From: mailinglist@capitol.hawaii.gov
To: HTHTestimony
Cc: mz9995@hotmail.com
Subject: Submitted testimony for SB305 on Feb 13, 2015 13:35PM
Date: Thursday, February 12, 2015 6:35:36 PM

SB305
Submitted on: 2/12/2015
Testimony for HTH on Feb 13, 2015 13:35PM in Conference Room 414

Submitted By	Organization	Testifier Position	Present at Hearing
Michael Zehner	Hawaii Smokers Alliance	Oppose	Yes

Comments: To include electronic smoking devices in this bill only promotes more misrepresentation of the product as "dangerous" without any scientific proof.

Please note that testimony submitted less than 24 hours prior to the hearing, improperly identified, or directed to the incorrect office, may not be posted online or distributed to the committee prior to the convening of the public hearing.

Do not reply to this email. This inbox is not monitored. For assistance please email webmaster@capitol.hawaii.gov

Chair Green, Vice-Chair Wakai, and members of the committee,

Thank you for the opportunity to testify in STRONG OPPOSITION to SB305. This bill is inappropriate based on current science and appears to be a corporate giveaway. Recent studies are showing what ecigarette proponents have known for years – ecigarettes are likely the most effective tool ever invented for quitting smoking. It is inappropriate for a taxpayer-funded healthcare organization to deny its own employees and patients the ability to use these tools, particularly in light of the lack of risk the products pose to users or bystanders.

Furthermore, the inclusion of the language in this bill regarding sanctioned "cessation programs" is a means of using taxpayer money to fund pharmaceutical corporations – these programs amount to distribution schemes for nicotine replacement therapies (patch, etc.) and cessation drugs. Research is showing that ecigarettes are more effective than these corporate options, and recent market information shows that their popularity has impacted these corporations' bottom lines. The agenda seems clear here, particularly when perusing legislators' donor lists.

Attached is a study showing the greater efficacy of ecigarettes in smoking cessation, and a study reviewing the current science on ecigarettes, which shows a very low risk profile.

P. Kuromoto

Addiction
RESEARCH REPORT
doi:10.1111/add.12623

Real-world effectiveness of e-cigarettes when used to aid smoking cessation: a cross-sectional population study

Jamie Brown[1,2], Emma Beard[1], Daniel Kotz[1,3], Susan Michie[2,4] & Robert West[1,4]

Cancer Research UK Health Behaviour Research Centre, University College London, London, UK,[1] Department of Clinical, Educational and Health Psychology, University College London, London, UK,[2] Department of Family Medicine, CAPHRI School for Public Health and Primary Care, Maastricht University Medical Centre, Maastricht, the Netherlands[3] and National Centre for Smoking Cessation and Training, London, UK[4]

ABSTRACT

Background and Aims Electronic cigarettes (e-cigarettes) are rapidly increasing in popularity. Two randomized controlled trials have suggested that e-cigarettes can aid smoking cessation, but there are many factors that could influence their real-world effectiveness. This study aimed to assess, using an established methodology, the effectiveness of e-cigarettes when used to aid smoking cessation compared with nicotine replacement therapy (NRT) bought over-the-counter and with unaided quitting in the general population. **Design and Setting** A large cross-sectional survey of a representative sample of the English population. **Participants** The study included 5863 adults who had smoked within the previous 12 months and made at least one quit attempt during that period with either an e-cigarette only ($n = 464$), NRT bought over-the-counter only ($n = 1922$) or no aid in their most recent quit attempt ($n = 3477$). **Measurements** The primary outcome was self-reported abstinence up to the time of the survey, adjusted for key potential confounders including nicotine dependence. **Findings** E-cigarette users were more likely to report abstinence than either those who used NRT bought over-the-counter [odds ratio (OR) = 2.23, 95% confidence interval (CI) = 1.70–2.93, 20.0 versus 10.1%] or no aid (OR = 1.38, 95% CI = 1.08–1.76, 20.0 versus 15.4%). The adjusted odds of non-smoking in users of e-cigarettes were 1.63 (95% CI = 1.17–2.27) times higher compared with users of NRT bought over-the-counter and 1.61 (95% CI = 1.19–2.18) times higher compared with those using no aid. **Conclusions** 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 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.

Keywords Cessation, cross-sectional population survey, e-cigarettes, electronic cigarettes, nicotine replacement therapy, NRT, quitting, smoking.

Correspondence to: Jamie Brown, Health Behaviour Research Centre, Department of Epidemiology and Public Health, University College London, 1-19 Torrington Place, London WC1E 6BT, UK. E-mail: jamie.brown@ucl.ac.uk
Submitted 27 February 2014; initial review completed 8 April 2014; final version accepted 12 May 2014

INTRODUCTION

Smoking is one of the leading risk factors for premature death and disability and is estimated to kill 6 million people world-wide each year [1]. The mortality and morbidity associated with cigarette smoking arises primarily from the inhalation of toxins other than nicotine contained within the smoke. Electronic cigarettes (e-cigarettes) provide nicotine via a vapour that is drawn into the mouth, upper airways and possibly lungs [2,3]. These devices use a battery-powered heating element activated by suction or manually to heat a nicotine solution and transform it into vapour. By providing a vapour containing nicotine without tobacco combustion, e-cigarettes appear able to reduce craving and withdrawal associated with abstinence in smokers [2,4,5], while toxicity testing suggests that they are much safer to the user than ordinary cigarettes [3].

E-cigarettes are increasing rapidly in popularity: prevalence of ever-use among smokers in the United

States appears to have increased from approximately 2% in 2010 to more than 30% in 2012, and the rate of increase appears to be similar in the United Kingdom [6–9]. Although there are concerns about their wider public health impact relating to the renormalization of smoking and promotion of smoking in young people, crucially two randomized controlled trials have suggested that e-cigarettes may aid smoking cessation [10,11]. However, there are many factors that influence real-world effectiveness, including the brand of e-cigarette, the way they are used and who chooses to use them [12]. Therefore, it is a challenge to establish probable contribution to public health through randomized efficacy trials alone. Moreover, this kind of evidence will take many years to emerge, and in the meantime the products are developing rapidly and countries require evidence on effectiveness to inform decisions on how to regulate them [13–19]. As a result, there is an urgent need to be able to make an informed judgement on the real-world effectiveness of currently popular brands as chosen by the millions of smokers across the world who are using them in an attempt to stop smoking [6–9].

Several studies have attempted to examine the relationship between the use of e-cigarettes and smoking status in the real world by surveying regular e-cigarette users [20–27]. These studies—including one using a longitudinal design [27]—have found that users consistently report that e-cigarettes helped them to quit or reduce their smoking. However, because the samples were self-selected, the results have to be interpreted with caution. In more general samples the evidence is less positive. One national study of callers to a quitline, which assessed the cross-sectional association of e-cigarette use and current smoking status at a routine follow-up evaluation of the quitline service, found that e-cigarette users compared with never users were less likely to be abstinent [28]. In a longitudinal study of a general population sample, e-cigarette users at baseline were no more likely to have quit permanently at a 12-month follow-up despite having reduced their cigarette consumption [29]. However, neither of these studies adjusted for important potential confounding variables and both evaluated the association between quitting and the use of e-cigarettes for any purpose, not specifically as an aid to quitting. It is crucial to distinguish between the issue of whether use of e-cigarettes in a quit attempt improves the chances of success of that attempt from the issue of whether the use of e-cigarettes, for whatever purpose, such as aiding smoking reduction or recreation, promotes or suppresses attempts to stop. In determining the overall effect on public health both considerations are important, but they require different methodologies to address them.

An ongoing national surveillance programme (the Smoking Toolkit Study) has been tracking the use of e-cigarettes as a reported aid to cessation among the general population in England since July 2009 [30]. This programme has established a method of assessing real-world effectiveness of aids to cessation by comparing the success rates of smokers trying to quit with different methods and adjusting statistically for a wide range of factors that could bias the results, such as nicotine dependence [31]. The method has been able to detect effects of behavioural support and prescription medications to aid cessation and found a higher rate of success when using varenicline than prescription nicotine replacement therapy (NRT) [32,33], supporting findings from randomized controlled trials and clinical observation studies [34–37]. This method cannot achieve the same level of internal validity as a randomized controlled trial, but clearly has greater external validity, so both are important in determining the potential public health contribution of devices hypothesized to aid cessation, such as e-cigarettes.

Given that smokers already have access to licensed NRT products, it is important to know whether e-cigarettes are more effective in aiding quitting. This comparison is particularly important for two reasons. First, buying a licensed NRT product from a shop, with no professional support, is the most common way of using it in England, and secondly, previous research has found that this usage was not associated with greater success rates than quitting unaided in the real-world [33]. It is therefore important to know whether e-cigarettes can increase abstinence compared to NRT bought over-the-counter.

The current study addressed the question of how effective e-cigarettes are compared with NRT bought over-the-counter and unaided quitting in the general population of smokers who are attempting to stop.

METHODS

Study design

The design was cross-sectional household surveys of representative samples of the population of adults in England conducted monthly between July 2009 and February 2014. To examine the comparative real-world effectiveness of e-cigarettes, the study compared the self-reported abstinence rates of smokers in the general population trying to stop who used e-cigarettes only (i.e. without also using face-to-face behavioural support or any medically licensed pharmacological cessation aid) with those who used NRT bought over-the-counter only or who made an unaided attempt, while adjusting for a wide range of key potential confounders. The surveys are part of the ongoing Smoking Toolkit Study, which is designed to provide information about smoking

prevalence and behaviour in England [30]. Each month a new sample of approximately 1800 adults aged ≥16 years are selected using a form of random location sampling, and complete a face-to-face computer-assisted survey with a trained interviewer. The full methods have been described in detail and shown to result in a sample that is nationally representative in its socio-demographic composition and proportion of smokers [30]. Approval was granted by the ethics committee of University College London, UK.

Study population

For the current study, we used aggregated data from respondents to the survey in the period from July 2009 (the first wave to track use of e-cigarettes to aid cessation) to February 2014 (the latest wave of the survey for which data were available), who smoked either cigarettes (including hand-rolled) or any other tobacco product (e.g. pipe or cigar) daily or occasionally at the time of the survey or during the preceding 12 months. We included those who had made at least one quit attempt in the preceding 12 months, assessed by asking: 'How many serious attempts to stop smoking have you made in the last 12 months? By serious attempt I mean you decided that you would try to make sure you never smoked again. Please include any attempt that you are currently making and please include any successful attempt made within the last year'. We included respondents who used either e-cigarettes or NRT bought over-the-counter during their most recent quit attempt, and an unaided group defined as those who had not used any of the following: e-cigarettes; NRT bought over-the-counter; a prescription stop-smoking medication; or face-to-face behavioural support. We excluded those who used either e-cigarettes or NRT bought over-the-counter in combination with one another, a prescription stop-smoking medication or face-to-face behavioural support.

Measurement of effect: quitting method

The use of different quitting methods were assessed for the most recent attempt by asking: 'Which, if any, of the following did you try to help you stop smoking during the most recent serious quit attempt?' and included: (i) e-cigarettes; (ii) NRT bought over-the-counter; (iii) no aid (i.e. had not used any of e-cigarettes, NRT bought over-the-counter, a prescription stop-smoking medication or face-to-face behavioural support).

Measurement of outcome: self-reported non-smoking

Our primary outcome was self-reported non-smoking up to the time of the survey. Respondents were asked: 'How long did your most recent serious quit attempt last before you went back to smoking?'. Those responding 'I am still not smoking' were defined as non-smokers. Previous research has shown that self-reported abstinence in surveys of this kind is not subject to the kind of biases observed in clinical trials where there is social pressure to claim abstinence [38].

Measurement of potential confounders

We measured variables potentially associated with the different quitting methods and that may also have an effect on the outcome. These potential confounders were chosen a priori. The most important factor was nicotine dependence, for which we used two questions. First, time spent with urges to smoke was assessed by asking all respondents: 'How much of the time have you felt the urge to smoke in the past 24 hours? Not at all (coded 0), a little of the time (i), some of the time (ii), a lot of the time (iii), almost all of the time (iv), all of the time (v)'. Secondly, strength of urges to smoke was measured by asking: 'In general, how strong have the urges to smoke been? Slight (i), moderate (ii), strong (iii), very strong (iv), extremely strong (v)'. This question was coded '0' for smokers who responded 'not at all' to the previous question. In this population these two ratings have been found to be a better measure of dependence (i.e. more closely associated with relapse following a quit attempt) than other measures [32,33,39]. The demographic characteristics assessed were age, sex and social grade (dichotomized into two categories: ABC1, which includes managerial, professional and intermediate occupations; and C2DE, which includes small employers and own-account workers, lower supervisory and technical occupations, and semi-routine and routine occupations, never workers and long-term unemployed). We also assessed the number of quit attempts in the last year prior to the most recent attempt, time since the most recent quit attempt was initiated (either more or less than 6 months ago), whether smokers had tried to quit abruptly or gradually and the year of the survey.

Analysis

Bivariate associations between the use of different quitting methods and potentially confounding socio-demographic and smoking history variables were assessed with χ^2 tests and one-way analyses of variance (ANOVA)s for categorical and continuous variables, respectively. Significant omnibus results were investigated further by *post-hoc* Sidak-adjusted χ^2 tests and *t*-tests.

Our measure of dependence (strength of urges to smoke) assumed that the score relative to other smokers would remain the same from pre- to post-quitting [32,33]. If a method of quitting reduced the strength of

urges to smoke more than another method, this would tend to underestimate the effectiveness of that intervention because the smokers using this method would appear to be less dependent. To test for this bias, we used an analysis of covariance (ANCOVA) to examine whether the difference in strength of urges to smoke in smokers versus non-smokers depended upon the method of quitting, adjusting for the time since the quit attempt started.

In the analysis of the associations between quitting method and abstinence, we used a logistic regression model in which we regressed the outcome measure (self-reported non-smoking compared with smoking) on the effect measure (use of e-cigarettes compared with either NRT bought over-the-counter or no aid). The primary analysis was an adjusted model that included the potential confounders listed above and two interaction terms: (i) between time since last quit attempt and time spent with urges, and (ii) between time since last quit attempt and strength of urges to smoke. These interaction terms were used to reflect the fact that urges to smoke following a quit attempt are influenced by whether an individual is currently abstinent and the duration of abstinence [32,33]. In addition to the model from the primary analysis ('fully adjusted model'; model 4), we constructed a simple model including only the effect measure ('unadjusted model'; model 1), a model that included the effect measure, year of the survey and all potential confounders except for the two measures of tobacco dependence, and a model that included all variables from the previous model and the two measures of tobacco dependence but without their interaction terms ('partially adjusted models'; models 2 and 3, respectively) to assess the extent of confounding by dependence. As *post-hoc* sensitivity analyses, the models were re-examined using different potential confounders from the ones specified a priori and reported in previous publications using the same methodology [32,33]. First, the time since the initiation of the quit attempt was included using the following six categories: 'in the last week'; 'more than a week and up to a month'; 'more than 1 month and up to 2 months'; 'more than 2 months and up to 3 months'; 'more than 3 months and up to 6 months'; and 'more than 6 months and up to a year'. Secondly, an additional index of dependence—the heaviness of smoking index (HSI) [40]—was included. The HSI was assessed by asking current smokers to estimate current cigarettes per day and time to first cigarette (the two items comprising HSI) and by asking non-smokers to recall these behaviours prior to their quit attempt. Finally, in *post-hoc* subgroup analyses all models were repeated (i) among those reporting smoking one or more than one cigarette per day (CPD) to determine whether inclusion of very light smokers might have had an influence on the results; (ii) among those completing the survey between 2012–14 once e-cigarette usage had become prevalent; and (iii) in the two subsamples of respondents who had started their most recent quit attempt less or more than 6 months ago, in order to assess the interplay between long-term effectiveness and the occurrence of differential recall bias. All analyses were performed with complete cases.

