireland. Purchasing does occur including from sources rarely used for tobacco such as online suppliers.
- Despite some experimentation with these devices among never smokers, EC are attracting very few young people who have never smoked into regular use.
- EC do not appear to be undermining the long-term decline in cigarette smoking in the UK among young people.
- Never smokers in the UK who try EC are more likely to have tried smoking subsequently than those who have not tried EC.
- A causal link has not been established and neither has progression to regular smoking. The 'common liability' hypothesis seems a plausible explanation for the relationship between EC and smoking experimentation.

Implications for research, policy and practice

- Trends in EC use and smoking among youth should continue to be monitored using standardised definitions of use. This should include the use of nicotine in EC and checks on the understanding of survey questions.
- Patterns of EC purchasing by young people should be closely monitored, particularly internet sales. Age of sale regulations are in place for EC and cigarettes and should be strongly enforced.
- Research is needed on trajectories of use – not just from EC experimentation to smoking, but also from smoking to EC use among young people.

6 Use of EC in adults

Introduction

The objective of this chapter is to provide an overview of available data on prevalence of trial and use of vaping devices/EC in adults in Great Britain and information on characteristics of EC use. This information will be followed by a brief overview of international evidence on prevalence of trial and use.

Surveys used to describe the situation in Great Britain are the 2016 Office for National Statistics (ONS) 'Adult smoking habits in Great Britain' (respondents aged 16 and over), the Smoking Toolkit Study from England (STS, respondents aged 16 and over) and the ASH Smokefree Great Britain surveys of adults (ASH-A, respondents aged 18 and over). In this chapter, EC use will be presented over time alongside smoking prevalence, followed by a breakdown of trial and use by smoking status and socio-demographic characteristics as available. Characteristics of EC use will be presented for all current EC users as well as broken down by vaping and smoking status, mainly relying on the ASH-A. International information will be summarised based on the literature review described in Chapter 2.

The surveys use different questions to determine EC trial and use. In the ASH-A, two questions determine EC use status. First "Which of the following statements BEST applies to you? a) I have never heard of e-cigarettes and have never tried them; b) I have heard of e-cigarettes but have never tried them; c) I have tried e-cigarettes but do not use them (anymore); d) I have tried e-cigarettes and still use them; e) Don't know". Options c) and d) combined are classed as 'ever tried' and those responding c) or d) are asked a follow-up question about how often they had used or currently used e-cigarettes which includes the option "Not applicable – I have only tried e-cigarettes once or twice" as well as five options ranging from "Everyday" to "Less than once a month" and an additional "Don't know". Those responding c) to the first question and "Not applicable – I have only tried e-cigarettes once or twice" are treated as past triers, those responding c) and any frequency of use in the follow-up question as past users. Those responding d) to the first question are treated as current users which includes a small percentage who have at the point of the survey only tried once or twice.

In the ONS, respondents were asked to select one response out of a) No, I have never used one and I will not use one in the future; b) No, I have never used one but I might use one in the future; c) Yes, I have used one in the past but no longer use one; d) Yes, I currently use one; e) I tried one, but did not go on to use it; f) I don't know what an e-cigarette is (spontaneous only). Little information is provided in publications, so the question wording is not available. Those responding c), d) or e) are combined as

having ever tried an EC; those responding c) or d) as ever users, and those responding d) as current users.

The STS uses a different approach and does not assess whether respondents have ever tried or used EC. Depending on smoking status, variations on the question “Are you using any of the following?” are asked, followed by a list of products including ‘Electronic cigarette’. Those who smoked cigarettes in the past year and have made any attempts to quit smoking are also asked about aids used, these also include EC as an option.

Evidence from recent GB surveys

Trial and use of EC in adults in GB

For 2016/17, the estimates for prevalence of current use were very similar across the three different surveys and ranged from 5.6% to 5.8%, regardless of different geographical coverage and slightly different minimum age of respondents (Figure 6 and Table 8). This prevalence translates to about 2.9 million current adult EC users in Great Britain.

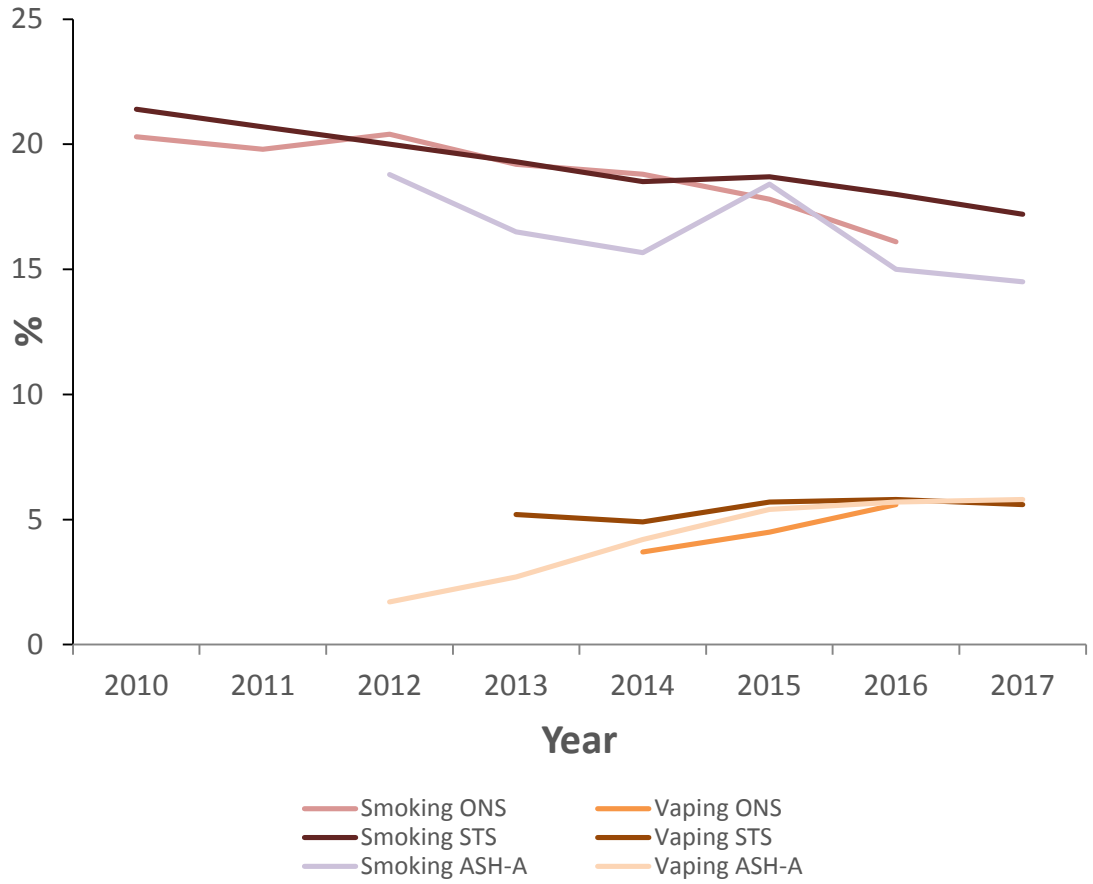
Figure 6 shows prevalence of EC use and smoking prevalence in adults from the three surveys over the last few years. This indicates that EC use prevalence has plateaued while smoking prevalence continues to decrease.

Table 8: Current prevalence of EC use and trial in adults

	ONS, 2016, %	ASH-A 2017, %	STS 2017, %
Ever tried EC	18.6	16.7	-
Current EC user	5.6	5.8	5.6

Notes: Unweighted ns: ONS 7,713; STS 20,395; ASH-A 12,696. Ages 16+ for ONS and STS, 18+ for ASH-A

Figure 6: Prevalence of smoking and EC use in the adult population in three national surveys



Notes: STS measured EC use from Quarter 4 in 2013, ASH-A is conducted in March. Ages 16+ for ONS and STS, 18+ for ASH-A

EC use and smoking status

Figures for EC use by smoking status vary a little across surveys (Table 9). This may at least partly be due to different questions and categorisations used to define smoking status. Additionally, the STS reports figures for past-year smokers (combining current smokers and those who stopped within the last 12 months) and long-term ex-smokers (those who stopped smoking more than 12 months ago) separately, whereas other surveys report data for current smokers and ex-smokers of any length of time. However, all recent surveys find the highest level of EC use among smokers (often referred to as 'dual use') and very low levels of EC use among never-smokers.

'Dual users' are not a homogenous group. This label includes a wide range of smoking and EC use patterns, from those who smoke many cigarettes a day and use EC only very occasionally to those who use EC many times a day and smoke only very occasionally, and every combination of behaviours in between. There has been little

research into different patterns of using EC while smoking and their effects on health or changes in smoking and EC use behaviour over time.

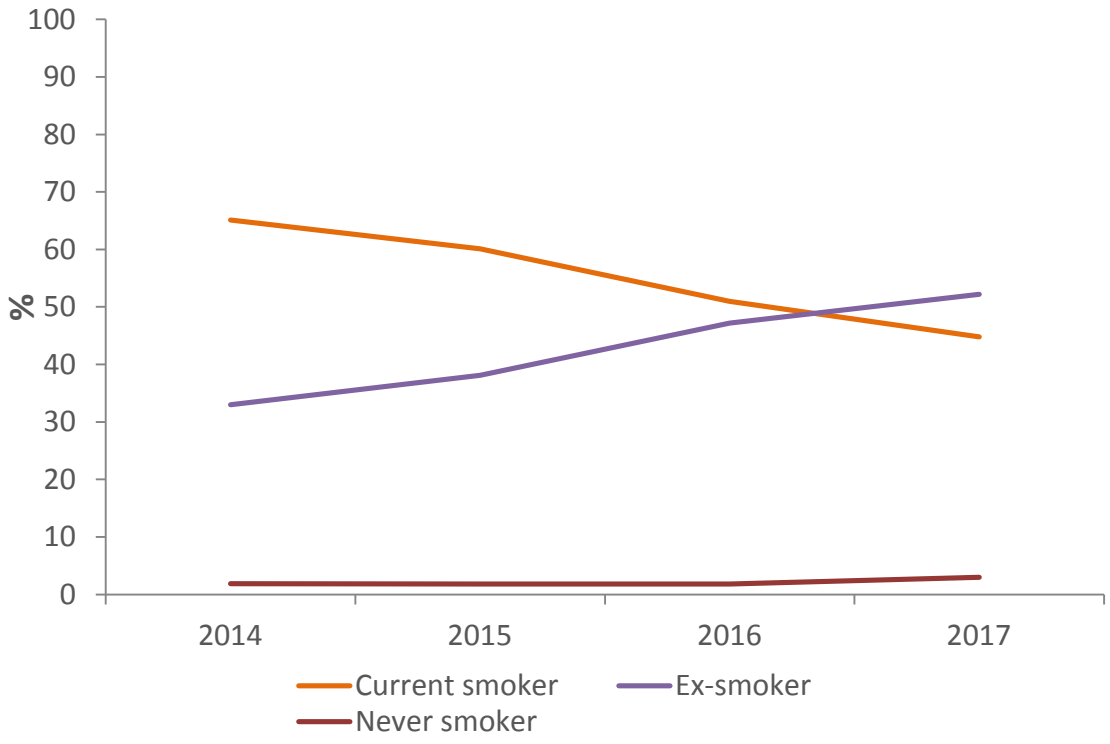
Table 9: Current EC use by smoking status, adults

	ONS, 2016	ASH-A, 2017	STS, 2017
Smoking status			
Current smokers/ past-year smokers in STS	13.7	18.0	20.1
Ex-smokers/ long-term (>1 year) ex-smokers for STS	12.1	9.5	8.7
Never-smokers	0.6	0.3	0.6

Notes: Unweighted ns: ONS 7,713; STS 20,395; ASH-A 12,696. Ages 16+ for ONS and STS, 18+ for ASH-A

The smoking status of those who use EC has changed over time; the proportion of smokers has been decreasing and the proportion of ex-smokers increasing so that the majority of EC users are now ex-smokers (Figure 7).

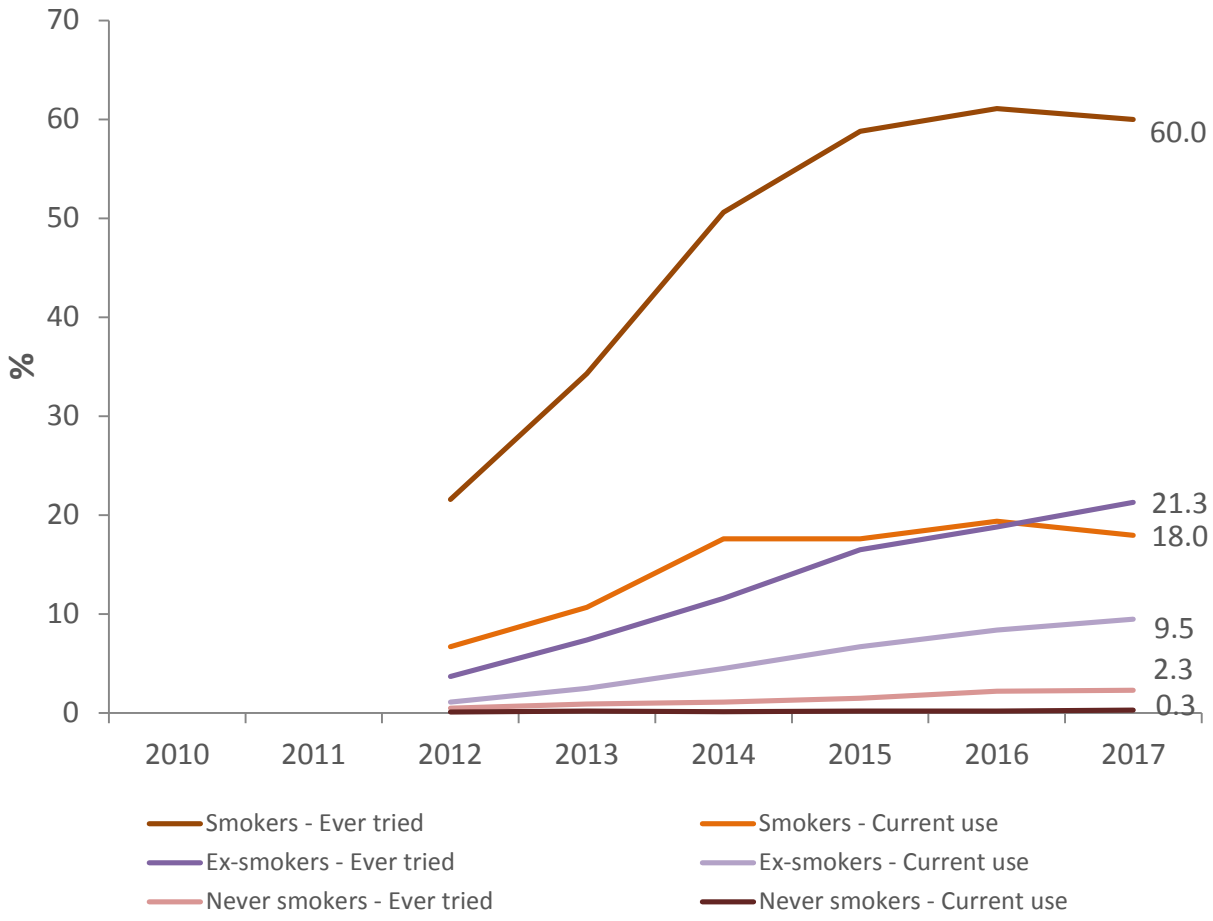
Figure 7: Smoking status of current EC users



Notes: ASH-A, reproduced (128). Unweighted bases in the appendix Age 18+

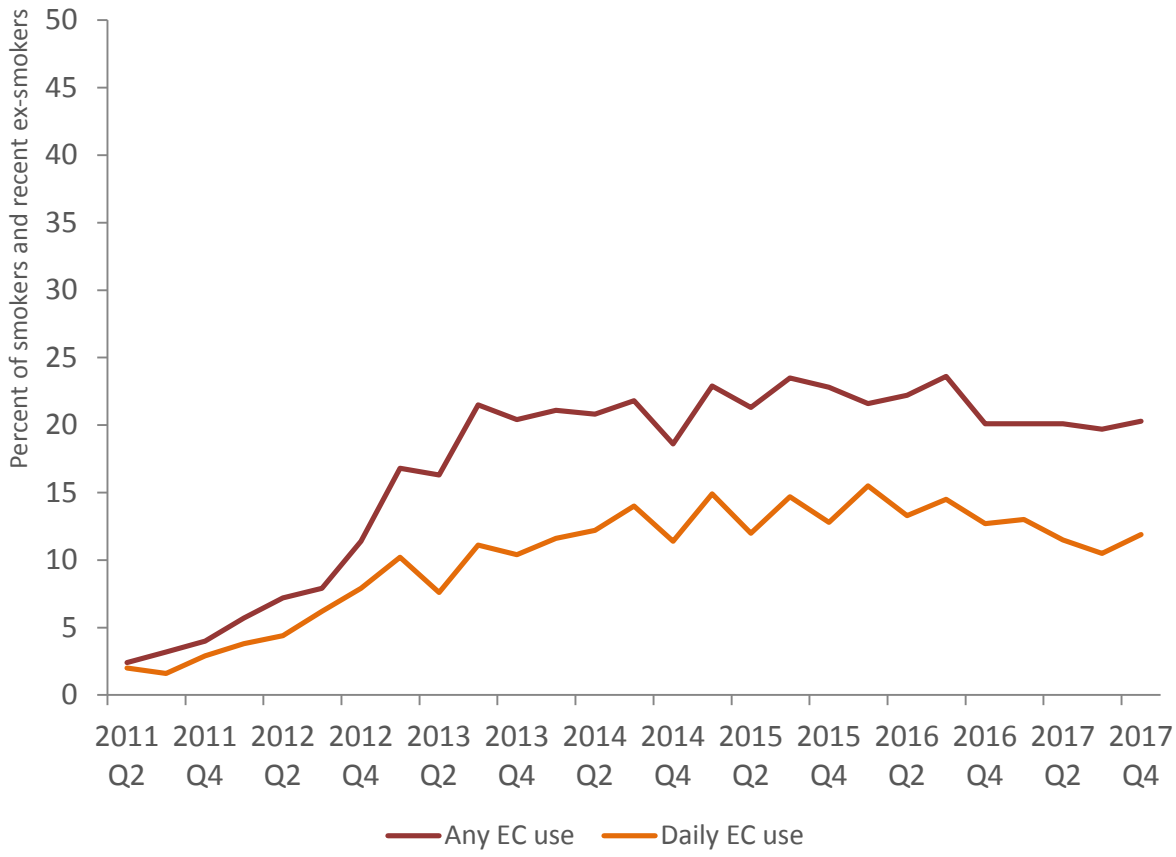
Figure 8 shows ever EC trial and current EC use by smoking status over time as recorded in the ASH-A survey. EC trial and use in current smokers seem to have levelled off with little change in use between 2014 and 2017; 40% of all current smokers have never tried EC. For comparison, in the 2016 survey, 59% of smokers had never tried NRT and 3% reported currently using NRT (19% for EC). In ex-smokers, use continues to increase. In never-smokers, EC use has remained very low since surveillance began in 2012 with the highest prevalence of 0.3% recorded in 2017. A similar picture emerges from the STS, where EC use among smokers and recent ex-smokers has plateaued (Figure 9) while use among long-term ex-smokers continues to increase (Figure 10). Similar to the ASH-A, the STS has recorded EC use among never smokers around 0.5%; interestingly, EC use has been at the same level as use of NRT in this group (Figure 10).

Figure 8: Ever trial and current use of EC in adults by smoking status over time



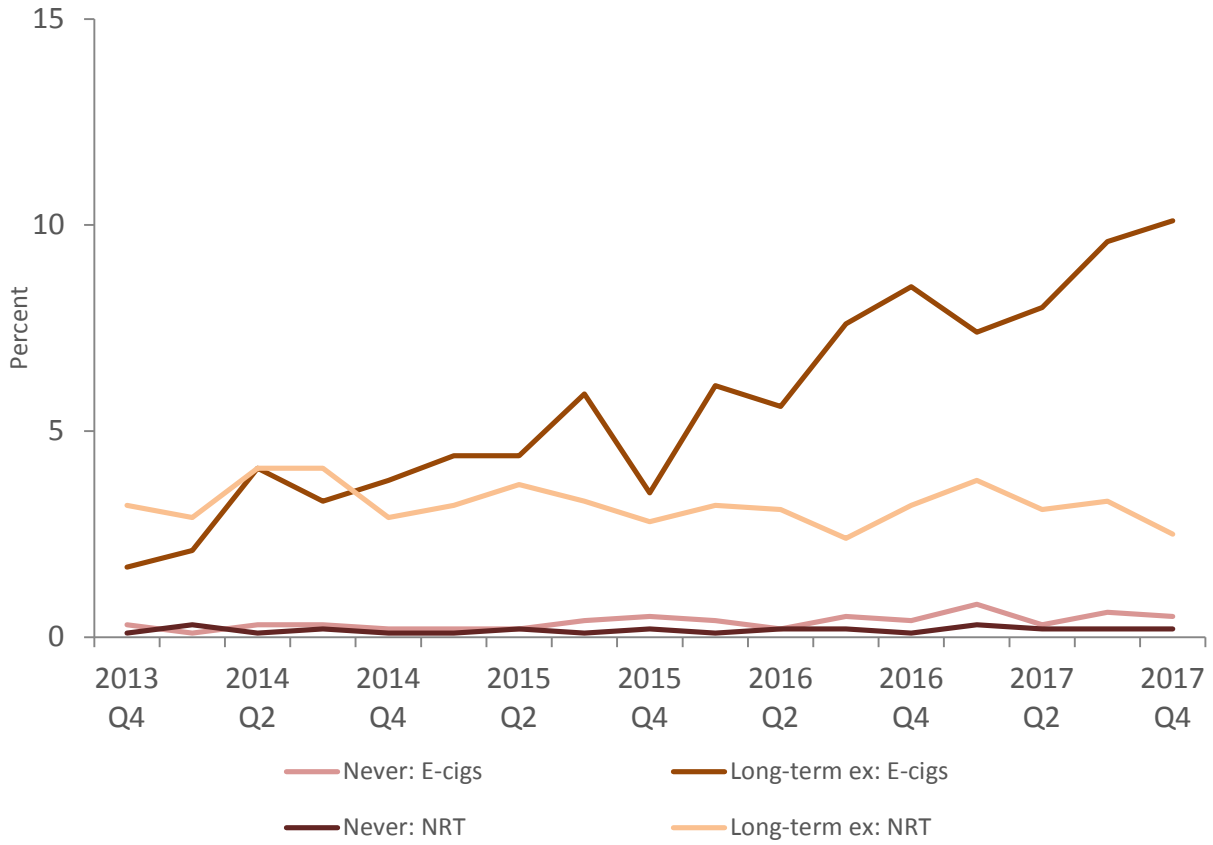
Notes: ASH-A. Unweighted bases in the appendix Ages 18+

Figure 9: Prevalence of EC use among smokers and recent ex-smokers



Notes: STS, N=27,389 adults (16+) who smoke or who stopped smoking in the past year

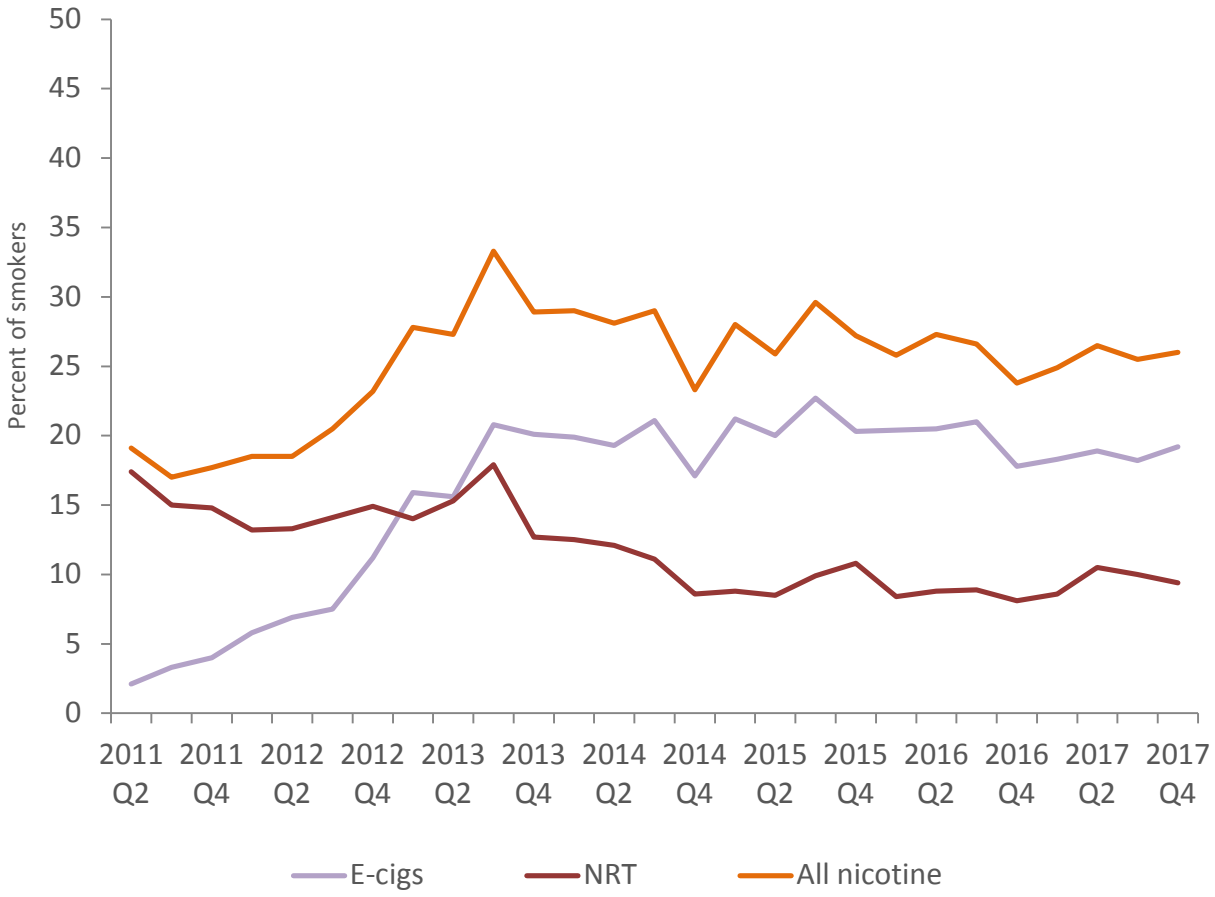
Figure 10: Use of NRT and EC by never smokers and long-term (>1 year) ex-smokers over time



Notes: STS. N=67,513 never and long-term ex-smokers aged 16+ from November 2013

STS data show a decline in the use of NRT alongside smoking and an increase in EC use alongside smoking (Figure 11). The extent to which EC use is cannibalising NRT is discussed in Chapter 7.

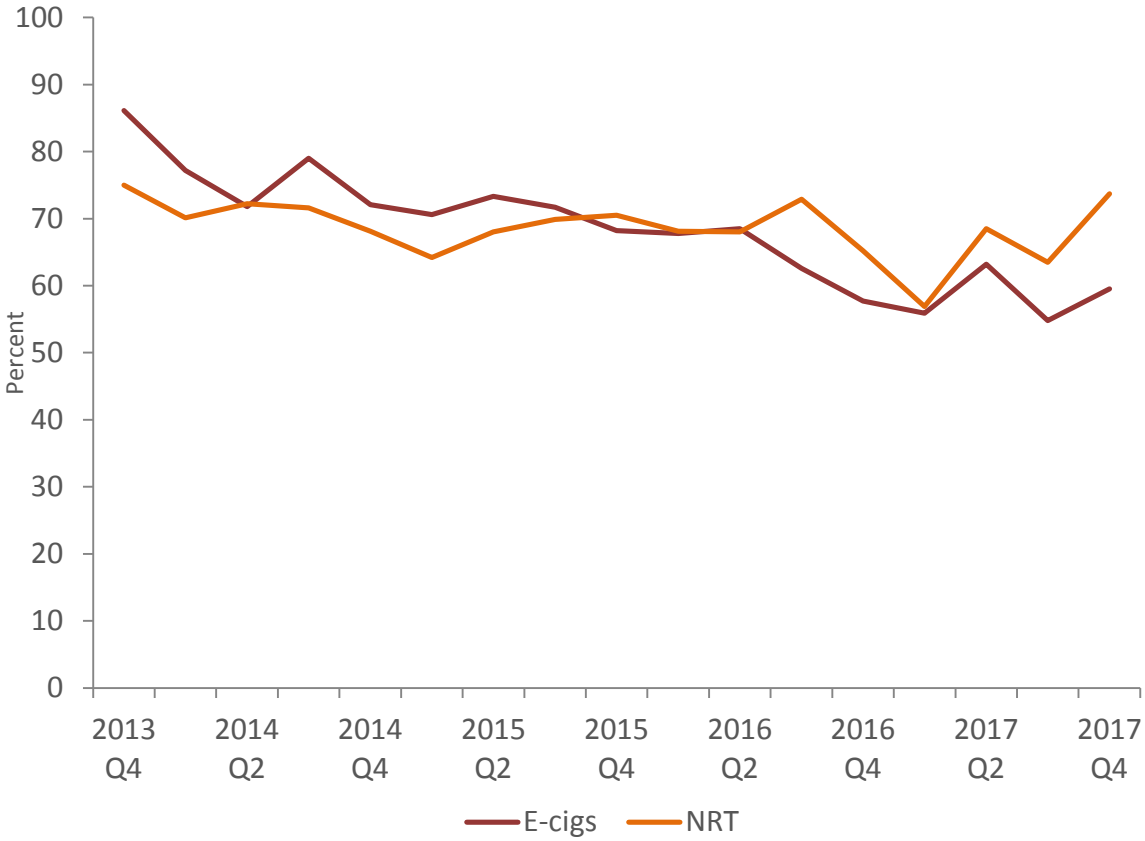
Figure 11: Use of nicotine products while smoking



Notes: STS. N=25,549 smokers aged 16+

Dual use of EC while smoking is unlikely to be associated with substantial reductions in harm, particularly when there is no substantial reduction in the number of cigarettes smoked (129). However, a comparison between dual users and smokers also indicated that dual use is not associated with an increase in harm. It is also worth noting that dual use is not specific to EC; very similar proportions of EC and NRT users also smoke or have smoked within the last year (Figure 12).

Figure 12: Proportion of EC users and NRT users who are 'dual users' (also smoke or have recently smoked)



Notes: STS, N=4,408 EC users and N=2,226 NRT users aged 16+

EC use and socio-demographics

Prevalence of current use in different socio-demographic groups is shown in Table 10. There does not appear to be a clear association with gender or a strong association with age, although all surveys report lower prevalence in the oldest and youngest age groups.

In terms of socioeconomic status, the association found depends on the population analysed (Table 11). In all adults in the general population (ONS and ASH-A), prevalence of EC use is higher in groups with lower socioeconomic status. This is expected due to a higher smoking prevalence in lower socioeconomic groups and the higher prevalence of EC use among smokers (ie groups with higher smoking prevalence are likely to have a higher EC use prevalence). In past-year smokers, the STS shows no clear gradient in prevalence of EC use, meaning that the socioeconomic differences seen in earlier years (5) have shrunk. This suggests that smokers from different socioeconomic status groups have a similar likelihood of using EC for quitting smoking although this remains to be tested empirically.

There are some regional variations; the proportion of adults using EC ranges from 3.0% in Wales to 11.5% in Yorkshire and the Humber and the proportion of smokers who have never tried EC ranges from 34.8% in Wales to 50.0% in the South West and in the West Midlands (Table 12).

Table 10: Current EC use by socio-demographics and smoking

	ONS, 2016, adults	ASH-A, 2017, adults	STS 2017, adult past-year smokers
Gender			
Men	6.3	6.4	20.2
Women	4.9	5.3	19.9

Notes: Unweighted ns: ONS 7,713; STS 20,395; ASH-A 12,696. Ages 16+ for ONS and STS, 18+ for ASH-A

Table 11: Prevalence of current EC use by age and socioeconomics

ONS, 2016 adults		ASH-A, 2017 adults		STS 2017 adult past-year smokers	
Age		**Age**		**Age**	
Under 25	5.8	Under 25	5.2	Under 25	19.8
25 to 34	6.9	25 to 34	6.3	25 to 34	20.3
35 to 49	7.1	35-44	6.9	35-44	22.0
50 to 59	6.5	45-54	6.9	45-54	21.4
60 and over	2.9	55+	4.6	55-64	20.1
				65+	14.2
Socioeconomics		**Socioeconomics**		**Socioeconomics**	
Degree	3.6	AB	4.3	AB	22.6
Higher education	5.9	C1	5.3	C1	20.0
A-Levels or Highers	6.5	C2	6.5	C2	20.8
ONC or National Level BTEC	8.2	D	7.3	D	16.8
O-Level, GCSE, CSE, Standard Grade*	6.4	E	7.5	E	20.9
Other qualifications	5.9				
No formal qualifications	5.3				

Notes: Unweighted ns: ONS 7,713; STS 20,395; ASH-A 12,696. Ages 16+ for ONS and STS, 18+ for ASH-A

AB: Higher & intermediate managerial, administrative, professional occupations; C1: Supervisory, clerical & junior managerial, administrative, professional occupations; C2: Skilled manual occupations; DE: Semi-skilled & unskilled manual occupations, Unemployed and lowest grade occupations.

**Calculated from O-Level or GCSE equivalent (grade A-C), GCSE (grade D-G), CSE (grade 2-5) or Standard Grade (level 4-6)*

Table 12: Regional prevalence of current EC use in adults in the general population and proportion of smokers who have never tried EC, ASH-A 2017

Region	Adult prevalence of EC use, %	Smokers who have never tried EC*, %
North East	3.8	45.2
North West	9.9	37.9
Yorkshire and the Humber	11.5	41.7
East Midlands	10.3	39.6
West Midlands	7.6	50.0
East of England	7.3	36.7
London	4.9	36.0
South East	6.1	38.2
South West	7.2	50.0
Wales	3.0	34.8
Scotland	5.5	35.4

** Including those who had never heard of EC and those who didn't know. Unweighted bases in the appendix. Age 18+*

Characteristics of EC use

This section mostly presents data from the ASH-A 2017; characteristics will be shown for current and past EC users by smoking status. Where the unweighted sample size is less than 50, percentages will not be reported because reliability of these figures would be low. This means that characteristics of use are not shown for never-smokers who currently use (n=15) or never-smokers who used more than once or twice in the past (n=45) in the ASH-A.

Frequency of use

Across different surveys, most respondents who say they currently use EC report daily EC use; 75% and 67% of current EC users reported daily use in the ONS 2016 and the ASH-A 2017 respectively. In the STS from 2013 to 2017, 62% of smokers who reported current EC use and 87% of ex-smokers who reported current EC use were daily users.

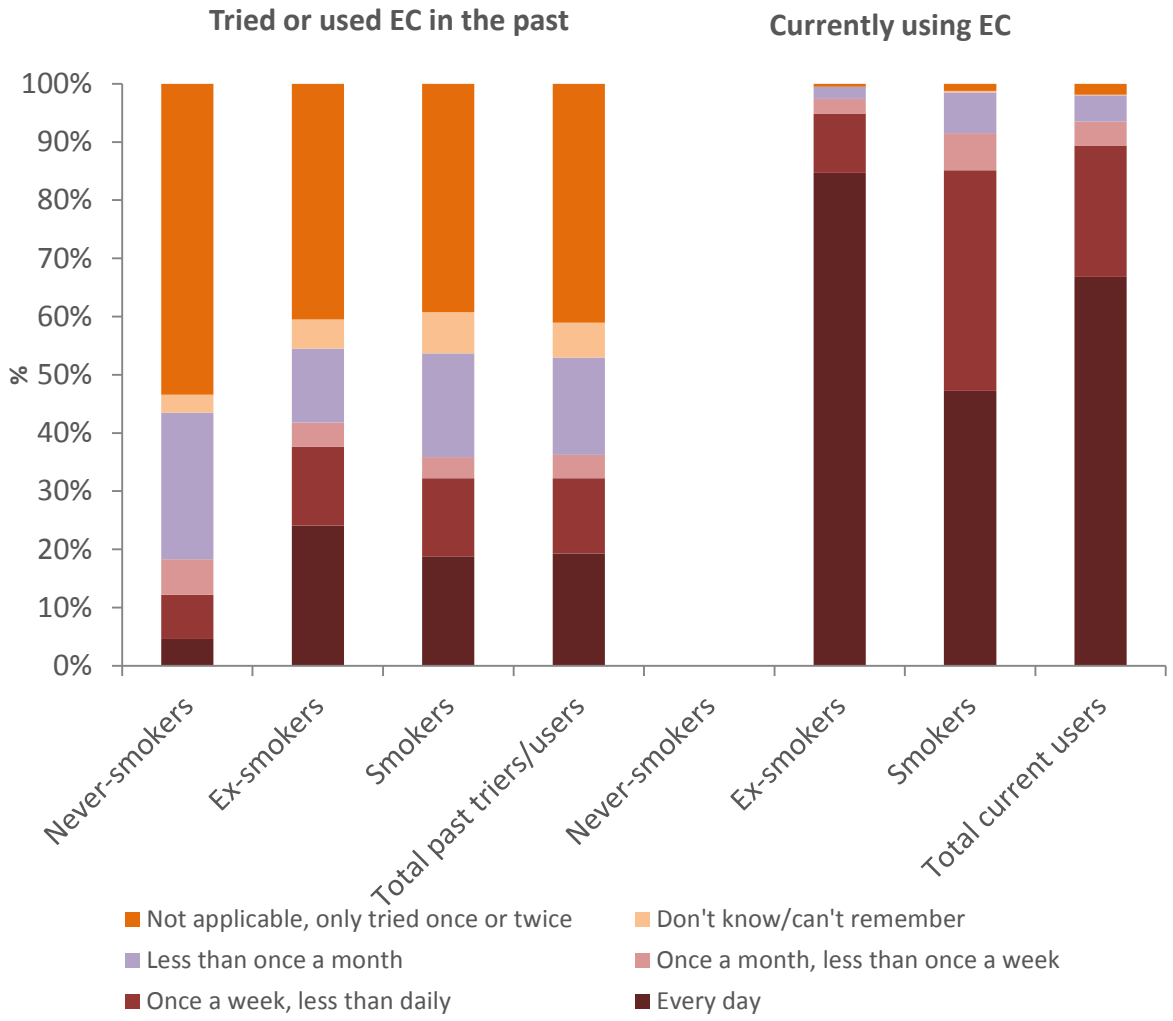
Among those who used or tried EC in the past, frequency of use looks very different (Figure 13); the most common response, regardless of smoking status, is that they only tried EC once or twice.

Among never-smokers who said they had ever used or tried an EC, experience with EC was mostly limited to trial. While 2.3% of never-smokers reported ever having tried or used EC, around half of those (50.7%) had only used EC once or twice. Among those who had used EC more often, the majority had used less than monthly (22.4% of all

never-smokers who had ever tried); 10.5% of never smokers who had ever tried EC reported they had used or were using every day (this equates to 0.2% of all never smokers or an unweighted n of 12 out of 6626 never smokers).

These data are in line with findings that frequent users are more likely to continue use from a longitudinal study in the US (130) which assessed frequency of EC use at baseline and again after a year. About 27% (95% CI: 18 to 40) of those who at baseline used on 1 to 5 days in the past month reported any use at follow-up, while 89% (95% CI: 78 to 100) of those who reported daily use at baseline also reported use at follow-up. To date, there is no evidence as to how EC use changes in the long-term, such as more than one year.

Figure 13: Frequency of EC use among past users or triers and current EC users by smoking status

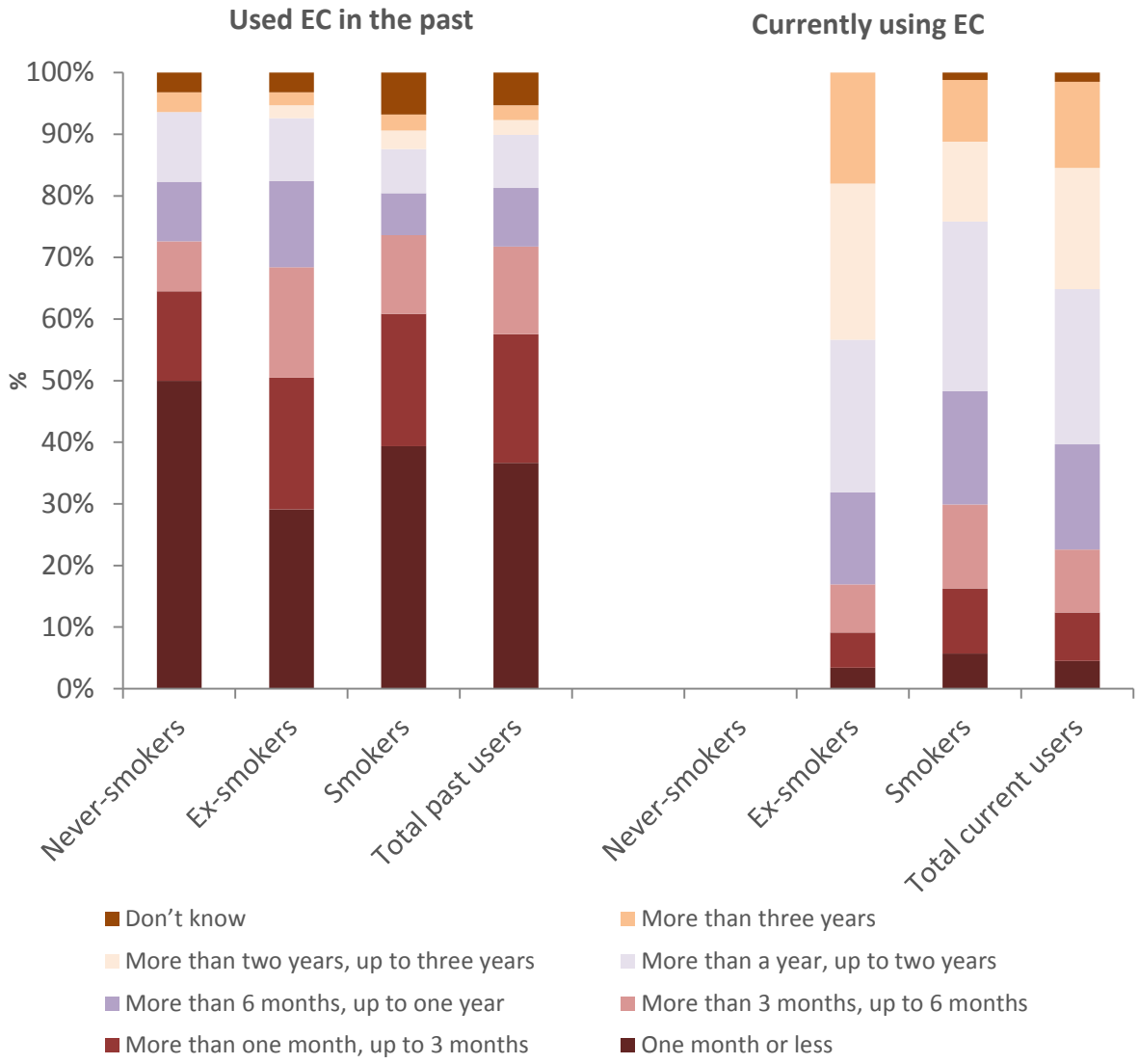


Notes: ASH-A 2017. Unweighted bases in the appendix. Age 18+

Duration of use

Current EC users appear to be mostly long-term users. About three quarters of current users (76.0%) have used for more than 6 months (83.0% among ex-smokers, 68.9% among smokers), including one third (33.7%) who have used EC for more than two years (Figure 14). Among those who used (not only tried once or twice) EC in the past, the majority (71.7%) used for less than 6 months, with half of those (36.6%) having used for a month or less.

