Review

Electronic Nicotine Delivery Systems
A review for clinicians

Michael Toumbis

6th Respiratory Dept., General Hospital of Chest Diseases "Sotiria", Athens, Greece

Key words:
- Electronic nicotine delivery systems,
- E-cigarettes,
- Epidemiology,
- Hazards and benefits

Correspondence:
Michael Toumbis, Pulmonologist, 6th Respiratory Dept., General Hospital of Chest Diseases, "Sotiria", 152 Mesogeion Ave, Athens, GR-115 27, Greece
E-mail: mtoumbis@gmail.com

ABSTRACT

The prevalence of the use of electronic nicotine delivery systems (ENDS) has increased rapidly in the past few years. In the absence of clear negative health messages, the decision of adults on whether or not to initiate ENDS use is influenced by various factors, including the pervasive promotion of ENDS as being effective in smoking cessation and a safe alternative to tobacco, which are unsubstantiated claims. The appeal of advertisements promoting ENDS as an enjoyable lifestyle choice and a high-tech product influences the choice of young people. Thus, the most common reasons for ENDS use in adults are its perceived safety and its efficacy as a cigarette cessation aid. Curiosity, flavors, and peer influence have been identified as the top reasons for ENDS use in adolescents and young people. Although ENDS are generally considered as a single product class, the systems constitute a diverse group with differences in the production and delivery of the various agents. The composition of the aerosol generated by ENDS depends on several factors, including, the electronic liquid constituents, the ENDS features, and user behavior. Currently available data indicate that ENDS aerosols are not harmless, especially with respect to body systems that are sensitive to various toxic effects. The literature on the effects of ENDS on the various body systems is sparse and marked by a lack of standardization in methods. The long-term effects of ENDS are as yet unknown. Studies of short-term exposure to ENDS aerosol document several biological and functional effects on the respiratory, cardiovascular, immune, and central nervous systems. At least under certain conditions, ENDS have been shown to deliver physiologically active quantities of nicotine, and can thus produce and/or maintain nicotine dependence. The current evidence is sufficient to justify cautioning pregnant women, women of reproductive age, children and adolescents about the hazards of ENDS use, because of the potential for fetal and adolescent nicotine exposure to have long-term consequences for brain development. Passive exposure to ENDS aerosol has not been well studied because ENDS are relatively

new products, but it is of concern, because of its potential adverse health effects for people who are involuntarily exposed. The majority of relevant studies concluded that passive exposure to ENDS aerosol may indeed pose a health risk. The evidence for the effectiveness of ENDS as a method for quitting or reducing tobacco smoking is limited and of low quality. Some studies demonstrated a significant relationship between ENDS use and increases in smoking cessation, while others found no association or a negative one. The findings of prospective studies on adolescent and young adult populations suggest that ENDS use is a clear and consistent indicator of the likelihood of subsequent initiation of cigarette and other combustible tobacco product use, at ages spanning from early adolescence through emerging adulthood.
Pneumon 2016, 29(4):1-28.

INTRODUCTION

The use of electronic nicotine delivery systems (ENDS) has increased rapidly in the past several years. With the increasing prevalence of ENDS use, there is growing discussion amongst public health organizations and the scientific community about its possible impact on tobacco control and public health. Among individuals there is strong debate about the public health benefits versus harms from ENDS use. The proponents argue that this is a novel product with the potential to accelerate the elimination of cigarette smoking. From this perspective, ENDS could represent an unprecedented opportunity to reduce the burden of tobacco-related death and disease on a massive scale. The opponents are concerned about minimizing unintended consequences, such as health hazards related to ENDS, dual use (ENDS and tobacco cigarette) that might undermine cigarette smoking cessation, and the possibility that ENDS will attract nonusers, including youth and former cigarette smokers[1-3].

This review presents the available recent literature on what ENDS are, survey data on use and awareness, the effects on the users and bystanders, and the utility of ENDS in helping smokers quit using tobacco.