RESULTS

A total of 6134 respondents reported a most recent quit attempt in the last 12 months that was either unaided ($n = 3477$) or supported by NRT bought over-the-counter ($n = 2095$), e-cigarettes ($n = 489$) or both ($n = 73$). Those using both were excluded as were those using a prescription stop-smoking medication or face-to-face behavioural support in combination with either NRT bought over-the-counter ($n = 173$) or e-cigarettes ($n = 25$). Thus, the study population consisted of 5863 smokers who had made an attempt to quit in the previous year, of whom 7.9% (464) had used e-cigarettes, 32.8% (1922) had used NRT bought over-the-counter and 59.3% (3477) had used no aid to cessation. Quitting method did not differ by sex or the number of quit attempts in the past year but was associated with age, social grade, time since the quit attempt started, CPD, smoking less than one CPD, the measures of dependence (time with and strength of urges and HSI) and whether the attempt had begun abruptly (see Table 1). The *post-hoc* comparisons showed that those who used either e-cigarettes or no aid were younger than those using NRT over-the-counter, and that those who used NRT over-the-counter or no aid were more likely to hold a lower social grade than those using e-cigarettes. As would be expected, given the recent advent of e-cigarettes, the quit attempts of e-cigarette users were less likely to have begun more than 6 months previously than those using NRT over-the-counter or no aid. Those using NRT bought over-the-counter smoked more cigarettes and scored higher than either of the other two groups on all measures of dependence. E-cigarette users smoked more cigarettes, and were more dependent by the strength of urges measure and HSI than those using no aid. Finally, those using no aid were more likely to have smoked less than one CPD and stopped abruptly than the other two groups.

Strengths of urges to smoke were higher in smokers than in non-smokers (see Table 2). However, the mean differences in strength of urges between smokers and non-smokers were similar across method of quitting: the interaction between smoking status (smokers versus non-smokers) and method of quitting in an ANCOVA of the strength of urges adjusted for the time since quit attempt started was not significant ($F_{(2,\ 5856)} = 1.50$, $P = 0.22$).

Non-smoking was reported among 20.0% (93 of 464) of those using e-cigarettes, 10.1% (194 of 1922) using

Table 1 Associations between characteristics of the sample and use of different quitting methods.

	E-cigarettes (n = 464)	*NRT over-the-counter[§] (n = 1922)*	*No aid (n = 3477)*	*P*
Mean (SD) age	39.0 (15.6)[a]	41.2 (15.3)[ab]	37.5 (16.2)[b]	***
% (*n*) Female	47.2 (219)	51.1 (982)	48.9 (1699)	NS
% Social grade C2DE	59.3 (275)[cd]	65.9 (1266)[c]	65.5 (2277)[d]	*
Mean (SD) cigarettes per day[¶]	12.6 (8.0)[ef]	13.8 (8.5)[eg]	10.9 (8.1)[fg]	***
% (*n*) < 1 cigarettes per day[¶]	0.7 (3)[h]	0.8 (15)[i]	2.8 (94)[hi]	***
% (*n*) Time since quit attempt started >26 weeks	23.7 (110)[jk]	36.4 (700)[j]	36.5 (1269)[k]	***
Mean (SD) quit attempts in the past year	1.6 (0.9)	1.6 (0.9)	1.5 (0.9)	NS
Mean (SD) time spent with urges to smoke (0–5)	1.9 (1.3)[l]	2.2 (1.3)[lm]	1.8 (1.3)[m]	***
Mean (SD) strength of urges to smoke (0–5)	2.0 (1.2)[no]	2.2 (1.1)[np]	1.8 (1.1)[op]	***
Mean (SD) heaviness of smoking index[†]	2.0 (1.5)[qr]	2.3 (1.5)[qs]	1.6 (1.5)[rs]	***
% (*n*) Abrupt attempt (no gradual cutting down first)	50.4 (234)[t]	52.5 (1010)[u]	59.0 (2051)[tu]	***

Different pairs of superscript letters indicate a significant difference ($P < 0.05$) between two groups after Sidak adjustment for multiple comparisons. *$P < 0.05$; ***$P < 0.001$; NS = not statistically significant ($P \geq 0.05$). [§]A subgroup of those using nicotine replacement therapy (NRT) over-the-counter provided information about the form of NRT ($n = 975$): 60.0% (585) used a patch, 21.0% (205) gum, 14.9% (145) an inhalator, 6.2% (60) lozenges, 1.2% (12) microtabs and 1.0% (10) nasal spray. NB: response options were not mutually exclusive and 11.1% (108) reported using more than one form. [¶]Data were missing for 156 respondents (e-cigarettes: 22; NRT over-the-counter: 34; no aid: 100). [†]Data were missing for 172 respondents (e-cigarettes: 23; NRT over-the-counter: 36; no aid: 113). SD = standard deviation.

Table 2 Differences between smokers and non-smokers in strength of urges to smoke by method of quitting.

Method of quitting	*n*	*Mean (SD) strength of urges to smoke in smokers*	*n*	*Mean (SD) strength of urges to smoke in non-smokers*	*Mean difference (95% CI) in strength of urges to smoke*
E-cigarettes	371	2.3 (1.1)	93	0.8 (1.1)	1.4 (1.2–1.7)
NRT over-the-counter	1728	2.3 (1.0)	194	1.2 (1.3)	1.2 (1.0–1.3)
No aid	2942	2.0 (1.0)	535	0.7 (1.1)	1.3 (1.2–1.4)

NB: the mean differences are calculated from exact rather than the rounded figures presented in columns 3 and 5 of this table. The mean difference in strength of urges to smoke was not different across the methods of quitting ($F_{(2, 5856)} = 1.50$, $P = 0.22$ for the interaction term between smoking status and method of quitting adjusted for the time since the quit attempt started). SD = standard deviation; CI = confidence interval; NRT = nicotine replacement therapy.

NRT over-the-counter and 15.4% (535 of 3477) using no aid. The unadjusted analyses indicated that e-cigarette users were more likely to be abstinent than either those using NRT bought over-the-counter [odds ratio (OR) = 2.23, 95% confidence interval (CI) = 1.70–2.93) or those who used no aid (OR = 1.38, 95% CI = 1.08–1.76; see model 1, Table 3). The primary analyses revealed that the fully adjusted odds of non-smoking in users of e-cigarettes were 1.63 (95% CI = 1.17–2.27) times higher compared with users of NRT bought over-the-counter and 1.61 (95% CI = 1.19–2.18) times higher compared with those using no aid (see model 4, Table 3). The relative magnitudes of the ORs from the fully adjusted model with the other three unadjusted and partially adjusted models illustrate the confounding effects of dependence (see Table 3).

In *post-hoc* sensitivity analyses, the associations between quitting method and non-smoking were re-examined using models including different potential confounders. In a model including the more fine-grained assessment of time since the initiation of the quit attempt than the measure presented in Table 1, the adjusted odds of non-smoking in users of e-cigarettes were 1.58 (95% CI = 1.13–2.21) times higher compared with users of NRT bought over-the-counter and 1.55 (95% CI = 1.14–2.11) times higher compared with those using no aid. In another model that included another measure of dependence (HSI; missing data 3%, $n = 172$), the adjusted odds of non-smoking in users of e-cigarettes were 1.63 (95% CI = 1.15–2.32) times higher compared with users of NRT bought over-the-counter and 1.43 (95% CI = 1.03–1.98) times higher compared with those using no aid.

In *post-hoc* subgroup analyses, very light smokers were shown to have little influence on the pattern of results: in repeated analyses among those 5595 smokers reporting smoking one or more than one CPD the adjusted odds of non-smoking in users of e-cigarettes were higher compared with users of NRT bought over-the-counter (OR = 1.59, 95% CI = 1.13–2.26) and compared with those using no aid (OR = 1.63, 95% CI = 1.18–2.24). Similarly, the exclusion of respondents

Table 3 Associations between quitting method and abstinence.

	(1) e-Cigarettes	*(2) NRT over-the-counter*	*(3) No aid*	*(1) versus (2)* *Model 1: OR (95% CI)* *Model 2: OR (95% CI)* *Model 3: OR (95% CI)* *Model 4: OR (95% CI)*	*(1) versus (3)* *Model 1: OR (95% CI)* *Model 2: OR (95% CI)* *Model 3: OR (95% CI)* *Model 4: OR (95% CI)*
Full sample (n = 5863)					
% (n) Self-reported non-smoking	20.0 (93/464)	10.1 (194/1922)	15.4 (535/3477)	2.23 (1.70–2.93)***	1.38 (1.08–1.76)*
				1.88 (1.40–2.52)***	1.21 (0.92–1.58)
				1.63 (1.17–2.28)**	1.62 (1.19–2.19)**
				1.63 (1.17–2.27)**	1.61 (1.19–2.18)**
Subsample: quit attempt started ≤26 weeks (n = 3784)					
% (n) Self-reported non-smoking	20.3 (72/354)	11.0 (135/1222)	14.6 (323/2208)	2.06 (1.50–2.82)***	1.49 (1.12–1.98)**
				1.80 (1.27–2.55)***	1.39 (1.01–1.90)*
				1.56 (1.06–2.29)*	1.88 (1.32–2.68)***
				–	–
Subsample: quit attempt started >26 weeks (n = 2079)					
% (n) Self-reported non-smoking	19.1 (21/110)	8.4 (59/700)	16.7 (212/1269)	2.56 (1.49–4.42)***	1.18 (0.72–1.94)
				1.98 (1.11–3.53)**	0.91 (0.54–1.55)
				1.64 (0.83–3.24)	1.10 (0.59–2.06)
				–	–

Model 1 = unadjusted; model 2 = adjusted for age, sex, social grade, time since quit attempt started, quit attempts in the past year, abrupt versus gradual quitting and year of the survey; model 3 = adjusted for the variables from model 2 and time spent with urges to smoke and strength of urges to smoke; model 4 = adjusted for the variables from model 3 and the interaction terms time since last quit attempt started × time spent with urges and time since last quit attempt started × strength of urges to smoke. NB: for the two subsample analyses, model 4 is redundant, as there is no variation in the time since quit attempt. *P < 0.05; **P < 0.01; ***P < 0.001. OR = odds ratio; CI = confidence interval; NRT = nicotine replacement therapy.

during a time when e-cigarette usage was relatively rare (2009–11) had little effect on the results: among those 2306 smokers responding between 2012–14 the adjusted odds of non-smoking in users of e-cigarettes were higher compared with users of NRT bought over-the-counter (OR = 1.59, 95% CI = 1.05–2.42) and those using no aid (OR = 1.46, 95% CI = 1.04–2.05). In a final subgroup analysis the models were re-examined among those who started their quit attempt more or less than 6 months ago: there was only evidence among those who began their attempts less than 6 months ago of higher odds of non-smoking in users of e-cigarettes compared with users of NRT bought over-the-counter or those using no aid in the fully adjusted models (see Table 3).

DISCUSSION

Respondents who reported having used an e-cigarette in their most recent quit attempt were more likely to report still not smoking than those who used NRT bought over-the-counter or nothing. This difference remained after adjusting for time since the quit attempt started, year of the survey, age, gender, social grade, abrupt versus gradual quitting, prior quit attempts in the same year and a measure of nicotine dependence.

The unadjusted results have value in that they demonstrate self-reported abstinence is associated with quitting method among those who use these methods to aid cessation in real-world conditions. However, this was not a randomized controlled trial and there were differences in the characteristics of those using different methods. For example, more dependent smokers tended to be more likely to use treatment, and smokers from lower social grades were less likely to use e-cigarettes. Although the adjustments go beyond what is typically undertaken in these types of real-world studies [28,29,41–44], it was not possible to assess all factors that may have been associated with the self-selection of treatment and we cannot rule out the possibility that an unmeasured confounding factor is responsible for the finding. For example, motivation to quit is likely to have been associated positively with the use of treatment. However, previous population studies have found that the strength of this motivation is not associated with success of quit attempts once started, so it is unlikely to explain our findings [45]. There are other variables which are typically related to abstinence that may also be related to the selection of treatment; for example, those using e-cigarettes may have been less likely to share their house with other smokers, had better mental health or greater social capital of a kind not measured by social grade. These possibilities mean the associations reported here must be interpreted with caution. Nevertheless, the data provide some evidence in forming a judgement as to whether the advent of e-cigarettes in the UK market is likely to be having a

positive or negative impact on public health, in a way that a randomized controlled trial is unable to do.

The finding that smokers who had used an e-cigarette in their most recent quit attempt were more likely to report abstinence than those who used NRT bought over-the-counter, and that the latter did not appear to give better results than not using any aid [33], contributes to the debate about how far medicine regulation can go in ensuring that products used for smoking cessation are or continue to be effective in the real world [14–17]. Randomized controlled trials are clearly important in identifying potential efficacy, but real-world effectiveness will depend upon a number of other contextual variables. The current study, together with previous randomized trials, suggests that e-cigarettes may prove to be both an efficacious and effective aid to smoking cessation [10,11]. In so far that this is true, e-cigarettes may substantially improve public health because of their widespread appeal [6–9] and the huge health gains associated with stopping smoking [46]. This has to be offset against any detrimental effects that may emerge, as the long-term effects on health have not yet been established. However, the existing evidence suggests the associated harm may be minimal: the products contain low levels of carcinogens and toxicants [3] and no serious adverse event has yet been reported in any of the numerous experimental studies. Regardless, the harm will certainly be less than smoking, and thus of greater importance is the possible long-term effect of e-cigarettes on cigarette smoking prevalence beyond helping some smokers to quit. For example, it has been suggested that e-cigarettes might re-normalize smoking, promote experimentation among young people who otherwise may not have tried smoking or lead to dual use together with traditional cigarettes, and thereby deter some smokers from stopping [47]. The current data do not address these issues. However, the rise in e-cigarette prevalence in England since 2010 has coincided with continued reduction in smoking prevalence [48].

If e-cigarette use is proving more effective than NRT bought over-the-counter, a number of factors may contribute to this [49]. A greater similarity between using e-cigarettes and smoking ordinary cigarettes in terms of the sensory experience could be one factor. Greater novelty is another. It is also possible that users of e-cigarettes use their products more frequently or for a longer period than those using NRT without professional support. These are all issues that need to be examined in future research.

This study was not designed to assess the comparative effectiveness of e-cigarettes and NRT or other medications obtained on prescription or behavioural support. The evidence still favours the combination of behavioural support and prescription medication as providing the greatest chance of success [33,34,37], which is currently offered free at the point of access by the NHS stop smoking services in the United Kingdom.

A major strength of the current study is the use of a large, representative sample of the English population. Additionally, the study benefits from having begun to track the use of e-cigarettes as an aid to cessation at a time when e-cigarettes were only an emerging research issue. The importance of adjusting for nicotine dependence in real-world studies of smoking cessation is illustrated by the difference in the ORs between the models with and without this adjustment. The optimal method of adjusting for dependence would be to assess this in all participants prior to their quit attempt. However, in a wholly cross-sectional study, we believe the particular method used to adjust for dependence, established in two previous studies, is valid [32,33]. One of the most commonly used alternative measures of dependence—HIS—relies upon the number of cigarettes smoked and time to first cigarette of the day [40]. When smokers relapse they tend to do so with reduced consumption, which can lead to a false estimation of prior dependence in cross-sectional studies. This potential confound was avoided in the primary analysis by using a validated measure involving ratings of current urges to smoke and statistical adjustment of the urges for the time since the quit attempt was initiated [39]. The value of strength of urges as a measure of dependence in cross-sectional research would be limited if different methods of stopping were linked differentially to lower or higher levels of urges in abstinent compared with relapsed smokers. For example, a method of stopping that led to a relatively higher reduction in urges could underestimate the effectiveness of that method by making it seem that those using it were less dependent. However, we have not previously found evidence in this population data set that urges to smoke in smokers versus quitters differs as a function of method [33], and it was true again in this study. Regardless, the pattern of results remained the same in both a sensitivity analysis that also included HSI and in a subgroup analysis that excluded very light smokers. It is unlikely, therefore, that differential dependence between the users of different treatments has led to a substantial over- or underestimation of the relative effectiveness of e-cigarettes in the current study. Nevertheless, future studies may be able to draw stronger inferences by including a broader array of dependence measures or assessing dependence prior to a quit attempt.

The study had several limitations. First, abstinence was not verified biochemically. In randomized trials, this would represent a serious limitation because smokers receiving an active treatment often feel social pressure to report abstinence. However, in population surveys the

social pressure and the related rate of misreporting is low and it is generally considered acceptable to rely upon self-reported data [38]. A related issue is the assessment of abstinence by asking respondents whether they were 'still not smoking'. This definition classified as abstinent those who had one or more lapses but resumed not smoking. This limitation would be serious if the rate of lapsing was associated with method of quitting, and should be assessed in future studies. By contrast, advantages of this measure were the assessment of prolonged abstinence, as advocated in the Russell Standard, and a clear relationship to the quit attempt in question. An alternative approach, with a view to survival analysis, may have been to assess the length of abstinence since quit date among all respondents, including those who had relapsed by the time of the survey. However, this assessment would have added noise and potential bias with smokers needing to recall the time of relapse and having different interpretations of their return to smoking (i.e. first lapse, daily but reduced smoking, or smoking at pre-quit level). The strength of our approach is that smokers only needed to know whether they were currently still not smoking.

