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Subject: SB63 Information

Hello Members of the Senate Finance Committee,

Please take a look at these documents that relate to the inclusion of vapor products in SB63. Most of the reports have been released since the end of the last legislative session, many being published in recent months. They are from both the US and other counties and all come to the same conclusion, vapor is not smoke and should not be treated as such, doing so would undermine efforts to help people stop their tobacco use. They show that vapor products are not the same as combustible products and should not be lumped together in smoke free bills as they do not produce smoke and there is no concern for bystanders. They also show the potential these product have to reduce tobacco use rates, reduce the amount of second hand smoke and first hand smoke in Alaska, decrease smoking related deaths and disease, thus lowering health care cost to the state. If the goal of SB63 is to protect and improve public health these new findings must be considered when forming policies. We all want to work together to make Alaska a healthier place to live and work making SB63 the best bill possible is part of that solution.

This is a study performed by the famous Mayo Clinic in Minnesota. They researched the feasibility of using vapor products to reduce smoking rate pre and post operation to reduces smoking related complications in their patients. They found this did work and that cigarette consumption was cut in half and 17% reported complete abstinence from cigarettes during the trial period.

This next document is the report put out this spring by Public Health England and the results of their extensive research on Vapor products in the UK. The first point they make in the Key Messages section that they want people to take away from the report is that smokers that smokers who have failed attempt to quit in the past should try Electronic cigarettes to stop smoking and that cessations services should include their use in the peoples's efforts to quit smoking. The second point they want people to see is that encouraging people to switch could reduce smoking related disease and death. They also state that vapor products are 95% safer than smoking in the sixth key message. This is a great report with lots of great information.

This next document also put out by Public Health England offers advice on making policy for public use and work place use. They state that Electronic Cigarettes or EC as they call them do not burn tobacco or produce smoke. They also state that there is "no evidence of harm to bystanders from exposure to e-cigarette vapour". They also state that EC "have the potential to make a significant contribution to its achievement" referring to the goal of being tobacco free by 2025. They also state that "To support smokers to stop smoking and stay smokefree, a more enabling approach may be appropriate in relation to vaping to make it an easier choice than smoking. In particular vapers should not be required to use

the same space as smokers, as this could undermine their ability to quit smoking and stay smoke free, particularly among those most heavily addicted." They also state that "to maximize the number of smokers switching to e-cigartette, vaping should be made a more convenient, as well as safer, option."

This study form Drexel University Peering through the mist concludes "Current state of knowledge about chemistry of liquids and aerosols associated with electronic cigarettes indicates that there is no evidence that vaping produces inhalable exposures to contaminants of the aerosol that would warrant health concerns by the standards that are used to ensure safety of workplaces."

Here is the press release from the results of last months report of a long term study by organizations both here and in the UK finding that cancer markers in people that use e-cigarettes is comparable to non smokers and could help reduce cancer rates.

This document is a report from the State Budget Solutions reporting that vapor product have the potential to save billions in Medicaid costs by reducing the amount of smoking related illness across the country. I know health care cost is a major category of our state's budget, if we could reduce that cost we could help reduce the deficit.

In this report funded by the FDA and the National Institute on Drug Abuse the author concludes "The primary aim of tobacco control policy should therefore be to discourage cigarette use while providing the means for smokers to more easily quit smoking, even if that means switching for some time to VNPs ratherthan quitting all nicotine use. Countries whose policies discourage VNP use run the risk of neutralizing a potentially useful addition to methods of reducing tobacco use." It also has flow charts showing the different results from use of vapor products many ending with former smokers.

Thank you for taking the time to look at and consider these reports, research, and policy suggestions. We can work together to create a bill to help current smokers kick their tobacco habits, former smokers stay some free and out of smoking areas where they would be more likely to take the habit back up, all while protecting the health of Alaskans across the state. Please remove references to vapor products from this bill, they do not produce smoke and do not belong in a smoke free bill. This simple change will help gain support for the bill and help improve public health in more ways than one.

Thanks again,

Alex McDonald

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Article Navigation

Feasibility of Electronic Nicotine Delivery Systems in Surgical Patients

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Abstract

Introduction:

Cigarette smoking is a known risk factor for postoperative complications. Quitting or cutting down on cigarettes around the time of surgery may reduce these risks. This study aimed to determine the feasibility of using electronic nicotine delivery systems (ENDS) to help patients achieve this goal, regardless of their intent to attempt long-term abstinence.

Methods:

An open-label observational study was performed of cigarette smoking adults scheduled for elective surgery at Mayo Clinic Rochester and seen in the pre-operative evaluation clinic between December 2014 and June 2015. Subjects were given a supply of ENDS to use prior to and 2 weeks after surgery. They were encouraged to use them whenever they craved a cigarette. Daily use of ENDS was recorded, and patients were asked about smoking behavior and ENDS use at baseline, 14 days and 30 days.

Results:

Of the 105 patients approached, 80 (76%) agreed to participate; five of these were later excluded. Among the 75, 67 (87%) tried ENDS during the study period. At 30-day follow-up, 34 (51%) who had used ENDS planned to continue using them. Average cigarette consumption decreased from 15.6 per person/d to 7.6 over the study period ($P < .001$). At 30 days, 11/67 (17%) reported abstinence from cigarettes.

Conclusion:

ENDS use is feasible in adult smokers scheduled for elective surgery and is associated with a reduction in perioperative cigarette consumption. These results support further exploration of ENDS as a means to help surgical patients reduce or eliminate their cigarette consumption around the time of surgery.

Implications:

Smoking in the perioperative period increases patients' risk for surgical complications and healing difficulties, but new strategies are needed to help patients quit or cut down during this stressful time. These pilot data suggest that ENDS use is feasible and well-accepted in surgical patients, and worthy of exploration as a harm reduction strategy in these patients.

Topic: smoking , surgical procedures, elective , surgical procedures, operative , cigarettes , electronic nicotine delivery system , perioperative period

Issue Section: Original Investigation

Introduction

Cigarette smoking increases the risks for postoperative complications in patients undergoing surgery, including cardiac, respiratory, and wound-related complications, and abstinence from smoking reduces these risks. [1] The duration of abstinence necessary for reduction of these risks is not known, but some evidence suggests that even a brief period of abstinence may be beneficial, [2,3] and that abstinence in the postoperative period itself may be helpful. [4] Numerous toxic compounds in cigarettes, including carbon monoxide, may contribute to risk, but available evidence suggests that patients benefit when nicotine replacement therapy (NRT) is used to achieve abstinence. [5] Although there are efficacious interventions available to help smokers quit, [6] including patients scheduled for elective surgery, the implementation of these interventions into clinical practice has proved challenging. For example, despite several years of active tobacco control efforts, at Mayo Clinic Rochester, approximately 40% of cigarette smokers still smoke on the morning of their surgical procedure (unpublished observations). Clearly, new strategies are needed to reduce exposure to cigarette smoke in the perioperative period.

Electronic nicotine delivery systems (ENDS) have recently exploded in popularity. [7,8] Also known as "electronic cigarettes" or "E-cigarettes," these devices vaporize nicotine solutions with some devices mimicking the look and feel of tobacco cigarettes. ENDS have been promoted as potential harm-reduction devices. [9] Although data are limited, some studies (but not all) suggest that at least some cigarette smokers are using ENDS to reduce or eliminate tobacco smoking. [10–14] Given that ENDS produce a nicotine-containing vapor, it is likely that any deleterious effects are less than conventional cigarettes, as many of the harmful constituents in tobacco smoke result from the combustion of tobacco leaf. Although the content of vapors produced by different ENDS varies and their long-term safety is not known, the levels of harmful substances found in ENDS are generally lower than those produced by combustible tobacco products. [15,16] ENDS are also available in a range of nicotine concentrations, including nicotine-free. However, the net public health effects of the widespread introduction of ENDS remain almost wholly unknown, and their potential impact (for good or harm) is a subject of considerable debate. [17]

NRT is a common component of efficacious interventions to help surgical patients quit smoking. [6] It is possible that ENDS, as a form of NRT, could be useful in helping smokers reduce or eliminate their smoking in the perioperative period, especially given emerging data that smokers may view ENDS more favorably than traditional NRT. [18] In pilot survey work, we have shown that smokers scheduled for elective surgery who are seen in Mayo Clinic Rochester Preoperative Evaluation Center express considerable interest in using ENDS to reduce their tobacco consumption. [19] However, it is not clear whether patients scheduled for surgery, who may have no experience with ENDS and many distractions in the busy perioperative period, would be able to consistently utilize these devices.

This study aimed to determine the feasibility and acceptability of ENDS in the perioperative period among cigarette smokers scheduled for elective surgery. A secondary objective was to determine how access to ENDS was associated with changes in cigarette consumption both preoperatively and up to 2 weeks following discharge from the surgical facility.

Methods

This study was approved by the Mayo Clinic Institutional Review Board, Rochester, Minnesota. Written informed consent was obtained.

Recruitment

Subjects were recruited from patients scheduled for elective surgery who were evaluated in the Mayo Clinic Preoperative Evaluation Center (POE), where approximately 15% of elective surgical patients at Mayo Clinic Rochester are seen. Patients undergoing a wide variety of elective procedures, including orthopedic, plastic and reconstructive, and oncologic procedures, are evaluated in this center. Inclusion criteria included age at least 18 years and current smoking (defined as >100 cigarettes lifetime consumption and self-report of smoking either every day or some days) prior to evaluation. For women of child-bearing potential, a negative pregnancy test was required. Exclusion criteria included current use of END (past use was not an

exclusion), current use of pharmacotherapy for nicotine dependence, pregnancy or lactation, and those whose surgeons specifically directed them not to use NRT prior to surgery. Eligible subjects were approached on a convenience basis and invited to participate, regardless of any intent to modify smoking behavior in the perioperative period; that is, subjects were not selected based on their willingness to quit or cut down smoking.

Study Procedures

After enrollment, study personnel delivered a brief intervention emphasizing the importance of quitting or cutting down on smoking in the perioperative period (Supplementary Appendix). The intervention also introduced the concept of ENDS, and provided instructions for their use. They were encouraged to use ENDS instead of cigarettes when they desired to smoke.

Study subjects were then given a supply of NJOY ENDS sufficient for use in the preoperative period and up to 2 weeks postoperatively in one of three varieties depending on patient preference and baseline cigarette consumption: NJOY KingsTraditional Gold (2.4% nicotine), NJOY Kings Traditional Bold (4.5% nicotine, offered to subjects smoking ≥15 cigarettes/d) and NJOY Kings Menthol (3% nicotine). The NJOY Traditional Gold product was selected because it is a single-use, disposable product that requires minimal training, and because there were published investigation of its pharmacokinetics at the time of study design. [20] According to the product label, each NJOY device delivers the equivalent of approximately one pack of tobacco cigarettes (20 cigarettes), although there is considerable variability in use patterns and recent data suggest that actual delivery does not achieve nicotine levels comparable to a cigarette. [10] The cost per device is $4.75, which is less expensive or comparable to purchasing regular cigarettes, depending on the pattern of ENDS use. Study subjects were supplied a sufficient number of devices to completely replace their use of tobacco cigarettes from the time of POE evaluation until 2 weeks after anticipated discharge from the surgical facility (median length of stay 1 day, IQR 0–2), along with an additional four devices to account for variability in use patterns. For example, the median time from POE evaluation to surgery is 1 day. Thus, a typical subject who smokes 20 cigarettes per day would have been given 15 NJOY ENDS, plus

an additional 4 to account for subject variability. Study subjects scheduled for surgery more than 1 week from the time of POE evaluation were given sufficient supply to support 1 week of preoperative and 2 weeks of postoperative ENDS use.

Study Measurements

Assessments were performed at baseline in the POE clinic, and at 14 and 30 days post discharge from the surgical facility. In addition, patients were asked to keep a daily diary of ENDS use for 1 week before surgery and 14 days after discharge.

Baseline

A survey administered via iPad (REDCap Survey, a secure, web-based electronic data capture tool hosted at Mayo Clinic) [21] queried demographic information, baseline measures of smoking history, and Surgical Risk and Health Concerns Indices assessing knowledge of how smoking affects surgical risk and health in general, respectively. [22] If subjects had used ENDS, additional items queried the reasons they used ENDS and their perceived benefits. Finally, the survey included items used in our prior work regarding interest in using ENDS to maintain perioperative abstinence (four items), perceived benefits in using ENDS to maintain perioperative abstinence (four items), and perceived barriers to using ENDS to maintain perioperative abstinence (five items). [19] The factor structure of ENDS-related indices, including internal consistency of scales and factor loading of each indicator was previously analyzed and found acceptable. [19]

Daily Diary Up to 14 Days Post Discharge

At the time of enrollment, subjects were given a paper diary in which to record their episodes of use of either ENDS or tobacco cigarettes over this period, as well as the number of ENDS finished each day. The diary also included binary response items (agree/disagree) to be completed at 14 days regarding their experience in using ENDS. Subjects were asked to return the diary via mail, and received $40 remuneration if they did so. Study personnel contacted participants by phone at 14 days to remind them to send the diary and survey. Study personnel first attempted to contact the subject on

day 14, and for up to 1 week after that time. If the patient reported losing the diary or not recording their use, study personnel verbally completed the 14-day survey with the patient during this phone call.

30 Days Post Discharge

Subjects were contacted by telephone to determine smoking behavior since surgery, ENDS utilization and a summary of ENDS use.

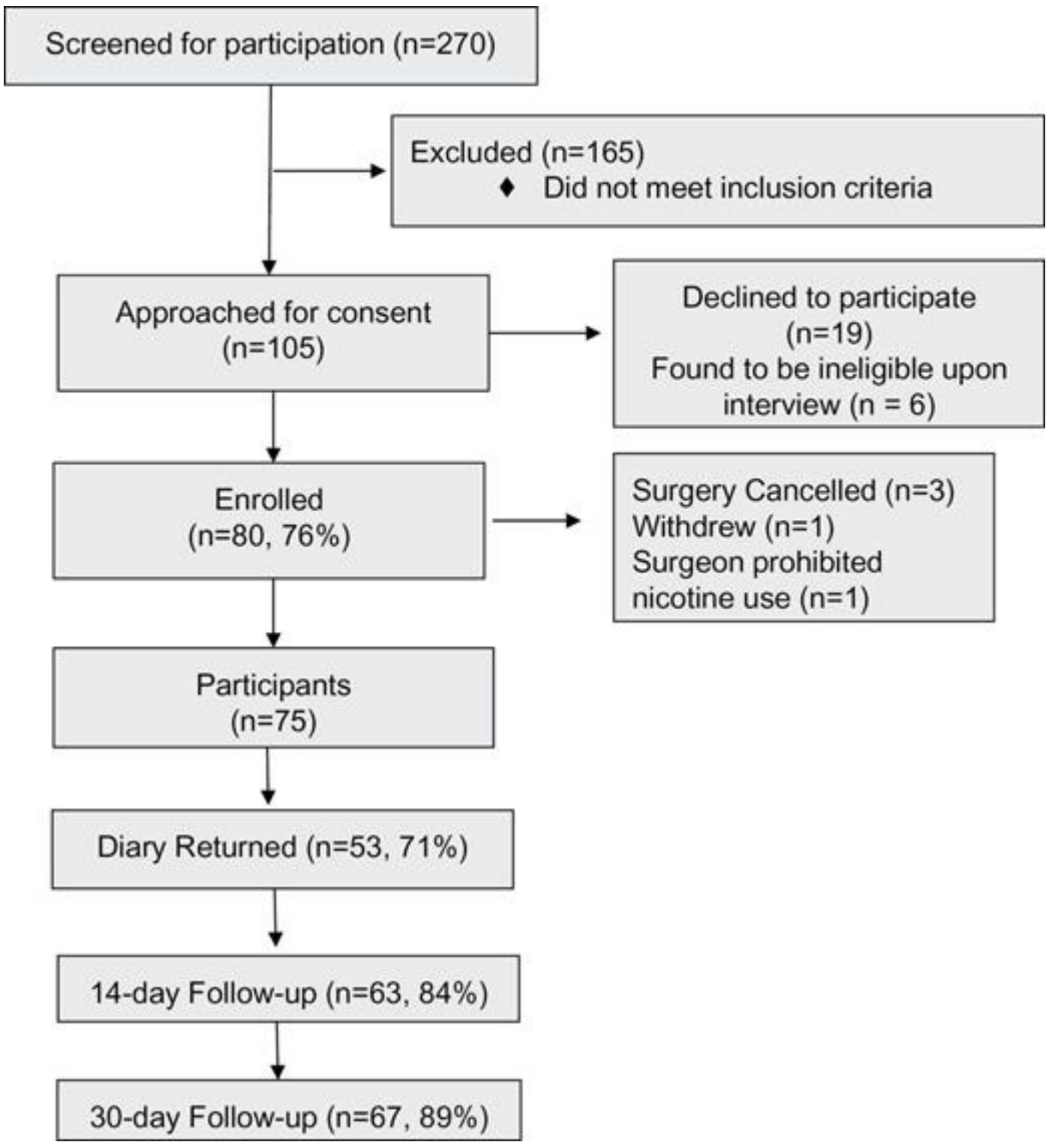
Statistical Analyses

The primary endpoints of this pilot study were the proportion of subjects who utilized ENDS before and after surgery and the number of times it was utilized. The secondary endpoint of this study was cigarette consumption. With a sample size of 80, this study was designed to have a power of 0.90 to detect a 20% decrease in cigarettes per day compared with baseline values. Descriptive statistics were used to characterize each of the primary and secondary endpoints listed above, with 95% CI used to present variability for proportions and standard deviation for continuous variables. Survey information was entered into REDCap directly by the participant (for enrollment survey) or indirectly by study personnel (for 14- and 30-day follow-up), which allowed for the automated export of data to statistical packages for analysis. Indices including the Surgical Risk Index, the Health Concerns Index, and three ENDS-related indices assessing interest in, perceived benefits of, and barriers to perioperative use, were scored and reported as mean ± standard deviation. The Surgical Risk Index was scored by summing the number of "yes responses." For the Health Concerns Index, each response was assigned a numerical value, with higher values indicating greater concern. For the ENDS-related indices, a score was calculated by averaging the numerical values assigned to each Likert response (1 = strongly disagree, 5 = strongly agree). Thirty-day outcomes were compared to baseline using Wilcoxon sign rank tests.

Results

A flow diagram of the recruitment process is illustrated in Figure 1 . Enrollment among patients who were eligible and approached for consent was high (76% of eligible patients enrolled). Of the 80 patients enrolled, five were excluded after enrollment (reasons shown in Figure 1). Of the 75 remaining participants, 53 (71%) returned the daily diaries; 63 (84%) and 67 (89%) were contacted at days 14 and 30, respectively. The median time from enrollment to surgery was 1 day [IQR 1–3.25].

Figure 1.



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Flow of patient recruitment, participation, and follow-up.

Baseline Characteristics

Most participants were older, male, at least high-school educated, and white (Table 1). Most also had a long history of cigarette consumption and had made at least one prior quit attempt, with about one-third making an attempt within the past year. Approximately half stated that they intended to remain abstinent after surgery, and approximately one in four felt that they were likely or very likely to succeed in doing so. Values of the Surgical Risk Index and Health Concerns Index were consistent with a strong appreciation of the risks of smoking to health.

Table 1.

Demographics and Baseline Data [a]

Age	60±9
Female gender	31 (42)
Education of high school/GED and beyond	71 (96)
Caucasian	106 (95)
Cigarettes/d	16±9.7
Prefer menthol cigarettes	4 (5)
Number of year of smoking	36±13.6
At least one quit attempt previously	63 (84)
Tried to quit within last year	28 (37)
No plan to quit smoking	9 (12)
Nicotine dependence (FTND score)	4.3±2.0
Surgical risk index (four items, max score = 4) [b]	2.9±1.4
Health concern index (three items, max score = 9) [b]	7.0±1.1

Plan to stay off cigarettes after surgery	52 (69)
Interest index (four items, max score = 20) [b]	17.6±2.1
Perceived benefits (four items, max score = 20) [b]	16.9±2.5
Barriers index (four items, max score = 20) [b]	9.9±2.6
Likely to stay off cigarettes after surgery	
Very likely	2 (3)
Likely	24 (32)
Neither likely nor unlikely	33 (44)
Unlikely	13 (17)
Very unlikely	3 (4)
Succeed at quitting smoking	
Extremely sure	1 (1.3)
Very sure	16 (21.3)
Somewhat sure	35 (48)
Not at all sure	22 (29.3)

[a] For proportions, values are given as *n* (%) for the 75 patients included in the analysis. Values for continuous variables are presented as mean ± standard deviation. FTND = Fagerstrom test for nicotine dependence; GED= general educational development, a marker of high school completion equivalence.

[b] Indices calculated as described in the methods.

Approximately two-thirds of participants had heard of ENDS, but had never tried them; most of the remainder had tried them, but no longer used them. Among those who had tried ENDS in the past (n = 24), the most common reason was to attempt abstinence from cigarettes. However, most of these individuals did not find them

useful for this purpose. Table 2 lists the interest in, perceived benefits of, and perceived barriers to using ENDS in the perioperative period for all participants. High proportions agreed or strongly agreed that they would be willing to use ENDS to help them eliminate or reduce regular cigarette use around the time of surgery, and similar proportions perceived health benefits of doing so. The corresponding values of the indices calculated from these responses regarding interest, perceived benefits, and perceived barriers were consistent with favorable perceptions of perioperative ENDS use (Table 1).

Table 2.

Interest, Perceived Benefits, and Barriers to E-Cigarette (E-Cig) Use

	1	2	3	4	5
Willing to try e-cigs to help me stay off or cut down regular cigarette around the time of surgery	44 (59)	30 (40)	1 (1)	0 (0)	0 (0)
If they were available free of charge, I would try to use them to help stay off or cut down regular cigarette use around the time of surgery	43 (57)	30 (40)	2 (3)	0 (0)	0 (0)
Even if I needed to buy them myself, it would be worth to try e-cigs to stay off or cut down regular cigarettes around the time of surgery	28 (37)	35 (47)	10 (13)	2 (3)	0 (0)
I think that e-cigarettes could help me stay off or cut down regular cigarette use around the time of surgery.	30 (40)	35 (47)	10 (13)	0 (0)	0 (0)
Using e-cigarettes instead of smoking regular cigarettes could help me do better after my surgery	27 (36)	37 (49)	11 (15)	0 (0)	0 (0)
E-cigarettes could help me cope with not being able to smoke regular cigarettes while in the hospital for my surgery	25 (33)	36 (48)	13 (17)	0 (0)	1 (1)
It would be better for my health if I could use e-cigarettes around the time of surgery rather than smoking regular cigarettes	30 (40)	36 (48)	9 (12)	0 (0)	0 (0)
Using e-cigarettes could help me improve my health around the time of surgery	29 (39)	35 (47)	11 (15)	0 (0)	0 (0)

Nicotine could cause problems for my surgery whether I get it by smoking or through e-cigarettes	15 (20)	33 (44)	24 (32)	2 (3)	1 (1)
It would be hard for me to learn how to use e-cigarettes around the time of my surgery	4 (5)	6 (8)	19 (25)	36 (48)	10 (13)
I have too many other things to worry about other than to try e-cigarettes around the time of surgery	3 (4)	6 (8)	19 (25)	36 (48)	11 (15)
E-cigarettes would be too expensive for me to use	3 (4)	3 (4)	36 (48)	28 (37)	5 (7)
I am concerned that e-cigarettes are not safe	2 (3)	5 (7)	28 (37)	32 (43)	8 (10)

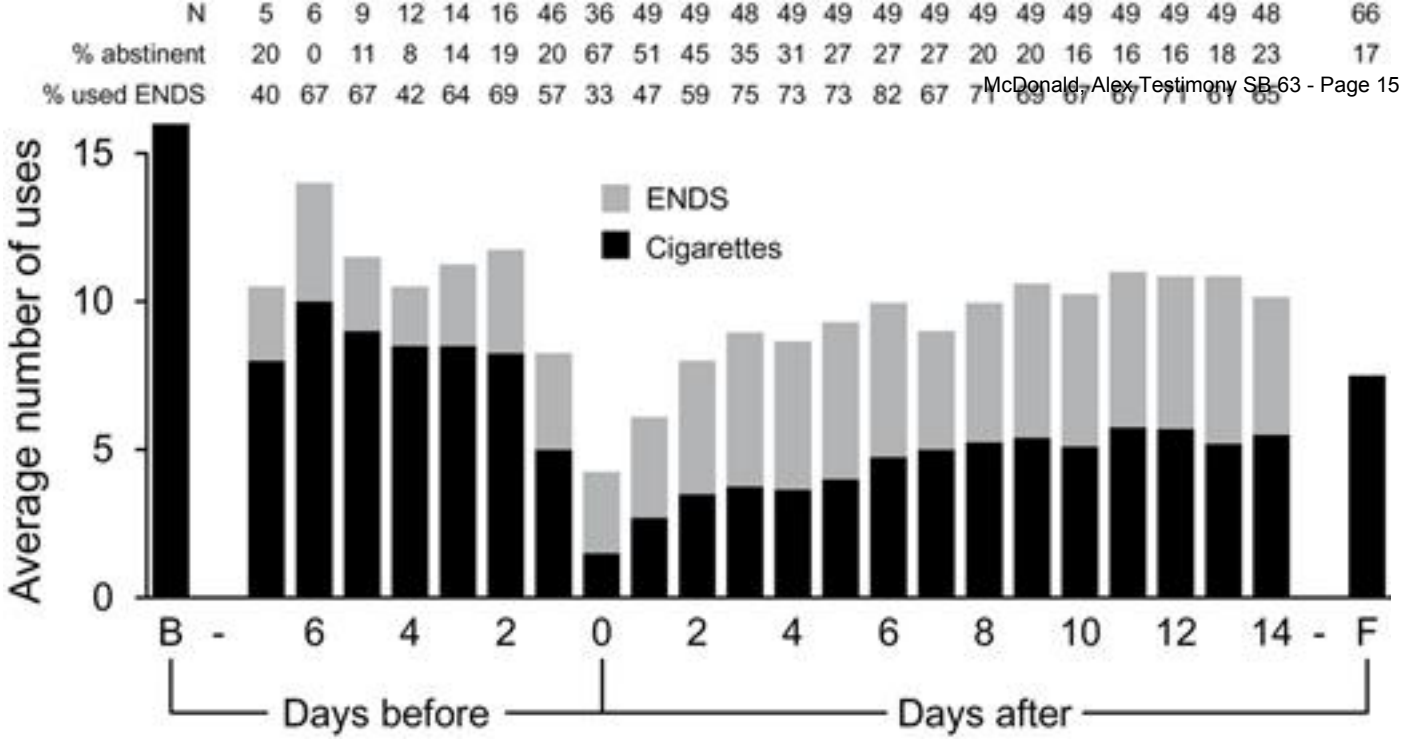
Values given as *n* (%) for the 75 participants. 1 = strongly agree; 2 = agree; 3 = neither agree nor disagree; 4 = disagree; 5 = strongly disagree.

ENDS Utilization (Primary Outcome)

For the 67 participants contacted on day 30, 58 (87%) reported at least one use of ENDS during the study period; 21 (32%) used ENDS before their surgery, and 58 (87%) used them afterward. At day 30, 34 (51%) of the 58 participants who had used the ENDS reported planning to continue using them in the future. Nine (16%) reported having finished their given ENDS supply and having already purchased additional ENDS for continued use.

ENDS use in the 53 participants who returned their daily diaries is presented in Figure 2 . The number of ENDS uses (defined as “e-times,” or number of episodes of ENDS use per day) was relatively stable from 1 week prior to surgery until 14 days after surgery (the period over which free ENDS were provided), as was the proportion of participants using ENDS. The relatively low absolute number of ENDS users from 2 to 7 days prior to surgery reflects the fact that most subjects were enrolled the day prior to surgery; regardless of when enrolled, approximately two-thirds of patients used ENDS preoperatively. On the day of surgery, 12 (33%) of participants used ENDS.

Figure 2.



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Cigarette and electronic nicotine delivery systems (ENDS) usage for study participants at the following timepoints: baseline (B, at enrollment), the 7 days before surgery (days −7 to −1), the day of surgery (day 0), the 14 days after surgery (days 1–14), and 30-day follow-up (F). The number of subjects reporting data each day (*N*) appears at the top of the figure, along with the proportion of subjects reporting who were abstinent from cigarettes on that day, and the proportions of subjects reporting who used ENDS at least once that day.

Of participants returning diaries, 46 answered items regarding their experiences using ENDS. Of these, 39 (85%) would be willing to try ENDS again for future surgeries, 29 (63%) felt that ENDS helped them cope with not smoking regular cigarettes, 33 (72%) felt that ENDS helped them quit or cut down on regular cigarettes, and 35 (76%) felt that their health was benefitted by their ENDS use.

Tobacco Use (Secondary Outcome)

At 30 days after discharge, 11 of the 67 participants contacted (17%) self-reported 7-day point prevalence abstinence from smoking. For these 67 participants, cigarette consumption at 30 days decreased significantly compared with baseline consumption (from 15.6 to 7.6 cigarettes per day, $P < .001$). Figure 2 presents cigarette use for the 53 participants who returned their daily diaries. The proportion of respondents who were abstinent on a given day in the preoperative period ranged from 0% to 20%. Two-thirds of those who reported their smoking behavior on the day of surgery maintained abstinence, with the proportion of abstainers ranging from 16% to 51% in the

subsequent 14 days. Over this postoperative period, on average approximately half of the instances of nicotine self-administration by subjects were via cigarettes, and half via ENDS.

Discussion

The major finding of this feasibility study was that when cigarette smokers scheduled for elective surgery were offered free ENDS at the time of pre-anesthesia evaluation, a high proportion utilized them in the perioperative period, with an associated reduction in cigarette consumption.

Consistent with our prior formative work, [19] interest in ENDS utilization was high in this pre-surgical population, as indicated by the baseline survey, the high enrollment rate and the high rate of utilization. This occurred despite the considerable life disruptions that surround the surgical experience, relatively high level of nicotine dependence, relatively low self-efficacy for maintaining abstinence, and no prior experience with ENDS for most patients. Approximately half of patients were sufficiently satisfied with their experience that they planned to continue ENDS use, and most would be willing to use ENDS again for future surgeries. These findings suggest that ENDS are potentially feasible and well-accepted in surgical patients who smoke. To our knowledge, there are no prior comparable studies reporting uptake of ENDS when their use is encouraged by healthcare professionals in a medical population.