PREVALENCE OF ENDS USE AMONG ADULTS

There are no data on ENDS use at the global level. However, several relevant surveys have been conducted in recent years. The most commonly reported prevalence measures are "ever use" (any ENDS use in an individual's lifetime) or "current use" (ENDS use in the 30 days before participating in a study). Although there are differences in the items explored and sampling methods, they document a clear trend towards increased awareness and use of ENDS.

Nationally representative samples of adults in the United States of America (USA) indicate that ENDS use prevalence is rising. Between 2010 and 2013, ever use of electronic cigarettes (ENDS) increased from 1.8% to 13%, while current use increased from 0.3% to about 4.1% ($p < 0.001$). Prevalence of use increased significantly across all demographic groups. In 2013, current use of an ENDS was highest among young adults aged 18-24 years (14.2%) and declined with age. Daily smokers (30.3%) and non-daily smokers (34.1%) were the most likely to use e-cigarettes currently, compared with former smokers (5.4%) and never-smokers (1.4%) ($p < 0.001$)[4-6].

In 2014, roughly the same prevalence of ever and current use of ENDS was found in a representative sample of civilian adults aged >18 years in the USA. It was estimated that 12.6% of adults had ever tried an ENDS, and about 3.7% currently used ENDS, with use differing by age, sex, race and origin. Current cigarette smokers (47.6%) and former smokers who had quit smoking within the past year (55.4%) were more likely to use ENDS than former smokers who had quit smoking over 1 year earlier (8.9%). and those who had never smoked (3.2%). Ever having used ENDS was highest among never smokers aged 18–24 (9.7%) and declined with age.

It appears that there has been an increase in the use of ENDS in the last years in Europe, also. According to Eurobarometer, which assessed the prevalence and determinants of ENDS use among persons aged ≥15 years in 27 European Union (EU) member countries only 7% of respondents had tried the products. The same survey conducted during 2014 showed that 12% of Europeans had used ENDS: 2% were currently using them and a further 3% had used them in the past but no longer did, while 7% had tried them in the past but never used them regularly[7]. Among those who reported that they had ever tried ENDS, 15.3% defined themselves as current users[8]. During 2014, ever ENDS use was reported by 31.1% of current smokers, 10.8% of former smokers and 2.3% of

never smokers. Extrapolated to the whole population, this means that approximately 48.5 million EU citizens were ever ENDS users[9]. Similar surveys have been conducted in several other countries around the world. The prevalence of current use among the adults of 7 countries ranged between 0.3% and 5.9% (mean 1.7%). Among current and former cigarette smokers, the mean prevalence of ever use of ENDS in 34 countries during 2010-2012 was reported to be around 17.5%, (range 1-34.3%), while the mean prevalence of current ENDS use in 5 countries was 2.75% (range 0.05-7%)[10].

PREVALENCE OF ENDS USE AMONG ADOLESCENTS

Epidemiological studies on the prevalence of ENDS use among adolescents (individuals aged 10-19 years old) are scarce. In the USA, nationally representative samples indicate that ENDS use has increased rapidly in recent years. According to data collected in 2011 and 2012, middle and high school students who reported being ever users increased from 3.1-3.2% to 6.5-6.8%, while current users increased from 0.6-1.8% to 2-2.8% over the year[11].

Substantial increases in ever and current ENDS use among middle and high school students were reported between 2011 and 2015. Current use of ENDS increased in middle school students from 0.6% to 5.3% (95%CI 4.6-6.2) and in high school students from 1.8% to 16% (95%CI 14.1-18). In 2015, it was estimated that 620,000 middle school students and 2,390,000 high school students were current ENDS users.[12,13]

The same trend is reported in several other parts of the world. During the period 2012-2014, among middle and high school students, adolescents and young adults, the mean prevalence of ever used ENDS ranged between 4.7% to 20% and of current use of ENDS ranged between 1.5% to 29.9%, according to various reports.[14,15]

PERCEPTIONS OF, AND REASONS FOR ENDS USE IN ADULTS

With an increasing prevalence of ENDS use being reported in multiple population groups, it is essential to understand what attracts people to this product. Initial research documented various reasons for using ENDS among smokers and current ENDS users. These reasons included: to reduce or quit smoking regular cigarettes, because ENDS are considered to be less harmful than tobacco; to protect the health of the social environment; to avoid smoking bans; because of the lower price; the better taste and smell of ENDS; out of curiosity; because the pleasure of the smoking process is mimicked by ENDS use[16-22].