Secondly, there was a reliance upon recall data. The assessment of the most recent quit attempt involved recall of the previous 12 months and introduced scope for bias. The bias associated with recall of failed quit attempts would be expected to reduce the apparent effectiveness of reported aids to cessation because quit attempts using such aids would be more salient than those that were unaided [31]. Therefore, recall bias should militate against finding a benefit of e-cigarettes compared with no aid to cessation. Consistent with this explanation, the effect size for e-cigarettes compared with no aid appeared lower in smokers who started their quit attempt more than 6 months ago than in smokers who started their quit attempt less than 6 months ago. Although the power to detect the associations in these subgroups was limited, the explanation that the lack of effect in the more distant attempts was related to differential recall bias is also supported by the absolute rate of non-smoking being higher in those making unaided attempts more than 6 compared with less than 6 months ago. Alternatively, the finding may reflect a reduced long-term effectiveness of e-cigarettes. Future longitudinal studies of e-cigarettes as aids to cessation in the general population may differentiate these explanations and would represent a valuable improvement upon the current study.

Thirdly, NRT over-the-counter and e-cigarettes both represent heterogeneous categories. In particular, there is considerable variability in nicotine vaporization between different types of e-cigarette [50,51]. Similarly, the simple definition of using one or the other aid to support an attempt is likely to have masked variability in how heavily, frequently and how long either NRT over-the-counter or e-cigarettes were used by different smokers [12,52–54]. It is also possible that there were differences between the groups in their experience of unanticipated side effects. It is precisely because of all these factors—type/brand of NRT over-the-counter or e-cigarette, intensity and frequency of usage and experience of unanticipated side effects—that it is important to examine real-world effectiveness. However, it also means that we cannot make more exact statements about relative effectiveness of different products and ways in which they may be used. Given this huge variability it may be many years before one could accumulate enough real-world data to address these questions. Finally, the prevalence of e-cigarettes has been increasing in England over the study period and this may affect real-world effectiveness. Although the evidence does not yet suggest an 'early adopters' effect—the current results persisted after adjusting for the year of survey and in a subgroup analysis limiting the data to a period when e-cigarette usage had become prevalent—these findings will need to be revisited to establish whether or not the apparent advantage of e-cigarettes is sustained.

In conclusion, among smokers trying to stop without any professional support, those who use e-cigarettes are more likely to report abstinence than those who use a licensed NRT 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.

Declaration of interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: JB's post is funded by a fellowship from the UK Society for the Study of Addiction; R.W. is funded by Cancer Research UK; Cancer Research UK, the Department of Health and Pfizer funded data collection for this study (including a Pfizer investigator initiated award), and that at the outset data collection for the Smoking Toolkit Study was also supported by GlaxoSmithKline and Johnson and Johnson; J.B., D.K. and E.B. have all received unrestricted research grants from Pfizer; R.W. undertakes research and consultancy and receives fees for speaking from companies that develop and manufacture smoking cessation medications (Pfizer, J&J, McNeil, GSK, Nabi, Novartis and Sanofi-Aventis); there are no other financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years, particularly electronic cigarette companies, and there are no other relationships or activities that could appear to have influenced the submitted work. Funding was provided for the conduct of this research and preparation of the manuscript. The funders had no

final role in the study design; in the collection, analysis and interpretation of data; in the writing of the report; or in the decision to submit the paper for publication. All researchers listed as authors are independent from the funders and all final decisions about the research were taken by the investigators and were unrestricted.

Transparency declaration

J.B. affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned have been explained.

STROBE statement

All authors declare that study hypotheses arose before any inspection of the data and that all STROBE recommendations were followed.

Acknowledgements

The research team is part of the UK Centre for Tobacco and Alcohol Studies. We would like to thank Martin Jarvis, Lion Shahab and Tobias Raupach for providing valuable comments on a draft of the manuscript. The full data set, which includes individual level data, and statistical code are all available from the corresponding author at jamie.brown@ucl.ac.uk. Participants gave informed consent for anonymized data sharing.

References

1. Lim S. S., Vos T., Flaxman A. D., Danaei G., Shibuya K., Adair-Rohani H. *et al*. A comparative risk assessment of burden of disease and injury attributable to 67 risk factors and risk factor clusters in 21 regions, 1990–2010: a systematic analysis for the Global Burden of Disease Study 2010. *Lancet* 2012; **380**: 2224–60.
2. Bullen C., McRobbie H., Thornley S., Glover M., Lin R., Laugesen M. Effect of an electronic nicotine delivery device (e cigarette) on desire to smoke and withdrawal, user preferences and nicotine delivery: randomised cross-over trial. *Tob Control* 2010; **19**: 98–103.
3. Goniewicz M. L., Knysak J., Gawron M., Kosmider L., Sobczak A., Kurek J. *et al*. Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. *Tob Control* 2014; **23**: 133–9.
4. Vansickel A. R., Cobb C. O., Weaver M. F., Eissenberg T. E. A clinical laboratory model for evaluating the acute effects of electronic 'cigarettes': nicotine delivery profile and cardiovascular and subjective effects. *Cancer Epidemiol Biomarkers Prev* 2010; **19**: 1945–53.
5. Dawkins L., Turner J., Hasna S., Soar K. The electronic-cigarette: effects on desire to smoke, withdrawal symptoms and cognition. *Addict Behav* 2012; **37**: 970–3.
6. Pearson J. L., Richardson A., Niaura R. S., Vallone D. M., Abrams D. B. e-Cigarette awareness, use, and harm perceptions in US adults. *Am J Public Health* 2012; **102**: 1758–66.
7. Zhu S.-H., Gamst A., Lee M., Cummins S., Yin L., Zoref L. The use and perception of electronic cigarettes and snus among the U.S. population. *PLOS ONE* 2013; **8**: e79332.
8. Dockrell M., Morison R., Bauld L., McNeill A. E-cigarettes: prevalence and attitudes in Great Britain. *Nicotine Tob Res* 2013; **15**: 1737–44.
9. Brown J., West R., Beard E., Michie S., Shahab L., McNeill A. Prevalence and characteristics of e-cigarette users in Great Britain: findings from a general population survey of smokers. *Addict Behav* 2014; **39**: 1120–25.
10. Bullen C., Howe C., Laugesen M., McRobbie H., Parag V., Williman J. *et al*. Electronic cigarettes for smoking cessation: a randomised controlled trial. *Lancet* 2013; **382**: 1629–37.
11. Caponnetto P., Campagna D., Cibella F., Morjaria J. B., Caruso M., Russo C. *et al*. EffiCiency and Safety of an eLectronic cigAreTte (ECLAT) as tobacco cigarettes substitute: a prospective 12-month randomized control design study. *PLOS ONE* 2013; **8**: e66317.
12. Vansickel A. R., Eissenberg T. Electronic cigarettes: effective nicotine delivery after acute administration. *Nicotine Tob Res* 2013; **15**: 267–70.
13. Lancet. E-cigarettes: a moral quandary. *Lancet* 2013; **382**: 914.
14. Cobb N. K., Abrams D. B. E-cigarette or drug-delivery device? Regulating novel nicotine products. *N Engl J Med* 2011; **365**: 193–5.
15. Cobb N. K., Cobb C. O. Regulatory challenges for refined nicotine products. *Lancet Respir Med* 2013; **1**: 431–3.
16. Hajek P., Foulds J., Houezec J. L., Sweanor D., Yach D. Should e-cigarettes be regulated as a medicinal device? *Lancet Respir Med* 2013; **1**: 429–31.
17. Etter J.-F. Should electronic cigarettes be as freely available as tobacco? Yes. *BMJ* (Clinical Research edn) 2013; **346**: 3845–6.
18. Borland R. Electronic cigarettes as a method of tobacco control. *BMJ* 2011; **343**: 6269–70.
19. Flouris A. D., Oikonomou D. N. Electronic cigarettes: miracle or menace? *BMJ* 2010; **340**: 311.
20. Etter J.-F. Electronic cigarettes: a survey of users. *BMC Public Health* 2010; **10**: 231.
21. Etter J-F B. C. Electronic cigarette: users profile, utilization, satisfaction and perceived efficacy. *Addiction* 2011; **106**: 2017–28.
22. Foulds J., Veldheer S., Berg A. Electronic cigarettes (e-cigs): views of aficionados and clinical/public health perspectives. *Int J Clin Pract* 2011; **65**: 1037–42.
23. Siegel M. B., Tanwar K. L., Wood K. S. Electronic cigarettes as a smoking-cessation tool: results from an online survey. *Am J Prev Med* 2011; **40**: 472–5.
24. Dawkins L., Turner J., Roberts A., Soar K. 'Vaping' profiles and preferences: an online survey of electronic cigarette users. *Addiction* 2013; **108**: 1115–25.
25. Goniewicz M. L., Lingas E. O., Hajek P. Patterns of electronic cigarette use and user beliefs about their safety and benefits: an internet survey. *Drug Alcohol Rev* 2013; **32**: 133–40.
26. Farsalinos K. E., Romagna G., Tsiapras D., Kyrzopoulos S., Spyrou A., Voudris V. Impact of flavour variability on electronic cigarette use experience: an internet survey. *Int J Environ Res Public Health* 2013; **10**: 7272–82.

Ther Adv Drug Saf
2014, Vol. 5(2) 67–86
DOI: 10.1177/2042098614524430

Safety evaluation and risk assessment of electronic cigarettes as tobacco cigarette substitutes: a systematic review

Konstantinos E. Farsalinos and Riccardo Polosa

***Abstract*:** Electronic cigarettes are a recent development in tobacco harm reduction. They are marketed as less harmful alternatives to smoking. Awareness and use of these devices has grown exponentially in recent years, with millions of people currently using them. This systematic review appraises existing laboratory and clinical research on the potential risks from electronic cigarette use, compared with the well-established devastating effects of smoking tobacco cigarettes. Currently available evidence indicates that electronic cigarettes are by far a less harmful alternative to smoking and significant health benefits are expected in smokers who switch from tobacco to electronic cigarettes. Research will help make electronic cigarettes more effective as smoking substitutes and will better define and further reduce residual risks from use to as low as possible, by establishing appropriate quality control and standards.

Keywords: electronic cigarettes, e-liquid, e-vapor, harm reduction, nicotine, safety, tobacco

Introduction

Complete tobacco cessation is the best outcome for smokers. However, the powerful addictive properties of nicotine and the ritualistic behavior of smoking create a huge hurdle, even for those with a strong desire to quit. Until recently, smokers were left with just two alternatives: either quit or suffer the harmful consequences of continued smoking. This gloomy scenario has allowed the smoking pandemic to escalate, with nearly 6 million deaths annually and a predicted death toll of 1 billion within the 21st century [World Health Organization, 2013]. But a third choice, involving the use of alternative and much safer sources of nicotine with the goal to reduce smoking-related diseases is now available: tobacco harm reduction (THR) [Rodu and Godshall, 2006].

Electronic cigarettes (ECs) are the newest and most promising products for THR [Polosa *et al.* 2013b]. They are electrically-driven devices consisting of the battery part (usually a lithium battery), and an atomizer where liquid is stored and is aerosolized by applying energy and generating heat to a resistance encircling a wick. The liquid used mainly consists of propylene glycol, glycerol, distilled water, flavorings (that may or may not be approved for food use) and nicotine. Consumers (commonly called 'vapers') may choose from several nicotine strengths, including non-nicotine liquids, and a countless list of flavors; this assortment is a characteristic feature that distinguishes ECs from any other THR products. Since their invention in 2003, there has been constant innovation and development of more efficient and appealing products. Currently, there are mainly three types of devices available [Dawkins, 2013], depicted in Figure 1. (1) First-generation devices, generally mimicking the size and look of regular cigarettes and consisting of small lithium batteries and cartomizers (i.e. cartridges, which are usually prefilled with a liquid that bathes the atomizer). Batteries may be disposable (to be used once only) or rechargeable. (2) Second-generation devices, consisting mainly of higher-capacity lithium batteries and atomizers with the ability to refill them with liquid (sold in separate bottles). In the most recent atomizers you can simply change the atomizer head (resistance and wick) while keeping the body of the atomizer, thus reducing the operating costs. (3) Third-generation devices (also called 'Mods', from modifications),

Correspondence to:
Konstantinos E. Farsalinos, MD
Onassis Cardiac Surgery Center, Sygrou 356, Kallithea 17674, Greece
kfarsalinos@gmail.com

Riccardo Polosa, PhD
Centro per la Prevenzione e Cura del Tabagismo (CPCT) and Institute of Internal Medicine, Università di Catania, Catania, Italy

Figure 1. Examples of electronic cigarette devices currently available on the market.

consisting of very large-capacity lithium batteries with integrated circuits that allow vapers to change the voltage or power (wattage) delivered to the atomizer. These devices can be combined with either second-generation atomizers or with rebuildable atomizers, where the consumers have the ability to prepare their own setup of resistance and wick.

Awareness and use (vaping) of ECs has increased exponentially in recent years. Data obtained from the HealthStyles survey showed that, in the US, awareness of ECs rose from 40.9–57.9% from 2010 to 2011, with EC use rising from 3.3–6.2% over the same time period [King *et al.* 2013]. In the United Kingdom, EC use in regular smokers increased from 2.7% in 2010 to 6.7% in 2012 [Dockrell *et al.* 2013]. Similar findings were obtained from the International Tobacco Control Four-Country Survey [Adkison *et al.* 2013]. A recent prospective study in Swiss army recruits showed that 12% of smokers who tried ECs progressed to daily use [Douptcheva *et al.* 2013]. It must be noted that this increase in EC use has occurred despite the concerns raised by public health authorities about the safety and appropriateness of using these products as alternatives to smoking [National Association of Attorneys General, 2013; Food and Drug Administration, 2009; Mayers, 2009].

The popularity of ECs may be due to their ability to deal both with the physical (i.e. nicotine) and the behavioral component of smoking addiction. In particular, sensory stimulation [Rose and Levin, 1991] and simulation of smoking behavior and cigarette manipulation [Hajek *et al.* 1989] are important determinants of a product's effectiveness in reducing or completely substituting smoking. These features are generally absent in nicotine replacement therapies (NRTs) and oral medications for nicotine dependence, whereas ECs are unique in that they provide rituals associated with smoking behavior (e.g. hand-to-mouth movement, visible 'smoke' exhaled) and sensory stimulation associated with it [Farsalinos *et al.* 2013b]. This explains why these products can be effective in reducing consumption of tobacco smoking [Bullen *et al.* 2013; Caponnetto *et al.* 2013b; Polosa *et al.* 2011] and are efficient as long-term substitutes of conventional cigarettes [Farsalinos *et al.* 2013b].

Methods

For this systematic review (Figure 2), we searched the PubMed electronic database by using keywords related to ECs and/or their combination (e-cigarette, electronic cigarette, electronic nicotine delivery systems). We obtained a total of 354 results, and selected 41 studies we judged relevant to research on EC safety/risk profile. Reference lists from these studies were also examined to identify relevant articles. We searched additional information in abstracts presented at scientific congresses (respiratory, cardiovascular, tobacco control, toxicology), and in reports of chemical analyses on EC samples that were available online. We also looked for selected studies on chemicals related to EC ingredients (e.g. nicotine, propylene glycol, glycerol, cinnamaldehyde, microparticles emission, etc.), but not specifically evaluated in EC research. In total, 97 publications were found, from which 15 chemical analyses of single or a limited number of EC samples were excluded because they were discussed in a review paper [Cahn and Siegel, 2011]. In total, 114 studies are cited in this paper.