This study also provides evidence that the use of ENDS in surgical patients was associated with a reduction in cigarette consumption. The potential of ENDS to impact smoking behavior has led to exploration of whether they could be effective tools to reduce or eliminate cigarette consumption, with variable results. [11] The current findings are consistent with prior observations in different settings that ENDS use is associated with modification of tobacco use. However, with this observational study design it is not possible to determine whether their use actually changed smoking behavior. Surgery itself serves as a “teachable moment” for changes in smoking behavior, [23] and patients may spontaneously reduce or eliminate consumption in the

absence of any intervention. Whether ENDS are efficacious in modifying smoking behavior in this setting requires further investigation using a control group not given ENDS. Nonetheless, these preliminary data are at least consistent with the concept that ENDS use could facilitate a reduction in cigarette consumption.

Given the apparent feasibility of ENDS use in surgical patients, several questions need to be explored before their use could be recommended in the perioperative period. Perioperative abstinence clearly reduces the risk for pulmonary and wound-related complications; whether reduced consumption would also be beneficial is unknown. Initial evidence suggests that dual use can reduce exposure to toxicants in cigarettes in the short term. [16] However, it is not clear, for patients unwilling to abstain, whether advocating a harm reduction strategy of replacing some portion of regular cigarette consumption with ENDS would be beneficial to surgical outcomes. Tobacco interventions incorporating approved NRT are efficacious to achieve sustained postoperative abstinence in the surgical population [6] ; the efficacy of ENDS remains to be determined. If efficacy were equivalent, ENDS would have the potential to be more effective in practice, given the high level of interest expressed in this and our prior study. As a further indication of potential interest, in a prior study of patch NRT in the same study setting (in which the intent to abstain also was not an inclusion criterion), [24] approximately 10% of those approached enrolled, compared with 76% in the present study. Given the relatively low nicotine delivery of the ENDS product used in the present study, it is possible that newer ENDS products that deliver nicotine at levels comparable to smoking could have an even greater impact on reducing or eliminating tobacco use.

In addition, the consequences of dual use beyond the immediate postoperative period would need to be considered, including the question of who could provide ongoing smoking cessation services and support to dual users, and if such use would potentially interfere with the “teachable moment” effect of surgery to promote spontaneous abstinence. [23] On the other hand, attempts to reduce consumption using NRT in smokers with an intention to quit significantly increases cessation rates, [10] raising the potential that ENDS could serve as an attractive means to initiate pharmacotherapy in this population who might otherwise not be willing to do so.

Finally, promotion of these devices by healthcare professionals given the rapidly

evolving state of ENDS development and regulation would be problematic. There is a wide array of available products, with potentially differing safety profiles (which themselves remain to be determined), and the FDA has not approved these devices for any type of smoking cessation or reduction. If ENDS were found in future studies to be effective in reducing perioperative risk, clinicians would likely insist upon a well-characterized, standardized ENDS product approved for this purpose.

Limitations of this study include the likelihood that those most interested in ENDS were more likely to enroll (although consent rates were high) and that results from this specialty practice in the upper Midwest, with a high proportion of Caucasian patients and many with greater than a high school education, may not apply to all practice settings. Also, as mentioned above, this pilot observational study did not have a control group, limiting our ability to determine any effect of ENDS on smoking behavior.

These results support further exploration of ENDS as a means to help surgical patients reduce or eliminate their cigarette consumption around the time of surgery.

Supplementary Material

Supplementary Appendix can be found online at http://www.ntr.oxfordjournals.org

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Declaration of Interests

SL has been funded by McNeil and GSK to test a nicotine delivery system for tobacco treatment.

DOW has been funded by Pfizer to develop a tobacco control curriculum for anesthesiology and surgery residents. IC, MN, SK, DS, and AH have nothing to disclose.

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Public Health England

Protecting and improving the nation's health

E-cigarettes: an evidence update

A report commissioned by Public Health England

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About Public Health England

Public Health England exists to protect and improve the nation's health and wellbeing, and reduce health inequalities. It does this through world-class science, knowledge and intelligence, advocacy, partnerships and the delivery of specialist public health services. PHE is an operationally autonomous executive agency of the Department of Health.

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Contents

Foreword

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

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

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

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

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

Duncan Selbie, Chief Executive, PHE

Key messages

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

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

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

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

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

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

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

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

Executive summary

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

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

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

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

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

Summary of Chapter 3: UK policy framework

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

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

Policy implications

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

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

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

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

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

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

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

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

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

Policy implications

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

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

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

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

Policy implications

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

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

Summary of Chapter 6: E-cigarettes and smoking behaviour

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

Policy implications

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

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

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

Summary of Chapter 7: Reasons for use and discontinuation

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

Policy implications

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

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

Summary of Chapter 8: Harm perceptions

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

Policy implications

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

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

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

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

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

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

Policy implications

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

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

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

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

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

Policy implications

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

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

Summary of Chapter 11: Other health and safety concerns

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

Policy implications

- The risks from fire or poisoning could be controlled through standard regulations for similar types of products, such as childproof containers (contained within the TPD but which are now emerging as an industry standard) and instructions about the importance of using the correct charger.

- Current products should comply with current British Standard operating standards.

- Records of EC incidents could be systematically recorded by fire services.

Summary of Chapter 12: International perspectives

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

Policy implications

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

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

1. Introduction

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

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

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

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

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

Description of e-cigarettes

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

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

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

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

Structure of report

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

2. Methodology

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

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

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

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

Smoking Toolkit Study (STS, University College London)

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

ASH Smokefree GB (adult and youth) surveys

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

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

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

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

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

ASH GB Smokers' survey 2014

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

ITC Policy Evaluation project

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

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

3. UK policy framework

E-cigarette regulations in England: current and proposed

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

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

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

EU Tobacco Products Directive (TPD) route

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

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

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

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

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

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

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

Medicines and Healthcare products Regulatory Agency (MHRA) licensing route

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

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

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

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

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

Summary of findings

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

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

Policy implications

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

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

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

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

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

Measures used

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

Use of e-cigarettes by adults

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

Population use of e-cigarettes

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

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

Table 1: Adult EC current use[1]

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

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

Never smokers and long-term ex-smokers

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

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

Smokers

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

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

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

Summary

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

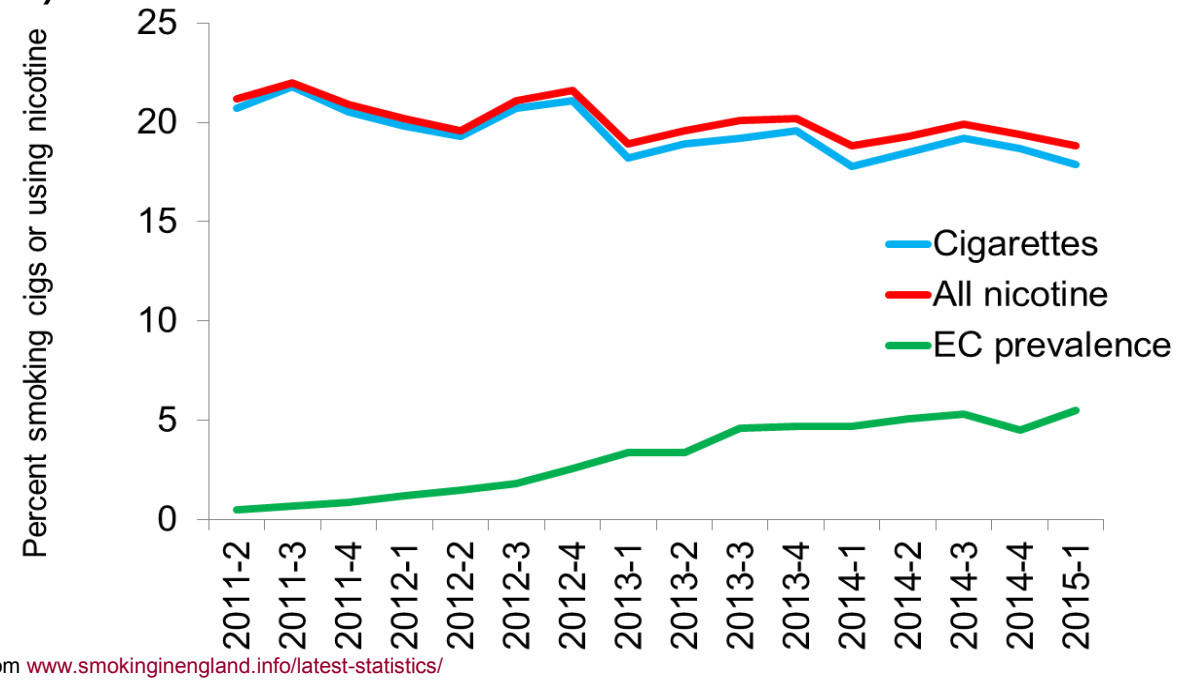
Trends in e-cigarette use among adults

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

Smoking Toolkit Study (STS) data

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

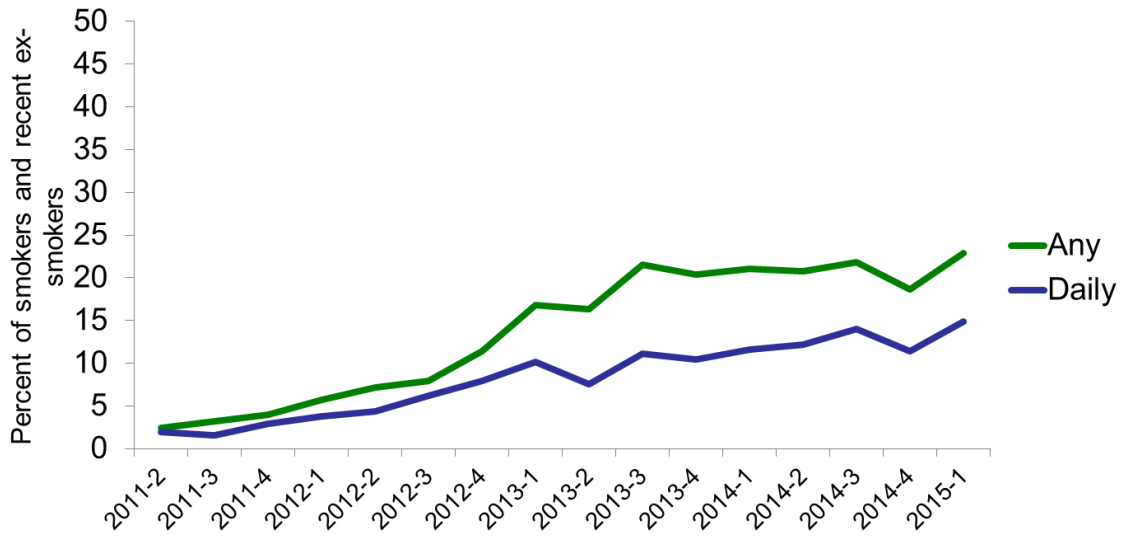
Figure 1: Prevalence of smoking and e-cigarette use among the adult English population (STS)



From www.smokinginengland.info/latest-statistics/

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

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



From www.smokinginengland.info/latest-statistics/

ASH Smokefree GB adult survey

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

Summary

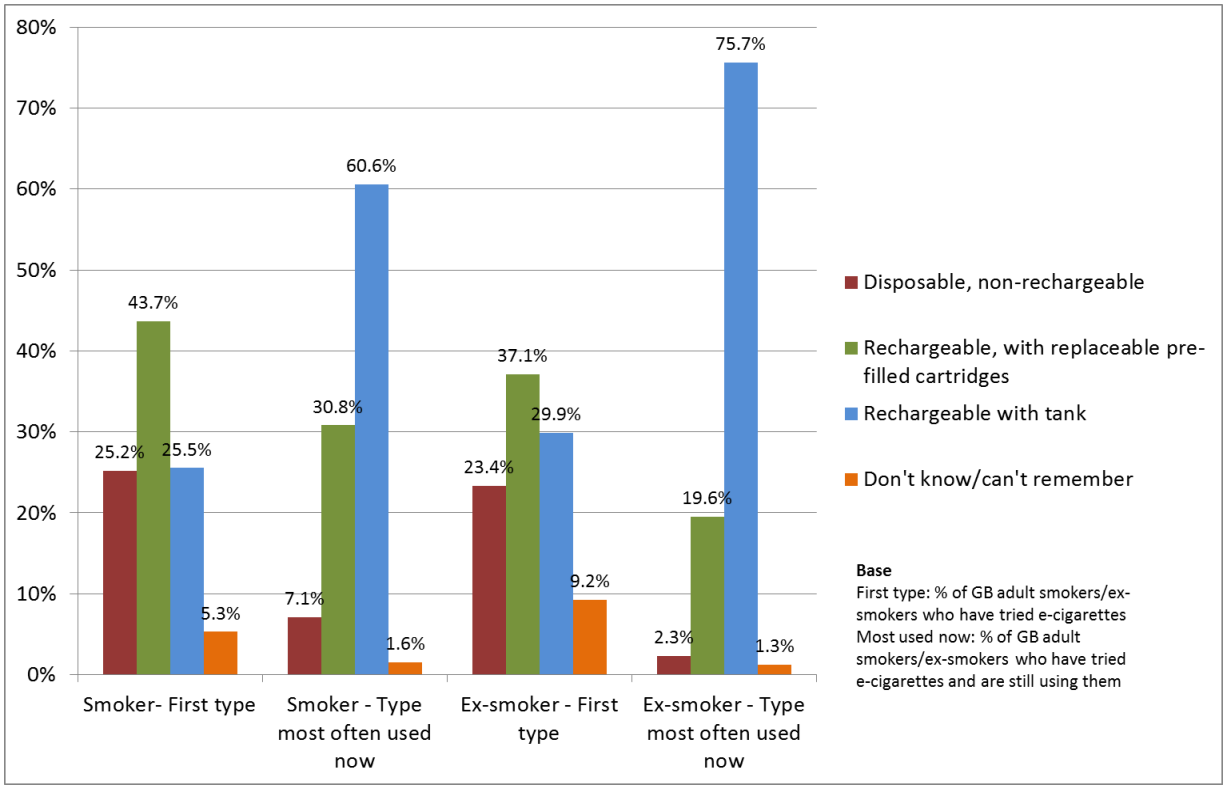
The prevalence of EC use among adults has plateaued. Most of the recent increase in use appears to be among ex-smokers. Cigarette smoking has declined over the period when EC use increased and overall nicotine use has also declined. These findings suggest that the advent of EC is not undermining and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

Types and flavours of e-cigarettes used among adults

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

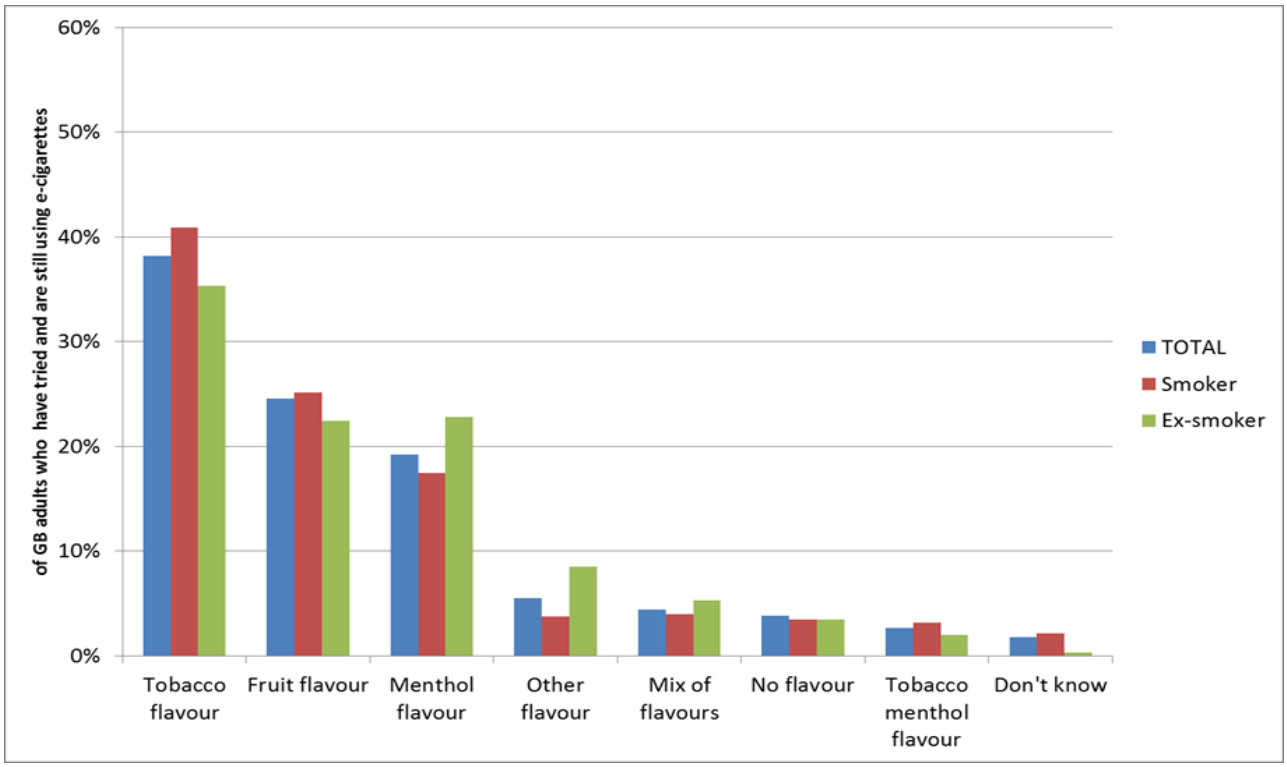
For those *still using EC* from the same survey, only 5% were *now mostly* using a disposable, 26% a rechargeable with replaceable pre-filled cartridges and 66% rechargeable with tank/reservoir filled with liquids (2% didn't know/couldn't remember). **This suggests that a considerable proportion of those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

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



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

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



Use of e-cigarettes among young people

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

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

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

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

Table 2: E-cigarette use among young people

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

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

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

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

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

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

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

Summary

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

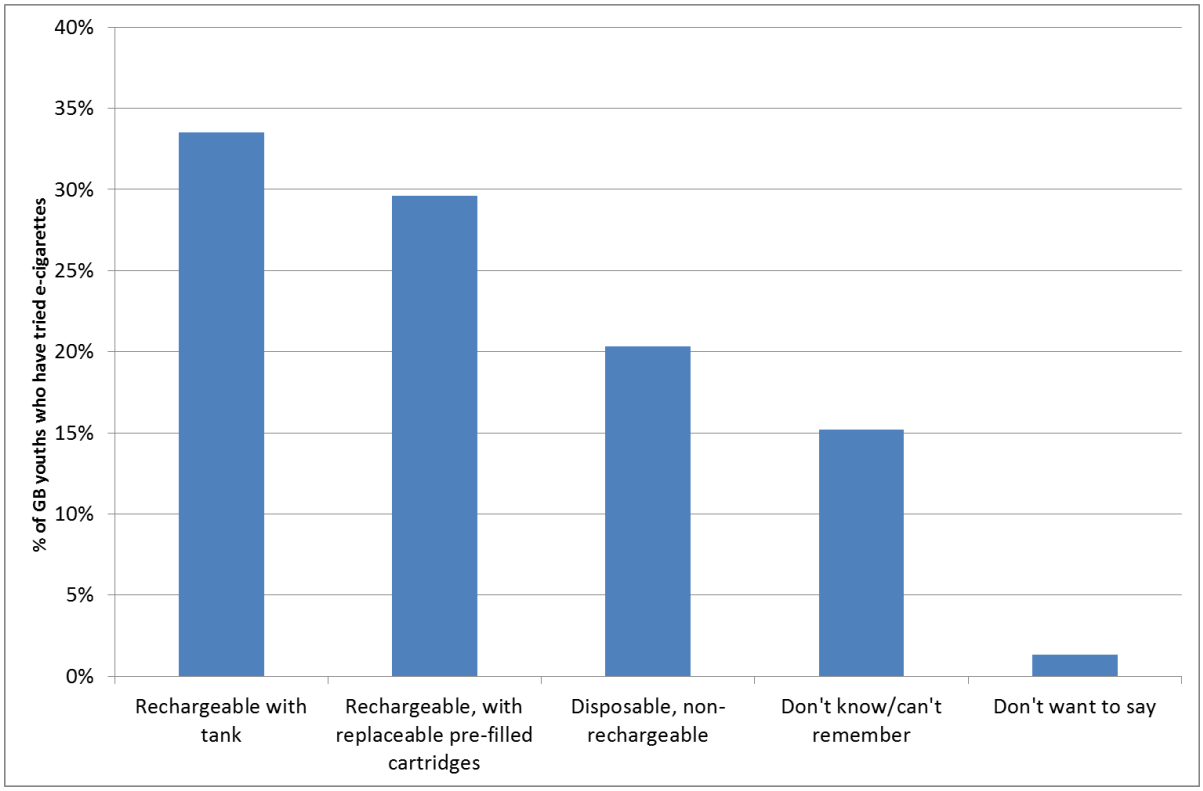
Trends in e-cigarette use among young people (ASH Smokefree GB youth)

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

Type and flavour among youth

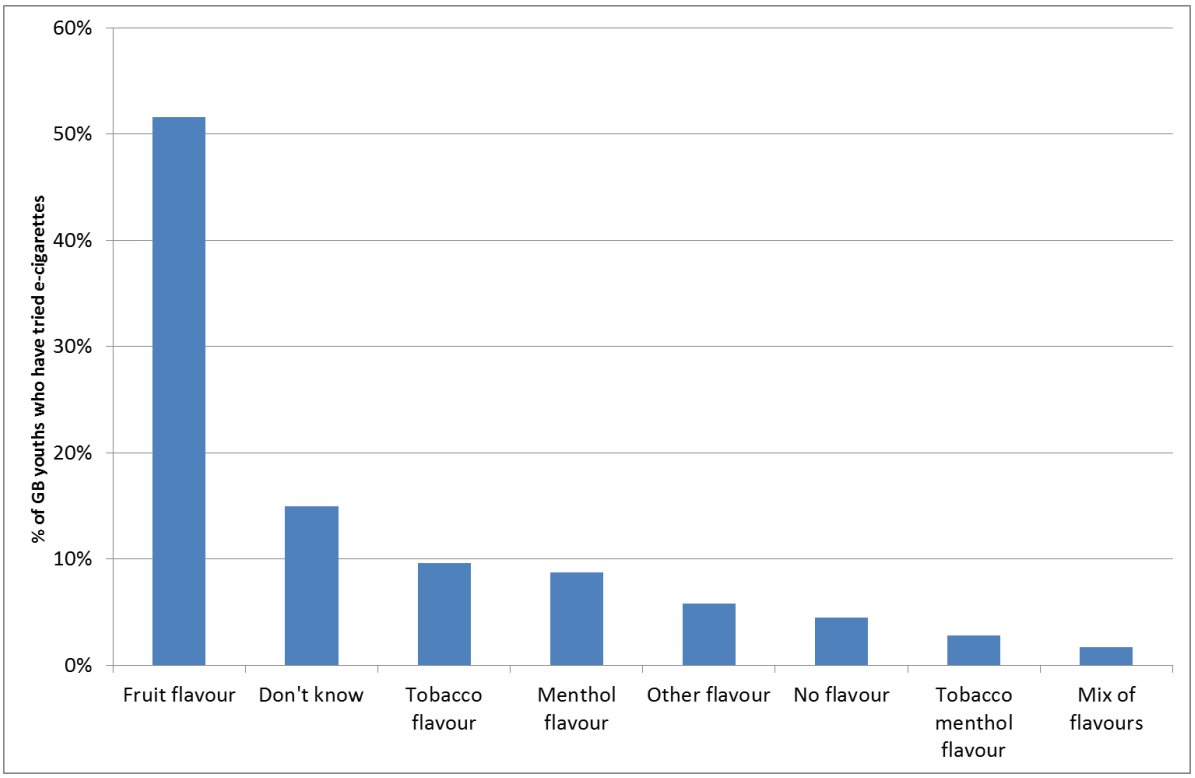
The proportion of youth reporting current use was too small to assess the most frequently used types or flavours in current users, so Figures 5 and 6 include everyone *who had tried* an EC. One third had first used a tank model and the most popular flavours among triers by far were fruit flavours. The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

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



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

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



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

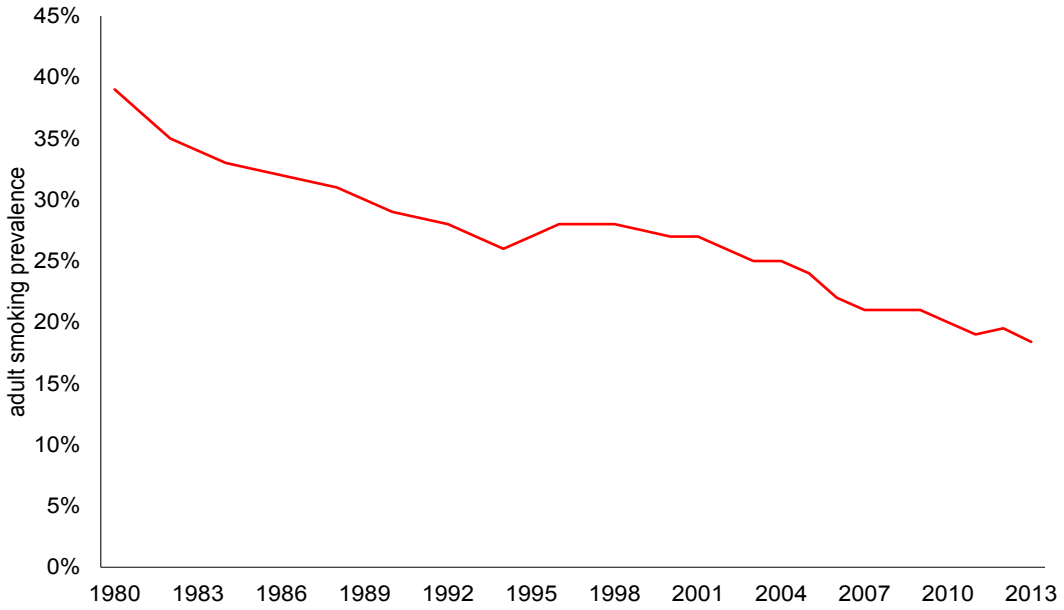
Concerns about impact of e-cigarette use on smoking

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

Recent trends in smoking prevalence

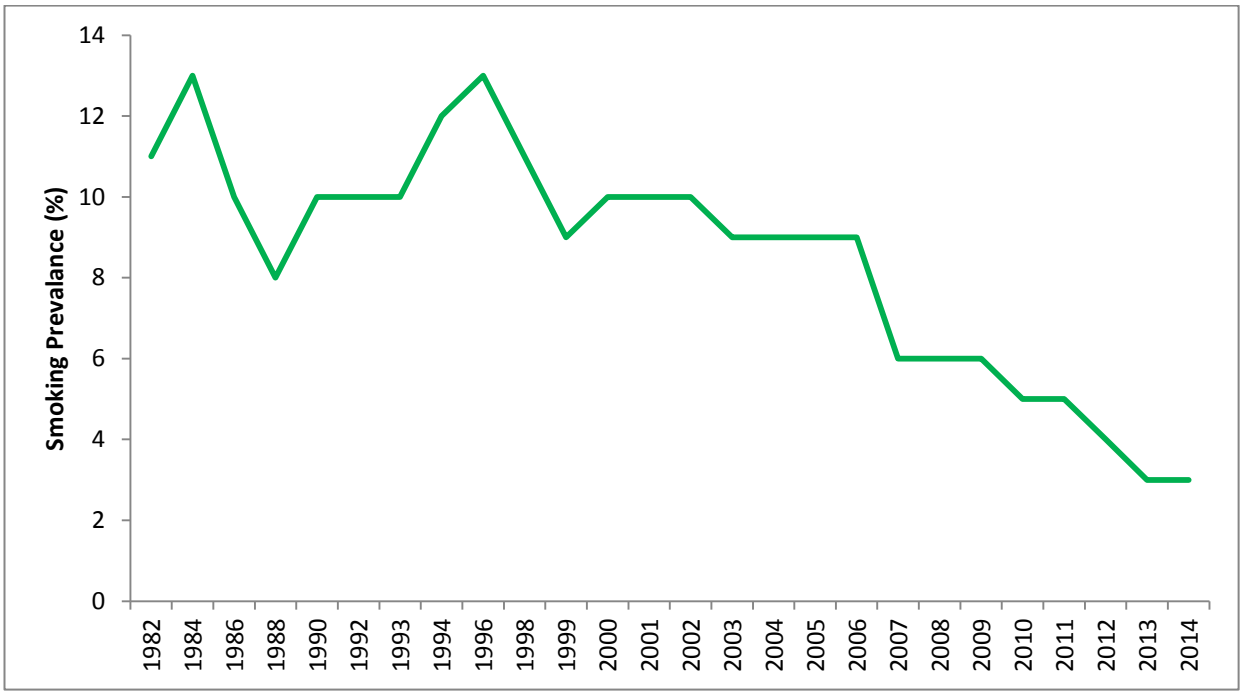
Since EC arrived on the market in England, smoking prevalence has continued to decline among both adults and youth (Figures 1, 7 and 8). Evidence to date therefore conflicts with any suggestion that EC are renormalising smoking. Whilst other factors may be contributing to the decline in smoking, it is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