Figure 14: Duration of EC use among past and current EC users by smoking status



Notes: ASH-A 2017. Unweighted bases in the appendix. Age 18+

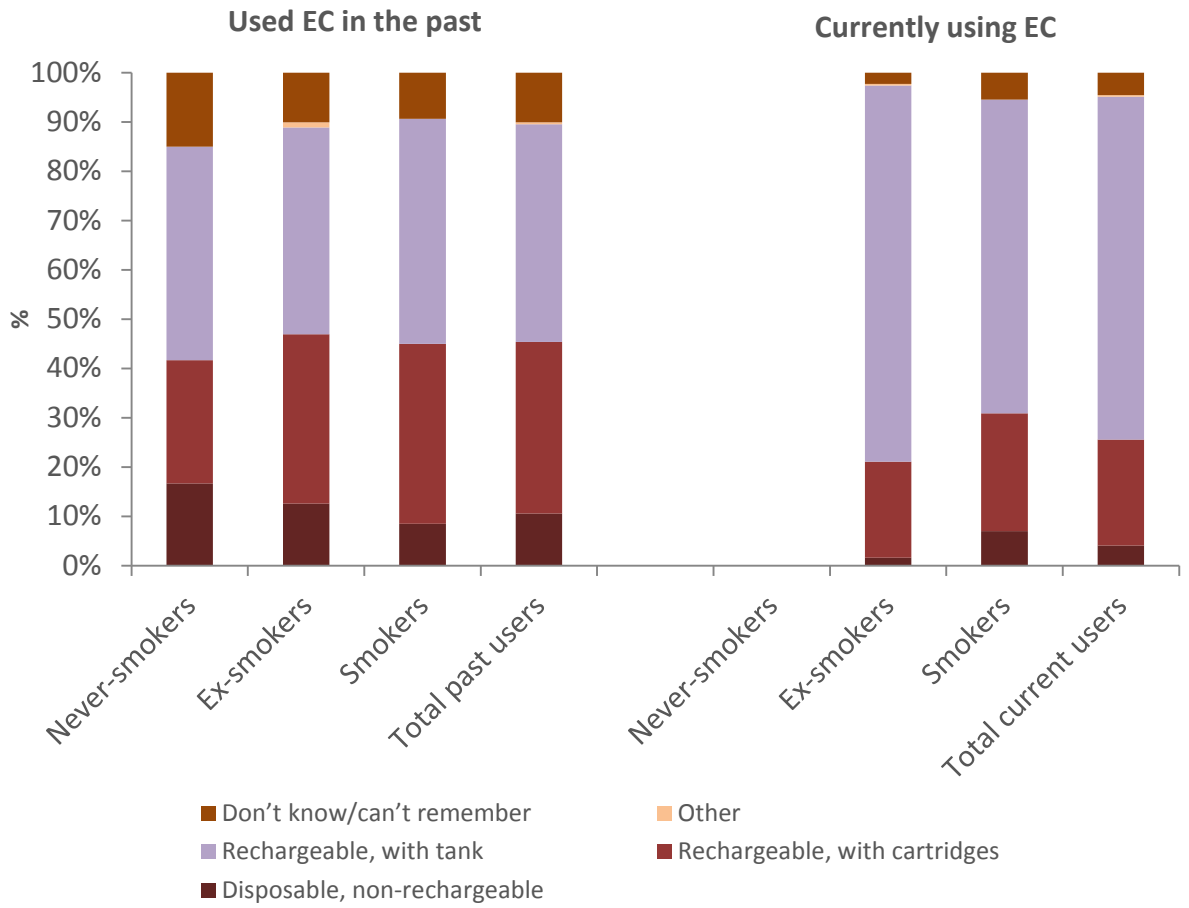
Device type

Devices with tanks that can be refilled with liquid continue to be the most popular type of devices among current EC users. In 2014, 40.8% of current EC users responded that they most often used a tank type; this increased to two thirds of current EC users in 2015 (66.2%) and remained at over two thirds in 2016 (71.0%) and 2017 (69.4%). Devices that use replaceable cartridges were used by 21.5% of EC users in 2017, similar to the previous two years (2015: 26.3%, 2016: 22.7%) and lower than in 2014 (46.7%). Past EC users (who had used EC more than once or twice) were less likely to have mostly used tank models (44.2%, Figure 15), potentially partly because their use occurred when these models were less popular or because continuing EC users move on to tank models.

The STS uses slightly different categories and also finds tank devices to be the most popular among EC users surveyed since August 2016. Split by smoking status, 57.6% of ex-smokers who used EC and 51.1% of smokers who used EC used this type of device, followed by modular systems [described as “A modular system that you refill with liquids (you use your own combination of separate devices: batteries, atomisers, etc.)”] that were used by 28.0% of ex-smokers and 22.8% of smokers who used EC. Eleven per cent of ex-smokers and 16.6% of smokers who used EC used cartridges.

The ONS used a simpler measure for type of device; here, 20.0% of EC users reported using one that resembles a cigarette, 73.9% one that does not resemble a cigarette and 6.1% some other kind.

Figure 15: Device types used by past and current EC users by smoking status

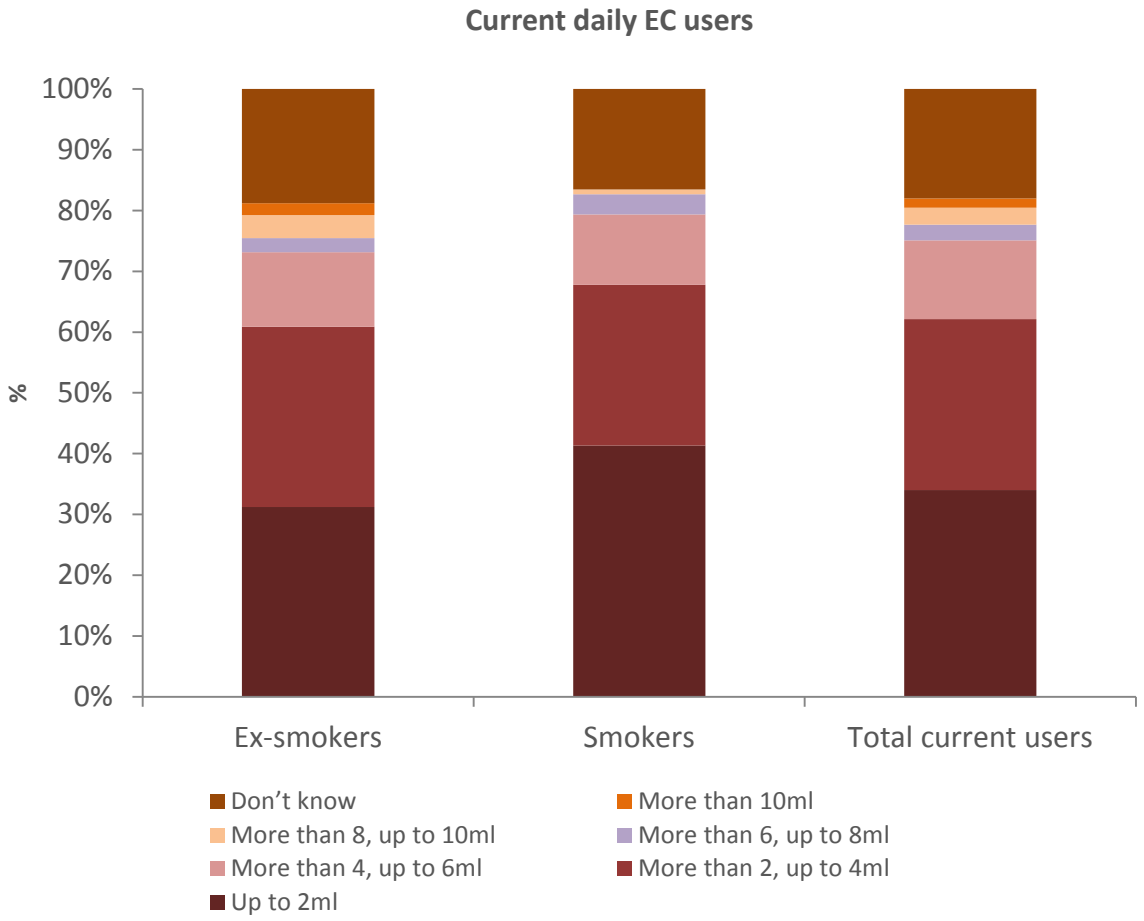


Notes: ASH-A 2017. Unweighted bases in the appendix. Age 18+

Amount of liquid

Only daily EC users were asked about the amount of liquid used. The majority (62.2%) of them reported using less than 4 mL per day and only a small percentage (1.5%) used more than 10 mL a day, the maximum amount allowed under the EU TPD to be sold in one refill bottle. Almost a fifth (18.1%) of daily EC users did not know how much liquid they use, indicating difficulty with self-report measures for consumption (Figure 16).

Figure 16: Amount of liquid used by daily EC users by smoking status



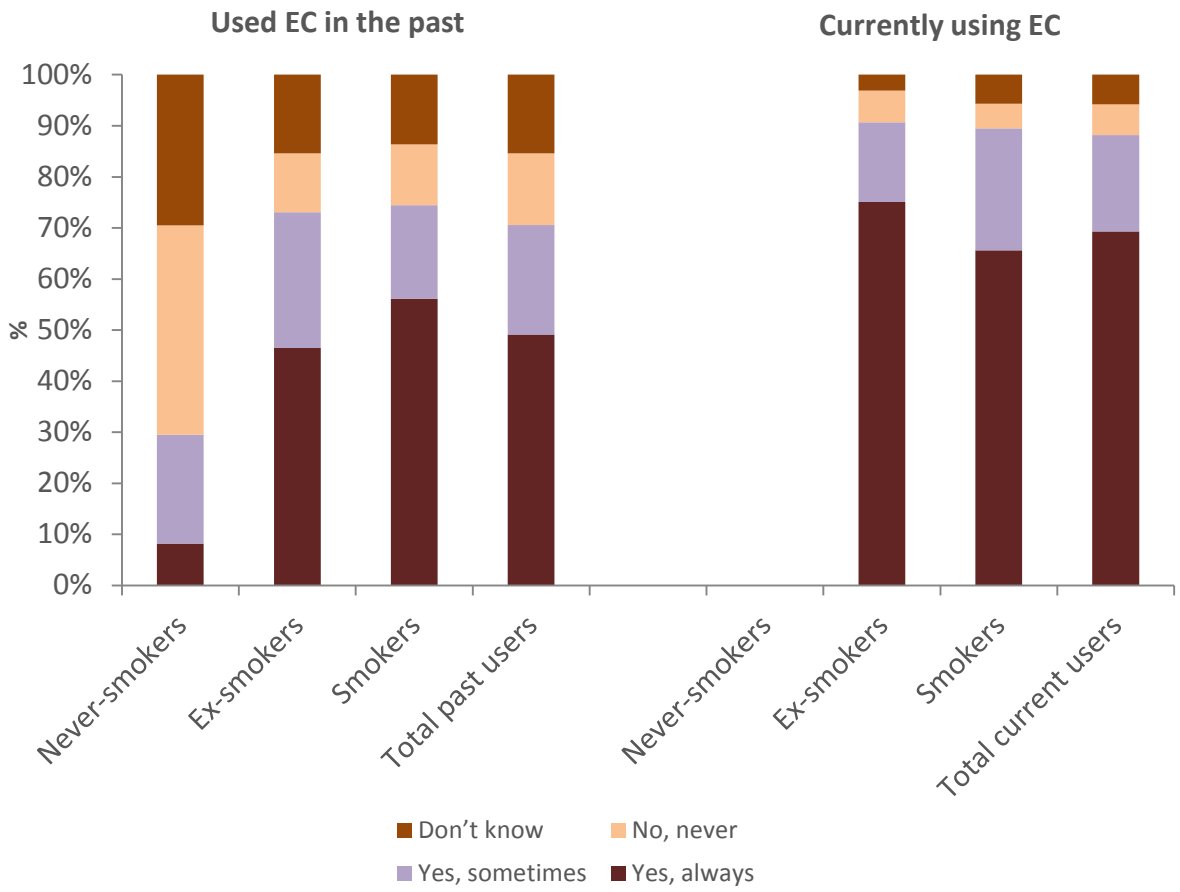
Notes: ASH-A 2017. Unweighted bases in the appendix. Age 18+

Nicotine

In the ASH-A, among current EC users, 69.3% always and 18.9% sometimes used nicotine (leaving 6.0% who never used nicotine and 5.8% who were unsure). Among past EC users who had used more than once or twice, 49.1% had always and 21.4% sometimes used nicotine. Notably, among never-smokers who had used EC, less than a third had used nicotine (29.5%) and most of those only sometimes. However, the same proportion of never-smokers who had used EC did not know whether they had used nicotine (Figure 17).

In the STS from August 2016 to July 2017, 84.5% of smokers and 88.1% of recent ex-smokers who use EC say that the EC or vaping device they mainly use contains nicotine.

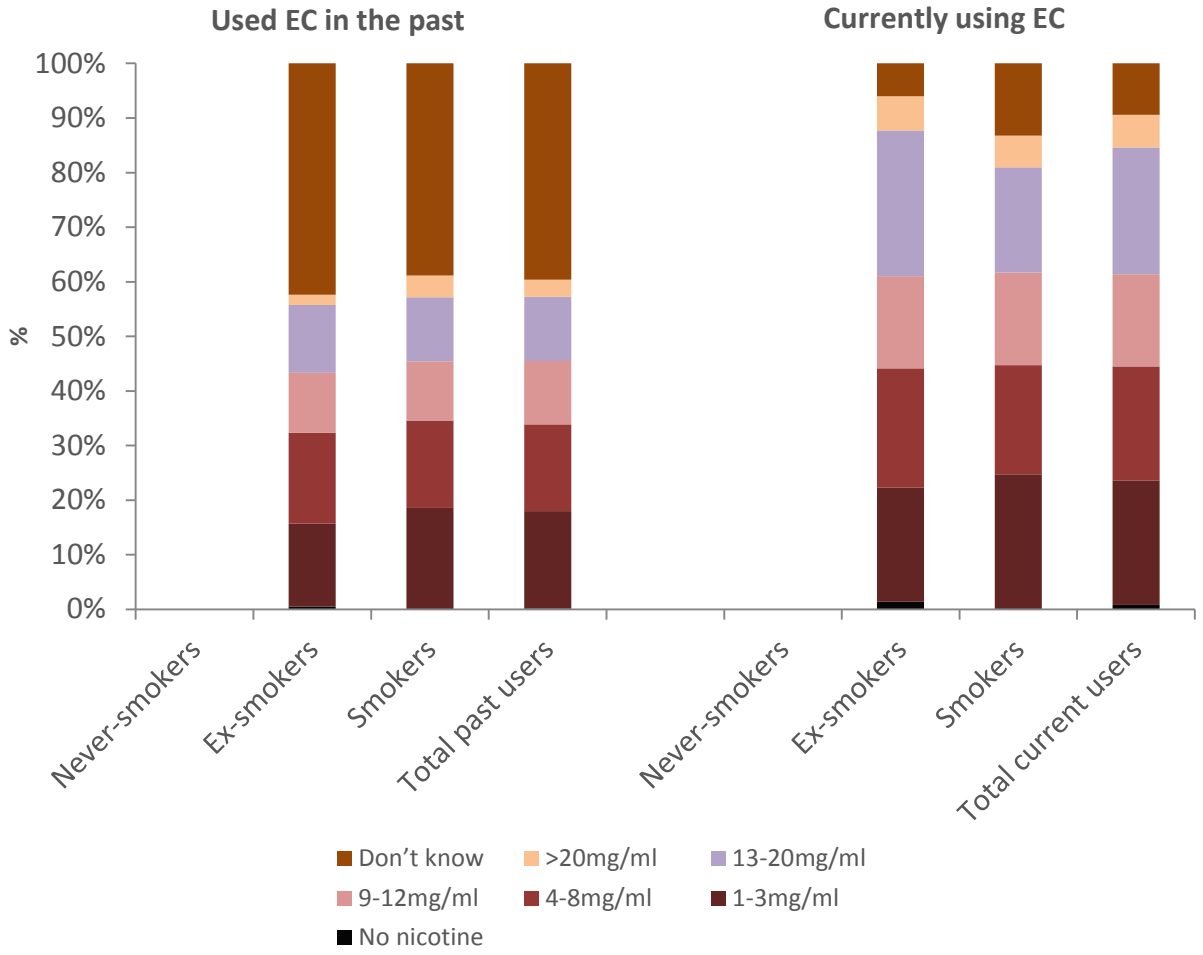
Figure 17: Use of nicotine-containing liquid used by past and current EC users by smoking status



Notes: ASH-A 2017. Unweighted bases in the appendix. Age 18+

In the ASH-A 2017 survey, those responding "always" or "sometimes" to using nicotine were asked about the concentration of nicotine in the liquid they used usually (strength). Among current EC users using nicotine, 6.0% used strengths over 20mg/mL which were still allowed in March 2017 when the survey was run, but not after 20 May 2017 under the EU TPD (Figure 18). The STS reports a similar figure for the time from August 2016 to June 2017 when 4.3% of smokers and 6.7% of ex-smokers who also used EC used strengths of 20mg/mL or more (note that this includes 20mg/mL, the upper threshold of legal concentrations). While among current EC users, 9.4% did not know or remember the strength, this was common among past EC users (39.6%).

Figure 18: Nicotine strength used by past and current EC users who at least sometimes used nicotine-containing liquid, by smoking status



Notes: ASH-A 2017. Unweighted bases in the appendix. Age 18+

Flavour

Overall, the most popular group of flavours among current EC users was fruit flavours (28.5%), followed by tobacco (26.9%, including 2.4% who used tobacco menthol flavour) and menthol or mint flavours (25.3%). The same order was found among current smokers who currently use EC (fruit 31.5%, tobacco 30.3% and menthol/mint 20.9%), while among ex-smokers, menthol/mint flavours were slightly more popular (30.2%) than fruit and tobacco (both 25.5%, all figures from the ASH-A 2017). Very few current EC users use no flavours (2.6%) or do not know the flavour (2.2%). Data on flavours were not collected for past EC users.

Place of purchase

In 2016/17, specialist vape shops were the most popular source for purchase of EC among past-year smokers; 49.2% of current smokers who used EC and 42.8% of ex-

smokers who used EC had purchased their device there, followed by 16.7% and 15.3% respectively who had purchased from a supermarket, 12.8% and 11.9% respectively from a newsagent and 9.9% and 11.9% from an online specialist vape shop (STS).

Main reasons for use

Surveys use different lists of reasons from which respondents can choose, but consistently find that the desire to stop smoking is an important reason. In the ASH-A 2017, across all adults (regardless of smoking status) who had ever tried EC, the most common reason was ‘just to give it a try’ (36.0%), followed closely by ‘to help me stop smoking entirely’ (35.6%) and ‘Because I had made an attempt to quit smoking already and I wanted an aid to help me keep off tobacco’ (24.5%). When excluding those who had tried once or twice, ‘to help me stop smoking entirely’ was the most common reason (42.0%), endorsed by 35.1% of current smokers, 54.5% of ex-smokers and 7.2% of never smokers who had used or were using EC. The ONS found similar percentages when asking EC users to select their main reason; ‘aid to stop smoking’ was the most frequently endorsed (46.6% overall, 50.1% among current smokers, 48.2% among ex-smokers, unweighted n for never smokers <50), followed by ‘less harmful than cigarettes’ (26.6%). Chapter 10 provides further information on harm perceptions.

Among smokers, trial, past use and current use of EC appears to be driven by different reasons. In one recent analysis of ASH-A 2016 data, among smokers who had ever tried or used EC, the most frequent reasons overall were ‘to give it a try’, ‘to help stop smoking’ and ‘to help reduce smoking’. However, reasons differed between groups with different EC use experience. Current users’ most frequent reason was ‘to reduce smoking’ (45.3%) followed closely by ‘to help stop smoking (37.4%). Current users were more likely to endorse smoking reduction compared with past users (24.2, adjusted odds ratio (AOR) = 2.40, 95% CI: 1.59–3.64) and to endorse overcoming smoking restrictions (26.0% versus 13.4%, AOR = 2.03, 95% CI: 1.22–3.38) For those who had tried EC but not gone on to use them, the most frequent reason was ‘to give it a try’ (50.8%), and compared with past users, they were more likely to endorse this reason (20.8%, AOR = 2.99, 95% CI: 1.99–4.50) and less likely to endorse ‘to help stop smoking’ (18.9%) which was the most popular reason among past users (36.8%, AOR = 0.46, 95% CI: 0.33–0.73)(14).

Motivation to stop smoking

Among all smokers in the ASH-A 2017, 18.3% were motivated to stop smoking with the intention to do so either in the next month or the next three months (131). Broken down by EC use status, 23.2% of smokers who were currently using EC gave these responses, compared with 13.2% of smokers who had never tried EC. Using 2016 data, a recent publication has analysed this association in more detail (14). Adjusting

for socio-demographics and dependence, current dual users were significantly more likely to be motivated to stop smoking in the next three months than those who had used EC in the past whose motivation was similar to those who had never tried EC suggesting that dual use may be a transient phase of heightened motivation to stop smoking.

Gaps in the available data

There are a few notable gaps in the available data. More information is needed to tease out whether ex-smokers are initiating EC use after a period of abstinence, their reasons for any uptake and whether this is associated with an increase or decrease of relapse to smoking.

Information on the impact of EC on health and economic inequalities associated with smoking are scarce.

Notably, no data are currently available to assess prevalence of trial and use of EC in disadvantaged groups with high smoking prevalence and smoking-related morbidity and mortality, such as those with mental health problems or offenders. In 2014, the Adult Psychiatric Morbidity Survey (132) included some questions on EC use as advised by Leonie Brose and Ann McNeill; however, the data have not yet been made available for analysis. Funding awarded to Leonie Brose has for the first time enabled the Smoking Toolkit Study to be extended with a mental health module; data are currently accruing.

International overview of EC use

A large number of surveys has been conducted, but often these are restricted to specific regions or populations for example college students in a particular US state. For this section, the focus was on national surveys with representative samples, surveys with other samples are however included in meta-analyses identified in the literature review. A limitation is that data on EC use prevalence can become outdated quickly; by the time survey data have been published in peer-reviewed publications, they may already be out of date.

Two meta-analyses have reviewed evidence from existing surveys on awareness, ever EC use and current EC use. One meta-analysis included all surveys of adults with a sample size of at least 200 (133) which provided information on awareness, ever use, current use (last 30 day use) or relative harm perceptions. In 28 studies published between 2009 and 2014, they found a pooled awareness of EC of 61.2%, ever use of 16.8% and past 30-day use of 11.1%. In line with findings from GB, figures differed by smoking status; ever use was 27.2% among current smokers and 2.5% among never smokers; past 30 day use was 16.8% for current smokers and 1.2% for never smokers.

A similar meta-analysis of data from 26 surveys published between 2011 and 2015 also found that current smokers were far more likely to use EC than non-smokers (adults: OR=14.7, 95% CI: 11.0 to 19.5) (134). These findings need to be interpreted in the light of some limitations. The included studies often did not survey a representative sample of the population, some restricted sampling to those with a specific smoking status (excluding never smokers which increases prevalence estimates) or even exclusively EC users. Although studies were from a range of countries, the majority was conducted in the US and as detailed elsewhere, past 30 day use overestimates actual use (for a discussion on this measure see Amato, Boyle and colleagues 2016, and Pearson, Hitchman and colleagues 2017 (135, 136)).

Other data from European countries

Peer-reviewed publications using the Eurobarometer survey (see Chapter 2 for details) published recently used 2012 and 2014 survey data (137-140). Data from the most recent Eurobarometer 2017 are available in a report (141). Across the 28 EU countries, 15% of those aged 15 and over have ever tried EC, including 2% who reported current EC use (decimal places not reported), which is unchanged since the previous survey in 2014. Current EC use ranges from 0% in Bulgaria, Croatia, Italy, Romania, Slovakia and Sweden to 5% in the UK. Similar to the UK, EC use remains concentrated among current and former smokers; overall, 4% of current smokers are current users, ranging from 0% (Bulgaria, Croatia, Hungary, Italy and Sweden) to 8% in the UK. Also, 4% of ex-smokers are current EC users with a range from 0% (Latvia, Lithuania, Luxembourg, Slovakia and Spain) to 14% in the UK. Among never-smokers, EC use is very rare. Across the EU, EC use is 0% among never-smokers and only in 5 countries is any use among never-smokers reported (all 1%, Austria, Belgium, Cyprus, Estonia and UK). In the EU, among those who use EC (base n=565), 67% use them daily, which translates to 1% of the EU population being daily EC users. The most popular flavours among current users were fruit flavours (47%), followed by tobacco (36%) and menthol/mint (22%). The most frequently mentioned reason for taking up EC was to stop or reduce tobacco consumption (61%). All other reasons were cited only by a minority; 31% said that they started using EC because they saw them as less harmful, and 25% cited the lower cost of EC (141).

A very small number of other representative surveys assessing EC use in European countries has been published; their findings are presented alongside the figures from the Eurobarometer for the country where applicable. A survey of people over the age of 14 living in Germany in 2016 reported weighted percentages of 11.8% for ever EC use and 1.4% for current EC use (142), broadly in line with the 14% and 2% reported by the Eurobarometer. EC had ever been used by 32.7% of ever smokers and 2.3% of never smokers; 4.3% and 0.1% respectively reported current EC use (compared with Eurobarometer 6% and 0%). A 2014 survey of a representative sample of 1,016 respondents aged 16 and over in Spain (143) found 10.3% ever use, including 2.0%

current use (compared with Eurobarometer 12% and 1%). Current EC use was 1.2% for never smokers, 1.1% among ex-smokers and 4.8% among current smokers (compared with Eurobarometer 0%, 0% and 2%). In Serbian adults aged 18 and over in 2014, ever EC use was reported as 9.5% and current use at 2.0%. As usual, the majority of current EC users were current or past cigarette smokers; there were no current EC users among never smokers in Serbia (0.0%, (144).

North America

US population information on current EC use in the recent peer-reviewed literature have been collected by the Population Assessment of Tobacco and Health (PATH) in 2013/14 and the National Health Interview Survey in 2014. Current EC use among adults was 5.5% in the PATH (n=32320) (145, 146), 3.7% in the National Health Interview Survey 2014 (n=36697) (147) and 3.5% in the National Health Interview Survey 2015 (148). Daily EC use was reported by 1.2% in the PATH and 1.1% in the National Health Interview Survey 2014. Some surveys also report the less accurate measure of past 30 day use (see above and (130, 135, 136)). A consumer-based survey in 2014 (n=4269) reported past 30 day EC use of 4.8% (149), PATH found 6.7% (146) and another 2014 survey found 4.9% (150).

Delnevo and colleagues broke down EC use in the National Health Interview Survey data by smoking status, separating current daily smokers (16.2% EC use), non-daily smokers (14.9% EC use), recent quitters who had quit in the last year (18.0% EC use), ex-smokers who had quit smoking 2 or 3 years ago (10.3% EC use), ex-smokers who had quit at least 4 years ago (0.8% EC use) and never smokers (0.4% EC use), demonstrating that use was extremely low among never smokers as well as long-term ex-smokers (147).

Among Canadians aged 15 and over, in 2013, 1.8% had used EC in the past 30 days; among current smokers, this was 9.6%, compared with 0.9% among ex-smokers and 0.3% among never-smokers *(151).*

Other countries

A handful of surveys for countries outside Europe and North America was identified. In a representative sample of 26021 respondents aged 15 and over in Taiwan in 2015, 2.7% reported ever EC use; this was 14.2% among smokers, 3.2% among ex-smokers and 0.8% among never smokers. Current EC use was not assessed (152). A small survey of respondents aged 15 to 65 in Hong Kong 2014 reported a weighted prevalence of 2.3% for ever EC use (11.8% among smokers, 4.3% among ex-smokers and 1.0% among never smokers; n=809). Again, current EC use was not assessed (153). Among adults in the Republic of Korea, the 2013 weighted prevalence of ever and current EC use were 6.6% and 1.1 %, respectively (n=5338). Current EC use was

reported by 21.8% of current smokers, 4.8% of ex-smokers and 0.7% of never smokers (154). One survey conducted among those aged 15 and over in Japan in 2015 has been published (155). It collapses use of EC and heated tobacco products and reports 6.6% ever use and 1.3% past 30 day use (weighted) which was 4.4% among smokers, 1.7% among ex-smokers and 0.3% among never smokers.

In New Zealand in 2014, a survey of 2594 respondents aged 15 and over reported weighted prevalence of 13.1% for ever EC use and 0.8% for current EC use. At 4%, current smokers reported the highest rate of current EC use (0.1% for ex-smokers and never-smokers) (156).

The International Tobacco Control (ITC) project measures current EC use among smokers and recent quitters in a large number of countries, however, published data date from 2009 to 2013 (157, 158); these data are currently being updated and will be published in Spring 2018. This will, for the first time, provide population-level information on EC use in lower or middle income countries.

Conclusions

Key findings

Prevalence

- In GB, prevalence of EC use in adults has plateaued at approximately 6% of the adult population.
- EC use among never smokers in GB remains very rare at less than 1%, similar to the level of use of NRT. Among never smokers who have ever used EC, a minority have used nicotine-containing liquids and the vast majority have not progressed to regular use.
- Prevalence of EC use and trial among smokers has plateaued while use and trial among ex-smokers continue to increase.
- Socioeconomic differences in EC use by smokers and recent ex-smokers have become smaller with no clear gradient in prevalence by occupational grade.
- Prevalence of dual use (use and smoking) is similar for EC users and NRT users.

Characteristics of use

- Most EC trial does not become regular use.
- Most current EC users use daily and have used EC for more than six months.
- Models with refillable tanks for liquids are the most widely used type.
- Since May 2017, nicotine concentration in liquids has been limited to a maximum of 20mg/mL. In March 2017, around 6% of EC users reported using higher nicotine

concentrations; substantial proportions had difficulties reporting these figures so more may have been affected by the limit.
- The most popular groups of flavours among current EC users are fruit (29%), tobacco (27%) and menthol/mint (25%).
- Specialist vape shops (physical premises rather than online) are the most popular place of purchase (>40%).
- The most common reason for EC use continues to be in order to stop smoking, and smokers who use EC on average have higher motivation to stop smoking than other smokers.

International

- Data can be outdated by the time of publication.
- Prevalence of current use in GB is at the higher end for countries in the EU where the average is 2% for current EC use. Prevalence estimates for current EC use in the US are around 4% to 6%, which is similar to GB.
- Across international surveys, a consistently low prevalence (<1%) of EC use has been reported among never-smokers; one exception is one Spanish survey at 1.2%.
- Prevalence figures found for smokers and ex-smokers vary more widely across surveys in different countries (4% to 22% among smokers and 0.1% to 5% among ex-smokers) .

Implications

Research

- As recommended in the 2015 PHE report, trends in EC use among adults should continue to be monitored using standardised definitions of use. Measures should include frequency and type of device used including different types of tank models.
- EC use among ex-smokers needs monitoring and further evidence to understand when and why they take up EC use and whether this is associated with an increase or decrease of relapse to smoking.
- More research is needed into different patterns of EC use while smoking and their effect on subsequent smoking behaviour to understand how best to move dual users to stop smoking.
- More research is needed on the impact of EC on health and economic inequalities associated with smoking, in particular on use of EC in disadvantaged groups with high smoking prevalence and smoking-related morbidity and mortality, such as those with mental health problems or offenders. Data that have been gathered from the Adult Psychiatric Morbidity Survey in England should be released for analysis.

Policy and practice

- As recommended in 2015 and as per existing National Institute for Health and Care Excellence (NICE) guidance, all smokers should be supported to stop smoking completely, including ‘dual users’ who smoke and use EC.
- Access to EC should be improved for smokers in disadvantaged groups.

7 The effect of EC use on smoking cessation and reduction

Introduction

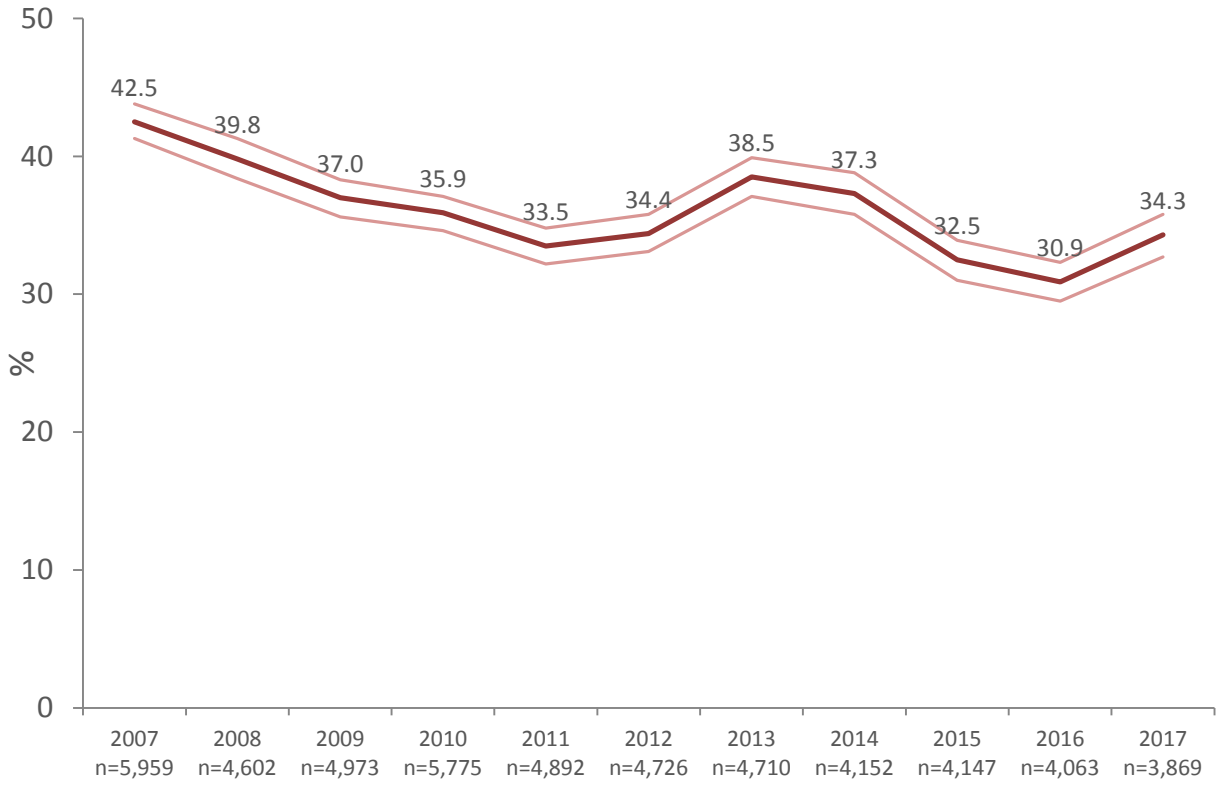
The objective of this chapter is to provide an overview of available data about the effect of EC on smoking cessation and reduction in England. First, we provide smoking cessation data from the Smoking Toolkit Study (a repeated monthly series of national household surveys of representative samples of approximately 1800 adults aged 16 and above on smoking) followed by details of EC use for smoking cessation and estimates of long-term quitters resulting from EC use. This is followed by an examination of the use of EC in treatment settings using data from English Stop Smoking Services. We then examine the use of EC on smoking cessation and reduction from systematic reviews of Randomised Controlled Trials (RCTs) and observational studies. We comment on comparable data in vulnerable groups where this exists.

Smoking cessation rates in England

The effect of EC on smoking cessation needs to be viewed within the context of overall smoking prevalence and cessation rates. As identified in the introduction, the official estimate of smoking prevalence has declined to 15.5% in 2016.

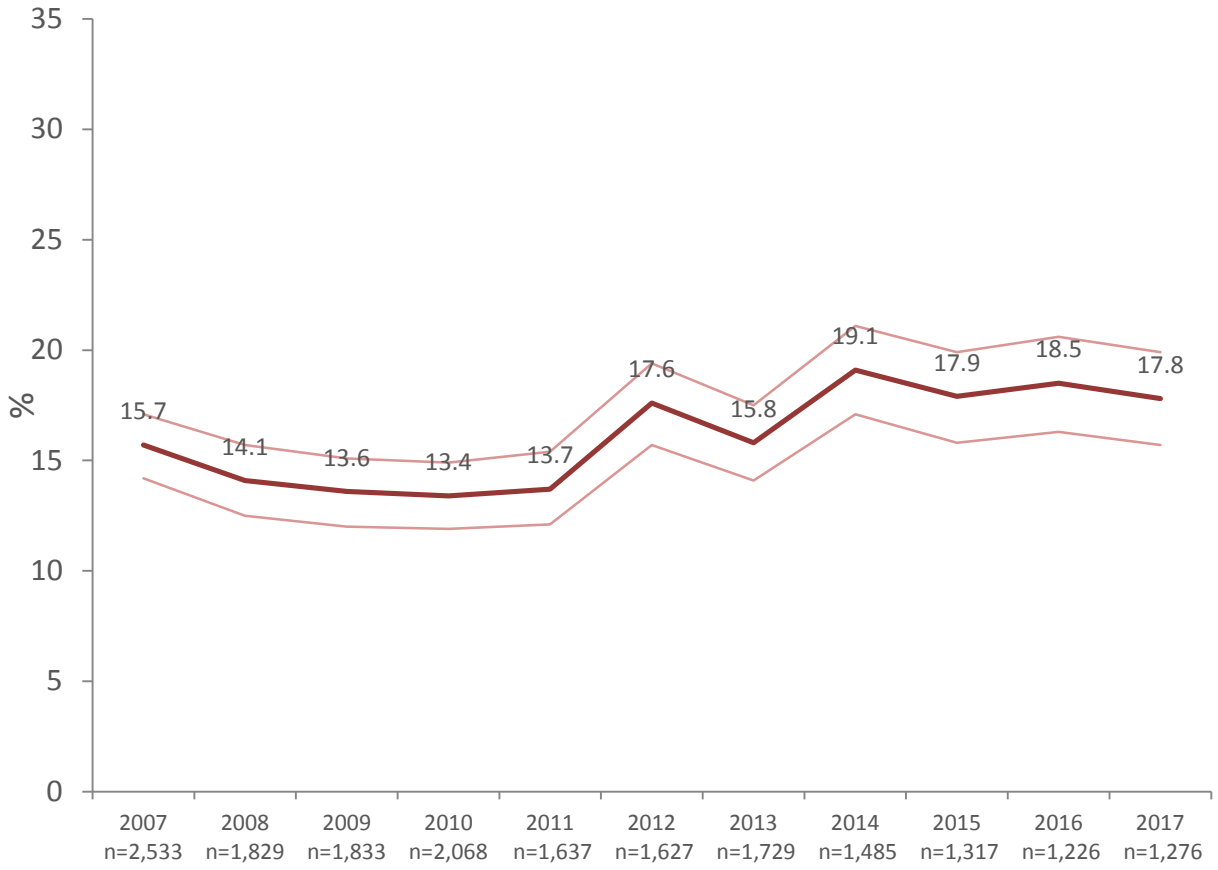
Figure 19 and Figure 20 present the proportion of people who tried to quit and were successful (defined as those who tried to stop in the preceding 12 months and reporting still not-smoking at time of the survey) between January 2007 and December 2017, using data from the Smoking Toolkit Study (STS). The proportion of people who reported trying to quit smoking declined annually between 2007 and 2011 and has been variable for the past six years.

Figure 19: Proportion of people who tried to stop smoking in past year



Base: Adults (age 16+) who smoked in the past year. Graph shows prevalence estimate, upper and lower 95% confidence intervals. From: http://www.smokinginengland.info/latest-statistics/ accessed 12/01/2018

Figure 20: Success rate for stopping in those who tried to quit



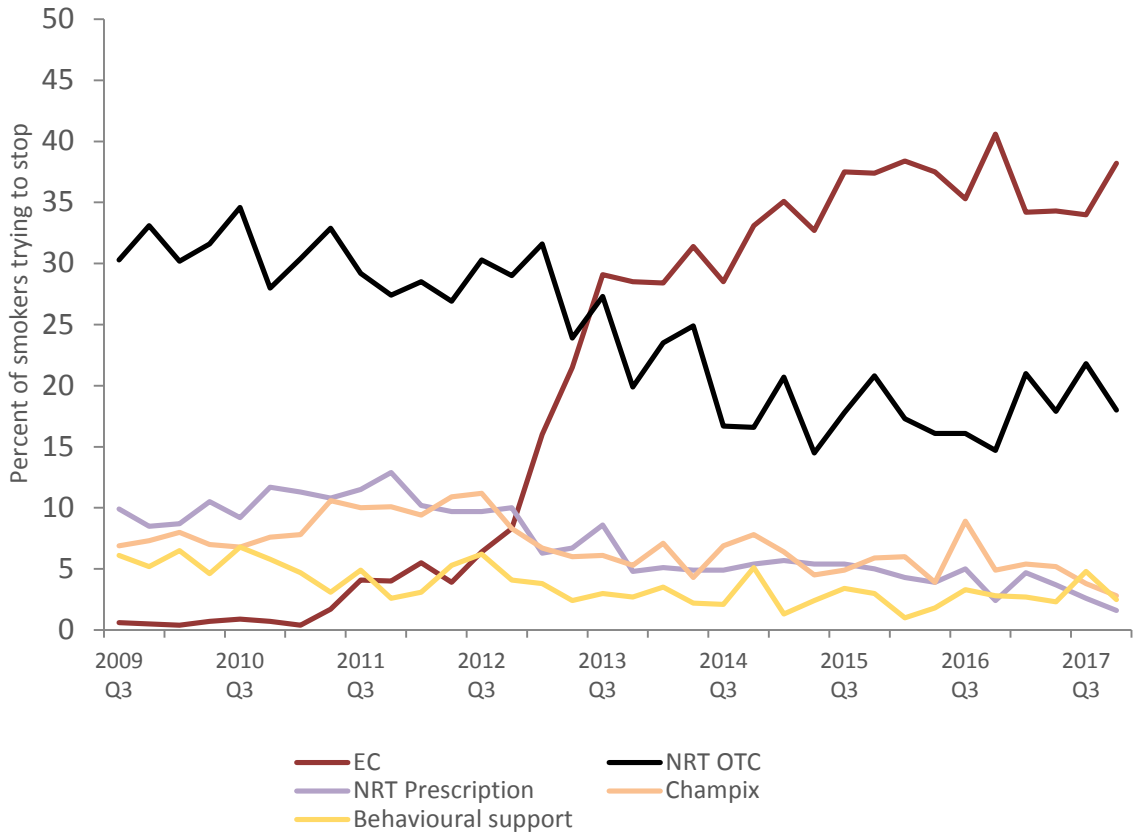
Base: Adults (age 16+) who smoked in the past year. Graph shows prevalence estimate, upper and lower 95% confidence intervals. From: http://www.smokinginengland.info/latest-statistics/ accessed 12/01/2018

In a report which examined quit success rates from 2007 to 2017, Brown and West (159) analysed data from 18,356 participants included in the STS. Using the definition of quit success above, they compared quit success rates for the first six months of 2017 with those in the previous 10 years and also assessed whether any trends in quit smoking success rates extended across different social groups. They found that quit success rates varied over time; the lowest rate (13.1%) was in 2010 and the highest (19.8%) in the first half of 2017; the quit rate in the first half of 2017 was significantly higher than the average for the previous 10 years (OR=1.33, 95% CI 1.09-1.62). Age, sex or the region the smoker lived in made no difference, whereas an increase in success rates was greater in people with lower socioeconomic status (OR=1.66, 95% CI 1.11-2.51). This is an important finding as it shows parity between the groups in quit success rates for the first time in over 10 years (and possibly ever). The authors commented that many factors may have contributed to these improvements in success rates, including an environment more conducive to quitting and the availability of a range of support for quitting including EC.

Use of EC for smoking cessation in England

The 2015 PHE report on EC (5) stated that since 2013, EC had been the most common quitting aid for smokers in England. The most recent data from the STS suggest this is still the case (Figure 21) although overall, the use of EC for quitting has plateaued since 2015. The popularity of EC as a quitting aid appeared to peak in the last quarter of 2016 when 40.6% of participants in the STS samples reported using an EC to quit smoking compared to 14.7% who used NRT bought over the counter from a shop (OTC) or on prescription (2.8%) and 4.7% who used varenicline. In the most recent STS findings (the last quarter of 2017), 38.2% of people reported they used an EC in their recent quit attempt compared with 18% who reporting using NRT OTC, or on prescription (1.6%) and 2.8% who used varenicline (Figure 21). From a visual inspection of the graph in Figure 21 the changes in use of EC and NRT OTC appear to be almost a mirror image of each other in that as EC use changes it is accompanied by a commensurate change in the use of NRT OTC. We discuss the issue of EC cannibalising the licensed NRT market later in the chapter.

Figure 21: Support used in most recent quit attempts



N=13,456 adults (age 16+) who smoke and tried to stop or who stopped in the past year; method is coded as any (not exclusive) use From: http://www.smokinginengland.info/latest-statistics/ accessed 12/01/2018

How EC might help smokers stop smoking

Figure 22 below shows how EC use might in theory help a smoker to stop smoking. The most obvious way is through use of an EC in a gradual or abrupt quit attempt. A second possibility is that a smoker who is not currently planning to stop tries an EC, perhaps out of curiosity or as an alternative to smoking in smoke-free settings and goes on to stop smoking without making a conscious decision to do so. Such smokers might not classify themselves as having made a 'quit attempt'. A third route is by preventing relapse to smoking in someone who has already stopped. In this scenario, a smoker who stopped smoking with or without the use of EC, may subsequently use an EC in a way that prevents relapse to smoking.

There are also ways that EC might also hinder quitting, such as if the dual use of tobacco cigarettes and EC prevents people from quitting because they feel reassured they are reducing tobacco related harm and are less motivated to quit. However, as discussed in chapter 6, a recent study found that current dual users were significantly more likely to be motivated to stop smoking in the next three months than those who had used EC in the past, whose motivation was similar to those who had never tried EC (14). Quitting may also be hindered if smokers who also use an EC find quitting harder.

Finally, successful quitters may try vaping and then, as a result, relapse to smoking. These routes are also included in Figure 22. Note that these are all theoretical impacts of using EC on quitting; what happens in practice needs to be examined empirically to establish a better of understanding about causal pathways. As there are no data yet on EC hindering quitting in England, they are not considered further here, but included in Figure 22. The assumptions underpinning estimates of additional quitters due to EC are discussed later in this chapter.