Risk differences compared with conventional cigarettes and the issue of nicotine

Conventional cigarettes are the most common form of nicotine intake. Smoking-related diseases are pathophysiologically attributed to oxidative stress, activation of inflammatory pathways and the toxic effect of more than 4000 chemicals and carcinogens present in tobacco smoke [Environmental Protection Agency, 1992]. In addition, each puff contains $>1 \times 10^{15}$ free radicals [Pryor and Stone, 1993]. All of these chemicals are emitted mostly during the combustion process, which is absent in ECs. Although the addictive potential of nicotine and related compounds is largely documented [Guillem *et al.*

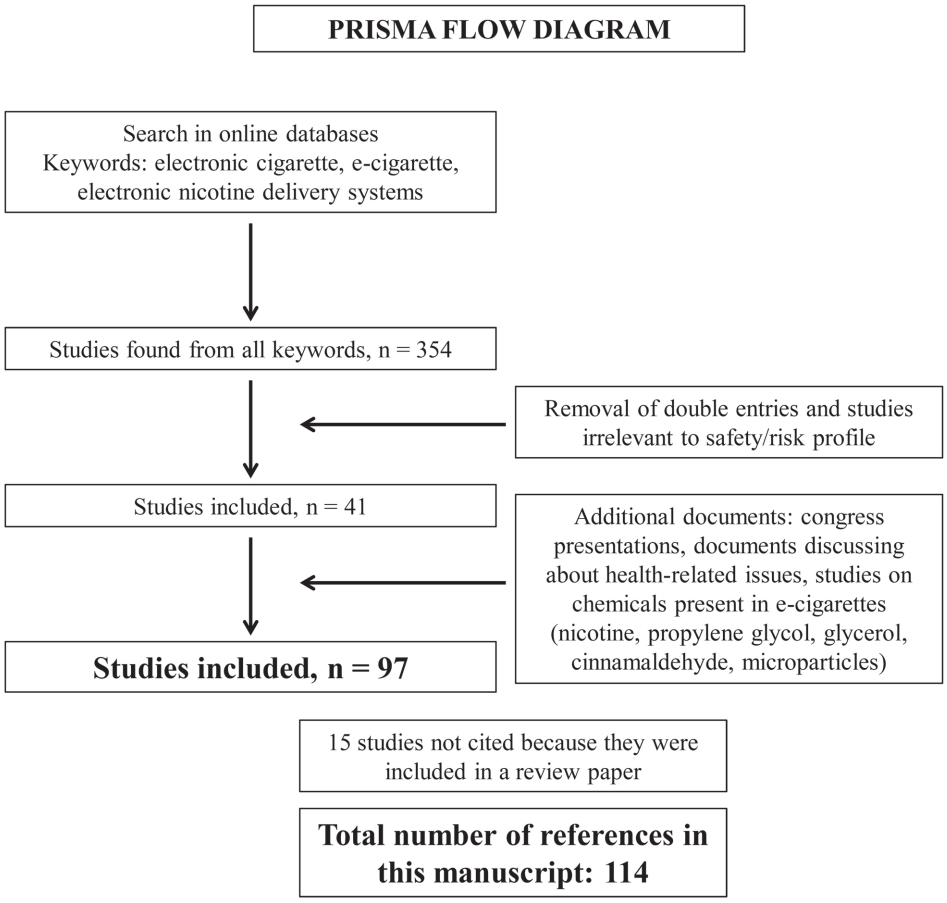

Figure 2. Methodology for literature research and selection of studies.

2005], much less dissemination has been given to the notion that nicotine does not contribute to smoking-related diseases. It is not classified as a carcinogen by the International Agency for Research on Cancer [WHO-IARC, 2004] and does not promote obstructive lung disease. A major misconception, commonly supported even by physicians, is that nicotine promotes cardiovascular disease. However, it has been established that nicotine itself has minimal effect in initiating and promoting atherosclerotic heart disease [Ambrose and Barua, 2004]. It does not promote platelet aggregation [Zevin *et al.* 1998], does not affect coronary circulation [Nitenberg and Antony, 1999] and does not adversely alter the lipid profile [Ludviksdottir *et al.* 1999]. An observational study of more than 33,000 smokers found no evidence of increased risk for myocardial infarction or acute stroke after NRT subscription, although follow up was only 56 days [Hubbard *et al.* 2005]. Up to 5 years of nicotine gum use in the Lung Health Study was unrelated to cardiovascular diseases or other serious side effects [Murray *et al.* 1996]. A meta-analysis of 35 clinical trials found no evidence of cardiovascular or other life-threatening adverse effects caused by nicotine intake [Greenland *et al.* 1998]. Even in patients with established cardiovascular disease, nicotine use in the form of NRTs does not increase cardiovascular risk [Woolf *et al.* 2012; Benowitz and Gourlay, 1997]. It is anticipated that any product delivering nicotine without involving combustion, such as the EC, would confer a significantly lower risk compared with conventional cigarettes and to other nicotine containing combustible products.

The importance of using nicotine in the long-term was recognized several years ago by Russell, indicating that the potential of nicotine delivery systems as long-term alternatives to tobacco should be explored in order to make the elimination of tobacco a realistic future target [Russell, 1991]. However, current regulations restrict the

long-term use of pharmaceutical or recreational nicotine products (such as snus) [Le Houezec *et al.* 2011]. In other words, nicotine intake has been demonized, although evidence suggests that, besides being useful in smoking cessation, it may even have beneficial effects in a variety of disorders such as Parkinson's disease [Nielsen *et al.* 2013], depression [McClernon *et al.* 2006], dementia [Sahakian *et al.* 1989] and ulcerative colitis [Guslandi, 1999]. Obviously, the addictive potential is an important factor in any decision to endorse nicotine administration; however, it should be considered as slight 'collateral damage' with minimal impact to vapers' health compared with the tremendous benefit of eliminating all disease-related substances coming from tobacco smoking. In fact, smokers are already addicted to nicotine; therefore the use of a 'cleaner' form of nicotine delivery would not represent any additional risk of addiction. Surveys have shown that ECs are used as long-term substitutes to smoking [Dawkins *et al.* 2013; Etter and Bullen, 2012]. Although consumers try to reduce nicotine use with ECs, many are unable to completely stop its intake, indicating an important role for nicotine in the ECs' effectiveness as a smoking substitute [Farsalinos *et al.* 2013b].

Nicotine overdose or intoxication is unlikely to occur with vaping, since the amount consumed [Farsalinos *et al.* 2013c] and absorbed [Nides *et al.* 2014; Dawkins and Corcoran, 2013] is quite low. Moreover, although not yet proven, it is expected that vapers will self-titrate their nicotine intake in a similar way to tobacco cigarettes [Benowitz *et al.* 1998]. Last, but not least, there is evidence suggesting that nicotine cannot be delivered as fast and effectively from ECs compared to tobacco cigarettes [Farsalinos *et al.* 2014]. Therefore, it seems that ECs have a huge theoretical advantage in terms of health risks compared with conventional cigarettes due to the absence of toxic chemicals that are generated in vast quantities by combustion. Furthermore, nicotine delivery by ECs is unlikely to represent a significant safety issue, particularly when considering they are intended to replace tobacco cigarettes, the most efficient nicotine delivery product.

Studies on the safety/risk profile of ECs

Findings on the safety/risk profile of ECs have just started to accumulate. However, this research must be considered work in progress given that the safety/risk of any product reflects an evolving body of knowledge and also because the product itself is undergoing constant development.

Existing studies about the safety/risk profile of ECs can be divided into chemical, toxicological and clinical studies (Table 1). Obviously, clinical studies are the most informative, but also the most demanding because of several methodological, logistical, ethical and financial challenges. In particular, exploring safety/risk profile in cohorts of well-characterized users in the long-term is required to address the potential of future disease development, but it would take hundreds of users to be followed for a substantial number of years before any conclusions are made. Therefore, most research is currently focused on *in vitro* effects, with clinical studies confined into evaluation of short-term use or pathophysiological mechanisms of smoking-related diseases.

Chemical studies

Chemical studies are relatively simple and cheap to perform and provide quick results. However, there are several disadvantages with this approach. Research is usually focused on the known specific chemicals (generally those known to be toxic from studies of cigarette smoke) and fails to address unknown, potentially toxic contaminants that could be detected in the liquid or the emitted aerosol. Problems may also arise from the detection of the chemicals in flavors. Such substances, although approved for use in the food industry, have largely unknown effects when heated and inhaled; thus, information on the presence of such substances is difficult to interpret in terms of *in vivo* effects. In fact, chemical studies do not provide any objective information about the effects of use; they can only be used to calculate the risk based on theoretical models and on already established safety levels determined by health authorities. An overview of the chemical studies performed on ECs is displayed in Table 2.

Laugesen performed the first studies evaluating the chemical composition of EC aerosols [Laugesen, 2008, 2009]. The temperature of the resistance of the tested EC was 54°C during activation, which is approximately 5–10% of the temperature of a burning tobacco cigarette. Toxic chemicals such as heavy metals, carcinogenic polycyclic aromatic hydrocarbons and phenols were not detected, with the exception of trivial amounts of mercury (0.17 ng per EC) and traces of formaldehyde and acetaldehyde. Laugesen

Table 1. Types of studies performed to determine safety and to estimate risk from EC use.

Type of studies	Research subject	Advantages	Disadvantages
Chemical studies	Evaluate the chemical composition of liquids and/or aerosol. Examine environmental exposure (passive 'vaping').	Easier and faster to perform. Less expensive. Could realistically be implemented for regulatory purposes.	Usually targeted on specific chemicals. Unknown effects of flavorings when inhaled. No validated protocols for vapor production. Provide no objective evidence about the end results (effects) of use (besides by applying theoretical models).
Toxicological studies	Evaluate the effects on cell cultures or experimental animals.	Provide some information about the effects from use.	Difficult to interpret the results in terms of human *in vivo* effects. More expensive than chemical studies. Need to test aerosol and not liquid. Standards for exposure protocols have not been clearly defined.
Clinical studies	Studies on human *in vivo* effects.	Provide definite and objective evidence about the effects of use.	Difficult and expensive to perform. Long-term follow up is needed due to the expected lag from initiation of use to possible development of any clinically evident disease. For now, limited to acute effects from use.

evaluated emissions based on a toxicant emissions score and reported a score of 0 in ECs compared with a score of 100–134 for tobacco cigarettes (Figure 3). The US Food and Drug Administration (FDA) also performed chemical analyses on 18 commercially available products in 2009 [Westenberger, 2009]. They detected the presence of tobacco-specific nitrosamines (TSNAs) but did not declare the levels found. Small amounts of diethylene glycol were also found in one sample, which was unlikely to cause any harm from normal use. Another study identified small amounts of amino-tandalafil and rimonambant in EC liquids [Hadwiger *et al.* 2010]. Subsequently, several laboratories performed similar tests, mostly on liquids, with Cahn and Siegel publishing a review on the chemical analyses of ECs and comparing the findings with tobacco cigarettes and other tobacco products [Cahn and Siegel, 2011]. They reported that TSNA levels were similar to those measured in pharmaceutical NRTs. The authors concluded that, based on chemical analysis, ECs are far less harmful compared with tobacco cigarettes. The most comprehensive study on TSNAs has been performed recently by a South Korean group, evaluating 105 liquids obtained from local retailers [Kim and Shin, 2013]. On average, they found 12.99 ηg TSNAs per ml of liquid, with the amount of daily exposure to the users estimated to be similar to users of NRTs [Farsalinos *et al.* 2013d]. The estimated daily exposure to nitrosamines from tobacco cigarettes (average consumption of 15 cigarettes per day) is estimated to be up to 1800 times higher compared with EC use (Table 3). Etter and colleagues evaluated the accuracy of nicotine labeling and the presence of nicotine impurities and degradation products in 20 EC liquid samples [Etter *et al.* 2013]. They found that nicotine levels were 85–121% of what was labeled, while nicotine degradation products were present at levels of 0–4.4%. Although in some samples the levels were higher than those specified in European Pharmacopoeia, they are not expected to cause any measurable harm to users.

Besides the evaluation for the presence of TSNAs, analyses have been performed for the detection of carbonyl compounds. It is known that the thermal degradation of propylene glycol and glycerol can lead to the emission of toxic compounds such as aldehydes [Antal *et al.* 1985; Stein *et al.* 1983]. Goniewicz and colleagues evaluated the emission of 15 carbonyls from 12 brands of ECs (mostly first-generation) [Goniewicz *et al.* 2013]. In order to produce vapor, researchers used a smoking machine and followed a regime of 1.8-second puffs with a very short 10-second interpuff interval, which does not represent realistic use [Farsalinos *et al.* 2013c]; although the puff duration was low, interpuff interval was remarkably short, which could potentially lead to overheating. In addition, the same puff number was used in all devices tested, although there was a significant difference in the design and liquid content between devices. Despite these limitations, out of 15 carbonyls, only 3 were detected (formaldehyde, acetaldehyde and acrolein); levels were

Table 2. Summary of chemical toxicity findings.

Study	What was investigated?	What were the key findings?	
		Liquid	Vapor
Laugesen [2009]	Evaluation of 62 toxicants in the EC vapour from Ruyan 16 mg and mainstream tobacco smoke using a standard smoking machine protocol.	N/A	No acrolein, but small quantities of acetaldehyde and formaldehyde found. Traces of TSNAs (NNN, NNK, and NAT) detected. CO, metals, carcinogenic PAHs and phenols not found in EC vapour. Acetaldehyde and formaldehyde from tobacco smoke were 55 and 5 times higher, respectively.
Westenberger [2009]	Evaluation of toxicants in EC cartridges from two popular US brands.	TSNAs and certain tobacco specific impurities were detected in both products at very low levels. Diethylene glycol was identified in one cartridge.	N/A
Hadwiger *et al.* [2010]	Evaluation of four refill solutions and six replacement cartridges advertised as containing Cialis or rimonambant.	Small amounts of amino-tandalafil and rimonambant present in all products tested.	N/A
Cahn and Siegel [2011]	Overview of 16 chemical toxicity studies of EC liquids/vapours.	TSNAs levels in ECs 500- to 1400-fold lower than those in conventional cigarettes and similar to those in NRTs. Other chemicals found very low levels, which are not expected to result in significant harm.	
Pellegrino *et al.* [2012]	Evaluation of PM fractions and PAHs in the vapour generated from cartomizers of an Italian EC brand.	N/A	PM fractions were found, but levels were 6–18 times lower compared with conventional cigarettes. Traces of PAHs detected.
Kim and Shin [2013]	TSNAs (NNN, NNK, NAT, and NAB) content in 105 refill liquids from 11 EC brands purchased in Korean shops.	Total TSNAs averaged 12.99 ng/ml EC liquid; daily total TSNA exposure from conventional cigarettes estimated to be up to 1800 times higher.	N/A
Etter *et al.* [2013]	Nicotine degradation products, ethylene glycol and diethylene glycol evaluation of 20 EC refill liquids from 10 popular brands	The levels of nicotine degradation products represented 0–4.4% of those for nicotine, but for most samples the level was 1–2%. Neither ethylene glycol nor diethylene glycol were detected.	N/A
Goniewicz *et al.* [2013]	Vapours generated from 12 brands of ECs and a medicinal nicotine inhaler using a modified smoking machine protocol	N/A	Carbonyl compounds (formaldehyde, acetaldehyde and acrolein), VOCs (toluene and trace levels of xylene), trace levels of TSNAs (NNN and NNK) and very low levels of metals (cadmium, nickel and lead) were found in almost all examined EC vapours. Trace amounts of formaldehyde, acetaldehyde, cadmium, nickel and lead were also detected from the Nicorette inhalator. Compared with conventional cigarette, formaldehyde, acetaldehyde and acrolein were 9–450 times lower; toluene levels 120 times lower; and NNN and NNK levels 380 and 40 times lower respectively.

(Continued)

Table 2. (Continued)

Study	What was investigated?	What were the key findings?	
		Liquid	Vapor
Williams *et al.* [2013]	Vapour generated from cartomizers of a popular EC brand using a standard smoking machine protocol	N/A	Trace levels of several metals (including tin, copper, silver, iron, nickel, aluminium, chromium, lead) were found, some of them at higher level compared with conventional cigarettes. Silica particles were also detected. Number of microparticles from 10 EC puffs were 880 times lower compared with one tobacco cigarette.
Burstyn [2014]	Systematic review of 35 chemical toxicity studies/ technical reports of EC liquids/vapours.	No evidence of levels of contaminants that may be associated with risk to health. These include acrolein, formaldehyde, TSNAs, and metals. Concern about contamination of the liquid by a nontrivial quantity of ethylene glycol or diethylene glycol remains confined to a single sample of an early technology product and has not been replicated.	

Abbreviations. CO, carbon monoxide; EC, electronic cigarette; NAT, N-Nitrosoanatabine; NNK, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone; NNN, N-Nitrosonornicotine; PAHs, polycyclic aromatic hydrocarbons; PM, particulate matter; TSNAs, tobacco-specific nitrosamines; VOCs, volatile organic carbons.

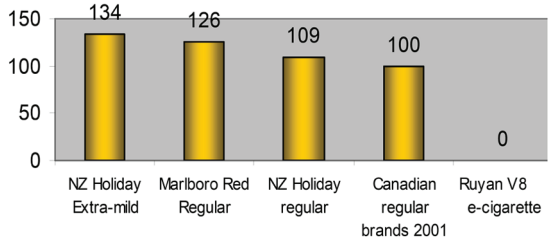

Figure 3. Toxic emissions score, adjusted for nicotine, for electronic cigarette and popular cigarette brands. (Reproduced with permission from Laugesen [2009]).