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



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

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



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

Gateway

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

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

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

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

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

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

Summary

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

Summary of findings

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

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

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

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

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

Policy implications

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

5. Smoking, e-cigarettes and inequalities

Smoking and inequalities

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

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

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

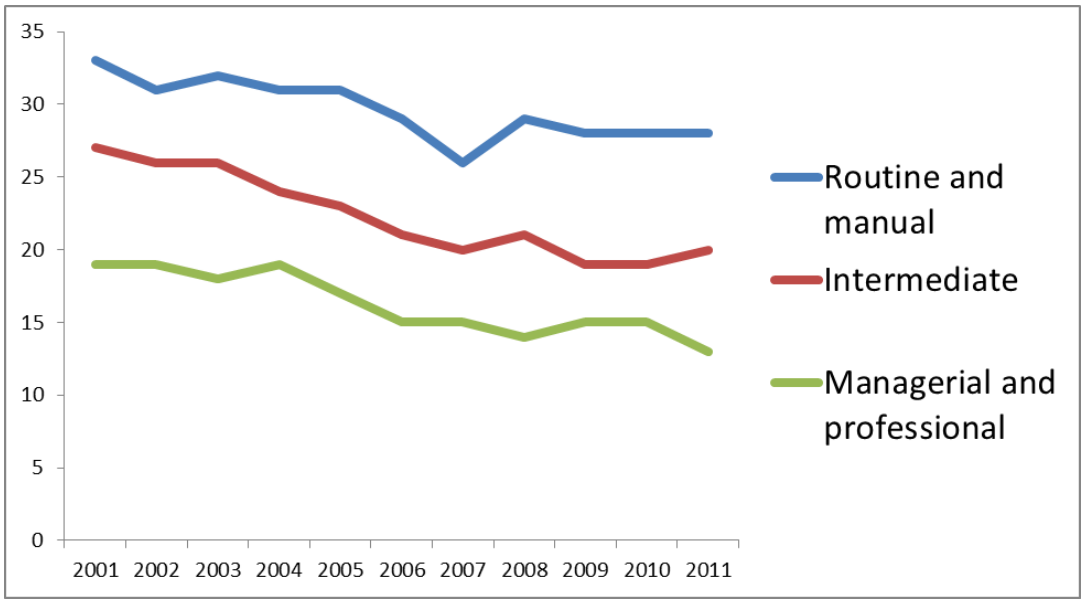
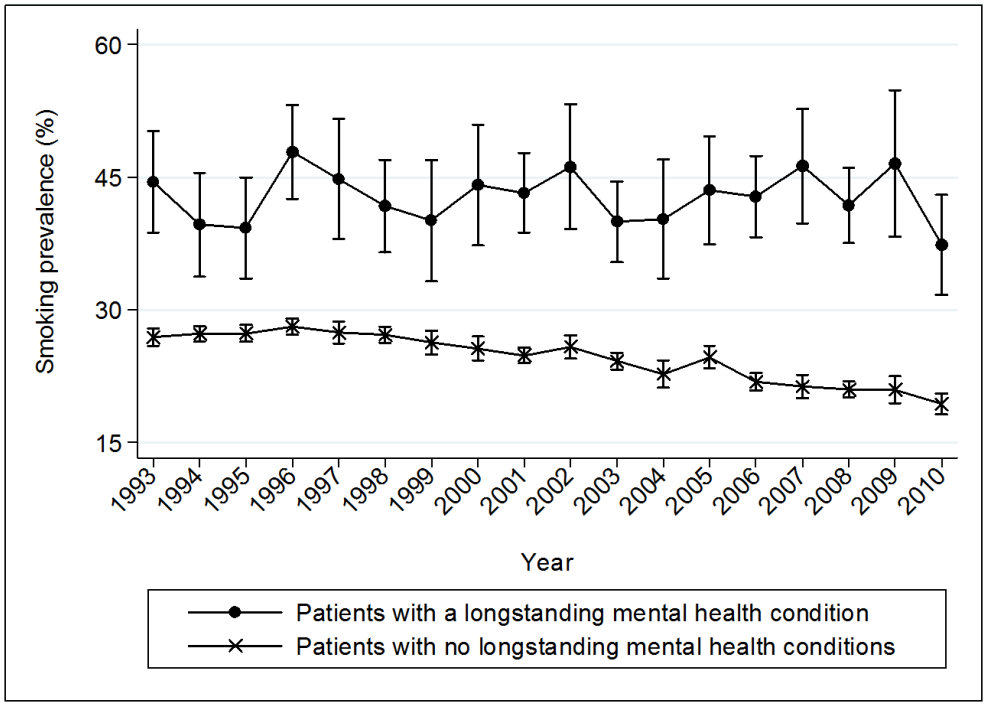


Figure 10: Smoking trends and mental health [27]

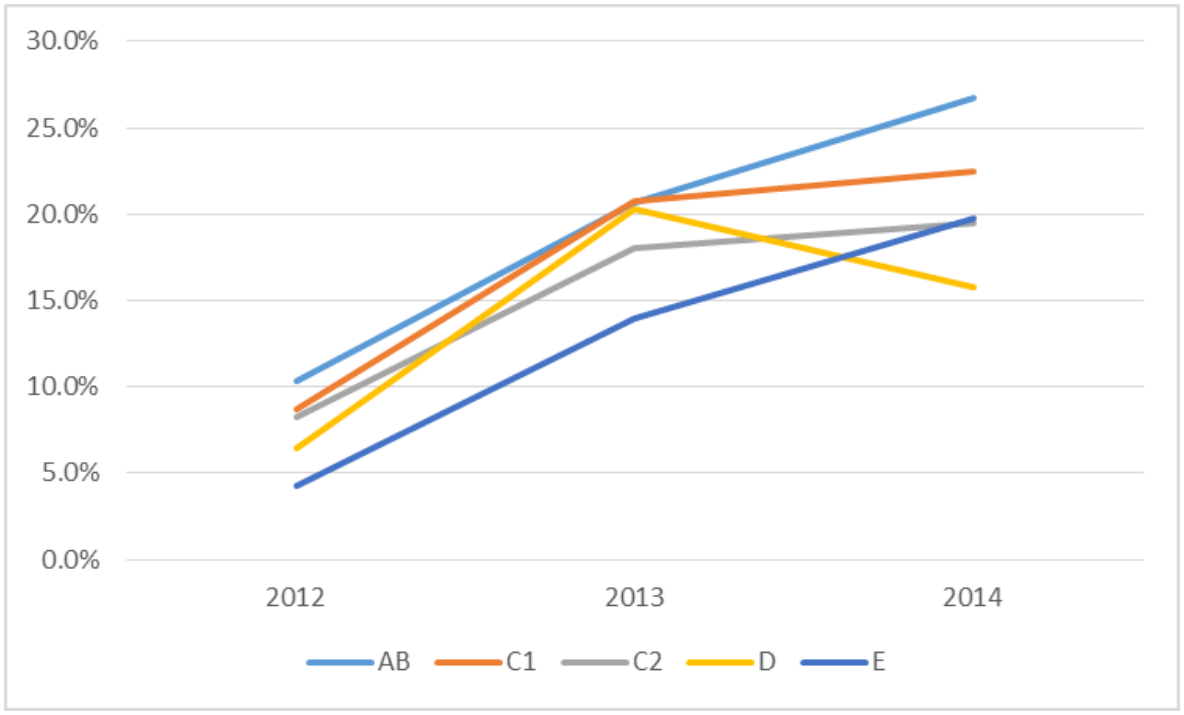


E-cigarette use and different social groups

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

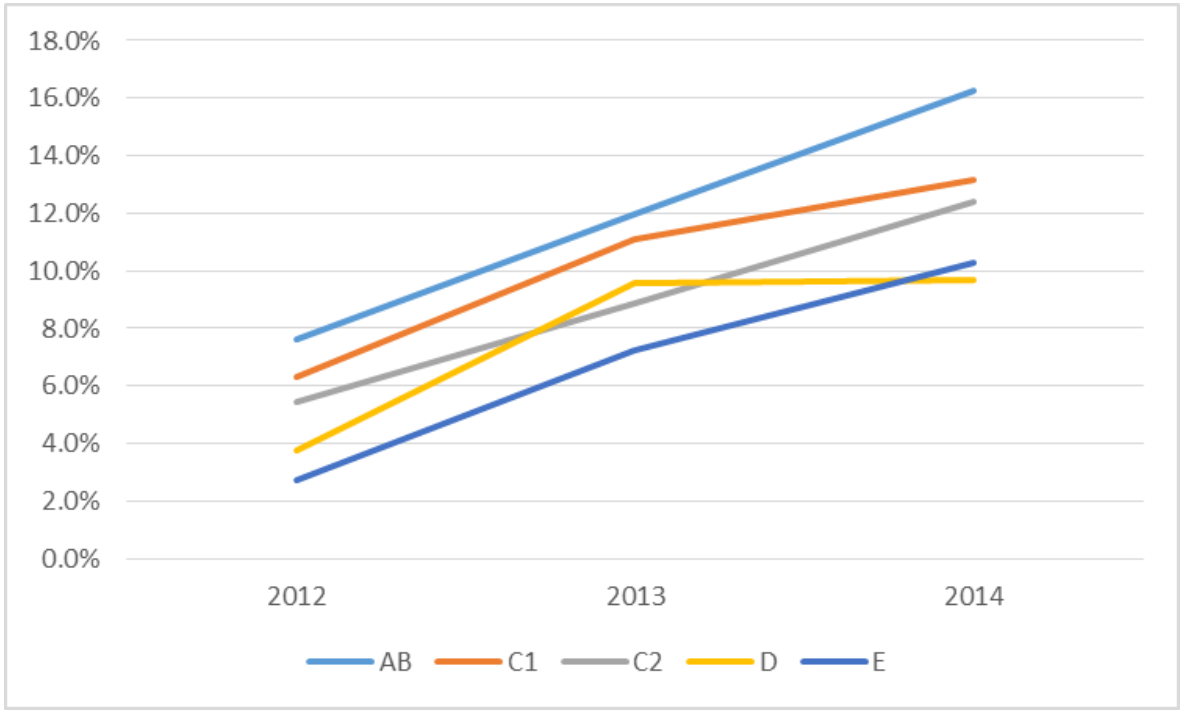
The STS data surveys show an increase in EC use in all social groups between 2012 and 2014 (Figures 11 and 12) but at a relatively similar rate such that socioeconomic differences are still apparent both for current and daily use of EC.

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



From www.smokinginengland.info/latest-statistics/

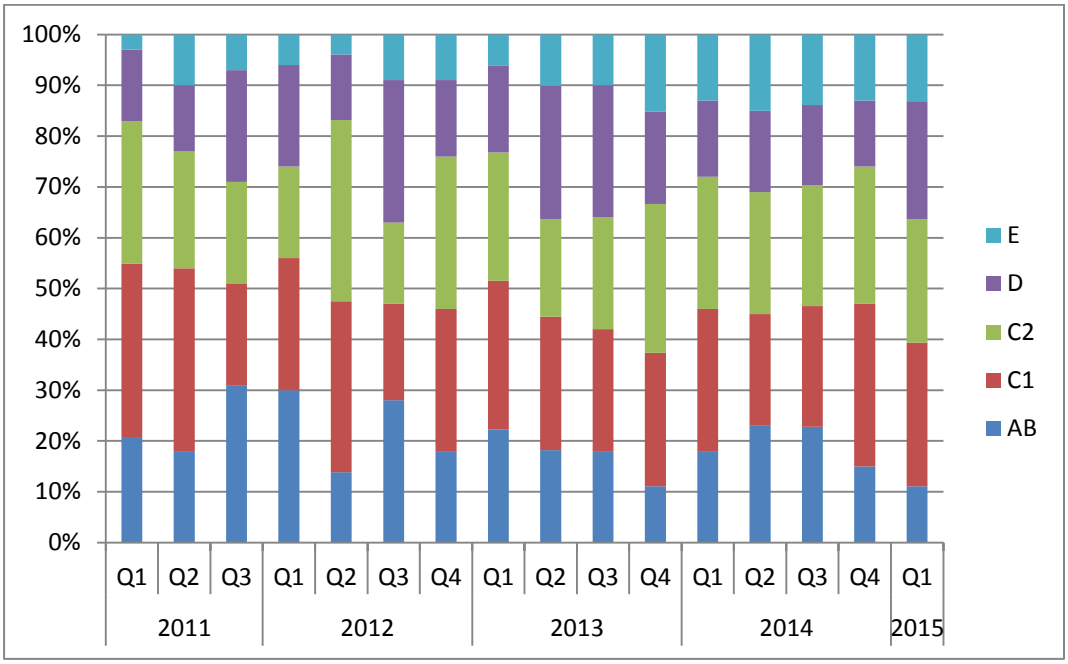
Figure 12: *Daily* use of e-cigarettes by social class among last year smokers (STS data)



From www.smokinginengland.info/latest-statistics/

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

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



From www.smokinginengland.info/latest-statistics/

E-cigarette use in other disadvantaged groups

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

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

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

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

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

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

Summary of findings

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

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

Policy implications

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

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

6. E-cigarettes and smoking behaviour

Introduction

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

Current recommendations for use of e-cigarettes to quit

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

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

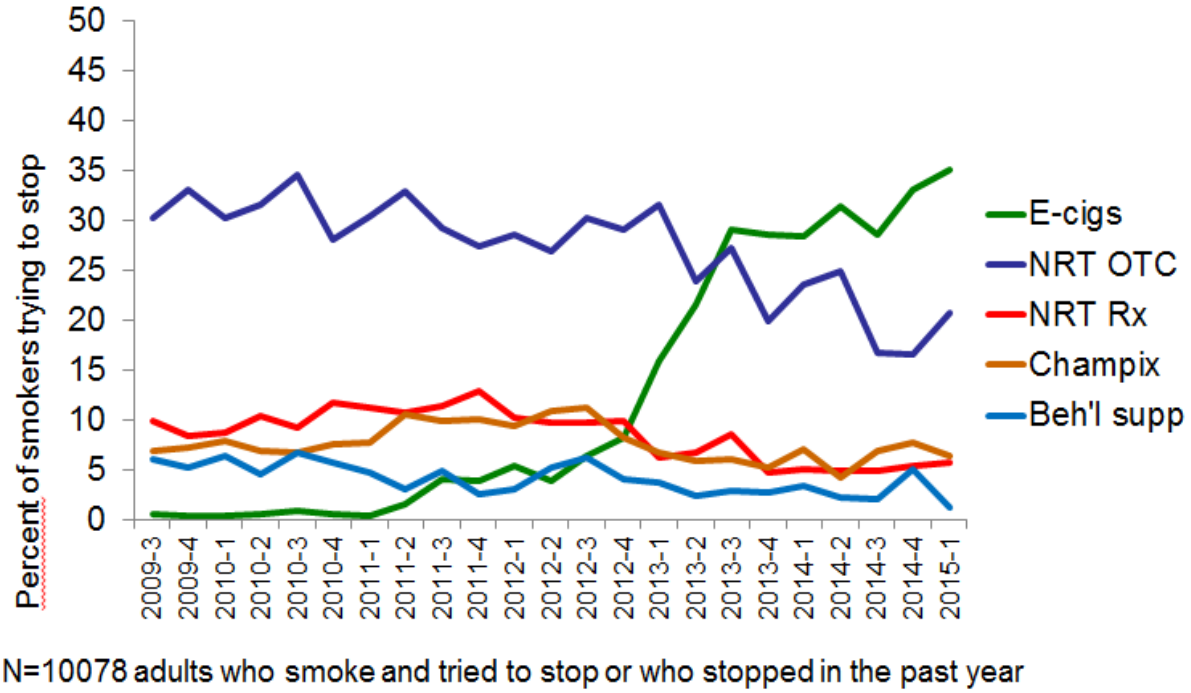
Use of e-cigarettes for stopping smoking

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

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

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

Figure 14: Support used in quit attempts



From: smokinginengland.info/latest-statistics

Randomised controlled trials

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

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

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

Population studies

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

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

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

Pilot studies

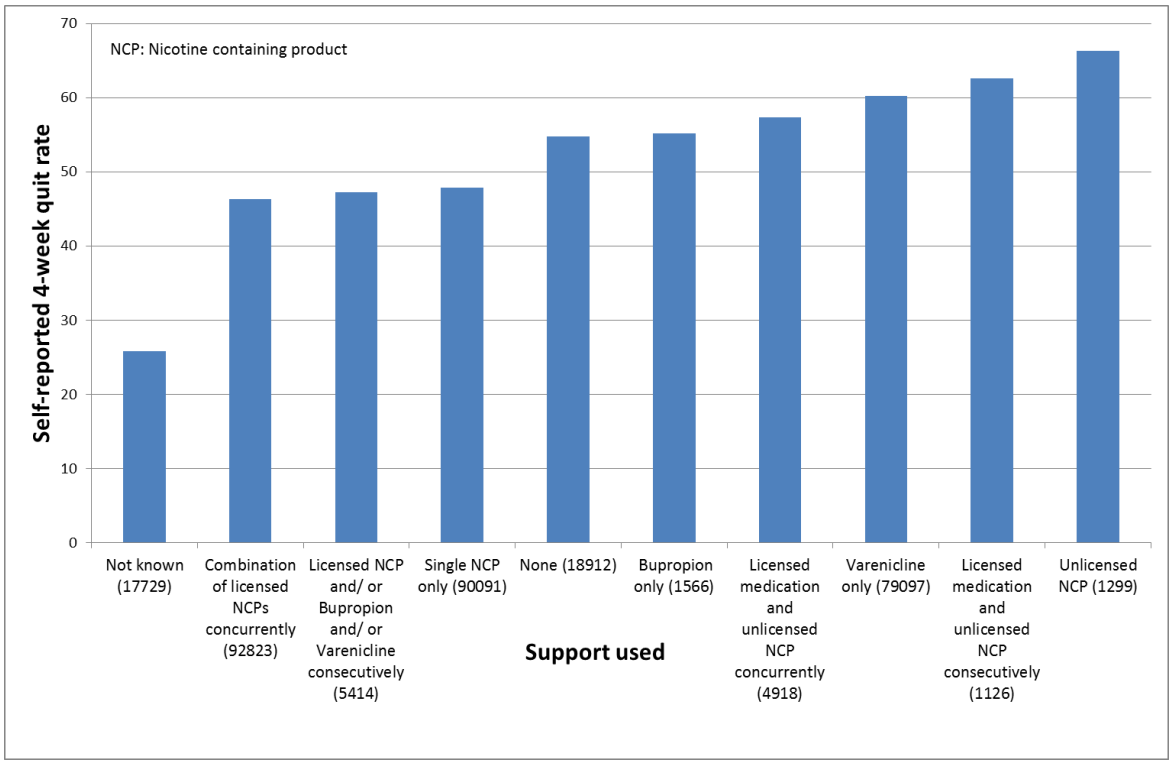
Polosa et al., 2014 [46] conducted a six-month pilot study of tank-type EC users with no control group among 72 smokers **who did not want to quit (smokers were enrolled after rejecting participation in smoking cessation program at a hospital)**. At six months, they found significant 50% and 80% reductions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

E-cigarettes and stop smoking services

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

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

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



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

Use of e-cigarettes while smoking

Population studies

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

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

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

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

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

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

Studies of smokers enrolled in smoking cessation programs

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

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

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

Summary of findings

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

Policy implications

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

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

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

7. Reasons for use and discontinuation

Reasons for using e-cigarettes

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

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

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

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

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

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

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

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

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

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

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

Reasons why trial does not become use

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

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

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

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

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

Summary of findings

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

Policy implications

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

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

8. Harm perceptions

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

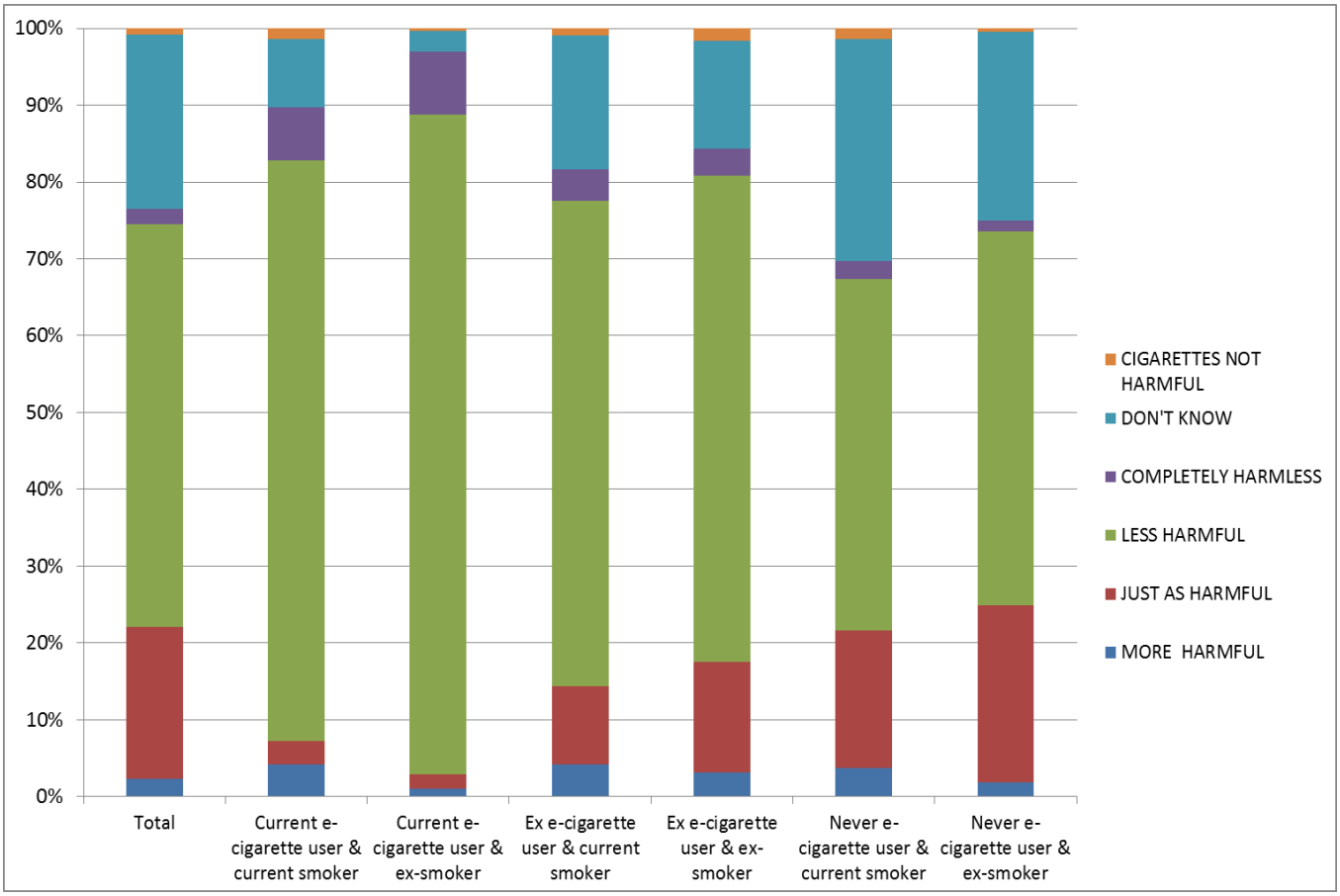
Harm perception relative to cigarettes

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

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

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

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



Trends in harm perceptions relative to cigarettes over time

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

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

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

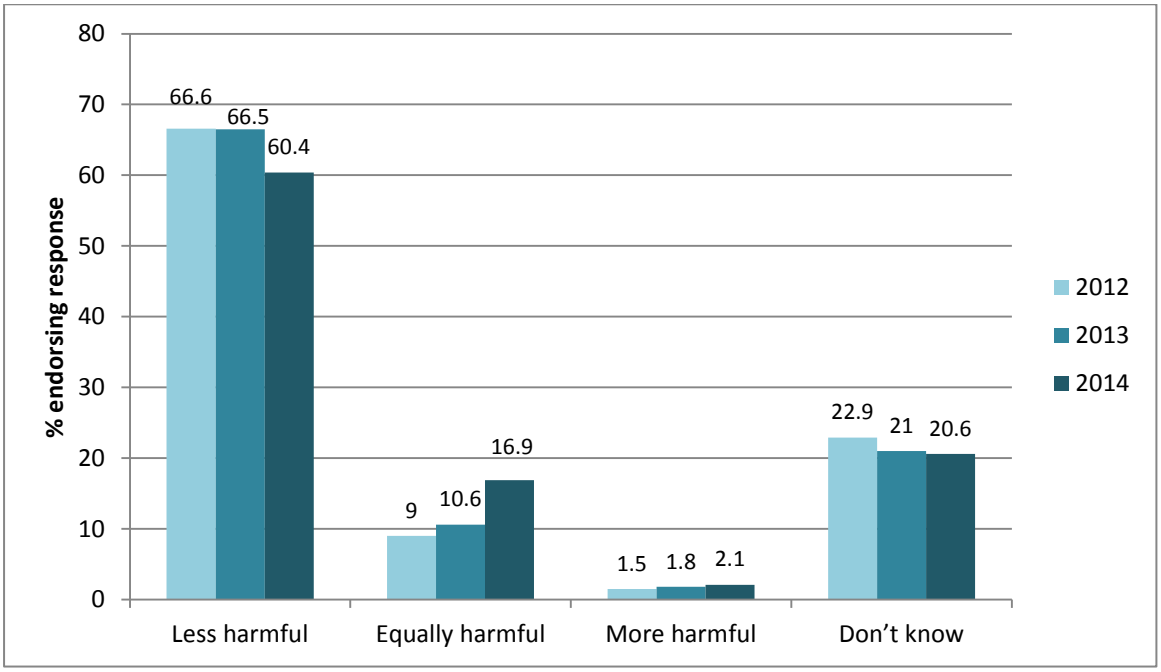
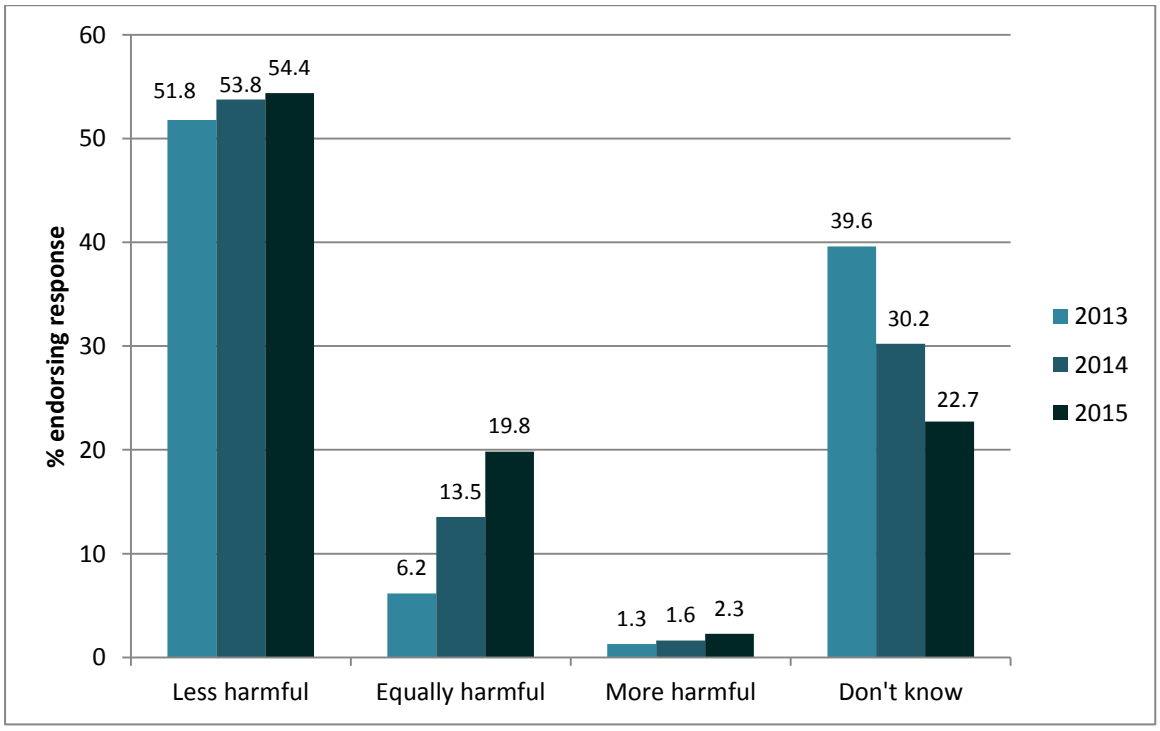
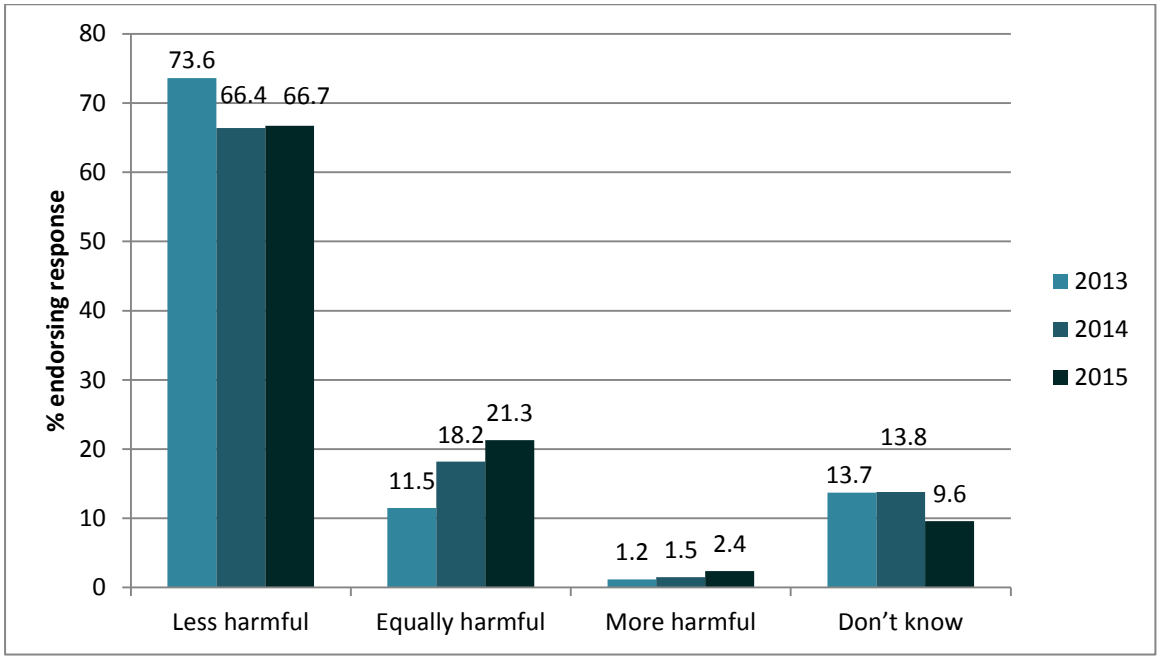


Figure 17: Perceptions of relative harmfulness of e-cigarettes in comparison with tobacco cigarettes. ASH Smokefree GB adult surveys (weighted)



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

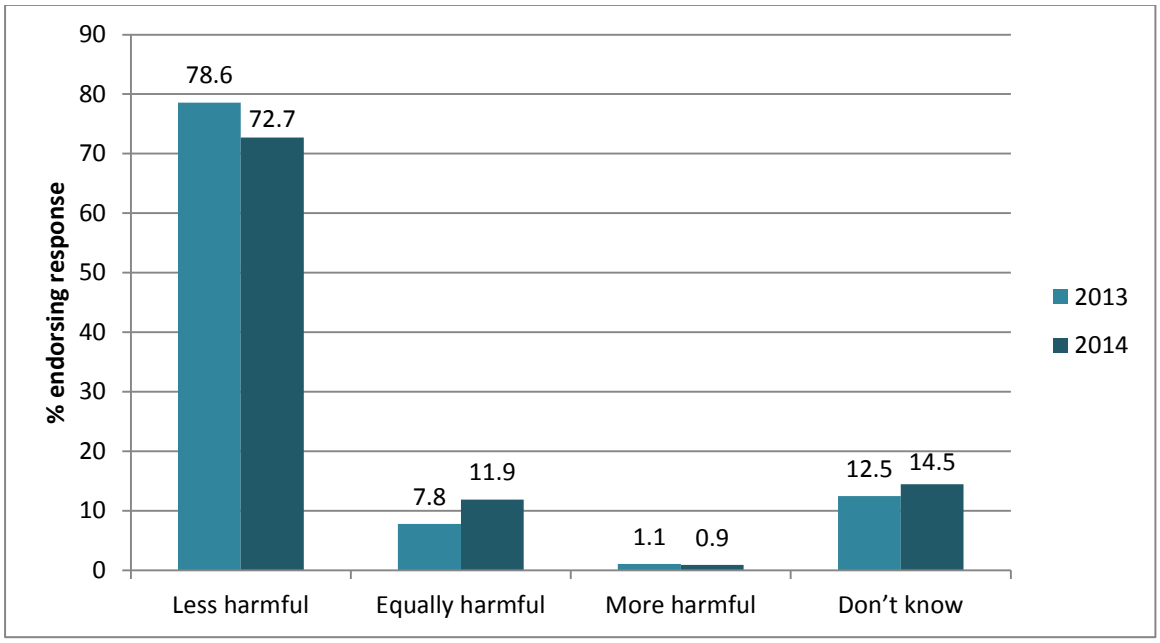
Figure 18: Perceptions of relative harmfulness of e-cigarettes in comparison with tobacco cigarettes. ASH Smokefree GB youth surveys (2013 and 2014) taken from Eastwood et al., in press[64].