Figure 22: How EC might impact on stopping smoking

Estimates of the impact of EC use on the number of long-term quitters

West and colleagues (160) and Beard and colleagues (161) have estimated the number of long-term additional quitters in England resulting from the use of EC *in quit attempts*, using Smoking Toolkit Study (STS) data and two different methods. Although their estimates are for 2014 and 2015, we include these studies here as they were published after the 2015 PHE report. Beard and colleagues (161) also assessed the temporal association between prevalence of *current* use of EC in smokers and recent ex-smokers (ie not necessarily within a quit attempt) on prevalence of quit attempts and success.

2014 estimate

West and colleagues (160) used an indirect method to estimate the number of additional long-term quitters generated by EC in 2014. In summary, using their STS data for 2014, they estimated:

1) A total of 891,000 smokers had used an EC to stop smoking (37.3% of all last year smokers had tried to stop at least once, 28.2% of whom used an EC without other support).

2) The *one year* (long-term) success rate of such quit attempts was 7.5% (50% more than the 5% estimated success rates for those without help or using a licensed nicotine product purchased OTC) (162) which would result in ~67,000 smokers successfully stopping.

3) As STS has identified no consistent changes in the proportion of smokers trying to quit that could be confidently attributable to EC use, they assumed that all these smokers would have made quit attempts even in the absence of EC. If these ~67,000 smokers had used no support/licensed nicotine OTC then 5% (ie two-thirds) would have stopped smoking leaving a residual 2.5% (~22,000) who additionally stopped because of EC. **This gives their upper estimate of ~22,000 additional long-term quits in 2014 caused by EC.**

4) For the lower bound estimate, they further assumed that EC was contributing to the decline in the use of prescription medications over time (which they estimated to be a decline of approximately 10% since EC started to become popular). They estimated that the decline in use of prescription medicines was approximately 10% of quit attempts (3.7% smokers in 2014, 313,000 smokers) and that an upper estimate for the contribution of EC to that decline was 80%, thus representing 250,000 smokers.

5) Thus they estimated that if EC had detracted from these methods of stopping, then of the initial 891k smokers using EC to quit, this would have resulted only in 641,000

additional smokers making quit attempts using EC, with an estimated success rate of 2.5% over and above had smokers used no support/licensed nicotine OTC, **giving ~16,000 additional long-term quits in 2014, their lower estimate**.

Contribution of EC to stopping smoking using time series analysis and 2015 estimate

The second study (161) used time series analyses of population trends to estimate more directly how population-level EC use had been associated with changes in quit attempts, quit success, and use of other support in quit attempts between 2006 and 2015 using STS data and data from people setting a quit date with English Stop Smoking Services.

In the discussion section of the paper, the authors estimated the number of additional long term quitters due to EC use in 2015. This study also allowed an assessment of the assumptions made in West and colleagues (160) described above. To control for possible changes in use of stop smoking support, a range of potential confounders were included in their analysis such as advertising expenditure and the introduction of several tobacco control policies. The prevalence of quit attempts and quit success was predicted from current smokers' prevalence of EC use and prevalence of EC use during a quit attempt.

Between 2006 and 2015, data was collected on 170,490 participants aged 16 years in the Smoking Toolkit Study. Of these, 41,301 were past year smokers and 37,765 were current smokers. The proportion who reported a quit attempt increased and then decreased overall changing from 45.4% at the start of the study to 31.2% in the last quarter of the study. There was an overall increase in the success rate of those who reported a quit attempt (from 10.6% in the last quarter of 2006 to 18.6% in the first quarter of 2015). Over the same period, current use of EC among smokers increased from negligible use in the last quarter of 2006 to 21.3% at the end of the study, and EC use in a quit attempt also rose from negligible use in the last quarter of 2006 to 35.0% in the first quarter of 2015.

The data did not show clear evidence of an association between prevalence of use of EC by smokers and *attempts* to quit smoking (supporting the assumption 3 discussed above (160)). However, the increase in prevalence of EC use by smokers was positively associated with the *success rates* of quit attempts and the association remained after adjustment for a range of confounding variables (161); for every percentage point increase in prevalence of EC use by smokers, the success rate of quit attempts increased by 0.098 percentage points. EC use in quit attempts was also positively associated with quit success, with every percentage point rise in prevalence of EC use in quit attempts associated with a 0.058 percentage point increase in the success of attempts.

The authors focused on the latter finding (that a one percentage point increase in EC use in quit attempts was associated with a 0.058 percentage point increase in quit successes) as this was likely to reflect a causal link and be a fairer point estimate. Using this finding, they estimated the impact on long-term quits as follows: 32.5% of 8m smokers (2.6m) made a quit attempt in 2015 and prevalence of EC use in quit attempts was 36%; this leads to 54,288 additional short to medium term (<1 year) quitters in 2015 compared with no use of EC in quit attempts. Assuming a 66% subsequent relapse rate, they estimated that EC may have contributed about 18,000 additional long-term ex-smokers in 2015 (a figure similar to the 2014 estimates).

Assumptions in quit estimates

The similarity in the estimates from West and colleagues (160) and Beard and colleagues (161) using different methods is reassuring. However, they both still rely on certain assumptions. Below, we discuss how the estimate might vary if key parameters were changed and then recalculated the estimates varying two parameters for 2014 and 2016 STS data.

Cannibalisation of other quit methods

An earlier study using Smoking Toolkit Study data suggested EC were not cannibalising the licensed NRT market (for smoking reduction, not quitting) (163). The more recent study described above (161) found no significant associations between EC use in quit attempts and the use of stop smoking services, NRT, OTC and prescription treatment overall. However, a significant association between EC use in quit attempts and the use of NRT on prescription was observed (for every percentage point increase in EC use in quit attempts, there would be a 0.098 percentage point decline in NRT use on prescription). During the study the mean proportion of quit attempts including NRT on prescription was 8.9 (Standard Deviation (SD) 2.45). This suggests that the lower bound 2014 estimate of 16,000 (160) is probably too conservative as they had allowed for a higher level of cannibalisation of other support methods than observed in Beard and colleagues (161). In our estimates below (Table 13) we have therefore varied this assumption, from 80% to 20% of the 10% decline in use of other methods.

Impact on relapse

As noted above, it is possible that using an EC in a quit attempt might result in a different relapse trajectory from the use of the other stop smoking support. This would affect the above estimates of long-term quitting, which would be larger if there is less relapse with EC, or smaller if there is more relapse with EC. Additionally, if some ex-smokers became EC users in order to prevent relapse (and this had worked), this would have resulted in the estimate for additional long-term quitters due to EC, being

an underestimate. As we are not aware of any data on this issue (and there is a need for research here), we have not altered this assumption below.

Success rates of quit attempts involving EC

This may now be higher than the 50% increase from 5% cited by West and colleagues, (160). The estimated 50% increase in success rates over and above no support/licensed nicotine OTC due to EC in quit attempts, derives from a previous study by the authors using the Smoking Toolkit Study data (162) when the type of products on the market were somewhat different, with fewer tank models being used (see Chapter 6 and ASH data and see below). We have recently replicated this study using a different dataset (ICGBS) which was presented at a conference, and therefore not yet peer reviewed (164). We aggregated data from the 2013, 2014 and 2016 waves to study the impact of using two different types of EC in quit attempts: non-tank (disposable or rechargeable model refillable with pre-filled cartridges) vs tank (rechargeable device with a tank that can be refilled with liquids or modular EC). The outcome was participant's self-reported smoking status at time of survey, regardless of length of abstinence. Participants stating that they had stopped smoking completely in the last year/since the last survey were classified as quit. A range of covariates (strength and frequency of urges to smoke, number of recent quit attempts, time since last quit attempt started, abrupt of reduction quit method, sex, age, social grade, survey year) were controlled for. Quit success rates were 31.2% for self-help/no help, 19.9% for non-tank EC, 38.0% for tank EC and 21.7% for licensed nicotine products OTC. In the fully adjusted analyses, using tank models increased the odds of quitting 2.19 times (OR 2.19 (1.50,3.19) compared with self-help/no help. The overall impact when tank and non-tank EC were combined was also significantly higher (OR 1.59, (1.19,2.13)) than self-help/no help.

The findings are in line with an earlier study using the ICGBS (20) which suggested that tank models were more effective than other EC as quit smoking aids. As approximately 70% of EC use involves tank models in 2017 (see Chapter 6), it is likely that the estimates of quitters generated by EC in more recent years would now be higher than the West and colleagues (160), and Beard and colleagues (161), estimates.

In our estimates below (Table 13) we have therefore varied the success rate over and above no help/licensed nicotine product from 50% to 100%, to estimate what impact that would have on the estimated number of smokers who have quit as a result of EC.

Updated quit rates based on STS 2016 data and varied parameters

As discussed above, we have recalculated the West and colleagues (160) indirect analysis varying two parameters: the success rate over and above no help/licensed nicotine product use (from 50% to 100%) and the percentage contribution of EC to the

decline in use of existing therapies (from 80% to 20%); we have then replicated the original and adjusted estimates using the 2016 STS data. The resulting figures are shown in Table 13 below, with the original estimates shaded grey.

Table 13 shows that varying the two parameters for 2014 gave the lowest estimate as ~21,000, and the highest estimate ~44,000). Using the same parameters as West and colleagues, 2014, for the 2016 year gave a lower estimate of ~22,000 and higher estimate ~29,000). Varying the two parameters for 2016, gave the lowest estimate as ~27,000 and the highest estimate ~57,000.

Table 13: Estimates for the additional contribution of EC to long term quitters for 2014 and 2016 using STS data (original estimates highlighted)

			2014		2016	
			Estimated success rate for EC above that of no help/licensed nicotine product			
			50%	100%	50%	100%
% contribution of EC to 10% decline in use of existing therapies	Upper estimate	0	22,245	44,489	28,662	57,324
	Lower estimate	80	15,934	31,868	22,275	44,550
	Upper estimate	0	22,245	44,489	28,662	57,324
	Lower estimate	20	20,667	41,334	27,065	54,131

It should be noted that we have not changed the assumption that in the absence of EC, the smokers trying to quit using EC would have tried to quit anyway. This is because there is no evidence of a consistent change in quit attempts due to the advent of EC and therefore it is not possible to attribute, with any confidence, a proportion of quit attempts that would not have happened in the absence of EC. Finally, as noted above, there are other routes to quitting smoking other than through traditional quit attempts, which have not been modelled.

Summary

Quit success rates in England are at the highest rates so far observed and for the first time, parity across different socioeconomic groups is observed. It is plausible that EC are contributing to this. Recent estimates of additional quitters resulting from the availability of EC, using the same dataset but two different methods, resulted in similar figures within the range of 18,000-22,000. Varying the assumptions, and updating these estimates for 2016, resulted in an upper bound estimate of around 57,000 additional quitters annually resulting from EC. While caution is needed with these figures, the evidence suggests that EC have contributed tens of thousands of *additional*

quitters in England annually. Insofar that success rates with EC have increased, then an updated time-series analysis including data from 2016 and 2017 may find a larger association between the use of EC and quit attempts, which may lead to larger estimates in the time since 2015.

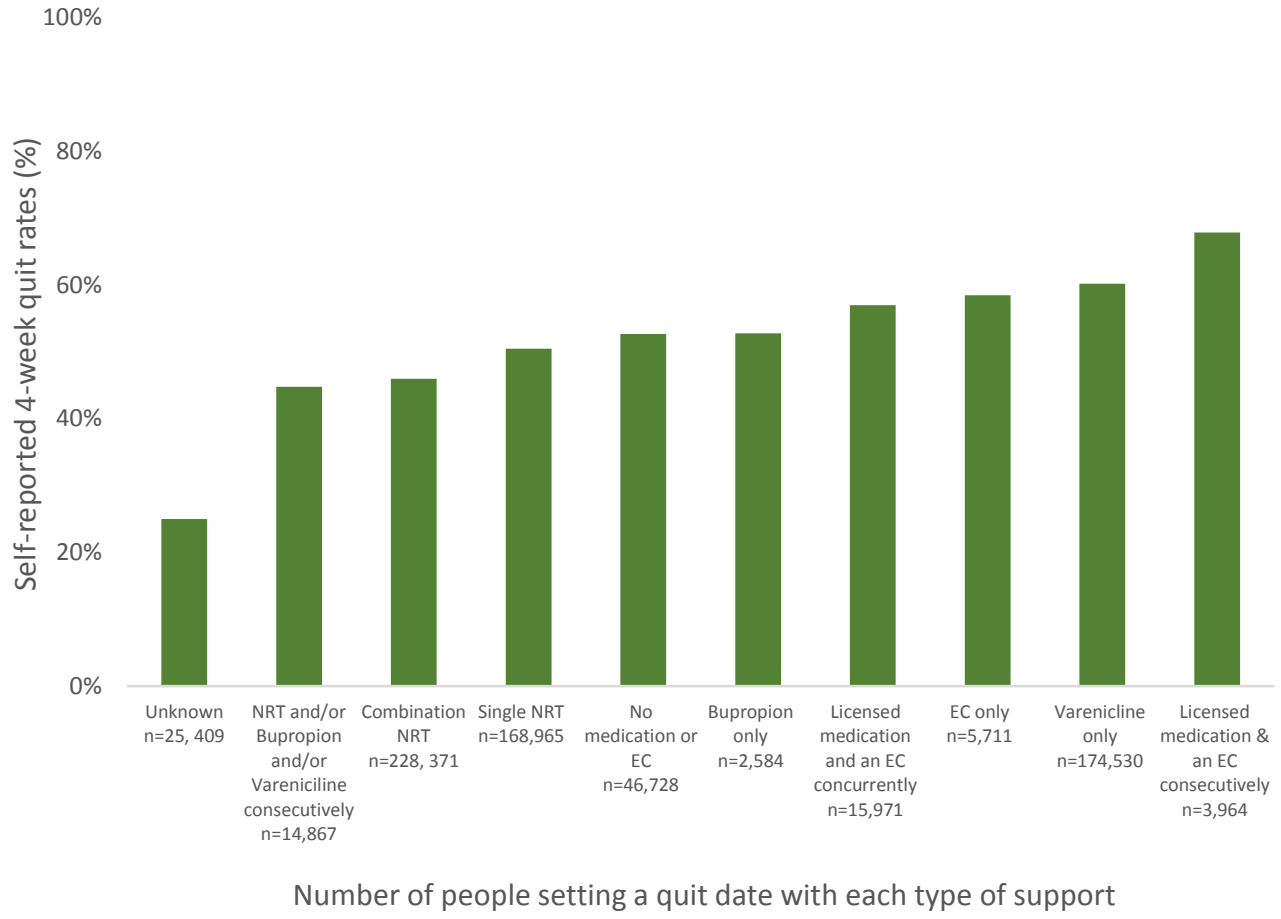
EC use in English Stop Smoking Services

Local authorities were given responsibility for public health by the Health and Social Care Act 2012. This transfer of functions was funded through a ring-fenced grant. The grant is used to commission a variety of services, including Stop Smoking Services. Stop Smoking Services offer smoking cessation support which involves the use of pharmacotherapies (NRT, varenicline, EC, bupropion, in combination or alone) and/or behavioural support. Data are collected from local authorities every three months about the number of treated smokers in each service, the number who successfully quit at 4 weeks (self-reported and carbon-monoxide (CO) verified) and key measures of the service including intervention type, intervention setting and type of pharmacotherapy received. A treated smoker is defined according to the Russell Clinical Standard (a clinical version of the Russell Standard for outcomes assessment in smoking cessation clinical trials) (165); a smoker who has at least one treatment session and sets a quit date is counted as a treated smoker, whereas a smoker who attends one treatment session but fails to attend future session is not counted in the data. A smoker is counted as a 'self-reported four-week quitter if they are assessed (face to face or by telephone) four weeks after the designated quit date (minus three days or plus 14 days) and declares that they have not smoked even a single puff on a cigarette in the past two weeks. A smoker is counted as a CO-verified four-week quitter if they are a self-reported four-week quitter and his/her expired-air CO is assessed four weeks after the designated quit date (minus three days or plus 14 days) and found to be less than 10ppm. Treated smokers lost to follow up (cannot be contacted for the four week follow up assessment) are counted as non-quitters. Since 2014, Stop Smoking Services have been asked to record if an EC was used in a quit attempt, either alone or in combination with a licensed medication. These data are naturalistic and do not allow us to control for things like the severity of tobacco dependence known to influence success rates or if the Stop Smoking Service was supportive of EC use. It is also possible that that the people using EC alone or in combination with licensed stop smoking medicines may differ from the rest of the smokers quitting with these services. However, these data provide valuable information about the use of EC within Stop Smoking Services and their contribution to quit success.

Between April 2015 and March 2017, 690,007 set a quit date and 51% were self-reported quitters at four-week follow up (37% were CO validated quitters). In 2016/17, the number of people setting a quit date with a Stop Smoking Service and the number of successful self-reported quitters fell for the fifth consecutive year (though the self-reported quit rate has remained relatively stable at 51-52% in recent years).

In both 2015-16 and 2016-17, the highest number of quit attempts involved combination NRT, though the highest quit rate was in people who used a licensed medicine and an EC consecutively. The number of treated smokers using each type of support and the quit rates between April 2015 and March 2017 are presented in Figure 23. These data suggest that smokers who are treated by a Stop Smoking service with behavioural support and use EC with or without additional licensed medication, have comparable quit success to smokers using a licenced medication.

Figure 23: Self-reported four-week successful quitters by pharmacotherapy type (2015-2017)

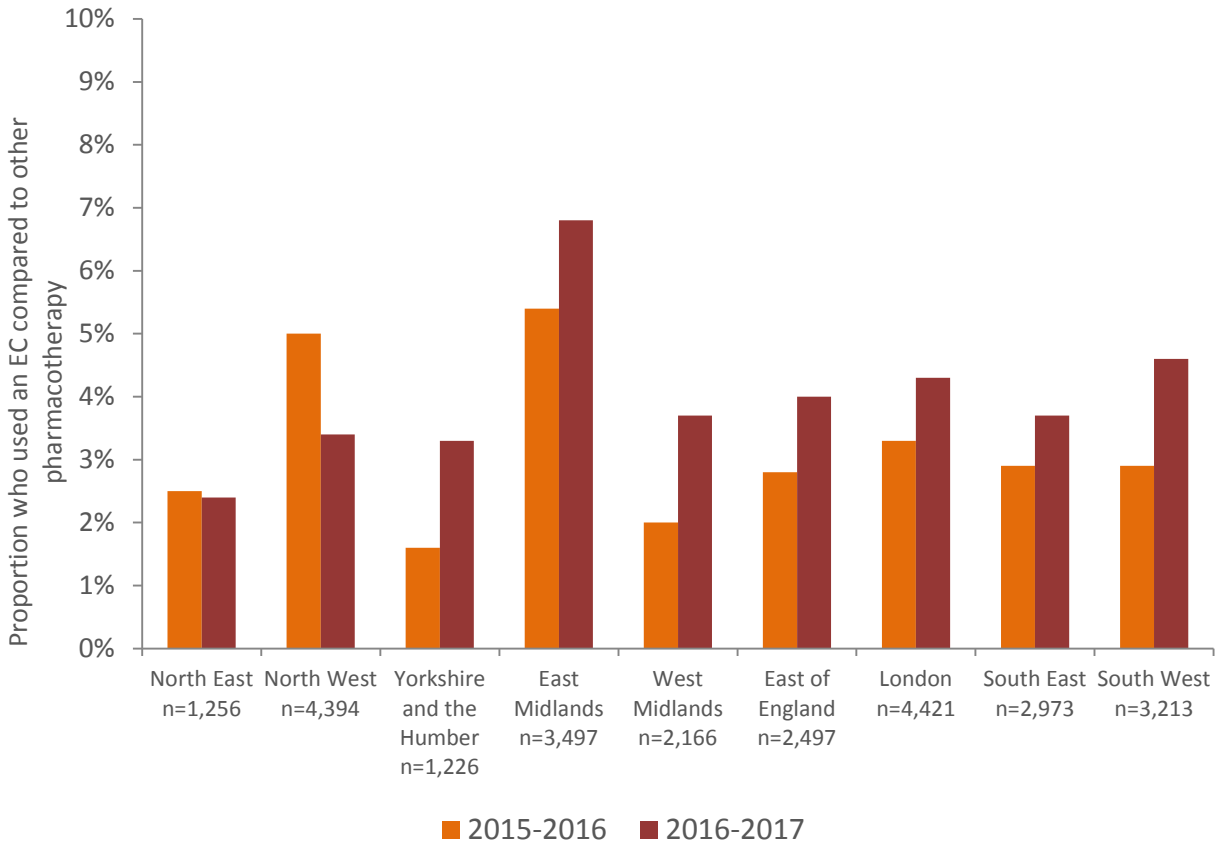


Notes: Data for all age groups

EC use by region

EC use as part of quit attempt varies by region (Figure 24). In 2015-16, Yorkshire and the Humber reported that 1.6% of the people who set a quit date with their services used an EC as part of their quit attempt compared to 5.4% in the East Midlands. In 2016-17, the North East region reported that 2.4% of the people who set a quit date with their services used an EC as part of their quit attempt compared to 6.8% in the East Midlands.

Figure 24: Proportion who used an EC relative to other type of pharmacotherapy* by region



*Notes: * EC use includes people who had used EC either alone or in combination with licenced medication concurrently or consecutively. Other type of pharmacotherapy excludes EC use, unknown use and people recorded as no medication used*

Similarly, quit rates vary between regions (Figure 25). For context, Figure 26 gives overall success rates by region for the same time period, although a range of factors will be influencing these success rates. In 2015-16, 45% of people in the North East region who used an EC as part of their quit attempt successfully quit (self-reported) compared to 70% in the East of England. In 2016-17, 49% of people in the South West region who used an EC as part of their quit attempt successfully quit (self-reported) compared to 68% in London.

Figure 25: Self-reported four-week successful quitters using an EC by region

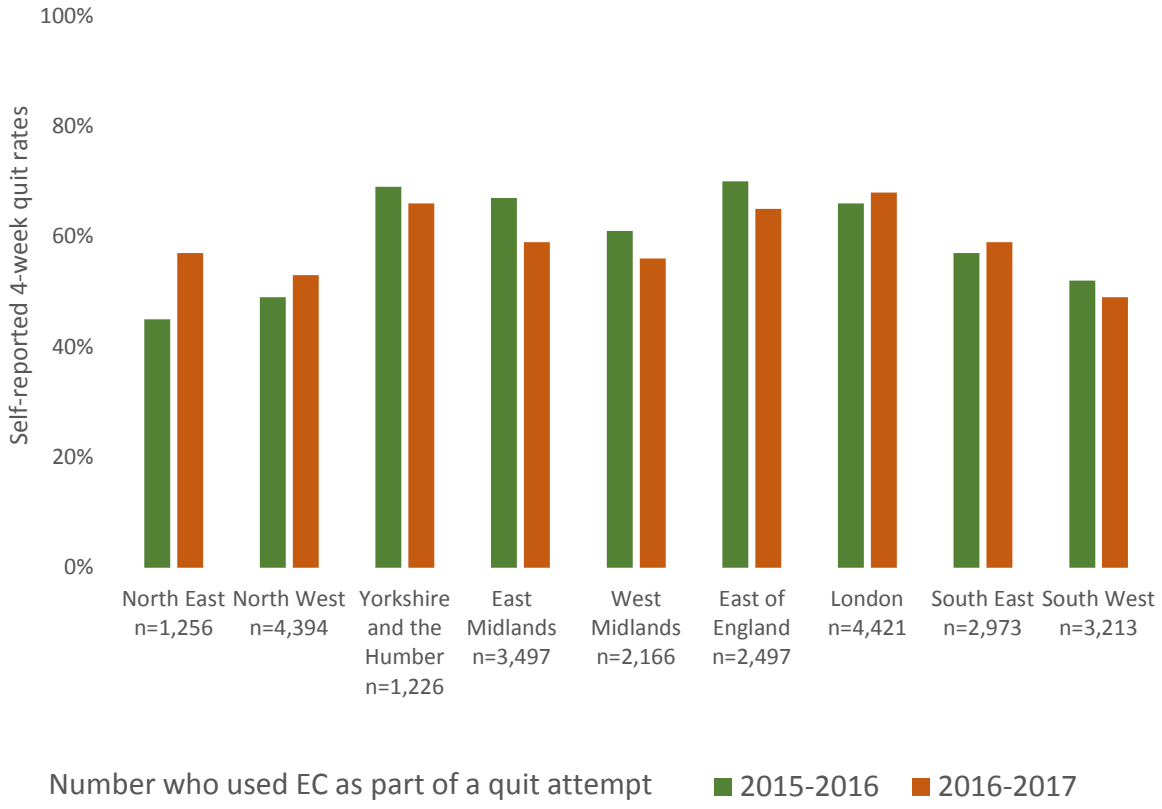
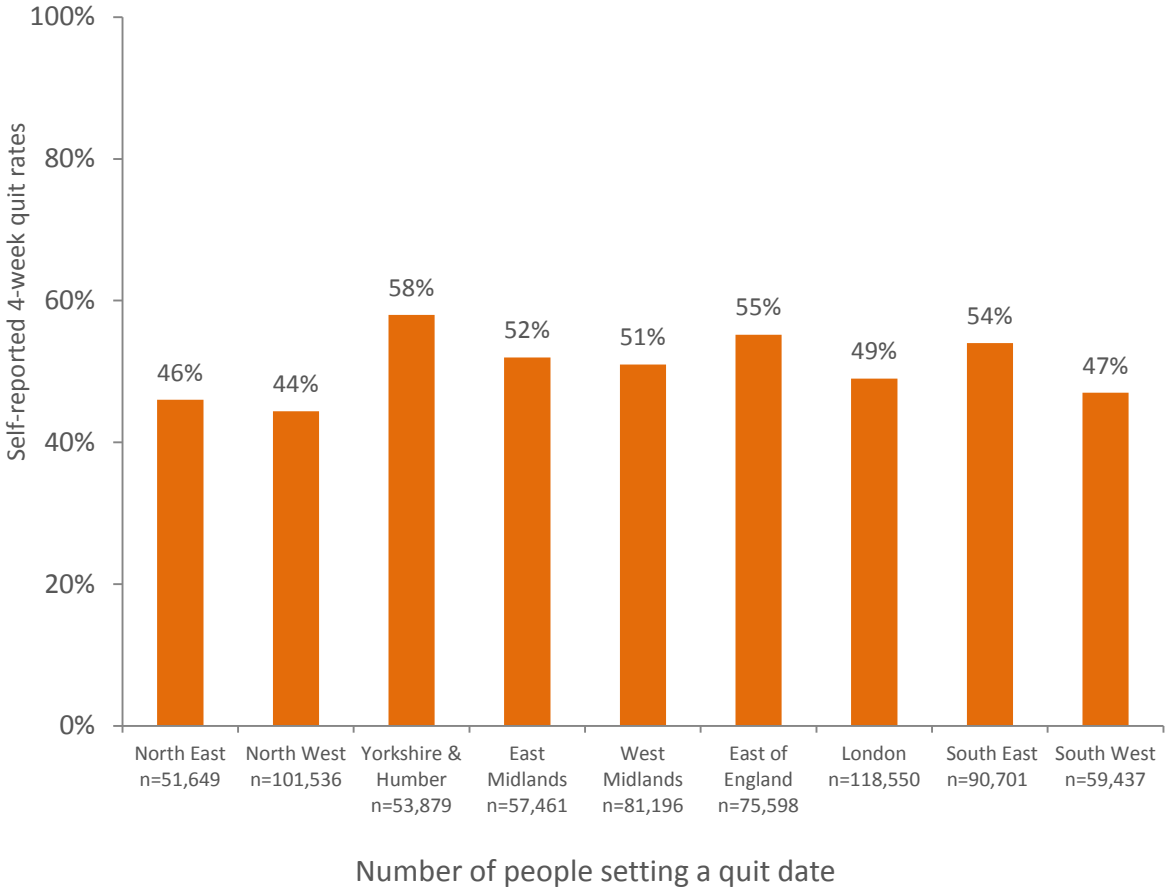


Figure 26: Self-reported four-week successful quitters by region (2015-2017)



In recent years there has been a reduction in the availability and use of Stop Smoking Services. In an annual Survey of Tobacco Control Leads in English local authorities conducted in June 2016, ASH reported that 59% of local authorities have cut their smoking cessation budgets, largely in response to the cut in the national public health grant and the wider cost pressures on local authority budgets (166). One in twenty local authorities no longer have a Stop Smoking Service beyond that offered by GPs and pharmacists and in 20% of Authorities, the Specialist Stop Smoking Service has been replaced by an integrated 'lifestyle' service of some kind. Without a specialist component, these services can be expected to be less effective in helping smokers quit.

Stop Smoking Services increase the chances of a successful quit attempt up to four-fold (167) and should be available to all smokers. As discussed above, the combination of EC with support from Stop Smoking Services is likely to optimise chances of stopping smoking when using an EC. Hence, all services should offer support to smokers wishing to use an EC to stop smoking. However, not all Stop Smoking Service practitioners are supportive of providing help to smokers wishing to use EC. In an online survey of 1,801 Stop Smoking Service practitioners and managers, (168) reported that less than 5% would recommend EC to all their clients.

It seems reasonable to propose that combining the most popular source of support (EC) used by smokers in the general population (identified from the STS data), with the most effective (Stop Smoking Service support), should be a recommended option available to all smokers.

Summary

EC use alone or in combination with licensed medication and behavioural support from a Stop Smoking Service, appear to be helpful in the short term. However, fewer smokers use an EC as part of a quit attempt with a Stop Smoking Service compared with licensed medication. If ECs are contributing to higher success rates, Stop Smoking Services in England may be missing an opportunity to maximise cessation outcomes for smokers who use their service.

Randomised controlled trials of EC use for smoking cessation or reduction (published since the last report)

Our literature search identified one RCT published since our previous report. Tseng and colleagues (169) compared the efficacy of a nicotine containing EC with a placebo EC on smoking reduction. Participants were daily smokers aged 21-35 who were not ready to quit smoking. They were randomised to receive either a disposable 4.5% nicotine EC (n=50) or a placebo EC (n=49) for three weeks. Participants in both groups were also given brief behavioural support about how to reduce their cigarette intake but minimal instructions on EC use. The main outcome was self- reported smoking reduction of at least 50% in the number of cigarettes smoked per day (CPD), three weeks after the start of the intervention. Both groups achieved significant reductions in overall number of cigarettes smoked per day. Compared with baseline, a significant reduction in CPD was observed at both study time periods (1 and 3 weeks) for the group who received the nicotine EC (from an average of 14 CPD to 6 CPD, $p < .001$) and the placebo EC (from an average of 15 CPD to 8 CPD, $p < .001$). The participants in the nicotine EC group were more likely to reduce by 50% or more at end of treatment, only after adjusting for EC consumption and baseline readiness to quit. The authors acknowledge that the study sample size was small and was underpowered to detect the small-moderate effect size observed in smoking reduction at the end-of-intervention, the intervention was brief and follow up period modest.

Overview of systematic reviews of EC use for smoking cessation or reduction

We identified 14 systematic reviews of EC for smoking cessation and /or reduction published since our last report; seven included a meta-analysis (170-176) and seven provided only a narrative synthesis (73, 177-181). The characteristics of the systematic reviews which included a meta-analysis are described in Table 14 and their primary studies in the Appendix.

Table 14: Characteristics of systematic reviews including a meta-analysis

Authors & funder	Date searched up to	Participants	1] Interventions 2] Comparators	Outcomes and length of follow up	No of studies included in each review	Method of synthesis	Tools used for 1] Risk of bias 2] Certainty of evidence
Rahman, 2015(175) Funder: No external funding	5/2014	Current smokers who had used an EC for 6 months or more	1] Nicotine EC 2] Placebo EC 2] NRT 2] No intervention	Self-reported or CO validated cessation at any follow up	RCT: 2 Uncontrolled intervention: 1 Observational (longitudinal or cross sectional):3	Pooled RR for 2 RCTs using a Mantel-Haenszel fixed effects model. Pooled ES for all included studies.	1] van Tulder Scale (182) 1] Downs and Black Scale (183)
Hartmann - Boyce, 2016(171) Funder: Cochrane Collaboration	31/1/16	Current cigarette smokers at enrolment into studies, motivated or unmotivated to quit	1] Nicotine EC. 2] Placebo EC. 2] Alternative smoking cessation aids, including NRT 2] No intervention. 1] EC added to standard treatment (behavioural orpharmacological or both) 2] Standard treatment alone	CO validated cessation at the longest follow-up point, (at least 6 months from the start of intervention)	RCT: 3 Uncontrolled intervention: 6 Observational (longitudinal or cross sectional):8	Pooled RR for 2 RCTs using a fixed-effect Mantel-Haenszel model. Other designs: narrative synthesis	1] Cochrane Risk of Bias tool (184) 2] GRADE (185)
Khoudigian, 2016(173) Funder: No external funding reported	26/5/14	Current cigarette smokers intending/not intending to quit	1] Nicotine EC 2] Placebo EC 2] NRT	Self-reported or CO validated cessation and reduction in number of cigarettes smoked per day at least 6 months follow up	RCT: 2 Various other designs: 3	Pooled RR or 2 RCTs using a random-effects Mantel-Haenszel model	1] Cochrane Collaboration's Risk of Bias Tool (184)

Vanderkam, 2016(176) Funder: No external funding reported	14/6/15	Current smokers	1] Nicotine EC 2] Placebo EC	Self-report or CO verified cessation and reduction on cigarette intake of at least 50% at 3 months or longer follow-u	RCT: 2 Uncontrolled intervention:3 Observational (longitudinal/ cross sectional): 9	Pooled RR for 2 RCTs using a random-effects Mantel-Haenszel model. Other designs: narrative synthesis	1] Cochrane Risk of Bias Tool (184)
Kalkhoran and Glantz, 2016(172) Funders: National Institutes of Health, National Cancer Institute, FDA Center for Tobacco Products	17/6/15	Current or past cigarette smokers intending/not intending to quit	1] EC use. including any past 30-day use, ever use 2] People who have not used an EC	Self-reported and/or biochemically-validated cessation at any duration of follow up	RCT: 1 Various other designs: 37	Pooled OR for 20 studies (various study designs)	1] Cochrane Risk of Bias Tool (184) 1] Modified ACROBAT-NRSI Tool (186)
Malas, 2016(174) Funder: Ministry of Health and Long-Term Care (Health System Research Fund, Canada)	1/2/16	Not reported	1] Nicotine EC 2] Placebo EC 2] NRT 2] No intervention	Self-reported and/or CO-validated cessation or reduction at any duration of follow up	RCT: 2 Observational (longitudinal/ cross sectional): 9	Pooled AORs by synthesising results of studies based on methodological quality using QualSyst tool	1] QualSyst 2]GRADE (185)
El Dib, 2017(170) Funder: WHO	29/12/15	“Cigarette smokers, regardless of whether the users were using them as part of a quit attempt”	1] EC with or without nicotine 2] No intervention 2] Stop smoking medication and/or behavioural support 2] Alternative EC with or without nicotine	Self-report or CO verified cessation and reduction on cigarette intake of at least 50% at 6 months or longer follow-up	RCT:3 Observational (longitudinal/ cross sectional): 9	Pooled RR for 2 RCTs and pooled OR for observational studies using a random-effect Mantel-Haenszel model	1] Modified version of the Cochrane Risk of Bias tool (187) 1] Modified Newcastle - Ottawa Scale (188) 2] GRADE (185)

The authors of the systematic reviews arrived at the same conclusion that further RCTs of EC are needed. However the reviews that included a meta-analysis produced different results; two found a positive effect (171, 175), four found an inconclusive effect (170, 173, 174, 176) and one found a negative effect (172) (Table 15). There appear to be several possible explanations for the discrepancies:

Types of studies included in a meta-analysis: Four reviews conducted a meta-analysis and/or sensitivity analysis that only included RCTs designed to evaluate the efficacy or effectiveness of an EC on cessation or reduction (171, 173, 175, 176); these studies are Bullen and colleagues, (189) and Caponnetto and colleagues (190) and were included in our previous report. The remainder of the reviews included studies within a meta-analysis (cross sectional and longitudinal studies) most of which were not specifically designed to test if EC resulted in cessation or reduction. Therefore one reason for the difference in findings across reviews is due to the inclusion of observational study designs, not specifically designed to test if EC resulted in cessation.

Types of participants included in a meta-analysis: Some reviews synthesised results from primary studies that enrolled only current smokers to their studies (171, 173, 175, 176); whereas other reviews included studies from a diverse range of participants, including current and ex-smokers, smokers who had 'tried an EC' but who continued to smoke. Studies which analyse results of smokers based on EC use at baseline by virtue of their design *have already excluded people who have successfully stopped smoking using an EC*. Such studies only keep patients in their study who are classed as treatment failures or who are in the middle of a quitting attempt where they may be cutting down to quit. Combining such diverse groups (with differing degrees of exposure to an EC) is likely to underestimate the effect of EC for cessation. Participants' motive, frequency and duration of EC use is also likely to influence findings, and combining studies of infrequent, brief EC use with more intensive long term EC use may influence review results.

Types of outcomes included in a meta-analysis: One of the main reasons for the differences between the results of the reviews relates to the length of follow up (whether review authors combined participants quit rates at 6 month or 12 month follow up) and how missing data was handled (on an intention to treat basis or complete case analysis). Two reviews reported cessation at the longest follow-up point from the start of the intervention (ie 6 months follow up for the Bullen and colleagues study and 12 month follow up for Caponnetto and colleagues (190), measured on an intention- to-treat basis (171, 175), two reviews reported consistent follow up points (at six months), also on an intention to treat basis (173, 176). The reason for the difference in the effect estimates between these four reviews related to the length of follow up: one participant in the Caponnetto control group (placebo EC) changed from being a non-quitter at six months follow up to a quitter at 12 months follow up (Table 16).

Table 15: Length of follow up of RCTs included in a meta-analysis

Study and length of follow up	Number who quit with a nicotine EC	Total participants	Number who quit with placebo EC	Total participants in study
Bullen, 2013(189): 6 months	21	289	3	73
Caponnetto 2013(190): 6 months	22	200	**3**	100
Caponnetto 2013(190): 12 months	22	200	**4**	100

The difference between the findings of El-Dib and colleagues and the two reviews by Rahman and colleagues and Hartmann-Boyce and colleagues relates to how missing data was handled. El-Dib's (170) complete cases analysis excluded 181 participants from the two RCTs whereas Rahman and colleagues (175) and Hartmann-Boyce and colleagues (171) included all randomised participants in an intention to treat analysis. In smoking cessation trials, it has been standard practice for several years that participants who do not complete follow up assessments or drop out of the trial early are counted as smokers. Therefore leaving them out of the analysis or filling in their missing data based on their last assessment (if they had quit), would lead to greater bias in efficacy comparisons (165).

Table 16: Results of systematic reviews that included a meta-analysis of cessation

Characteristics	Rahman, 2015 (175)	Hartmann-Boyce, 2016 (171)	Khoudigian, 2016 (173)	Vanderkam, 2016 (176)	Kalkhoran & Glantz, 2016 (172)	Malas, 2016 (174)	El Dib, 2017 (170)
Studies synthesised, (length of follow up)	Bullen, 2013(189) (6 months) Caponnetto, 2013 (190) (12 months).	Bullen, 2013 (6 months) Caponnetto, 2013 (12 months)	Bullen, 2013 (6 months) Caponnetto, 2013 (6 months)	Bullen 2013 (3 months & 6 months) Caponnetto, 2013 (6 months)	Combined 1 RCT (Bullen 2013) with 17 longitudinal (interventional & non-interventional) & 3 cross sectional	Combined 1 RCT (Adriaens, 2014) with 4 longitudinal (interventional & non-interventional)	Bullen, 2013 (6 months) Caponnetto 2013 (12 months)
Method for participants lost to follow up	Included participants with missing data and counted them as still smoking	Included participants with missing data and counted them as still smoking	Included participants with missing data and counted them as still smoking	Included participants with missing data and counted them as still smoking	Unclear	Not reported	Excluded participants with missing data and counted complete cases
Effect Estimate	RR 2.29, (95%CI 1.05-4.96) p=0.04	RR 2.29, (95%CI 1.05-4.96) p=0.04	RR 2.02, (95%CI 0.97-4.22) p=0.06	RR 1.91, (95%CI 0.93-3.89) p=0.08	OR 0·72, (95% CI 0·57-0·91)	AOR 0.10, (95% CI: 0.05, 0.22) - 6.07 (95% CI: 1.11, 33.18)	RR 2.03, (95% CI 0.94-4.38) p=0.07
Authors' conclusion	EC use is associated with smoking cessation & reduction	EC with nicotine, compared with placebo EC, helped smokers to stop smoking long-term	Non-statistically significant trend toward smoking cessation in adults using nicotine EC exists compared with other therapies or placebo.	The use of EC with nicotine decreases tobacco consumption among regular smokers	EC are associated with significantly less quitting among smokers	While the majority of studies demonstrate a positive relationship between EC use and smoking cessation, the evidence remains inconclusive	It is impossible to make strong inferences regarding whether EC use promotes, has no effect or hinders smoking cessation

Summary of systematic reviews

We identified 14 systematic reviews of EC for smoking cessation and /or reduction published since our last report, seven of which included a meta-analysis. The authors of the systematic reviews all concluded that further RCTs of EC are needed. However, the reviews that included a meta-analysis produced different results because of methodological differences. Two found a positive effect, four found an inconclusive effect and one found a negative effect for EC use on cessation.

The standardisation of the reporting of smoking cessation trials has been greatly improved since the publication of the Russell Standard (165). Researchers continue to add other outcome measures in the context of their own trials and this is to be encouraged. However, when reporting trial outcomes, a core set of outcomes, as per the Russell Standard should be encouraged. Similarly, the standardisation of systematic reviews and meta-analytical methods have been improved since the development of the Cochrane Collaboration of Researchers, and we encourage reviewers to report a core set of outcomes using similar methods to the Cochrane Collaboration, in addition to their own outcomes.

Improving the methodological quality of EC research

Villanti and colleagues (181) provide the most recent narrative systematic review to be published and while a narrative synthesis was employed, we include it because the authors propose a set of standards for research on EC use and cessation. To improve the scientific rigor of EC research, Villanti and colleagues (181) have proposed a hierarchy of methodological criteria for considering whether a study provides sufficient evidence to assess if EC use leads to smoking cessation or reduction (box 1) and tested their proposed hierarchy in a systematic review. They searched relevant literature up to the beginning of February 2017 and included any type of research design from studies that claimed to have evaluated the impact of EC use on abstinence from tobacco cigarettes or the reduction in number of tobacco cigarettes consumed. Their search identified 91 identified papers; after assessing if studies assessed the outcome of interest, EC use as the exposure and study design (criterion 1-3), seven studies remained, though only four articles from three RCTs were considered to have met all six of their proposed criteria (169, 189).

Box 1: Hierarchy of methodological criteria for assessing EC use for smoking cessation/reduction (181)

Criterion	Description
Criterion1	Does the study examine and adequately measure the outcome of interest (cigarette smoking abstinence or reduction)?
Criterion 2	Does the study examine EC use specifically for smoking cessation or reduction as the exposure of interest (were EC specifically used with the intention to quit or reduce smoking?)
Criterion 3	Does the study use an appropriate design with control or comparison groups to address the potential impact of EC use on smoking cessation or reduction?
Criterion 4	Does the study measure EC use (exposure) before measuring smoking cessation or reduction (the final outcome)?
Criterion 5	Does the study evaluate the dose and duration of exposure, to determine adherence and adequate delivery of active ingredients for a sufficient time period?
Criterion 6	Does the study evaluate the type and quality of the EC product used?

Villanti and colleagues (191) reach a similar conclusion to the most recent Cochrane Review (171) even though Villanti and colleagues arrived at their conclusion using a slightly different process. The Villanti paper may be expected to contribute to improved rigour in EC research; although no observational studies met all their criteria (192). The strict inclusion and exclusion criteria of RCTs often have limited applicability to patients in real-world clinical settings or people in the general population who smoke or use EC. Therefore, the conclusion drawn from Villanti and colleagues' systematic review using their new hierarchy may be conservative. Likewise, the requirement of maintaining fidelity to an intervention, such as using EC, within certain parameters (eg type, dose, duration and frequency) is also discordant with what happens in real life. As EC technology has become more sophisticated and varied, and the people who use EC more heterogeneous, new and flexible ways of conducting observational studies and RCTs to allow for user experimentation (eg trial and error of different types of EC products), as well as the inclusion of patient/user reported outcome measures that are relevant and meaningful to EC users are necessary (192).

EC use for smoking cessation or reduction in vulnerable groups

Smoking prevalence in vulnerable groups such as those with a mental illness, substance misuse disorder, people who are homeless or prisoners remain considerably higher than in the general population (193-196). Similar treatments to those that are effective for general population smokers are also effective for people who smoke who have a severe mental illness (197, 198) or substance misuse disorder (199). Historically, smokers from vulnerable groups have been offered fewer opportunities to stop smoking compared to smokers in the general population, although there is now a concentrated focus on reducing harm from smoking in this population following recent

policy initiatives (200). As the evidence base rapidly grows for EC use in the general population, it is important that researchers include vulnerable populations when testing EC for smoking cessation or harm reduction. It is also important that practitioners and policy makers ensure equal opportunities to all potential cessation aids for these populations.