9–450 times lower compared with emissions from tobacco cigarettes (derived from existing literature but not tested in the same experiment). Formaldehyde and acetaldehyde were also emitted from the nicotine inhalator, although at lower levels. In addition, they examined for the presence of 11 volatile organic carbons and found only trace levels of toluene (at levels from 0.2–6.3 μg per 150 puffs) and xylene (from 0.1–0.2 μg per 150 puffs) in 10 of the samples; toluene levels were 120 times lower compared with tobacco cigarettes (again derived from existing literature but not tested in the same experiment).

Given that ECs have several metal parts in direct contact with the e-liquid, it is quite obvious to expect some contamination with metals in the vapor. Goniewicz and colleagues examined samples for the presence of 12 metals and found nickel, cadmium and lead emitted [Goniewicz *et al.* 2013]; the levels of nickel were similar to those present in a pharmaceutical nicotine inhalator, while lead and cadmium were present at 2–3 times higher levels compared with the inhalator. Still, the absolute levels were very low (few nanograms per 150 puffs). Williams *et al.* [2013] focused their research on the presence of heavy metals and silicate particles emitted from ECs. They tested poor quality first-generation cartomisers and found several metals emitted in the aerosol of the EC, specifying that in some cases the levels were higher compared with conventional cigarettes. As mentioned earlier, it is not unusual to find trace levels of metals in the vapor generated by these products under experimental conditions that bear little relevance to their normal use; however, it is unlikely that such small amounts pose a serious threat to users' health. Even if all the aerosol was absorbed by the consumer (which is not the case since most of the aerosol is visibly exhaled), an average user would be exposed to 4–40 times lower amounts for most metals than the maximum daily dose allowance from impurities in medicinal products [US Pharmacopeia, 2013]. Silicate particles were also found in the EC aerosol. Such particles come from the wick material, however the authors did not clarify whether crystalline silica oxide particles were found, which are responsible for respiratory disease. In total, the number of microparticles (< 1000 nm) estimated to be inhaled by EC users from 10 puffs were 880 times lower compared

Table 3. Levels of nitrosamines found in electronic and tobacco cigarettes. Prepared based on information from Laugesen [2009], Cahn and Siegel [2011] and Kim and Shin [2013].

Product	Total nitrosamines levels (ng)	Daily exposure (ng)	Ratio[4]
Electronic cigarette (per ml)	13	52[1]	1
Nicotine gum (per piece)	2	48[2]	0.92
Winston (per cigarette)	3365	50 475[3]	971
Newport (per cigarette)	3885	50 775[3]	976
Marlboro (per cigarette)	6260	93 900[3]	1806
Camel (per cigarette)	5191	77 865[3]	1497

[1]Based on average daily use of 4ml liquid
[2]Based on maximum recommended consumption of 24 pieces per day
[3]Based on consumption of 15 cigarettes per day
[4] Difference (number-fold) between electronic cigarette and all other products in daily exposure to nitrosamines

with one tobacco cigarette. Similar findings concerning microparticles were reported by Pellegrino and colleagues who found that, for each particulate matter fraction, conventional cigarettes released 6–18 times higher amounts compared with the EC tested [Pellegrino *et al.* 2012].

Burstyn has recently reviewed current data on the chemistry of aerosols and the liquids of ECs (including reports which were not peer-reviewed) and estimated the risk to consumers based on workplace exposure standards (i.e. Threshold Limit Values [TLVs]) [Burstyn, 2014]. After reviewing all available evidence, the author concluded that there was no evidence that vaping produced inhalable exposure to contaminants of aerosol that would warrant health concerns. He added that surveillance of use is recommended due to the high levels of propylene glycol and glycerol inhaled (which are not considered contaminants but ingredients of the EC liquid). There are limited data on the chronic inhalation of these chemicals by humans, although there is some evidence from toxicological studies (which are discussed later in this paper).

In conclusion, chemical studies have found that exposure to toxic chemicals from ECs is far lower compared with tobacco cigarettes. Besides comparing the levels of specific chemicals released from tobacco and ECs, it should be taken into consideration that the vast majority of the >4000 chemicals present in tobacco smoke are completely absent from ECs. Obviously, surveillance of use is warranted in order to objectively evaluate the *in vivo* effects and because the effects of inhaling flavoring substances approved for food use are largely unknown.

Toxicological studies

To date, only a handful of toxicological studies have been performed on ECs, mostly cytotoxicity studies on established cell lines. The cytotoxicity approach also has its flaws. Findings cannot be directly applied to the *in vivo* situation and there is always the risk of over- (as well as under-)estimating the interpretation of the toxic effects in these investigational models. An ample degree of results variability is to be expected from different cell lines and, sometimes, also within the same cell line. Comparing the potential cytotoxicity effects of EC vapor with those resulting from the exposure of cigarette smoke should be mandatory, but standards for vapor production and exposure protocols have not been clearly defined.

Bahl and colleagues [Bahl *et al.* 2012] performed cytotoxicity tests on 36 EC liquids, in human embryonic stem cells, mouse neural stem cells and human pulmonary fibroblasts and found that stem cells were more sensitive to the effects of the liquids, with 15 samples being moderately cytotoxic and 12 samples being highly cytotoxic. Propylene glycol and glycerol were not cytotoxic, but a correlation between cytotoxicity and the number and height of the flavoring peaks in high-performance liquid chromatography was noted. Investigations were just restricted to the effect of EC liquids and not to their vapors, thus limiting the importance of the study findings; this is not a trivial issue considering that the intended use of these products is by inhalation only and that it is unlikely that flavoring substances in the EC liquids will still be present in the aerosol in the same amount due to differences in evaporation temperature [Romagna *et al.* 2013]. Regrettably, a set of experiments with cigarette smoke extracts as

comparator was not included. Of note, the authors emphasized that the study could have underestimated the cytotoxicity by 100 times because when they added the EC liquids to the cell, medium final concentration was 1%. However, cells were cultured for 48 hours with continuous exposure to the liquid, while in real use the lungs come in contact with aerosol instead of liquid, the contact lasts for 1–2 seconds per puff and most of the aerosol is visibly exhaled. Finally, Cinnamon Ceylon, the liquid found to be mostly cytotoxic in this study, was not a refill liquid but a concentrated flavor which is not used in ECs unless it is diluted to 3–5%.

Romagna and colleagues [Romagna *et al.* 2013] performed the first cytotoxicity study of EC vapor on fibroblast cells. They used a standardized ISO 10993-5 protocol, which is used for regulatory purposes of medical devices and products. They tested the vapor of 21 liquid samples containing the same amount of nicotine (9 mg/ml), generated by a commercially available EC device. Cells were incubated for 24 hours with each of these vapors and with smoke from a conventional cigarette. Only one sample was found to be marginally cytotoxic, whereas cigarette smoke was highly cytotoxic (approximately 795% more cytotoxic), even when the extract was diluted up to 25% of the original concentration.

The same group also investigated the cytotoxic potential of 20 EC liquid samples in cardiomyoblasts [Farsalinos *et al.* 2013a]. Vapor was produced by using a commercially available EC device. Samples contained a wide range of nicotine concentrations. A base liquid mixture of propylene glycol and glycerol (no nicotine and no flavorings) was also included as an additional experimental control. Four of the samples examined were made by using cured tobacco leaves in a steeping process, allowing them to impregnate a mixture of propylene glycol and glycerol for several days before being filtered and bottled for use. Of note, this was the first study which evaluated a limited number of samples with an EC device delivering higher voltage and energy to the atomizer (third-generation device). In total, four samples were found to be cytotoxic; three of them were liquids made by using cured tobacco leaves, with cytotoxicity observed at both 100% and 50% extract concentration, while one sample (cinnamon flavor) was marginally cytotoxic at 100% extract concentration only. In comparison, smoke from three tobacco cigarettes was highly cytotoxic, with toxicity observed even when the extract was diluted to 12.5%. The samples made with tobacco leaves were three times less cytotoxic compared with cigarette smoke; this was probably due to the absence of combustion and the significantly lower temperature of evaporation in EC use. Concerning high-voltage EC use, the authors found slightly reduced cell viability without any of the samples being cytotoxic according to the ISO 10993-5 definition. Finally, no association between cell survival and the amount of nicotine present in the liquids was noted.

A recent study evaluated in more detail the cytotoxic potential of eight cinnamon-flavored EC liquids in human embryonic stem cells and human pulmonary fibroblasts [Behar *et al.* 2014]. The authors found that the flavoring substance predominantly present was cinnamaldehyde, which is approved for food use. They observed significant cytotoxic effects, mostly on stem cells but also on fibroblasts, with cytotoxicity associated with the amount of cinnamaldehyde present in the liquid. However, major methodological issues arose from this study. Once again, cytotoxicity was just restricted to EC liquids and not to their vapors. Moreover, the authors mentioned that the amount of cinnamaldehyde differed between liquids by up to 100 times, and this raises the suspicion of testing concentrated flavor rather than refills. By searching the internet and contacting manufacturers, based on the names of samples and suppliers mentioned in the manuscript, it was found that at least four of their samples were not refills but concentrated flavors. Surprisingly, the levels of cinnamaldehyde found to be cytotoxic were about 400 times lower than those currently approved for use [Environmental Protection Agency, 2000].

Few animal studies have been performed to evaluate the potential harm of humectants in EC liquids (i.e. propylene glycol and glycerol) when given by inhalation. Robertson and colleagues tested the effects on primates of inhaling propylene glycol vapor for several months and found no evidence of toxicity on any organ (including the lungs) after post-mortem examination of the animals [Robertson *et al.* 1947]. Similar observations were made in a recent study in rats and dogs [Werley *et al.* 2011]. Concerns have been raised in human use, based on studies of people exposed to theatrical fog [Varughese *et al.* 2005; American Chemistry Council, 2003] or propylene glycol used in the aviation industry [Wieslander *et al.* 2001]. Irritation of the respiratory tract was found, but no permanent lung injury or other

long-term health implications were detected. It should be reminded that, in these circumstances, nonpharmaceutical purity propylene glycol is used and in some cases oils are added, making it difficult to interpret the results in the context of EC use. Evidence for the potential harm of inhaled glycerol is sparse. A study using Sprague–Dawley rats found minimal to mild squamous metaplasia of the epiglottis epithelium in the high-dose group only, without any changes observed in lungs or other organs [Renne *et al.* 1992]. No comparative set of experiments with cigarette smoke was included, but it is well known that exposure to tobacco smoke in similar animal models leads to dramatic changes in the lungs, liver and kidneys [Czekaj *et al.* 2002].

In conclusion, toxicological studies have shown significantly lower adverse effects of EC vapor compared with cigarette smoke. Characteristically, the studies performed by using the liquids in their original liquid form have found less favorable results; however, no comparison with tobacco smoke was performed in any of these studies, and they cannot be considered relevant to EC use since the samples were not tested in the form consumed by vapers. More research is needed, including studies on different cell lines such as lung epithelial cells. In addition, it is probably necessary to evaluate a huge number of liquids with different flavors since a minority of them, in an unpredictable manner, appear to raise some concerns when tested in the aerosol form produced by using an EC device.

Clinical studies and research surveys

Clinical trials can be very informative, but they require monitoring of hundreds of users for many years to adequately explore the safety/risk profile of the products under investigation. Research surveys of EC users, on the other hand, can quickly provide information about the potential harm of these products and are much cheaper to run. However, self-reported data, highly self-selected study populations, and the cross-sectional design are some of the most common limitations of research surveys. Taken together, findings from surveys and follow-up studies of vapers have shown that EC use is relatively safe.

Polosa and colleagues followed up smokers for 24 months, after a 6-month period of intervention during which ECs were given [Polosa *et al.* 2013a]. Only mild symptoms such as mouth and throat irritation and dry cough were observed. Farsalinos and colleagues retrospectively evaluated a group of 111 EC users who had completely quit smoking and were daily EC users for a median period of 8 months [Farsalinos *et al.* 2013b]. Throat irritation and cough were the most commonly reported side effects. Similar findings have been observed in surveys [Dawkins *et al.* 2013; Etter *et al.* 2011]. However, it is expected that dedicated users who have more positive experiences and fewer side effects compared with the general population participate in such studies, therefore interpretation should be done with caution. The only two existing randomized controlled trials have also included detailed EC safety analysis. The ECLAT study [Caponnetto *et al.* 2013b], a three-arm, controlled, randomized, clinical trial designed to compare efficacy and safety of a first-generation device with 7.2, 5.4, or 0 mg nicotine cartridges, reported clinically significant progressive health improvements already by week two of continuous use of the device, and no serious adverse events (i.e. major depression, abnormal behavior or any event requiring an unscheduled visit to the family practitioner or hospitalization) occurred during the study. The ASCEND study [Bullen *et al.* 2013], a three-arm, controlled, randomized, clinical trial designed to compare the efficacy and safety of a first-generation device (with or without nicotine) with nicotine patches, reported no serious adverse events in any of the three study groups.

Few clinical studies have been performed to evaluate the short-term *in vivo* effects of EC use in current or former smokers. Vardavas and colleagues evaluated the acute effects of using an EC for 5 minutes on respiratory function [Vardavas *et al.* 2012]. Although they did not report the results of commonly-used spirometry parameters, they found that a sensitive measure of airways resistance and nitric oxide levels in exhaled breath were adversely affected. Similar elevations in respiratory resistance were reported by other research groups [Palamidas *et al.* 2013; Gennimata *et al.* 2012], who also documented some bizarre elevation in exhaled carbon monoxide levels after EC use; this finding has been challenged by several other studies [Farsalinos *et al.* 2013f; Nides *et al.* 2014; Van Staden *et al.* 2013]. Schober and colleagues found that EC use led to elevated exhaled nitric oxide [Schober *et al.* 2013], contradicting the findings from Vardavas and colleagues [Vardavas *et al.* 2012]. Characteristically, none of the above studies performed any comparative tests after smoking tobacco cigarettes. Flouris and colleagues found

that only smoking had an acute adverse effect on respiratory function [Flouris *et al.* 2013]; no difference was observed after the group of smokers was exposed to active or passive EC use.

Two studies have evaluated the short-term effects of ECs on the cardiovascular system. Farsalinos and colleagues evaluated the acute effects of using ECs with an 11 mg/ml nicotine-containing liquid on hemodynamics and left ventricular function, in comparison with the effects of cigarette smoking [Farsalinos *et al.* 2012]. They found that EC use resulted in a slight elevation in diastolic blood pressure while, after smoking, both systolic and diastolic blood pressure and heart rate were significantly elevated. Obviously, this was due to the relatively low nicotine content of the EC (which is considered medium strength). Diastolic dysfunction was observed in smokers after smoking, which was in line with findings from previous studies. However, no adverse effects were observed in EC users after using the device *ad lib* for 7 minutes. Another study by the same group [Farsalinos *et al.* 2013f], evaluated the acute effects of EC use on coronary flow. In particular, they measured the flow velocity reserve of the left anterior descending coronary artery by echocardiography after intravenous infusion of adenosine, representing the maximal ability of the artery to deliver blood to the myocardium. Smoking was associated with a decline in flow velocity reserve by 16% and an elevation in resistance to flow by 19%. On the contrary, no difference was observed in any of these parameters after using the EC. Blood carboxyhemoglobin levels were also measured in participants; baseline values were significantly higher in smokers compared with vapers and were further elevated after smoking but were not altered after EC use. Similar observations for carboxyhemoglobin levels were observed by Van Staden and colleagues [Van Staden *et al.* 2013].

A clinical case report of a smoker suffering from chronic idiopathic neutrophilia was published. According to that report [Farsalinos and Romagna, 2013], switching from smoking to EC use led to a reversal of the condition after 6 months. In addition, C-reactive protein levels, which were consistently elevated for more than 6 years, decreased to normal levels. Another case report of a patient with lipoid pneumonia was published, with the condition attributed to glycerin-based EC liquids used by the patient [McCauley *et al.* 2012]. However, glycerin is an alcohol (polyol) and thus it is impossible to cause lipoid pneumonia. Only oil-based liquids could be the cause for this condition; such liquids should not be used with ECs.

One study evaluated the acute effects of tobacco and EC use on white blood cell count [Flouris *et al.* 2012]. Smoking one tobacco cigarette caused an immediate elevation in white blood cells, neutrophils and lymphocytes, indicating acute inflammatory distress. On the contrary, no differences were observed after using ECs.