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

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

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



Harm perception relative to nicotine replacement therapy (NRT)

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

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

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

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

Summary of findings

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

Policy implications

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

9. E-cigarettes, nicotine content and delivery

Background

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

Toxicity of nicotine

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

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

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

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

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

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

Review methods

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

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

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

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

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

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

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

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

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

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

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

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

Summary

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

Nicotine in e-liquids

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

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

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

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

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

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

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

The data generated so far provide answers to three questions:

Do e-liquids pose a poisoning hazard?

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

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

How accurate is product labelling?

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

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

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

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

Summary

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

Nicotine in e-vapour

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

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

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

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

N.A., not available.

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

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

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

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

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

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

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

Summary

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

Nicotine delivery to e-cigarette users

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

The two key questions in this field are:

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

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

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

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

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

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

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

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

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

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

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

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

Table 8: Studies examining nicotine intake in vapers

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

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

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

Summary of findings

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

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

Policy implications

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

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

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

Introduction

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

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

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

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

Aldehydes in vapour from e-cigarettes

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

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

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

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

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

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

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

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

Summary

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

Effects of e-cigarette vapour on mice lungs

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

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

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

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

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

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

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

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

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

Summary

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

Particles in e-cigarette vapour

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

Impact of media reports that e-cigarettes are dangerous

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

Summary of findings

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

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

Policy implications

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

11. Other health and safety concerns

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

Poison reports

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

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

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

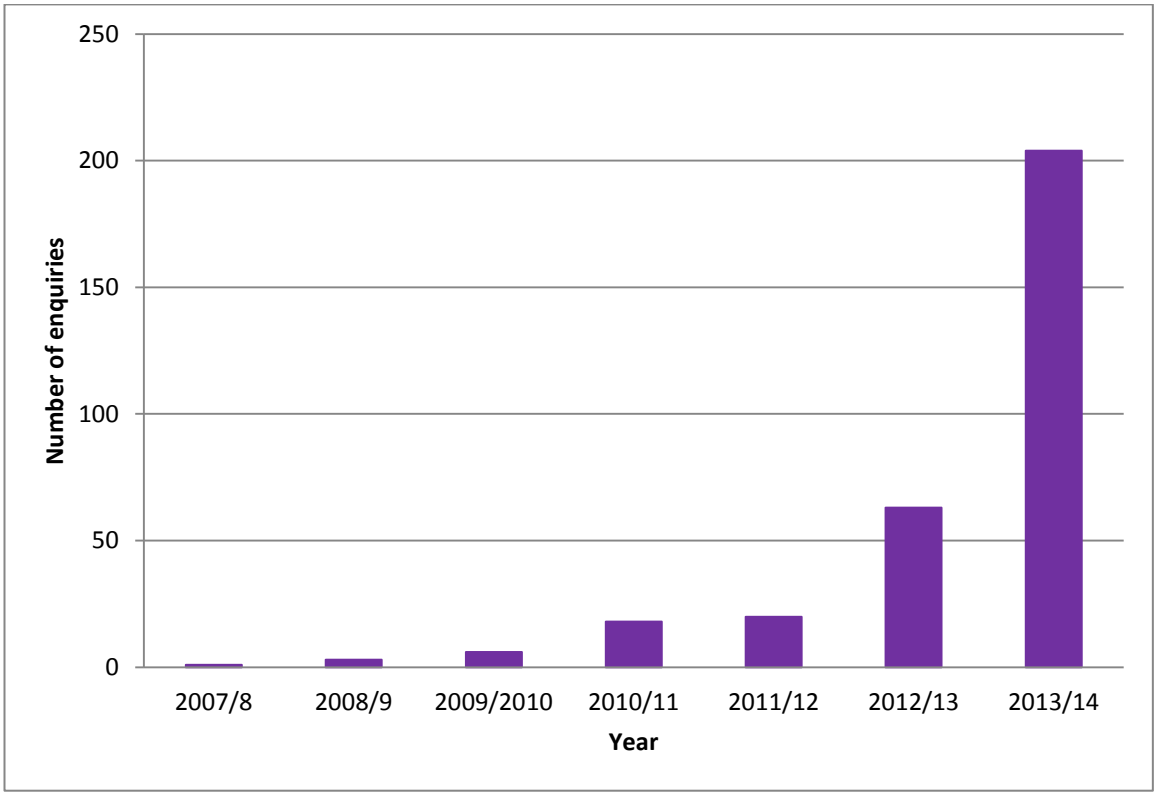


Figure 21: Number of enquiries about e-cigarettes to NPIS by age

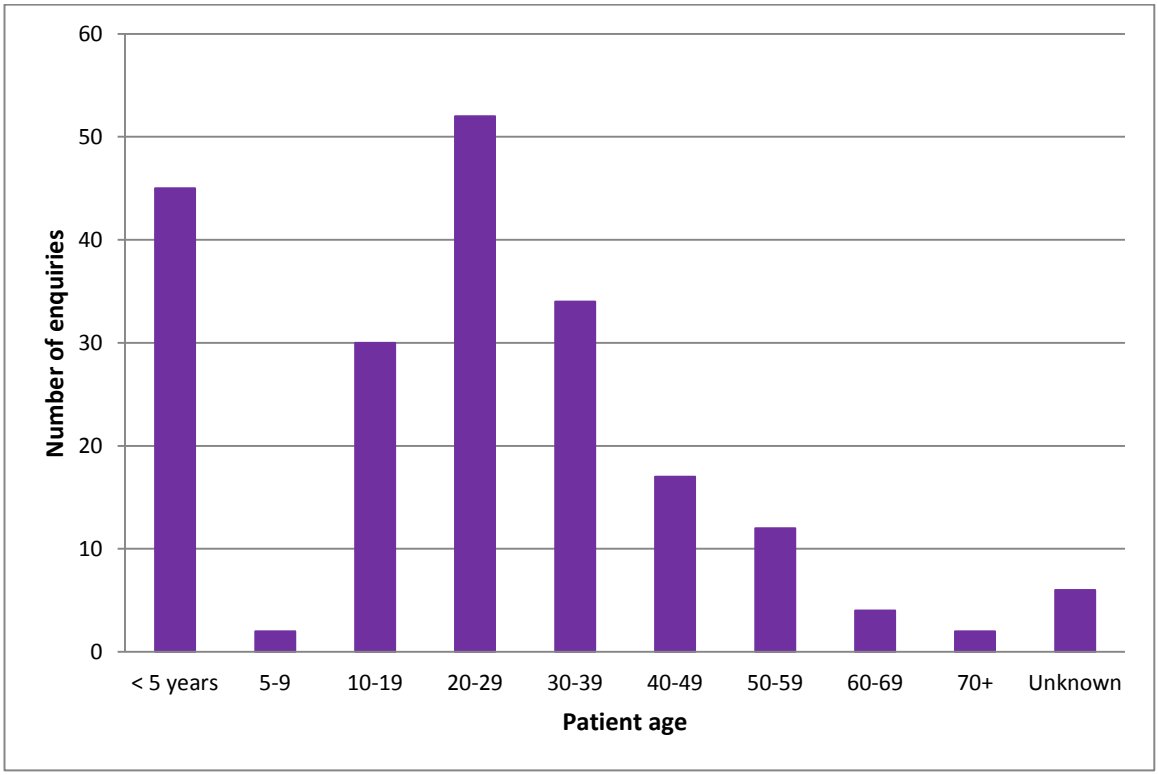
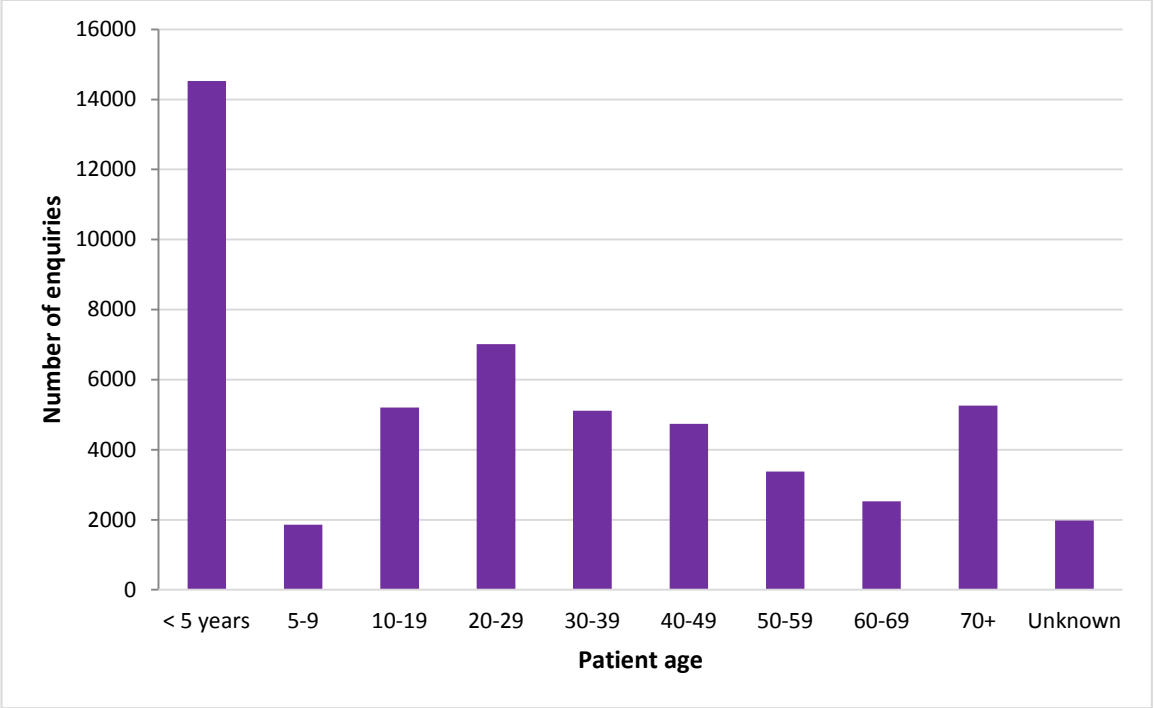


Figure 22: Age of poisoned patients overall reported in telephone enquiries to NPIS 2013/4



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

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

Fire

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

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

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

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

Summary of findings

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

Policy implications

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

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

12. International perspectives

Overview

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

Use of e-cigarettes among adults internationally

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

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

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

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

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

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

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

Use of e-cigarettes among youth internationally

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

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

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

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

The cases of Australia and Canada

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

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

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

Summary of findings

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

Policy implications

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

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

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Declaration of interests

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

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

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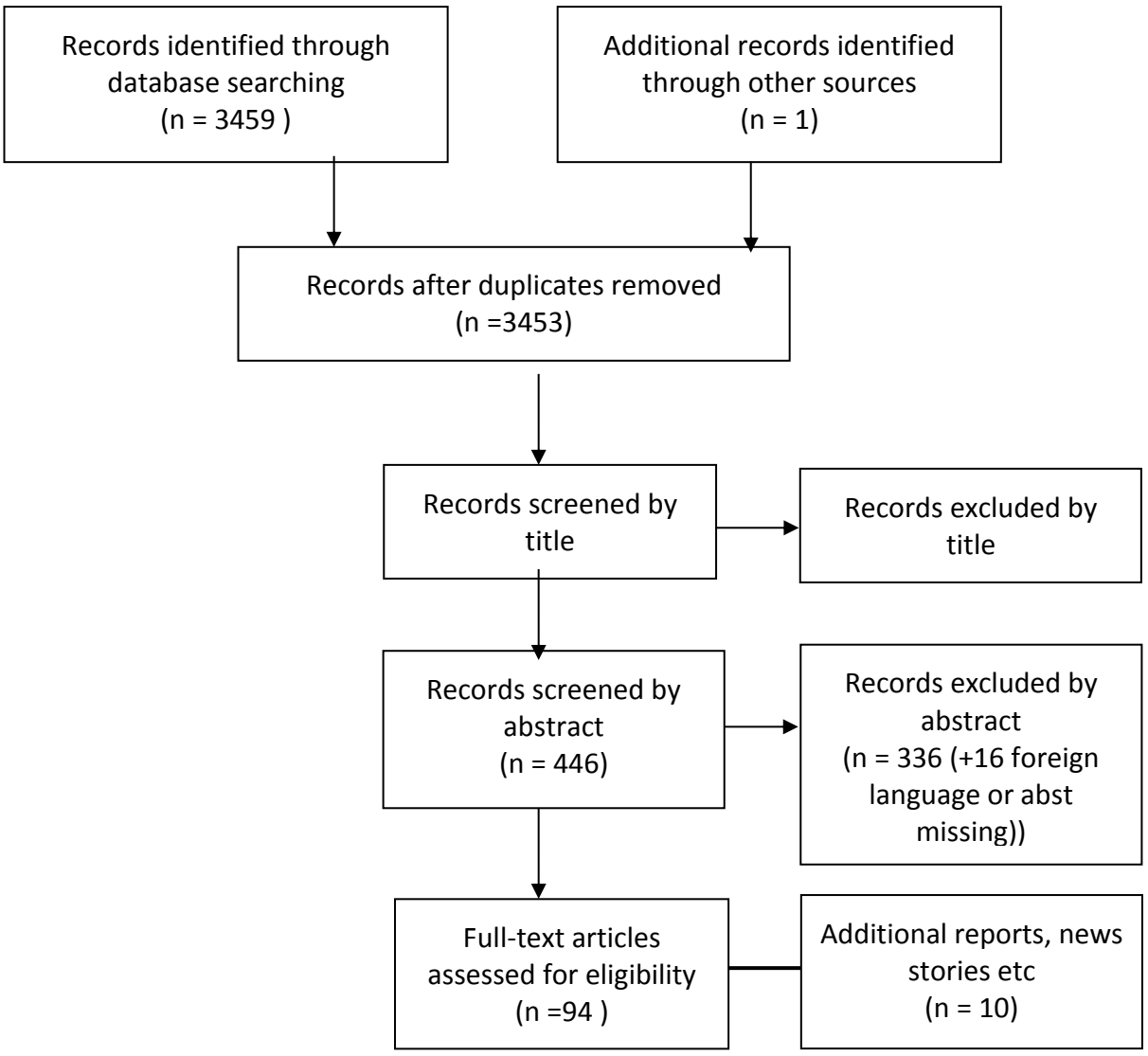
Appendices

APPENDIX A: PRISM Flow Diagram[5]



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

APPENDIX B: Measures of e-cigarette use

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

Surveys

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

Smoking Toolkit Study (STS)

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

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

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

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

Nicotine gum
Nicotine lozenge

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

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

ASH Smokefree GB adult survey

Which of the following statements BEST applies to you?

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

The fourth option constitutes 'current use'

ASH Smokefree GB youth survey

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

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

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

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

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

Internet cohort survey

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

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

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

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

Other studies

Amrock et al., 2015 (US)

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

Biener & Hargraves, 2014 (US)

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

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

Borderud et al., 2014 (US)

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

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

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

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

What electronic cigarette equipment do you currently use the most?

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

Brown et al., 2014 (England)

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

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

Canadian Tobacco, Alcohol and Drugs Survey 2013 (CTADS)

Trial

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

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

Last 30 day use

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

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

CDC/NYTS and Dutra and Glantz

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

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

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

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

Gravely et al., 2014 (Netherlands)

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

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

Gravely et al., 2014 (China)

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

1. Yes
2. No

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

"Have you ever bought or tried electronic cigarettes?"

Hummel et al., 2014 (Netherlands)

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

Lee et al., 2014 (US)

E-cigarette use questions were:

Have you ever used e-cigarettes?

1. yes
2. no

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

1. yes
2. no

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

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

Moore et al., 2015 (Welsh study HBSC)

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

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

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

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

Pearson et al., 2014 (US)

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

Pepper et al., 2014 (US)

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

Richardson et al., 2014 (US)

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

Rutten et al., 2014 (US)

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

Schmidt et al., 2014 (US)

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

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

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

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

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

Ever use: Have you ever tried electronic cigarettes?

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

Early studies

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

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

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

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

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

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

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

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

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

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

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

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

3) Nicotine concentration and chemical composition of e-liquid

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

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

4) Type of EC device

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

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

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

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

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

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

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

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

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

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

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

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

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

Public Health England

Protecting and improving the nation's health

Use of e-cigarettes in public places and workplaces

Advice to inform evidence-based policy making

About Public Health England

Public Health England exists to protect and improve the nation's health and wellbeing, and reduce health inequalities. It does this through world-class science, knowledge and intelligence, advocacy, partnerships and the delivery of specialist public health services. PHE is an operationally autonomous executive agency of the Department of Health.

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Contents

Introduction

Smoking is a uniquely harmful activity. Despite continued declines in smoking rates, it remains the leading cause of preventable illness and premature death in England, with the damage spreading far beyond smokers, to their families and others around them, to their communities and to wider society. The estimated total annual cost of smoking to society in England, including lost productivity and health and social care costs, is £13.9bn.[i]

Legislation under the Health Act 2006, which prohibits smoking in enclosed public places and workplaces, on public transport and in vehicles used for work, is based on conclusive scientific evidence of the direct health harm caused to bystanders through the inhalation of secondhand smoke.

E-cigarette use, known as vaping, is not covered by smokefree legislation. E-cigarettes do not burn tobacco and do not create smoke. While debate continues about their absolute level of safety, the consensus across England's public health community is that e-cigarettes are significantly safer for users than smoked tobacco. An independent review of the latest evidence[ii] published by Public Health England (PHE) in 2015 found that, based on the international peer-reviewed evidence, vaping is around 95% safer for users than smoking. It also confirmed the findings of PHE's 2014 independent evidence review,[iii] that there is no evidence of harm to bystanders from exposure to e-cigarette vapour and the risks to their health are likely to be extremely low.

E-cigarettes and the endgame for tobacco

Around 2.8m adults in Great Britain use e-cigarettes. Almost all are smokers or ex-smokers.[iv] E-cigarettes have rapidly become the most popular stop smoking aid in England[v] and a developing body of evidence[vi] shows that they can be effective. While experimentation with e-cigarettes among young people has increased over recent years, regular use remains rare and almost entirely confined to current or ex-smokers.[vii]

PHE's ambition is to secure a tobacco-free generation by 2025. We believe e-cigarettes have the potential to make a significant contribution to its achievement. Realising this potential depends on fostering an environment in which e-cigarettes can provide a route out of smoking for England's eight million smokers, without providing a route into smoking for children or non-smokers.

Balancing risks and opportunities

The role of e-cigarettes in tackling tobacco dependency, especially in the long term, is hotly debated within public health and wider society. We don't yet know everything there is to know about e-cigarettes and their impact. For that reason, some commentators cite the 'precautionary principle' in support of prohibition until more evidence is available. Our stance on the precautionary principle is that it requires analysis of the consequences of action and inaction, in this context prohibition as well as toleration. Both approaches demand evaluation, neither is without its risks. Our aim is to build an evidence-based consensus around an approach to e-cigarettes that harnesses the potential benefits to individual and public health while managing the risks.

Appropriate regulation is essential to ensure that e-cigarettes are as safe and effective as possible and to protect against uptake among young people. The UK has one of the most comprehensive regulatory systems for e-cigarettes in the world, with high standards of quality and safety, and tight restrictions on promotion and advertising. The 2015 prohibition on selling e-cigarettes to under-18s, and on adults buying them on behalf of under-18s, has provided additional protection for children and young people.

It is also essential that we continue to monitor the evidence on uptake of e-cigarettes, their health impact on individuals and populations, and their effectiveness for smoking cessation as the technology and products develop.

Finally, if e-cigarettes are to do their job of making smoking less of a social norm, they must be clearly positioned as products that help adult smokers to quit. In this way, vaping becomes synomyous with the rejection of smoking.

Concerns on e-cigarettes, the evidence and the implications

The main concerns surrounding e-cigarettes focus on their uptake by young people, their potential to renormalise smoking, safety for users and bystanders, and their effectiveness as quitting aids. A summary of the current evidence is on page 11.

Further concerns regarding e-cigarette use in public places include the possible reversal of advances in clean air achieved by banning smoking in public places, and a potential normalisation of nicotine addiction. These concerns will resonate with some people, and are especially relevant to risk assessments for particular settings. For instance, when developing its policy on e-cigarette use, it would be rational for a school to prioritise the risk of youth uptake and to decide to treat e-cigarettes in the same way as other age-restricted products and prohibit them onsite.

How to use this guide

Policies and practice on e-cigarette use in public places and workplaces are evolving and need to continue to do so in the light of the emerging evidence. Action on Smoking and Health and the Chartered Institute of Environmental Health took a lead in this field with the publication in 2015 of their 'five questions' briefing.[viii]

PHE has produced this guide in consultation with public health partners and other stakeholders.* It is deliberately non-prescriptive, because no one-size-fits-all answer exists to the issue of e-cigarette use in public places and workplaces. Instead, by setting out some key principles for an approach that fits with our current knowledge and protects against the unintended consequences of being either too permissive or too prohibitive, it can help organisations develop their own policies.

*For details see 'Report of PHE stakeholder 'conversation' on use of e-cigarettes in enclosed public places and workplaces', Public Health England, July 2016

Use of e-cigarettes in public places and workplaces: key principles to guide policy making

These five principles guide the development of evidence-based policies that maximise the potential for e-cigarettes to improve public health while managing the risks in any particular setting. It is recommended that policies are kept under regular review to take account of developments in the evidence base and changes in the regulatory environment.

1. Make clear the distinction between vaping and smoking

Smoking is defined clinically[ix] and in law,[x] and e-cigarette use does not meet the definition in either context. Based on the international peer-reviewed evidence, e-cigarettes carry a fraction of the risk of cigarettes and have the potential to help drive down smoking rates and improve public health. To the extent that they cut the number of smoking role models, reduce public smoking and provide a role model for the rejection of smoking, e-cigarettes can help to denormalise smoking. Therefore policies should make clear the distinction between vaping and smoking.

Considerations for policy development:

- while taking account of the specific circumstances applying to a public place or workplace, policies on e-cigarette use should be evidence-based and should aim to maximise the benefits while managing any identified risks
- when communicating an organisation's policy on e-cigarette use, make clear the distinction between vaping and smoking, and the evidence on the relative risks for users and bystanders
- to avoid confusion, do not use smoking terminology when referring to e-cigarettes. E-cigarette use is often known as 'vaping' and e-cigarette users are often known as 'vapers'
- NICE guidance for NHS secondary care recommends that estates should become completely smokefree, indoors and outdoors. Managers should seek to develop approaches to e-cigarettes that support smokefree sites

2. Ensure policies are informed by the evidence on health risks to bystanders

International peer-reviewed evidence indicates that the risk to the health of bystanders from exposure to e-cigarette vapour is extremely low. This is in contrast to the conclusive evidence of harm from exposure to secondhand smoke, which provides the

basis for UK smokefree laws. The evidence of harm from secondhand exposure to vapour is not sufficient to justify the prohibition of e-cigarettes. Managers of public places and workplaces should ensure that this evidence informs their risk assessments.

Considerations for policy development:

- e-cigarette use is not covered by smokefree legislation and should not routinely be included in the requirements of an organisation's smokefree policy
- reasons other than the health risk to bystanders may exist for prohibiting e-cigarette use in all or part of a public place or workplace, such as commercial considerations and professional etiquette
- people with asthma and other respiratory conditions can be sensitive to a range of environmental irritants, which could include e-cigarette vapour. The interests of such individuals should be taken into account when developing policies and adjustments made where necessary
- vaping can in certain circumstances be a nuisance or distraction for people nearby. Where a decision is taken to allow vaping in an enclosed place, policies could consider some simple etiquette guidelines for vapers, such as minimising the production of visible vapour

3. Identify and manage risks of uptake by children and young people

E-cigarette use is not recommended for young people. In the UK protection is in place via prohibitions on the sale of e-cigarettes to under-18s and purchase by adults on behalf of under-18s, and restrictions on advertising. However, because adult smokers use e-cigarettes to quit smoking and stay smokefree, the products can help reduce children's and young people's exposure to secondhand smoke and smoking role models. In developing policies on e-cigarette use in child and youth settings it is appropriate to guard against potential youth uptake, while balancing this with the need to foster an environment where it is easier for adults not to smoke.

Considerations for policy development:

- UK data shows little evidence that young people who try e-cigarettes progress to regular use, other than those who had previously smoked. Managers of child and youth settings such as schools have a particular responsibility in managing the risk of youth uptake of e-cigarettes and might want to treat e-cigarettes as they would any other age-restricted product
- while it is not recommended to allow adults who use or work in child and youth settings to vape in view of children, consider ways to make it easier to vape than to smoke. Approaches might include allowing vaping in a designated adults-only indoor area or allowing vaping but prohibiting smoking in outdoor areas

- while it is preferable for young people neither to smoke nor to vape, when assessing the risks policies should give priority to supporting young people not to smoke

4. Support smokers to stop smoking and stay smokefree

E-cigarettes are used almost exclusively by smokers and ex-smokers and are now the most popular stop smoking aid in England. To support smokers to stop smoking and stay smokefree, a more enabling approach may be appropriate in relation to vaping to make it an easier choice than smoking. In particular, vapers should not be required to use the same space as smokers, as this could undermine their ability to quit smoking and stay smokefree, particularly among those most heavily addicted.

Considerations for policy development:

- e-cigarettes have significant potential to help reduce tobacco use and the serious harm it causes to smokers, those around them and wider society. Recognition of this should be at the centre of policies on e-cigarette use in public places and workplaces
- while e-cigarettes are not currently available as licensed medicines, it is expected that products will come onto the market that can be prescribed on the NHS by GPs and other healthcare professionals alongside other stop smoking medicines
- to maximise the number of smokers switching to e-cigarettes, vaping should be made a more convenient, as well as safer, option
- while smokefree law protects people from the harm of secondhand smoke, forcing smokers outdoors has increased public visibility of smoking, including to children and young people. Having a more enabling approach to vaping can mitigate this and help make smoking less of a social norm
- smokers can achieve their desired blood plasma nicotine level with one cigarette every hour or so, and in a short space of time. Vaping provides a generally lower blood nicotine level and takes longer to reach a desired level, requiring frequent interim top-ups This difference should be taken into account, particularly when developing policies for workplaces
- it is never acceptable to require vapers to share the same outdoor space with smokers. Where a designated outdoor smoking area has been provided in a public place or workplace, vapers should be allowed to vape elsewhere

5. Support compliance with smokefree law and policies

Compliance with smokefree requirements can be maintained and supported by emphasising a clear distinction between smoking and vaping. Managers should indicate accurately where vaping is permitted or prohibited, and communicate the policy clearly to everyone it affects.

Considerations for policy development:

- UK smokefree law prohibiting smoking in enclosed public places and workplaces is well established, and compliance levels are high. While some e-cigarettes physically resemble cigarettes, the distinctive odour and ash of lit tobacco makes it generally easy to distinguish between someone who is vaping and someone who is smoking.
- policies on e-cigarette use should be communicated clearly so that everybody using a public place or workplace is aware of the policy and understands where vaping is or is not allowed. Where appropriate, this could include signs.
- the Action on Smoking and Health / Chartered Institute of Environmental Health 'five questions' briefing* advises: "It should be remembered that offering a safe and effective alternative to smoking tobacco to people who are addicted to nicotine may help support compliance with smokefree legal requirements and make smokefree policies easier to implement."

*'Will you permit or prohibit electronic cigarette use on your premises? Five questions to ask before you decide', ASH/CIEH, October 2015

Summary of the current evidence on e-cigarettes

Prevalence and patterns of use

Adults

An estimated 2.8m adults in Great Britain currently use e-cigarettes. Of these, 1.4m are smokers and 1.3m have completely stopped smoking. The principal reasons given for e-cigarette use are to support cutting down or quitting tobacco use and to help avoid relapse to smoking. Regular use of e-cigarettes among never smokers is negligible at 0.2%.