Similar, but also different, reasons for using ENDS were revealed by a number of relevant quality research projects on ENDS use. In a large national study of USA adults aged 18 to >65 years (n=3,878) who had ever used ENDS, the most common reasons for trying were curiosity (53%), because a friend or family member used, gave, or offered ENDS (34%), and as an aid to quitting or reducing smoking (30%). Nearly two-thirds (65%) of people who started using ENDS later stopped using them. Discontinuation was more common among those whose main reason for trying was not goal-oriented (e.g., curiosity), in contrast to goal-oriented (e.g., quitting smoking) (81% *vs*. 45%, $p < 0.001$)[23].

In the International Tobacco Control (ITC) Netherlands survey, with 1,550 participants aged over 15 years, ENDS users reported using them mainly to reduce their smoking (79%) or because they considered ENDS to be less harmful than regular cigarettes (77.2%). Price was also clearly important, as a majority (61%) reported that they started to use ENDS because they considered them to be cheaper than regular cigarettes, and concerns about the price of cigarettes were similarly positively associated with trying ENDS. Less often, they mentioned the better taste of ENDS compared with regular cigarettes (18.1%).[24]

In a multi-module online concept mapping (CM) study with 108 adults, 11 interrelated components or clusters that characterized reasons for using ENDS were recognized. In decreasing order of mean participant ratings, the clusters were: method of smoking cessation, perceived health benefits, private regard, convenience, conscientiousness (i.e., setting a good example and being a leader for others), pleasurable effects, unanticipated benefits (regaining smell, taste), perceived agency, therapeutic effects (some reported calming effects, including promoting relaxation, nerve calming, stress reduction, or helping to clear the mind), hobby/interests, networking/social impacts. Importantly, reasons related to cessation methods, perceived health benefits, private regard, convenience and conscientiousness were rated significantly higher than other categories/types of reasons related to ENDS use ($p < 0.05$)[25].

Assuming that ENDS users report using flavors in their devices solely because of the taste, may ignore other important roles that flavors may play in ENDS use. For example, in a study of 46 adult ENDS users, five broad

thematic clusters of statements were ranked as reasons for using flavored liquid in their devices, namely increased satisfaction/enjoyment, better feel/taste than cigarettes, variety/customization, food craving suppression, and social impact. Statements in the first two clusters were rated significantly higher than statements from the other clusters ($p < 0.05$). Some statements indicated that flavors were perceived as masking agents for nicotine or other unpleasant tastes associated with cigarette smoking, making ENDS use more palatable. Thus, the statements generated in this study indicate that flavorings make ENDS an appealing product for reasons other than just tasting pleasant[26].

Gender differences have been identified in the initiation and continuation of ENDS use. In a study of 1,815 adults (aged ≥18 years) males were found to be more likely to report initiating ENDS use to quit smoking because of health concerns, whereas females were more likely to base their decision on recommendations from family and friends. Regarding maintenance of ENDS use, males reported higher attribution related to positive reinforcement (enjoyment), while females reported higher negative reinforcement (stress reduction or mood management). Males reported more positive expectations from ENDS, including taste, social facilitation, and energy, whereas women rated ENDS higher for weight control. These findings parallel previously established gender differences in cigarette use and expectations from smoking[27].

It is apparent that the motivation for ENDS use is not based solely on perceived safety and efficacy as a cessation aid, but that ENDS are devices that are used for a variety of reasons.

PERCEPTIONS AND REASONS FOR ENDS USE IN ADOLESCENTS AND YOUNG ADULTS

There is a great concern about the potential for initiation and continued use of ENDS by young people, especially those who are not current traditional cigarette smokers. In initial findings, quitting smoking does not appear to be a primary reason for ENDS use in this group. Curiosity, flavors, and peer influence were identified as top reasons for ENDS use in 7 middle schools, high schools, and colleges in Connecticut[28]. Enjoyment was the primary reason for using ENDS among undergraduates at 4 colleges in New York State[29]. In a USA national study of teen flavored tobacco use, the primary reason for ENDS use was flavoring, followed closely by the perception of ENDS doing less harm than cigarettes[30].