In conclusion, clinical studies evaluating the effects of short-term EC use on selected cardiovascular and respiratory functional outcomes have shown that even if some harmful effects of vaping are reported, these are considerably milder compared with smoking conventional cigarettes. However, it is difficult to assess the prognostic implications of these studies; longer-term data are needed before any definite conclusions are made.

Passive vaping

Passive smoking is an established risk factor for a variety of diseases [Barnoya and Navas-Acien, 2013]. Therefore, it is important from a public health perspective to examine the impact of EC use on bystanders. Indirect data can be derived from chemical studies in vapor mentioned above, which show that the potential of any significant adverse effects on bystanders is minimal. In fact, since sidestream exposure is nonexistent in EC (aerosol is produced only during activation of the device, while tobacco cigarettes emit smoke even when no puffs are taken), such studies are undoubtedly overestimating the risk of environmental exposure.

Few studies have focused on second-hand vaping. McAuley and colleagues [McAuley *et al.* 2012], although mentioning indoor air quality in the title of their study and finding minimal health-related impact, did not in fact evaluate second-hand vaping because aerosol was produced from an EC device and was evaluated without previously being inhaled by any user. Moreover, there were some problems with cross-contamination with tobacco cigarette smoke, which made the results somewhat questionable, at least for some of the parameters tested. Schripp and colleagues [Schripp *et al.* 2013] evaluated the emissions from an EC by asking a volunteer to use three different EC devices in a closed 8 m^3 chamber. From a selection of 20 chemicals analyzed, only formaldehyde, acrolein, isoprene, acetaldehyde and acetic acid were

detected. The levels were 5–40 times lower compared with emissions from a conventional cigarette. For formaldehyde, the authors specifically mentioned that the levels were continuously rising from the time the volunteer entered the room, even before he started using the EC. Moreover, no acute elevation was observed when the smoker used the three EC devices, contrary to the acute elevation and spiking of levels when a tobacco cigarette was lit. The authors concluded that formaldehyde was not emitted from the ECs but was due to human contamination, since low amounts of formaldehyde of endogenous origin can be found in exhaled breath [Riess *et al.* 2010]. Romagna and colleagues [Romagna *et al.* 2012] evaluated chemicals released in a realistic setting of a 60 m^3 room, by asking five smokers to smoke *ad lib* for 5 hours and five vapers to use ECs *ad lib* for a similar period of time on two separate days. Nicotine, acrolein, toluene, xylene and polycyclic aromatic hydrocarbons were detected in room air after the smoking session, with the amount of total organic carbon (TOC) reaching to 6.66 mg/m^3. In contrast, after the EC session, only glycerol was detected in minimal levels (72 $\mu g/m^3$), while TOC reached a maximum level of 0.73 mg/m^3. Characteristically, the amount of TOC accumulated after 5 hours of EC use was similar to the amount found after just 11 minutes of smoking. The study on heavy metals mentioned previously [Williams *et al.* 2013] could also be used to examine any potential risk of bystanders' exposure to toxic metals. The levels of heavy metals found in vapor were minimal, and considering the dispersion of these molecules in the whole room air, it is unlikely that any of these metals could be present in measurable quantities in the environment. Therefore, the risk for bystanders would be literally nonexistent. Contrary to that, Schober and colleagues [Schober *et al.* 2013] found that levels of aluminum were raised by 2.4 times in a 45 m^3 room where volunteers were asked to use ECs for 2 hours. This is a highly unexpected finding which cannot be supported by the findings of the study by Williams and colleagues [Williams *et al.* 2013]; because the levels found in the latter could not result in such elevation of the environmental levels of aluminum, unless nothing is retained in or absorbed from the lungs. Moreover, Schober and colleagues [Schober *et al.* 2013] found that levels of polycyclic aromatic hydrocarbons (PAHs) were raised by 20% after EC use. However, a major methodological problem of this study is that control environmental measurements were performed on a separate day and not on the same day of EC use. This is a major limitation, because the levels of environmental PAHs have significant diurnal and day-to-day variations [Ravindra *et al.* 2008]; therefore, it is highly likely that the differences in levels of PAHs (which are mainly products of combustion and are not expected to be emitted from EC use) represented changes due to environmental conditions and not due to EC use. Bertholon and colleagues [Bertholon *et al.* 2013] examined the EC aerosol exhaled from a user, in comparison with exhaled smoke from a smoker. The authors found that particle size diameters were 0.29–0.033μm. They observed that the half life of EC aerosol was 11 seconds compared with 20 minutes for cigarette smoke, indicating that risk of passive vaping exposure is significantly lower compared with passive smoking.

The recent findings by Czogala and colleagues [Czogala *et al.* 2013] led to similar conclusions. The authors compared the emissions of electronic and conventional cigarettes generated by experienced dual users in a ventilated full-sized room and found that ECs may emit detectable amounts of nicotine (depending on the specific EC brand tested), but no carbon monoxide and volatile organic carbons. However, the average ambient levels of nicotine of ECs were 10 times lower than those of conventional cigarettes (3.32 ± 2.49 *versus* 31.60 ± 6.91 $\mu g/m^3$).

In his review and comparison with TLVs, Burstyn found that emissions from ECs to the environment are not expected to pose any measurable risk for bystanders [Burstyn, 2014].

An issue that needs further clarification relates to the findings of microparticles emitted from ECs. In most studies, these findings are presented in a way implying that the risk is similar to environmental or smoking microparticles. In reality, it is not just the size but the composition of the microparticles that matters. Environmental microparticles are mainly carbon, metal, acid and organic microparticles, many of which result from combustion and are commonly called particulate matter. Particulate matter exposure is definitely associated with lung and cardiovascular disease [Peters, 2005; Seaton *et al.* 1995]. In the case of ECs, microparticles are expected to consist mostly of propylene glycol, glycerol, water and nicotine droplets. Metal and silica nanoparticles may also be present [Williams *et al.* 2013], but, in general, emissions from ECs are incomparable to environmental particulate matter or cigarette smoke microparticles.

Flouris and colleagues [Flouris *et al.* 2013] performed the only clinical study evaluating the respiratory effects of passive vaping compared with passive smoking. Researchers found significant adverse effects in spirometry parameters after being exposed to passive smoking for 1 hour, while no adverse effects were observed after exposure to passive vaping.

Although evaluating the effects of passive vaping requires further work, based on the existing evidence from environmental exposure and chemical analyses of vapor, it is safe to conclude that the effects of EC use on bystanders are minimal compared with conventional cigarettes.

Miscellaneous safety issues

Specific subpopulations: psychiatric and chronic obstructive pulmonary disorder patients

A challenging population subgroup with unique smoking patterns is that of psychiatric patients and in particular schizophrenic patients. This subpopulation is characterized by a very high smoking prevalence [De Leon and Diaz, 2005] with an excess of smoking-related mortality [Brown *et al.* 2000]. Currently, only NRTs are recommended to treat nicotine dependence in this specific subpopulation, but in general they are not particularly effective [Aubin *et al.* 2012]. ECs could be used as an alternative to smoking products in this group. Caponnetto and colleagues performed a prospective 12-month pilot study to evaluate the efficacy of EC use in smoking reduction and cessation in a group of 14 patients with schizophrenia [Caponnetto *et al.* 2013a]. In 50% of participants, smoking consumption went from 30 to 15 cigarettes per day at 52 weeks of follow up, while 14.3% managed to quit smoking. Importantly, no deterioration in their psychiatric condition was observed, and side effects were mild and temporary. The results were promising although an outdated EC device was used in this study.

There is also anecdotal evidence that successful smoking cessation could be attained by using an EC in smokers with other psychiatric conditions such as depression [Caponnetto *et al.* 2011a]. Both patients described in this case series stated that EC use was well tolerated and no adverse events were reported.

Considering that first-line oral medications for nicotine addiction are contraindicated in such patients (prescribing information for bupropion and varenicline carry a 'black-box' warning for certain psychiatric conditions), ECs may be a promising tool in these challenging patient groups.

Another subpopulation that may benefit from regular EC use is that of respiratory patients with chronic obstructive pulmonary disease (COPD), a progressive disease characterized by a persistent inflammatory response to tobacco smoke that generally leads to decline in lung function, respiratory failure, cor pulmonale and death. Consequently, smoking cessation plays a crucial part in the management of COPD patients. However, the available evidence in the medical literature indicates that COPD patients who smoke respond poorly to smoking cessation efforts [Schiller and Ni, 2006]. To date, no formal efficacy and safety assessment of EC use in COPD patients has been conducted. There is only evidence from a case report of inveterate smokers with COPD and a documented history of recurring relapses, who eventually quit tobacco smoking on their own by using an EC [Caponnetto *et al.* 2011b]. Significant improvement in quality of life and reduction in the number of disease exacerbations were noted. EC use was well tolerated with no reported adverse events.

Accidental nicotine exposure

Accidental ingestion of nicotine, especially by children, or skin contact with large amounts of liquid or highly concentrated nicotine solution can be an issue. However, the historically referenced lethal dose of 60 mg has recently been challenged in a review by Mayer [Mayer, 2013]; he found that the lethal levels currently reproduced in every document originated from dubious experiments performed in the 19th century. Based on post-mortem studies, he suggested that the acute dose associated with a lethal outcome would be 500–1000 mg. Taking into account that voluminous vomiting is the first and characteristic symptom of nicotine ingestion, it seems that far higher levels of nicotine need to be ingested in order to have lethal consequences.

A surveillance system of adverse events has been developed by the FDA, which identifies safety concerns in relation to tobacco products. Since 2008, 47 adverse events were reported for ECs

[Chen, 2013]. Eight of them were serious events such as hospitalizations for pneumonia, heart failure, seizures and hypotension and burns. A case of second-degree burns was caused by a battery explosion, which is generally a problem observed in lithium batteries and has occurred in other products (such as mobile phones). The author emphasized that the reported events were not necessarily associated with EC use but may have been related to pre-existing conditions or other causes. No condition was characteristically associated with EC use.

A recent review of the California Poison Control System database from 2010 to 2012 identified 35 cases (14 children) associated with EC exposure (accidental exposure in 25 cases) [Cantrell, 2013]. A total of five patients were evaluated in an emergency department and all were discharged within 4 hours. Nausea, vomiting, dizziness and oral irritation were most commonly reported. Taken together, data from surveillance systems of adverse events suggest that short-term adverse effects and accidental exposures to EC cartridges are unlikely to result in serious toxicity.

Notwithstanding, avoiding preventable contact with highly concentrated nicotine solution remains important; this can be achieved by specific labeling of the products, child-proof caps and proper education of consumers. There is no evidence that nicotine-containing EC liquids should be treated in any different way compared with other consumer products used every day in households (such as bleach, washing machine powder, etc.).

Electrical accidents and fires

The electronic equipment of ECs may be the cause for accidents. ECs are mainly composed of lithium batteries. There have been reports of explosions of batteries, caused either by prolonged charging and use of improper chargers or by design defects. Similar accidents have occurred with batteries of other popular devices, such as mobile phones. Therefore, this does not occur specifically with ECs, however, quality standards of production should be used in order to avoid such accidents.

Smoking is a major cause of residential fires. Between 2008 and 2010, an estimated annual average of 7600 smoking-related fires occurred in residential buildings in the US [US Fire Administration, 2012]. They account for only 2% of all residential building fires but for 14% of fire deaths. Since ECs are activated only when used by the person and there is no combustion involved, there is the potential to avoid the risk of smoking-related fires.

Use by youngsters and nonsmokers

Although beyond the scope of this review, it is important to briefly discuss the potential for addiction from EC use. It should be acknowledged that nicotine is addictive, although recent studies have shown that several other chemicals present in tobacco are associated with a significant enhancement of the addictiveness of nicotine [Lotfipour *et al.* 2011; Rose, 2006; Guillem *et al.* 2005]. Still, nicotine intake should not be recommended to nonsmokers. Smokers are already addicted to nicotine, thus ECs will be a cleaner form of nicotine intake, while at the same time they will maintain their sensory stimulation and motor simulation of smoking; these are important aspects of the addiction to smoking. Regulatory authorities have expressed concern about EC use by youngsters or by never-smokers, with ECs becoming a gateway to smoking or becoming a new form of addiction. However, such concerns are unsubstantiated; research has shown that EC use by youngsters is virtually nonexistent unless they are smokers. Camenga and colleagues [Camenga *et al.* 2013] examined the use of ECs and tobacco in a group of adolescents, in a survey conducted in three waves. In the first wave of the survey (February 2010), 1719 adolescents were surveyed from which only one nonsmoker was found to be using ECs. In the second and third wave of the surveys, only five nonsmoking adolescents were using ECs. In fact, these are adolescents who reported first ever use of ECs in the past 30 days; therefore they were not necessarily regular or daily EC consumers. The increased prevalence of EC use from 0.9% in 2010 to 2.3% in 2011 concerned smoking adolescents, therefore it should be considered a positive finding that smokers are experimenting with the significantly less harmful ECs. Similarly, the Medicines and Healthcare Products Regulatory Agency (MHRA) found that less than 1% of EC users are never-smokers [MHRA, 2013]. Data from the Centers for Disease Control [2013] National Youth Tobacco Survey reported doubling in EC experimentation by 13–18 year old students from 1.1% in 2011 to 2.1% in 2012; however, 90.6% of them were smokers. From the whole population, only 0.5% were nonsmokers experimenting with ECs.

Once again, participants were asked about ever experimenting with an EC in the past 30 days, not regular or daily EC use. Recently, a survey of more than 75,000 students in South Korea was published [Lee *et al.* 2013]. Although they found that 12.6% of them were daily smokers (8.6% were using only tobacco cigarettes and 3.6% were using both tobacco and ECs), only 0.6% of nonsmokers had used ECs in the past 30 days. Although the above mentioned data have been used as arguments to support the fact that a new epidemic of nicotine addiction through the use of ECs is appearing, in reality they are showing that any experimentation with ECs is done by smokers. This is in fact a positive finding, and could lead to reduced smoking prevalence through adoption of EC use. Therefore, ECs could serve as gateway from smoking; on the contrary, there is no evidence indicating that they could be a gateway to smoking. It is promising to see that penetration of EC use in youngsters is virtually nonexistent, especially when you take into consideration that there is currently no official regulation in most countries to prohibit the access to ECs by youngsters.

Conclusion

Existing evidence indicates that EC use is by far a less harmful alternative to smoking. There is no tobacco and no combustion involved in EC use; therefore, regular vapers may avoid several harmful toxic chemicals that are typically present in the smoke of tobacco cigarettes. Indeed, some toxic chemicals are released in the EC vapor as well, but their levels are substantially lower compared with tobacco smoke, and in some cases (such as nitrosamines) are comparable with the amounts found in pharmaceutical nicotine products. Surveys, clinical, chemistry and toxicology data have often been mispresented or misinterpreted by health authorities and tobacco regulators, in such a way that the potential for harmful consequences of EC use has been largely exaggerated [Polosa and Caponnetto, 2013]. It is obvious that some residual risk associated with EC use may be present, but this is probably trivial compared with the devastating consequences of smoking. Moreover, ECs are recommended to smokers or former smokers only, as a substitute for conventional cigarettes or to prevent smoking relapse; thus, any risk should be estimated relative to the risk of continuing or relapsing back to smoking and the low efficacy of currently approved medications for smoking cessation should be taken into consideration [Moore *et al.* 2009; Rigotti *et al.* 2010;Yudkin *et al.* 2003]. Nonetheless, more research is needed in several areas, such as atomizer design and materials to further reduce toxic emissions and improve nicotine delivery, and liquid ingredients to determine the relative risk of the variety of compounds (mostly flavorings) inhaled. Regulations need to be implemented in order to maintain the current situation of minimal penetration of EC use in nonsmokers and youngsters, while manufacturers should be forced to provide proof for the quality of the ingredients used and to perform tests on the efficiency and safety of their products. However, any regulatory decisions should not compromise the variability of choices for consumers and should make sure that ECs are more easily accessible compared with their main competitor, the tobacco cigarette. Consumers deserve, and should make, informed decisions and research will definitely promote this. In particular, current data on safety evaluation and risk assessment of ECs is sufficient enough to avert restrictive regulatory measures as a consequence of an irrational application of the precautionary principle [Saitta *et al.* 2014].

ECs are a revolutionary product in tobacco harm reduction. Although they emit vapor, which resembles smoke, there is literally no fire (combustion) and no 'fire' (suspicion or evidence that they may be the cause for disease in a similar way to tobacco cigarettes). Due to their unique characteristics, ECs represent a historical opportunity to save millions of lives and significantly reduce the burden of smoking-related diseases worldwide.