Early e-cigarettes all looked like cigarettes, however rapid innovation has resulted in a range of product designs. Rechargable devices with a reservoir/tank have increased in popularity, with over two thirds of vapers (71%) using this type of product in 2016. Cigalike or pen-type devices with pre-filled cartridges are used by 23% of vapers and only 3% use disposable products.[xi]

Young people

Evidence from UK studies indicates that while young people's awareness of, and experimentation with, e-cigarettes has increased, regular use remains rare and almost entirely confined to those who are current smokers or have smoked in the past.

Around 12% of British youth have ever tried e-cigarettes. Around 2% use e-cigarettes at least monthly and 0.5% weekly. Among young people who have never smoked, regular use (at least monthly) is 0.3% or less.

Overall, the youth data suggests that e-cigarettes are attracting very few young people who have never smoked into regular use.[xii]

E-cigarettes and smoking – renormalising or denormalising?

Concerns have been expressed that the presence of e-cigarettes might act to renormalise smoking, undermining decades of work to tackle the harm from tobacco. So far, there is no evidence that e-cigarettes are acting as a route into smoking for children or non-smokers. The authors of PHE's independent review of the latest evidence found that: "Since EC [e-cigarettes] were introduced to the market, smoking prevalence among adults and youth has declined. Hence there is no evidence to date

that EC are renormalising smoking, instead it's possible that their presence has contributed to further declines in smoking, or denormalisation of smoking."

The gateway hypothesis – the theory that the use of one drug leads to the use of another drug – features prominently in the academic and public discourse on e-cigarettes in relation to young people. In their review, the authors address this, pointing out that "The gateway theory is ill defined and we suggest its use be abandoned until it is clear how it can be tested in this field. Whilst never smokers are experimenting with EC, the vast majority of youth who regularly use EC are smokers. Regular EC use in youth is rare." [xiii]

Safety

For users

E-cigarettes are not risk free, but based on current evidence they carry a fraction of the risk of cigarettes. The authors of PHE's independent review of the latest evidence concluded that using an e-cigarette (known as 'vaping') is around 95% safer than smoking.[xiv] In an authors' note published to accompany the report, they explain that this estimate is based on the facts that:

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

Their overall assessment is that on current evidence, there is no doubt that smokers who switch to vaping dramatically reduce the risks to their health.

For bystanders

There is no published scientific evidence of harm to bystanders from exposure to e-cigarette vapour and the available evidence indicates that any risk of harm is extremely low, especially when compared with tobacco smoke.

In their independent evidence review conducted for PHE and published in 2014, Professor John Britton and Dr Ilze Bogdanovica concluded that: "Electronic cigarettes do not produce smoke so the well-documented effects of passive exposure of others to cigarette smoke are clearly not relevant…laboratory work suggests that electronic cigarette use in an enclosed space exposes others to nicotine at levels about one tenth

generated by a cigarette, but little else. The health risks of passive exposure to electronic cigarette vapour are therefore likely to be extremely low."[xvi] Following their assessment of the latest evidence, the authors of PHE's 2015 evidence review reached a similar conclusion: "EC [e-cigarettes] release negligible levels of nicotine into ambient air with no identified health risks to bystanders."[xvii]

Effectiveness for smoking cessation

PHE is clear that the best way for smokers to protect their health and the health of those around them is to stop immediately, completely and permanently. We also recognise that not all smokers are ready or able to stop in one step, and for those people we support the approaches set out in the NICE public health guidance on tobacco harm reduction (PH45). These include: cutting down to quit, reducing the amount smoked and temporary abstinence from smoking, with or without using licensed nicotine-containing products. Our advice is for smokers to switch to e-cigarettes and for e-cigarette users to stop smoking completely.

E-cigarettes have rapidly become the most popular stop smoking aid in England.[xviii] In PHE's independent review of the latest evidence, the authors conclude that: "Recent studies support the [2014] Cochrane Review[xix] findings that EC [e-cigarettes] can help people to quit smoking and reduce their cigarette consumption. There is also evidence that EC can encourage quitting or cigarette consumption reduction even among those not intending to quit or rejecting other support. It is not known whether current EC products are more or less effective than licensed stop-smoking medications, but they are much more popular, thereby providing an opportunity to expand the number of smokers stopping successfully…The evidence on EC used *alongside smoking* on subsequent quitting of smoking is mixed."[xx]

Evidence indicates that e-cigarettes are particularly effective when combined with additional support from local stop smoking services: in 2014-15, smokers in England who combined e-cigarette use with behavioural support had the highest quit rates, with two out of three quitting successfully.[xxi]

A much-cited study by researchers at King's College London and University College London found that the type of e-cigarette used and the frequency of use had an impact on outcomes. They concluded that daily use of tank models may give smokers a better chance of quitting.[xxii]

Impact on compliance with smokefree legislation

The ASH/CIEH guide 'Developing an organisational approach to the use of electronic cigarettes on your premises' advises that: "There are concerns that the appearance and use of electronic cigarettes could undermine our high levels of compliance with smoke-

free requirements. However, burning tobacco produces a distinctive and pervasive smell as well as deposits of ash. The Chartered Institute of Environmental Health advises that attempts to pass off smoking as using an electronic cigarette should be able to be detected by a diligent investigator."[xxiii]

The CIEH policy on use of electronic cigarettes in indoor workplaces and public places acknowledges that the organisation has been made aware of enforcement problems occurring in Wales, including some cases being lost when the enforcement officer's evidence is insufficient to secure a conviction. Taking this into account, the policy states: "A statutory prohibition on the use of nicotine vapourisers because of a limited number of smokefree legislation enforcement failures cannot be justified. This would be particularly perverse if the evidence is accepted of the effectiveness of nicotine vapourisers in assisting smokers to stop or reduce their smoking and all other risks are considered to be acceptable."

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Peering through the mist: systematic review of what the chemistry of contaminants in electronic cigarettes tells us about health risks

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Abstract

Background

Electronic cigarettes (e-cigarettes) are generally recognized as a safer alternative to combusted tobacco products, but there are conflicting claims about the degree to which these products warrant concern for the health of the vapers (e-cigarette users). This paper reviews available data on chemistry of aerosols and liquids of electronic cigarettes and compares modeled exposure of vapers with occupational safety standards.

Methods

Both peer-reviewed and “grey” literature were accessed and more than 9,000 observations of highly variable quality were extracted. Comparisons to the most universally recognized workplace exposure standards, Threshold Limit Values (TLVs), were conducted under “worst case” assumptions about both chemical content of aerosol and liquids as well as behavior of vapers.

Results

There was no evidence of potential for exposures of e-cigarette users to contaminants that are associated with risk to health at a level that would warrant attention if it were an involuntary workplace exposures. The vast majority of predicted exposures are < <1% of TLV. Predicted exposures to acrolein and formaldehyde are typically <5% TLV. Considering exposure to the aerosol as a mixture of contaminants did not indicate that exceeding half of TLV for mixtures was plausible. Only exposures to the declared major ingredients -- propylene glycol and glycerin -- warrant attention because of precautionary nature of TLVs for exposures to hydrocarbons with no established toxicity.

Conclusions

Current state of knowledge about chemistry of liquids and aerosols associated with electronic cigarettes indicates that there is no evidence that vaping produces inhalable exposures to *contaminants* of the aerosol that would warrant health concerns by the standards that are used to ensure safety of workplaces. However, the aerosol generated during vaping as a whole (contaminants *plus declared ingredients*) creates personal exposures that would justify surveillance of health among exposed persons in conjunction with investigation of means to keep any adverse health effects as low as reasonably achievable. Exposures of bystanders are likely to be orders of magnitude less, and thus pose no apparent concern.

Keywords

Vaping e-cigarettes Tobacco harm reduction Risk assessment Aerosol Occupational exposure limit

Background

Electronic cigarettes (also known as e-cigarettes) are generally recognized as a safer alternative to combusted tobacco products (reviewed in [1]), but there are conflicting claims about the degree to which these products warrant concern for the health of the vapers (e-cigarette users). A vaper inhales aerosol generated during heating

of liquid contained in the e-cigarette. The technology and patterns of use are summarized by Etter [1], though there is doubt about how current, complete and accurate this information is. Rather conclusive evidence has been amassed to date on comparison of the chemistry of aerosol generated by electronic cigarettes to cigarette smoke [2, 3, 4, 5, 6, 7, 8]. However, it is meaningful to consider the question of whether aerosol generated by electronic cigarettes would warrant health concerns on its own, in part because vapers will include persons who would not have been smokers and for whom the question of harm reduction from smoking is therefore not relevant, and perhaps more importantly, simply because there is value in minimizing the harm of those practicing harm reduction.

One way of approaching risk evaluation in this setting is to rely on the practice, common in occupational hygiene, of relating the chemistry of industrial processes and the emissions they generate to the potential worst case of personal exposure and then drawing conclusions about whether there would be interventions in an occupational setting based on comparison to occupational exposure limits, which are designed to ensure safety of unintentionally exposed individuals. In that context, exposed individuals are assumed to be adults, and this assumption appears to be suitable for the intended consumers of electronic cigarettes. “Worst case” refers to the maximum personal exposure that can be achieved given what is known about the process that generates contaminated atmosphere (in the context of airborne exposure considered here) and the pattern of interaction with the contaminated atmosphere. It must be noted that harm reduction notions are embedded in this approach since it recognizes that while elimination of the exposure may be both impossible and undesirable, there nonetheless exists a level of exposure that is associated with negligible risks. To date, a comprehensive review of the chemistry of electronic cigarettes and the aerosols they generate has not been conducted, depriving the public of the important element of a risk-assessment process that is mandatory for environmental and occupational health policy-making.

The present work considers both the contaminants present in liquids and aerosols as well as the declared ingredients in the liquids. The distinction between exposure to declared ingredients and contaminants of a consumer product is important in the context of comparison to occupational or environmental exposure standards. Occupational exposure limits are developed for unintentional exposures that a person does not elect to experience. For example, being a bread baker is a choice that does not involve election to be exposed to substances that cause asthma that are part of the flour dust (most commonly, wheat antigens and fungal enzymes). Therefore, suitable occupational exposure limits are created to attempt to protect individuals from such risk on the job, with no presumption of “assumed risk” inherent in the occupation. Likewise, special regulations are in effect to protect persons from unintentional exposure to nicotine in workplaces (http://www.cdc.gov/niosh/docs/81-123/pdfs/0446.pdf; accessed July 12, 2013), because in environments where such exposures are possible, it is reasonable to protect individuals who do not wish to experience its effects. In other words, occupational exposure limits are based on protecting people from involuntary and unwanted exposures, and thus can be seen as more stringent than the standards that might be used for hazards that people intentionally choose to accept.

By contrast, a person who elects to lawfully consume a substance is subject to different risk tolerance, as is demonstrated in the case of nicotine by the fact that legally sold cigarettes deliver doses of nicotine that exceed occupational exposure limits [9]: daily intake of 20 mg of nicotine, assuming nearly 100% absorption in the lungs and inhalation of 4 m^3 of air, corresponds to roughly 10 times the occupational exposure limit of 0.5 mg/m^3 atmosphere over 8 hours [10]. Thus, whereas there is a clear case for applicability of occupational exposure limits to contaminants in a consumer product (e.g. aerosol of electronic cigarettes), there is no corresponding case for applying occupational exposure limits to declared ingredients desired by the consumer in a lawful product (e.g. nicotine in the aerosol of an electronic cigarette). Clearly, some limits must be set for voluntary exposure to compounds that are known to be a danger at plausible doses (e.g. limits on blood alcohol level while driving), but the regulatory framework should reflect whether the dosage is intentionally determined and whether the risk is assumed by the consumer. In the case of nicotine in electronic cigarettes, if the main

reason the products are consumed is as an alternative source of nicotine compared to smoking, then the only relevant question is whether undesirable exposures that accompany nicotine present health risks, and the analogy with occupational exposures holds. In such cases it appears permissible to allow at least as much exposure to nicotine as from smoking before admitting to existence of new risk. It is expected that nicotine dosage will not increase in switching from smoking to electronic cigarettes because there is good evidence that consumers adjust consumption to obtain their desired or usual dose of nicotine [11]. The situation is different for the vapers who want to use electronic cigarettes without nicotine and who would otherwise not have consumed nicotine. For these individuals, it is defensible to consider total exposure, including that from any nicotine contamination, in comparison to occupational exposure limits. In consideration of vapers who would never have smoked or would have quit entirely, it must be remembered that the exposure is still voluntary and intentional, and comparison to occupational exposure limits is legitimate only for those compounds that the consumer does not elect to inhale.

The specific aims of this review were to:

1. 1.

   Synthesize evidence on the chemistry of liquids and aerosols of electronic cigarettes, with particular emphasis on the contaminants.

2. 2.

   Evaluate the quality of research on the chemistry of liquids and aerosols produced by electronic cigarettes.

3. 3.

   Estimate potential exposures from aerosols produced by electronic cigarettes and compare those potential exposures to occupational exposure standards.

Methods

Literature search

Articles published in peer-reviewed journals were retrieved from *PubMed* (http://www.ncbi.nlm.nih.gov/pubmed/) available as of July 2013 using combinations of the following keywords: “electronic cigarettes”, “e-cigarettes”, “smoking alternatives”, “chemicals”, “risks”, “electronic cigarette vapor”, “aerosol”, “ingredients”, “e-cigarette liquid”, “e-cig composition”, “e-cig chemicals”, “e-cig chemical composition”, “e-juice electronic cigarette”, “electronic cigarette gas”, “electronic cigars”. In addition, references of the retrieved articles were examined to identify further relevant articles, with particular attention paid to non-peer reviewed reports and conference presentations. Unpublished results obtained through personal communications were also reviewed. The Consumer Advocates for Smoke-free Alternatives Association (CASAA) was asked to review the retrieved bibliography to identify any reports or articles that were missed. The papers and reports were retained for analysis if they reported on the chemistry of e-cigarette liquids or aerosols. No explicit quality control criteria were applied in selection of literature for examination, except that secondary reporting of analytical results was not used. Where substantial methodological problems that

precluded interpretation of analytical results were noted, these are described below. For each article that contained relevant analytical results, the compounds quantified, limits of detection, and analytical results were summarized in a spreadsheet. Wherever possible, individual analytical results (rather than averages) were recorded (see Additional file 1). Data contained in Additional file 1 is not fully summarized in the current report but can be used to investigate a variety of specific questions that may interest the reader. Each entry in Additional file 1 is identified by a *Reference Manage ID* that is linked to source materials in a list in Additional file 2 (linked via *RefID*); copies of all original materials can be requested.

Comparison of observed concentrations in aerosol to occupational exposure limits

For articles that reported mass or concentration of specific compounds in the aerosol (generated by smoking machines or from volunteer vapers), measurements of compounds were converted to concentrations in the "personal breathing zone",[a] which can be compared to occupational exposure limits (OELs). The 2013 Threshold Limit Values (TLVs) [10] were used as OELs because they are the most up to date and are most widely recognized internationally when local jurisdictions do not establish their own regulations (see http://www.ilo.org/safework/info/publications/WCMS_113329/lang--en/index.htm; accessed July 3, 2013). TLVs are more protective that of US Occupation Safety and Health Administration's Permissible Exposure Limits because TLVs are much more often updated with current knowledge. However, all OELs generally agree with each other because they are based on the same body of knowledge. TLVs (and all other OELs) aim to define environmental conditions to which nearly all persons can be exposed to all day over many years without experiencing adverse health effects. Whenever there was an uncertainty in how to perform the calculation, a "worst case" scenario was used, as is the standard practice in occupational hygiene, where the initial aim is to recognize potential for hazardous exposures and to err on the side of caution. The following assumptions were made to enable the calculations that approximate the worst-case personal exposure of a vaper (Equation 1):

$$\left[\mathrm{mg}/\mathrm{m}^3\right] = \mathrm{mg}/\mathrm{puff} \times \mathrm{puffs}/(8\ \mathrm{hr\ day}) \times 1/\left(\mathrm{m}^3\ \text{air inhaled in 8 hr}\right)$$

$$\left[\mathrm{mg}/\mathrm{m}^3\right] = \mathrm{mg}/\mathrm{puff} \times \mathrm{puffs}/(8\,\mathrm{hr\ day}) \times 1/\left(\mathrm{m}^3\ \text{air inhaled in 8 hr}\right) \quad (1)$$

1. 1.

   Air the vaper breathes consists of a small volume of aerosol generated by e-cigarettes that contains a specific chemical plus pristine air;

2. 2.

   The volume of aerosols inhaled from e-cigarettes is small compared to total volume of air inhaled;

3. 3.

   The period of exposure to the aerosol considered was 8 hours for comparability to the standard working shift for which TLVs were developed (this does not mean only 8 hours worth of vaping was considered but, rather, a day's worth of exposure was modeled as being concentrated into just 8 hours);

4. 4.

   Consumption of 150 puffs in 8 hours (an upper estimate based on a rough estimate of 150 puffs by a typical vaper in a day [1]) was assumed. (Note that if vaping over 16 hours "day" was considered then air into which contaminants from vaping are diluted into would have to increase by a factor of 2, thereby lowering estimated exposure; thus, the adopted approach is entirely still in line with "worst case" assessment);

5. 5.

   Breathing rate is 8 liters per minute [12, 13];

6. 6.

   Each puff contains the same quantity of compounds studied.

The only exception to this methodology was when assessing a study of aerosol emitted by 5 vapers in a 60 m^3 room over 5 hours that seemed to be a sufficient approximation of worst-case "bystander" exposure [6]. All calculated concentrations were expressed as the most stringent (lowest) TLV for a specific compound (i.e. assuming the most toxic form if analytical report is ambiguous) and expressed as "percent of TLV". Considering that all the above calculations are approximate and reflecting that exposures in occupational and general environment can easily vary by a factor of 10 around the mean, we added a 10-fold safety factor to the "percent of TLV" calculation. This safety factor accounts for considerable uncertainty about the actual number and volume of puffs since the number of puffs is hard to estimate accurately with reports as high as 700 puffs per day [14]. Details of all calculations are provided in an Excel spreadsheet (see Additional file 3).

No systematic attempt was made to convert the content of the studied liquids into potential exposures because sufficient information was available on the chemistry of aerosols to use those studies rather than making the necessary simplifying assumptions to do the conversion. However, where such calculations were performed in the original research, the following approach was used: under the (probably false – see the literature on formation of carbonyl compounds below) assumption of no chemical reaction to generate novel ingredients, composition of liquids can be used to estimate potential for exposure if it can be established how much volume of liquid is consumed in given 8 hours, following an algorithm analogous to the one described above for the aerosols (Equation 2):

$$\left[\mathrm{mg}/\mathrm{m}^3\right] = \mathrm{mg}/(\mathrm{mL\ \ liquid}) \times (\mathrm{mL\ \ liquid})/\mathrm{puff} \times \mathrm{puffs}/(8\ \ \mathrm{hr\ \ day}) \times 1/\left(\mathrm{m}^3\ \ \mathrm{air\ inhaled\ \ in\ \ 8\ \ hr}\right)$$

$$\left[\mathrm{mg}/\mathrm{m}^3\right] = \mathrm{mg}/(\mathrm{mL\ liquid}) \times (\mathrm{mL\ liquid})/\mathrm{puff} \times \mathrm{puffs}/(8\ \mathrm{hr\ day}) \times 1/\left(\mathrm{m}^3\ \mathrm{air\ inhaled\ in\ 8\ hr}\right)$$

(2)

Comparison to cigarette smoke was not performed here because the fact that e-cigarette aerosol is at least orders of magnitude less contaminated by toxic compounds is uncontroversial [2, 3, 4, 5, 6, 7, 8].

The study adhered to the PRISMA guidelines for systematic reviews (http://www.prisma-statement.org/).

Results and discussion

General comments on methods

In excess of 9,000 determinations of single chemicals (and rarely, mixtures) were reported in reviewed articles and reports, typically with multiple compounds per electronic cigarette tested [2, 3, 4, 5, 6, 7, 8, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43]. Although the quality of reports is highly variable, if one assumes that each report contains some information, this asserts that quite a bit is known about composition of e-cigarette liquids and aerosols. The only report that was excluded from consideration was work of McAuley *et al*.[24] because of clear evidence of cross-contamination – admitted to by the authors – with cigarette smoke and, possibly, reagents. The results pertaining to non-detection of tobacco-specific nitrosamines (TSNAs) are potentially trustworthy, but those related to polycyclic aromatic hydrocarbons (PAH) are not since it is incredible that cigarette smoke would contain fewer PAHs, which arise from incomplete combustion of organic matter, than aerosol of e-cigarettes that do not burn organic matter [24]. In fairness to the authors of that study, similar problems may have occurred in other studies but were simply not reported, but it is impossible to include a paper in a review once it is known for certain that its quantitative results are not trustworthy. When in doubt, we erred on the side of trusting that proper quality controls were in place, a practice that is likely to increase appearance of atypical or erroneous results in this review. From this perspective, assessment of concordance among independent reports gains higher importance than usual since it is unlikely that two experiments would be flawed in the same exact manner (though of course this cannot be assured).

It was judged that the simplest form of publication bias – disappearance of an entire formal study from the available literature – was unlikely given the exhaustive search strategy and the contested nature of the research question. It is clearly the case that only a portion of all industry technical reports were available for public access, so it is possible that those with more problematic results were systematically suppressed, though there is no evidence to support this speculation. No formal attempt was made to ascertain publication bias *in situ* though it is apparent that anomalous results do gain prominence in typical reviews of the literature: diethylene glycol [44, 45] detected at non-dangerous levels (see details below) in one test of 18 of early-technology products by the US Food and Drugs Administration (FDA) [23] and one outlier in measurement of formaldehyde content of exhaled air [4] and aldehydes in aerosol generated from one e-cigarette in Japan [38]. It must be emphasized that the alarmist report of aldehydes in experiments presented in [38] is based on the concentration in generated aerosol rather than air inhaled by the vaper over prolonged period of time (since vapers do not inhale only aerosol). Thus, results reported in [38] cannot be the basis of any claims about health risk, a fallacy committed both by the authors themselves and commentators on this work [45].

It was also unclear from [38] what the volume of aerosol sampled was – a critical item for extrapolating to personal exposure and a common point of ambiguity in the published reports. However, in a personal exchange with the authors of [38] [July 11, 2013], it was clarified that the sampling pump drew air at 500 mL/min through e-cigarette for 10 min, allowing more appropriate calculations for estimation of health risk that are presented below. Such misleading reporting is common in the field that confuses concentration in the aerosol (typically measured directly) with concentration in the air inhaled by the vaper (never determined directly and currently requiring additional assumptions and modeling). This is important because the volume of aerosol inhaled (maximum ~8 L/day) is small compared to the volume of air inhaled daily (8 L/min); this point is illustrated in the Figure 1.

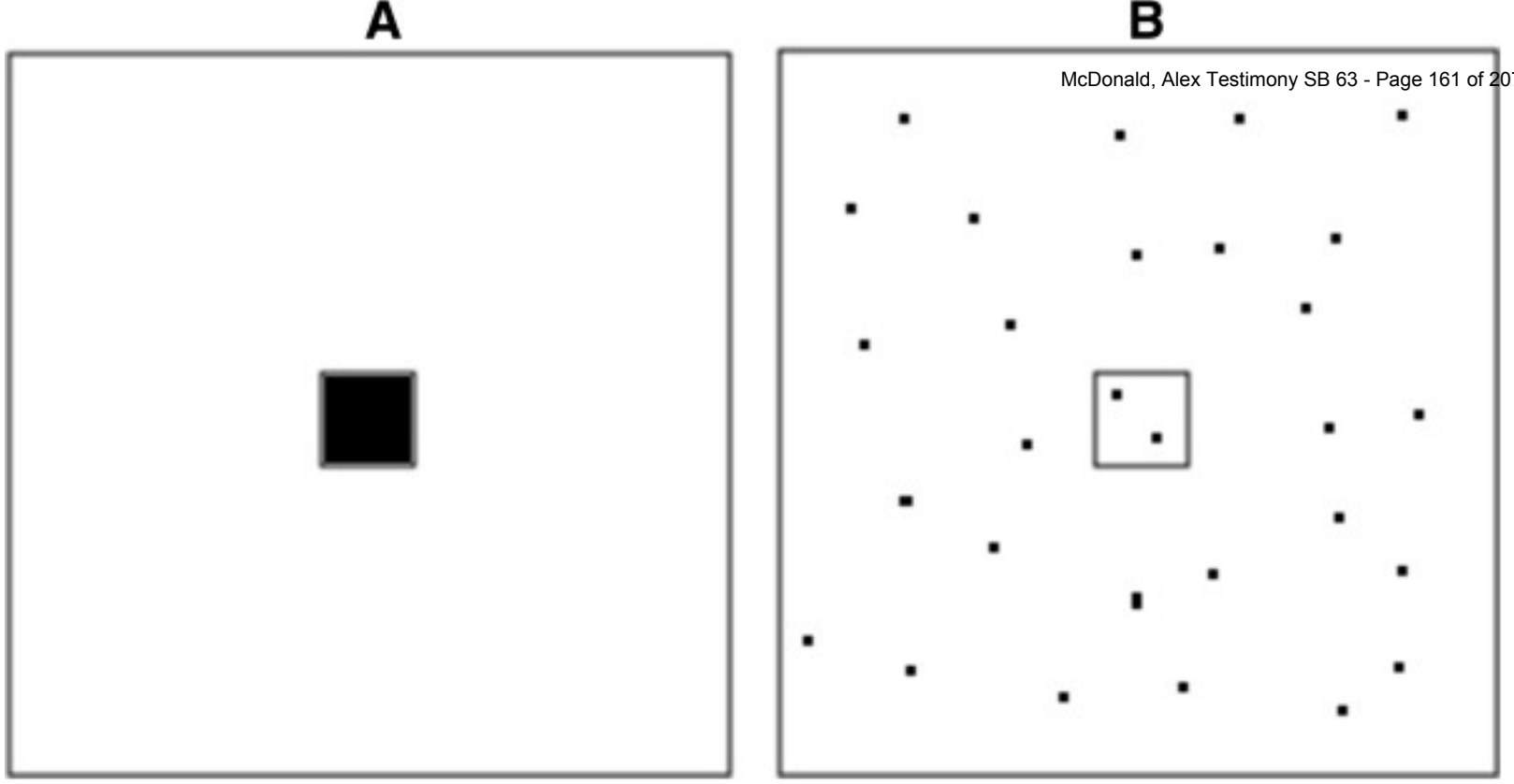

Figure 1

Illustrating the difference between concentrations in the aerosol generated by vaping and inhaled air in a day. *Panel* Ashows a black square that represents aerosol contaminated by some compound as it would be measured by a "smoking machine" and extrapolated to dosage from vaping in one day. This black square is located inside the white square that represents total uncontaminated air that is inhaled in a day by a vaper. The relative sizes of the two squares are exaggerated as the volume of aerosol generated in vaping relative to inhaled air is much smaller than is illustrated in the figure. *Panel* Bshows how exposure from contaminated air (black dots) is diluted over a day for appropriate comparison to occupational exposure limits that are expressed in terms of "time-weighted average" or average contamination over time rather than as instantaneous exposures. Exposure during vaping occurs in a dynamic process where the atmosphere inhaled by the vaper alternates between the smaller black and larger white squares in *Panel* A. Thus, the concentration of contaminants that a vaper is exposed to over a day is much smaller than that which is measured in the aerosol (and routinely improperly cited as reason for concern about "high" exposures).

A similar but more extreme consideration applies to the exposure of bystanders which is almost certainly several orders of magnitude lower than the exposure of vapers. In part this is due to the absorption, rather than exhalation, of a portion of the aerosol by the vapers: there is no equivalent to the "side-stream" component of exposure to conventional cigarettes, so all of the exposure to a bystander results from exhalation. Furthermore, any environmental contamination that results from exhalation of aerosol by vaper will be diluted into the air prior to entering a bystander's personal breathing zone. Lastly, the number of puffs that affect exposure to bystander is likely to be much smaller than that of a vaper unless we are to assume that vaper and bystander are inseparable.

It is unhelpful to report the results in cigarette-equivalents in assessments that are not about cigarette exposure, as in [43], because this does not enable one to estimate exposures of vapers. To be useful for risk assessment, the results on the chemistry of the aerosols and liquids must be reported in a form that enables the calculations in Equations 1 and 2. It must be also be noted that typical investigations consisted of qualitative and quantitative phases such that quantitative data is available mostly on compounds that passed the qualitative screen. In the qualitative phase, presence of the compounds above a certain limit of detection is determined. In the quantitative phase, the amount of only the compounds that are detected in the qualitative phase is estimated.

This biased all reports on concentration of compounds towards both higher levels and chemicals which a particular lab was most adept at analyzing.

Declared Ingredients: comparison to occupational exposure limits

Propylene glycol and glycerin

Propylene glycol and glycerin have the default or precautionary 8-hour TLV of 10 mg/m^3 set for all organic mists with no specific exposure limits or identified toxicity (http://www.osha.gov/dts/chemicalsampling/data/CH_243600.html; accessed July 5, 2013). These interim TLVs tend to err on the side of being too high and are typically lowered if evidence of harm to health accumulates. For example, in a study that related exposure of theatrical fogs (containing propylene glycol) to respiratory symptoms [46], "mean personal inhalable aerosol concentrations were 0.70 mg/m^3 (range 0.02 to 4.1)" [47]. The only available estimate of propylene concentration of propylene glycol in the aerosol indicates personal exposure on the order of 3–4 mg/m^3 in the personal breathing zone over 8 hours (under the assumptions we made for all other comparisons to TLVs) [2]. The latest (2006) review of risks of occupational exposure to propylene glycol performed by the Health Council of the Netherlands (known for OELs that are the most protective that evidence supports and based exclusively on scientific considerations rather than also accounting for feasibility as is the case for the TLVs) recommended exposure limit of 50 mg/m^3 over 8 hours; concern over short-term respiratory effects was noted [http://www.gezondheidsraad.nl/sites/default/files/200702OSH.pdf; accessed July 29, 2013]. Assuming extreme consumption of the liquid per day via vaping (5 to 25 ml/day and 50-95% propylene glycol in the liquid),[b] levels of propylene glycol in inhaled air can reach 1–6 mg/m^3. It has been suggested that propylene glycol is very rapidly absorbed during inhalation [4, 6] making the calculation under worst case scenario of all propylene glycol becoming available for inhalation credible. It must also be noted that when consuming low-nicotine or nicotine-free liquids, the chance to consume larger volumes of liquid increases (large volumes are needed to reach the target dose or there is no nicotine feedback), leading to the upper end of propylene glycol and glycerin exposure. Thus, estimated levels of exposure to propylene glycol and glycerin are close enough to TLV to warrant concern. However, it is also important to consider that propylene glycol is certainly not all absorbed because visible aerosol is exhaled in typical vaping. Therefore, the current calculation is in the spirit of a worst case assumption that is adopted throughout the paper.