Curiosity was identified as one of the leading reasons for adolescents to try ENDS[28]. In a nationally representative sample of 22,007 USA students attending public and private schools in grades 6–12 (age range 9 to 19 years), among students who had never used ENDS, "high curiosity" was reported by 13.4% and "some curiosity" by 12.4%, while 74.1% reported no curiosity about ENDS. High school students displayed higher levels of curiosity than middle school students. Greater curiosity was observed among those with a lower perception of harm from these products and those who had previously tried a combustible tobacco product. Thus, one-quarter of middle and high school students who had never used ENDS were curious about the products, with curiosity being greater among those with a lower perception of harm from these products. These findings underscore the importance of continued efforts to assess factors that influence curiosity about ENDS[31].

In a nationally representative, cross-sectional USA survey on 4,066 students in the 8th, 10th, and 12th grades (age range 15 to 19 years), the more common reasons for ever using ENDS were experimentation (53%), taste (37.2%), boredom (23.5%), having a good time (22.4%), and relaxation (21.6%). Reasons associated with quitting or reducing regular cigarette use were not commonly found among that group of adolescents, echoing other research findings[28]. Adolescents who had ever used regular cigarettes were more likely than never smokers to report almost all reasons for ENDS use, but quitting smoking was among their least common reasons. Adolescents who used ENDS frequently reported taste as a primary reason[32].

In a study examining the reasons of adolescents and young adults for ENDS experimentation and discontinuation in middle school, high school and college students in Connecticut, the top reasons for experimentation were curiosity (54.4%), appealing flavors (43.8%) and peer influence (31.6%), and the top reasons for discontinuation were responses related to losing interest (23.6%), perceiving ENDS as "uncool" (16.3%), and health concerns (12.1%). Availability of flavors was thus the second most endorsed reason, following curiosity for experimentation. School level differences showed that flavors are particularly important to high school students. This finding confirms that appealing ENDS flavors (e.g., candy) are particularly attractive to adolescents[28].

Generally, flavor is one of several significant product appeal factors that influence willingness to try ENDS. More than 8,000 ENDS flavors are available in the market[33]. Certain flavors, such as fruit and confectionary or candy-like

aromas, appeal to children, younger never-smokers and young ENDS beginners, and may therefore play a role in motivating experimentation in this group.[30,34-38]

One possible source of curiosity of adolescents and young people about ENDS is exposure to advertising. Research suggests that prior exposure to tobacco marketing is associated with curiosity and future tobacco use among adolescents[37]. A review of longitudinal studies on adolescents aged 18 years or younger revealed that subjects who were more aware of, or receptive to, tobacco advertising were more likely to have experimented or become smokers at follow-up[38]. This phenomenon may also apply to ENDS use.

ENDS PROMOTION

ENDS are being marketed to consumers in a variety of media and formats, including television commercials, sports and cultural sponsorship, celebrity endorsement, social networking, online advertising and point-of-sale displays.[39] Some forms of marketing clearly emulate the very successful tobacco advertising, asserting an independent identity and a lifestyle choice, aligning users with celebrities, fashionable and youthful places and exciting activities. Some ENDS are marketed as being not only socially acceptable but also socially superior[40]. Unsubstantiated claims of safety and smoking cessation are frequent marketing themes aimed specifically at smokers[41]. Current data indicate that spending on ENDS advertising has been increasing since 2011.[42,43] Relevant studies from the USA showed that ENDS advertising expenditure in magazines, television, newspapers, and the Internet grew from $6.4 million in 2011 to $60 million in 2013[44,45].