Funding

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Conflict of interest statement

Riccardo Polosa is a Professor of Medicine and is supported by the University of Catania, Italy. He has received lecture fees and research funding from GlaxoSmithKline and Pfizer, manufacturers of stop smoking medications. He has also served as a consultant for Pfizer and Arbi Group Srl (Milano, Italy), the distributor of Categoria™ e-Cigarettes. His research on electronic cigarettes is currently supported by LIAF (Lega Italiana AntiFumo).

Konstantinos Farsalinos is a researcher at Onassis Cardiac Surgery Center. He has never been funded by the pharmaceutical or the tobacco

industry. For some of his studies, the institution has received financial compensation from electronic cigarette companies for the studies' cost. His salary is currently being paid by a scholarship grant from the Hellenic Society of Cardiology.

References

Adkison, S., O'Connor, R., Bansal-Travers, M., Hyland, A., Borland, R., Yong, H.H. *et al.* (2013) Electronic nicotine delivery systems: international tobacco control four-country survey. *Am J Prev Med* 44: 207–215.

Ambrose, J. and Barua, R. (2004) The pathophysiology of cigarette smoking and cardiovascular disease: an update. *J Am Coll Cardiol* 43: 1731–1737.

American Chemistry Council (2003) Ethylene Glycols: Considerations Against Use in Theatrical Fogs/Mist and Artificial Smoke. Available at: http://www.americanchemistry.com/ProductsTechnology/Ethylene-Glycols-2/PDF-Ethylene-Glycols-Fog-Information-Sheet.pdf (Accessed: 20 November 2013).

Antal, M., Mok, W., Roy, J. and T-Raissi, A. (1985) Pyrolytic sources of hydrocarbons from biomass. *J Anal Appl Pyrol* 8: 291–303.

Aubin, H., Rollema, H., Svensson, T. and Winterer, G. (2012) Smoking, quitting, and psychiatric disease: A review. *Neurosci Biobehav Rev* 36: 271–284.

Bahl, V., Lin, S., Xu, N., Davis, B., Wang, Y. and Talbot, P. (2012) Comparison of electronic cigarette refill fluid cytotoxicity using embryonic and adult models. *Reprod Toxicol* 34: 529–537.

Barnoya, J. and Navas-Acien, A. (2013) Protecting the world from secondhand tobacco smoke exposure: where do we stand and where do we go from here? *Nicotine Tob Res* 15: 789–804.

Behar, R., Davis, B., Wang, Y., Bahl, V., Lin, S. and Talbot, P. (2014) Identification of toxicants in cinnamon-flavored electronic cigarette refill fluids. *Toxicol In Vitro* 28: 198–208.

Benowitz, N. and Gourlay, S. (1997) Cardiovascular toxicity of nicotine: implications for nicotine replacement therapy. *J Am Coll Cardiol* 29: 1422–1431.

Benowitz, N., Zevin, S. and Jacob, P. III (1998) Suppression of nicotine intake during ad libitum cigarette smoking by high-dose transdermal nicotine. *J Pharmacol Exp Ther* 287: 958–962.

Bertholon, J., Becquemin, M., Roy, M., Roy, F., Ledur, D., Annesi Maesano, I. *et al.* (2013) Comparison of the aerosol produced by electronic cigarettes with conventional cigarettes and the shisha. *Rev Mal Respir* 30: 752–757.

Brown, S., Inskip, H. and Barraclough, B. (2000) Causes of the excess mortality of schizophrenia. *Br J Psychiatry* 177: 212–217

Bullen, C., Howe, C., Laugesen, M., McRobbie, H., Parag, V., Williman, J. *et al.* (2013) Electronic cigarettes for smoking cessation: a randomised controlled trial. *Lancet* 382: 1629–1637.

Burstyn, I. (2014) Peering through the mist: Systematic review of what the chemistry of contaminants in electronic cigarettes tells us about health risks. *BMC Public Health* 14: 18.

Cahn, Z. and Siegel, M. (2011) Electronic cigarettes as a harm reduction strategy for tobacco control: a step forward or a repeat of past mistakes? *J Public Health Policy* 32: 16–31.

Camenga, D., Delmerico, J., Kong, G., Cavallo, D., Hyland, A., Cummings, K. *et al.* (2013) Trends in use of electronic nicotine delivery systems by adolescents. *Addict Behav* 39(1): 338–340.

Cantrell, F. (2013) Adverse effects of e-cigarette exposures. *J Community Health* 15 December 2013 (Epub ahead of print). DOI: 10.1007/s10900-013-9807-5

Caponnetto, P., Auditore, R., Russo, C., Cappello, G. and Polosa, R. (2013a) Impact of an electronic cigarette on smoking reduction and cessation in schizophrenic smokers: a prospective 12-month pilot study. *Int J Environ Res Public Health* 10: 446–461.

Caponnetto, P., Campagna, D., Cibella, F., Morjaria, J., Caruso, M., Russo, C. *et al.* (2013b) EffiCiency and Safety of an eLectronic cigAreTte (ECLAT) as tobacco cigarettes substitute: a prospective 12-month randomized control design study. *PLoS One* 8: e66317.

Caponnetto, P., Polosa, R., Auditore, R., Russo, C. and Campagna, D. (2011a) Smoking cessation with e-cigarettes in smokers with a documented history of depression and recurring relapses. *Int J Clin Med* 2: 281–284.

Caponnetto, P., Polosa, R., Russo, C., Leotta, C. and Campagna, D. (2011b) Successful smoking cessation with electronic cigarettes in smokers with a documented history of recurring relapses: a case series. *J Med Case Rep* 5: 585.

Centers for Disease Control and Prevention (CDC) (2013) Notes from the field: electronic cigarette use among middle and high school students - United States, 2011-2012. *MMWR Morb Mortal Wkly Rep* 62: 729–730.

Chen, I. (2013) FDA summary of adverse events on electronic cigarettes. *Nicotine Tob Res* 15: 615–616.

Czekaj, P., Pałasz, A., Lebda-Wyborny, T., Nowaczyk-Dura, G., Karczewska, W., Florek, E. *et al.* (2002) Morphological changes in lungs, placenta, liver and kidneys of pregnant rats exposed to cigarette smoke. *Int Arch Occup Environ Health* 75 (Suppl): S27–S35.

Czogala, J., Goniewicz, M., Fidelus, B., Zielinska-Danch, W., Travers, M. and Sobczak, A. (2013) Secondhand exposure to vapors from electronic cigarettes. *Nicotine Tob Res* (11 December 2011 (Epub ahead of print). DOI: 10.1093/ntr/ntt203

Dawkins, L. (2013) Electronic cigarettes: what are they and are they effective? E-Cigarette Summit, London, UK (oral presentation). Available at: http://e-cigarette-summit.com/wp-content/uploads/2013/12/Summit-Presentations.pdf [accessed 22 December 2013].

Dawkins, L. and Corcoran, O. (2013) Acute electronic cigarette use: nicotine delivery and subjective effects in regular users. *Psychopharmacology (Berl)* 231: 401–407.

Dawkins, L., Turnern, J., Roberts, A. and Soar, K. (2013) 'Vaping' profiles and preferences: an online survey of electronic cigarette users. *Addiction* 108: 1115–1125.

De Leon, J. and Diaz, F. (2005). A meta-analysis of worldwide studies demonstrates an association between schizophrenia and tobacco smoking behaviors. *Schizophr Res* 76: 1351–1357.

Dockrell, M., Morison, R., Bauld, L. and McNeill, A. (2013) E-Cigarettes: prevalence and attitudes in Great Britain. *Nicotine Tob Res* 15: 1737–1744.

Douptcheva, N., Gmel, G., Studer, J., Deline, S. and Etter, J.F. (2013) Use of electronic cigarettes among young Swiss men. *J Epidemiol Community Health* 67: 1075–1076.

Environmental Protection Agency (1992) EPA Report/600/6-90/006F. Respiratory health effects of passive smoking: lung cancer and other disorders. Washington, DC. Available at: http://oaspub.epa.gov/eims/eimscomm.getfile?p_download_id=36793 (Accessed: 20 November 2013).

Environmental Protection Agency (2000) Cinnamaldehyde (040506) fact sheet. Available at: http://www.epa.gov/pesticides/chem_search/reg_actions/registration/fs_PC-040506_1-Oct-98.pdf (Accessed: 20 November 2013).

Etter, J. and Bullen, C. (2011) Electronic cigarette: users profile, utilization, satisfaction and perceived efficacy. *Addiction* 106: 2017–2028.

Etter, J., Zäther, E. and Svensson, S. (2013) Analysis of refill liquids for electronic cigarettes. *Addiction* 108: 1671–1679.

Farsalinos, K. and Romagna, G. (2013) Chronic idiopathic neutrophilia in a smoker, relieved after smoking cessation with the use of electronic cigarette: a case report. *Clin Med Insights Case Rep* 6: 15–21.

Farsalinos, K., Romagna, G., Allifranchini, E., Ripamonti, E., Bocchietto, E., Todeschi, S. *et al.* (2013a) Comparison of the cytotoxic potential of cigarette smoke and electronic cigarette vapour extract on cultured myocardial cells. *Int J Environ Res Public Health* 10: 5146–5162.

Farsalinos, K., Romagna, G., Tsiapras, D., Kyrzopoulos, S. and Voudris, V. (2013b) Evaluating nicotine levels selection and patterns of electronic cigarette use in a group of "vapers" who had achieved complete substitution of smoking. *Subst Abuse* 7: 139–146.

Farsalinos, K., Romagna, G., Tsiapras, D., Kyrzopoulos, S. and Voudris, V. (2013c) Evaluation of electronic cigarette use (vaping) topography and estimation of liquid consumption: implications for research protocol standards definition and for public health authorities' regulation. *Int J Environ Res Public Health* 10: 2500–2514.

Farsalinos, K., Romagna, G. and Voudris, V. (2013d) Authors miss the opportunity to discuss important public health implications. *J Chromatogr A* 1312: 155–156.

Farsalinos, K., Spyrou, A., Tsimopoulou, K., Stefopoulos, C., Romagna, G. and Voudris, V. (2014). Nicotine absorption from electronic cigarette use: comparison between first and new-generation devices. *Sci Rep* (in press).

Farsalinos, K., Tsiapras, D., Kyrzopoulos, S., Savvopoulou, M., Avramidou, E., Vasilopoulou, D. *et al.* (2012) Acute effects of using an electronic nicotine-delivery device (e-cigarette) on myocardial function: comparison with the effects of regular cigarettes. *Eur Heart J* 33(Abstract Supplement): 203.

Farsalinos, K., Tsiapras, D., Kyrzopoulos, S., Stefopoulos, C., Spyrou, A., Tsakalou, M. *et al.* (2013f) Immediate effects of electronic cigarette use on coronary circulation and blood carboxyhemoglobin levels: comparison with cigarette smoking. *Eur Heart J* 34(Abstract Supplement): 13.

Flouris, A., Chorti, M., Poulianiti, K., Jamurtas, A., Kostikas, K., Tzatzarakis, M. *et al.* (2013) Acute impact of active and passive electronic cigarette smoking on serum cotinine and lung function. *Inhal Toxicol* 25: 91–101.

Flouris, A., Poulianiti, K., Chorti, M., Jamurtas, A., Kouretas, D., Owolabi, E. *et al.* (2012) Acute effects of electronic and tobacco cigarette smoking on complete blood count. *Food Chem Toxicol* 50: 3600–3603.

Food and Drug Administration (2009) FDA and Public health experts warn about electronic cigarettes.

Available at: http://www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/ucm173222.htm (Accessed: 20 November 2013).

Gennimata, S., Palamidas, A., Kaltsakas, G., Tsikrika, S., Vakali, S., Gratziou, C. *et al.* (2012) Acute effect of e-cigarette on pulmonary function in healthy subjects and smokers. Presented at the European Respiratory Society's Annual Congress, Poster P1053. Available at: https://www.ersnetsecure.org/public/prg_congres.abstract?ww_i_presentation=59718 (Accessed: 20 November 2013).

Goniewicz, M., Knysak, J., Gawron, M., Kosmider, L., Sobczak, A., Kurek, J. *et al.* (2013) Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. *Tob Control.* DOI: 10.1136/tobaccocontrol-2012-050859. (Published online: 6 March 2013).

Greenland, S., Satterfield, M. and Lanes, S. (1998) A meta-analysis to assess the incidence of adverse effects associated with the transdermal nicotine patch. *Drug Safety* 18: 297–308.

Guillem, K., Vouillac, C., Azar, M., Parsons, L., Koob, G., Cador, M. *et al.* (2005) Monoamine oxidase inhibition dramatically increases the motivation to self-administer nicotine in rats. *J Neurosci* 25: 8593–8600.

Guslandi, M. (1999) Nicotine treatment for ulcerative colitis. *Br J Clin Pharmacol* 48: 481–484.

Hadwiger, M., Trehy, M., Ye, W., Moore, T., Allgire, J. and Westenberger, B. (2010) Identification of amino-tadalafil and rimonabant in electronic cigarette products using high pressure liquid chromatography with diode array and tandem mass spectrometric detection. *J Chromatogr A* 1217: 7547–7555.

Hajek, P., Jarvis, M., Belcher, M., Sutherland, G. and Feyerabend, C. (1989) Effect of smoke-free cigarettes on 24 h cigarette withdrawal: a double-blind placebo-controlled study. *Psychopharmacology (Berl)* 97: 99–102.

Hubbard, R., Lewis, S., Smith, C., Godfrey, C., Smeeth, L., Farrington, P. *et al.* (2005) Use of nicotine replacement therapy and the risk of acute myocardial infarction, stroke, and death. *Tob Control* 14: 416–421.

Kim, H. and Shin, H. (2013) Determination of tobacco-specific nitrosamines in replacement liquids of electronic cigarettes by liquid chromatography-tandem mass spectrometry. *J Chromatogr A* 1291: 48–55.

King, B., Alam, S., Promoff, G., Arrazola, R. and Dube, S. (2013) Awareness and ever use of electronic cigarettes among US adults, 2010–2011. *Nicotine Tob Res* 15(9): 1623–1627.

Laugesen, M. (2008) Safety Report on the Ruyan® e-cigarette Cartridge and Inhaled Aerosol. Available at: http://www.healthnz.co.nz/RuyanCartridgeReport30-Oct-08.pdf (Accessed: 18 November 2013).

Laugesen, M. (2009). Ruyan®E-cigarette Bench-top tests. Society for Research on Nicotine and Tobacco (SRNT) Dublin, Poster 5-11. Available at: http://www.healthnz.co.nz/DublinEcigBenchtopHandout.pdf [accessed 20 November 2013].

Le Houezec, J., McNeill, A. and Britton, J. (2011) Tobacco, nicotine and harm reduction. *Drug Alcohol Rev* 30: 119–123.

Lee, S., Grana, R. and Glantz, S. (2013) Electronic cigarette use among Korean adolescents: a cross-sectional study of market penetration, dual use, and relationship to quit attempts and former smoking. *J Adolesc Health*. DOI: 10.1016/j.jadohealth.2013.11.003. (Published online: 22 November 2013).

Lotfipour, S., Arnold, M., Hogenkamp, D., Gee, K., Belluzzi, J. and Leslie, F. (2011) The monoamine oxidase (MAO) inhibitor tranylcypromine enhances nicotine self-administration in rats through a mechanism independent of MAO inhibition. *Neuropharmacology* 61: 95–104.

Lúdvíksdóttir, D., Blöndal, T., Franzon, M., Gudmundsson, T. and Säwe, U. (1999) Effects of nicotine nasal spray on atherogenic and thrombogenic factors during smoking cessation. *J Intern Med* 246: 61–66.

Mayer, B. (2013). How much nicotine kills a human? Tracing back the generally accepted lethal dose to dubious self-experiments in the nineteenth century. *Arch Toxicol* 88: 5–7.

Mayers, M. (2009) FDA acts to protect public health from electronic cigarettes. Campaign for Tobacco-Free Kids statement. Available at: http://www.tobaccofreekids.org/press_releases/post/id_1166 (Accessed: 20 November 2013).

McAuley, T., Hopke, P., Zhao, J. and Babaian, S. (2012) Comparison of the effects of e-cigarette vapor and cigarette smoke on indoor air quality. *Inhal Toxicol* 24: 850–857.

McCauley, L., Markin, C. and Hosmer, D. (2012) An unexpected consequence of electronic cigarette use. *Chest* 141(4): 1110–1113.

McClernon, F., Hiott, F., Westman, E., Rose, J. and Levin, E. (2006) Transdermal nicotine attenuates depression symptoms in nonsmokers: a double-blind, placebo-controlled trial. *Psychopharmacology (Berl)* 189: 125–133.