Nicotine

Nicotine is present in most e-cigarette liquids and has TLV of 0.5 mg/m^3 for average exposure intensity over 8 hours. If approximately 4 m^3 of air is inhaled in 8 hours, the consumption of 2 mg nicotine from e-cigarettes in 8 hours would place the vaper at the occupational exposure limit. For a liquid that contains 18 mg nicotine/ml, TLV would be reached upon vaping ~0.1-0.2 ml of liquid in a day, and so is achieved for most anyone vaping nicotine-containing e-cigarettes [1]. Results presented in [25] on 16 e-cigarettes also argue in favor of exceedance of TLV from most any nicotine-containing e-cigarette, as they predict >2 mg of nicotine released to aerosol in 150 puffs (daily consumption figure adopted in this report). But as noted above, since delivery of nicotine is the purpose of nicotine-containing e-cigarettes, the comparison to limits on unintended, unwanted exposures does not suggest a problem and serves merely to offer complete context. If nicotine is present but the liquid is labeled as zero-nicotine [25, 44], it could be treated as a contaminant, with the vaper not intending to consume nicotine and the TLV, which would be most likely exceeded, is relevant. However, when nicotine content is disclosed, even if inaccurately, then comparison to TLV is not valid. Accuracy in nicotine content is a concern with respect to truth in advertising rather than unintentional exposure, due to presumed (though not yet tested) self-regulation of consumption by persons who use e-cigarettes as a source of nicotine.

Overall, the declared ingredients in the liquid would warrant a concern by standards used in occupational hygiene, provided that comparison to occupational exposure limits is valid, as discussed in the introduction. However, this is not to say that the exposure is affirmatively believed to be harmful; as noted, the TLVs for propylene glycol and glycerin mists is based on uncertainty rather than knowledge. These TLVs are not derived from knowledge of toxicity of propylene glycol and glycerin mists, but merely apply to any compound of no known toxicity present in workplace atmosphere. This aspect of the exposure from e-cigarettes simply has little precedent (but see study of theatrical fogs below). Therefore, the exposure will provide the first substantial collection evidence about the effects, which calls for monitoring of both exposure levels and outcomes, even though there are currently no grounds to be concerned about the immediate or chronic health effects of the exposure. The argument about nicotine is presented here for the sake of completeness and consistency of comparison to TLVs, but in itself does not affect the conclusions of this analysis because it should not be modeled as if it were a contaminant when declared as an ingredient in the liquid.

Contaminants

Polycyclic aromatic hydrocarbons

Polycyclic aromatic hydrocarbons (PAH) were quantified in several reports in aerosols [5, 6, 43] and liquids [7, 19, 42]. These compounds include well-known carcinogens, the levels of which are not subject to TLV but are instead to be kept "as low as reasonably achievable" [10]. For PAH, only non-carcinogenic pyrene that is abundant in the general environment was detected at 36 ng/cartridge in 5 samples of liquid [7]; PAHs were not detected in most of the analyses of aerosols, except for chrysene in the analysis of the aerosol of one e-cigarette [43].

Tobacco-specific nitrosamines

The same risk assessment considerations that exist for PAH also hold for carcinogenic tobacco-specific nitrosamines (TSNAs) [48] for which no occupational exposure limits exist because (a) these exposures do not appear to occur in occupational settings often enough to warrant development of TLVs, and (b) it is currently accepted in establishing TLVs that carcinogens do not have minimal thresholds of toxicity. As expected, because the TSNAs are contaminants of nicotine from tobacco leaf, there is also evidence of association between nicotine content of the liquid and TSNA concentrations, with reported concentrations <5 ng/cartridge tested [7]. Smaller studies of TSNA content in liquids are variable, with some not reporting any detectable levels [18, 33, 35] and others clearly identifying these compounds in the liquids when controlling for background contamination (n = 9) [23]. Analyses of aerosols indicate that TSNAs are present in amounts that can results in doses of < ng/day [5, 33] to μg/day [8] (assuming 150 puffs/day) (see also [43]). The most comprehensive survey of TSNA content of 105 samples of liquids from 11 manufactures indicates that almost all tested liquids (>90%) contained TSNAs in μg/L quantities [36]. This is roughly equivalent to 1/1000 of the concentration of TSNAs in modern smokeless tobacco products (like snus), which are in the ppm range [48]. For example, 10 μg/L (0.01 ppm) of total TSNA in liquid [36] can translate to a daily dose of 0.025–0.05 μg from vaping (worst case assumption of 5 ml liquid/day); if 15 g of snus is consumed a day [49] with 1 ppm of TSNAs [48] and half of it were absorbed, then the daily dose is estimated to be 7.5 μg, which is 150–300 times that due to the worst case of exposure from vaping. Various assumptions about absorption of TSNAs alter the result of this calculation by a factor that is dwarfed in magnitude compared to that arising from differences considered above. This is reassuring because smokeless tobacco products, such as snus, pose negligible cancer risk [50], certainly orders of magnitude smaller than smoking (if one considers the chemistry of the products alone). In general, it appears that the cautious approach in face of variability and paucity of data is to seek better understanding of the predictors of presence of TSNA in liquids and aerosols so that measures for minimizing exposure to TSNAs from aerosols can be devised. This can include considering better control by manufactures

who extract the nicotine from tobacco leaf.

Volatile organic compounds

Total volatile organic compounds (VOC) were determined in aerosol to be non-detectable [3] except in one sample that appeared to barely exceed the background concentration of 1 mg/m^3 by 0.73 mg/m^3[6]. These results are corroborated by analyses of liquids [19] and most likely testify to insensitivity of employed analytic methods for total VOC for characterizing aerosol generated by e-cigarettes, because there is ample evidence that specific VOC are present in the liquids and aerosols.[c] Information on specific commonly detected VOC in the aerosol is given in Table 1. It must be observed that these reported concentrations are for analyses that first observed qualitative evidence of the presence of a given VOC and thus represent worst case scenarios of exposure when VOC is present (i.e. zero-level exposures are missing from the overall summary of worst case exposures presented here). For most VOC and aldehydes, one can predict the concentration in air inhaled by a vaper to be < <1% of TLV. The only exceptions to this generalization are:

1. (a)

   acrolein: ~1% of TLV (average of 12 measurements) [40] and measurements at a mean of 2% of TLV (average of 150 measurements) [41] and

2. (b)

   formaldehyde: between 0 and 3% of TLV based on 18 tests (average of 12 measurements at 2% of TLV, the most reliable test) [40] and an average of 150 results at 4% of TLV [41].

Table 1

Exposure predictions based on analysis of aerosols generated by smoking machines: volatile organic compounds

Compound	N#	Estimated concentration in personal breathing zone		Ratio of most stringent TLV (%)		Reference
		PPM	mg/m^3	Calculated directly	Safety factor 10	
	1	0.005		0.02	0.2	[5]
	3	0.003		0.01	0.1	[4]
	12	0.001		0.004	0.04	[8]

Acetaldehyde	1	0.00004		0.0001	0.001	[3]
	1	0.0002		0.001	0.008	[3]
	150	0.001		0.004	0.04	[40, 41]
	1	0.008		0.03	3	[38]
Acetone	1	0.002		0.0003	0.003	[38]
	150	0.0004		0.0001	0.001	[40, 41]
Acrolein	12	0.001		1	13	[8]
	150	0.002		2	20	[40, 41]
	1	0.006		6	60	[38]
Butanal	150	0.0002		0.001	0.01	[40, 41]
Crotonaldehyde	150		0.0004	0.01	0.1	[40, 41]
Formaldehyde	1	0.002		0.6	6	[5]
	3	0.008		3	30	[4]
	12	0.006		2	20	[8]
	1	<0.0003		<0.1	<1	[3]
	1	0.0003		0.1	1	[3]
	150	0.01		4	40	[40, 41]

	150	0.01		4	40	[40, 41]
	1	0.009		3	30	[38]
Glyoxal	1		0.002	2	20	[38]
	150		0.006	6	60	[40, 41]
o-Methylbenzaldehyde	12		0.001	0.05	0.5	[8]
p,m-Xylene	12		0.00003	0.001	0.01	[8]
Propanal	3	0.002		0.01	0.1	[4]
	150	0.0006		0.002	0.02	[40, 41]
	1	0.005		0.02	0.2	[38]
Toluene	12	0.0001		0.003	0.03	[8]
Valeraldehyde	150		0.0001	0.0001	0.001	[40, 41]

[#]Average is presented when N > 1.

Levels of acrolein in exhaled aerosol reported in [6] were below 0.0016 mg/m^3 and correspond to predicted exposure of <1% of TLV (Table 2). It must re-emphasized that all calculations based on one electronic cigarette analyzed in [38] are best treated as qualitative in nature (i.e. indicating presence of a compound without any particular meaning attached to the reported level with respect to typical levels) due to great uncertainty about whether the manner in which the e-cigarette was operated could have resulted in overheating that led to generation of acrolein in the aerosol. In fact, a presentation made by the author of [38] clearly stated that the "atomizer, generating high concentration carbonyls, had been burned black" [40, 41]. In unpublished work, [40] there are individual values of formaldehyde, acrolein and glyoxal that approach TLV, but it is uncertain how typical these are because there is reason to believe the liquid was overheated; considerable variability among brands of electronic cigarettes was also noted. Formaldehyde and other aldehydes, but not acrolein, were detected in the analysis one e-cigarette [43]. The overwhelming majority of the exposure to specific VOC that are predicted to result from inhalation of the aerosols lie far below action level of 50% of TLV at which exposure has to be mitigated according to current code of best practice in occupational hygiene [51].

Table 2

Exposure predictions for volatile organic compounds based on analysis of aerosols generated by volunteer vapers

Compound	N#	Estimated concentration in personal breathing zone (ppm)	Ratio of most stringent TLV (%)		Reference
			Calculated directly	Safety factor 10	
2-butanone (MEK)	3	0.04	0.02	0.2	[4]
	1	0.002	0.0007	0.007	[6]
2-furaldehyde	3	0.01	0.7	7	[4]
Acetaldehyde	3	0.07	0.3	3	[4]
Acetic acid	3	0.3	3	30	[4]
Acetone	3	0.4	0.2	2	[4]
Acrolein	1	<0.001	<0.7	<7	[6]
Benzene	3	0.02	3	33	[4]
Butyl hydroxyl toluene	1	4E-05	0.0002	0.002	[6]
Isoprene	3	0.1	7	70	[4]
Limonene	3	0.009	0.03	0.3	[4]
	1	2E-05	0.000001	0.00001	[6]

m,p-Xyelen	3	0.01	0.01	0.1	[4]
Phenol	3	0.01	0.3	3	[4]
Propanal	3	0.004	0.01	0.1	[4]
Toluene	3	0.01	0.07	0.7	[4]

[#]Average is presented when N > 1.

Finding of an unusually high level of formaldehyde by Schripp *et al*.[4] – 0.5 ppm predicted vs. 15-minute TLV of 0.3 ppm (not given in Table 2) – is clearly attributable to endogenous production of formaldehyde by the volunteer smoker who was consuming e-cigarettes in the experimental chamber, since there was evidence of build-up of formaldehyde prior to vaping and liquids used in the experiments did not generate aerosol with detectable formaldehyde. This places generalizability of other findings from [4] in doubt, especially given that the only other study of exhaled air by vapers who were not current smokers reports much lower concentrations for the same compounds [6] (Table 2). It should be noted that the report by Romagna *et al*.[6] employed more robust methodology, using 5 volunteer vapers (no smokers) over an extended period of time. Except for benzene, acetic acid and isoprene, all calculated concentrations for detected VOC were much below 1% of TLV in exhaled air [6]. In summary, these results do not indicate that VOC generated by vaping are of concern by standards used in occupational hygiene.

Diethylene glycol and ethylene glycol became a concern following the report of their detection by FDA [44], but these compounds are not detected in the majority of tests performed to date [3, 15, 17, 19, 23]. Ten batches of the liquid tested by their manufacture did not report any diethylene glycol above 0.05% of the liquid [42]. Methods used to detect diethylene glycol appear to be adequate to be informative and capable of detecting the compound in quantities <<1% of TLV [15, 17, 23]. Comparison to TLV is based on a worst case calculation analogous to the one performed for propylene glycol. For diethylene glycol, TLV of 10 mg/m^3 is applicable (as in the case of all aerosols with no know toxicity by inhalation), and there is a recent review of regulations of this compound conducted for the Dutch government by the Health Council of the Netherlands (jurisdiction with some of the most strict occupational exposure limits) that recommended OEL of 70 mg/m^3 and noted lack of evidence for toxicity following inhalation [http://www.gezondheidsraad.nl/sites/default/files/200703OSH.pdf; accessed July 29; 2013]. In conclusion, even the quantities detected in the single FDA result were of little concern, amounting to less than 1% of TLV.

Inorganic compounds

Special attention has to be paid to the chemical form of compounds when there is detection of metals and other elements by inductively coupled plasma mass spectrometry (ICP-MS) [8, 26]. Because the parent molecule that occurs in the aerosol is destroyed in such analysis, the results can be misleading and not interpretable for risk assessment. For example, the presence of sodium (4.18 μg/10 puffs) [26] does not mean that highly reactive and toxic sodium metal is in the aerosol, which would be impossible given its reactivity, but most likely means the presence of the ubiquitous compound that contains sodium, dissolved table salt (NaCl). If so, the corresponding

daily dose of NaCl that arises from these concentrations from 150 puffs is about 10,000 times lower than allowable daily intake according to CDC (http://www.cdc.gov/features/dssodium/; accessed July 4, 2013). Likewise, a result for presence of silica is meaningless for health assessment unless the crystalline form of SiO_2 is known to be present. When such ambiguity exists, a TLV equivalence calculation was not performed. We compared concentrations to TLVs when it was even remotely plausible that parent molecules were present in the aqueous solution. However, even these are to be given credence only in an extremely pessimistic analyst, and further investigation by more appropriate analytical methods could clarify exactly what compounds are present, but is not a priority for risk assessment.

It should also be noted that one study that attempted to quantify metals in the liquid found none above 0.1-0.2 ppm levels [7] or above unspecified threshold [19]. Table 3 indicates that most metals that were detected were present at <1% of TLV even if we assume that the analytical results imply the presence of the most hazardous molecules containing these elements that can occur in aqueous solution. For example, when elemental chromium was measured, it is compared to TLV for insoluble chromium IV that has the lowest TLV of all chromium compounds. Analyses of metals given in [43] are not summarized here because of difficulty with translating reported units into meaningful terms for comparison with the TLV, but only mercury (again with no information on parent organic compound) was detected in trace quantities, while arsenic, beryllium, chromium, cadmium, lead and nickel were not. Taken as the whole, it can be inferred that there is no evidence of contamination of the aerosol with metals that warrants a health concern.

Table 3

Exposure predictions based on analysis of aerosols generated by smoking machines: inorganic compounds [#]

Element quantified	Assumed compound containing the element for comparison with TLV	N[##]	Estimated concentration in personal breathing zone (mg/m^3)	Ratio of most stringent TLV (%)		Reference
				Calculated directly	Safety factor 10	
Aluminum	Respirable Al metal & insoluble compounds	1	0.002	0.2	1.5	[26]
Barium	Ba & insoluble compounds	1	0.00005	0.01	0.1	[26]
Boron	Boron oxide	1	0.02	0.1	1.5	[26]
Cadmium	Respirable Cd & compounds	12	0.00002	1	10	[8]

Chromium	Insoluble Cr (IV) compounds	1	3E-05	0.3	3	[26]
Copper	Cu fume	1	0.0008	0.4	4.0	[26]
Iron	Soluble iron salts, as Fe	1	0.002	0.02	0.2	[26]
Lead	Inorganic compounds as Pb	1	7E-05	0.1	1	[26]
		12	0.000025	0.05	0.5	[8]
Magnesium	Inhalable magnesium oxide	1	0.00026	0.003	0.03	[26]
Manganese	Inorganic compounds, as Mn	1	8E-06	0.04	0.4	[26]
Nickel	Inhalable soluble inorganic compounds, as Ni	1	2E-05	0.02	0.2	[26]
		12	0.00005	0.05	0.5	[8]
Potassium	KOH	1	0.001	0.1	1	[26]
Tin	Organic compounds, as Sn	1	0.0001	0.1	1	[26]
Zinc	Zinc chloride fume	1	0.0004	0.04	0.4	[26]
Zirconium	Zr and compounds	1	3E-05	0.001	0.01	[26]
Sulfur	SO_2	1	0.002	0.3	3	[26]

[#]The actual molecular form in the aerosol unknown and so worst case assumption was made if it was physically possible (e.g. it is not possible for elemental lithium & sodium to be present in the

aerosol); there is no evidence from the research that suggests the metals were in the particular highest risk form, and in most cases a general knowledge of chemistry strongly suggests that this is unlikely. Thus, the TLV ratios reported here probably do not represent the (much lower) levels that would result if we knew the molecular forms.

[##]Average is presented when $N > 1$.

Consideration of exposure to a mixture of contaminants

All calculations conducted so far assumed only one contaminant present in clean air at a time. What are the implications of small quantities of various compounds with different toxicities entering the personal breathing zone at the same time? For evaluation of compliance with exposure limits for mixtures, Equation 3 is used:

$$\mathrm{OEL}_{\mathrm{mixture}} = \sum_{i-1}^{n} \left(C_i / TL\,V_i \right), \mathrm{OEL}_{\mathrm{mixture}} = \sum_{i\text{-}1}^{n} \left(C_i / TLV_i \right),$$

(3)

where C_i is the concentration of the i^{th} compound ($i = 1,\ldots,n$, where $n > 1$ is the number of ingredients present in a mixture) in the contaminated air and TLV_i is the TLV for the i^{th} compound in the contaminated air; if $\mathrm{OEL}_{\mathrm{mixture}} > 1$, then there is evidence of the mixture exceeding TLV.

The examined reports detected no more than 5–10 compounds in the aerosol, and the above calculation does not place any of them out of compliance with TLV for mixture. Let us imagine that 50 compounds with TLVs were detected. Given that the aerosol tends to contain various compounds at levels, on average, of no more than 0.5% of TLV (Tables 1 and 3), such a mixture with 50 ingredients would be at 25% of TLV, a level that is below that which warrants a concern, since the "action level" for implementation of controls is traditionally set at 50% of TLV to ensure that the majority of persons exposed have personal exposure below mandated limit [51]. Pellerino *et al*.[2] reached conclusions similar to this review based on their single experiment: contaminants in the liquids that warrant health concerns were present in concentrations that were less than 0.1% of that allowed by law in the European Union. Of course, if the levels of the declared ingredients (propylene glycol, glycerin, and nicotine) are considered, the action level would be met, since those ingredients are present in the concentrations that are near the action level. There are no known synergistic actions of the examined mixtures, so Equation 3 is therefore applicable. Moreover, there is currently no reason to suspect that the trace amounts of the contaminants will react to create compounds that would be of concern.

Conclusions

By the standards of occupational hygiene, current data do not indicate that exposures to vapers from contaminants in electronic cigarettes warrant a concern. There are no known toxicological synergies among compounds in the aerosol, and mixture of the contaminants does not pose a risk to health. However, exposure of vapers to propylene glycol and glycerin reaches the levels at which, if one were considering the exposure in connection with a workplace setting, it would be prudent to scrutinize the health of exposed individuals and examine how exposures could be reduced. This is the basis for the recommendation to monitor levels and effects of prolonged exposure to propylene glycol and glycerin that comprise the bulk of emissions from electronic cigarettes other than nicotine and water vapor. From this perspective, and taking the analogy of work on theatrical fogs [46, 47], it can be speculated that respiratory functions and symptoms (but not cancer of respiratory tract or non-malignant respiratory disease) of the vaper is of primary interest. Monitoring upper airway irritation of vapers and experiences of unpleasant smell would also provide early warning of exposure to

compounds like acrolein because of known immediate effects of elevated exposures (http://www.atsdr.cdc.gov/toxprofiles/tp124-c3.pdf; accessed July 11, 2013). However, it is questionable how much concern should be associated with observed concentrations of acrolein and formaldehyde in the aerosol. Given highly variable assessments, closer scrutiny is probably warranted to understand sources of this variability, although there is no need at present to be alarmed about exceeding even the occupational exposure limits, since occurrence of occasional high values is accounted for in established TLVs. An important clue towards a productive direction for such work is the results reported in [40, 41] that convincingly demonstrate how heating the liquid to high temperatures generates compounds like acrolein and formaldehyde in the aerosol. A better understanding about the sources of TSNA in the aerosol may be of some interest as well, but all results to date consistently indicate quantities that are of no more concern than TSNA in smokeless tobacco or nicotine replacement therapy (NRT) products. Exposures to nicotine from electronic cigarettes is not expected to exceed that from smoking due to self-titration [11]; it is only a concern when a vaper does not intend to consume nicotine, a situation that can arise from incorrect labeling of liquids [25, 44].

The cautions about propylene glycol and glycerin apply only to the exposure experienced by the vapers themselves. Exposure of bystanders to the listed ingredients, let alone the contaminants, does not warrant a concern as the exposure is likely to be orders of magnitude lower than exposure experienced by vapers. Further research employing realistic conditions could help quantify the quantity of exhaled aerosol and its behavior in the environment under realistic worst-case scenarios (i.e., not small sealed chambers), but this is not a priority since the exposure experienced by bystanders is clearly very low compared to the exposure of vapers, and thus there is no reason to expect it would have any health effects.

The key to making the best possible effort to ensure that hazardous exposures from contaminants do not occur is ongoing monitoring of actual exposures and estimation of potential ones. Direct measurement of personal exposures is not possible in vaping due to the fact the aerosol is inhaled directly, unless, of course, suitable biomarkers of exposure can be developed. The current review did not identify any suitable biomarkers, though cotinine is a useful proxy for exposure to nicotine-containing liquids. Monitoring of potential composition of exposures is perhaps best achieved though analysis of aerosol generated in a manner that approximates vaping, for which better insights are needed on how to modify “smoking machines” to mimic vaping given that there are documented differences in inhalation patterns [52] that depend on features of e-cigarettes [14]. These smoking machines would have to be operated under a realistic mode of operation of the atomizer to ensure that the process for generation of contaminants is studied under realistic temperatures. To estimate dosage (or exposure in personal breathing zone), information on the chemistry of the aerosol has to be combined with models of the inhalation pattern of vapers, mode of operation of e-cigarettes and quantities of liquid consumed. Assessment of exhaled aerosol appears to be of little use in evaluating risk to vapers due to evidence of qualitative differences in the chemistry of exhaled and inhaled aerosol.

Monitoring of liquid chemistry is easier and cheaper than assessment of aerosols. This can be done systematically as a routine quality control measure by the manufacturers to ensure uniform quality of all production batches. However, we do not know how this relates to aerosol chemistry because previous researchers did not appropriately pair analyses of chemistry of liquids and aerosols. It is standard practice in occupational hygiene to analyze the chemistry of materials generating an exposure, and it is advisable that future studies of the aerosols explicitly pair these analyses with examination of composition of the liquids used to generate the aerosols. Such an approach can lead to the development of predictive models that relate the composition of the aerosol to the chemistry of liquids, the e-cigarette hardware, and the behavior of the vaper, as these, if accurate, can anticipate hazardous exposures before they occur. The current attempt to use available data to develop such relationships was not successful due to studies failing to collect appropriate data. Systematic monitoring of quality of the liquids would also help reassure consumers and is best done by independent laboratories rather than manufactures to remove concerns about impartiality (real or perceived).

Future work in this area would greatly benefit from standardizing laboratory protocols (e.g. methods of

extraction of compounds from aerosols and liquids, establishment of "core" compounds that have to be quantified in each analysis (as is done for PAH and metals), development of minimally informative detection limits that are needed for risk assessment, standardization of operation of "vaping machine", etc.), quality control experiments (e.g. suitable positive and negative controls without comparison to conventional cigarettes, internal standards, estimation of % recovery, etc.), and reporting practices (e.g. in units that can be used to estimate personal exposure, use of uniform definitions of limits of detection and quantification, etc.), all of which would improve on the currently disjointed literature. Detailed recommendations on standardization of such protocols lie outside of scope of this report.

All calculations conducted in this analysis are based on information about patterns of vaping and the content of aerosols and liquids that are highly uncertain in their applicability to "typical" vaping as it is currently practiced and says even less about future exposures due to vaping (e.g. due to development of new technology). However, this is similar to assessments that are routinely performed in occupational hygiene for novel technology as it relied on "worst case" calculations and safety margins that attempt to account for exposure variability. The approach adopted here and informed by some data is certainly superior to some currently accepted practices in the regulatory framework in occupational health that rely purely on description of emission processes to make claims about potential for exposure (e.g. [53]). Clearly, routine monitoring of potential and actual exposure is required if we were to apply the principles of occupational hygiene to vaping. Detailed suggestions on how to design such exposure surveillance are available in [54].

While vaping is obvious not an occupational exposure, occupational exposure standards are the best available option to use. If there were a standard for voluntary consumer exposure to aerosols, it would be a better fit, but no such standard exists. The only candidate standard is the occupational standard, which is conservative (more protective) when considered in the context of voluntary exposures, as argued above, and any suggestion that another standard be used needs to be concrete and justified.

In summary, analysis of the current state of knowledge about the chemistry of contaminants in liquids and aerosols associated with electronic cigarettes indicates that there is no evidence that vaping produces inhalable exposures to these contaminants at a level that would prompt measures to reduce exposure by the standards that are used to ensure safety of workplaces. Indeed, there is sufficient evidence to be reassured that there are no such risks from the broad range of the studied products, though the lack of quality control standards means that this cannot be assured for all products on the market. However, aerosol generated during vaping on the whole, when considering the declared ingredients themselves, if it were treated in the same manner as an emission from industrial process, creates personal exposures that would justify surveillance of exposures and health among exposed persons. Due to the uncertainty about the effects of these quantities of propylene glycol and glycerin, this conclusion holds after setting aside concerns about health effects of nicotine. This conclusion holds notwithstanding the benefits of tobacco harm reduction, since there is value in understanding and possibly mitigating risks even when they are known to be far lower than smoking. It must be noted that the proposal for such scrutiny of "total aerosol" is not based on specific health concerns suggested by compounds that resulted in exceedance of occupational exposure limits, but is instead a conservative posture in the face of unknown consequences of inhalation of appreciable quantities of organic compounds that may or may not be harmful at doses that occur during vaping.

Key conclusions

- Even when compared to workplace standards for involuntary exposures, and using several conservative (erring on the side of caution) assumptions, the exposures from using e-cigarettes fall well below the threshold for concern for compounds with known toxicity. That is, even ignoring the benefits of e-cigarette use and the fact that the exposure is actively chosen, and even comparing to the levels that are considered unacceptable to people who are not benefiting from the exposure and do not want it, the

exposures would not generate concern or call for remedial action.

- Expressed concerns about nicotine only apply to vapers who do not wish to consume it; a voluntary (indeed, intentional) exposure is very different from a contaminant.

- There is no serious concern about the contaminants such as volatile organic compounds (formaldehyde, acrolein, etc.) in the liquid or produced by heating. While these contaminants are present, they have been detected at problematic levels only in a few studies that apparently were based on unrealistic levels of heating.

- The frequently stated concern about contamination of the liquid by a nontrivial quantity of ethylene glycol or diethylene glycol remains based on a single sample of an early-technology product (and even this did not rise to the level of health concern) and has not been replicated.

- Tobacco-specific nitrosamines (TSNA) are present in trace quantities and pose no more (likely much less) threat to health than TSNAs from modern smokeless tobacco products, which cause no measurable risk for cancer.

- Contamination by metals is shown to be at similarly trivial levels that pose no health risk, and the alarmist claims about such contamination are based on unrealistic assumptions about the molecular form of these elements.

- The existing literature tends to overestimate the exposures and exaggerate their implications. This is partially due to rhetoric, but also results from technical features. The most important is confusion of the concentration in aerosol, which on its own tells us little about risk to heath, with the relevant and much smaller total exposure to compounds in the aerosol averaged across all air inhaled in the course of a day. There is also clear bias in previous reports in favor of isolated instances of highest level of chemical detected across multiple studies, such that average exposure that can be calculated are higher than true value because they are "missing" all true zeros.

- Routine monitoring of liquid chemistry is easier and cheaper than assessment of aerosols. Combined with an understanding of how the chemistry of the liquid affects the chemistry of the aerosol and insights into behavior of vapers, this can serve as a useful tool to ensure the safety of e-cigarettes.

- The only unintentional exposures (i.e., not the nicotine) that seem to rise to the level that they are worth further research are the carrier chemicals themselves, propylene glycol and glycerin. This exposure is not known to cause health problems, but the magnitude of the exposure is novel and thus is at the levels for concern based on the lack of reassuring data.

Endnotes

[a]Atmosphere that contains air inhaled by a person.

[b]This estimate of consumption was derived from informal reports from vaping community; 5 ml/day was identified as a high but not rare quantity of consumption and 25 ml/day was the high end of claimed use, though some skepticism was expressed about whether the latter quantity was truly possible. High-quality formal studies to verify these figures do not yet exist but they are consistent with report of Etter (2012).

[c]The term "VOC" loosely groups together all organic compounds present in aerosol and because the declared ingredients of aerosol are organic compounds, it follows that "VOC are present".

Authors' information

IB is trained in both occupational hygiene and epidemiology and thus is an expert in bring information that these two fields contribute to risk assessment and policy-making. IB does not and never has used any tobacco products. Current research was completed by him as independent research contract during otherwise unpaid summer months. IB is an Associate Professor at Drexel University and felt obliged to disclose his primary academic appointment but this work was completed outside of the structures of Drexel University.