During the period 2011-2013, youth exposure to television ENDS advertisements increased 256%, and young adult exposure increased 321%[50]. YouTube is the most popular video sharing website in the world. A recent study assessing ENDS content on You Tube showed that among 196 unique videos found, 94% were "pro" ENDS, 4% were neutral, and only 2% were "anti" ENDS[40]. One of the most prevalent topics in the "pro" e-cigarette videos was the claim that ENDS constitute a safer and healthier alternative to conventional cigarettes, delivering the experience of smoking while eliminating the health risks associated with tobacco smoke. Another topic highlighted in the "pro" e-cigarette videos, attractive to smokers wanting to quit smoking, was the claim that ENDS can aid smoking cessation. Furthermore, ENDS were presented as enjoyable and socially acceptable products, produced in multiple flavors (e.g., chocolate, strawberry), colors and fancy packaging, and they are endorsed by famous actors and even fictional cartoon characters. All these characteristics are probably attractive to adolescents and young adults. The target audience was primarily young people in the USA, the UK and Canada, and "pro" e-cigarette videos were watched more frequently and rated much more favorably than "anti" videos.

Twitter appears to be an important marketing platform for ENDS. A study of tweets related to ENDS revealed them to be overwhelmingly commercial, and a substantial proportion mentioned smoking cessation.

An unquantified extent of ENDS advertising uses deceptive health claims and its targeting includes the youth sector[41-42,47-51].

In the absence of clear negative health messages about ENDS, it is likely that opinions about e-cigarettes, and consequently the decision of young people on whether or not to initiate ENDS use, are influenced by "selling" factors, including the pervasive marketing of ENDS through social media (e.g., YouTube and Twitter) as a "sexy" and safe alternative to tobacco cigarettes, the appeal of the "high tech" nature of ENDS, and the availability of many flavors (e.g., fruit and candy). These influences may also discourage ENDS cessation among young current users.

A study of college freshmen associated the appeal of ENDS advertisements with the intent to use them[52]. Data from the 2014 National Youth Tobacco Survey on 22,007 US middle and high school students were analyzed to examine the association between exposure to ENDS marketing and susceptibility to and use of ENDS[58]. Exposure to ENDS marketing, including internet, print, retail, and TV/movies, was significantly associated with an increased likelihood of ever and current use of ENDS among middle and high school students. Marketing exposure was also associated with susceptibility to the use of ENDS among current non-users. Multivariate models demonstrate that as the number of channels of ENDS marketing exposure increased, the likelihood of use and susceptibility also increased. These findings suggest that young people who are exposed to ENDS marketing via multiple channels are more likely to use ENDS.

Overall, unsubstantiated claims of safety and smoking cessation are frequent themes in ENDS marketing. Furthermore, ENDS are advertised as enjoyable and socially acceptable products. Promotion of ENDS may influence the decision of adults and young people to use them for a variety of reasons. Regulations recently approved in the

USA and the EU – the main ENDS markets in size – are expected to limit or impede ENDS promotion.[54,55]

ENDS AND THEIR FEATURES

ENDS, of which e-cigarettes are the prototype, deliver an aerosol by heating a solution, also called electronic liquid (e-liquid), which users inhale. Each device includes a battery, a reservoir that contains the e-liquid, and an aerosolization chamber with a heating element. Although they are generally considered as a single product class, these systems constitute a diverse group with potentially significant differences in the production of toxicants and delivery of nicotine. The design of ENDS devices was originally based on the format of conventional cigarettes, but it has since evolved, with later-generation devices permitting users to refill a single device with different liquids and to customize the heating element. They were shaped to look like their conventional tobacco counterparts, e.g., cigarettes, cigars, cigarillos, pipes, or hookahs. Later versions take the form of everyday items, such as pens and USB memory sticks, or are larger cylindrical or rectangular devices.[56,57]

The devices are classified into 4 generations or models, with substantial differences, such as the way in which the solution is stored, the method of heater activation, the electrical power flowing through the heater, and the overall appearance. The first generation (G1) of ENDS devices are roughly the same size as regular tobacco cigarettes. They are not rechargeable or refillable and are intended to be discarded after product stops producing aerosol. Second generation ENDS devices (G2) usually look like pens or laser pointers, and they are considerably larger than those of first generation. They may contain a prefilled or refillable cartridge and often come with a manual switch allowing regulation of the length and frequency of puffs. Third generation ENDS devices (G3), called 'tank-like', come in many different sizes and shapes, are considerably larger than the earlier models and have mechanical or regulated modifications ("mod"). Mechanical mods have no electronic circuit and feature only a fire button, a battery compartment and a connector. Regulated mods are more complex, incorporating control hardware by which the user can modify the voltage and/or wattage. The most recent, advanced and innovative devices belong to the fourth generation of ENDS (G4). Their mods have the possibility to adjust voltage/wattage, to control the temperature, to handle very low ohm builds, and to adjust airflow. These devices can be classified into closed and open systems. Closed systems are those that are not refillable or rechargeable, while the remaining devices belong to the open systems.[58,59]