Since the previous PHE report (5), we have found no published RCTs of EC for smoking cessation or reduction in the above mentioned vulnerable groups. There has been one uncontrolled study of EC use in smokers with severe mental illness and one in people who smoke who are maintained on methadone. Pratt and colleagues (201) provided EC for four weeks and instructions on how to use them, to 21 people with schizophrenia or bipolar disorder and assessed participants weekly for four weeks. Nineteen participants completed weekly assessments. Thirteen (68%) of participants were female, their mean age was 42 and they had been smoking for an average of 24 years. Between baseline and four weeks, two participants quit and 17 reduced their mean tobacco cigarette intake from 192 to 67 cigarettes/week ($p = 0.005$), confirmed by reduction in breath CO levels from 27 ppm to 15 ppm ($p=0.004$). Temporary and mild side-effects were reported by 58% of participants and included dry/sore throat, nausea, dizziness, and cough. Pratt and colleagues (201) also captured subjective experiences of using an EC and reported participants commented that they perceived that EC were healthier and helped them feel more accepted by non-smokers. However, some participants felt that the EC did not provide the same “hit” they were used to and some participants reported that they tended to use their regular tobacco instead of the EC when they were experiencing emotional distress.

Stein and colleagues (202) provided EC for six weeks and instructions how to use them to 12 smokers who were maintained on methadone. Participants were all male, and their mean age was 46 years. Participant’s reduced their CPD by an average of 13.4 at nine weeks follow up and one participant quit. Temporary and mild side-effects were reported by the minority of clients and included headache, cough and sore throat. Both studies had high adherence rates to EC and low attrition rates.

A similar uncontrolled pilot study of EC (203) with smokers with serious mental illness not intending to stop smoking soon and who were accessing community services, currently under peer review, found similar reductions in tobacco use and measures of smoke intake while using the EC.

International overview of EC use for smoking cessation or reduction

The previous section on systematic reviews is largely international literature; here we provide a brief summary on national surveys with representative samples and finish with a framework for considering the potential deaths that could be averted by hypothetically replacing cigarettes with EC.

In Chapters 6 and 10 we report data from the Eurobarometer 2017 study (EC special Eurobaromter 458 (141)) about EC use in 28 Member States of the European Union. Of 3,612 respondents who reported they currently smoked or used to smoke and have at least tried EC, 14% indicated that using EC enabled them to stop smoking tobacco entirely and 17% reported they had reduced their tobacco consumption due to the use of EC, but did not stop using tobacco entirely. Men (43%) were slightly more likely than women (37%) to say that using EC helped them reduce their tobacco consumption: nearly half (46%) of those aged 55 or over said that using EC helped them cut their use of tobacco, compared with less than a third (32%) of those aged between 15 and 24. The longer someone spent smoking, the more likely they were to say that EC helped them stop or reduce their tobacco consumption. More than two-thirds of former daily smokers (67%) found EC helpful, compared to 58% of former occasional smokers (58%).

In the US, Zhu and colleagues (204) used the US Current Population Survey-Tobacco Use Supplement included data from five surveys, (2001-02, 2003, 2006-07, 2010-11, and 2014-15) to assess the relationship between EC use and smoking cessation in a representative sample of the US population. Of 161,054 respondents to the 2014-15 survey, 22,548 were current smokers, and 2136 recent quitters. EC users were more likely than non-users to make a quit attempt (65.1% v 40.1%), and more likely to succeed in quitting (8.2% v 4.8%). The overall quit attempt rate in 2014-15 (45.9%) was significantly higher compared with the previous surveys. The overall population smoking cessation rate increased between 2010-2011 (4.5%) and 2014-15 (5.6%) representing approximately 350 000 additional US smokers who quit in 2014-15. Zhu and colleagues (204) explain the limitations of their study design and data collection methods and suggest there may be many reasons other than the use of EC that contributed to an increase in quit attempts and quit success (eg an increase in federal tobacco tax and national media campaigns). However, their findings are consistent with Beard and colleagues (161) discussed earlier in this chapter.

Modelling the overall impact of EC

Mathematical and computational modelling play an increasingly important role in guiding public health policy, though are not without their limitations; in this section we report two studies about the potential population impact of EC use in the US. Cherng and colleagues (205) used an agent-based modelling approach to examine hypothetical scenarios of EC use by smoking status and the effects of EC on the initiation and cessation of tobacco smoking). Using multiple sources of data from national surveys, census and epidemiological studies, the model simulated a population of U.S. adults, aged 18 to 85, and their smoking and EC use status. The model included four nicotine-use states: 1) exclusive EC user, 2) exclusive cigarette smoker, 3) dual user of both EC and cigarettes and 4) never user of either product. Cherng and colleagues (205) found larger reductions in smoking prevalence than

potential impact on smoking initiation. They reported if EC increased individual-level smoking cessation probabilities by 20%, the model estimated a 6% reduction in smoking prevalence by 2060 compared to baseline model (no effects) outcomes. In contrast, prevalence of EC use among never smokers would have to rise dramatically from current estimates, with EC increasing smoking initiation by more than 200% relative to baseline model estimates in order to achieve a corresponding 6% increase in smoking prevalence by 2060.

In the second modelling study, Levy and colleagues (206) present a framework for considering all the potential contributions that EC might make to population health. They modelled the potential deaths that could be averted in the US by hypothetically replacing cigarettes with EC using a model that took account of potential cohort effects. They compared projected smoking rates and health outcomes over a 10 year period (2016-2026) using a *Status Quo Scenario* (essentially a world where EC do not exist) with two *Substitution scenarios* (a world where cigarettes are replaced with EC, taking an optimistic and pessimistic view) (Box 2). *The Status Quo Scenario* focused on cigarette use only with the population classified as never, current and former cigarette smokers. Smoking rates were projected forward using age and sex-specific initiation and cessation rates. The number of smoking related deaths of current smokers was calculated by age, sex and year as the product of their excess mortality risks (ie current smoker mortality rate minus never smoker mortality rate) multiplied by the number of smokers. A parallel process was used to calculate estimates for former smokers. Their findings are in Box 2.

Box 2: Assumptions for substitution scenarios (207)

OPTIMISTIC SCENARIO	PESSIMISTIC SCENARIO
Replacing 10% of cigarette by EC users over 10 years, so that a residual of 5% cigarette smoking prevalence remains in 2026	Replacing 10% of cigarette by EC users over 10 years, so that a residual of 10% cigarette smoking prevalence remains in 2026
Never smokers who would have smoked cigarettes instead become EC users at the same rates as initiation of cigarette use in the Status Quo Scenario after the 5% smoking prevalence is reached	EC initiation is assumed to occur at 150% of the Status Quo smoking initiation rate to reflect some renormalisation of nicotine
EC users each year quit at the same age-specific and sex-specific cessation rate as smokers in the Status Quo Scenario	EC users each year quit at half the rate of cigarette smokers in the Status Quo Scenario
An excess risk of EC use at 5% of cigarette excess risk is applied to current EC users	An excess risk of EC use at 40% of cigarette excess risk is applied to current EC users
Predicted potential 6.6 million fewer premature deaths and an estimated 86.7 million fewer life years lost	Predicted potential 1.6 million fewer premature deaths and an estimated 20.8 million fewer life years lost.

Conclusions

Key findings

- In the first half of 2017, quit success rates in England were at their highest rates so far observed and for the first time, parity across different socioeconomic groups was observed. It is plausible that EC have contributed to this.
- Recent estimates of additional quitters resulting annually from the availability of EC, using the same dataset (STS) but two different methods, resulted in similar figures within the range of 16,000-22,000. Varying the assumptions, and updating these estimates for 2016, resulted in an upper bound estimate of around 57,000 additional quitters annually resulting from EC (lower bound around 22,000). While caution is needed with these figures, the evidence suggests that EC have contributed tens of thousands of additional quitters in England.
- EC use alone or in combination with licensed medication and behavioural support from a Stop Smoking Service, appear to be helpful in the short term. However, fewer smokers use an EC as part of a quit attempt with a Stop Smoking Service compared with licensed medication.

- We identified 14 systematic reviews of EC for smoking cessation and /or reduction published since our last report, seven of which included a meta-analysis. The authors of the systematic reviews arrived at the same conclusion that further randomised controlled trials of EC are needed. However, the reviews that included a meta-analysis produced different results; two found a positive effect on cessation for EC use, four found an inconclusive effect for cessation and one found a negative effect.

Implications

Research

- An important focus of future research is longer-term relapse trajectories of people who use EC for quitting compared with other stop smoking treatments and also assess whether the uptake of EC after quitting can prevent relapse back to smoking.
- Funders should consider that although RCTs may yield higher internal validity this is at the cost of lower generalisability. Future robust observational and RCTs should consider allowing for user experimentation (eg trial and error of different types of EC products), as well as the inclusion of study outcomes that are relevant and meaningful for EC users.
- Funders should commission research about the effect of EC on smoking cessation in vulnerable populations (eg people who smoke who have a mental illness, substance misuse disorder, homeless or prison populations).

Policy and practice

- Stop smoking practitioners and health professionals should provide behavioural support to smokers who want to use an EC to help them quit smoking.
- Stop smoking practitioners and health professionals supporting smokers to quit should receive education and training in use of EC in quit attempts.
- Local authorities should continue to fund and provide Stop Smoking Services in accordance with the evidence base.

8 Poisonings, fires and explosions

Introduction

The objective of this chapter is to summarise the evidence on poisonings, fires and explosions attributed to EC and their component parts. These incidents are examined in two categories: harm caused by exposure to e-liquids (poisoning) and harm caused by malfunctioning EC (injuries from fires and exploding EC or EC batteries). Incidents of this nature often gain media attention (208-211), yet little is known about their prevalence and context. This chapter will summarise the evidence available and, where possible, will provide context by reporting risks from other commercially available products. The health implications of inhaling vapour during regular EC use are discussed in Chapter 9 and are not covered here. This chapter presents data from peer reviewed literature published since January 2015, a FOI request sent to Fire Rescue Services (FOI-F) and a FOI request sent to burn treatment centres (FOI-B); these data sources are described in Chapter 2. Of the 29 FOI requests issued to burn treatment centres, data was returned from nine. We are very grateful to those centres that did provide data, however the total response was insufficient to draw either inference or conclusions, therefore the data are not presented in this report.

EC Poisoning

E-liquids typically consist of a solution containing PG, VG, nicotine and flavourings. This section reviews the evidence on cases of poisoning resulting from exposure to e-liquids that far exceeds that from routine EC use but which nevertheless provide valuable background and context to poisoning from e-liquids.

The data here are presented in four sections: National Poison Information Service (NPIS) data for the UK, UK case reports, non-UK case reports and activity reports from international poison treatment centres.

National Poisons Information Service Data (NPIS)

The NPIS collates and summarises UK wide data from its telephone and online (TOXBASE) poison enquiry services as described in Chapter 2 (in 2015 a TOXBASE app was introduced for iOS and Android mobile devices which is not discussed further here as it only accounts for less than 2% of all queries received). The NPIS records enquiries made by clinicians and the public about the assessment and treatment of poisoning cases. Unlike hospital records it can capture incidents that involve accident and emergency services (A&E) attendance but that do not require a hospital admission.

In 2016/17 the NPIS recorded 662,105 TOXBASE user sessions. The most commonly accessed pages were those for Paracetamol (99,584) Ibuprofen (27,675), Sertraline (25,524), Diazepam (23,913) and Codeine phosphate (23,322). The NPIS reported a total of 43,611 patient-related *telephone* enquiries for all causes of poisoning in 2016/17, a reduction from 48,000 the previous year. These included 1,210 for enquiries for drugs of misuse, 694 for iron poisoning, 498 for dishwashing tablets, 419 for carbon monoxide, and 295 enquiries for automotive screenwashes.

For EC poisoning, the NPIS reported 230 patient-related telephone enquiries in 2016/17 compared to 272 such enquiries in 2015/16. Of the 230 enquiries in 2016/17, 185 were recorded as accidental poisoning, 32 intentional poisoning and 13 “all other” or “unknown” (Figure 27). The vast majority (95%) of EC *telephone* poisoning enquiries recorded by NPIS between 2015 and 2017 were recorded as minor, or no toxicity; 2% resulted in moderate toxicity; 1% (n=2) in severe toxicity and 2% of unknown toxicity (Figure 28). Both incidences of severe toxicity in 2016/17 involved a cardiac arrest. There were 608,868 user sessions of the online NPIS service TOXBASE concerning all poisoning causes in 2015/16, and 602,012 user sessions in 2016/17. *Online* enquiries for EC were down from 3,724 in 2015 to 2,664 for the 10 months of 2017 (the number from the equivalent 10 months in 2015 were 3,044).

Figure 27: Telephone enquiries of EC poisoning by cause 2015 - 2017: NPIS data (all ages)

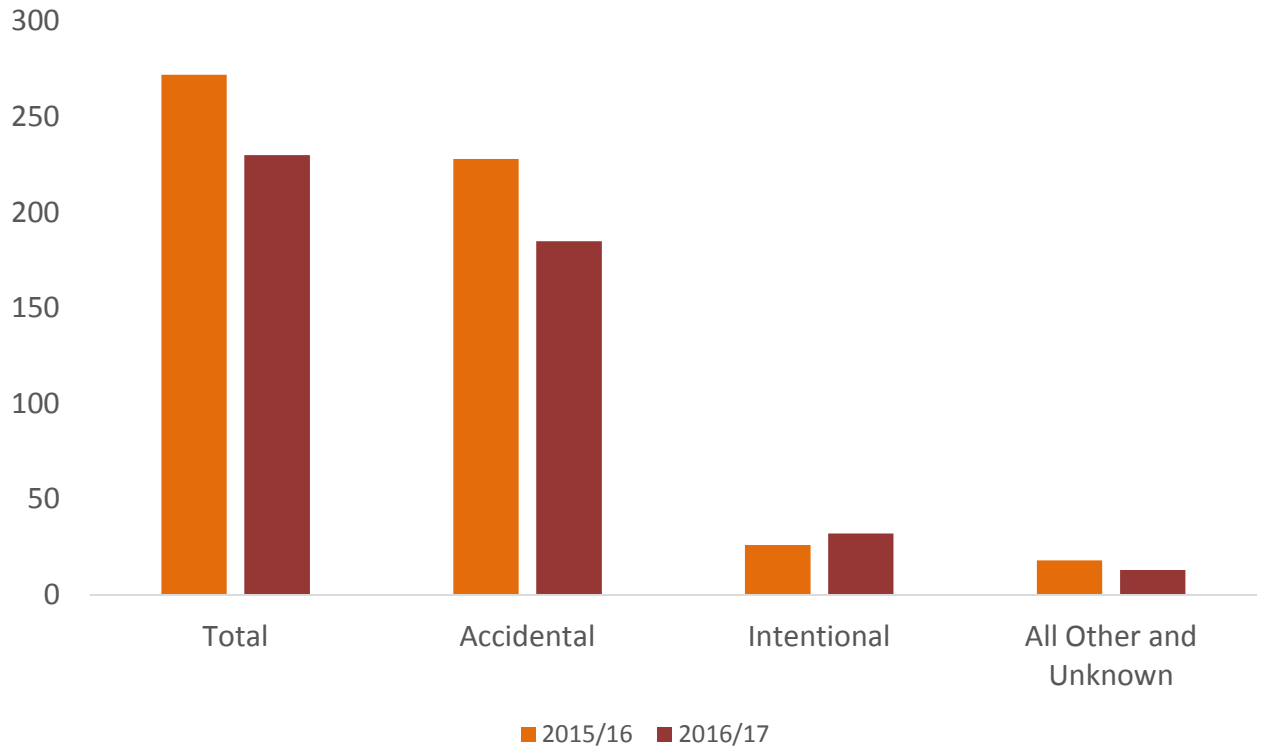
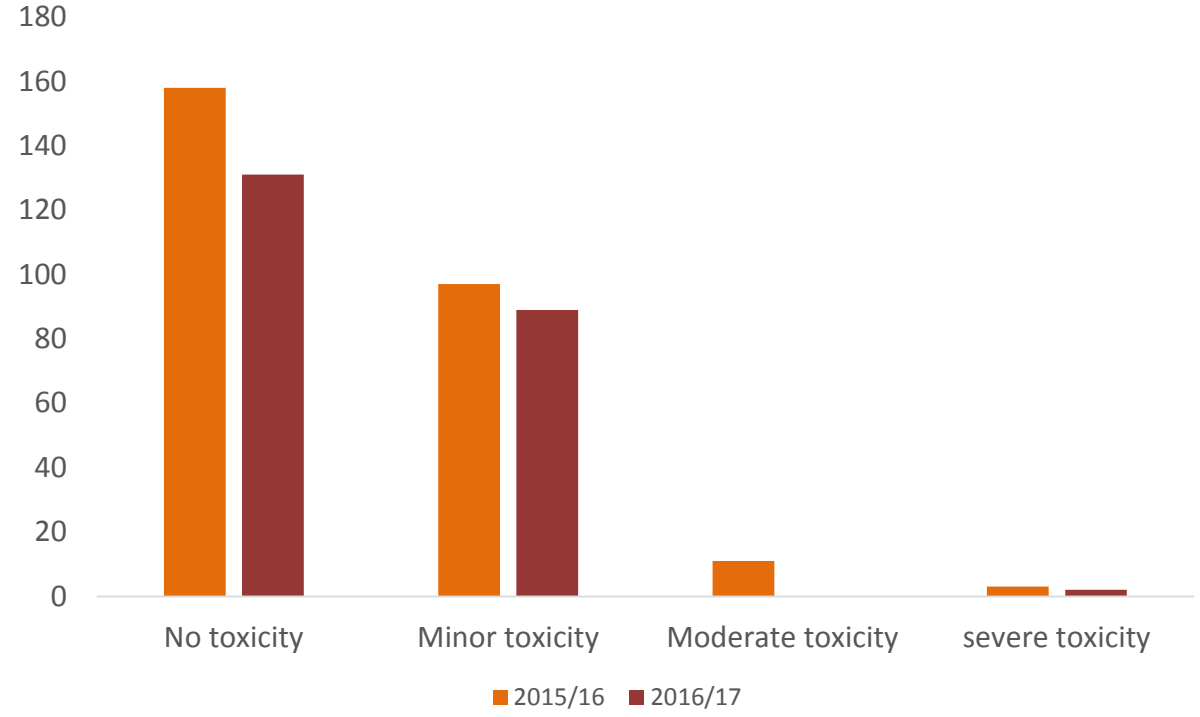


Figure 28: EC poisoning by level of toxicity 2015 - 2017 NPIS Data (all ages)



Review of UK case reports from the literature

There were no peer-reviewed case reports from the UK identified by our literature search. We did identify a letter to an academic journal and a conference abstract that described poisoning by EC. Despite the limitations of these articles they can provide some detail and context to poisoning events and are often used to highlight emerging issues. The research letter reported accidental application of e-liquid to a person's eye after confusing the e-liquid for eye-drops (212). The letter reported that the liquids were stored adjacently in the same cabinet. The person was treated for eye irritation but suffered no long-term damage. The conference abstract reported a man who presented at A&E having ingested two bottles of e-liquid (213). He was treated with benzodiazepines to control and prevent seizures and was discharged after 36 hours and suffered no long-term effects.

Review of case reports from outside the UK

We identified ten papers detailing 11 case reports of EC poisoning outside the UK (Table 17).

Accidental exposure

Five cases described accidental exposure to e-liquid. In two of these cases the e-liquid was mistaken for a medication. In one case report a parent gave 5mL of e-liquid to their 15-month old child mistaking it for cold medicine (214). A second case was of a parent who had prepared and stored e-liquid in an old liquid ibuprofen bottle. They then mistakenly gave 10mL of e-liquid to their six-year-old child believing it to be ibuprofen (215). In other cases, children were reported to have ingested e-liquid from bottles that had no safety cap or child resistant lid (216, 217) one of these incidents resulted in death (216) (Table 17).

Intentional exposure to e-liquid and exposures of uncertain intent

Three cases involved intentional use of e-liquid in a suicide attempt. One reported IV injection of 4mL of 32mg/mL liquid. The patient survived following medical intervention (218). Another case involved subcutaneous injection of between 100 and 400mL e-liquid of uncertain strength resulting in a fatality (219). The third case involved oral ingestion of e-liquid of unknown quantity or strength also, resulting in a fatality (220). An additional three case reports, two of which were fatal, were uncertain about whether the ingestion was intentional or accidental (218, 221, 222) (Table 17).

Table 17: Non–UK e-liquid poisoning case studies from the peer reviewed literature

Author, Publication year, country	Number of cases	Gender	Age	Type of liquid/container	Storage	Intent	Route	Outcome/symptoms
Bartschat, 2015(222) Germany	1	Male	34	Three empty 50mL vials of e-liquid were found. Bottles marked as 72mg/mL	In bedroom; liquids ordered online	Inconclusive.	Oral	Fatal
Chen, 2015(220) US	1	Female	24	Two empty 15mL vials of concentrated liquid nicotine (100mg/mL) were found	Not stated	Intentional suicide attempt	Oral	Fatal
Eggleston, 2016(216) US	1	Male	18 months	100mg/mL nicotine bottle size not stated. In an uncapped, non-child-resistant container	Not stated	Accidental	Oral	Fatal
Gill, 2015(217) Canada	1	Female	2	One 60mL bottle over 3/4s full was found containing 24 mg/mL nicotine. Liquid was grape flavoured; the bottle was similar to an eye dropper, had no safety cap and had cartoon monkeys on it	Not stated - but the toddler was found with the bottle in her hand	Accidental	Oral	Patient vomited for 30 minutes
Lam, 2017(223) China	1	Male	24	A nicotine free flavoured mix, with liquid from an unmarked bottle purchased online as "liquid cannabis". The patient reported to have ingested two drops.	Not stated	Accidental	Oral	Acute confusion, agitation, visual hallucinations, rapid irregular heart rhythm
Noble, 2017(215) US	1	Female	6	E-liquid was stored in an ibuprofen container. The patient was given 10mL of e-liquid which was analysed and found to be 70.3mg/mL nicotine - pH 8.97.	In the fridge (in a liquid ibuprofen bottle having been mixed at home)	Accidental E-liquid was mistakenly given to the patient as ibuprofen	Oral	Vomiting, sweating, visual disturbance, muscle twitching, incontinence and brief loss of consciousness

Author, Publication year, country	Number of cases	Gender	Age	Type of liquid/container	Storage	Intent	Route	Outcome/symptoms
Rasanen, 2017(219) Finland	1	Female	29	Patient injected between 100 and 400 mg of e-liquid of undisclosed strength. This was combined with an undisclosed intake of diazepam and alcohol.	Not stated	Intentional suicide attempt	Subcutaneous injection	Fatal
Seo, 2016(214) South Korea	1	Female	15 months	5mL of liquid nicotine, (10mg/mL); the e-liquid was mistaken for cold medicine.	Not stated	Accidental	Oral	Fatal
Sommerfeld, 2016(218) Poland	2	Female	21	The patient drank 30mL e-liquid with a concentration of 12mg/mL (12.4mg/mL on analysis)	Not stated	Not stated	Oral	Vomited profusely 15 minutes after ingestion. Abdominal pain, motor agitation, anxiety and difficulty breathing. Low pulse and blood pressure. The patient returned to normal after 12 hours and was discharged after 40 hours.
Sommerfeld, 2016 Poland		Male	32	32mg/mL nicotine (32.2mg/mL on analysis). Injected approx. 4mL.	Not stated	Intentional suicide attempt	IV Injection	Abnormal slow breathing and loss of consciousness after approx. 1hr
You, 2016(221) South Korea	1	Male	39	EC with liquid bottle was found. 7.2mg/mL	Not stated	Not stated	Oral	Fatal

Review of data from poison centres outside the UK

The literature review identified six articles of EC incidents from poison treatment centres, all based outside the UK (Table 18). Five articles were from the US and one was from the EU (this study did not analyse any data from UK poison centres). Four articles reported EC poisoning for all age groups and two focused on EC poisoning events in children. Three articles from the US reported activity at a regional level, and two provided national statistics (224, 225). Accordingly, some poisoning incidences may contribute to both regional and national reports and so caution must be used when comparing or combining these data.

In reports that included all age groups, there were 3,609 incidences reported in children aged five or under compared to 2,755 in all other age ranges. These reports covered all of the US, as well as ten EU member states; each report included data from between 3 and 5 years. Most of these poisoning events were accidental; however intentional overdose and self-harm incidents were also reported. Intentional incidents accounted for 5 to 18% of the total number of EC poisonings where reported. The most common route of exposure was ingestion followed by inhalation, with these making up over three quarters of events in all reports. Dermal, ocular and “other” routes of exposure were also reported. The most commonly reported side-effect was vomiting, with the following adverse health effects also reported: drowsiness, tachycardia, agitation, dizziness, headache, eye pain, red eye, conjunctivitis, blurred vision, corneal abrasion, lethargy, throat conditions, abdominal conditions, diarrhoea, breathing conditions and tremor. There were two fatalities (224), one accidental ingestion of e-liquid by a child aged under five, and one suicide attempt involving injection of e-liquid.

In the two studies that focused specifically on children, over half of the events reported by Forrester (226) and Kamboj and colleagues (225) involved children under two years old, with marginally more incidents attributed to males in both studies. Here ingestion was again the most common route of administration accounting for 93% (Forrester) and 82% (Kamboj and colleagues) of cases, with low levels (<5%) reported for dermal, inhalation and ocular routes. Vomiting was the most common side-effect, with other adverse health effects including coughing and choking, eye pain, respiratory arrest, seizures, and tachycardia. Forrester and colleagues reported one “major effect”; Kamboj and colleagues reported five “major effects” and one fatality where a one year old accessed an open refill container. Kamboj compared this to two “major effects” and no deaths from tobacco cigarette poisonings during the same period, noting that overall the number of EC poisonings in children was less than a quarter of the number of poisonings from cigarettes during the same period

Table 18: E-liquid poisoning summaries from poison centres

All ages

Article	Location and date range	Proportion by age (n)[1]	EC *n*	Cigarettes *n*	Gender	Intent[2]	Data source	Route of administration %
Chatham Stephens et al., 2016 (224)	US 2010-2014	0-5 = 58% *(3,341)* 6-10 = 1.9% *(108)* 11-19 = 5.5% *(314)* 20+ = 34.7% *(2,001)*	5,807	20,372	54% male 46% female	Not reported	Calls to the US national repository and surveillance system	Ingestion = 65.8% Inhalation/nasal = 11.0% Eye = 8.6% Multiple routes = 8% Skin = 6.5% Ear = 0.2%
Ordonez et al., 2015 (227)	Texas, US 2009-2014	0 – 5 = 53% *(119)* 6-19 – 6% *(13)* 20+ = 41% *(93)*	225	1,893	49% male 51% female	87% unintentional 5% intentional	Exposures reported to the Texas Poison Center network	Ingestion = 78% Multiple routes = 10% Inhalation = 9% Dermal = 8% Ocular = 4%
Weiss et al., 2016 (228)	Wisconsin, US 2010-2015	0 – 5 = 58.2% *(57)* 6 – 19 = 11.2% *(11)* 20+ = 30.6% *(30)*	98	671	Not provided	86.7% unintentional 8.1% intentional	Calls to Wisconsin Poison Centre	Ingestion = 66.3% Inhalation = 14.3% Ocular = 6.1% Dermal = 2.0% Other = 9.3%
Vardavas et al., 2017 (229)	Ten EU Member states 2012-2015	0 – 5 = 33.2% *(92)* 6 – 18 = 9.8% *(27)* 19+ = 57.0% *(158)*	277	N/A	51% male 49% female	71.3% unintentional 17.8% intentional	Data from poison information centres from ten EU States	Ingestion = 67.5% Respiratory = 16.6% Dermal = 9.0% Ocular = 7.6% Other = 2.2%

Studies focusing on children

Article	Location and date range	Age range~	EC *n*	Cigarettes *n*	Gender	Intent*	Data source	Route of administration
Forrester, 2015 (226)	Texas, US 2010-2014	0 = 8.9% *(18)* 1 = 35.2% *(64)* 2 = 38.5% *(85)* 3 = 11.8% *(28)* 4 = 3.9% *(5)* 5 = 1.6% *(3)*	203	N/A	51.2% male 48.8% females	All accidental	Exposures reported to the Texas Poison Center network concerning children under five years old	All alone or in combination Ingestion = 93.1% Dermal = 11.3% Ocular = 3.0% Inhalation = 2.0% Multiple routes = 9.9%
Kamboj et al., 2016 (225)	US 2012-2015	0 = 8.9% *(267)* 1 = 35.2% *(1,452)* 2 = 38.5% *(1,591)* 3 = 11.8% *(487)* 4 = 3.9% *(161)* 5 = 1.6% *(67)*	4,128	17,512	55.2% Male 44.6% Female 0.2% Unknown	All accidental	NPDS The National Poison Data System holds data on calls to all US poison control centres	Ingestion = 81.5% Ingestion = 9.7% Dermal = 3.3% Inhalation/nasal = 3.2% Ocular = 1.6% Other = 0.5% Unknown = 0.1%

[1] Total calls may differ from sum of ages as age was not always recorded. [2] Intent of all events not known so percentages do not always combine to make 100

EC fires and explosions

EC along with many other personal and portable electrical appliances use rechargeable lithium-ion batteries. In common with all types of batteries, lithium-ion batteries can fail; this is usually typified by a slow decline in performance to the point where the battery needs replacing. On rare occasions, a battery may fail by discharging all its stored energy at once. This can be triggered by mechanical damage, exposure to extreme heat, unsafe charging, short-circuiting or by design and manufacturing faults within the battery. This type of immediate failure is known as “thermal runaway” and can occur in all battery types (230). When thermal runaway occurs, the pressure and temperature of the battery increases and can cause the battery to vent flammable gasses at high pressure (231). This can cause the battery and device in which it is stored to be propelled at high velocity. This has the potential to be more extreme in lithium-ion batteries than in other types of batteries because of the large amount of energy they can store. The immediate and dramatic nature of such events means that they are often given a high media profile (208-210). Lithium-ion batteries are commonly used in consumer electronics and although their instability and potential for fire is rare, it has been documented in other products such as mobile phones (232). It is because of the use of lithium-ion batteries that we sought to compare EC fires/explosions with those attributed to mobile phones.

This section of the chapter summarises data from FOI requests made by the authors to UK fire rescue services and burn treatment centres as described in Chapter 2. We will also summarise the peer reviewed literature published since January 2015 on EC fires, burns and explosions.

Data from individual UK Fire Rescue Services

Forty-nine fire rescue services responded to the FOI request described in Chapter 2. Six were unable to provide any data, citing high costs or that the data requested were not available. Data on fires and false alarms attributed to EC were available for 41 fire rescue services (Figure 29); and data on both EC and mobile phone incidents from 2015 to 2017 were available for 38 fire rescue services (Figure 30). For 2017 data, fire rescue services reported data that was available at the time of the FOI request (August 2017).

Call outs for EC related fires increased from 2015 to 2016, with 93% of this increase attributed to false alarms. In 2016 (the most recent full year data) fire services included in this analysis recorded a total of 269 call outs comprising 202 false alarms and 67 fires. There were nine casualties reported in 2015, 11 in 2016 and four in the data available for 2017. No fatalities were recorded in the data available between 2015 and 2017.

Figure 29: EC fires and false alarms recorded by 41 fire rescue services 2015-2017

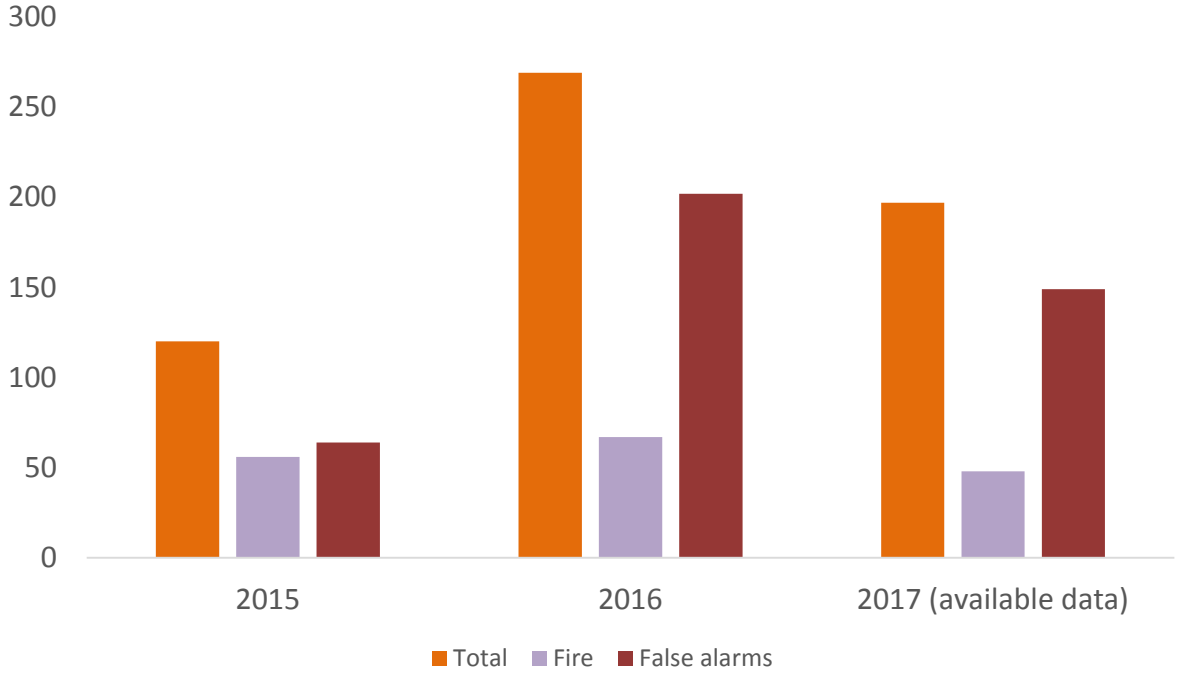
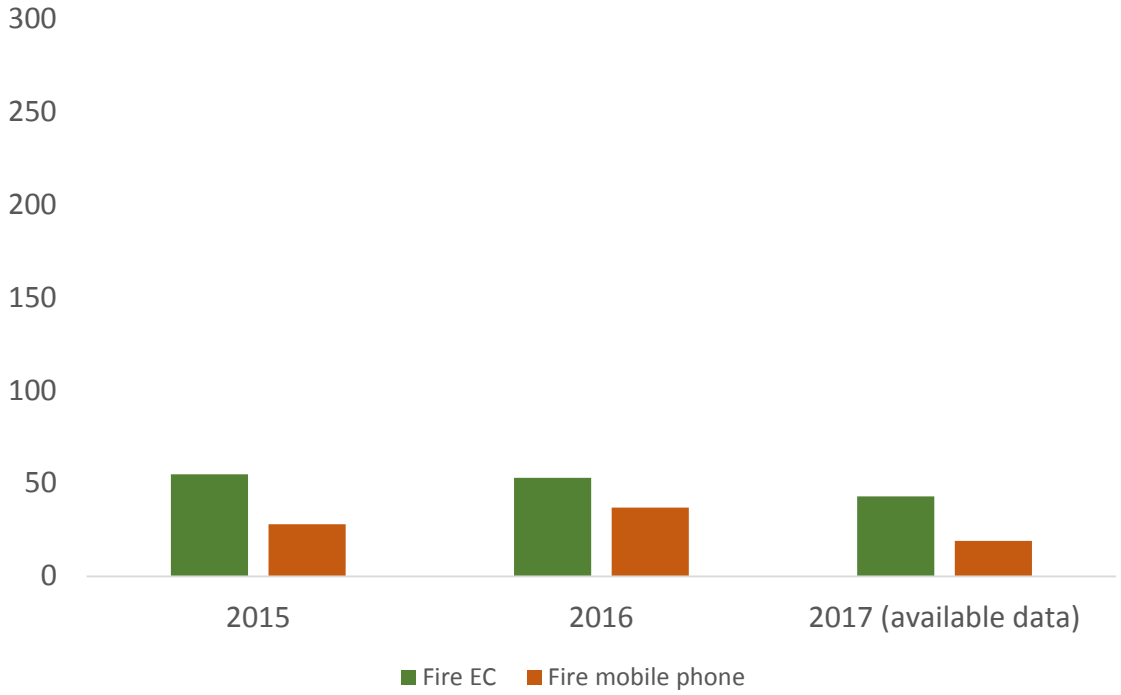


Figure 30: Fire attributable to EC and mobile phones for 38 fire services 2015-2017



Data on EC and mobile phones from 2015 to 2017 were provided by 38 fire rescue services (Figure 30). False alarms were excluded from this analysis because EC can trigger false alarms by either observers mistaking the vapour for smoke, or by the vapour triggering fire detection mechanisms (correspondence to the authors from Tyne and Wear, Royal Berkshire, and East Sussex Fire and Rescue Services). Mobile phones do not cause false alarms in these ways and so comparisons of false alarms between devices are not appropriate in this context. There were 151 fires related to EC

and 84 related to mobile phones between 2015 and 2017, and no fatalities recorded for either EC or mobile phones in this analysis.

National fire statistics

National data on fires attributed to smokers' materials are available from official Home Office statistics (25). These are drawn from all 52 fire rescue services and from mandatory recording procedures which do not apply to EC, so are not directly comparable with the FOI-F data presented above but provide useful context.

In the UK in 2015/16 there were 3,608 fires caused by smokers' materials causing 584 non-fatal casualties and 77 fatalities. In 2016/17 there were 3,156 fires caused by smokers' materials causing 479 non-fatal casualties and 68 fatalities.

London fire brigade

In their response to the FOI request, London Fire Rescue Service volunteered additional data on both EC and cigarettes enabling a direct comparison of EC and cigarette data from a single service. It is important to note that these data was used in the FOI analyses above and will have also fed into the national data in the same time period for EC.

Table 19 compares fires attributed to EC and to smokers' materials in London between 2015 and August 2017. London Fire Rescue Service reported 3,527 fires attributed to smokers' materials compared to 13 attributed to EC. Cigarettes were associated with 395 injuries and 44 fatalities compared to no injuries or fatalities recorded in the same time period for EC.

Table 19: Fires recorded in London

	Total		2015		2016		2017 (Available data)	
	EC	Smoking related	EC	Smoking related	EC	Smoking related	EC	Smoking related
Total Fires	13	3,527	4	1,346	6	1,214	3	967
Injuries	0	395	0	130	0	145	0	120
Fatalities	0	44	0	14	0	22	0	8

Limitations

The FOI-F data has considerable limitations. Recording of EC as the cause of fire is not mandatory, and requires use of a free-text box. The reliance on searching a free text box for EC events means that events may be excluded if they are misspelled or

abbreviated. The numbers reported from different services were varied. For example, one service reported a nil return against our criteria, where another reported 79 call outs indicating the potential for a wide range in recording practices across fire services in the UK. This is also reflected in the discrepancies between
Figure 29 and Figure 30 which include data from different numbers of fire services.

There are no data sources that are sufficient to determine the prevalence of EC poisonings fires or explosions in the UK given that such questions are not included in population wide surveys. Individual cases within the data presented here are confidential and cannot be identified. It is therefore possible for single incidents to be reported to the NPIS and to be written up as a case study and hence be included more than once in this summary. Similarly, there may be potential overlap between regional and national poison centre reports in the US. It is also likely that these data underestimate incidences of poisonings, fires and explosions attributable to EC. Not all incidences are reported to health, fire or medical services, and incidences that are reported may not always be recorded as related to EC.

Case reports concerning injury from fires and explosions

We reviewed the literature on injuries from EC fires and explosions following the protocol outlined in Chapter 2. The search identified 25 articles, three of which are case reports or case series from the UK and 21 of which were non-UK case reports or case series. There were three additional articles from the international literature, one was a review of EC fires and explosions in the US using information reported to federal agencies, and two were retrospective audits of referrals to burn centres.

Case reports originating from the UK

We identified three articles describing six case studies of EC related burns in the UK (233-235) (Table 20). All patients were male and their average age was 33 years. In five cases, patients sustained burn injuries as a result of an EC exploding in their trouser pocket. One of these reported having coins in the same pocket as the EC. One case occurred while the EC was charging.

Injuries included superficial partial thickness and mixed depth thermal burns covering 1-7% of the total body surface area; injuries occurred to the lower extremities (foot, thigh, genitals) and hands, one case included alkali chemical burns from the lithium battery. Treatment included wound management with one person needing a skin graft. In addition to describing three cases, Arnoult and colleagues (233) included information about a further nine male patients aged 24-63 who sustained superficial partial thickness and mixed depth thigh burn injuries from EC batteries, although information about the context and cause of these injuries was not included.

Case reports originating outside the UK

We identified 21 papers describing 43 cases from outside the UK (18 in the US, one each from Canada, Germany and Malaysia) (see table in appendix). Forty-one patients were male and two were female and their average age was 29 years. Twenty-three cases described patients who had sustained injuries as a result of an EC (and/or EC battery) exploding while being carried in a trouser pocket; four of which reported they were carrying keys and/or coins in their pocket at the time of the explosion. There were 13 explosions that occurred when the EC device was in the patient's mouth, four while holding it, one while modifying their device and one during a motorcycle accident.

Injuries included thermal and chemical burns to the face, hands, thighs, buttocks and genitals; puncture wounds, fractures, loss of teeth and eye injuries. Thirty-six cases resulted in burn injury; the mean total surface area of the burn was 6% (range 0.5% to 27.5%) in 27 cases. Treatment included wound management, dental and maxillofacial surgery; 13 patients required a skin graft.

Table 20: UK case reports concerning injuries caused by EC explosion

Author, year and setting	Number of cases	Gender	Age	Circumstance of EC explosion	Nature of injury	Treatment	Details of EC
Arnaout et al., 2017 (233), UK.	3	Male	22	While charging	1% TSBA superficial partial thickness burns to hands and sole of right foot	Wound management	Rechargeable device
		Male	22	While in right trouser pocket	1% TSBA mixed depth burn to right thigh and scrotum, superficial, partial thickness burns to left hand	Wound management	Not reported
		Male	49	While in trouser pocket with coins (lithium battery only)	7% TBSA, superficial partial thickness burns to right thigh	Wound management	Rechargeable device
Nicoll et al., 2016 (234), UK	2	Male	39	While in trouser pocket (lithium battery only)	4% TSBA, superficial partial thickness burns to his right thigh, minor superficial burns to the right hand	Skin graft	EC showed no sign of damage before explosion
		Male	30	While in trouser pocket (lithium battery only)	3% superficial partial thickness burns to his right thigh. Superficial burns were also sustained to the right hand.	Wound management	Not reported
Walsh et al., 2016 (235) , UK	1	Male	35	While in right trouser pocket (with keys)	1.5% Total Body Surface Area, mixed depth burn to right thigh	Wound management	Not reported

Additional international literature

Rudy and Durmowitz (236) reviewed EC fires and explosions in the US. They searched media outlets, five US federal agencies and the scientific literature, identifying 92 events related to EC overheating, catching fire or exploding. There were 45 incidents involving injury to 47 people, and 67 incidents involved property damage. The majority of injuries sustained were burns (thermal = 33, chemical = 4) and the remainder were blast injuries (fractures and lacerations to the upper extremities). Most incidents happened during charging (n=44) with fewer occurring while inhaling or between puffs (n=20); the remainder occurred during transportation or storage. It was suggested in some occurrences that EC user actions may have contributed to the malfunction, for example when using a substitution charger, charging a non-rechargeable battery, using a recalled or incorrect battery or using an EC near oxygen containers. This review was limited by inconsistent and incomplete primary reports, lack of device identifiers and device damage, reliance of voluntary reporting to agencies and the possibility of undetected duplicate cases reported to Federal agencies and the media.

A retrospective case note audit of referrals to three burn centres in California, US, (237) identified 29 patients who had sustained injuries caused by EC explosions between February 2015 and July 2016 as well as one patient in 2014. Twenty-four of the 30 patients (80%) were male and their average age was 30 years. Explosion of a fully assembled EC was described in 16 cases and an isolated battery in 10 cases; with the EC status unclear in the remaining four cases. Patients sustained burn injuries to the lower part of the body (legs and genitalia) and upper part (hands, torso and face). The burn size ranged from less than 1 to 8% of the total body surface area, with a mean total body surface area of 4%. Nine patients (30%) received surgical intervention.

In a retrospective case note audit of referrals to one burn centre in California (a different burn centre to the one reported by Ramirez and colleagues (237)), US, Toy and colleagues (238) identified 24 male patients and one female patient who sustained a burn injury from an EC. Their average age was 34 years. The majority (72%) of burn injuries occurred when the EC (and/or EC battery) exploded in the patient's pocket, the remainder while in use. Thigh and genital areas were the most commonly affected areas of the body. The area of burns averaged 4.1% total body surface area with a range of 1% to 9% and five patients required a skin graft.

Limitations of case reports

Case reports and case series have long been accepted as a way to present unusual, uncontrolled observations regarding symptoms, clinical findings and novel treatments and are often written to educate other clinicians. However, as a methodology, they are limited; they are not chosen from representative population samples and cannot be generalised, they rely on the patients’ recall of events and the observer’s subjectivity

can bias the quality and interpretation of the observation (ie information bias). Case reports often deal with rare and atypical events and can be easily over- interpreted or misinterpreted, as they often have an emotional appeal on readers. In the case of EC the above information cannot therefore provide information on incidence or prevalence of explosions and cannot be generalised to the current 2.9 million EC users in the UK. Although explosion events are very rare, the case reports can alert us to precautions that can be taken to minimise further events and guide clinical treatment decisions.