MHRA Commission on human medicines, Working Group on nicotine containing products (NCPS) (2013). Current use of electronic cigarettes. Available

at: http://www.mhra.gov.uk/home/groups/comms-ic/documents/websiteresources/con286845.pdf (Accessed: 20 November 2013).

Moore, D., Aveyard, P., Connock, M., Wang, D., Fry-Smith, A. and Barton, P. (2009) Effectiveness and safety of nicotine replacement therapy assisted reduction to stop smoking: systematic review and meta-analysis. *BMJ* 338: b1024.

Murray, R., Bailey, W., Daniels, K., Bjornson, W., Kurnow, K., Connett, J. *et al.* (1996) Safety of nicotine polacrilex gum used by 3,094 participants in the Lung Health Study. Lung Health Study Research Group. *Chest* 109: 438–445.

National Association of Attorneys General (2013) FDA regulation on E-cigarettes. Available at: http://www.naag.org/assets/files/pdf/E%20Cigarette%20Final%20Letter%20(5)(1).pdf (Accessed: 20 November 2013).

Nides, M., Leischow, S., Bhatter, M. and Simmons, M. (2014) Nicotine blood levels and short-term smoking reduction with an electronic nicotine delivery system. *Am J Health Behav* 38: 265–274.

Nielsen, S., Franklin, G., Longstreth, W., Swanson, P. and Checkoway, H. (2013) Nicotine from edible Solanaceae and risk of Parkinson disease. *Ann Neurol* 74: 472–477.

Nitenberg, A. and Antony, I. (1999) Effects of nicotine gum on coronary vasomotor responses during sympathetic stimulation in patients with coronary artery stenosis. *J Cardiovasc Pharmacol* 34: 694–699.

Palamidas, A., Gennimata, S., Kaltsakas, G., Tsikrika, S., Vakali, S., Gratziou, C. *et al.* (2013) Acute effect of an e-cigarette with and without nicotine on lung function. Presented at the European Respiratory Society's Annual Congress, Poster P1054. Available at: http://www.ersnet.org/learning_resources_player/abstract_print_13/files/100.pdf (Accessed: 20 November 2013).

Pellegrino, R., Tinghino, B., Mangiaracina, G., Marani, A., Vitali, M., Protano, C. *et al.* (2012) Electronic cigarettes: an evaluation of exposure to chemicals and fine particulate matter (PM). *Ann Ig* 24: 279–288.

Peters, A. (2005) Particulate matter and heart disease: evidence from epidemiological studies. *Toxicol Appl Pharmacol* 207: 477–482.

Polosa, R. and Caponnetto, P. (2013) Time for evidence-based e-cigarette regulation. *Lancet Oncol* 14: 582–583.

Polosa, R., Caponnetto, P., Morjaria, J., Papale, G., Campagna, D. and Russo, C. (2011) Effect of an electronic nicotine delivery device (e-Cigarette) on smoking reduction and cessation: a prospective 6-month pilot study. *BMC Public Health* 11: 786.

Polosa, R., Morjaria, J., Caponnetto, P., Campagna, D., Russo, C., Alamo, A. *et al.* (2013a) Effectiveness and tolerability of electronic cigarette in real-life: a 24-month prospective observational study. *Intern Emerg Med.* DOI: 10.1007/s11739-013-0977-z (Published online: July 2013).

Polosa, R., Rodu, B., Caponnetto, P., Maglia, M. and Raciti, C. (2013b) A fresh look at tobacco harm reduction: the case for the electronic cigarette. *Harm Reduct J* 10: 19.

Pryor, W. and Stone, K. (1993) Oxidants in cigarette smoke: radicals, hydrogen peroxide, peroxynitrate, and peroxynitrite. *Ann NY Acad Sci* 686: 12–28.

Ravindra, K., Wauters, E. and Van Grieken, R. (2008) Variation in particulate PAHs levels and their relation with the transboundary movement of the air masses. *Sci Total Environ* 396: 100–110.

Renne, R., Wehner, A., Greenspan, B., Deford, H., Ragan, H., Westenberg, R. *et al.* (1992) 2-Week and 13-Week Inhalation Studies of Aerosolized Glycerol in Rats. *Inhal Toxicol* 4: 95–111.

Riess, U., Tegtbur, U., Fauck, C., Fuhrmann, F., Markewitz, D. and Salthammer, T. (2010) Experimental setup and analytical methods for the non-invasive determination of volatile organic compounds, formaldehyde and NOx in exhaled human breath. *Anal Chim Acta* 669: 53–62.

Rigotti, N., Pipe, A., Benowitz, N., Arteaga, C., Garza, D. and Tonstad, S. (2010) Efficacy and safety of varenicline for smoking cessation in patients with cardiovascular disease: A randomized trial. *Circulation* 121: 221–229.

Robertson, O., Loosli, C., Puck, T., Wise, H., Lemon, H. and Lester, W. Jr (1947) Tests for the chronic toxicity of propylene glycol and triethylene glycol on monkeys and rats by vapor inhalation and oral administration. *J Pharmacol Exp Ther* 91: 52–76.

Rodu, B. and Godshall, W. (2006) Tobacco harm reduction: An alternative cessation strategy for inveterate smokers. *Harm Reduct J* 3: 37.

Romagna, G., Allifranchini, E., Bocchietto, E., Todeschi, S., Esposito, M. and Farsalinos, K. (2013) Cytotoxicity evaluation of electronic cigarette vapor extract on cultured mammalian fibroblasts (ClearStream-LIFE): comparison with tobacco cigarette smoke extract. *Inhal Toxicol* 25: 354–361.

Romagna, G., Zabarini, L., Barbiero, L., Bocchietto, E., Todeschi, S., Caravati, E. *et al.* (2012) Characterization of chemicals released to the environment by electronic cigarettes use (ClearStream-Air project): is passive vaping a reality?

SRNT Europe Annual Congress, Helsinki, Finland. Poster RRP18. Available at: http://www.srnteurope.org/assets/srnt-e2012abstractbook.pdf [accessed 20 November 2013].

Rose, J. (2006) Nicotine and nonnicotine factors in cigarette addiction. *Psychopharmacology (Berl)* 184: 274–285.

Rose, J. and Levin, E. (1991) Inter-relationships between conditioned and primary reinforcement in the maintenance of cigarette smoking. *Br J Addict* 86: 605–609.

Russell, M. (1991) The future of nicotine replacement. *Br J Addict* 86: 653–658.

Sahakian, B., Jones, G., Levy, R., Gray, J. and Warburton, D.(1989) The effects of nicotine on attention, information processing, and short-term memory in patients with dementia of the Alzheimer type. *Br J Psychiatry* 154: 797–800.

Saitta, D., Ferro, G. and Polosa, R. (2014) Achieving appropriate regulations for electronic cigarettes. *Ther Adv Chronic Dis* 3 February 2014 (Epub ahead of print). DOI: 10.1177/2040622314521271

Schiller, J. and Ni, H. (2006) Cigarette smoking and smoking cessation among persons with chronic obstructive pulmonary disease. *Am J Health Promot* 20: 319–323.

Schober, W., Szendrei, K., Matzen, W., Osiander-Fuchs, H., Heitmann, D., Schettgen, T. *et al.* (2013) Use of electronic cigarettes (e-cigarettes) impairs indoor air quality and increases FeNO levels of e-cigarette consumers. *Int J Hyg Environ Health.* DOI: 10.1016/j.ijheh.2013.11.003. (Published online: 6 December 2013).

Schripp, T., Markewitz, D., Uhde, E. and Salthammer, T. (2013) Does e-cigarette consumption cause passive vaping? *Indoor Air* 23: 25–31.

Seaton, A., MacNee, W., Donaldson, K. and Godden, D. (1995) Particulate air pollution and acute health effects. *Lancet* 345: 176-178.

Stein, Y., Antal, M. and Jones, M. (1983) A study of the gas-phase pyrolysis of glycerol. *J Anal Appl Pyrol* 4: 283–296.

US Fire Administration (2012) Smoking-related Fires in residential buildings (2008-2010). Topical Fire Report Series 13. Available at: http://www.usfa.fema.gov/downloads/pdf/statistics/v13i6.pdf (Accessed: 20 November 2013).

US Pharmacopeia (2013) Elemental impurities limits. Available at: http://www.usp.org/sites/default/files/usp_pdf/EN/USPNF/key-issues/c232_final.pdf (Accessed: 20 November 2013).

Van Staden, S., Groenewald, M., Engelbrecht, R., Becker, P. and Hazelhurst, L. (2013) Carboxyhaemoglobin levels, health and lifestyle perceptions in smokers converting from tobacco cigarettes to electronic cigarettes. *S Afr Med J* 103: 865–868.

Vardavas, C., Anagnostopoulos, N., Kougias, M., Evangelopoulou, V., Connolly, G. and Behrakis, P. (2012) Short-term pulmonary effects of using an electronic cigarette: impact on respiratory flow resistance, impedance, and exhaled nitric oxide. *Chest* 141: 1400–1406.

Varughese, S., Teschke, K., Brauer, M., Chow, Y., van Netten, C. and Kennedy, S. (2005) Effects of theatrical smokes and fogs on respiratory health in the entertainment industry. *Am J Ind Med* 47: 411–418.

Werley, M., McDonald, P., Lilly, P., Kirkpatrick, D., Wallery, J., Byron, P. *et al.* (2011) Non-clinical safety and pharmacokinetic evaluations of propylene glycol aerosol in Sprague-Dawley rats and Beagle dogs. *Toxicology* 287: 76–90.

Westenberger, B. (2009) Evaluation of e-Cigarettes. St.Louis, MO: Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Division of Pharmaceutical Analysis. Available at: http://www.fda.gov/downloads/drugs/Scienceresearch/UCM173250.pdf (Accessed: November 10, 2013).

WHO-IARC (2004) IARC monographs on the evaluation of carcinogenic risks to humans. Volume 83, tobacco smoke and involuntary smoking. Available at: http://monographs.iarc.fr/ENG/Monographs/vol83/mono83.pdf. (Accessed: 20 November 2013).

Wieslander, G., Norbäck, D. and Lindgren, T. (2001) Experimental exposure to propylene glycol mist in aviation emergency training: acute ocular and respiratory effects. *Occup Environ Med* 58: 649–655.

Williams, M., Villarreal, A., Bozhilov, K., Lin, S. and Talbot, P. (2013) Metal and silicate particles including nanoparticles are present in electronic cigarette cartomizer fluid and aerosol. *PLoS One* 8: e57987.

World Health Organization (2013) Tobacco fact sheet No 339. Updated July 2013. Available at: http://www.who.int/mediacentre/factsheets/fs339/en/ (Accessed: 18 November 2013).

Woolf, K., Zabad, M., Post, J., McNitt, S., Williams, G. and Bisognano, J. (2012) Effect of nicotine replacement therapy on cardiovascular outcomes after acute coronary syndromes. *Am J Cardiol* 110: 968–970.

Yudkin, P., Hey, K., Roberts, S., Welch, S., Murphy, M. and Walton, R. (2003) Abstinence from smoking eight years after participation in randomised controlled trial of nicotine patch. *BMJ* 327: 28–29.

Zevin, S., Benowitz, N. and Jacob, P. (1998) Dose-related cardiovascular and endocrine effects of transdermal nicotine. *Clin Pharmacol Ther* 64: 87–95.

27. Etter J. F., Bullen C. A longitudinal study of electronic cigarette users. *Addict Behav* 2014; **39**: 491–4.
28. Vickerman K. A., Carpenter K. M., Altman T., Nash C. M., Zbikowski S. M. Use of electronic cigarettes among state tobacco cessation quitline callers. *Nicotine Tob Res* 2013; **15**: 1787–91.
29. Adkison S. E., O'Connor R. J., Bansal-Travers M., Hyland A., Borland R., Yong H.-H. *et al*. Electronic nicotine delivery systems: international tobacco control Four-Country Survey. *Am J Prev Med* 2013; **44**: 207–15.
30. Fidler J. A., Shahab L., West O., Jarvis M. J., McEwen A., Stapleton J. A. *et al*. 'The smoking toolkit study': a national study of smoking and smoking cessation in England. *BMC Public Health* 2011; **11**: 479.
31. Borland R., Partos T. R., Cummings K. M. Systematic biases in cross-sectional community studies may underestimate the effectiveness of stop-smoking medications. *Nicotine Tob Res* 2012; **14**: 1483–7.
32. Kotz D., Brown J., West R. Effectiveness of varenicline versus nicotine replacement therapy for smoking cessation with minimal professional support: evidence from an English population study. *Psychopharmacology (Berl)* 2014; **231**: 37–42.
33. Kotz D., Brown J., West R. 'Real-world' effectiveness of smoking cessation treatments: a population study. *Addiction* 2014; **109**: 491–9.
34. Brose L. S., West R., McDermott M. S., Fidler J. A., Croghan E., McEwen A. What makes for an effective stop-smoking service? *Thorax* 2011; **66**: 924–6.
35. Brose L. S., West R., Stapleton J. A. Comparison of the effectiveness of varenicline and combination nicotine replacement therapy for smoking cessation in clinical practice. *Mayo Clin Proc* 2013; **88**: 226–33.
36. Cahill K., Stead L. F., Lancaster T. Nicotine receptor partial agonists for smoking cessation. *Cochrane Database Syst Rev* 2012; **4**: CD006103.
37. Stead L. F., Lancaster T. Combined pharmacotherapy and behavioural interventions for smoking cessation. *Cochrane Database Syst Rev* 2012; **10**: CD008286.
38. Wong S. L., Shields M., Leatherdale S., Malaison E., Hammond D. Assessment of validity of self-reported smoking status. *Health Rep* 2012; **23**: 47–53.
39. Fidler J., Shahab L., West R. Strength of urges to smoke as a measure of severity of cigarette dependence: comparison with the Fagerström Test for Nicotine Dependence and its components. *Addiction* 2010; **106**: 631–8.
40. Fagerström K., Furberg H. A comparison of the Fagerström Test for Nicotine Dependence and smoking prevalence across countries. *Addiction* 2008; **103**: 841–5.
41. Pierce J. P., Gilpin E. A. Impact of over-the-counter sales on effectiveness of pharmaceutical aids for smoking cessation. *JAMA* 2002; **288**: 1260–4.
42. Lee C-w K. J. Factors associated with successful smoking cessation in the United States, 2000. *Am J Public Health* 2007; **97**: 1503–9.
43. Hagimoto A., Nakamura M., Morita T., Masui S., Oshima A. Smoking cessation patterns and predictors of quitting smoking among the Japanese general population: a 1-year follow-up study. *Addiction* 2010; **105**: 164–73.
44. Yang J., Hammond D., Driezen P., O'Connor R. J., Li Q., Yong H. H. *et al*. The use of cessation assistance among smokers from China: findings from the ITC China Survey. *BMC Public Health* 2011; **11**: 75.
45. Vangeli E., Stapleton J., Smit E. S., Borland R., West R. Predictors of attempts to stop smoking and their success in adult general population samples: a systematic review. *Addiction* 2011; **106**: 2110–21.
46. West R. The clinical significance of 'small' effects of smoking cessation treatments. *Addiction* 2007; **102**: 506–9.
47. Chapman S. Should electronic cigarettes be as freely available as tobacco cigarettes? No. *BMJ* 2013; **346**: 3840–1.
48. Brown J., West R. Smoking prevalence in England is below 20% for the first time in 80 years. *BMJ* 2014; **348**: 1378.
49. Wagener T. L., Siegel M., Borrelli B. Electronic cigarettes: achieving a balanced perspective. *Addiction* 2012; **107**: 1545–8.
50. Goniewicz M. L., Kuma T., Gawron M., Knysak J., Kosmider L. Nicotine levels in electronic cigarettes. *Nicotine Tob Res* 2013; **15**: 158–66.
51. Goniewicz M. L., Hajek P., McRobbie H. Nicotine content of electronic cigarettes, its release in vapour and its consistency across batches: regulatory implications. *Addiction* 2014; **109**: 500–7.
52. Etter J-F B. C. Saliva cotinine levels in users of electronic cigarettes. *Eur Respir J* 2011; **38**: 1219–20.
53. Bansal M. A., Cummings K. M., Hyland A., Giovino G. A. Stop-smoking medications: who uses them, who misuses them, and who is misinformed about them? *Nicotine Tob Res* 2004; **6**: S303–S10.
54. Etter J.-F. Levels of saliva cotinine in electronic cigarette users. *Addiction* 2014; **109**: 825–9.