ENDS solutions (e-liquids)

E-liquids generally consist of nicotine, solvents and humectants, usually propylene glycol (PG), vegetable glycerin (VG), or a mixture of these, and one or more flavorings. The concentration of nicotine ranges from 0 to 36 mg/ml. Some solutions are labeled with low, medium, or high nicotine levels, without standard definitions for these categories[60]. The actual concentration may differ from the product labeling; in some instances, trace amounts of nicotine have been detected in e-liquids advertised as containing 0 mg/ml of nicotine[61].

Because the nicotine in e-liquids is derived from the tobacco plant, the liquid may contain other tobacco related toxicants, such as tobacco-specific nitrosamines (TSNAs) that are known carcinogens[62]. In several studies TSNAs have been found in the liquid and the aerosol produced when the heater is activated, but at much lower levels than in tobacco cigarettes[63].

It is of note that more than 8,000 flavorings are available in the ENDS market[33]. Humectants, along with many of the flavorings in e-liquids, are commonly used as food additives and are considered to be safe for oral ingestion, but data on the safety of long-term inhalation of these substances are very limited.

Analysis of commercially available e-liquids and aerosols by gas or liquid chromatography and mass spectroscopy has identified constituents other than the above ingredients. Acetone, acrolein, 1,3 butadiene, clyclohexane, diethylene glycol, ethylene glycol, ethanol, formaldehyde and tobacco alkaloids are some of the additional compounds detected in ENDS products[64]. These constituents were generally found in concentrations lower than those associated with toxicity in foods or oral pharmaceuticals, although some were at levels high enough to raise concerns about safety[65].

The composition of the aerosol generated by ENDS depends on several factors, including the e-liquid constituents, the electrical characteristics of the heating element, the temperature reached, the characteristics of the wick and the puffing topography.

ENDS AEROSOL

The ENDS aerosolization process involves heat gen-

erated by an electric current as it flows through a wire that surrounds a wick saturated with liquid. The high temperature of the liquid at the heating element is followed by rapid cooling to form an aerosol, which is inhaled directly by the user through a mouthpiece. The process of aerosolization is thus fundamentally different from the combustion of tobacco, and consequently the composition of the ENDS aerosol is quite different from that of tobacco cigarette smoke. In general, the e-liquid constituents, features of the ENDS device, puff topography and user experience all impact aerosol yield and delivery to the users.

The impact of e-liquid constituents on aerosol yield

The concentration of nicotine in e-liquid appears to directly affect its yield in the resulting aerosol and several, but not all studies, have shown a positive relationship between the nicotine concentration in the e-liquid and the nicotine yield[66,67]. The presence of nicotyrine in the e-liquid may increase nicotine delivery in ENDS users[68].

The creation of the aerosol can be affected by the boiling point of PG (188ºC) and VG (290º C). The boiling point of VG requires the element to reach a higher temperature, which may influence toxicant emissions. In addition, VG yields larger particles than PG, and the distribution of these particles in the lung is not affected by the presence of nicotine or flavors[69].

PG, on the other hand, yields higher amounts of aldehydes[70]. The levels of carbonyl compounds in ENDS vapors are strongly affected by product characteristics, including the type of nicotine solvent and battery voltage. The highest levels of carbonyls have been observed in vapors generated from PG-based solutions[71]. Furthermore, it has been found that a PV/VG mixture produced more ROS than either one alone[72]. Flavorants in e-liquid also contribute to the aerosol constituent yield, but there have been no systematic studies addressing this issue.