Conclusions

Key findings

Poisonings

- There are recorded cases of poisoning from e-liquid in the UK. These have predominantly involved accidental ingestion with fewer incidences of other routes (eg ocular or dermal) of exposure.
- Intentional poisoning using e-liquids has been reported in self-harm and suicide attempts.
- Toxic effects from EC poisoning are usually short in duration and of minimal severity; severe cases and fatalities, while very rare, have been recorded.
- EC poisonings reported to medical centres most commonly occur in children under five years old. Toxic effects for this age group are usually short in duration and non-severe. Fatalities, while very rare, have also been recorded in this age group.
- Incidents of poisoning in children are often preventable and have involved liquids stored non-securely, in unmarked containers or in containers without safety caps.

Fires

- EC fires are recorded at the discretion of individual fire rescue services in the UK. Information provided to us through a FOI request suggest that, where recorded, they occur in low numbers and are vastly outweighed by fires caused by smokers' materials. There were no fatalities from fires caused by EC in the reporting period.
- EC and/or their batteries are recorded as the cause of fires by UK fire rescue services. The root cause of EC fires is likely to be through a malfunctioning lithium-ion battery.

Explosions

- Exploding EC can cause severe burns and injuries that require intensive and prolonged medical treatment especially when they explode in users' hands, pockets or mouths.
- Incidents are very rare. The cause is uncertain but appears to be related to malfunctioning lithium-ion batteries.

Implications

Research

- Research is required on the prevalence of e-liquid poisoning, fires and explosions caused by EC in England. This will require some synthesis of existing datasets.
- Research on presence and effectiveness of safety features and instructions should be part of a future review of the EU TPD.

Policy and practice

- Monitoring of fires caused by EC should be recorded by Fire Rescue Services in a mandatory way (similar to "cooking appliances", "smokers' materials" and "other electrical appliances") and should not continue to rely on free text entry.
- EC can trigger fire/smoke detectors and therefore consumers should be advised to move away from detectors when using them.
- It is too early to assess the impact of the EU TPD in reducing poisonings, fires or explosions, or whether further regulations are needed. Therefore, continued monitoring is required to assess effectiveness of EU TPD regulations (such as childproof containers), in reducing accidental ingestion of e-liquid.
- Regulations should require that labelling on e-liquid bottles advises customers to store products away from similar looking medicines such as eye drops, ear drops and children's medicine.
- Regulations should require that labelling reinforces advice on the safe storage and transportation of batteries used by EC. For example, advice should be given that EC should not be carried in pockets with coins, keys or other metallic objects, and that the correct charger should always be used.

9 Health risks of EC

Introduction

The 2015 PHE report (5) reviewed studies that had raised concerns about potential health risks resulting from using EC. It identified that most toxins responsible for health damage from smoking are absent in EC aerosol and that those that are present are there at much lower levels (below 5% and mostly below 1%) than in tobacco cigarettes. Regarding ingredients specific to EC, no significant health risks had been identified at the time. We therefore concluded that the new studies did not demonstrate substantial new risks and thus did not change the conclusions of previous reviews that EC were substantially less harmful than smoking (4). We considered a 5% residual risk to be a cautious estimate allowing for uncertainty over risks in the longer term. Since the 2015 PHE report, the Royal College of Physicians (RCP) has also reviewed evidence on the safety of EC and concluded that they were "*unlikely to exceed 5% of the harm from smoking tobacco*". Over the past two years, many new studies were published of which several raised concerns regarding EC safety.

This chapter reviews the new evidence to update conclusions on potential health risks from using EC. In this chapter, we focus on studies that provide new relevant information, EC adverse events from the MHRA Yellow Card reporting system, reviews and high profile studies. We start with a brief consideration of approaches to assess health risks of vaping and a summary of the adverse reactions data. Following this, the Chapter organises the new findings into thematic sections according to the safety concerns they cover, beginning with overall effects and followed by studies concerning propylene glycol and glycerine, aldehydes, flavours, metals and passive vaping. Nicotine was discussed in Chapter 4, therefore the discussion below focuses on other EC constituents. Within each section, where appropriate, we report the different categories of studies including: animal and cell studies; studies of the chemical composition of EC aerosol; and, studies of toxin intake and vaping effects in EC users. As EC are a product that is competing with tobacco cigarettes, the focus of the review is mainly on risks of vaping compared to risks of smoking. In addition, given we believe that biomarkers of exposure might be particularly informative at this time, we include a more detailed analysis of four candidate biomarkers of exposure, an analysis not yet peer reviewed but which brings together different study findings and is therefore relevant. Finally, we have an additional section at the end in which we explore the misreporting of some studies and possible reasons why this may be happening.

Considerations for assessing the health risks of EC

There are different approaches to assessing risks of vaping, with each posing certain methodological challenges. The weakest evidence comes from animal and cell studies, because their relevance for estimating effects of vaping for human exposure is unclear. In addition, it can be difficult to emulate realistic vaping conditions and generate realistic dosing of EC aerosol. However, such studies can provide indications of which constituents of EC aerosol human research should focus on. Another approach is to look at the chemical composition of EC aerosol. Such studies are essential and can obviously generate important information, but they too can suffer from using EC settings that generate unrealistic exposure.

The strongest evidence for relative risks of EC and tobacco cigarettes will eventually come from actual health outcomes in cohorts of EC users compared to cohorts of smokers and non-smokers. However, this will take time. EC prevalence has only been at a measurable level since about 2011/12, not long enough to measure long term impacts of vaping on health. There is also the issue that most EC users are former or current smokers and smoking-related health risks can persist for a long time, therefore assessment of harm/risk from EC has to account for the possible damage related to current or past smoking. Cohort studies will need to include ex-smokers quitting with different methods as well as those who switched to vaping, those who carry on smoking, and those who never smoked.

An additional approach is to study switching to EC versus quitting smoking among smokers with established smoking-related disease – these studies might expose any benefits or risks sooner than in studies largely of healthy smokers. Reported adverse reactions to EC can also be assessed from research studies of EC users, and any mandatory reporting schemes.

An alternative option is to assess biomarkers of potential or actual harm, such as lung function, premalignant lesions or chromosomal aberrations. Here, changes might occur more quickly and before health outcomes can be measured, thereby ameliorating problems with time lags. It does not, however, necessarily help to discriminate between the effects of smoking and the effects of EC use among people who have used both. Special attention needs to be given to the extent to which any acute effects indicated by biomarkers translate into chronic effects and relevant health outcomes.

A further option is to look at biomarkers of exposure such as measuring internal exposure to eg constituents of tobacco smoke or EC aerosol which can be measured in bodily fluids – one such example are tobacco specific nitrosamines which can be measured in urine samples. This has the benefit of accumulating evidence quickly about short term and reversible harms. Such biomarkers must be reasonably specific to the exposure and related to a disease to provide evidence of harm. Advantages of

using biomarkers of exposure include that they are less affected by prior exposure to smoking and they can be observed in users of the products.

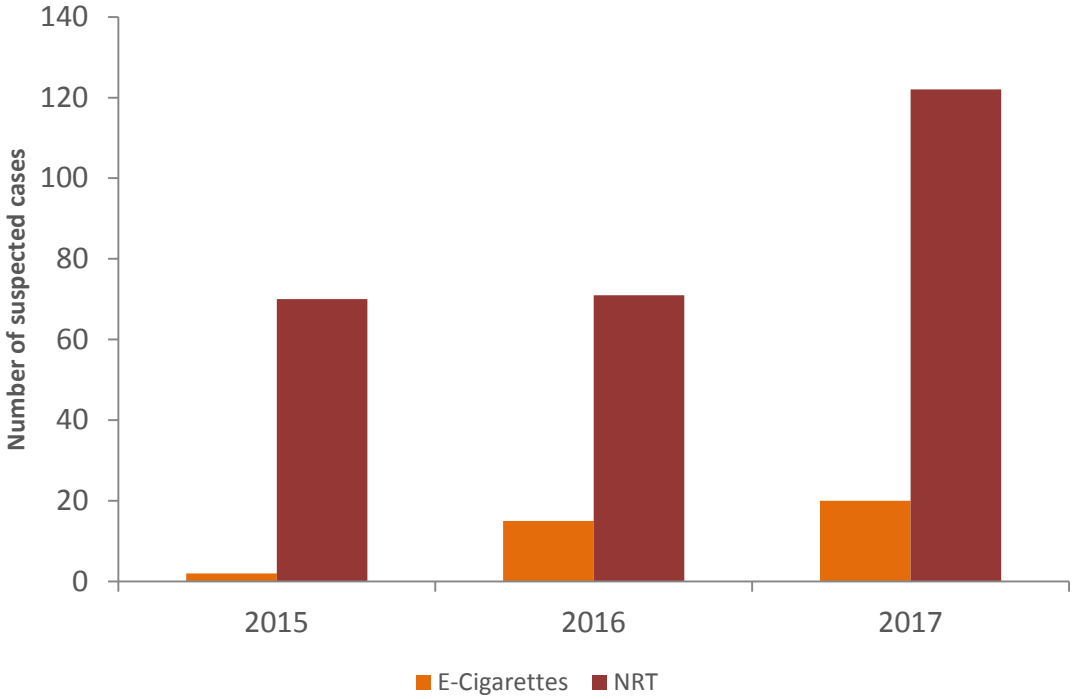
Adverse reactions

MHRA Yellow Card Scheme

No population-based studies on adverse outcomes of EC use were identified in the search. Instead, we report data from the Yellow Card Scheme. Run by the MHRA, is a reporting system to record suspected adverse reactions to medicines from health professionals, manufacturers or members of the public. To coincide with implementation of the EU TPD 2014/14/EU (see Chapter 3), on 20 May 2016 the MHRA extended its Yellow Card reporting system to include EC and e-liquids, although some reports had been received prior to this date. Consumers and healthcare professionals can report both side-effects and product safety concerns. A report can be made when a medicine (or EC) is suspected to have led to an adverse reaction. The person making the report does not need proof that the medicine/EC caused the symptoms, only to suspect that it may have, or that there was a close temporal relationship to the administration of the medicine/EC. The MHRA provided us with anonymised reports for spontaneous suspected adverse reactions for EC along with details of spontaneous suspected adverse drug reactions for Nicotine Replacement Therapy (NRT) products for context. Due to differences in adverse reaction reporting requirements between marketing authorisation holders of nicotine containing licensed medicines and EC producers it is not possible to directly compare the number of reports, therefore we have included this information for context only. Adverse reaction reporting rates are influenced by the seriousness of adverse reactions, their ease of recognition, the extent of use of a particular product, and may be stimulated by promotion and publicity about a product. There is a requirement for all medicinal products to have details of reporting to the Yellow Card Scheme in their product information; however this does not extend to EC.

A total of 37 reports were received with a suspected adverse reaction to EC between 1 January 2015 and 20 October 2017, 263 reports were received associated with a suspected adverse drug reaction to NRT during the same reporting period (Figure 31). EC reports listed 23 EC or e-liquid brands (two brands were indicated twice and it was unreported in 12 cases). The dose of e-liquid content was reported in 14 cases and ranged from 3-24mg (mean= 12.5mg). As reported in Chapter 6, there are approximately 2.9 million adult EC users in GB in 2017. In the same survey (ASH-A) in 2016 1.18% of participants responded that they had “tried NRT products and still use them” from which we can estimate that approximately 600,000 people were using NRT in GB.

Figure 31: Number of reports of a suspected adverse reaction to EC or NRT



It is not possible to determine from this data source if an EC or NRT caused or contributed to a suspected adverse reaction or if it was coincidental. We also do not have information if the EC user was also a smoker or if the NRT user was a smoker and/or used an EC. There may also be differences between propensity to report EC and NRT suspected adverse reactions, for example if consumers are more likely to perceive EC as a consumer product than medicinal, compared to NRT. As ECs are not subject to the same regulations around safety reporting as licensed medication there is no legal obligation for manufacturers to provide the MHRA with reports; therefore it is not possible to directly compare two different products.

Between 2015 and 2017, the 37 reports included 99 suspected adverse reactions (with many individuals reporting multiple adverse reactions such as nausea and headache). The most commonly reported adverse reaction related to gastrointestinal disturbance (n=19, eg nausea) and respiratory problems (n=17, eg cough). One report was of a non-fatal cardiac arrest. Additional data from the Yellow Card Scheme noted that this patient had a relevant cardiac history. In the same reporting period, the 263 NRT reports included 649 suspected adverse drug reactions including one report of suicide where NRT was recorded.

Adverse reaction reports from research studies

In the most recent Cochrane systematic review of the effect of EC on cessation (see chapter 7 for details about primary studies), Hartmann-Boyce and colleagues (171) concluded that none of the studies included in the review found that smokers who used

EC for up to two years had an increased health risk compared to smokers who did not use EC. Ten studies included in the review assessed adverse effects; the findings are described narratively in the review and were not subject to a meta-analysis. In an RCT by Bullen and colleagues (189) the event rate was 0·8 events per person month in the nicotine EC group and NRT patch group, and 0·9 in placebo EC group and the difference was not significant (incidence rate ratio 1·05, 95% CI 0·82–1·34, p=0·7). In an RCT by Caponnetto (190) there was no difference in the frequency of adverse events at three or 12-month follow-up between the three groups receiving 1) an EC containing a 7.2mg nicotine cartridge for 12 weeks; 2) an EC containing a 7.2mg nicotine cartridge for six weeks and 3) a nicotine free EC for 12 weeks. The frequency of adverse events decreased significantly over time, with the exception of throat irritation. Eight cohort studies reported they assessed adverse effects though only five provided numbers and/or proportions of adverse events (189, 190, 239-243). Duration of EC use for these five studies was between one week and 6 months and the most common adverse effects reported were dry cough, mouth and throat irritation.

Overall effects of EC vapour exposure in users

In the absence of long-term use data, the RCP discussed the likely effects of EC use, in relation to the main constituents of concern. The RCP report (68) commented that most reviews raising concerns about constituents, related to their presence, rather than absolute levels which are "*generally the more important determinant of toxicity*". They commented that all of the constituents identified were at lower levels than in cigarette smoke, but that long-term use of even these low levels could be problematic although "*the magnitude of these risks relative to those of sustained tobacco smoking is likely to be small*".

Recent studies

Animal and cell studies

A recent study (244) exposed laboratory rats weighing around 250 grams to a variable voltage EC with a setting that is avoided by human users when using the particular device used in the study (15 Watts). The volume of exposure to the animals (6-second puffs with 5-second inter-puff interval delivered for 5 days a week for 4 weeks) was also discordant with the puffing regime observed in people who use EC. In comparison, EC users typically take puffs of under 3 seconds with 18 second inter-puff intervals (245). Also, there was no comparison with rats exposed to tobacco smoke. The authors detected a range of effects. The title of the paper ('*E-cigarettes induce toxicological effects that can raise the cancer risk*') did not mention that the study focused on animals forced to vape in these conditions, rather than human EC users. The abstract concluded '*Our results demonstrate that exposure to e-cigs could endanger human*

health, particularly among younger more vulnerable consumers' (244), which did not appear to be borne out by the study.

Another study exposed cells to EC vapour or cigarette smoke (246) and found that EC vapour generated some damage after several weeks of exposure, while smoke killed the cells within 24 hours. The abstract did not mention the cigarette smoke results and the press release claimed that the study showed the dangers of vaping.

Composition of EC and EC aerosol

A recent study (247) was accompanied by a press release claiming that 'cancer-causing benzene was found in EC vapours operated at high power'. The authors did not find any benzene in vapour from cartridge-based EC that used benzoic acid (this can be transformed to benzene, but this does not seem to happen at normal vaping temperatures). They then created their own benzoic acid-containing e-liquid and submitted it to high 'dry puff' temperatures and this did generate benzene - albeit in levels lower than those in ambient air (248).

In a separate study (249), published data on emissions from cigarettes and EC and their cancer potencies were used to calculate lifetime cancer risk using daily consumption estimates. EC cancer potencies were largely found to be only a small fraction of those of smoking (0.4%). Where findings exceeded 1% of the risks of smoking, the relationship between formaldehyde levels and user aversion (248) suggests that they were associated with dry puffs.

Studies with EC users

Biomarker data

A presentation at a meeting of American Urological Association in 2017 reported finding two out of five putative carcinogens in the urine of 12 of 13 EC users. It is not clear what the levels of the carcinogens were – only the abstract of the conference presentation was published (250) - but both chemicals (o-toluidine and 2-naphthylamine) are normally found in urine of non-smokers as well (251). Neither has been reported in EC liquid or aerosol so far, so their presence or absence remains to be verified.

A comparison was recently published of biomarkers of nicotine and a range of carcinogens and toxins - three TSNAs and 14 Volatile Organic Compounds (VOCs, including aldehydes and acrolein, a major contributor to the respiratory effects of smoking)- in the body fluids of smokers, EC users who stopped smoking, NRT users who stopped smoking, and dual users of EC or NRT and cigarettes (129). There were no differences in nicotine intake. NRT-only and EC-only users had significantly lower

levels of all biomarkers than groups that continued to smoke. The messages from this study were that: i) EC only users were comparable to NRT users in terms of exposure to the toxins and carcinogens studied; ii) dual users did not differ in toxin intake from smokers and should be encouraged to stop smoking altogether. For the latter finding, it is not known whether the dual users were heavier smokers prior to taking up EC and further research is needed to explore toxin intake across the range of dual use (eg predominantly smokers or predominantly EC users).

A recent study of smokers who switched to vaping for two weeks, supported these findings. There was no change in nicotine intake, but a substantial reduction in exposure to a range of carcinogens and toxicants (252).

Other data from switching/cessation studies

Several small sample or uncontrolled studies have suggested some benefits in smokers switching to vaping on some respiratory and other measures. Smokers who switched to vaping during the ECLAT study in Italy (Chapter 7) and who had elevated blood pressure initially lowered their systolic blood pressure compared to baseline (253). A tobacco – industry funded study randomised smokers to switch partially or completely to vaping or stop using nicotine products altogether for a period of five days (15 smokers per study condition). The study findings suggested little difference between vapers and abstainers in terms of blood pressure, heart rate, lung function (one-second forced expiratory volume and forced vital capacity), exhaled CO and nitrous oxide (254).

An uncontrolled longitudinal study of 16 smokers with asthma who switched to vaping found improvements in lung function and respiratory symptoms which were maintained up to 24 months after switching (255). This was also observed in dual users.

An on-line survey asked established EC users about any changes in the incidence of respiratory infections following their switch to vaping (256): 29% reported no change, 5% reported worsening, and 66% reported an improvement.

Other data from adolescent studies

Adolescents who tried EC were reported to have increased rates of '*chronic bronchitic symptoms*' (257). Participants were asked about wheezing, cough, phlegm and 'bronchitis' (definition not provided). The unadjusted analysis suggested an association between trying an EC in the past three months and bronchitis, but this association disappeared when smoking status was controlled for. EC experimentation in the past remained associated with 'bronchitis' in the current year, but also with a significant decrease in wheezing.

Self-reported asthma symptoms among adolescents were associated with current EC use even after controlling for smoking within the past 30 days in one study(258). Past asthma was significantly associated with current EC use which suggests confounding. Further studies are needed in this area.

Summary

In summary, a study of cancer potencies of EC emissions suggested that these are largely less than 0.4% of smoking. There are no similar data-based estimates available for cardiovascular and lung risks. There are chemicals whose presence or absence in EC vapour remains to be assessed, but the main carcinogens and toxins that are inhaled by smokers have been detected in smokers who switched to EC use at levels that are much lower and similar to those in NRT users. Adolescents who tried vaping reported more respiratory symptoms than those who did not. Some small scale or uncontrolled studies have noted improvements in asthma and in respiratory infections in smokers who switched to vaping, but more research is needed in this area.

Propylene glycol (PG) and glycerine

Propylene glycol and glycerine, both organic compounds, are used in varying proportions to make the e-liquids for EC. The RCP report (3) summarised that in relation to both PG and glycerine, studies with animals have been generally reassuring in relation to health consequences. There was some evidence, from one study in humans, that PG was an airways irritant and a further one of a relationship between exposure in the home and asthma and rhinitis in children. Glasser (73) reported that PG and vegetable glycerine in EC liquids were not cytotoxic for any human and animal cell types. Indeed, a recent case study reported a resolution of recurrent tonsillitis in a non-smoker who started to use EC, proposing that such effects could be due to bactericidal properties of PG. It has been suggested that a controlled trial with nicotine free EC in non-smoking patients (so they are not given nicotine) with recurrent throat infections could provide more definitive answers (259).

Aldehydes

Heating PG or glycerine can release aldehydes such as formaldehyde, acrolein and acetaldehyde, which are also produced during smoking. The 2015 PHE report discussed the phenomenon of ‘dry puff’ when the e-liquid is overheated which creates an aversive taste that EC users avoid. A study published at the end of 2015 (260) which used these conditions reported that, at a maximum power setting of a variable voltage EC, the EC emitted up to 15 times more formaldehyde than tobacco cigarettes. EC users however do not vape under these conditions. The phenomenon has been compared to toasters that can burn toasts so severely that the resulting char contains a range of carcinogens, but the taste would be so aversive that people would be very

unlikely to eat it. In a recent replication of the above study, using the same apparatus and conditions, experienced EC users reported dry puffs well below the power setting at which high aldehyde levels were detected (248).

Recent studies

Composition of EC and EC aerosol

A recent study also reported very high aldehyde emissions, from an EC using a top-coil device and silica wick, operated at 3.8 and 4.8V (261). The results were unprecedented and an attempt at replication using even higher settings failed to replicate the phenomenon (262). The same settings in newer devices which do not overheat the e-liquid, generate aldehyde emissions that are much below regulatory limits and much lower than in cigarette smoke (262). This tallies with a study showing that newer EC devices that use bottom coils produce less aldehydes than earlier EC devices (263).

Another study (264) found that aldehydes in EC aerosol generated at normal settings were either absent or present at low levels, well below safety limits for cumulative exposure that is normally used for assessing exposure hazards. However, levels of one of these aldehydes, formaldehyde, exceeded a threshold (the American Conference of Governmental Industrial Hygienists acute (one inhalation) exposure) ceiling limit of 0.3 ppm (0.38mg/m3) in over 50% of the samples and the median was nearly twice as high as the ceiling limit. This appeared of concern but no comparison with smoking was provided. Smokers are commonly exposed to acute concentrations of 60-130 mg/m3, ie at least a hundred times higher (265). In addition to this, the acute exposure presented as if it was exceeding the exposure limit was in fact far below the ceiling limit. The authors' calculation assumed that the full inhalation consists of the EC puff. In reality, 45-80mL puffs from EC get mixed with air so that the resulting 500mL inhalation dilutes the puff contents at least six-fold.

Another recent study compared tobacco smoke and six e-liquid refills and their resultant aerosol emissions (using a realistic setting and puffing regime) on a range of chemical constituents (266). The e-liquids were accurately labelled and contained none or only a very small fraction of potentially harmful chemicals including trace elements, metals, pesticides and polycyclic aromatic hydrocarbons (PAHs) compared to tobacco smoke. Compared to tobacco smoke, levels of carbonyls were <1 vs 1,540 ng/mL for acetaldehyde; none to 2.2 vs 171 ng/mL for acrolein and 0.4 to 1.5 vs 82ng/mL for formaldehyde.

Studies with EC users

One of the aldehydes, acrolein, that is considered to present a particularly strong health risk as a potent respiratory irritant, produces a specific and stable primary metabolite

(3-HPMA) and this allows estimates of its actual intake in EC users. The 2015 PHE report included studies which demonstrated lower aldehyde including acrolein levels in switchers (smoking to vaping) and dual users (267, 268). These findings have now been confirmed by further studies which have found levels in EC users that are much lower than those in smokers and similar to those in non-smokers ((252) and (129) described above).

Summary

In summary, although EC can release aldehydes and the levels can be high if the e-liquid is overheated, the overheating generates an aversive taste and this ensures that such emissions are avoided. At normal vaping temperatures, aldehyde content in EC aerosol is only a small fraction of levels inhaled by smokers.

Flavours

The RCP report summarised that flavours used in e-liquids are generally recognised as safe (GRAS) but this is in relation to eating or drinking, rather than inhalation following being heated.

One of the most commonly heard safety concerns about flavourings used in e-liquids is that flavours that contain diacetyl might cause bronchiolitis obliterans (also referred to as *'popcorn lung)*', a serious disease that has been linked to the exposure to high levels of this chemical in popcorn plant workers. Diacetyl has been detected in some EC flavourings, but at hundreds of times lower levels than observed in cigarette smoke (269). Given that even at these levels, smoking is not a major risk factor for this rare disease, the diacetyl content in EC flavourings is unlikely to pose much risk. In any case though, manufacturers are now avoiding flavourings that use this. The Glasser review (73) reported that in cytotoxicity studies, cinnamon flavour was found to be the most cytotoxic when comparing different flavours. Concerns about tobacco flavoured e-liquids having potentially higher tobacco specific nitrosamine (TSNA) levels do not appear to be founded; one study found that tobacco flavoured e-liquids (sometimes made through using natural extracts of tobacco), did not have higher TSNAs but possible higher nitrate content than other e-liquids; nevertheless they were all consistently (orders of magnitude) lower than levels in tobacco smoke (270).

Recent studies

Animal and cell studies

Several in-vitro studies have examined flavourings. For example, cells which were exposed to direct contact with flavouring chemicals (not EC aerosol) for 24 hours

showed signs of damage (271). Similar results were reported with directly exposed human umbilical vein endothelial cells. Some flavourings showed some negative impact, but less than tobacco smoke, even at high EC extract concentrations (272).

In another study, bronchial epithelial cells were exposed to EC aerosol with various flavourings, tobacco smoke or air. Some flavourings in EC aerosol generated adverse effects on the cells, but again this was less than tobacco smoke (273). The actual levels of chemical constituents responsible for the effect were not established. It is not known whether EC release higher levels of relevant compounds than occupational safety limits, and this issue warrants further attention.

The exact relevance of these cell studies for human vaping is unclear. However, these types of studies can help to provide information on the relative risks of different flavourings overall, which could be used by EC users for guidance and provides information for quality standards.

Composition of EC and EC aerosol

A new concern was raised by a study that reported that e-liquid flavourings released high levels of aldehydes (274). Such levels were previously only found with dry puffs as discussed above in the section on aldehydes. In this instance, the authors reported that while flavoured e-liquids produced aldehydes, unflavoured e-liquids used with the same device settings released no aldehydes at all, suggesting that it was the flavours which were causing the aldehyde production. The report is in contrast to other studies that detected no such phenomenon (275, 276). Indeed, the Klager and colleagues (264) study reported above, looked specifically at correlations between a range of flavourings and aldehydes and detected no significant relationship.

We are aware of a recent replication of the original study using the same EC device and e-liquids. The manuscript has been submitted for publication (277). One of the flavoured liquids generated aldehydes at levels statistically higher than the unflavoured sample, but at very low levels, much below environmental safety limits and several-fold lower than in the replicated study. The replication results tally with previous studies and suggest that the earlier finding was likely to be an artefact of problems with laboratory procedures, equipment or data analysis. Further studies of effects of flavouring on aldehydes will provide definitive answers.

Summary

In summary, while no clear evidence that specific flavourings pose health risks has been identified so far, there are suggestions that inhaled chemicals in some flavourings could be a source of preventable risks. Further research on the presence and effects of inhaled flavourings is warranted.

Metals

Previous studies found several metals in EC liquid and aerosol, but at very low levels, comparable to those in nicotine inhaler, and considerably below the levels found in cigarette smoke. A comparison of the levels detected in these studies with several safety norms confirmed this (278). The RCP report (68) concluded that this was probably not a major concern because of the low levels and that they could be reduced further by manufacturing improvements. These were perceived to be unlikely to pose any risks to health.

Recent studies

Composition of EC and EC aerosol

A recent study (279) analysed metals in e-liquids removed from cartridges of five ‘cigalike’ EC brands. (The pre-filled cartridges in which e-liquid is exposed to metal continuously for weeks to months can be expected to have higher metal content than refillable tank systems). The authors presented a list of dangers associated with various metals when ingested or inhaled in large doses, but the study provided no indication of whether the levels actually detected could pose any risks. The levels were expressed in different metrics than in previous studies. Using conservative assumptions, they are concordant with previous findings and so signal very low risk. The study, however, identified one issue that is of relevance. EC products differed in metal emissions. This could be related to the age of different cartridges, but also to materials used in atomisers and coils, and requires further study.

A later study (280) confirmed that EC products differ in nickel and chromium levels released in the aerosol from the heating coil and that this is reflected in salivary and, to a lesser extent, also in urinary levels of these metals in EC users using these products. This does not necessarily signal a health risk as the metal levels were very low, with urine nickel concentrations lower than population norms. Levels of chromium (which is non-toxic apart from chromium IV that is unlikely to be generated by EC) were higher, but still in the range that could be influenced by environment and diet. As with the previous study though, the finding is informative as it suggests that manufacturing practices can and should be adopted that keep metal emissions to a minimum, and users should avoid nickel or nichrome coils.

Summary

In summary, the levels of metals identified in EC aerosol do not give rise to any significant safety concerns. However, product differences show that metal emissions,

however small, are unnecessary. EC that generate minimal metal emissions should become an industry standard.

Passive vaping

There is no side-stream vapour emitted from the end of EC, just the exhaled aerosol entering the atmosphere. In the 2015 PHE report, we discussed a particular concern about nicotine being deposited on surfaces raised from one study, but this did not reflect levels of vaping and had indicated very low levels; we concluded that there were no identified health risks to bystanders. Particle exposure was another concern that we discussed in the 2015 PHE report in which we concluded that it was the content of the particles, rather than their presence or size which had health implications. Given the low levels of toxins we report above in the EC aerosol, there are unlikely to be health implications. The Glasser review (73) found that second-hand vapour studies showed that non-users may be exposed to nicotine vapour but the level of exposure was low, and exposure to other compounds were also very low, or at trace or non-detectable levels when compared with second-hand smoke. Glasser and colleagues (73) however reported that it was unclear if any levels were sufficient to be of biological concern to humans and that more definitive studies were needed before conclusions about harm can be made. We discuss several new studies below.

Recent studies

Composition of EC and EC aerosol

A recent modelling of passive exposure suggested that bystanders could be exposed to aldehydes (281), but the modelling was based on the study discussed above that used a laboratory set-up generating dry puffs (261).

Studies with EC users

A recent study (tobacco industry funded) examined air in an experimental chamber with air exchange rate typical for office buildings where 10-11 EC users used different EC devices for four hours (282). A wide range of potential toxicants was evaluated. Negligible levels of chemicals were detected, which were much below permissible exposure limits. In addition, with regards to concerns about metals in EC aerosol reviewed above, no emissions of nickel or chromium were detected. There was also no significant increase in nicotine deposits on surfaces.

A study analysing the exhaled breath of EC users reported that of chemicals inhaled, only 6% of nicotine, 8% of PG and 16% of glycerine was exhaled (79). This therefore suggests that 94% of nicotine is retained by EC users. Indeed, a study that examined

surface samples from homes of EC users found no difference in nicotine levels compared to homes of non-tobacco users (283).

In relation to particles, an extensive study measured indoor air quality in 193 households with children under 14 to assess the impact of a range of occupant activities and home characteristics (284). The study included week-long airborne particle measurements. Cigarette and marijuana smoking as well as other activities such as burning candles and variables such as home type affected mean weekly particle counts, but vaping (present in 43 out of 193 homes) had no discernible effect.

Concentrations of vaping-related chemicals in the air of a vape shop were well below occupational exposure limits and nicotine was undetectable (285). Other unpublished reports on the results of checking air quality in vape shops by California Department of Public Health and by the National Institute for Occupational Safety and Health in Cincinnati reported that even in a shop with relatively poor ventilation where 13 customers used EC during the shift, creating a visible cloud, a range of flavouring compounds and formaldehyde were all below the lowest occupational exposure limit and nicotine was virtually undetectable (285).

Summary

In summary, to date there have been no identified health risks of passive vaping to bystanders.

Comparison of studies assessing biomarkers for exposure

In this section we summarise evidence from twelve, mostly new, studies, with different methodologies and designs (Table 21), that evaluated differences in four candidate biomarkers for exposure between smokers and EC users (286). The participants varied across the studies, in some cases smokers who used EC for just a few hours, in others, smokers who had switched to EC for a year or more. Unadjusted raw data was used and the amount for EC users was divided by the amount observed for smokers, to give a percentage reduction compared with smoking. Levels observed in people not smoking (either smokers abstaining or never-smokers) are taken into account only in the final section. Four of the studies were funded by the manufacturer of ECs tested, presenting a conflict of interest which may bias findings. It should be emphasised that this assessment has not been peer reviewed but a version of it was presented at a recent conference (286).

Table 21. Study characteristics

Authors	Design	Duration	Population	Groups/comparisons	Funding
Cravo et al, 2016 (287)	RCT	12 weeks	Smokers, n=387	Switched to EC use, n=286 Continued cigarette smoking, n=101 (Part in confinement[1])	Fontem Ventures B.V., subsidiary of Imperial Brands plc
D'Ruiz et al, 2016 (288) O'Connell et al, 2016 (289)	RCT	5 days	Smokers, n=105	Switched to EC use, n=45 Switched to dual use EC + cigarette, n=45 Nicotine abstinence, n=15 (All in confinement)	Fontem Ventures B.V., subsidiary of Imperial Brands plc
Goniewicz et al, 2017 (252)	Longitudinal cohort	2 weeks	Smokers, n=20	Before (baseline) and after encouragement to switch to using EC (provided)	Ministry of Science and Higher Education, Poland; National Institutes of Health, US
Hecht et al, 2015 [H] (267) Kotandeniya et al, 2015 [K] (290)	Historical comparison	N/A	EC users, n=55 Smokers, n=262	n=28 [H] +27 [K] Smokers, n=224 [H] +38 [K]	National Cancer Institute at the National Institutes of Health, US

Authors	Design	Duration	Population	Groups/comparisons	Funding
Martin et al, 2016 (291)	Cross-sectional	N/A	EC users (regularly for ≥6 months and ≤5 cigarettes per week), smokers, non-smokers, n=39	EC users, n=12 Smokers, n=14 Non-smokers, n= 13	National Institutes of Health, US; Foods and Drug Administration, Center for Tobacco Products, US
McRobbie et al, 2015 (268)	Longitudinal cohort	4 weeks	Smokers, n=33, supported to quit	Baseline before quit date compared with follow-up 4 weeks post quit date, EC provided from quit date. At follow-up: Not smoking, using EC, n=16; smoking, using EC, n=17	UK Medicines and Healthcare Products Regulatory Agency
Pulvers et al, 2016 (292)	Longitudinal cohort	4 weeks	Smokers willing to switch to EC, n=40	Before (baseline) and after encouragement to switch to EC (provided). Throughout follow-up 6 exclusive EC users.	University of Minnesota, US; California State University San Marcos, US
Shahab et al, 2017 (129) Nelson et al, 2015 (293) Additional unpublished data[2]	Cross-sectional	N/A	EC users (≥6 months use), NRT users (≥6 months use), smokers, ex-smokers (≥6 months quit), n=181/n=144 Never-smokers[2]	EC-only users (ex-smokers), n=36 EC users and smokers, n=36 NRT users and smokers, n=36 NRT-only users (ex-smoker), n=36 Smokers, no NRT or EC, n=37 (only in Shahab et al)	Cancer Research UK; Society for the Study of Addiction, UK; National Institute on Drug Abuse and National Cancer Institute, National Institutes of Health, US; Roswell Park Alliance Foundation, US

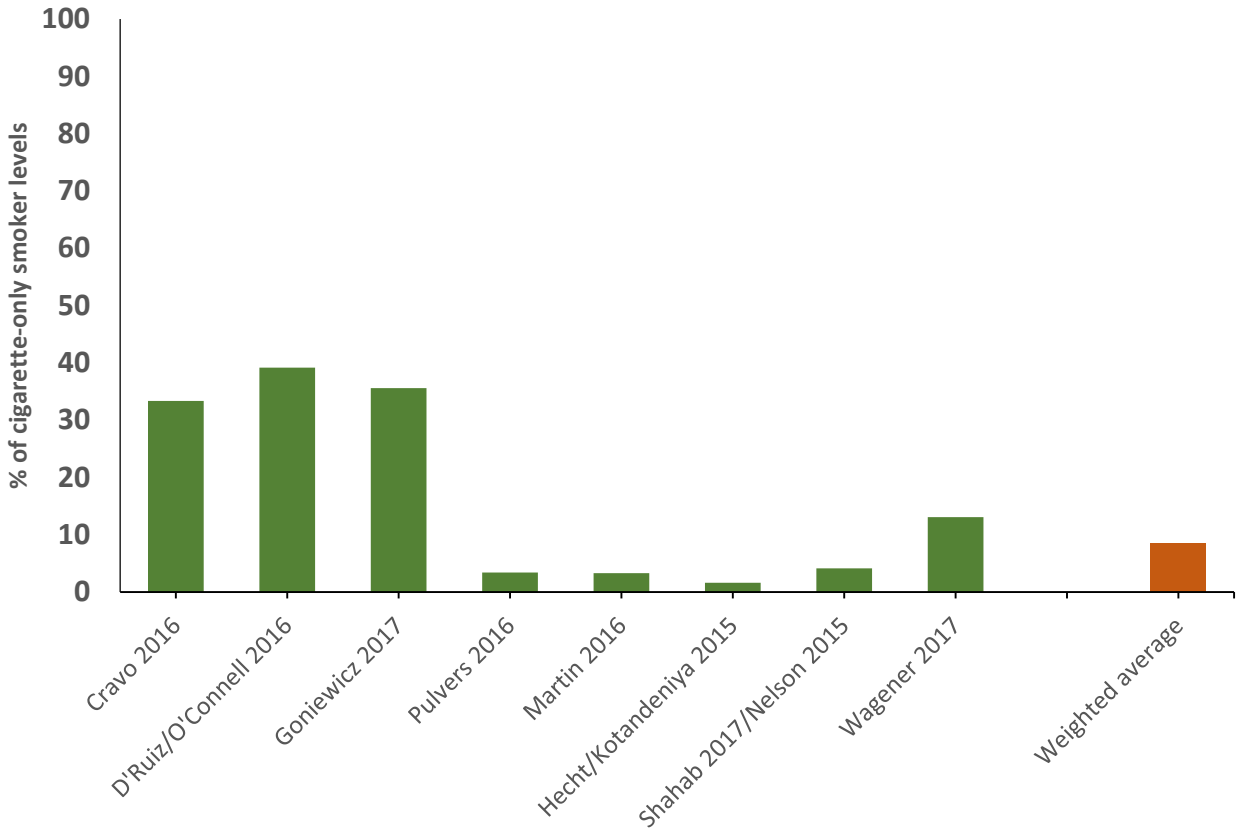
Authors	Design	Duration	Population	Groups/comparisons	Funding
Wagener et al, 2017 (294)	Cross-sectional	12h abstinence followed by 2h EC use session	Smokers, EC users, n=30	EC users, n=20 Smokers, n=10	Intramural funds, US; Oklahoma Tobacco Settlement Endowment Trust, US; Oklahoma Shared Clinical and Translational Resource, US
Vansickel et al, 2010 (295)	Cross-over	For each product 12h abstinence followed by 2.5h use session	Smokers, n=32	EC use Cigarette Unlit cigarette	National Cancer Institute, US Public Health Service
Walele et al, 2016 (296)	Cross-over	For each product overnight abstinence followed by 3h use session	Smokers, n=12	EC NRT inhalator Cigarette (All in confinement)	Fontem Ventures, Imperial Tobacco Group [Imperial Brands]
Yan & D'Ruiz, 2015 (297)	Cross-over	For each product: 36h abstinence followed by 1.5h use session	Smokers, n=23	EC Cigarette	LOEC Inc, subsidiary of Lorillard [BAT]

[1] *Confinement means that participant stayed in a controlled environment and were not given access to other products.*
[2] *Available on request.*

4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol (NNAL)

NNAL is a marker for exposure to nitrosamines (nicotine-derived nitrosamine ketone (NNK)) which are potent lung carcinogens. It is specific to tobacco use and linked to subsequent cancer risk (298) and its urinary half-life is about 10 days (299). There were 10 published papers reporting on eight studies between 2015 and 2017 that evaluated tank-type EC (total n=658). Figure 32 shows NNAL levels in EC users as a percentage of NNAL levels in those who smoked cigarettes. Overall, there was a 91.4% average difference in NNAL levels (weighted by sample size in each study); this increased to 96.4% when restricting only to those who had been abstinent from smoking for at least four weeks (129, 267, 290, 292, 293).

Figure 32: Level of NNAL in EC use relative to smoking

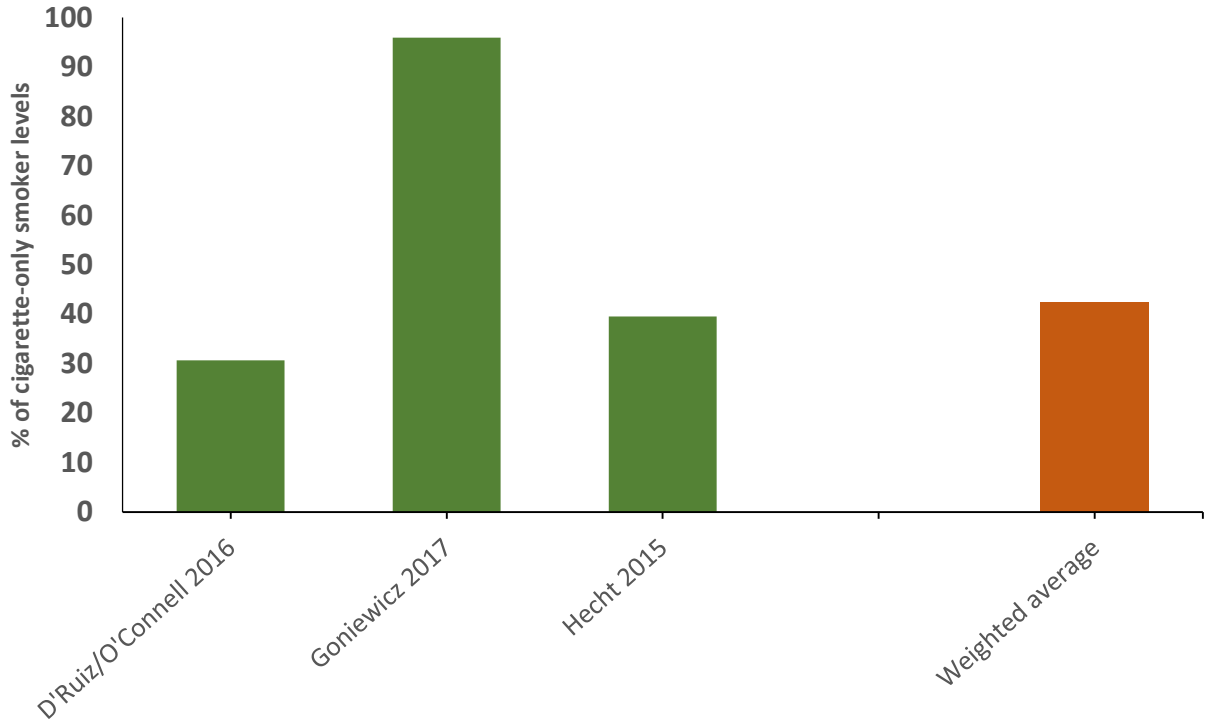


1-hydroxypyrene (1-HOP)

1-HOP is a urinary metabolite of the non-carcinogen pyrene, and is a biomarker for polycyclic aromatic hydrocarbons which include carcinogens such as benzo[a]pyrene (300). Its urinary half-life is about 20 hours (301). There were four papers covering three studies between 2015 and 2017 with a total of 271 participants; mostly evaluating

tank-type EC. The studies showed an average difference in 1-HOP of 57.6% in EC users relative to smokers. However, one of the studies (252) found only a 4.1% difference, although it is important to note that this study did not require abstinence from smoking or substantial reduction in cigarettes smoked (Table 21; Figure 33). Excluding this study resulted in an average difference in 1-HOP of 61.9% in EC users relative to smokers.