Declarations

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Electronic supplementary material

12889_2013_7486_MOESM1_ESM.xlsx Additional file 1: Summary of chemical analyses of e-cigarettes extracted from the literature.(XLSX 57 KB)
12889_2013_7486_MOESM2_ESM.rtf Additional file 2: **Key to identifying articles listed in** Additional file 1. (RTF 60 KB)
12889_2013_7486_MOESM3_ESM.xlsx Additional file 3: Calculations conducted to compare reported results to threshold limit values. Spreadsheet that implemented calculations summarized in the article. (XLSX 71 KB)
Below are the links to the authors' original submitted files for images.
12889_2013_7486_MOESM4_ESM.tif Authors' original file for figure 1

Competing interests

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E-cigarettes safer than smoking says long-term study

Category: **Press release** 6 February 2017 Cancer Research UK

E-cigarettes are less toxic and safer to use compared to conventional cigarettes, according to research* published in *Annals of Internal Medicine* today (Monday).

Cancer Research UK-funded scientists found that people who swapped smoking regular cigarettes for e-cigarettes or nicotine replacement therapy (NRT) for at least six months, had much lower levels of toxic and cancer causing substances in their body than people who continued to use conventional cigarettes.

For the first time, researchers analysed the saliva and urine of long-term e-cigarette and NRT users, as well as smokers, and compared body-level exposure to key chemicals.**

Ex-smokers who switched to e-cigarettes or NRT had significantly lower levels of toxic chemicals and carcinogens*** in their body compared to people who continued to smoke tobacco cigarettes. But, those who used e-cigarettes or

"This study adds to growing evidence that e-cigarettes are a much safer alternative to tobacco, and suggests the long term effects of these products will be minimal." - *Alison Cox, Cancer Research UK*

NRT while continuing to smoke, did not show the same marked differences, highlighting that a complete switch is needed to reduce exposure to toxins.

Dr Lion Shahab, senior lecturer in the department of epidemiology and public health at UCL, and lead author of the publication, said: “Our study adds to existing evidence showing that e-cigarettes and NRT are far safer than smoking, and suggests that there is a very low risk associated with their long-term use.

“We’ve shown that the levels of toxic chemicals in the body from e-cigarettes are considerably lower than suggested in previous studies using simulated experiments. This means some doubts about the safety of e-cigarettes may be wrong.

“Our results also suggest that while e-cigarettes are not only safer, the amount of nicotine they provide is not noticeably different to conventional cigarettes. This can help people to stop smoking altogether by dealing with their cravings in a safer way.”

Alison Cox, Cancer Research UK’s director of cancer prevention, said: “Around a third of tobacco-caused deaths are due to cancer, so we want to see many more of the UK’s 10 million smokers break their addiction.”

“This study adds to growing evidence that e-cigarettes are a much safer alternative to tobacco, and suggests the long term effects of these products will be minimal.

“Understanding and communicating the benefits of nicotine replacements, such as e-cigarettes, is an important step towards reducing the number of tobacco-related deaths here in the UK.”

ENDS

For media enquiries please contact the Cancer Research UK press office on +44 203 469 8300 or, out-of-hours, the duty press officer on +44 7050 264 059.

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Notes to Editor

**Previous research into the toxicity of e-cigarettes has focused on assessing concentrations of potentially harmful chemicals within the products themselves, or the vapor they produce.

***Levels of TSNAs (tobacco-specific nitrosamines) and VOCs (volatile organic compounds) metabolites were examined – these compounds have well-established smoking-related toxicological and carcinogenic risks.

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E-Cigarettes Poised to Save Medicaid Billions

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STATE BUDGET SOLUTIONS POLICY ANALYSIS

MARCH 31, 2015

E-Cigarettes Poised to Save Medicaid Billions

J. Scott Moody, Chief Executive Officer and Chief Economist

Electronic cigarettes (e-cigs) have only been around since 2006, yet their potential to dramatically reduce the damaging health impacts of traditional cigarettes has garnered significant attention and credibility. Numerous scientific studies show that e-cigs not only reduce the harm from smoking, but can also be a part of the successful path to smoking cessation.

The term "e-cig" is misleading because there is no tobacco in an e-cig, unlike a traditional, combustible cigarette. The e-cig uses a battery-powered vaporizer to deliver nicotine via a propylene-glycol solution—which is why "smoking" an e-cig is called "vaping." The vapor is inhaled like a smoke from a cigarette, but does not contain the carcinogens found in tobacco smoke.

Unlike traditional nicotine replacement therapy (NRT), such as gum or patches, e-cigs mimic the physical routine of smoking a cigarette. As such, e-cigs fulfill both the chemical need for nicotine and physical stimuli of smoking. This powerful combination has led to the increasing demand for e-cigs—8.2% use among nondaily smokers and 6.2% use among daily smokers in 2011.[1]

The game-changing potential for dramatic harm reduction by current smokers using e-cigs will flow directly into lower healthcare costs dealing with the morbidity and mortality stemming from smoking combustible cigarettes. These benefits will particularly impact the Medicaid system where the prevalence of cigarette smoking is twice that of the general public (51% versus 21%, respectively).

Based on the findings of a rigorous and comprehensive study on the impact of cigarette smoking on Medicaid spending, the potential savings of e-cig adoption, and the resulting tobacco smoking cessation and harm reduction, could have been up to $48 billion in Fiscal Year (FY) 2012.[2] This savings is 87% higher than all state cigarette tax collections and tobacco settlement collections ($24.4 billion) collected in that same year.

Unfortunately, the tantalizing benefits stemming from e-cigs may not come to fruition if artificial barriers slow their adoption among current smokers. These threats range from the Food and Drug Administration regulating e-cigs as a pharmaceutical to states extending their cigarette tax to e-cigs. To be sure, e-cigs are still a new product and should be closely monitored for long-term health effects. However, given the long-term fiscal challenges facing Medicaid, the prospect of large e-cigs cost savings is worth a non-interventionist approach until hard evidence proves otherwise.

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Prevalence of Smoking in the Medicaid Population

According to the Centers for Disease Control and Prevention, in 2011, 21.2% of Americans smoked combustible cigarettes. However, as shown in Table 1, the smoking rate varies considerably across states with the top three states being Kentucky (29%), West Virginia (28.6%), and Arkansas (27%) and the three lowest states being Utah (11.8%), California (13.7%), and New Jersey (16.8%).[3]

Table 1
Smokers Represent Significantly Larger Proportion of Medicaid Recipients than General Population
2011

State	Percent Smokers		Medicaid Enrollment	Number of Smokers on Medicaid
	Medicaid	General Population		
United States	51%	21.2% (median)	68,372,045	36,461,209
Alabama	52%	24.3%	938,313	487,923
Alaska	68%	22.9%	135,059	91,840
Arizona	49%	19.2%	1,989,470	974,840
Arkansas	54%	27.0%	777,833	420,030
California	45%	13.7%	11,500,583	5,175,262
Colorado	61%	18.3%	733,347	447,342
Connecticut	49%	17.1%	729,294	357,354
Delaware	58%	21.7%	223,225	129,471
Florida	46%	19.3%	3,829,173	1,761,420
Georgia	42%	21.2%	1,925,269	808,613
Hawaii	62%	16.8%	313,629	194,450
Idaho	62%	17.2%	409,456	253,863
Illinois	58%	20.9%	2,900,614	1,682,356
Indiana	68%	25.6%	1,208,207	821,581
Iowa	61%	20.4%	544,620	332,218
Kansas	54%	22.0%	363,755	196,428
Kentucky	65%	29.0%	1,065,840	692,796
Louisiana	43%	25.7%	1,293,869	556,364
Maine	63%	22.8%	327,524	206,340
Maryland	51%	19.1%	1,003,548	511,809
Massachusetts	53%	18.2%	1,504,611	797,444
Michigan	64%	23.3%	2,265,277	1,449,777
Minnesota	54%	19.1%	989,600	534,384
Mississippi	35%	26.0%	775,314	271,360
Missouri	66%	25.0%	1,126,505	743,493
Montana	70%	22.1%	136,442	95,509
Nebraska	64%	20.0%	284,000	181,760
Nevada	62%	22.9%	363,357	225,281
New Hampshire	80%	19.4%	152,182	121,746
New Jersey	36%	16.8%	1,304,257	469,533
New Mexico	50%	21.5%	571,621	285,811
New York	54%	18.1%	5,421,232	2,927,465
North Carolina	63%	21.8%	1,892,541	1,192,301
North Dakota	63%	21.9%	85,094	53,609
Ohio	65%	25.1%	2,526,533	1,642,246
Oklahoma	58%	26.1%	852,603	494,510
Oregon	67%	19.7%	690,364	462,544
Pennsylvania	70%	22.4%	2,443,909	1,710,736
Rhode Island	48%	20.0%	221,041	106,100
South Carolina	41%	23.1%	978,732	401,280
South Dakota	69%	23.0%	134,798	93,011
Tennessee	58%	23.0%	1,488,267	863,195
Texas	43%	19.2%	4,996,318	2,148,417
Utah	54%	11.8%	366,271	197,786
Vermont	67%	19.1%	184,088	123,339
Virginia	58%	20.9%	1,016,419	589,523
Washington	67%	17.5%	1,371,987	919,231
West Virginia	67%	28.6%	411,218	275,516
Wisconsin	63%	20.9%	1,292,799	814,463
Wyoming	62%	23.0%	76,372	47,351
District of Columbia	51%	20.8%	235,665	120,189

Source: Centers for Disease Control and Prevention, Centers for Medicare and Medicaid Services, and State Budget Solutions

Additionally, the smoking rate varies dramatically by income level. Nearly 28% of people living below the poverty line smoke while 17% of people living at or above the poverty line smoke.[4]

As a consequence, the level of smoking prevalence among Medicaid recipients is more than twice that of the general public, 51% versus 21%, respectively. However, this too varies considerably across states with the top three states being New Hampshire (80%), Montana (70%), and Pennsylvania (70%) and the three lowest states being Mississippi (35%), New Jersey (36%), and South Carolina (41%).[5]

In absolute terms, the U.S. Medicaid system includes 36 million smokers out of a total Medicaid enrollment of over 68 million. As such, this places much of the health burden and related financial cost of smoking on the Medicaid system which strains the system and takes away scarce resources from the truly needy.

Economic Benefit of Smoking Cessation and Harm Reduction

Smoking creates large negative externalities due to adverse health impacts. Table 2 shows the results of a comprehensive study that quantified the two major costs of smoking in 2009-lost productivity and healthcare costs.[6]

Lost productivity occurs when a person dies prematurely due to smoking or misses time from work due to smoking. This cost the economy $185 billion in lost output in 2009.

Smokers incur higher healthcare costs when those individuals require medical services such as ambulatory care, hospital care, prescriptions, and neonatal care for conditions caused by smoking. This cost the economy $116 billion in extra medical treatments.

Overall, in 2009 alone, the negative externalities of smoking cost the U.S. economy $301

billion in lost productivity and higher healthcare costs. Not surprisingly, these costs were centered in high population states such as California ($26.9 billion), New York ($20.6 billion), and Texas ($20.4 billion).

Literature Review On E-cig Impact On Harm Reduction Through Reduced Toxic Exposure and Smoking Cessation

E-cigs have only been around since 2006, yet their potential to dramatically reduce the damaging health impacts of traditional combustible cigarettes has garnered significant attention and credibility. Numerous scientific studies are showing that e-cigs not only reduce the harm from smoking, but is also a successful path to smoking cessation.

In perhaps the most comprehensive e-cig literature review to date, Neil Benowitz et al. (2014) identified eighty-one studies with original data and evidence from which to judge e-cig effectiveness for harm reduction.[7] They concluded:

"Allowing EC (electronic cigarettes) to compete with cigarettes in the market-place might decrease smoking-related morbidity and mortality. Regulating EC as strictly as cigarettes, or even more strictly as some regulators propose, is not warranted on current evidence. Health professionals may consider advising smokers unable or unwilling to quit through other routes to switch to EC as a safer alternative to smoking and a possible pathway to complete cessation of nicotine use."

There are two ways that e-cigs benefit current smokers. First, there is harm reduction for the smoker by removing exposure to the toxicity associated with the thousands of compounds, many carcinogenic, found in the burning of tobacco and the resulting smoke. Second, smoking cessation efforts by the smoker are enhanced by simultaneously fulfilling both the chemical need for nicotine and physical stimuli of smoking.

In the last few years the academic literature has exploded with articles on these two topics. The following is a selection of some of the most recent studies and their conclusions.

Reduced Toxic Exposure

Igor Burstyn (2014) concludes, "Current state of knowledge about chemistry of liquids and aerosols associated with electronic cigarettes indicates that there is no evidence that vaping produces inhalable exposures to contaminants of the aerosol that would warrant health concerns by the standards that are used to ensure safety of workplaces . . . Exposures of bystanders are likely to be orders of magnitude less, and thus pose no apparent concern."[8]

Table 2
Comprehensive Costs of Smoking
(Billions of Dollars)
2009

State	Lost Productivity			Healthcare Costs	Total Smoking Costs
	Premature Death	Workplace	Total		
United States	117.1	67.5	184.6	116.4	301.0
Alabama	2.7	1.2	3.9	1.7	5.6
Alaska	0.2	0.2	0.4	0.3	0.7
Arizona	1.9	1.3	3.2	1.9	5.1
Arkansas	1.7	0.7	2.4	1.1	3.4
California	9.6	5.7	15.2	11.6	26.9
Colorado	1.3	1.2	2.5	1.6	4.1
Connecticut	1.2	0.7	1.8	1.7	3.6
Delaware	0.4	0.2	0.6	0.4	1.1
District of Columbia	0.3	0.1	0.4	0.5	0.9
Florida	7.9	4.4	12.3	7.3	19.6
Georgia	3.7	2.4	6.2	2.9	9.0
Hawaii	0.4	0.2	0.7	0.4	1.1
Idaho	0.4	0.3	0.7	0.4	1.1
Illinois	5.0	2.9	7.9	4.8	12.7
Indiana	3.0	2.1	5.1	2.6	7.7
Iowa	1.2	0.7	1.9	1.1	3.0
Kansas	1.0	0.6	1.6	1.0	2.6
Kentucky	2.6	1.3	3.9	1.8	5.7
Louisiana	2.4	0.9	3.3	1.8	5.1
Maine	0.6	0.3	0.9	0.7	1.6
Maryland	2.1	1.3	3.4	2.2	5.6
Massachusetts	2.2	1.3	3.4	3.7	7.1
Michigan	4.5	2.4	7.0	4.0	11.0
Minnesota	1.5	1.5	3.0	2.3	5.4
Mississippi	1.8	0.7	2.4	1.0	3.5
Missouri	3.0	1.5	4.5	2.7	7.2
Montana	0.3	0.2	0.6	0.4	0.9
Nebraska	0.6	0.5	1.1	0.7	1.8
Nevada	1.1	0.7	1.7	0.9	2.6
New Hampshire	0.5	0.3	0.8	0.6	1.4
New Jersey	2.9	1.8	4.7	3.6	8.3
New Mexico	0.5	0.4	0.9	0.6	1.5
New York	6.9	3.9	10.8	9.8	20.6
North Carolina	4.1	2.2	6.3	3.4	9.7
North Dakota	0.2	0.2	0.4	0.3	0.7
Ohio	5.7	2.9	8.6	5.2	13.9
Oklahoma	2.1	0.9	3.0	1.3	4.3
Oregon	1.3	0.8	2.1	1.3	3.4
Pennsylvania	5.4	3.2	8.5	5.7	14.2
Rhode Island	0.4	0.2	0.7	0.6	1.3
South Carolina	2.3	1.0	3.3	1.6	4.9
South Dakota	0.3	0.2	0.5	0.3	0.8
Tennessee	3.6	1.7	5.3	2.6	7.9
Texas	7.9	4.9	12.8	7.6	20.4
Utah	0.4	0.3	0.7	0.4	1.1
Vermont	0.2	0.1	0.4	0.3	0.7
Virginia	2.9	2.0	4.8	2.7	7.5
Washington	2.1	1.3	3.4	2.4	5.7
West Virginia	1.1	0.5	1.6	0.9	2.5
Wisconsin	2.0	1.4	3.4	2.4	5.8
Wyoming	0.2	0.2	0.4	0.2	0.6

Source: See Endnote 6 and State Budget Solutions

Neal Benowitz, et al. (2013) concludes, "The vapour generated from e-cigarettes contains potentially toxic compounds. However, the levels of potentially toxic compounds in e-cigarette vapour are 9-450-fold lower than those in the smoke from conventional cigarettes, and in many cases comparable with the trace amounts present in

pharmaceutical preparation. Our findings support the idea that substituting tobacco cigarettes with electronic cigarettes may substantially reduce exposure to tobacco-specific toxicants. The use of e-cigarettes as a harm reduction strategy among cigarette smokers who are unable to quit, warrants further study."[9]

Kostantinos E Farsalinos et al. (2014) concludes, "Although acute smoking inhalation caused a delay in LV (Left Ventricular) myocardial relaxation in smokers, electronic cigarette use was found to have no such immediate effects in daily users of the device. This short-term beneficial profile of electronic cigarettes compared to smoking, although not conclusive about its overall health-effects as a tobacco harm reduction product, provides the first evidence about the cardiovascular effects of this device."[10]

Smoking Cessation

Emma Beard et al. (2014) concludes, "Among smokers who have attempted to stop without professional support, those who use e-cigarettes are more likely to report continued abstinence than those who used a licensed NRT [Nicotine Replacement Therapy] product bought over-the-counter or no aid to cessation. This difference persists after adjusting for a range of smoker characteristics such as nicotine dependence."[11]

Christopher Bullen et al. (2013) concludes, "E-cigarettes, with or without nicotine, were modestly effective at helping smokers to quit, with similar achievement of abstinence as with nicotine patches, and few adverse events . . . Furthermore, because they have far greater reach and higher acceptability among smokers than NRT [Nicotine Replacement Therapy], and seem to have no greater risk of adverse effects, e-cigarettes also have potential for improving population health."[12]

Pasquale Caponnetto et al. (2013) concludes, "The results of this study demonstrate that e-cigarettes hold promise in serving as a means for reducing the number of cigarettes smoked, and can lead to enduring tobacco abstinence as has also been shown with the use of FDA-approved smoking cessation medication. In view of the fact that subjects in this study had no immediate intention of quitting, the reported overall abstinence rate of 8.7% at 52-weeks was remarkable."[13]

Konstantinos E. Farsalinos et al. (2013) concludes, "Participants in this study used liquids with high levels of nicotine in order to achieve complete smoking abstinence. They reported few side effects, which were mostly temporary; no subject reported any sustained adverse health implications or needed medical treatment. Several of the side effects may not be attributed to nicotine. In addition, almost every vaper reported significant benefits from switching to the EC [e-cigarette]. These observations are consistent with findings of Internet surveys and are supported by studies showing that nicotine is not cytotoxic, is not classified as a carcinogen, and has minimal effects on the initiation or propagation of atherosclerosis . . . Public health authorities should consider this and other studies that ECs are used as long-term substitutes to smoking by motivated exsmokers and should adjust their regulatory decisions in a way that would not restrict the availability of nicotine-containing liquids for this population."[14]

Potential E-cig Medicaid Cost Savings

To date, the academic literature strongly suggests that e-cigs hold the promise of dramatic harm reduction for smokers simply by switching from combustible tobacco cigarettes to e-cigs. This harm reduction is due to both its positive impact on smoking cessation and

Table 3
Smoking Costs on Medicaid by State
(Millions of Dollars)
Fiscal Year 2012

State	Medicaid Spending	Smoking Costs as Percent of Medicaid Spending	Smoking Costs on Medicaid
United States	415,154	11%	45,667
Alabama	5,027	9%	452
Alaska	1,348	15%	202
Arizona	7,905	18%	1,423
Arkansas	4,160	11%	458
California	50,165	11%	5,518
Colorado	4,724	17%	803
Connecticut	6,759	7%	473
Delaware	1,485	10%	148
District of Columbia	2,111	11%	232
Florida	17,907	11%	1,970
Georgia	8,526	10%	853
Hawaii	1,493	11%	164
Idaho	1,452	14%	203
Illinois	13,393	11%	1,473
Indiana	7,486	15%	1,123
Iowa	3,495	10%	350
Kansas	2,667	12%	320
Kentucky	5,702	12%	684
Louisiana	7,358	12%	883
Maine	2,413	14%	338
Maryland	7,687	12%	922
Massachusetts	12,926	11%	1,422
Michigan	12,460	13%	1,620
Minnesota	8,894	11%	978
Mississippi	4,466	9%	402
Missouri	8,727	14%	1,222
Montana	973	15%	146
Nebraska	1,722	15%	258
Nevada	1,739	11%	191
New Hampshire	1,187	15%	178
New Jersey	10,389	6%	623
New Mexico	3,430	12%	412
New York	53,306	11%	5,864
North Carolina	12,282	11%	1,351
North Dakota	744	12%	89
Ohio	16,352	13%	2,126
Oklahoma	4,642	12%	557
Oregon	4,587	15%	688
Pennsylvania	20,393	11%	2,243
Rhode Island	1,856	8%	148
South Carolina	4,848	11%	533
South Dakota	749	16%	120
Tennessee	8,798	11%	968
Texas	28,286	11%	3,111
Utah	1,903	14%	266
Vermont	1,353	15%	203
Virginia	6,906	11%	760
Washington	7,560	18%	1,361
West Virginia	2,790	11%	307
Wisconsin	7,096	13%	923
Wyoming	528	16%	85

Note: States do not sum to Total due to rounding.
Source: See Endnote 15 and State Budget Solutions

reduced exposure to toxic compounds in cigarette smoke.

As a result, we can expect the healthcare costs of smoking to decline over time as the adoption of e-cigs by smokers continues to grow. Additionally, we can expect greater rates of adoption as e-cigs continue to evolve and improve based on market feedback-a dynamic that has never existed with other nicotine replacement therapies.

As discussed earlier, the potential savings to the economy are very large. In terms of healthcare alone, most of that cost is currently borne by the Medicaid system where the prevalence of cigarette smoking is twice that of the general public, 51% versus 21%, respectively. So what are the potential healthcare savings to Medicaid?

Brian S. Armour et al. (2009) created an impressive economic model to estimate how much smoking costs Medicaid based on data from the Medical Expenditure Panel Survey and the Behavioral Risk Factor Surveillance System.[15]

Overall, their model ". . . included 16,201 adults with weighting variables that allowed us to generate state representative estimates of the adult, noninstitutionalized Medicaid population."

The study concluded that 11% of all Medicaid expenditures can be attributed to smoking. Additionally, among the states these costs ranged from a high of 18% (Arizona and Washington) to a low of 6% (New Jersey).

This study uses their percentage of Medicaid spending due to smoking and applies it to the latest year of available state-by-state Medicaid spending. As shown in Table 3, in FY 2012, smoking cost the Medicaid system $45.7 billion. Of course, the largest states bear the brunt of these costs such as New York ($5.9 billion), California ($5.5 billion), and Texas ($3.1 billion).

To put this potential savings to Medicaid into perspective, in FY 2012, state governments and the District of Columbia combined collected $24.4 billion in cigarette excise taxes and tobacco settlement payments. As shown in Table 4, the potential Medicaid savings exceeds cigarette excise tax collections and tobacco settlement payments by 87%.

However, this varies greatly by state with high ratios in the South Carolina (435%), Missouri (409%), and New Mexico (260%), Arizona (238%), and California (238%) and low ratios in New Jersey (-39%), New Hampshire (-31%), Rhode Island (-17%), Connecticut (-13%), and Hawaii (-4%). Overall, 45 states and D.C. stand to gain more from potential Medicaid savings than through lost cigarette tax collections and tobacco settlement payments.

Note that many of the five states with negative ratios are distorted because excise tax collections are based on where the initial sale occurred and not where the cigarettes were ultimately consumed. This can vary greatly because of cigarette smuggling and cross-border shopping created by state-level differentials in cigarette excise taxes.[16]

For instance, New Hampshire has long been a source for out-of-state cigarette purchase from shoppers living in Massachusetts, Maine, and Vermont because of its lower cigarette excise tax. As such, the ratio is too high for Massachusetts, Maine, and Vermont and too low for New Hampshire. The same applies to New Jersey and Connecticut vis-à-vis New York and, more specifically, New York City, which levies its own cigarette tax on top of the state tax.

Hawaii is an exception due to its physical isolation which creates monopoly rents. Rhode Island levies a very high cigarette excise tax, but not relatively high enough compared to neighboring Connecticut and Massachusetts to drive a lot of cross-border shopping.

Other Potential E-cig Cost Savings

Another area of cost savings from greater e-cig adoption is the reduction in smoke and fire dangers in subsidized and public housing. According to a recent study, smoking imposes three major costs:

1. Increased healthcare costs from exposure to second hand smoke within and between housing units.

2. Increased renovation costs of smoking-permitted housing units.

3. Fires attributed to cigarettes.

As shown in Table 5, the study estimates that smoking imposes a nationwide cost of nearly $500 million.[17] The top three states facing the greatest expenses are New York ($125 million), California ($72 million), and Texas ($24 million) while the top three states with the lowest expenses are Wyoming ($0.6 million), Idaho ($0.8 million), and Montana ($1 million).

Table 5
Smoking Costs on Subsidized and Public Housing
(Millions of Dollars)
2012

State	Smoking Costs
United States	496.8
New York	124.7
California	72.4
Texas	28.3
Massachusetts	24.0
Florida	23.2
Ohio	21.7
Pennsylvania	17.7
New Jersey	15.8
Louisiana	14.4
North Carolina	13.9
Illinois	13.3
Tennessee	12.9
Michigan	12.8
Alabama	12.4
Georgia	11.6
Connecticut	10.7
Missouri	9.4
Indiana	8.3
Virginia	7.8
Mississippi	7.2
Kentucky	7.1
Minnesota	7.1
South Carolina	7.0
Maryland	7.0
Arkansas	6.8

Table 4
Smoking Costs on Medicaid Exceed State Cigarette Tax Collections and Tobacco Settlement Payments
(Millions of Dollars)
Fiscal Year 2012

State	State Cigarette Tax Collections (a)	Tobacco Settlement Payments (b)	Smoking Costs on Medicaid	Smoking Costs on Medicaid as a Percent of State Cigarette Tax Collections and Tobacco Settlement Payments
United States	17,226	7,190	45,667	87%
Alabama	126	94	452	106%
Alaska	67	30	202	108%
Arizona	319	101	1,423	238%
Arkansas	247	51	458	54%
California	896	736	5,518	238%
Colorado	203	91	803	173%
Connecticut	418	124	473	-13%
Delaware	121	27	148	1%
District of Columbia	36	38	232	214%
Florida	381	365	1,970	164%
Georgia	227	141	853	132%
Hawaii	122	49	164	-4%
Idaho	48	25	203	177%
Illinois	606	274	1,473	67%
Indiana	465	130	1,123	89%
Iowa	225	66	350	20%
Kansas	104	58	320	98%
Kentucky	277	102	684	81%
Louisiana	133	141	883	222%
Maine	140	51	338	77%
Maryland	411	146	922	66%
Massachusetts	574	254	1,422	72%
Michigan	965	256	1,620	33%
Minnesota	422	167	978	66%
Mississippi	157	110	402	50%
Missouri	105	135	1,222	409%
Montana	87	30	146	24%
Nebraska	68	38	258	145%
Nevada	103	40	191	34%
New Hampshire	215	43	178	-31%
New Jersey	792	231	623	-39%
New Mexico	75	39	412	260%
New York	1,632	738	5,864	147%
North Carolina	295	141	1,351	210%
North Dakota	28	32	89	49%
Ohio	843	295	2,126	87%
Oklahoma	293	77	557	50%
Oregon	256	79	688	106%
Pennsylvania	1,119	337	2,243	54%
Rhode Island	132	47	148	-17%
South Carolina	26	73	533	435%
South Dakota	60	24	120	42%
Tennessee	279	139	968	131%
Texas	1,470	475	3,111	60%
Utah	124	36	266	66%
Vermont	80	35	203	77%
Virginia	192	117	760	145%
Washington	471	151	1,361	119%
West Virginia	110	64	307	77%
Wisconsin	653	131	923	18%
Wyoming	26	19	85	90%

(a) Includes all forms of tobacco taxes.
(b) Includes Master Settlement Agreement and individual state payments.
Source: Department of Commerce: Census Bureau, Internal Revenue Service, and State Budget Solutions

Applying Cigarette Taxes to E-cigs?

Many policymakers around the country have suggested applying the existing cigarette tax, wholly or in part, to e-cigs. This is bad public policy and is based on a fundamental misunderstanding of the cigarette tax.

The cigarette tax is what economists call a "Pigovian Tax" which is designed to mitigate negative externalities of certain actions. Cigarette smoking creates many negative externalities such as

Oklahoma	6.8
Wisconsin	6.5
Washington	5.0
Arizona	4.9
Colorado	4.5
West Virginia	4.3
Oregon	4.3
Maine	4.2
Rhode Island	4.0
Hawaii	3.8
Iowa	3.8
New Mexico	3.0
Kansas	2.9
Nebraska	2.1
Nevada	1.9
Vermont	1.9
New Hampshire	1.9
Utah	1.4
Delaware	1.3
North Dakota	1.2
South Dakota	1.1
Montana	1.0
Idaho	0.8
Wyoming	0.6
Alaska	N.A.
District of Columbia	N.A.
Source: See Endnote 17 and State Budget Solutions	

harmful health consequences to the user or to those in near proximity (second-hand smoke).

As detailed in this study, the negative externalities associated with traditional smoking are all but eliminated by e-cigs. Without evidence of actual negative externalities, applying the existing cigarette tax to e-cigs is simply bad public policy.

Conclusion

Policymakers have long sought to reduce the economic damage due to the negative health impact of smoking. They have used tactics ranging from cigarette excise taxes to subsidizing nicotine replacement therapies. To be sure, smoking prevalence has fallen over time, but there is more that can be done, especially given the fact that so much of the healthcare burden of smoking falls on the already strained Medicaid system.

As with any innovation, no one could have predicted the sudden arrival into the marketplace of the e-cig in 2006. Since e-cigs fulfill both the chemical need for nicotine and physical stimuli of smoking the demand for e-cigs has grown dramatically. The promise of a relatively safe way to smoke has the potential to yield enormous healthcare savings. The most current academic research verifies the harm reduction potential of e-cigs.

As shown in this study, the potential savings to Medicaid significantly exceeds the state revenue raised from the cigarette excise tax and tobacco settlement payments by 87%. As such, the rational policy decision is to adopt a non-interventionist stance toward the evolution and adoption of the e-cig until hard evidence proves otherwise. While cigarette tax collections will fall as a result, Medicaid spending will fall even faster. This is a win-win for policymakers and taxpayers.