The impact of ENDS features on aerosol yield

ENDS are activated by batteries with several voltages ranging from 3 to 6 V, and the resistances of the heating element range from 1.0 to 6.5 Ohms. The heating element is usually made from nichrome wire (80% nickel, 20% chrome) but may be made from Kanthal (iron, chromium 20-30%, aluminum 4-8%) or ceramic. The number of heating elements influences the net resistance. Together voltage and resistance determine the power output ($P=V^2/R$ in Watts), which affects the yield and content of ENDS aerosols[73]. The power can thus be raised by increasing the battery voltage or by lowering the heating element resistance, to increase the nicotine yield. For example, a 2.5-fold increase in power achieved by increasing the voltage was shown to result in 4 to 5-fold increases in nicotine yield[73]. A recent study demonstrated that some 3.3-V ENDS paired with relatively low-resistance heating elements (i.e., 1.5V), used with 36 mg/ml liquid nicotine, can result in plasma nicotine concentrations after 10 puffs higher than those usually recorded in combustible tobacco cigarette smokers under similar conditions[74].

The average ISO nicotine yield for a single traditional cigarette ranges from 0.5 to 1.5 mg/cigarette. While machine-smoked ENDS nicotine yields are not directly comparable with those from traditional cigarettes, several studies found that the ENDS nicotine yield is much lower (more than 50%), than that of traditional cigarettes, but with high variability of nicotine delivery among ENDS brands and smoking methods[75-79]. Several studies have demonstrated that some models of ENDS deliver very little, while others can deliver at least as much nicotine as a combustible tobacco cigarette[80-83].

In one study, exhaled CO (eCO), cotinine levels, plasma nicotine concentration and liquid consumption were measured in 30 participants (10 smokers, 9 G2 and 11 G3 ENDS users). In the smokers respectively 4 and 7 times higher levels of eCO were recorded than in G2 or G3 users ($p<0.0001$), and during the vaping session, G3 users achieved significantly higher plasma nicotine concentrations than G2 users[84].

The aerosolization process occurs at various temperature ranges. It has been estimated that the theoretical vaporization temperature of the heating element may reach up to 350ºC[85], which is sufficiently high to induce physical changes in e-liquids and chemical reactions between the constituents of e-liquids. Both VG and PG have been shown to decompose at high temperatures, generating low molecular weight carbonyl compounds with established toxic properties (e.g., formaldehyde, acetaldehyde, acrolein, and acetone). It has been found that if e-liquid is dripped directly onto the heating element the concentration of aldehyde in the resulted aerosol is equal to or higher than that of tobacco cigarettes, due to the higher temperature of the element.[86] In a systematic study of this effect, increases in voltage from 3.2 to 4.8 resulted in 4- to 200-fold increases in formaldehyde, acetaldehyde and acetone yield in the vapor[70]. The levels of formaldehyde in the aerosol from high-voltage devices were in the range of levels reported in tobacco smoke (1.6–52 μg/cigarette)[88].

These findings suggest that under certain conditions ENDS might expose users to the same or even higher levels of carcinogenic formaldehyde than tobacco smoke.

The impact of puffing topography on aerosol yield

The user's puffing behavior may have significant effects on the production and delivery of the aerosol. The parameters of puff topography are mainly the puff duration, the puff number, the puff volume and velocity, and the inter-puff interval. In a study on puff topography it was found that puff duration varied significantly among ENDS users, ranging between 1.9 and 8.3s and that the mean puff duration was significantly longer in ENDS users (4.3±1.5s) than in conventional cigarette smokers (2.4±0.8s)[89]. Similar results were documented in a subsequent video study with 80 individuals using a G2 device[79]. When the combined influence of puff duration and velocity on nicotine yield in aerosol was examined[90] it was found that ENDS users with longer puffs produced higher nicotine yields than tobacco smokers with shorter puffs, while puff velocity had no effect on nicotine yield. Combining these puffing topography findings, ENDS users appear to be characterized by longer puff duration and lower inhalation compared with conventional tobacco smokers. These characteristics result in greater delivery of nicotine, and perhaps of other toxicants. While a faster, deeper puff increases the delivery of nicotine and other constituents in tobacco smokers, it may diminish the delivery from ENDS, due to cooling of the heating element, and a longer puff duration may be more effective.