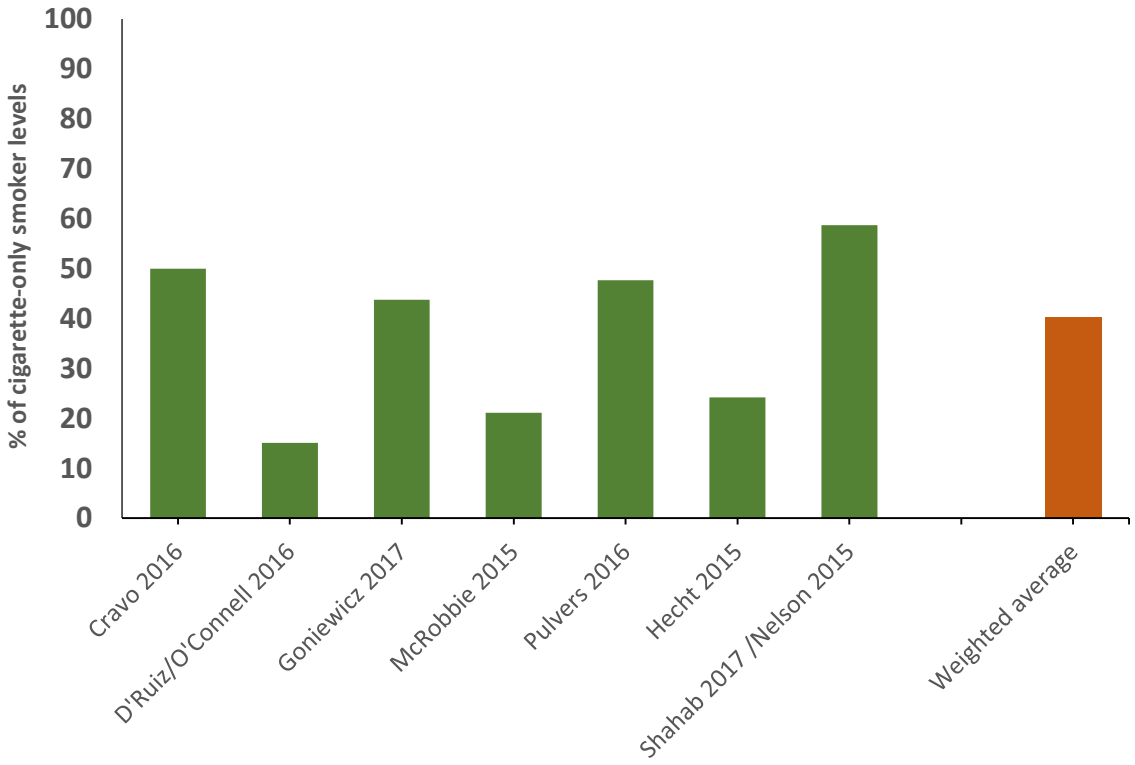
Figure 33: Level of 1-HOP in EC use relative to smoking



3-hydroxypropylmercapturic acid (3-HPMA)

This is a marker of the volatile organic compound acrolein, a potent respiratory irritant (302). It is relatively specific to tobacco use, toxic and is a short-chain aldehyde; several short-chain aldehydes have been linked to cancer (303). Its urinary half-life is about one day (304). There were eight papers covering seven studies published between 2015 and 2017 with 658 participants in total; again mostly evaluating tank-type EC. They found an average difference in 3-HPMA levels of 59.6% in EC users compared to cigarette smokers (Figure 34).

Figure 34: Level of 3-HPMA in EC use relative to smoking

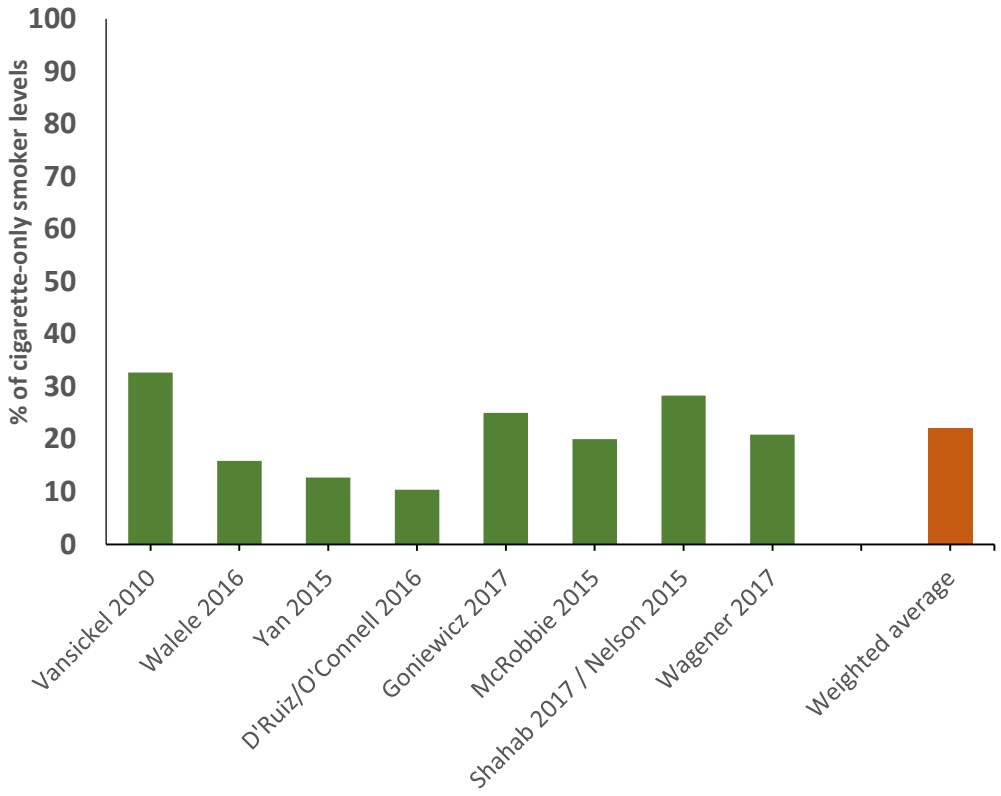


Carbon Monoxide (CO)

CO is a highly toxic gas (265) that is the product of incomplete combustion, produced when smoking tobacco and linked to CVD (305). In exhaled breath it has a half-life of about 5 hours (306).

Between 2010 and 2017, there were nine papers reporting on eight studies (total n=245) measuring exhaled CO levels among EC users; these studies included earlier cigalike and tank-type EC. Across the studies there was an average difference of 77.9% in CO levels (Figure 35).

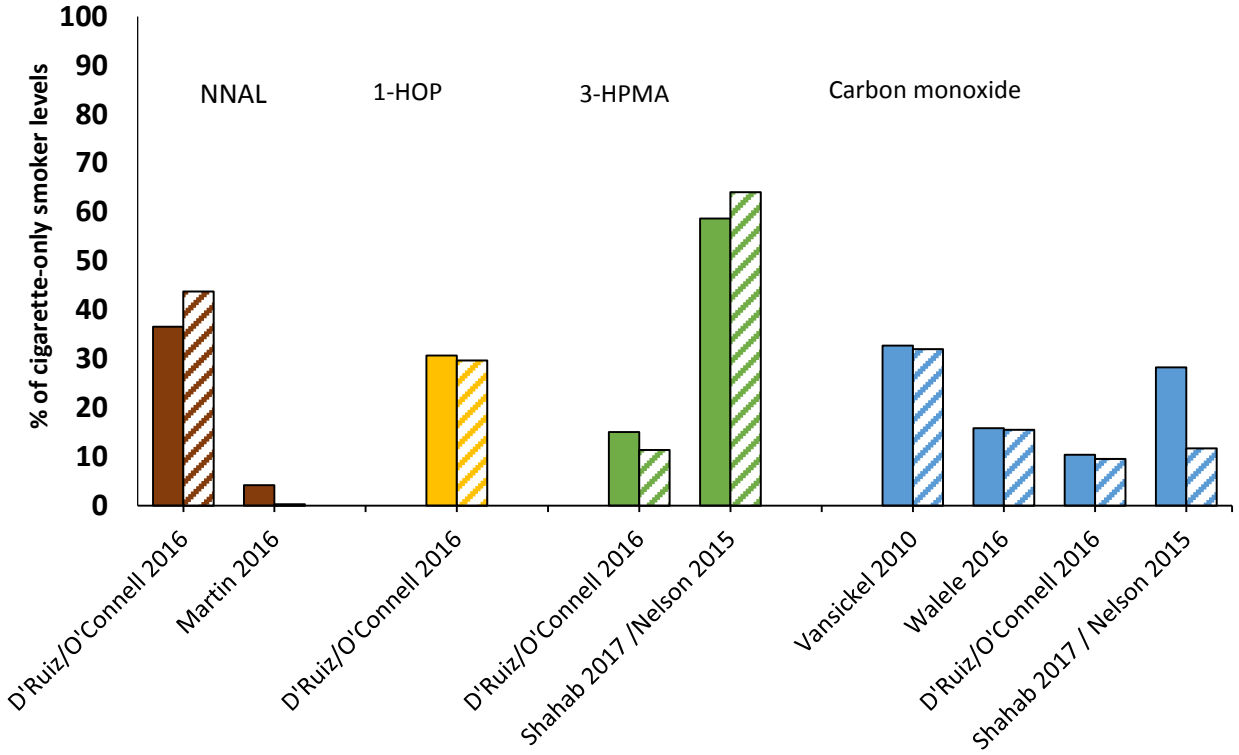
Figure 35: Level of CO in EC use relative to smoking



Comparison with smokers abstaining or non-smoker levels

Importantly, five of the studies also compared the levels of some or all of these biomarkers in smokers who had switched to EC with the levels in non-smokers or smokers abstaining/using NRT, and found those levels comparable (Figure 36). While some comparisons were with smokers only abstaining for a short period (Table 21), overall this suggests how some of these biomarkers have other endogenous and exogenous sources which can result in exposure. Hence there cannot be a reduction of 100% when comparing the risk of EC with smoking.

Figure 36: Levels of biomarkers of exposure in EC use and never-smokers or smokers abstaining relative to smokers.



Notes: Full bars are levels observed in EC use; striped bars are levels observed in non-smoking groups (D'Ruiz/O'Connell nicotine abstinence condition; Martin non-smokers; Shahab/Nelson never smokers; Vansickel unlit cigarette condition ; Walele NRT inhalator condition; see Table 21 for length and details of studies).

Limitations

There are limitations with these data as only a few specific biomarkers are included in these analyses, and it is unclear whether there are linear or threshold effects (ie would a 95% reduction in exposure represent a 95% reduction in harm). Most of the non-smoker comparisons were with smokers abstaining for short periods. It should also be noted that some of the studies were tobacco industry funded. Additionally, the mode of delivery may affect risks of harm, and harm may change with changing patterns of use and products.

Summary

The biomarker data assessed in this section are consistent with significant reductions in harmful constituents and in EC users some biomarkers show similar levels to non-smokers or smokers abstaining from smoking.

Misreporting of scientific studies

Over the past few years, a number of research findings have been presented as documenting serious risks of vaping and received widespread coverage. Of course all studies have strengths and weaknesses in their research designs, and that includes those that demonstrate that EC use is much less harmful than smoking. However, the way the results of some studies with particular limitations have been designed and reported, and then subsequently presented in the media, may have caused serious concerns about EC use as shown by growing misperceptions of the health risks of EC in Chapter 10.

We believe that there are a number of contributory reasons for this:

1. Studies that compare EC and tobacco cigarette exposures and show the latter as much more toxic are not viewed as newsworthy (eg Husari and colleagues (307))
2. Understandably, journals, authors and research organisation press offices are keen to seek publicity for articles in order to gain impact, resulting in press releases. Sometimes, these do not accurately represent the article on which they are based.
3. Study findings can be further exaggerated when discussed in the media.
4. Posters or presentations at conferences, when there is not yet a peer-reviewed article to accompany them, are sometimes reported as if they have been through peer review and taken as definitive findings.

These are some recent headings in the media generated from some of the studies previously described in this chapter:

- *E-cigarettes are no better than regular smoking*' (http://www.dailymail.co.uk/health/article-3377730/E-cigarettes-NO-better-regular-smoking-Toxins-devices-cause-cancer-nicotine-FREE.html)
- '*Cancer alert'* headlines (eg http://www.mirror.co.uk/science/e-cig-cancer-alert-smokers-10004747; http://www.dailymail.co.uk/news/article-4303316/Chemicals-e-cigs-cause-cancer.html
- '*Bladder cancer*' headlines eg http://www.dailymail.co.uk/health/article-4514542/E-cigarette-smokers-high-bladder-cancer-risk.html

None of these headlines would be justifiable from the research studies they refer to. However, it is understandable how some of these headlines were generated from press materials accompanying the papers or, in one case, conference presentation.

As we have seen, the most frequent source of concerns is from animal and in-vitro studies which have unclear relevance for human exposure. They also typically avoided

comparisons with smoking. Often the studies suffer from one or both of two major methodological problems.

The first is that EC exposure was much greater than the level of exposure to which human EC users would be exposed. For example, in in-vitro studies, cells are bathed in e-liquid or exposed directly to EC aerosol. In animal studies, laboratory animals that are a fraction of the size of humans and much more sensitive to nicotine and other chemicals, including strong smells, are exposed to emissions that are of much higher magnitude than those to which human EC users are exposed relative to body weight. The animals are also sometimes severely distressed over extended periods of time. Systemic poisoning and an aftermath of chronic distress are then interpreted as a sign of the toxicity of vaping.

The second problem, as discussed in detail above, is that when the e-liquid is overheated it releases toxic aldehydes, but this is not applicable to human EC users because overheated e-liquid generates acrid aversive tasting emissions which EC users avoid. When the toxic products from overheated e-liquid are detected in the bodies of animals, or affect tissues and cells, this is again claimed to show risks of vaping, despite the fact that EC users do not generate, or absorb, these chemicals.

The consequences of this inaccurate or inadequate reporting are that the general public is misled. This could induce smokers to carry on smoking rather than switching and EC users to relapse to smoking. While such inaccurate reporting is not confined to the tobacco harm reduction and EC field, the impact is rarely as large. Smoking is uniquely dangerous and each year in England around 80,000 smokers die because of tobacco use (2) . There are few other scientific areas where the gains and losses to public health are so high. It is very likely that these reports and headlines are playing a key role in the persistent misperceptions that the public have about the relative risks of EC and tobacco cigarettes as explored in Chapter 10 of this report.

Conclusions

Key findings

- One assessment of the published data on emissions from cigarettes and EC calculated the lifetime cancer risks. It concluded that the cancer potencies of EC were largely under 0.5% of the risk of smoking.
- Comparative risks of cardiovascular disease and lung disease have not been quantified but are likely to be also substantially below the risks of smoking. Among EC users, two studies of biomarker data for acrolein, a potent respiratory irritant, found levels consistent with non-smoking levels.
- There have been some studies with adolescents suggesting respiratory symptoms among EC experimenters. However, small scale or uncontrolled switching studies from smoking to vaping have demonstrated some respiratory improvements.
- EC can release aldehydes if e-liquids are overheated, but the overheating generates an aversive taste.
- To date, there is no clear evidence that specific flavourings pose health risks but there are suggestions that inhalation of some could be a source of preventable risks.
- To date, the levels of metals identified in EC aerosol do not give rise to any significant safety concerns, but metal emissions, however small, are unnecessary.
- Biomarkers of exposure assessed to date are consistent with significant reductions in harmful constituents and for a few biomarkers assessed in this chapter, similar levels to smokers abstaining from smoking or non-smokers were observed.
- One study showed no reductions across a range of biomarkers for dual users (either for nicotine replacement therapy or EC dual users).
- To date, there have been no identified health risks of passive vaping to bystanders.
- Reporting of some academic studies has been misleading.

Implications

Research

- More research is needed with human users about biomarkers of exposure, risk and harm and health effects over time.
- More research with biomarkers across the range of different combinations of dual use is needed.
- Any adverse effects of passive vaping should be monitored.

Policy

- Policy makers and regulators should ensure that EC are manufactured in a way that minimises harm. An advantage of EC is that particular constituents can be removed or minimised in a way that is not feasible with tobacco cigarettes.
- Regulations should therefore be flexible to ensure any emerging evidence of constituent harmfulness can be acted upon, such that products are modified to remove any components shown to pose avoidable risks.
- Consumers and health professionals should be encouraged to use the Yellow Card Scheme for reporting adverse reactions to EC use.
- Vaping poses only a small fraction of the risks of smoking and switching completely from smoking to vaping conveys substantial health benefits over continued smoking. The previous estimate that, based on current knowledge, vaping is at least 95% less harmful than smoking remains a good way to communicate the large difference in relative risk unambiguously so that more smokers are encouraged to make the switch from smoking to vaping. It should be noted that this does not mean EC are safe.
- The lack of difference in biomarkers between dual users and smokers found so far underlines the need to encourage and support dual users to stop smoking altogether.

10 Perceptions of relative harms of nicotine, EC and smoking

Introduction

The 2015 PHE report (5) described an increase over time in the proportion of the population believing EC to be at least as harmful as cigarettes. The objective of this chapter is to update the previous findings with the latest data available for Great Britain for adults and youth and to provide a brief overview of recent findings from other countries.

Evidence from recent GB surveys

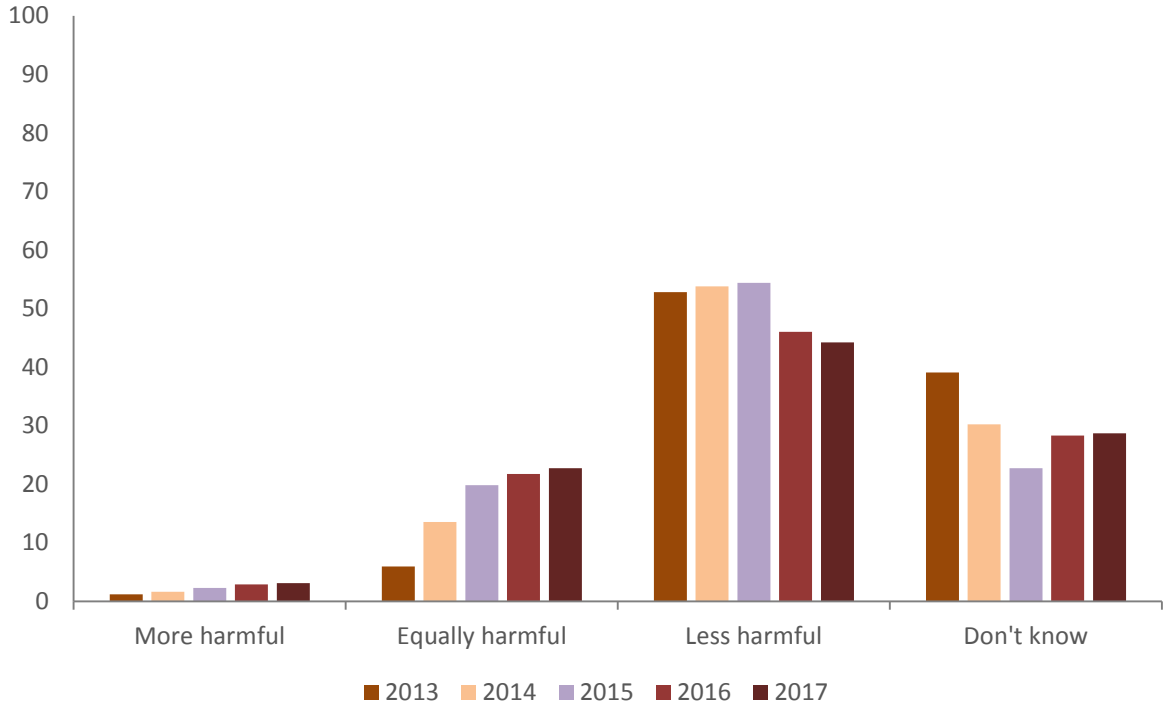
ASH-A, ASH-Y, ONS, STS and the ICGBS all include questions about (relative) harm perceptions of different products.

Adults' perception of harm of EC relative to cigarettes

Among adults in Great Britain, the ASH-A shows that the previously observed trend of increased perceived relative harm of EC has continued (5, 21). In 2017, 44.2% perceived EC as less harmful than cigarettes, the lowest percentage since tracking started in 2013, and 25.8% perceived them to be equally (22.7%) or more harmful (3.1%), which is the highest percentage recorded (28.7% don't know, Figure 37).

The ONS also asked about relative perceived harm among all adults, without providing a 'don't know' option. Here, about 74% responded that EC were less harmful than cigarettes (21.1% about as harmful, 5.1% more harmful). The difference between the two surveys could suggest that if forced to choose a response, respondents are likely to pick less harmful but possibly without particular confidence in this response.

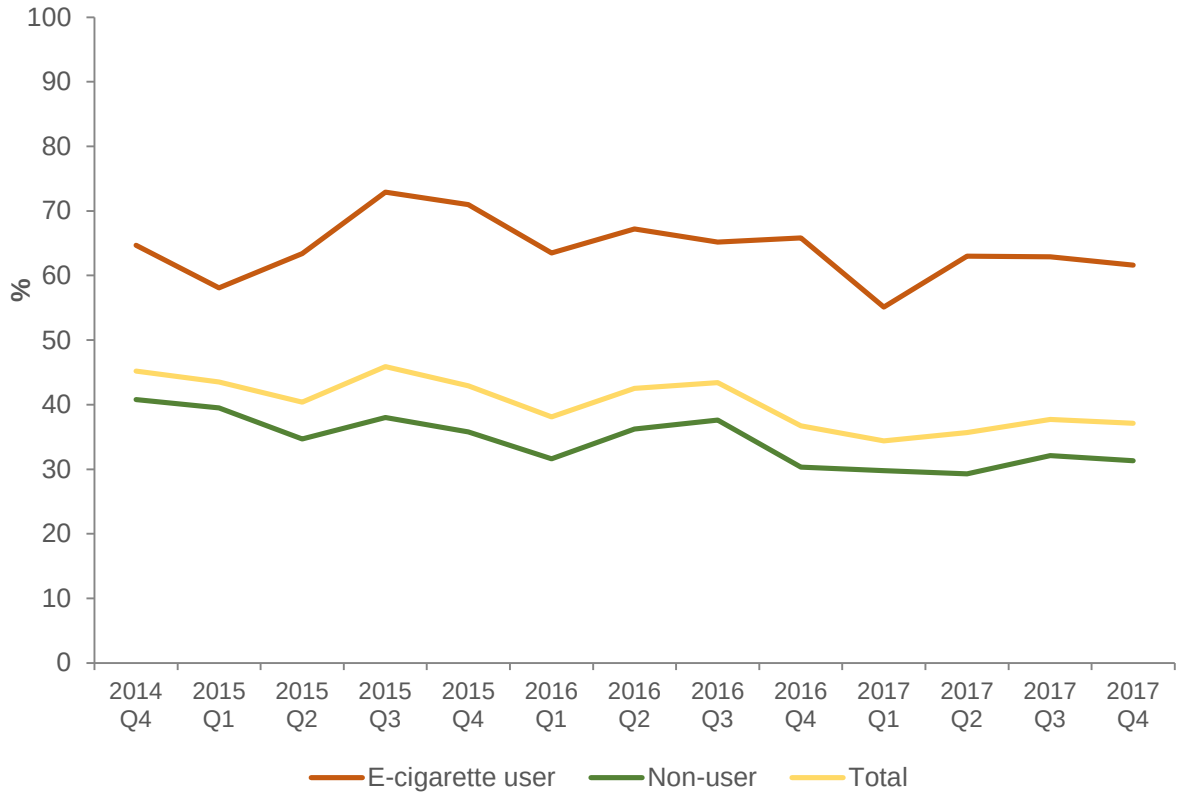
Figure 37: Perception of relative harm of EC compared with cigarettes over time. ASH-A



Notes: Adults aged 18+. Unweighted base sizes in the appendix

A downward trend in accurate understanding of the relative risks of cigarette smoking and EC use has also been observed among current smokers in the STS, where a declining minority believe EC are less harmful than cigarettes (Figure 38). Smokers who also use EC are more likely to perceive EC to be less harmful than smokers not using them.

Figure 38: Perception that EC are less harmful than cigarettes in smokers over time



Notes: STS. N=10,029 current smokers aged 16+

Although accurate perception seems to be a little higher among smokers in the ASH-A 2017 than in the STS, breaking down the ASH-A 2017 data by smoking and EC use status, it becomes apparent that relative harm perceptions of EC are particularly poor among groups who could benefit from EC use. It is lowest among current smokers who have never tried EC, where only one third (33.1%) think that EC are less harmful than cigarettes. Among smokers who tried or used EC in the past and stopped EC use but still smoke, only half (51.5%) think that EC are less harmful than smoking (Table 22). In comparison, 90% of ex-smokers who use EC accurately perceived EC as less harmful than cigarettes.

Table 22: Proportion selecting accurate response by smoking and EC use status. ASH-A 2017

Smoking status	EC use status	EC less harmful than cigarettes, %	NRT less harmful than cigarettes, %[1]	Portion of health risk of smoking due to nicotine – none or very small, %[1]
Never smokers	**Any/all**	**42.4**	**57.9**	**4.6**
	Never used EC	42.0	59.2	9.2
	Ever tried/used[2]	55.8	56.5	4.6
Ex-smokers	**Any/all**	**45.2**	**61.6**	**9.7**
	Never used EC	37.5	61.6	5.9
	Used /tried in the past	58.3	63.0	18.9
	Current EC use	89.8	65.7	30.4
Smokers	**Any/all**	**48.9**	**52.9**	**13.5**
	Never used EC	33.1	53.4	10.6
	Used/tried in the past	51.5	53.7	14.8
	Current EC use	73.9	56.7	18.4

[1] The figures for any/all are in some instances lower than the figures for all subgroups shown; this is because the additional subgroup consisting of those who did not know or provide their vaping status (1.9%) mostly also responded 'don't know' to these questions, thereby lowering the overall average.

[2]Tried or used in the past or currently, combined for never smokers due to small ns, combined unweighted n=110. Unweighted ns for EC question: Never smokers n=6,256, ex-smokers n=4,276, smokers n=1,569.

Notes: Adults aged 18+. Unweighted ns for NRT and nicotine questions: Never smokers n=6,626, ex-smokers n=4,438, smokers n=1,632

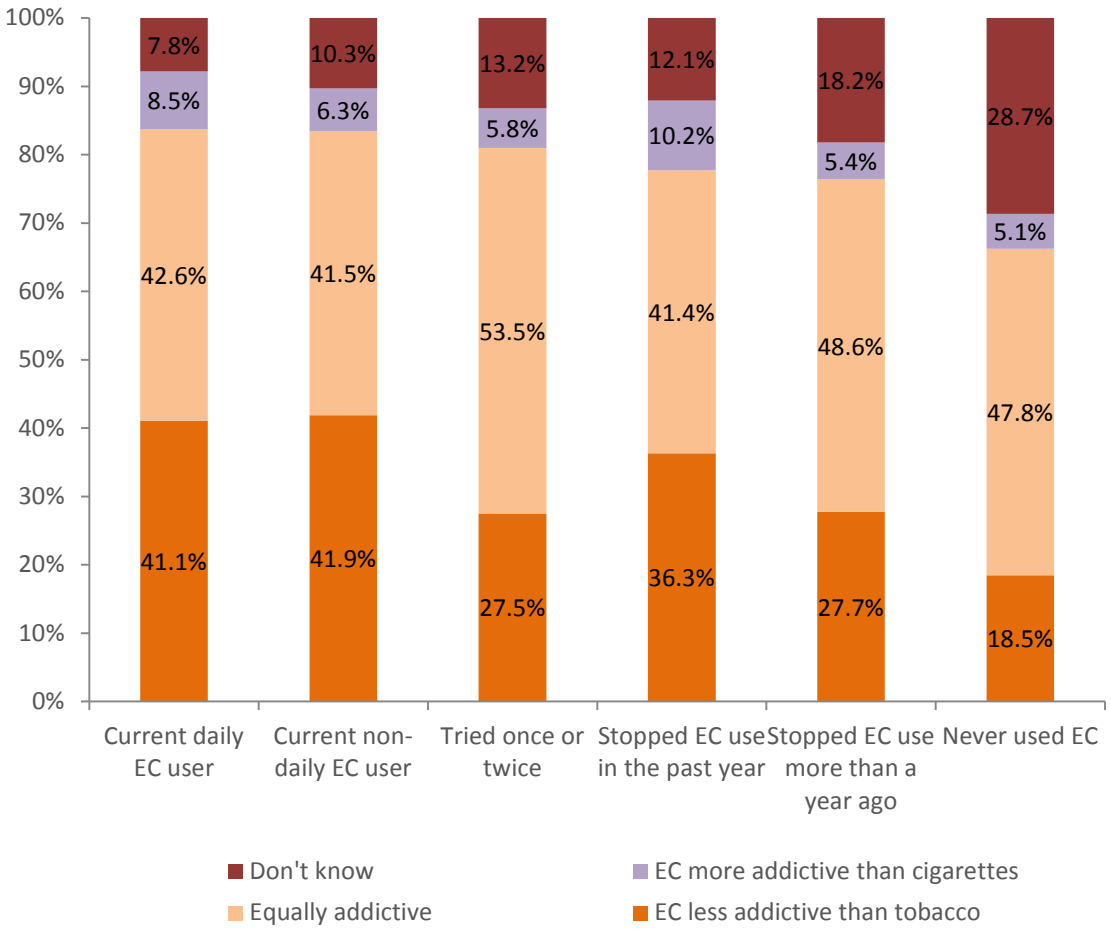
To further assess perception of relative harm and the effect of replacing tobacco cigarettes with vaping, the ICGBS asked respondents to estimate the change in health harms including perception of harm reduction achieved by replacement. Responses differentiated complete replacement (10/10 CPD replaced by EC) and partial replacement (5/10 cigarettes). Very small proportions believed that replacement would increase health harms a little or a lot (3.5% for complete, 3.8% for partial replacement). Considerable minorities thought that complete (12.2%) or partial replacement (18.4%) of cigarettes would not have any effect on health harms; 29.4% and 45.4% respectively responded that health harms would be a little reduced. Only 38% of the sample of smokers and ex-smokers thought that complete replacement would reduce health harms a lot, compared with 15% for partial replacement. While it may be desirable that fewer smokers think that partial replacement will be beneficial, it is striking that only a minority think that their health would benefit from what would in effect be smoking cessation.

Addictiveness

Little evidence has been collected on perceptions of addictiveness of EC. In the ICGBS, 6.3% thought that EC/vaping devices are more addictive than tobacco cigarettes, 47.2% that they are equally addictive, 29.0% that EC are less addictive and 17.5% didn't know. There was some variation across groups with different levels of EC use experience (Figure 39).

Future research should aim to assess to what extent the perception of addictiveness contributes to the misperceptions of relative harmfulness of EC compared with cigarettes.

Figure 39: Perceived addictiveness of EC relative to tobacco cigarettes



Notes: ICGBS 2016. N=3,431 adult smokers, ex-smokers and EC users aged 18+

Perceived health impact of EC on others

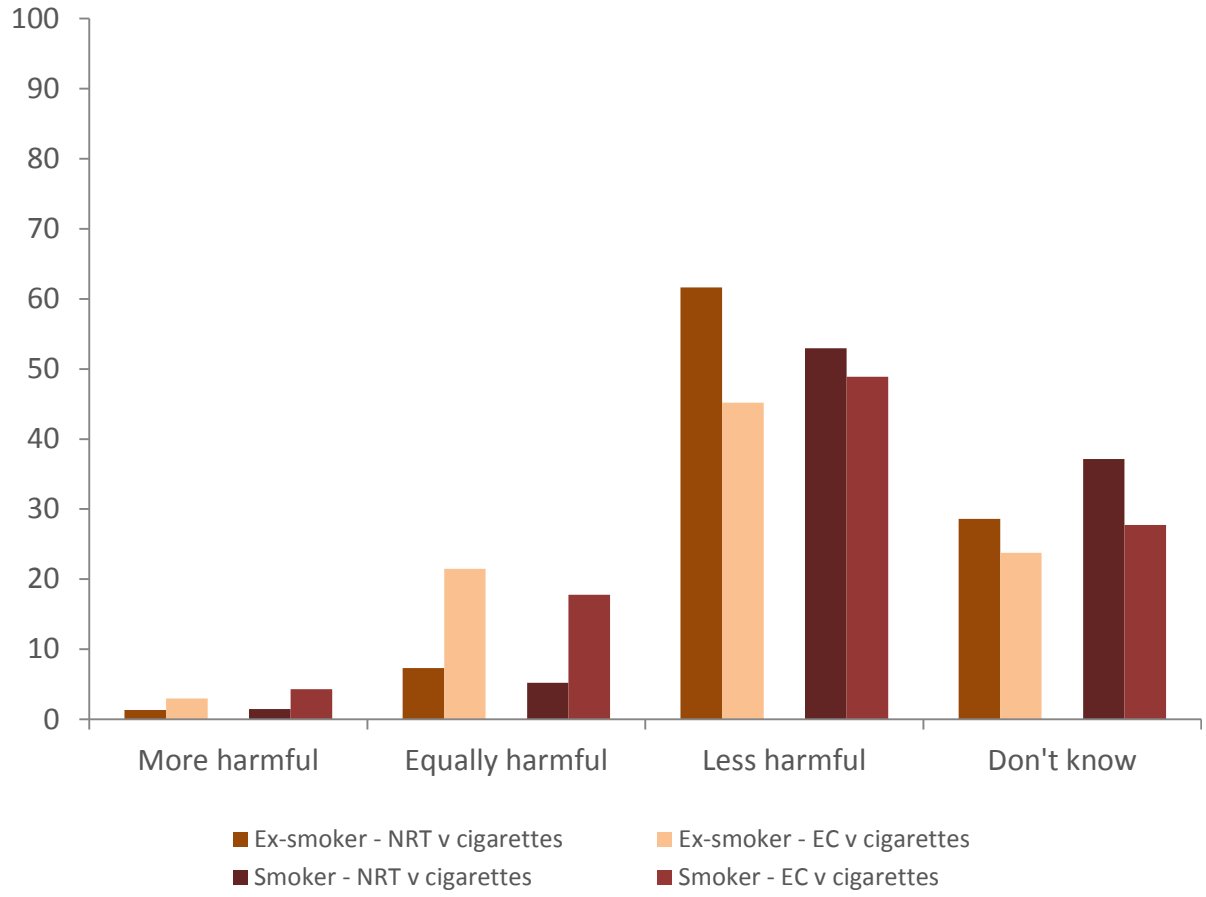
Only the ONS asked about perceptions of health impact of EC on individuals who are exposed to them but do not use them directly. Responses were presented separately for current and ex EC users and those who had never been a user (but may have tried) EC. The latter group was further divided into those who were current or ex-smokers and those who had never smoked. Among ever EC users, 72.9% believed that EC would have no health impact on those exposed second-hand and 23.9% that they would have a damaging impact. Among never EC users who were current or ex-smokers, 53.9% believed EC would have no impact and 42.1% believed they would have a damaging impact. Among never EC users who had never smoked, this was 49.6% and 46.1% respectively. Raw data for this survey were not available, so the data could not be split primarily by smoking status. It would be useful to be able to specifically assess smokers' thoughts on the health impact on others of EC relative to smoking, eg do they think those around them would benefit from not being exposed to smoke but to EC emissions instead?

Perceived relative harm for NRT, EC and cigarettes

Perceived harm for NRT relative to cigarettes is inaccurate in large proportions of the general adult population. In the ASH-A 2017, just over half (58.4%) responded that NRT is any less harmful than smoking cigarettes and there is less variation by smoking and vaping status than for EC harm perception (Table 22). This means that the lack of knowledge extends to smokers and ex-smokers with only small majorities thinking that NRT is less harmful than cigarettes (Figure 40). Particularly among smokers, there is little difference between relative harm perception for NRT (52.9% less harmful than cigarettes) and EC (48.9% less harmful than cigarettes) (Figure 40).

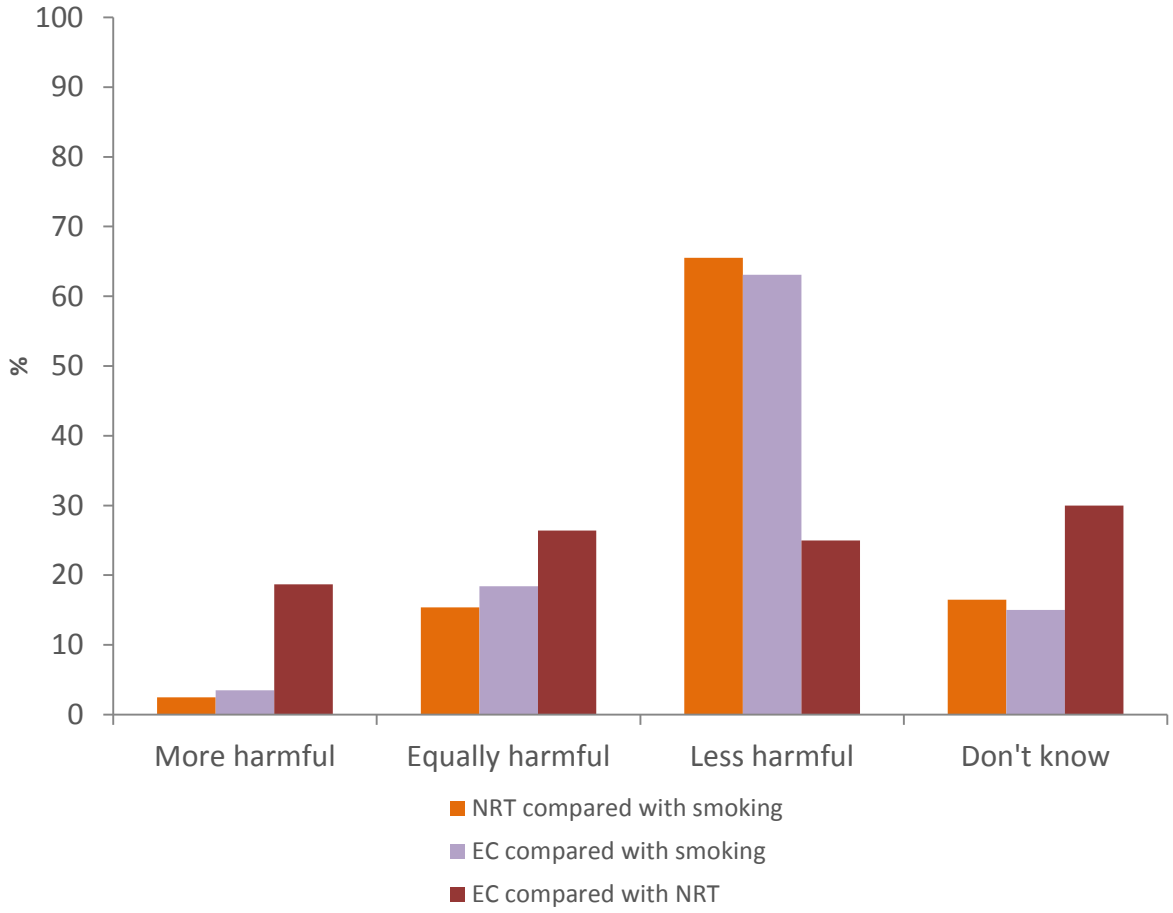
The ICGBS also included questions about perceived harm of EC and NRT relative to cigarettes. Proportions responding more, equally, and less harmful were almost identical for both types of products relative to cigarette smoking (Figure 41). In this survey, these questions were followed by a direct comparison of EC and NRT; respondent's views were fairly evenly distributed across response options and the modal response was 'don't know' (30.0%), suggesting smokers and ex-smokers may find the difference in harm between EC and NRT difficult to judge (Figure 41).

Figure 40: Perceived harm of NRT and EC relative to cigarettes among smokers and ex-smokers



Notes: ASH-A 2017. Unweighted base sizes in the appendix. Adults aged 18+

Figure 41: Perceived relative harm of EC and NRT



Notes: ICGBS 2016. N=3,431 adult smokers, ex-smokers and EC users aged 18+

Perceived harms of nicotine

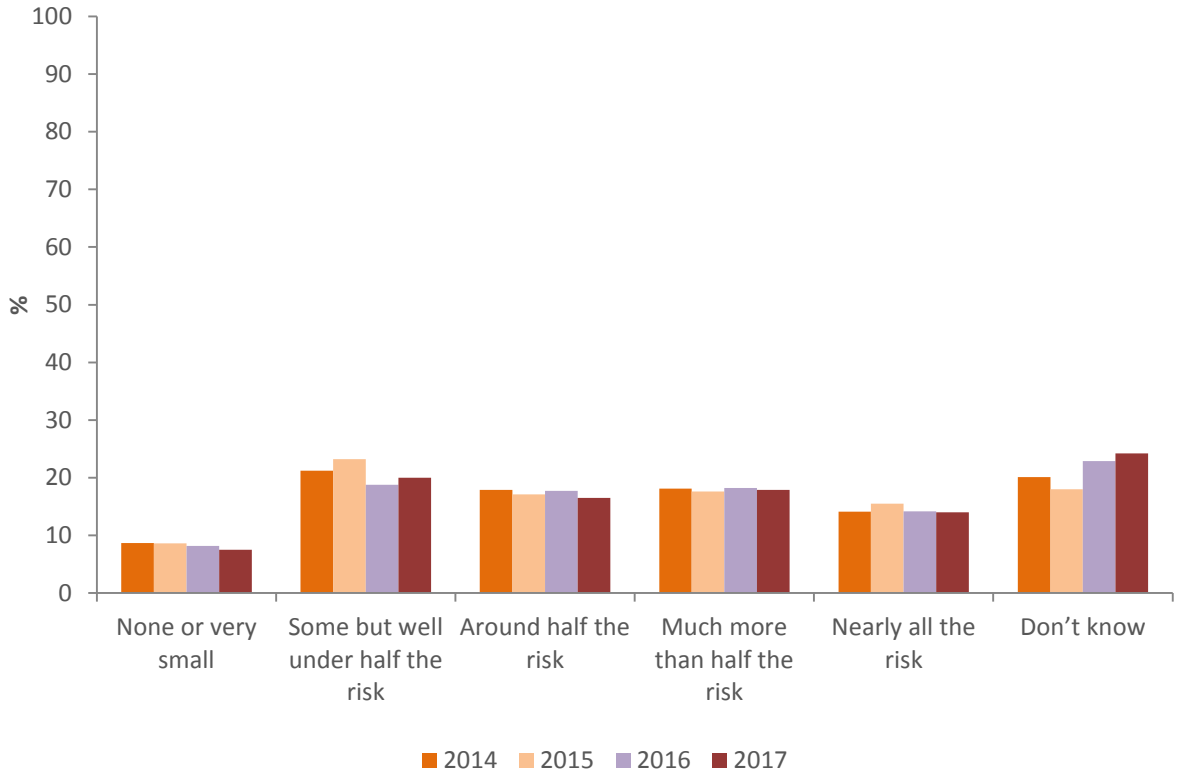
The common factor for cigarettes, NRT and (most) EC is nicotine, and misperceptions of relative harm may be linked to the perception of nicotine (see also eg (308) for an association between perceived nicotine content and perceived harm of cigarettes).

Knowledge about the portion of harm of smoking attributable to nicotine in the general adult population is poor and not improving. In 2017, only 7.5% thought that none or a very small part of the risk of smoking comes from nicotine (the correct response) whereas 14.0% thought that it was nearly all the risk; almost a quarter (24.2) of the population chose ‘don’t know’ (Figure 42). Smokers overall may be slightly better informed with 13.5% thinking it is none or a very small part of the risk and 6.0% that it is nearly all the risk, although again 24.6% did not know. However, among smokers who have never tried EC, only 10.6% give the correct response (Table 22), repeating the pattern seen for relative harm perception of EC use vs smoking among smokers with different EC use status. It is interesting that the highest accurate response to this question was given by ex-smokers who were current EC users (30.4%). Responses from the ICGBS which surveys smokers and ex-smokers, are in line with the population

data for these groups with 12.9% thinking that only a very small portion of the risk of smoking is due to nicotine.

The ICGBS also asked whether respondents believed that nicotine is the chemical in cigarettes that causes most of the cancer and a considerably proportion of respondents (39.5%) erroneously believed this to be true. This question was not included in any of the other recent surveys, but these results are in line with older data from the ITC study for smokers and ex-smokers in the UK, US, Canada and Australia (309); for more detail see Figure 44 and Figure 45.

Figure 42: Perceived portion of the harms of smoking due to nicotine, ASH-A, 2017



Notes: Unweighted base sizes in the appendix. Adults aged 18+

Harm perceptions among youth

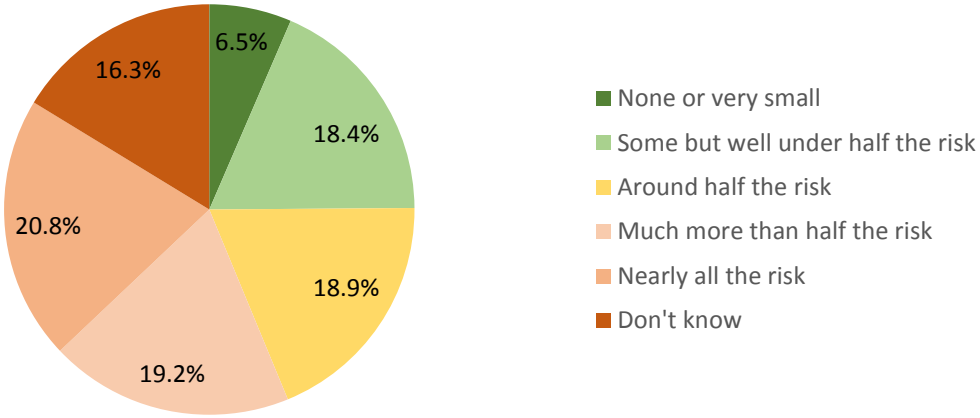
For youth, a recent publication reports harm perception in the ASH-Y over time among those aware of EC (8) and shows a similar trend to adults. In 2013, 73.4% of youth aware of EC thought that EC were less harmful than cigarettes and this dropped significantly to 62.3% in 2016 (8). In 2017, this perception was held by only 61.9% of youth (Eastwood, personal communication).

An analysis using the 2016 ASH-Y found that accurate perception was more likely among youth 14 years and older, those who had tried or used EC sometimes (compared with those who had never used EC), those who had at least one family member who used EC and those who thought that the public either approve or neither

approve nor disapprove of EC use. Respondents' own smoking status was not associated with perception (116).