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Addiction Debate

A framework for evaluating the public health impact of e-cigarettes and other vaporized nicotine products

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Abstract

The use of vaporized nicotine products (VNPs), especially e-cigarettes and, to a lesser extent, pressurized aerosol nicotine products and heat-not-burn tobacco products, are being adopted increasingly as an alternative to smoking combusted products, primarily cigarettes. Considerable controversy has accompanied their marketing and use. We propose a framework that describes and incorporates patterns of VNP and combustible cigarette use in determining the total amount of toxic exposure effects on population health. We begin by considering toxicity and the outcomes relevant to population health. We then present the framework and define different measures of VNP use; namely, trial and long-term use for exclusive cigarette smokers, exclusive VNP and dual (cigarette and VNP) use. Using a systems thinking framework and decision theory we considered potential pathways for current, former and never users of VNPs. We then consider the evidence to date and the probable impacts of VNP use on public health, the potential effects of different policy approaches and the possible influence of the tobacco industry on VNP and cigarette use.

Introduction

In the United States, smoking rates have fallen by 50% since their peak in the 1960s as a result of tobacco control policies [1], but smoking still contributes to high rates of premature mortality. The 2014 Surgeon General's Report stated: 'the burden of death and disease from tobacco in the U.S. is overwhelmingly caused by cigarettes and other combusted tobacco products; rapid elimination of their use will dramatically reduce this burden'.

While all are agreed that efforts to discourage combustible tobacco products, especially cigarettes, should continue, there is more controversy about the marketing of new vaporized nicotine products (VNPs), especially e-cigarettes, because of disagreements about whether they will complement or undermine successful tobacco control efforts [2, 3]. VNP use has increased markedly in many high-income countries [4-7] as a result of increased marketing [8, 9], the use of VNPs for smoking cessation [10] and policies that have made cigarettes less affordable [11]. In the United States, increasing e-cigarette use [5, 6] has been accompanied by an unusually large reduction in adult [12] and youth [6, 13] smoking prevalence.

Although the types of available VNPs vary and are evolving rapidly [14, 15], these products expose users to substantially lower levels of toxicants than combustible cigarettes [16-18]. Consequently, VNPs could reduce harm to never smokers who would have otherwise initiated long-term cigarette use, and reduce harm to current smokers by helping them to quit, to switch to exclusive VNP use or to substantially reduce their smoking. If, however, VNP use encourages the long-term use of cigarettes, or VNPs are used by those who would not have otherwise smoked, the net societal benefit would be diminished and VNPs could incur population-level harm.

Despite growing evidence of the possible benefits of VNPs, 55 of 123 countries surveyed [19] have bans or laws that prohibit or restrict the sale of VNPs and 71 have laws that regulate the minimum purchase age, marketing or taxation of VNPs. In April 2014, the US Food and Drug Administration (FDA)'s Center for Tobacco Products proposed deeming regulations that would assert their jurisdiction over e-cigarettes [20]. Before imposing regulations, the FDA must consider scientific evidence on the probable benefit and harm to individuals and the population as a whole.

This paper proposes a systems-level model [21] of the possible harm-increasing and harm-reducing effects that is used to estimate the potential net effects of VNPs on population health. This framework employs decision theory to consider potential pathways of cigarette and VNP product use by current, former and never smokers. We begin by considering the toxicity of VPN. We then present the framework and consider different measures of use, distinguishing trial from different forms of long-term use. Finally, we consider the available evidence and probable impacts on public health, the potential effects of different policies and the possible influence of the tobacco industry on VNP and cigarette use. We focus on the United States, where VNPs are now largely unregulated.

Mortality risks of exclusive and dual VNP use

A multi-criteria decision analysis [22] estimated that exclusive VNP use is associated with 5% of the mortality risks of smoking. This is comparable to the estimated risks of low-nitrosamine smokeless tobacco [23]. In the absence of long-term experience the precise percentage of reduced harm may be difficult to quantify, but studies using major biomarkers of cancer and other chemicals in e-cigarettes indicate substantially lower

(e.g. 9–450 times) levels compared to cigarette smoke [16-18].

For dual users, VNP use may translate to a lower quantity and duration of cigarettes smoked. Both may decrease lung cancer and chronic obstructive pulmonary disease (COPD) risk [24, 25], with the amount depending upon the proportion of total harm exposure obtained from each source. Studies find considerable variation in VNP use and quantity of cigarettes smoked [26], including ≥ 50% reduction in consumption. The potential to reduce risk is likely to depend upon the age of initial dual use. Although much use now begins at later ages, VNP use is likely to occur at earlier ages in more recent cohorts of smokers, and thereby provide a greater reduction in cigarette use and toxic exposures over longer periods of use. In addition, initiating VNP use before cigarette smoking may delay or prevent smoking initiation and thereby reduce smoking risks.

Framework and measures of use

The use of tobacco products over a prolonged period is necessary to detect reductions in life expectancy [25, 27]. This is also likely to apply to the use of VNPs. We consider short-term ('trial') use, which may determine transitions to long-term ('prolonged') use and may help to gauge the immediate effects of public policies. Possible transitions are shown for never, current and former smokers in Figs 1-3. Harm-reducing effects are indicated by '+' and harm-increasing effects by '–'; '?' indicates that the amount of change depends upon the pattern of use. In each case, the impact on population health will depend upon how VNP use influences the long-term prevalence of: exclusive cigarette smoking, exclusive VNP use, dual use and abstinence compared to the counterfactual scenario in the absence of VNPs.

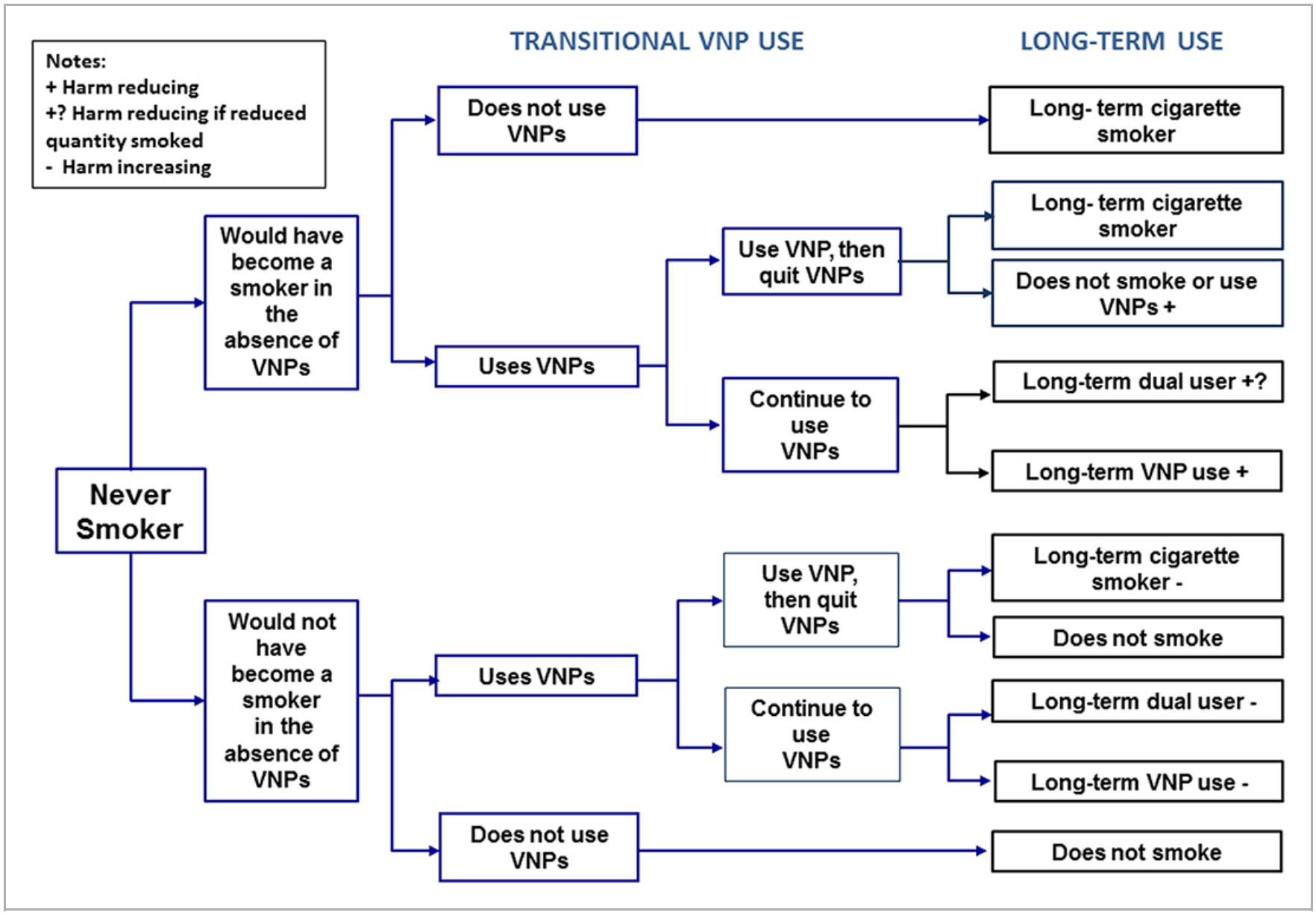

Figure 1.

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The public health impact of vaporized nicotine product (VNP) use among never smokers

Studies on e-cigarettes to date have measured mainly ‘ever use’ or ‘past 30-day use’ [28], with the ratio of current to ever use averaging 30% across 27 European countries [29] in 2012 and 30% among US college students [30] and adults [31]. While current use is often described by past-30 day use, evidence suggests that much reported use is infrequent [31] and so unlikely to lead to substantial harm to health. Harm is determined by how many users transition to more frequent use of cigarettes or VNPs. More established use can be assessed by inquiring about the number of days used in the last month [29, 32], daily use [33] and number of times used [34-36].

Accurate measures of long-term exclusive and dual use require sufficient time to transition from smoking, possibly through dual use, to final use states (e.g. abstinence from either cigarettes or from VPNs or both) [37]. For example, recent former cigarette smokers (quit ≤ 1 year) were twice as likely as longer-term former smokers (quit 2–3 years) and four times as likely as current cigarette smokers [31] to be daily VNP users. In addition, transitions may differ by cohort depending upon perceived risk, ability of available products to satisfy cravings or withdrawal symptoms, differences between early and late adopters, socio-economic status and current tobacco control policies [38, 39].

Transitions from never smoker

As shown in Fig. 1, a never smoker may transition from trying VNP to exclusive VNP use, exclusive cigarette use, dual use or quit using cigarettes and VNPs. The population health impact depends critically upon whether the never smoker who tries VNPs would have smoked cigarettes in the absence of VNPs. Health impacts are harm-increasing when VNPs lead to someone who would otherwise never smoke to initiate cigarette smoking. VNP and dual use are harm-reducing when those who would otherwise smoke cigarettes transition to no use, substantially reduce their cigarette use or exclusively use VNPs.

Studies indicate that adolescents and young adult VNP users are far more likely to have already smoked cigarettes than to have never smoked [40]. A 2014 Great Britain survey (ages 11–18) found past month use at 0.2% among never smokers and 13.5% among smokers. Only 8.2% of those who ever used a VNP smoked a cigarette for the first time after using VNPs compared to 69.8% who smoked a cigarette before trying a VNP [41]. Studies of youth and young adult use from the United States [30, 42, 43] and other countries [44-47] using different use measures have found current smokers to be at least 15 times more likely to use VNPs than never smokers.

Only a few studies have considered more established VNP use [48, 49]. Of 13.4% of high school students reporting any past 30-day VNP use, 74% had tried VNPs on 1–9 days, while ≥ 20 days use was reported by only 15.5% of users, who comprised 2% of the population [48]. Among college students, cigarette smokers were more likely to continue VNP use (8.0%) than non-smokers 90.4%), and more non-smokers who tried VNPs were non-users at follow-up (96.8%) than smokers (68.1%) [49].

Adolescents and young adults who use VNPs are most likely to be those at higher risk of initiating cigarette smoking [50, 51]. Young VNP experimenters are more likely to engage in other risky behaviors [30, 52, 53]

and have executive function deficits [54, 55] like those found in cigarette smokers [55, 56]. These findings suggest that a common liability model is more plausible than a gateway from VNP use to cigarette smoking [57, 58]. In testing the role of common liability and gateway effects of VNP use, statistical techniques are required to control adequately for the factors that determine initial VNP use and the transition from experimental to regular use, i.e. those that correct for confounding and selection bias [59, 60].

Transitions from current cigarette smoking

Figure 2 shows that the public health impact on VNP use on cigarette smokers will depend upon how VNP use affects the likelihood of quit success, i.e. how many smokers would quit in their absence. The effect of VNPs on cessation is likely to depend upon their desirability and the ability to deliver nicotine at a sufficient dose to reduce craving or withdrawal symptoms from cigarettes [4, 61]. Both may vary with product type and preparedness of smokers to use them for prolonged periods. Several studies have reported higher smoking cessation rates among users of VNP tank systems [61]. Other studies indicate that more regular use (e.g. daily) of VNPs is correlated with being an ex-smoker [31, 33, 34], increased numbers of quit attempts and greater reductions in number of cigarettes smoked [62].

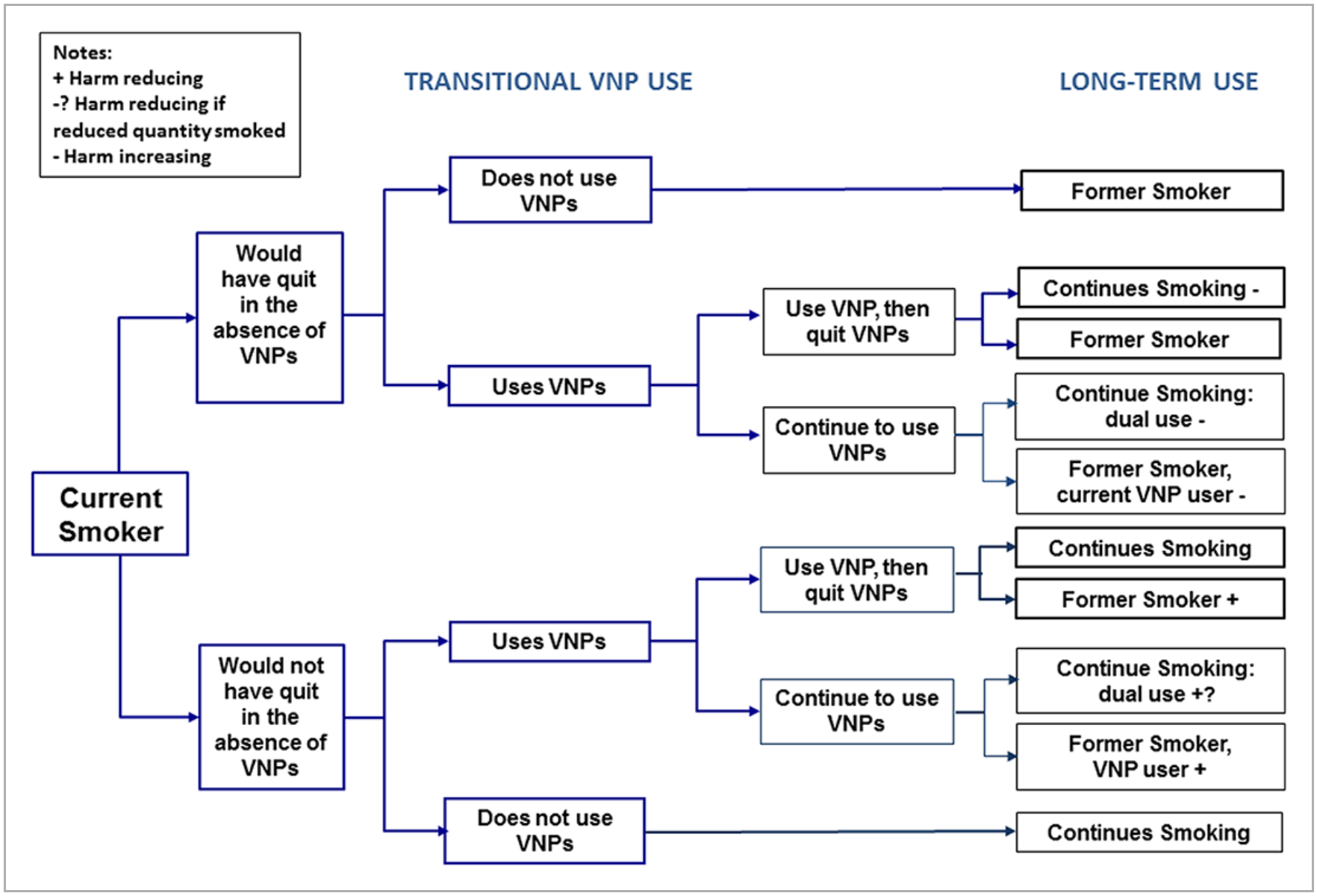

Figure 2.

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The public health impact of vaporized nicotine product (VNP) use among smokers

Two randomized controlled trials have found that VNPs can help some smokers to quit or reduce their cigarette consumption [63, 64]. Rates of smoking cessation in the VNP groups were similar to those seen in clinical trials of nicotine replacement therapy (NRT) [65]. In uncontrolled prospective studies, one with carbon monoxide (CO) testing found a similar success rate [66], while four others found higher rates of smoking abstinence [67-70]. One review [71] that reported lower cessation rates among VNP users included studies that were not prospective, defined ever-use or past 30-day use as sufficient exposure to VNPs to impact abstinence, and suffered from other methodological weaknesses (e.g. selection bias). A more recent review [72] concluded: 'Smokers who have tried other methods of quitting without success could be encouraged to try e-cigarettes to stop smoking… There is evidence that EC can encourage quitting or cigarette consumption reduction'.

Because VNPs are more widely available and often more appealing to smokers than conventional NRT [10], they have the potential for having a larger impact on the rate of smoking cessation in the population [2, 73]. However, evidence suggests that VNPs are not especially attractive to longer-term ex-smokers; only 0.8% of long-term former smokers who had quit for more than 4 years used VNPs compared to 13% of recent quitters [31].

Ultimately, the ability to identify the public health impact of VNP use will depend upon measurement of factors that predict willingness to try VNPs and transitions to long-term VNP use by different groups (i.e. current smokers, ex-smokers, never smokers). For example, quit success may depend upon intent (e.g. whether it is used to quit) and on whether smokers who use VNPs are more addicted or have a history of unsuccessful use of other cessation techniques [10, 61, 74, 75]. Some studies [29, 75, 76] find that current VNP use is associated with past quit attempts. One study found that the relationship between VNP use and cigarette smoking cessation depended upon the ability to statistically control for factors related to success of past quit attempts and intention to quit [74].

Transitions from former smoker

Figure 3 shows that VNP use may increase harm for former smokers who would not have otherwise relapsed if, after trying VNPs, they relapse to exclusive or dual cigarette use. It will reduce harm in former smokers who use VNPs to prevent a relapse to cigarette smoking. Beneficial effects of VNP use are suggested by a longitudinal observational study [77] that found 6% of former smokers who used VNP daily at baseline relapsed to cigarette smoking at 1 month and 6% at 1 year. Eight per cent of recent quitters relapsed to occasional smoking at 1 month and 5% at 1 year, but none relapsed to daily smoking. These rates compare favorably to typical relapse rates for smoking after cessation using other methods [78]. However, we do not yet have enough evidence on the effects of VNP use on relapse, because of their limited use by former smokers who did not use VNPs before quitting [79, 80].

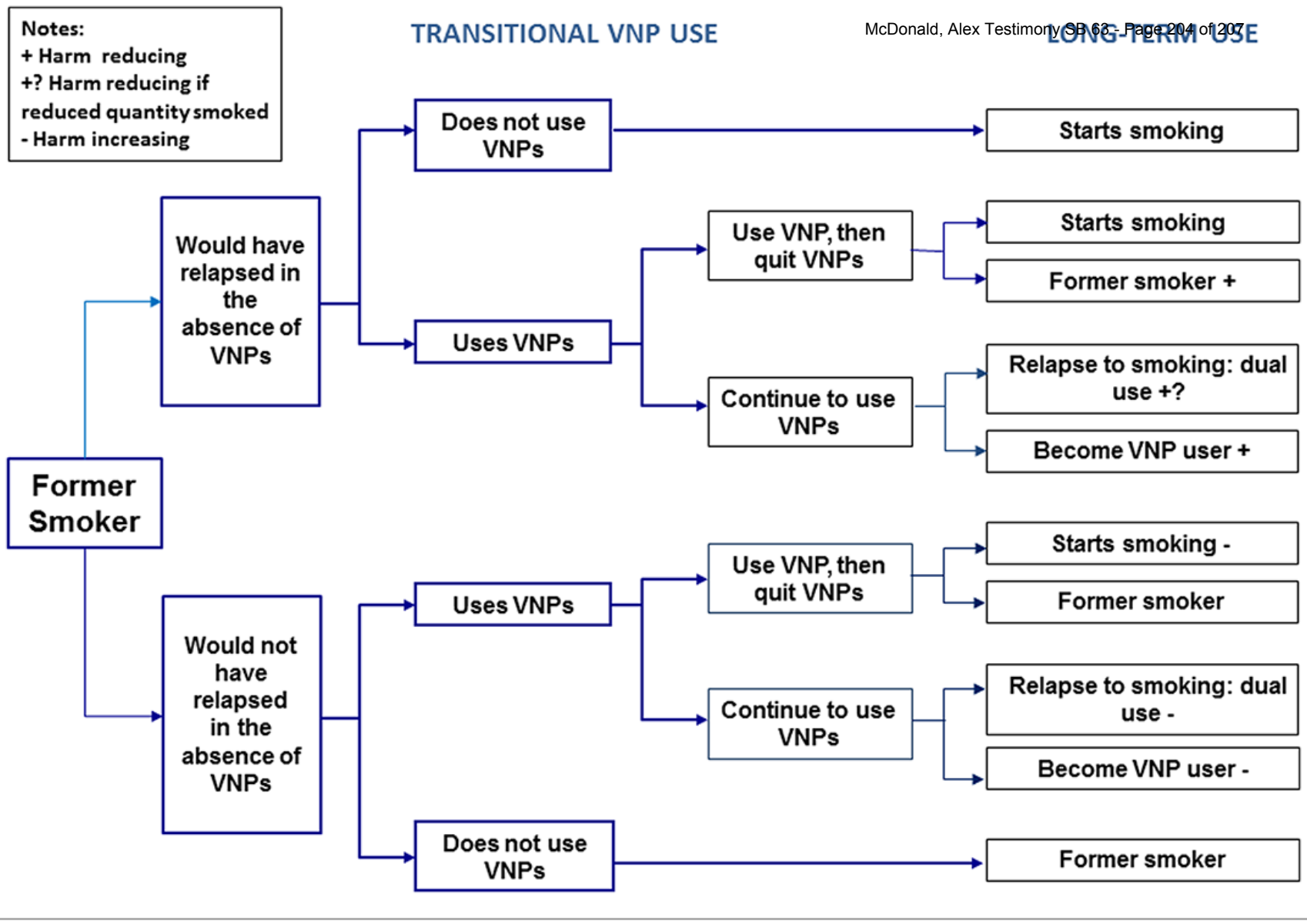

Figure 3.

Open in figure viewer

The public health impact of vaporized nicotine product (VNP) use among former smokers

The role of policy: intended and unintended effects

Any assessment of the effect of policies towards VNPs depends upon understanding that cigarettes and VNPs are potentially substitutable goods [81-83]. Liberal regulation of VNPs may mean that transitions to VNPs result in more long-term VNP use rather than their short-term use as cessation aids. Conversely, restrictive policies towards VNPs may mean that cigarette smokers are less likely to switch to VNPs. A recent study [83], for example, found that states with minimum VNP purchase age laws had lower rates of VNP uptake and more cigarette uptake than states without such restrictions.

Stronger cigarette control policies (e.g. bans on menthol and other flavors to reduce their appeal, toxicity or addictiveness) may encourage cessation by those smokers who are more likely to quit. As many as 40% of smokers make a quit attempt each year in most high-income nations, but only 3–5% remain abstinent for 6 months or longer [84, 85], indicating that many smokers who try to quit soon relapse to smoking. Studies [32, 75] indicate that most smokers use VNPs with the intention of quitting smoking cigarettes. While stronger cigarette policies may lead initially to dual use, they may also lead to complete cessation of cigarettes if the

policies are sufficiently strong.

The effect of policies towards VNPs will depend upon how they affect dual versus exclusive use. Product regulations that limit toxicity may increase VNP use as a substitute for smoking, especially if that information is publicized, and thereby reduce substantially the risk per unit exposure. However, if regulations discourage VNP innovations that make VNPs more attractive to smokers, they reduce cessation among smokers who would use better VNPs. Outright bans on VNP sales may be more likely to discourage cessation than reduce VNP use, as indicated by their use in countries where VNP sales are prohibited [86, 87]. Bans may not stop some young people from taking up vaping, as experience with cannabis use shows.

Concerns have been raised that cigarette smoking will be re-normalized by VNP use [88, 89]. This issue can be addressed by the media and public health campaigns that encourage norms that are hostile to cigarette smoking and at the same time distinguishing clearly between VNP and cigarette risks, discouraging dual use and encouraging exclusive VNP use. Indeed, the availability of VNPs may provide a justification for stronger policies to discourage cigarette smoking because smokers, particularly those of lower socio-economic status and with mental health issues, are given a less risky and potentially less costly alternative way to service their need for nicotine.

The role of the traditional tobacco and vaping industries

In coordinating tobacco and VNP control strategies, we need to gauge how they will influence the ‘four Ps’ of tobacco marketing: Product, Price, Promotion and Place [90, 91].

The VNP industry is made up of many different manufacturers, most of whom are not affiliated with cigarette companies. By contrast, the cigarette, cigar and smokeless tobacco industries are largely consolidated and controlled by a few large multi-national cigarette companies. With the rapid growth of the VNP market [92], major cigarette makers such as Phillip Morris (MarkTen, IQOS, Marlboro Heat Stick), Imperial (Blu), Reynolds American (Vuse, Revo) and BAT (Vype) have introduced VNP products. However, cigarette companies do not control VNPs as they do the rest of the tobacco business; many manufacturers of e-cigarettes such as NJOY do not sell cigarettes, and there are thousands of vape shops that are independent of the cigarette industry. The diversity of the VNP business influences the distribution channels and the cost differential between VNP and conventional tobacco products.

Cigarette companies that have entered the smokeless tobacco market [93, 94] have encouraged dual rather than exclusive use, and are likely to do the same with VNPs. By contrast, VNP companies that are unaffiliated with cigarette manufacturers want smokers to switch completely from cigarettes to VNPs. Product content regulations that create regulatory hurdles that only large firms can surmount are likely to favor the cigarette industry and discourage innovation by firms outside the cigarette industry. For example, a regulation restricting VNP tank devices will favor firms selling the ‘cigalike’ VNPs sold by cigarette companies [70] that are less attractive to smokers [62].

Increasing VNP prices by taxing them in the same way as cigarettes will discourage youth VNP use, but also discourage use by smokers of lower socio-economic status who are trying to switch or quit. However, if VNP taxes are accompanied by even higher cigarette taxes, youth VNP use may be reduced and initiation into smoking discouraged, while switching and cessation among current smokers would be encouraged [95]. In the case of marketing restrictions, retailer point-of-sale restrictions, which limit subsidies by cigarette manufacturers to provide shelf space and price promotions, can reduce price discounting and discourage

advertisement displays [96]. This could provide greater shelf space for VNP products to be sold by independent firms.

Final comments

From a public health perspective, VNP policies should aim to discourage experimental and regular use of VNPs by never smokers who would not have smoked otherwise while encouraging innovations in VNP products that promote smoking cessation. The evidence suggests a strong potential for VNP use to improve population health by reducing or displacing cigarette use in countries where cigarette prevalence is high and smokers are interested in quitting. Rising VNP use is a global phenomenon in low- and middle-income countries as well as in high-income countries [86]. However, evidence is lacking on their impact in countries where cigarette smoking prevalence is low (e.g. sub-Saharan African countries) or where interest in quitting among smokers may be low (e.g. China).

The primary aim of tobacco control policy should therefore be to discourage cigarette use while providing the means for smokers to more easily quit smoking, even if that means switching for some time to VNPs rather than quitting all nicotine use. Countries whose policies discourage VNP use run the risk of neutralizing a potentially useful addition to methods of reducing tobacco use. We must collect clearer information on VNP use and its consequences to assess this potential more effectively. Although large cross-sectional surveys can be used to estimate transition probabilities [97] we need longitudinal data, such as the large-scale longitudinal US Population Assessment of Tobacco and Health (PATH) survey and the International Tobacco Control surveys [86], to track transitions more directly to and from VNP use. As we gain clearer knowledge of the effects of cigarette- and VNP-oriented policies, a long-term view that reduces the use of the most toxic combusted tobacco nicotine delivery products will become a more realistic goal.

Our framework identifies the critical information required, but this information will need to be continually updated. VNPs will change over time, and the extent of product innovation will depend upon industry structure and how tobacco control policies are applied to cigarettes and VNPs. As the product and population of users change, the characteristics of experimenters and long-term VNP users, their transitions to exclusive and dual cigarette and VNP use and associated health risks may change. While there is more uncertainty about the health risks of exclusive and dual VNP use than of cigarette use, the substantially lower levels of toxins than cigarettes make VNPs far less harmful, although by exactly how much is unclear. If the harms of VNP use are substantially greater than indicated by current evidence, then policies will be needed to discourage long term VNPs use.

Clearly, we need more effective measures of longer-term and longitudinal patterns of VNP use, product toxicity and addictive potential and appropriate methods to study critical transitions in patterns of VNP and cigarette use. With multiple potential interactions between VNP and cigarette use and the differential effects of policies on these use rates, modeling provides a ‘virtual population laboratory’ to synthesize existing evidence, to project future trends and to compare the impact of different possible interventions [98-101]. However, until clearer data are available, our ability to understand the impact of VNP use will need to be based on careful and prudent extrapolations of their probable benefits and harms from shorter-term evidence.

Declaration of interests

K. Michael Cummings has provided testimony on behalf of plaintiffs in cases against the tobacco industry.

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