Nicotine knowledge among youth is also poor; in 2017, 6.5% thought that none or a very small part of the risk of smoking comes from nicotine and about a fifth thought it was nearly all the risk (Figure 43). In the 2016 ASH-Y data, accurate nicotine knowledge was higher among those who were 16 years and older and those who had at least one family member smoking. Again, respondents' own smoking status was not associated with nicotine knowledge (116).

Figure 43: Perceived harm of EC relative to cigarettes in youth. ASH-Y, 2017



Notes: Unweighted base n=1977, aged 11-18.

International overview

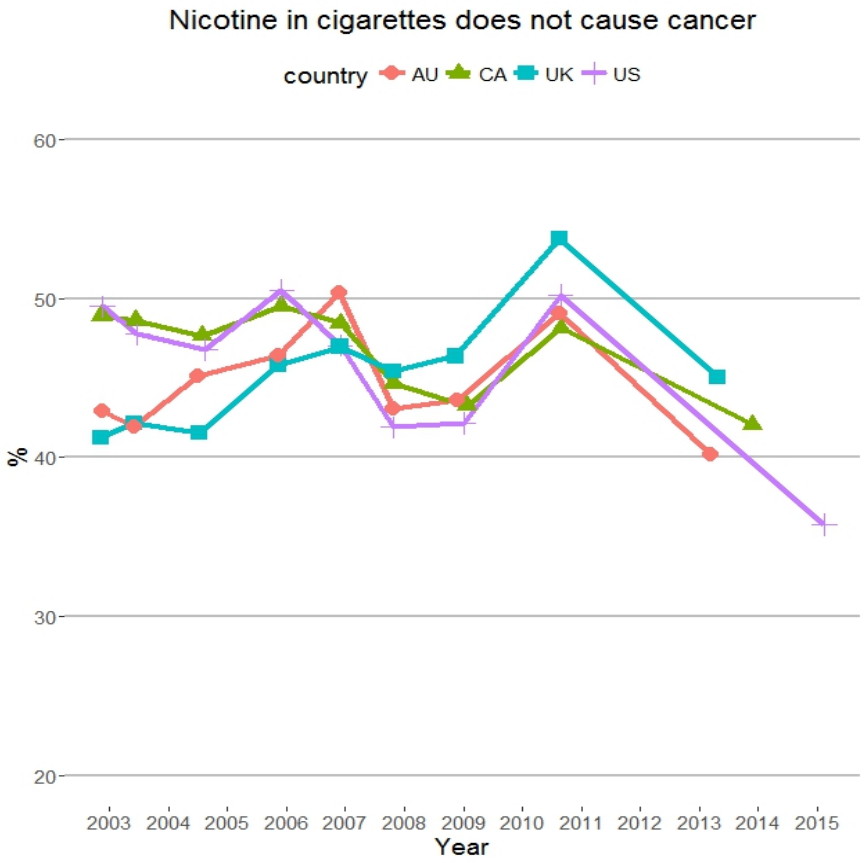
Many surveys, mostly from the US, have included questions about perceived harmfulness. This section will focus on reviews and surveys reporting on national samples of adults or youth.

ITC project

The ITC Project has collected data on nicotine perceptions over time among smokers in four industrialised countries, Australia, Canada, UK and US. Given these are cohort data with replenishment, binary generalised estimating equation models were used to estimate the adjusted percentage of smokers correctly responding that nicotine in cigarettes does not cause cancer, for each country. The adjusted estimates controlled for sex, age group, income, education, daily vs. non-daily smoking status, Heaviness of Smoking Index, use of NRT, survey mode and time in sample. The general pattern in the UK is similar compared with the other three countries although more recently, the level of misperceptions seems to be slightly lower in the UK than in the other countries

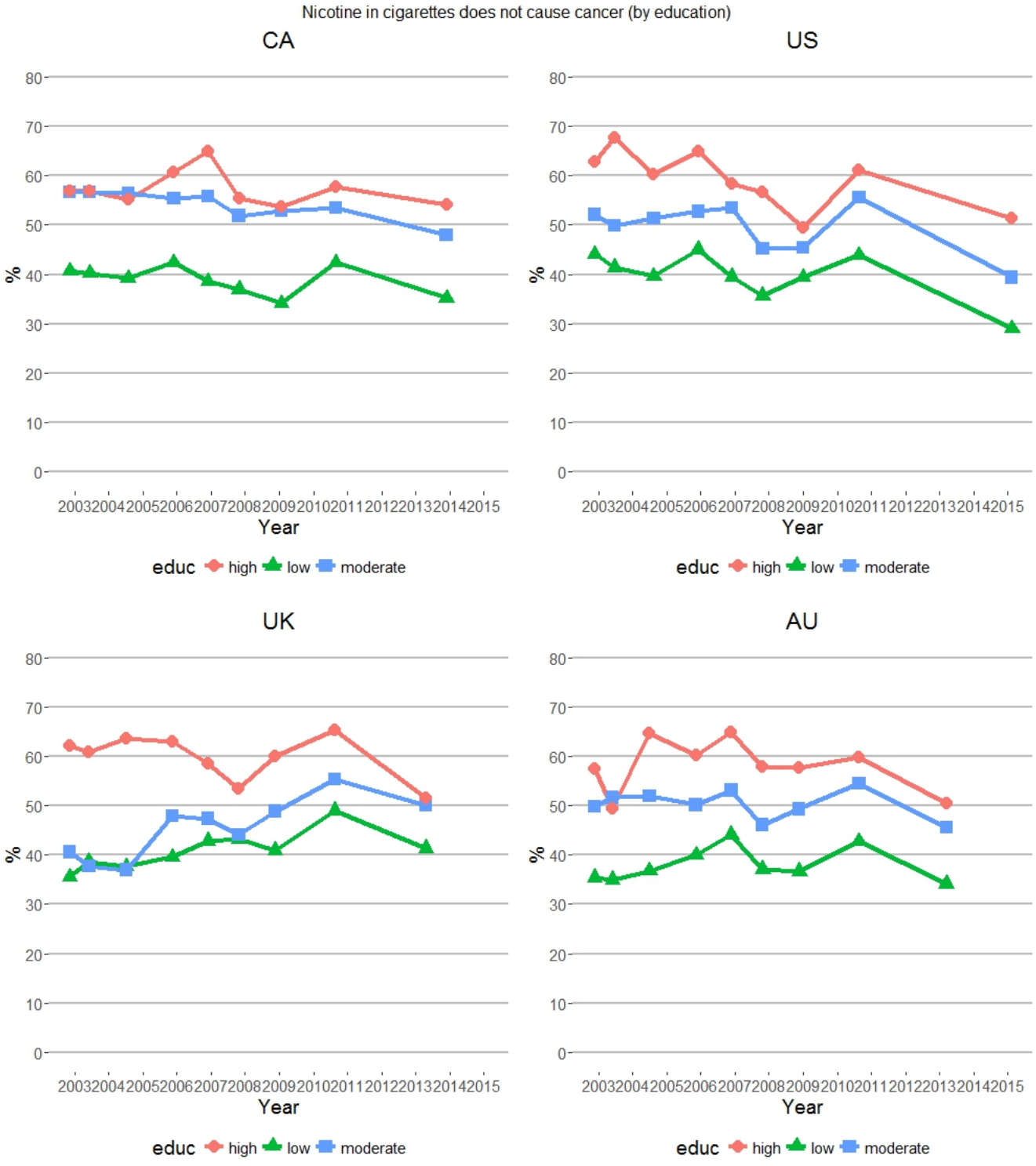
(Figure 44). Misperceptions vary consistently by indicators of socioeconomic status across the four countries, with more disadvantaged smokers and recent ex-smokers having higher rates of misperceptions (Figure 45).

Figure 44: Proportion correctly responding that nicotine in cigarettes does not cause cancer in the ITC 4 country study over time



Notes: Adult smokers and ex-smokers aged 18+

Figure 45: Proportion correctly responding that nicotine in cigarettes does not cause cancer in the ITC 4 country study over time by educational level



Notes: Adult smokers and ex-smokers aged 18+

The ITC Project has also collected data on perceived harmfulness of EC relative to tobacco cigarettes among smokers across a variety of countries (Table 23). These data show that misperceptions of relative harm abound in other countries too, with smokers in England being better informed than in most other countries.

Table 23: Percentage of adult smokers across different countries thinking EC are equally as harmful or more harmful than cigarettes (ITC data)

Country	Year	'EC equally or more harmful than cigarettes', % [1]
High income		
Republic of Korea	2016	66
United States	2016	37
Netherlands	2015	32
Canada	2016	30
England [2]	2016	24
Australia [2]	2016	22
Uruguay	2014	19
Middle income		
Malaysia	2013	70
Zambia	2014	57
Thailand	2012	54
Mexico	2014-15	38
Bangladesh	2014-15	37
Brazil	2012-13	22
China	2013-15	15

[1] *Among smokers who have heard of EC.*

[2] *Figure from ITC, amended from presentation by Professor Geoffrey T Fong at European Network for Smoking and Tobacco Prevention (ENSP) conference, Athens, 2017.*

The data for Australia and England are preliminary and unweighted. The data for England are adjusted for oversampling of 18-24 year olds; there was no such oversampling in Australia

Two reviews of studies from any country have included perceived harm of EC relative to cigarettes. Reviewing 50 samples from 23 studies, Czoli and colleagues found that in 70% of samples a majority perceived EC to be less harmful than cigarettes (310). The comprehensive review of studies by Glasser and colleagues (73) concluded that generally, EC are perceived to be less harmful and less addictive than cigarettes regardless of the respondent's tobacco use status. They also concluded that evidence from the US and GB shows that the belief that EC are less harmful has eroded over time, with more individuals mistakenly believing EC are as harmful or more harmful than cigarettes (73).

Other data from European countries

As far as we are aware, peer-reviewed publications using Eurobarometer data and reporting on harm perception (139) have not yet used the latest wave, but 2017 Eurobarometer data are available in a report (141). In contrast to most other surveys, the Eurobarometer asks about absolute perceived harm to the health of users, rather than relative risks. In 2017, just over half (55%) of EU citizens thought that EC are harmful to the health of their users, an increase of three percentage points since the

last survey in 2014. In 22 out of 28 countries, at least half of respondents agreed that EC are harmful and in seven of these countries, over three quarters gave this answer (Estonia 75%, Luxembourg and Cyprus 76%, Denmark 79%, Latvia 80%, Lithuania 80%, Finland 81% and the Netherlands 85%). The lowest proportion agreeing with this statement was found in Italy (34%). The proportion of respondents who think that EC are harmful has increased in almost all countries since the previous survey. For the UK, the Eurobarometer reports that 50% thought EC were harmful. The meaning of an absolute harm question without any option of grading the response or a comparator is somewhat difficult to interpret.

One representative survey of those aged 14 and over conducted in Germany in 2016 (142) found that 20.7% of respondents believed EC to be less dangerous than cigarettes, 46.3% equally dangerous, and 16.1% believed they were even more dangerous (17.0% no response). This was similar among current smokers, where only 25.5% believed that EC are less dangerous and 15.9% believed EC to be more dangerous than cigarettes.

United States

For US adults, data on relative perceived harm from the Health Information National Trends Surveys (HINTS) 2012 to 2014 have been published. Among those who were aware of EC (77% in 2012 to 94% in 2014), perception that EC were less harmful than cigarettes declined from 50.7% in 2012 to 43.1% in 2014 (311). In a separate publication, data from the Health Information National Trends Survey (HINTS-FDA) 2015 show absolute harm perception of different products; 90.5% perceived cigarettes and 48.7% EC to be very harmful; cigarettes were perceived to be moderately harmful by another 8.9% while 41.9% perceived EC to be moderately harmful (312). Another representative survey of US adults, the Tobacco Products and Risk Perception Survey waves 2012, 2014 and 2015 also show a decline in the proportion believing EC to be less harmful than cigarettes (39.4% in 2012, 35.2% in 2014 and 30.7% in 2015) and steep increases in the proportions believing EC to be equally (11.5% to 35.7%) or more harmful (1.3% to 4.1%) than cigarettes (313).

The HINTS-FDA and the Tobacco Products and Risk Perception Survey each also included a question on addictiveness. Under a third (28.7%) of adults believed that using EC was very addictive and 21.1% that it was moderately addictive, compared with 76.8% and 10.5% for cigarettes (314). The proportion of adults agreeing that people can become addicted to EC increased from 32.0% in 2012 to 67.6% in 2015 (313).

One review summarised US studies examining perceptions of EC during pregnancy and found that mostly, these were perceived to be less harmful than cigarettes but this was accompanied by considerable uncertainty (315). This lack of information is further

supported by findings from one national survey of US adults where 11.1% believed using EC during pregnancy was less harmful than smoking, 51.0% believed it was equally harmful, 11.6% believed it was more harmful, and 26.2% did not know (316).

Among US youth, data are available from the PATH and the NYTS. In the first wave of the PATH in 2013-14, perceived relative harm was measured using both a direct measure asking respondents to compare EC with cigarettes and an indirect measure that asked about the harm to the user separately for each product. In the direct measure, 50.2% of the 12 to 17-year old respondents perceived EC to be less harmful than cigarettes; this was true for 67.3% when using an indirect measure (317). Data from the 2012 and 2014 NYTS (318) are unusual compared with other youth and adult surveys in that they show an increase in the proportion of respondents perceiving EC to be less harmful than cigarettes. In 2012, 30.6% responded that they perceived EC to be less harmful which increased to 50.7% in 2014, a figure which is comparable with the PATH direct measure. This increase is mirrored by a decrease in the proportion who were unaware of EC or who didn't know enough to respond to the question (50.9% in 2012 to 30.6% in 2014). The NYTS also asked about addictiveness compared with cigarettes; 31.3% thought EC were less addictive, 29.7% equally addictive, 5.4% more addictive and 33.8% were unaware of the product or didn't know enough to answer the question (318).

Conclusions

Key findings

- Perceived relative harm of EC compared with cigarettes has continued to increase; less than half of adults in GB think EC are less harmful than smoking.
- NRT is subject to similar misperceptions and only just over half of adults in GB think that NRT is any less harmful than smoking.
- Adult smokers are poorly informed about relative risks of different products.
  - Only half of smokers believe that EC are less harmful than smoking and this decreases to one third among smokers who have never tried EC.
  - In contrast to evidence to date, it appears that a majority of smokers and ex-smokers does not think that complete replacement of cigarettes with EC would lead to major health benefits.
  - Only half of all adult smokers believe that NRT is any less harmful than smoking
- As the common factor for cigarettes, NRT and (most) EC is nicotine, these misperceptions may be linked to the perception of nicotine.
  - When adults in GB are asked what proportion of the health harms of smoking is due to nicotine, the accurate response (most health harms are not caused by nicotine) is the least common response consistently chosen by 8-9%. Smokers' knowledge around nicotine is similarly poor.

  - Four in ten smokers and ex-smokers incorrectly think nicotine in cigarettes is the cause of most of the smoking-related cancer.
  - Misperceptions around nicotine and cancer are greater in more disadvantaged groups.
- It is unclear to what extent the perception of addictiveness underpins the perception of harm.
- Among youth in GB, perceived harm of EC relative to cigarettes has also increased over time and nicotine knowledge is similarly poor (7% correctly responded that none or a small portion of the harms of smoking is due to nicotine).
- Where available, international data show similar misperceptions around nicotine and relative harmfulness of EC and smoking as in England. International data also support the trends of increased harm perception of EC with the exception of one survey in youth in the US.

Implications

Research

- Future research should aim to assess causes and effects of misperceptions of the relative harmfulness of EC and NRT compared with cigarettes, including to what extent the perception of addictiveness contributes to these misperceptions.

Policy and practice

- Misperceptions of nicotine and different nicotine-containing products need to be addressed. These have deteriorated further since the 2015 PHE report in 2015 which called for clear and accurate information on relative harms (5).
  - Misperceptions of the relative harms of NRT and EC compared with cigarettes need to be addressed, particularly among smokers who would benefit from switching to NRT or EC.
  - Knowledge about the role of nicotine in the development of cancers and other diseases caused by smoking needs improvement.

11 Indicative EC pricing

Introduction

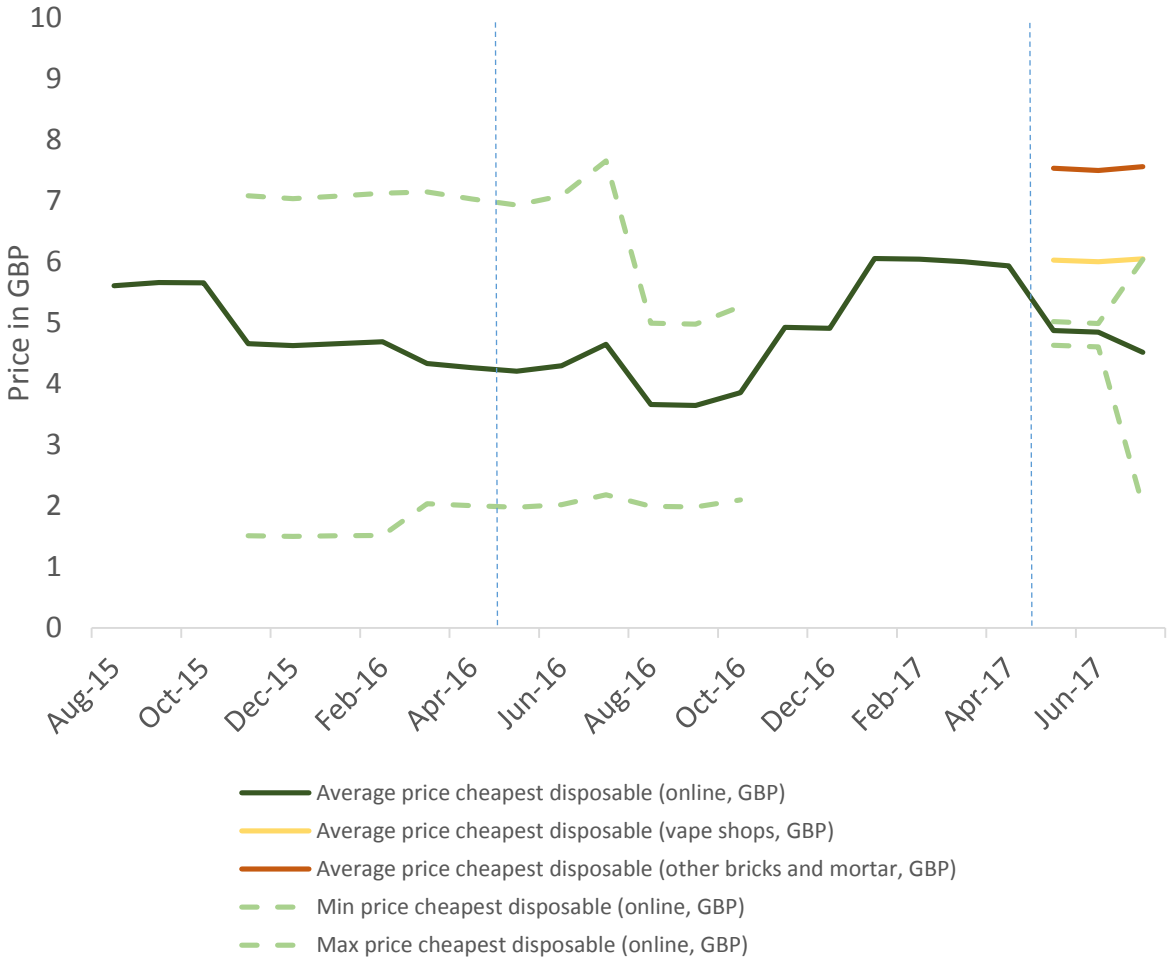
To illustrate the price range of EC, the ECigIntelligence Global Database was used.

Price of different products

Cheapest disposable EC

The price of the cheapest disposable EC has fluctuated from less than 4 GBP to 6 GBP over the time period from August 2015 to July 2017 (Figure 46). For cheapest disposable EC, online prices were generally lower than those of specialisded vape shops. Other brick and mortar shop prices appeared to be the highest.

Figure 46: Average monthly price of cheapest disposable EC



Cheapest closed system kit

The average price of the cheapest closed system kit remained between 10 and 20 GBP between August 2015 and June 2017, with an increasing trend observed towards the end of the study period which was probably due to a considerable increase in the maximum price of cheapest closed system kit. Although average price data for EC sold in vape shops were available only for a few months at the end of study period, they suggest that prices were slightly higher in vape shops than online (Figure 47).

Figure 47: Average monthly price of the cheapest closed system kit

Cheapest pre-filled clearomiser/cartomiser

The price of the cheapest pre-filled clearomiser/cartomiser has remained relatively stable, at around 2 GBP throughout the study period. It appears that in May/ June 2017 the average price increased, but this is likely to be explained by a steep increase in the maximum price of the cheapest pre-filled clearomiser on some websites (Figure 48).

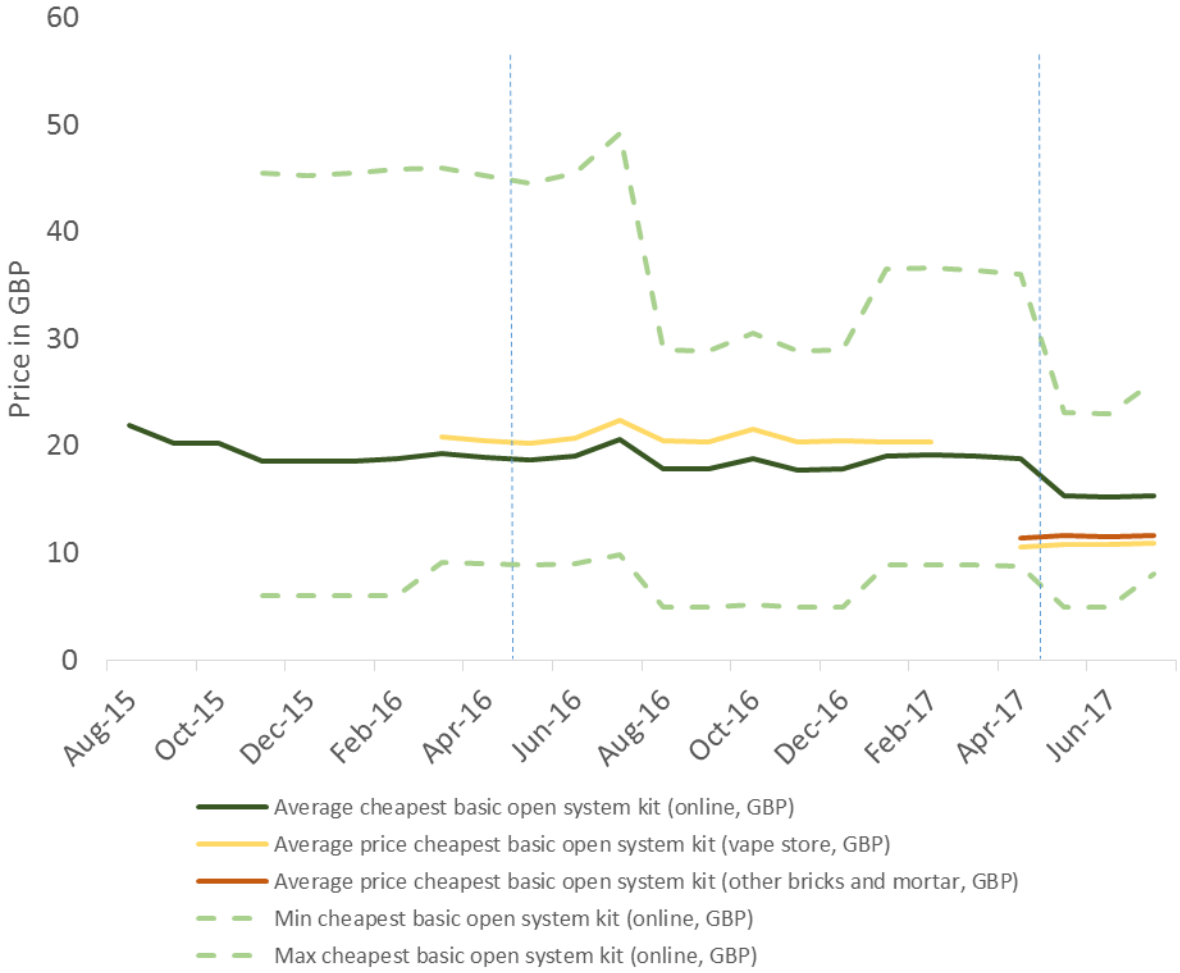
It is possible that the increase in minimum price after April 2017 is related to implementation of the TPD, but in order to explore causality long term trends are required. As with other products, the average price of pre-filled clearomisers/cartomisers was considerably lower when purchased online.

Figure 48: Average monthly price of cheapest pre-filled clearomiser/ cartomiser

Cheapest basic open system kit

The price of the cheapest basic open system kit has remained relatively constant, but decreased towards the end of the study period, and unlike other products was slightly higher from online suppliers towards the end of the study period (Figure 49).

Figure 49: Average monthly price of the cheapest basic open system kit



Cheapest clearomiser

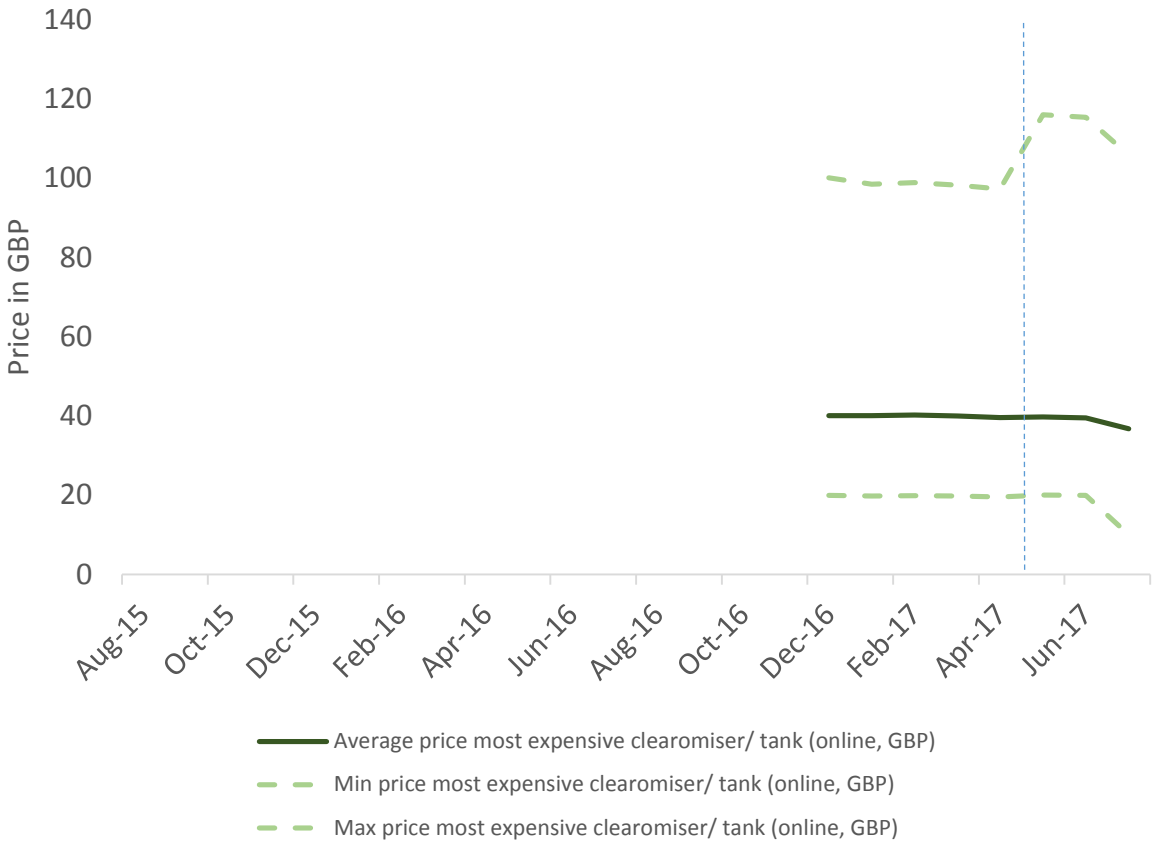
As with the average monthly price of a basic open system kit, the average price of the cheapest clearomiser has remained relatively stable during the study period. However, an increase towards the end of the study period has been observed, possibly due to an increase in the maximum prices of the cheapest clearomisers (Figure 50). Prices from vape shops , available only in the last few months of the study period, appeared lower than from online retailers.

Figure 50: Average monthly price of the cheapest clearomiser

Most expensive clearomiser/tank

Prices of the most expensive clearomiser/ tank have been available in the dataset since December 2016. The prices have remained almost unchanged, and only minor fluctuations in minimum and maximum prices have been observed (Figure 51).

Figure 51: Average monthly price of the most expensive clearomiser/ tank



Variable wattage/variable voltage kits

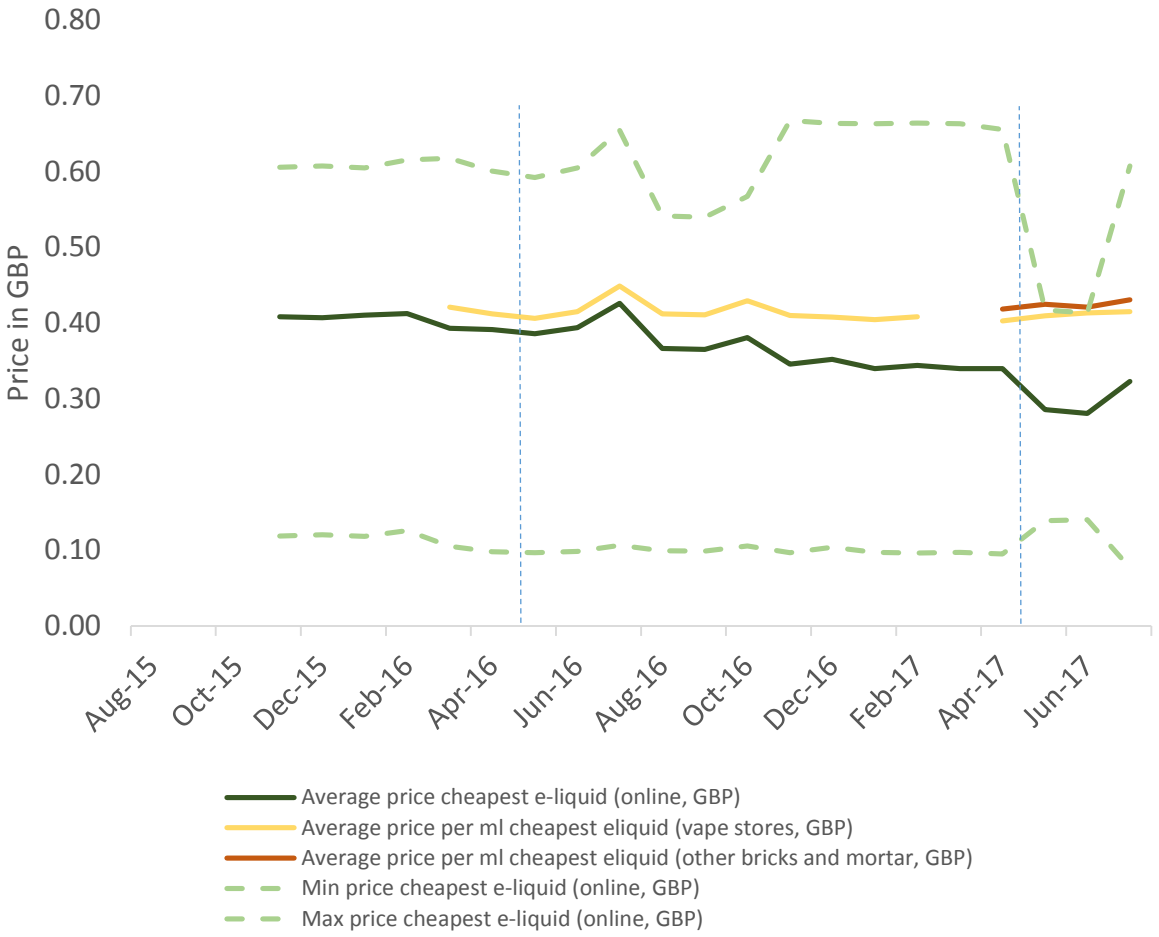
The average monthly price of variable wattage/ variable voltage kits has been available only since March 2016 and has remained stable over time with a slight decrease towards the end of the study period (Figure 52). However, in this category, the range of prices available from various online sources is wide, from about 20 GBP to 130 GBP. As with other open system kits described above, average prices of these products in vape shops appear to be below those observed in online retailers.

Figure 52: Average monthly price of variable wattage/ variable voltage kit

Cheapest e-liquid

The average price of the cheapest e-liquid has decreased over time, and appears to have been higher in vape shops than online (Figure 53). It appears that despite restrictions on e-liquid bottle size included in the EU TPD price of e-liquid per mL has not increased.

Figure 53: Average monthly price per 1mL of the cheapest e-liquid



Limitations

These data are descriptive and most of the data presented refer to the cheapest EC product online. It is difficult to investigate trends particularly in relation the implementation of the TPD given the relatively short period of time since full implementation; in addition some data points are missing.

Conclusions

Key Findings

- Price varies considerably between products, and there appear to be differences between online and bricks and mortar shop prices, with closed system products tending to be cheaper online, and open system kits cheaper in bricks and mortar shops.
- Generally, average maximum and minimum prices seem to have remained relatively stable from August 2015 to July 2017 for all product categories.
- There appear to have been no major and consistent changes in price over the first year since implementation of the EU TPD.

Implications

- Current available data provide minimum, maximum and average prices, but do not provide detail on nicotine levels, brands and flavours that would be helpful to our understanding of market developments.
- Currently EC products are available in a wide range of prices and therefore affordable to various types of EC users. Any changes in pricing need to ensure that EC are affordable to smokers to avoid discouraging smokers from switching away from smoked tobacco which would be counter-productive in public health terms. There should therefore be a competitive advantage for the prices of EC compared to combustible tobacco products.

12 Heated tobacco products

Introduction

Heated tobacco products are products that do not combust tobacco like cigarettes but heat it to a lower temperature with the aim of avoiding the harmful products of combustion; they are often referred to as ‘heat-not-burn’ tobacco products. In contrast to EC, heated tobacco products in general apply heat to tobacco, instead of liquids. There is however a range of different types of heated tobacco products, and some classifications include products where vapour is produced from non-tobacco sources and then passed over processed tobacco to be flavoured (319). Typically, heated tobacco products are rechargeable and include a holder, and tobacco sticks, plugs or capsules to be heated with an electronically controlled heating element.

Heated tobacco products have been launched by tobacco companies since the 1980s (320, 321) but failed to attract consumers. The heated tobacco products described in the current literature are also manufactured by tobacco companies. Philip Morris International’s (PMI’s) heated tobacco product IQOS was launched initially in test markets in cities in Japan, Italy and Switzerland in 2014 before expanding into all of Japan and other countries. As of July 2017, it was available in 27 countries worldwide including Great Britain (322). In some countries IQOS is branded as Marlboro, representing co-branding with cigarettes. PMI is preparing city tests for further products such as TEEPS (https://www.pmi.com/smoke-free-products). Other heated tobacco products currently include glo by BAT which was first available in Japan in late 2016, followed by a small number of other countries (Canada, Switzerland, Korea), and Ploom TECH by Japan Tobacco International which was launched in Japan and Switzerland in summer 2017.

In Great Britain, IQOS has been available from a dedicated shop in London since December 2016 and more recently also online and a couple of other outlets in London. Other heated tobacco products are expected to be launched in the UK soon, therefore the UK government is seeking to develop a specific taxation category for heated tobacco products (319). Before being put on the market, heated tobacco products need to be notified to PHE (see chapter 3). In the US, PMI has submitted an application equivalent to millions of pages to the FDA to be able to market its heated tobacco products as a modified risk tobacco product (323).

The objective for this chapter was to review the existing peer-reviewed evidence on emissions and use of current heated tobacco products and to supplement this with recent evidence from UK surveys.

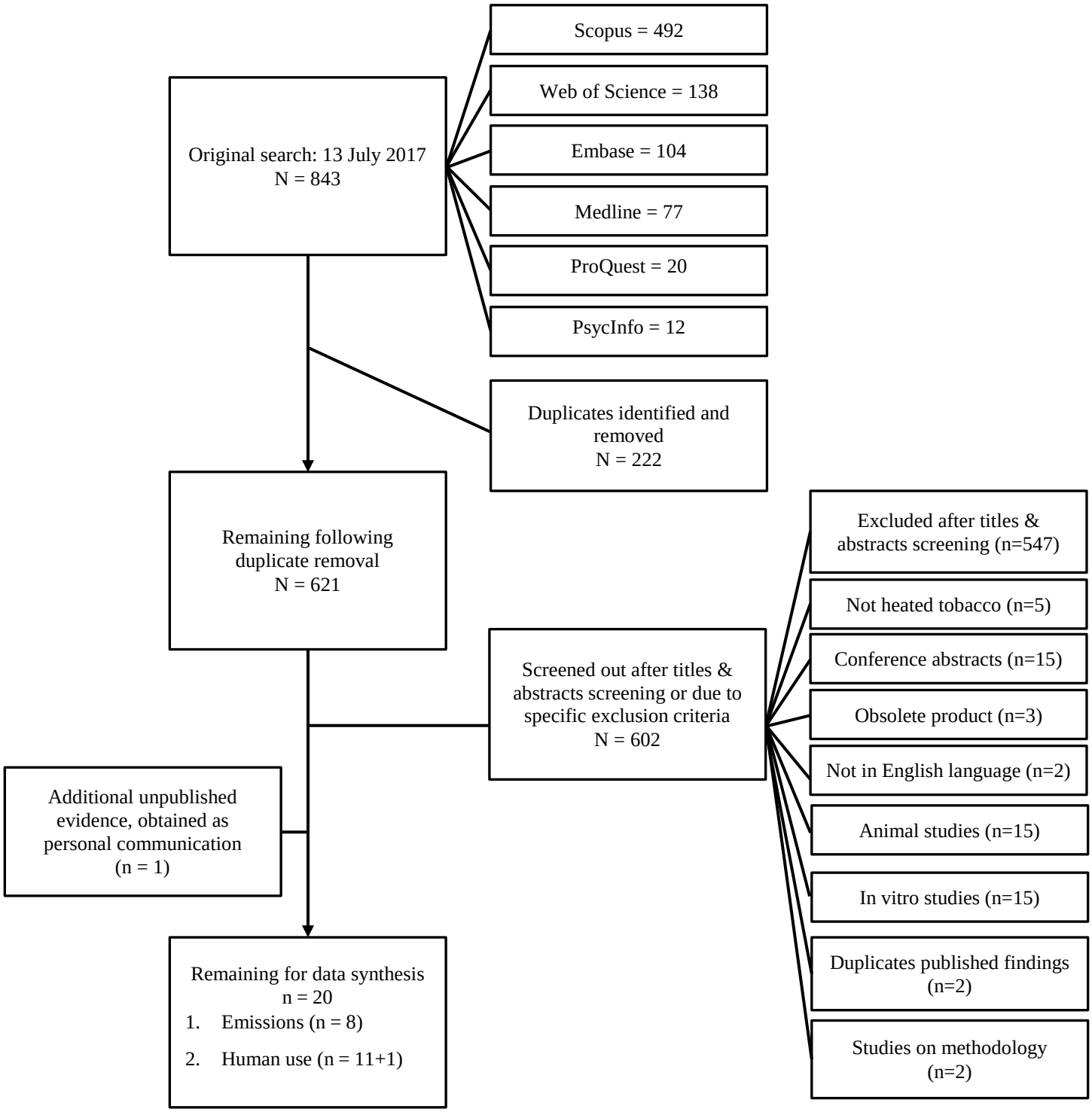
Systematic review of existing literature

Description of studies

From 843 records identified after the initial search, 19 studies were included in the review (Figure 54). Of these, seven studies were funded independently of the tobacco industry, eleven were funded by the manufacturer of IQOS and one study was funded by a competitor tobacco company (Table 24).

Manufacturers researching their own products or competitor products experience a conflict of interest which may bias findings and interpretations, so results need to be interpreted with caution (324). A further study we became aware of through contact with the study authors was also included, making a total of 20 studies.

Figure 54: Heated tobacco products review flowchart



Different types of products assessed in these studies were categorised as:

i. Loose-leaf tobacco vaporiser: One study focused on Pax by Ploom.
ii. Carbon heated tobacco product: This predecessor of TEEPS by PMI was the focus of one study. A specifically designed electric lighter lights the carbon heating source which then heats a tobacco plug. Twelve puffs of the Carbon Heated Tobacco Product (CHTP) are reported to yield 3 mg tar, 2 mg glycerol, 0.4 mg nicotine, and 1 mg of CO (325).
iii. Tobacco heating system 2.1 (THS 2.1): Developed by PMI, a predecessor of IQOS, was assessed in two studies.
iv. Tobacco heating system 2.2 (THS 2.2), available commercially as IQOS: THS2.2/IQOS was assessed in 16 studies. According to the manufacturer, compared with THS 2.1, THS 2.2 has a slightly lower operating heating temperature of <350°C (326) compared with <400°C (327), higher ISO nicotine yield per tobacco stick (0.5 mg (326) compared with 0.3 mg (328, 329)) and 'improved puff by puff consistency and improved sensory satisfaction' (330).
v. Other commercially available heated tobacco products: glo and Ploom/Ploom TECH were included alongside IQOS in two studies from Japan.

Eight of the included studies were laboratory studies on heated tobacco product emissions (331-338). These compared IQOS emissions with emissions from factory-made (331-333, 335-338) or hand-rolled (335) tobacco cigarettes, EC (332, 334-336) and a nicotine inhalator (334). Four were independently funded.

Nine publications reported on six RCTs using a few different products (Table 24), one of them published in two parts, and two cross-over design experimental trials in human participants (total *n* = 796)(325, 326, 328, 329, 339-343). One of these studies was independently funded (339), the other eight were funded by the manufacturer and all published by the same set of authors.

One publication was a case report (*n* = 1, (344)), one reported findings from a national cross-sectional survey from Japan (*n* = 8240, (155)); both independently funded. In addition to the studies identified from the literature, we included an independently funded update to the survey in Japan (345) that was not yet published at the time of the literature search but which the authors shared with us.

Table 24: Summary of included heated tobacco product studies

Authors, year of publication	Funder, country	Study design	Heated tobacco product and reference products [1]	Main aim
Mainstream emissions				
Auer, Concha-Lozano et al. 2017(331)	Not reported, Switzerland	Laboratory comparison study using smoking machines	IQOS Cigarette	To compare levels of HPHC in mainstream IQOS emissions with those in mainstream cigarette smoke
Farsalinos, Yannovits et al. 2017(332)	No funding, Greece	Laboratory comparison study using smoking machines	IQOS Cigarette EC: (i) Cigalike (ii) eGo-style, 2nd generation (pen-style tank) (iii) variable wattage (tank)	To compare levels of nicotine in mainstream IQOS emissions with nicotine in different type of EC aerosol and in mainstream cigarette smoke
Schaller, Keller et al. 2016(337)	PMI, Switzerland	Laboratory comparison study using smoking machines	THS 2.2 Cigarette	To compare levels of HPHC in mainstream emissions and smoke
Schaller, Pijnenburg et al. 2016(338)	PMI, Switzerland	Laboratory comparison study using smoking machines	THS 2.2 Cigarette	To compare levels of HPHC in mainstream IQOS emissions from regular and menthol tobacco sticks with those in mainstream cigarette smoke
Sidestream & environmental emissions				
Mitova, Campelos et al. 2016(333)	PMI, Switzerland	Laboratory comparison study using smoking volunteers	THS 2.2 Cigarette	To compare levels of environmental smoke/emissions
O'Connell, Wilkinson et al. 2015(334)	IT, United Kingdom	Laboratory comparison study using smoking volunteers	THS 2.2 Nicorette inhalator EC (cigalike)	To compare levels of sidestream emissions
Protano, Manigrasso et al. 2016(335)	Non-sponsored, Italy	Laboratory comparison study using smoking volunteers	THS 2.2 Cigarette Hand-rolled cigarette EC (pen-style tank)	To compare levels of environmental smoke/emissions
Ruprecht, De Marco et al. 2017(336)	National Cancer Institute Italy & University of Southern California, not reported	Laboratory comparison study using smoking volunteers	THS 2.2 Cigarette EC (cartridge)	To compare levels of environmental smoke/emissions

Authors, year of publication	Funder, country	Study design	Heated tobacco product and reference products [1]	Main aim
Effects of use by humans				
Brossard, Weitkunat et al. 2017(341)	PMI, Japan	Randomised crossover experimental trial	THS 2.2 Cigarette Nicotine gum	To compare nicotine delivery and effects on urge to smoke
Haziza, de La Bourdonnaye, Merlet et al. 2016(328)	PMI, Japan	RCT	THS 2.2 Cigarette	To compare exposure to HPHC during 5 days of use
Haziza, de La Bourdonnaye, Skiada, et al. 2016 (329)	PMI, Poland	RCT	THS 2.2 Cigarette	To compare exposure to HPHC during 5 days of use
Kamada, Yamashita et al. 2016 (344)	None reported, Japan	Case report	IQOS	To report a case of acute eosinophilic pneumonia following use
Lopez, Hiler et al. 2016 (339)	National Institutes of Health & FDA, United States	Randomised crossover experimental trial	Pax LLTV Cigarette eGo EC (pen-style tank)	To compare nicotine delivery, expired air CO and abstinence symptom suppression
Ludicke, Baker et al. 2017 (326)	PMI, Poland	RCT	THS 2.1 Cigarette	To compare exposure to HPHC during 5 days of use in confinement
Ludicke, Haziza et al. 2016 (325)	PMI, Poland	RCT	CHTP Cigarettes	To compare exposure to HPHC during 5 days of use in confinement
Ludicke, Picavet et al. 2017c (343)	PMI, Japan	RCT	THS 2.2 Cigarette	To compare exposure to HPHC during 5 days of use in confinement and further 85 days of use in an ambulatory setting [2]
Ludicke, Picavet et al. 2017b (342)	PMI, Japan	RCT	THS 2.2 Cigarette	To compare effect on biologically and clinically relevant risk markers during 90 days of use
Picavet, Haziza et al. 2016 (340)	PMI, United Kingdom	RCT	THS 2.1 Cigarette	To compare nicotine delivery and effects on urge to smoke
Epidemiology				
Tabuchi, Kiyohara et al. 2016 (155)	Ministry of Health, Labour and Welfare Japan	Cross-sectional survey, nationally representative sample	IQOS, Ploom/Ploom TECH, glo	To report awareness and use of heated tobacco products in a nationally representative sample
Tabuchi, Gallus et al. 2017 (345)	Ministry of Health, Labour and Welfare & Society for the Promotion of Science, Japan	Follow-up survey of participants in Tabuchi et al, 2016 (155)	IQOS, Ploom/Ploom TECH, glo	To assess population interest, rate of use, predictors of use, and perceived effects of second-hand aerosol

[1] *Labels as provided by study authors, additional EC categories in brackets*

[2] *Confinement means that participant stayed in a controlled environment and were not given access to other products. Ambulatory refers to a period of use outside of that controlled environment.*

Abbreviations: CHTP: carbon heated tobacco product; Cigarette: Factory-made cigarette; HPHC: harmful and potentially harmful compounds; IT: Imperial Tobacco (now Imperial Brands); LLTV: loose-leaf tobacco vaporiser; PMI: Philip Morris International; THS 2.1: tobacco heating system 2.1.; THS 2.2: tobacco heating system 2.2 (commercially available as IQOS)

Heated tobacco product nicotine and emissions

Nicotine levels in tobacco sticks

An independent study (332) reported that a regular IQOS tobacco stick contained 15.2 ± 1.1 mg of nicotine per gram of tobacco and a menthol tobacco stick contained 15.6 ± 1.7 mg of nicotine per gram of tobacco. Based on the reported average weight of a tobacco stick of 320 mg (327), this equates to 4.9–5 mg of nicotine in each IQOS tobacco stick. For comparison, commercially available cigarettes have around 10–14 mg nicotine per gram of tobacco (346) and the mean amount per cigarette has been reported as 8.7 mg (347) or 10–15 mg (348). However, the content of products before use is less relevant than what is inhaled by the user and those around them. Smokers usually take in about 1-2mg nicotine per cigarette (348).

Emissions

For cigarettes, emissions can be categorised into mainstream, sidestream and environmental (or second-hand) tobacco smoke. Mainstream tobacco smoke is usually defined as the smoke that the user draws in (349). Laboratory studies use machines to measure the mainstream that would be inhaled by a smoker. Sidestream smoke is smoke that is emitted from the burning end of a cigarette or other tobacco product (349). Environmental tobacco smoke or second-hand smoke is the combination of exhaled mainstream smoke and sidestream smoke and ambient air (349). To categorise the studies in this section, we transfer this categorisation to heated tobacco products as mainstream, sidestream and environmental emissions. All eight studies that focused on heated tobacco product emissions (Table 24) assessed IQOS products; we present the results based on the studies' key focus on i) mainstream emissions, ii) sidestream and environmental heated tobacco product emissions.

Mainstream emissions

Nicotine levels

The available evidence suggests that nicotine levels in mainstream heated tobacco product aerosol are lower than those in cigarette smoke. Two independent (331, 332) and two manufacturer-funded studies (337, 338) reported on nicotine levels in heated tobacco product aerosol. The studies used different reference cigarettes and different machine smoking regimes, either the ISO regime (ISO; 35 mL puff volume, 30 s intervals between puffs, 14 puffs on average during 5–6 minutes) or the Health Canada Intense regime (HCI; 55 mL puff volume, 2 s puff duration, 30 s intervals between puffs, 14 puffs on average during 5–6 minutes). Generally, for cigarettes, the HCI regime yields higher levels of Harmful and Potentially Harmful Compounds (HPHC) (350) than

the ISO regime but neither are representative of human smoking behaviour and exposure (351). These regimes were also used for the heated tobacco products and EC, sometimes with adaptations.

One independent study (331) followed the ISO puffing regime and used BAT's Lucky Strike Blue Lights (7 mg tar, 0.6 mg nicotine) as a reference cigarette, another independent study (332) used the HCI regime and PMI's Marlboro Regular reference cigarette (10 mg tar, 0.8 mg nicotine). The two studies funded by the manufacturer (337, 338) used the HCI regime and University of Kentucky 3R4F reference cigarette (9.4 mg tar, 0.7 mg nicotine). The independent study that used the ISO regime (331) reported an average yield of 0.3 mg of nicotine in the aerosol from a single tobacco stick. The other three studies (332, 337, 338) used the HCI puffing regime and reported nicotine levels in the aerosol which were similar across studies. For regular tobacco sticks, they found a mean and SD of 1.40 ± 0.16 mg (332), 1.38 ± 0.2 mg (338) and 1.32 ± 0.16 mg nicotine (337) and for menthol sticks they reported 1.38 ± 0.11 mg (332) and 1.21 ± 0.09 mg (337) nicotine. Across the four studies, the relative level of nicotine in the heated tobacco product aerosol compared with nicotine in cigarette smoke was reported at 84% (331), 73% (338), 72% (332) and 70% (337).

One study (332) compared nicotine levels in heated tobacco product aerosol with nicotine in aerosol from EC using the HCI puffing regime with increased 4 seconds puffing duration. The heated tobacco product delivered more nicotine than a cigalike EC (0.86 ±0.08 mg, $p<0.001$), but less than an 'eGo-style' (pen-style tank) EC (1.73 ± 0.09 mg, $p<0.001$) or a variable wattage tank style EC (1.84 ± 0.11 mg, $p<0.001$).

Harmful and potentially harmful compounds

One independent (331) and two manufacturer-funded studies (337, 338) reported levels of HPHC in mainstream heated tobacco product aerosol compared with cigarette smoke. Different machine puffing regimes and reference cigarettes were used across studies, so results cannot be directly compared. The three studies reported proportions of HPHC in aerosol from regular tobacco sticks for the heated tobacco product compared with HPHC levels in smoke from reference cigarettes; for some, they found similar proportions, others differ widely (Table 25).

When comparing levels of polycyclic aromatic hydrocarbons in heated tobacco product aerosol and cigarette smoke, the independent study (331) used reference data from 50 US cigarette brands (350). However, as a critique from PMI noted (352), Auer and colleagues (331) had inadvertently used incorrect reference values for these constituents (data obtained under HCI instead of ISO regimes). Therefore, for the purposes of this chapter, we recalculated the ratios and provide both the originally published and the recalculated ratios in the comparison of relative levels of three polycyclic aromatic hydrocarbons across the three studies (Table 25).

Auer and colleagues also assessed further constituents and reported a much higher concentration of the polycyclic aromatic hydrocarbon acenaphthene for the heated tobacco product relative to cigarettes (295% reported in the publication; 580% if using ISO reference values). Acenaphthene was not included in the manufacturer studies; the manufacturer commented that the compound is not included in any regulatory lists and that Auer's method may have been faulty, and that they 'could not detect it [acenaphthene] in the IQOS aerosol' (352).

Table 25: Level of constituents in mainstream heated tobacco product (IQOS) aerosol relative to mainstream cigarette smoke (only showing constituents measured in all three studies)

	Schaller, Pijnenburg et al. 2016 (338)	Schaller, Keller et al. 2016 (337)		Auer, Concha-Lozano et al. 2017 (331)
Tobacco stick	Regular	Regular	Menthol	Regular
Reference cigarette	3R4F	3R4F	3R4F	Lucky Strike Blue
Puffing regimen	HCI	HCI	HCI	ISO
Levels relative to cigarette				
Nicotine (mg/stick)	73%	70%	64%	84%
Gases				
Nitric oxide (µg/stick)	3%	3%	3%	6%
Carbonyls				
Acetaldehyde	12%	14%	13%	22%
Propionaldehyde	12%	12%	11%	26%
Formaldehyde	11%	10%	8%	74%
Acrolein	7%	7%	6%	82%
Crotonaldehyde	<6%	6%	5%	4%
Acetone	5%	6%	5%	13%
Polycyclic aromatic hydrocarbons				
Benzo[a]pyrene (ng/stick)	7%	9%	8%	4%*/ 8%**
Benz [a]anthracene (ng/stick)	10%	5%	9%	6%*/ 11%**
Pyrene (ng/stick)	10%	<6%	10%	7%*/ 15%**

** Originally reported proportions*

*** We calculated these proportions based on mean values of polycyclic aromatic hydrocarbons in mainstream smoke of 50 commercial US cigarettes measured by the ISO smoking regimen as reported by (Vu, Taylor et al. 2015)*

Sidestream and environmental emissions

Published evidence disagrees on the extent to which heated tobacco products produce environmental emissions and the composition of these emissions.

Four studies, two independent (335, 336), one manufacturer-funded (333) and one funded by a competing tobacco company (334), compared environmental heated tobacco product emissions with environmental tobacco smoke from factory-made (333, 335, 336) or hand-rolled (335) tobacco cigarettes, or aerosol from a nicotine inhalator (334) and different EC (334-336). The studies were heterogeneous in the methods used and in the reporting of results, therefore only key findings are summarised here.

Two studies (334, 335) reported few measurements of individual compounds and only provided some general conclusions about environmental heated tobacco product emissions. The independent study (335) reported that the tested EC and heated tobacco product generated four times lower levels of submicronic particles, an indicator of second-hand smoking, compared with environmental tobacco smoke from regular or hand-rolled cigarettes. Despite low levels of emissions, the study authors concluded that the tested EC and heated tobacco products still posed health risks to users and bystanders (335). The study funded by the competing tobacco company (334) reported that IQOS produced a significantly greater level of sidestream emissions than a nicotine inhalator or an EC: the heated tobacco product emissions were detectable when the device was activated but not used, which contradict the manufacturer's claims that IQOS 'does not emit a true sidestream aerosol' (333).

The second independent study (336) reported levels of particulate matter of different sizes (>1.0 µm, >0.3 µm, and 10-1000 nm) and HPHC in environmental heated tobacco product emissions. In simulated indoors conditions with 1.54 air changes per hour levels of nano-sized (10-1000 nm) particulate matter in environmental heated tobacco product emissions reached up to 23.8% of the levels detected in environmental tobacco cigarette smoke; levels for other size particulate matter in environmental heated tobacco product emissions ranged from 0.7% to 7.3%. Regarding HPHC in environmental heated tobacco product emissions, acrolein concentration reached 1.8%-2.3% of levels detected in environmental cigarette smoke, acetaldehyde reached 5.0%-5.9%, and formaldehyde 6.9%-7.1%. For EC, these were not detectable, with the exception of nano-sized particles (5.7%-7.0% of cigarettes), acetaldehyde (0.2%-0.3%) and formaldehyde (3.1%-3.7%). The study concluded that environmental emissions from heated tobacco products were substantially higher than from EC but significantly lower than those detected in environmental tobacco smoke from a cigarette. The study authors also noted the presence of carbonyls in environmental heated tobacco product emissions as a concern that heated tobacco product use might affect bystanders (336).

In contrast to other three studies, the manufacturer-funded study (333) concluded that the tested heated tobacco product did not produce particulate matter and also reported lower levels of environmental heated tobacco product emissions compared with environmental tobacco smoke from a cigarette. In simulated indoors condition with 1.2 air changes per hour, no change in particulate matter markers was detected and levels

of HPHC in air after heated tobacco product use ranged from 5.8% for benzene to 40.5% for formaldehyde compared with cigarette smoke.

Heated tobacco product use by human participants and effects of use

We summarise nine articles that compared levels of exposure to biomarkers of HPHC, nicotine delivery characteristics, human puffing topography, effect on urges to smoke and subjective satisfaction with heated tobacco products. The six RCTs (one of them reported in two papers) and two studies with a crossover design are presented by the type of heated tobacco product they assessed.

Loose-leaf tobacco vaporiser

One independent study (339) used a crossover design (so that each of the 15 participants went through all three conditions) to compare the loose-leaf tobacco heated tobacco product Pax, cigarettes and pen-style EC. The study compared nicotine delivery, levels of expired air CO concentration and suppression of nicotine abstinence symptoms after short periods of use. The short period of use consisted of 10 puffs separated by 30 seconds and each period was separated by 60 minutes. The highest plasma nicotine levels were reported after cigarette use (24.4 ng/mL), lower levels were found after heated tobacco product use (14.3 ng/mL) and the lowest after EC use (9.5 ng/mL). Baseline expired air CO was around 5 parts per million for all conditions. After two periods of smoking a cigarette, this increased significantly (up to 16.9 parts per million, $p<0.001$), which contrasted with small but significant decreases after single periods of heated tobacco product and EC use ($ps<0.05$); no differences between the latter two were observed. Nicotine delivery was associated with suppression of nicotine abstinence symptoms; smoking a cigarette suppressed them most, use of the heated tobacco product was less effective, and use of the EC was least effective. Based on participants' responses to a specifically modified version of Direct Effects of Product Scale questionnaire, the study authors concluded that the heated tobacco product and the EC were less satisfying than cigarettes.

Carbon heated tobacco product

One manufacturer-funded RCT (325) compared levels of exposure to HPHC between smokers who were randomised to using a CHTP (predecessor to TEEPS), to continue smoking, or to abstain from smoking, for five days in 'confinement', ie in a controlled environment without access to other products (n=112). After switching, smokers in the CHTP group were reported to demonstrate less exposure to HPHC than participants who continued smoking (Table 26). Smokers in the CHTP group altered their behaviour: they took more frequent and longer puffs, showed higher average and total puff volumes. On day five, product consumption by those randomised to the CHTP was reported to be 19.7 compared with 18.8 cigarettes among smokers randomised to

continued cigarette smoking. At the end of the five-day confinement period, nicotine equivalents measured in urine in the CHTP group was reported at 19.1 ng/mL compared with 17.2 ng/mL in the cigarette smoking group, plasma cotinine for the past 24 hours was 319.8 mg versus 289.8 mg; these differences were not statistically significant.

Tobacco heating system 2.1 (THS 2.1)

Two manufacturer-funded RCTs (326, 340) reported findings on THS 2.1. One trial (340) compared the pharmacokinetic nicotine delivery profile of THS 2.1 with non-menthol and smokers' preferred cigarettes (n=28). After single use, THS 2.1 and cigarettes were reported to be similar in how fast plasma nicotine levels reached peak (median for both: 8 minutes), reduction of urges to smoke, and in the nicotine half-life length (2.6 hours for THS 2.1 and 2.5 hours for a cigarette). However, compared with cigarettes, THS 2.1 delivered lower peak levels of nicotine after single and a day's *ad libitum* use (70% and 62%, respectively) and participants consumed fewer tobacco sticks than smokers smoked cigarettes during an *ad libitum* use day (10.9 tobacco sticks versus 16.7 CPD). THS 2.1 was perceived less rewarding in sensory and physical effects when used *ad libitum*; on the modified cigarette evaluation scores (353), THS 2.1 was rated significantly lower on four out of five subscales (Smoking satisfaction, Psychological rewards, Enjoyment of respiratory tract sensation and Craving reduction). The other trial (326) compared exposure levels to HPHC in smokers randomised to using THS 2.1 with smokers randomised to continued smoking; both groups were in confinement for five days (n=40). The exposure to HPHC was reported to be lower in the THS 2.1 group (Table 26). In contrast to the previous study findings that showed less use during one day, in this five-day study smokers in the THS 2.1 group used up to 35% more tobacco sticks than the other group cigarettes (27.2 and 20.1 respectively). Despite compensatory puffing (increased frequency, duration and volume), THS 2.1 users achieved only 85% and 88% of nicotine and cotinine of the cigarette group on the last confinement day. Modified cigarette evaluation scores were again significantly lower for THS 2.1 on the same four subscales.

Tobacco heating system 2.2 (THS 2.2)

The review identified a single case report related to use (344), one publication on a manufacturer randomised cross-over study and four publications reporting on three manufacturer-funded RCTs (328, 329, 341-343) using THS 2.2 which is equivalent to the commercially available IQOS.

The case report (344) described a case of acute eosinophilic pneumonia in a 20-year-old man from Japan who used 20 IQOS tobacco sticks per day for six months and 40 IQOS tobacco sticks a day for two weeks before hospitalisation. Based on the relationship between cigarette smoking and this type of pneumonia, the case report

authors presumed that the rapid increase in the daily use of tobacco sticks had caused the onset of the acute eosinophilic pneumonia.

The randomised cross-over study (341) was conducted in Japan and assessed pharmacokinetic nicotine delivery properties of regular and menthol THS 2.2 compared with cigarettes (n=44) and nicotine gum (n=18). The study authors concluded that the use of regular and menthol THS 2.2 delivered nicotine in a similar way as smoking regular and menthol cigarettes. In detail, compared with cigarettes, nicotine pharmacokinetics for regular and menthol tobacco sticks were similar to each other and similar to cigarettes: peak plasma concentrations for regular and menthol tobacco sticks and cigarettes were reached in six minutes, actual exposure to nicotine was comparable (ratio THS 2.2 : cigarettes: 96.3% for regular, 98.1% for menthol), as was nicotine half-life (93.1% and 102.3%). Peak nicotine concentration ratio for regular tobacco sticks versus cigarettes was 103.5% and 88.5% for menthol tobacco sticks versus cigarettes. Relative to nicotine gum, the results are less clear, probably due to the small sample. Regular tobacco sticks appeared to outperform menthol sticks for actual exposure to nicotine (127.2% and 55.9%) and peak nicotine concentration (240.2% and 101.6%); however, with only 18 participants, this may be due to chance. Relative to gum, nicotine half-life was 87.3% for regular and 92.1% for menthol tobacco sticks.

Four papers reported on the three RCTs. Two manufacturer-funded RCTs, one conducted in Japan (328) and the other in Poland (329), compared the exposure to HPHC in smokers who were in confinement randomised to using regular THS 2.2 for five days, to continued smoking of their preferred non-menthol cigarette, or to smoking abstinence (both RCTs n=160). Two papers (342, 343) reported findings from one manufacturer-funded RCT comparing menthol THS 2.2 with menthol cigarettes conducted in Japan where exposure to HPHC and change in health risk markers were assessed after five days in confinement and a further 85 days in ambulatory setting. This RCT also had a third group of participants randomised to abstain from smoking.

The three RCTs reported daily product use at the end of five days in confinement and provided contrasting results; in the trial in Japan (328), the THS 2.2 group used significantly fewer (on average 20%) tobacco sticks than the smoking group smoked cigarettes, while in the trial in Poland (329), the THS 2.2 group used significantly more (on average 25%) tobacco sticks than the other group cigarettes. In the menthol study (343), daily use of tobacco sticks and cigarettes did not differ.

Publications on all three RCTs reported lower levels of exposure to biomarkers of HPHC in smokers who switched to using THS 2.2 compared with smokers who continued smoking (Table 26), (328, 329, 342). Across the three studies, the reduction in exposure to HPHC in the THS 2.2 groups approached that reported in the groups randomised to smoking abstinence.

The three RCTs also reported similar findings on puffing topography, the ability of THS 2.2 to supress urges to smoke and modified cigarette evaluation scores. THS 2.2 users throughout all three studies demonstrated different puffing behaviours that may indicate compensatory puffing (increased puffing frequency, duration and number of puffs compared with the smoking group). THS 2.2 was reported to supress urges to smoke similarly to smoking cigarettes and was in all three studies rated lower on sensory and psychological satisfaction than cigarettes (significantly lower scores for THS 2.2 on four out of five modified Cigarette Evaluation Questionnaire (mCEQ) subscales in two studies (329, 343) and on one subscale in the other study (328).

The RCT with a 90-day follow-up (342) additionally measured changes in a set of risk markers associated with CVD (eg endothelial functions, cholesterol metabolism, platelet functions, inflammation and oxidative stress). When compared with smokers who continued to smoke menthol cigarettes, smokers who had been randomised to using menthol THS 2.2 were reported to show improvements in risk markers associated with endothelial dysfunction, oxidative stress, inflammation, and high-density lipoprotein cholesterol counts, with the changes reportedly approaching those in the group randomised to complete abstinence. However, participants may have been non-compliant with study conditions. Reportedly, 92.5% participants randomised to smoking abstinence and 89.7% randomised to exclusive heated tobacco product use were compliant throughout the 85 days of ambulatory use. However, compliance was defined as not having used more than two menthol CPD since the last visit and not more than half a cigarette per day on average. Consumption was assessed by self-reported electronic diary entries, and while expired CO was measured, results were not reported, thereby not following standard practice (165) (354). This suggests that both ‘abstinent’ participants and heated tobacco product participants may have been smoking. If heated tobacco product users had also smoked, any reduction in biomarkers relative to smokers would be conservative; however, comparison with the abstinence group should be treated with particular caution as the extent of abstinence is unclear. Study validity is further undermined because the study used a per-protocol approach instead of intention to treat analysis which compromises the validity of randomisation (355) and is in contravention to trial standards outlined eg in the CONSORT statement (356).

Table 26: Product use and level of exposure to HPHC in heated tobacco product users relative to cigarette smokers

	Ludicke, Haziza et al. 2016 (325)	Ludicke, Baker et al. 2017 (326)	Haziza, de La Bourdonnaye, Merlet, et al. 2016 (328)	Haziza, de La Bourdonnaye, Skiada, et al. 2016 (329)	Ludicke, Picavet et al. 2017a; 2017b (342, 343)
Heated tobacco product	Carbon heated tobacco product	THS 2.1, 0.3mg nicotine, 5.0mg* glycerol	Non-menthol THS 2.2, 0.5mg nicotine, 4.9mg glycerol	Non-menthol THS 2.2, 0.5mg nicotine, 4.9mg glycerol	Menthol THS 2.2, 1.2mg nicotine, 3.9mg glycerol
Reference product	Non-menthol cigarette, preferred brand	Non-menthol cigarette, preferred brand	Non-menthol cigarette, preferred brand	Non-menthol cigarette, preferred brand	Menthol cigarette, preferred brand
Mean (SD) product use (heated tobacco vs reference)	19.7 (7.8) vs 18.8 (4.4)	27.2 (9.1) vs 20.1 (3.2)	9.9 (3.9) vs 12.5 (3.5)	20.7 (8.1) vs 16.6 (3.8)	13.9 (4.3) vs 13.6 (4.7)
Biomarkers for HPHC, Mean (95% CI if available)					
Carbon monoxide (CO)	39%	23% (21%–26%)	47% (44%–50%)	24% (22%–25%)	45%
Acrolein	26%	28% (23%–33%)	53% (46%–61%)	42% (38%–46%)	52%
1,3-butadiene	10%	12% (9%–16%)	23% (18%–29%)	8% (7%–10%)	13%
Benzene	16%	7% (5%–10%)	16% (13%–19%)	6% (5%–7%)	11%
Nicotine-derived nitrosamine ketone (NNK)	52%	33% (25%–44%)	49% (42%–57%)	44% (39%–48%)	44%
Pyrene	57%	43% (36%–51%)	46% (41%–52%)	44% (40%–49%)	38%
N-nitrosonornicotine (NNN)	not reported	12% (9%–16%)	30% (24%–38%)	24% (18%–33%)	29%
4-Aminobiphenyl	16%	41% (31%–53%)	18% (15%–22%)	15% (13%–17%)	21%
1-aminonaphthalene	not reported	not reported	4% (4%–5%)	4% (3%–5%)	6%
2-aminonaphthalene	19%	11% (8%–14%)	18% (15%–21%)	12% (10%–13%)	14%
o-toluidine	49%	58% (48%–71%)	51% (42%–60%)	42% (36%–48%)	41%
Acrylonitrile	not reported	15% (12%–18%)	21% (18%–25%)	13% (12%–15%)	18%
Ethylene oxide	not reported	not reported	47% (40%–55%)	32% (27%–38%)	51%
Crotonaldehyde	not reported	not reported	38% (32%–45%)	23% (20%–25%)	43%
Benzo(a)pyrene	not reported	not reported	30% (25%–36%)	28% (23%–33%)	28%
Nicotine equivalents	111%	87% (76%–100%)	105% (92%–120%)[1]/ 99%[2]	105% (92%–120%)	118%
Nicotine	not reported	85% (62%–115%)	113% (91%–140%)[1]/ 90%[2]	113% (91%–140%)	not reported
Cotinine	110%	88% (75%–103%)	96% (71%–131%)	111% (91%–136%)	not reported

All figures from fifth day of confinement (including only studies that used at least 5 days of confinement)

** Reported as 50mg in publication, authors confirmed this was a typo and should be 5.0mg*

[1] Originally reported proportions

[2] Proportions we calculated based on raw study figures

Epidemiological studies on heated tobacco product use

The literature search identified one independently-funded survey on awareness and use of heated tobacco products in Japan in 2015 (155), which was conducted about three months after the launch of IQOS and about a year after the launch of Ploom. EC are not generally available in Japan. Additionally, we report unpublished findings from a follow-up to that survey (357).

The 2015 survey (155) provided evidence from a nationally representative sample of 8,240 respondents aged 15 to 69 years. Survey questions did not distinguish between EC and heated tobacco products; almost half of Japan's population (48%) were aware of EC and/or heated tobacco products, 6.6% had ever used these products, and 1.3% used them in the last 30 days. Data by product type were only reported for ever use which showed that 0.5% of the population had ever used Ploom and 0.6% had ever used IQOS. The as yet unpublished data on heated tobacco use in Japan in 2017 (357) are based on annual surveys following up the 2015 sample (follow-up rate 65.6% in 2016 and 52.2% in 2017) and suggest growth in IQOS use. These data include past 30 day use for different products for 2015 allowing comparisons over time; in 2015, 0.3% reported using IQOS in the last 30 days, this increased to 0.6% in 2016 and 3.6% in 2017 (never smokers 1.3%, ex-smokers 2.1%, current smokers with intention to quit 18.8%, current smokers without intention to quit 10.3%). Last 30-day use of other commercially available heated tobacco products in 2017 was reported at 1.2% for Ploom/ploom TECH and 0.8% for glo (the same respondent may have used more than one product). Smoking rates remained unchanged across survey waves (22.1% in 2015, 22.0% in 2017). It is also reported that among the 7% of never-smokers who had been exposed to second-hand heated tobacco aerosol, nearly half reported at least one acute symptom, although these symptoms were not serious (357).

Data and trends from Japan are not easily transferrable to the UK because in contrast to the UK, EC are not legal in Japan giving heated tobacco products a very different starting position. Nevertheless, data from Japan show rapid penetration of a non-combustible tobacco product into the market.

Additional survey data from GB

These data are unpublished and therefore not included in the preceding systematic review. The STS and ASH-A have introduced questions on heated tobacco products. In the ASH-A 2017, 9.3% reported awareness of heated tobacco products and 1.7% had tried or were using the products. Among those who had ever tried heated tobacco products, 38.7% had tried it once or twice and 12.7% had been using it daily. However, survey participants were asked about heated tobacco products prior to answering about EC, which is likely to have had led to overestimations of awareness and use of heated tobacco products (see Brose and colleagues (358) for more details). The hypothesis that the ASH-A represents an overestimation is strongly supported by data from the STS. Between January and July 2017, nearly 12,000 respondents were surveyed. The STS did not ask about awareness of the product, only about use. Last-year smokers (n=2,185) were asked about use of heated tobacco products in recent quit attempts (n=4 reported use), to help cut down the amount smoked (n=6), in situations where not allowed to smoke (n=1) or for any other reason (n=0). Among never and long-term ex-smokers (n=9,777), n=5 said they were using heated tobacco products.

Conclusions

Key findings

- In mid 2017 heated tobacco products were commercially available in 27 countries and further country launches were planned. Three tobacco manufacturers were promoting heated tobacco products: ‘IQOS’ was promoted by PMI, ‘glo’ by BAT, and ‘Ploom TECH’ by Japan Tobacco International.
- Out of 20 studies that were included in this review, 12 were funded by manufacturing companies so there is a lack of independent research.
- There is a variety of heated tobacco products, including some that deliver via both vapour and combustion.
- Most studies published at the time of the search for this review evaluated IQOS, none evaluated glo or Ploom TECH. An updated version of the review inlcuding later publications is in preparation to be published separately.
- In Great Britain, in 2017, awareness and ever use of heated tobacco products were very rare.
- Nicotine in mainstream aerosol from heated tobacco products reached 70%–84% of the nicotine detected in smoke from reference cigarettes.
- The tested heated tobacco products delivered more nicotine in aerosol than a cigalike EC and less nicotine than tank style EC.
- Pharmacokinetics and delivery of nicotine after single use of a heated tobacco product were generally comparable with smoking a cigarette. However, studies that compared *ad libitum* use of heated tobacco products with smoking cigarettes

consistently reported lower nicotine levels in heated tobacco product users compared with smokers.
    - Probably to compensate, smokers who were switched to using heated tobacco products adjusted their puffing behaviour.
- Heated tobacco product use reduced urges to smoke, but smokers consistently reported heated tobacco product use to be less rewarding compared with smoking a cigarette.
- Compared with cigarettes, heated tobacco products are likely to expose users and bystanders to lower levels of particulate matter and harmful and potentially harmful compounds (HPHC). The extent of the reduction found varies between studies.
- The limited evidence on environmental emissions from use of heated tobacco products suggests that harmful exposure from heated tobacco products is higher than from EC, but further evidence is needed to be able to compare products.
- Japan, where EC are not available, has the most diverse heated tobacco product market with three tobacco manufacturers participating. Past 30 day use for the most frequently used product increased from 0.3% in 2015 to 3.7% in 2017, suggesting rapid penetration of heated tobacco products.

Implications

Research

- There is a need for more research that is independent of commercial interests.
- Different types of heated tobacco products will have different characteristics and effects, presenting a challenge for research
- Research is needed on relative risk of heated tobacco products to users and those around them compared with cigarettes and EC.
- Evidence is needed on appeal of heated tobacco products to smokers and non-smokers, particularly among youth.
- Effects on smoking need to be researched, this includes whether they replace or complement cigarettes. Due to co-branding of some products with cigarettes and the more similar sensory profile, findings may be different than for EC.
- Future studies, whether funded by manufacturers or independently should ensure conduct of studies in line with established guidelines such as definitions of abstinence from smoking, using intention-to-treat analysis and registering trial protocols prior to the start of participant recruitment.
- The appropriateness of different methods for measuring emissions and their translation from cigarettes to heated tobacco products should be evaluated to be able to recommend a gold standard.
- Prevalence and market share should be monitored, particularly in markets targeted by manufacturers.

  - In line with recommendations for EC use (135), measures should go beyond lifetime use or past 30 day use to assess current use; uptake and use should be assessed by smoking status.
  - Monitoring should include transitions between smoking, EC use and heated tobacco product use.

Policy and practice

- The available evidence suggests that heated tobacco products may be considerably less harmful than tobacco cigarettes and more harmful than EC.
- With a diverse and mature EC market in the UK, it is currently not clear whether heated tobacco products provide any advantage as an additional potential harm reduction product.
- Depending on emerging evidence on their relative risk to combustible tobacco and EC, regulatory levers such as taxation and accessibility restrictions should be applied to favour the least harmful options alongside continued efforts to encourage and support complete cessation of tobacco use.

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Appendices

1 ASH-A unweighted base sizes

1. By smoking status over time (age 18+)

	2012	2013	2014	2015	2016	2017
Total	12,436	12,171	12,269	12,055	12,157	12,696
Never-smokers	5,967	5,973	5,995	6,129	6,099	6,626
Ex-smokers	4,132	4,303	4,498	3,889	4,354	4,438
Smokers	2,337	1,895	1,776	2,037	1,704	1,632

2. By EC use and smoking status, 2017 (age 18+)

	Never smokers	Ex-smokers	Smokers	Total
Never heard of them/don't know	370	162	63	595
Never tried	6,146	3,491	600	10,237
Tried or used in the past	95	424	676	1,195
Currently using	15	361	293	669
Total	6,626	4,438	1,632	12,696

3. By EC use and smoking status for those who have used EC more than once or twice, 2017 (age 18+)

	Never smokers	Ex-smokers	Smokers	Total
Used in the past	45	253	405	703
Currently using	15	361	293	669
Total	60	614	698	1,372

2 Table of primary studies included in systematic reviews of EC for cessation or reduction (chapter 7)

Reviews	Rahman 2015 (175)		Hartmann-Boyce 2016 (171)		Khoudigian 2016 (173)		Vanderkam 2016 (176)		Kalkhoran & Glantz 2016 (172)		Malas 2016 (174)		El Dib 2016 (170)	
Primary studies	Incl. in review	Incl. in m-a	Incl. in review	Incl. in m-a	Incl. in review	Incl. in m-a	Incl. in review	Incl. in m-a	Incl. in review	Incl. in m-a	Incl. in review	Incl. in m-a	Incl. in review	Incl. in m-a
RCTs														
Adriaens 2014 (359)			✓						✓		✓	✓	✓	
Bullen 2010 (360)					✓									
Bullen 2013 (189)	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		✓	✓
Caponnetto 2013 (190)	✓	✓	✓	✓	✓	✓	✓	✓	✓				✓	✓
O'Brien 2015 (361)							✓		✓					
Uncontrolled intervention studies														
Caponnetto 2013b (362)			✓						✓					
Dawkins 2012 (363)					✓									
Dawkins 2013a (364)					✓									
Ely 2013 (365)			✓						✓					
Hajek 2015 (366)									✓	✓			✓	
Humair 2014 (367) [1]									✓					
McRobbie 2015 (268)[1]									✓					
Pacifici 2015 (368)			✓											
Polosa 2011 (243) *			✓				✓		✓					
Polosa 2014a (242)			✓				✓							
Polosa 2014b (369)	✓	✓	✓				✓		✓		✓	✓		
Polosa 2014c (370)			✓						✓					
Polosa 2015 (371)			✓						✓					

Reviews	Rahman 2015 (175)		Hartmann-Boyce 2016 (171)		Khoudigian 2016 (173)		Vanderkam 2016 (176)		Kalkhoran & Glantz 2016 (172)		Malas 2016 (174)		El Dib 2016 (170)	
Observational studies (non-intervention)														
Adkison 2013 (372)									✓	✓	✓	✓		
Al-Delaimy 2015 (373)			✓						✓	✓			✓	✓
Berg 2014 (374)							✓		✓					
Biener & Hargraves 2015 (375)							✓		✓	✓	✓	✓	✓	✓
Borderud 2014 (376)			✓						✓	✓			✓	✓
Brose 2015 (17)			✓				✓		✓				✓	✓
Brown 2014 (19)	✓	✓							✓	✓	✓		✓	✓
Choi 2014 (377)			✓						✓	✓				
Christensen 2014 (378)									✓	✓	✓	✓		
Dawkins 2013b (379)									✓		✓	✓		
Etter 2014 (380)	✓	✓	✓				✓		✓					
Gallus 2014 (381)									✓					
Goniewicz 2013 (382)											✓	✓		
Grana 2014 (383)			✓				✓		✓	✓	✓	✓		
Harrington 2015 (384)									✓	✓			✓	✓
Hitchman 2015 (20)							✓		✓	✓			✓	✓
Manzoli 2015(385)			✓				✓		✓	✓			✓	✓
McQueen 2015 (386)									✓	✓				
Pavlov 2015 (387)									✓	✓				
Pearson 2015 (388)							✓		✓	✓				
Prochaska 2014 (389)			✓						✓	✓			✓	✓
Shi 2015 (390)									✓	✓				
Siegel 2014 (391)	✓	✓							✓					
Sutfin 2015 (392)									✓	✓				
Tackett 2015 (393)									✓		✓	✓		
Vickerman 2013 (394)							✓		✓	✓			✓	✓

[1] *Conference abstract *same study*

3 Non–UK case reports concerning injuries caused by EC explosion (Chapter 8)

Author, publication year and location	n of cases	Gender	Age	Circumstance of EC explosion	Nature of injury	Treatment	Details of EC
Archambeau et al., 2016 (395) US	1	Male	59	In mouth while vaping	Fractures to skull and nose, black eye, laceration to lips. Pneumocephalus.	Oral and maxillofacial surgery	Bought it online 2 days previously, no modifications made
Bauman et al., 2017 (396)	3	Male	58	While in right trouser pocket	7% TBSA combination of deep partial-thickness and full-thickness burns to the back and side of left thigh	Wound management. Skin graft	Reported as unclear
US		Male	20	While in right trouser pocket (with coins and keys)	4% TBSA superficial, partial-thickness burn to the right thigh	Wound management	Immediately prior to the injury, the patient had changed the used battery
		Male	37	While in right trouser pocket	11% TBSA deep partial-thickness to full-thickness burn to left thigh and buttock	Wound management and skin graft	The lithium battery in his EC was over 1-year old
Bohr et al., 2016 (397) Germany	1	Male	24	While in right trouser pocket	8% TBSA superficial and deep burn and soot-particle contamination to right leg	Wound management	Tank style EC
Brooks et al., 2017 (398) US	1	Male	18	In mouth while vaping	Loss of three teeth and damaged a further three. External/intra oral lacerations. Fracture to nose.	Wound management and four teeth extracted	Had been vaping for approx. an hour and occurred after refilling EC with e-liquid.
Colaianni et al., 2016 (399)	3	Male		In mouth while vaping	Loss and fracture of several teeth. External/intra oral lacerations.	Sutures and dental care	Not reported
US		Male		While in right trouser pocket	Third-degree burn injuries to legs and second-degree burn injuries to genitalia and/or hands	Skin graft	Not reported
		Male		While in right trouser pocket	Third-degree burn injuries to legs and second-degree burn injuries to genitalia and/or hands	Skin graft	Not reported
Cason et al., 2016 (400) US	1	Male	23	In mouth while vaping	Multiple fractures to hard palate (roof of mouth) and nose. Loss of teeth. Fractured finger. Corneal abrasion.	Surgical repair of his hard palate	Not reported
Foran et al., 2017 (401) US	1	Male	30	While holding the EC	First and second-degree burns to left hand. Material from EC device embedded deep in tissue from high pressure injection	Wound management and surgery to finger immediately and 5 months later	Not reported
Harshman et al., 2017 (402) Canada	2	Male	31	While in trouser pocket along with coins (EC battery	10% TBSA mixed partial thickness and full-thickness burns to his right thigh, buttock and leg, and left inner thigh	Wound management and skin graft	Not reported
		Male	36	While in trouser pocket along with coins and keys (EC battery)	3% TBSA deep partial and full thickness burns to his right thigh and superficial partial thickness burns to right hand	Wound management and skin graft	Not reported

Author, publication year and location	n of cases	Gender	Age	Circumstance of EC explosion	Nature of injury	Treatment	Details of EC
Harrison and Hicklin, 2016 (403) US	1	Male	28	In mouth while vaping	Tooth loss and damage, burns to tongue, lips and gum	Teeth extraction, gum surgery and teeth implants	EC had just been charged (with a charger purchased separately to EC)
Jablow and Sexton, 2015 (404) US	1	Male	30	While in trouser pocket (lithium battery only)	8% TBSA superficial partial-thickness burn to right leg	Wound management	Not known
Jiwani et al., 2017 (405) US	10	Male	26	While in trouser pocket	5.5% Mixed partial and full thickness ***burn to*** left thigh and lower leg, groin and scrotal area	Wound management	Not reported
		Male	46	While in his lap	4.4% TBSA partial thickness burn to left thigh	Wound management	Not reported
		Male	19	Battery explosion (circumstance not reported)	3.5% TBSA mixed partial and full thickness Left hand and forearm, left thigh	Skin graft	Not reported
		Male	29	While in trouser pocket	4.5% TBSA full-thickness burn to left thigh	Skin graft	Not reported
		Male	19	Motorcycle crash inducing ignition of EC in trouser pocket	2% TBSA mixed partial and full thickness burn to right thigh	Wound management	Not reported
		Female	18	In mouth while vaping	1% TBSA partial thickness burn to right hand, dental and face trauma	Wound management	Not reported
		Male	38	While in trouser pocket	5% TBSA mixed partial and full thickness to right thigh	Skin graft	Not reported
		Male	22	While in trouser pocket (with keys)	3% TBSA burn to left thumb left thigh	Wound management	Not reported
		Male	29	Vaporiser explosion (circumstances not reported)	27.25% TBSA mixed deep partial and full thickness burns to Bilateral upper extremities, face, ear, anterior chest, abdomen	Skin graft and elective contracture releases of his axillary region and both hands at later date	Not reported
		Male	22	While in trouser pocket	3.25 TBSA mixed partial thickness burn to right thigh and right hand	Wound management	Not reported
Khairudin et al., 2016 (406) Malaysia	1	Male	18	While modifying the EC	Laceration to right eyelid and conjunctival. Traumatic mydriasis, anterior uveitis. Cataract.	Irrigation and suturing of the eyelid and conjunctival laceration wounds	Modifying the tank of the mechanical EC, changing the original coil to a homemade copper coil
Kite et al., 2016 (407)	2	Male	19	In mouth while vaping	External/intra oral lacerations. Loss of three teeth, fractures to four teeth	Oral and maxillofacial surgery	Homemade vaporizer
		Male	24	While holding EC	3% TBSA deep partial thickness, second-degree burns to chest and left forearm. Full thickness skin and soft tissue loss to right palm and fingers. Metal and chemical deposits in soft tissue of the hand	Surgery and eventually amputation of finger	Lone Wulf Mechanical Mod cigarette.

Author, publication year and location	n of cases	Gender	Age	Circumstance of EC explosion	Nature of injury	Treatment	Details of EC
Kumetz et al., 2016 (408) US	2	Male	29	In mouth while vaping	External/intra oral burns, lip lacerations and superficial burns. Loss and fracture of several teeth. Post-traumatic stress disorder.	Oral and maxillofacial surgery	Refillable rechargeable device
		Female	23	While in trouser pocket	4% TBSA partial and full thickness burn to the right thigh. Partial-thickness burns to palm and 3 fingers on right hand		Not reported
Norii and Plate, 2017 (409) US	1	Male	27	In mouth while vaping	Fractures of two vertebrae. Fractures to two teeth. Partial thickness burns to lips. Abrasion on tongue.	Surgery to remove EC component from spine	Occurred after replacement of a new battery
Paley et al., 2016 (410) US	2	Male	45	In mouth while vaping	First-degree burns to face and right hand. Loss of two teeth. Lacerations to both corneas and irises. Damage to eyesight.	Eye surgery	Not reported
		Male	16	While holding EC at chest level	Burns to face, neck, and hands and both corneas	Treatment for burns unspecified; irrigation and topical treatment to eyes.	Vape pen
Patterson et al., 2016 (411) US	2	Male	46	While in trouser pocket	1% TBSA partial thickness burns to left thigh, penis and two fingers of left hand	An 'operative intervention'	Not reported
		Male	41	In mouth while vaping	0.5% TBSA burn to face, lip laceration, corneal abrasion	Wound management	Not reported
Roger et al., 2016 (412) US	1	Male	18	In mouth while vaping	Oral and abdominal burns (severity not specified), oral lacerations, tooth loss and fracture	Reconstructive surgery and dental implants	Not reported
Shastry and Langdorf, 2016 (413) US	1	Male	26	In mouth while vaping	Small area of second-degree burns. Foreign body penetration in abdomen and chest; small penetrating foreign bodies in thumb	Wound care	Patient was a paid tester for an EC company. Was using an experimental customizable, device with a lithium-ion battery
Sheckter et al., 2016 (414) US	3	Male	34	While in trouser pocket	15 % TBSA[1]; deep partial-thickness and full-thickness burn of the right leg	Skin graft	Not reported
		Male	19	While in trouser pocket	7 % TBSA mixed partial- and full-thickness burn to the thigh and calf	Skin graft	Not reported
		Male	35	While in trouser pocket	2 % TBSA partial- and full-thickness burn to right thigh	Wound management	Not reported
Treitl et al., 2017 (415) US	3	Male	25	While in trouser pocket (lithium battery only)	6% TBSA partial thickness burns to the left thigh and knee	Wound management	Not reported
		Male	43	While in trouser pocket (battery only)	3–4% TBSA partial and full thickness burns to his right thigh, scrotum, and penis. < 1% TBSA partial thickness burns to hands. Neuropathic pain 4 months post event.	Wound management and transferred to burn centre	Not reported
		Male	30	While in trouser pocket (battery only)	10% TBSA, partial thickness burns, as well as 2–3% TBSA full-thickness burns to his left calf	Wound management and transferred to a burn centre for skin graft	Not reported

[1] *TBSA = total body surface area*