The impact of user experience and behavior on aerosol constituent

Studies in inexperienced users suggest that ENDS deliver modest amounts of nicotine[91-94], while in contrast, recent studies in experienced and current ENDS users showed that such ENDS users may achieve systemic nicotine concentrations akin to those of traditional cigarettes smokers. Furthermore, these studies suggest that ENDS use may support dependence behaviors in the experienced user[95-97].

Aerosol constituents of commercially available ENDS

The constituents of the aerosol generated by ENDS and inhaled by the user are more directly related to health than are the ingredients of e-liquids. Most ENDS products have not been tested by independent scientists, but the limited testing that has been made has revealed wide variations in the nature of the toxicity of liquid contents and the derived emissions[57].

Analysis of commercially available ENDS aerosols by gas or liquid chromatography and mass spectroscopy has confirmed the presence of the listed ingredients such as VG, PG and nicotine, but has also revealed several other compounds, including acetaldehyde, acetone, acrolein, formaldehyde, N'-nitrosonornicotine (NNN), 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (NNK), certain metals (cadmium, lead, nickel, tin, copper), and toluene[98-103].

As described above, the concentration of the various constituents in the ENDS aerosol depends on several factors and under certain conditions it can be equal to or even higher than that in tobacco smoke. The nicotine contained in the aerosol from 13 puffs of an ENDS with e-liquid containing 18 mg/ml nicotine has been estimated to be equivalent to the amount in the smoke of a typical tobacco cigarette, which contains approximately 0.5 mg of nicotine. The concentration of formaldehyde inhaled in mainstream ENDS aerosol has been estimated to be approximately 400 μg/m^3 in a typical G2 ENDS. This is greater than the 30-minute short-term average limit for continuous exposure that was established to prevent sensory irritation in the general population[98]. Although the concentration of carbonyl compounds found in ENDS aerosol is substantially lower than that in tobacco cigarette smoke, it increases when the voltage used to generate the aerosol is raised. For example, the levels of formaldehyde in aerosol from high-voltage devices were found to be in the range reported in tobacco smoke (i.e., 1.6–52 μg/cigarette).[104] Increases in voltage from 3.2 to 4.8 have been shown to result in a 4- to 200-fold increase in formaldehyde, acetaldehyde and acetone yield[105]. A laboratory study showed that ENDS aerosol and tobacco cigarette smoke contain similar amounts of reactive oxygen species and that the size of the particles distributed in ENDS aerosol was in the respirable range that leads to small-airway or alveolar deposition, with a mass median aerodynamic diameter of 1.03 μm[102].

The presence of chromium, nickel, and lead, and also tin, silver, and aluminum, have been reported in ENDS aerosol, including metal nanoparticles. Lead and chromium concentrations were within the range found in the smoke from conventional cigarettes, while nickel was 2 to 100 times higher in ENDS aerosol than in Marlboro brand cigarette smoke[101]. Inhaled lead has adverse health effects and elemental chromium is a respiratory irritant, while the hexavalent chromium that could be

formed during high temperature oxidation is a known human carcinogen[106].

Aerosol particle size is a critical parameter that defines the delivery of toxicants to the human respiratory system, determining both the delivery and the deposition efficiency in each region of the respiratory tract. It is also well known that inhaled nanoparticles and submicron particles may be deposited efficiently by diffusion in all regions of the respiratory tract.[107,108]

Information on ENDS aerosol particle size is sparse and insufficient for definitive conclusions to be drawn. In several studies the particle size distribution, and the number of particles delivered by ENDS were observed to be similar to those of conventional cigarettes, with most particles in the ultrafine range (≈100–200 nm).

A study using real-time measurement of ENDS aerosol size showed bimodal behavior, with comparable concentrations of nanoparticles (11-25 nm count median diameter) and submicron particles (96-175 nm count median diameter). The authors assumed that the nanoparticles contain metals (and/or metal oxides), and other unknown chemicals of low volatility [101,109-112.]

Overall, investigation of potentially toxic substances in ENDS aerosol has shown that a number of such substances are present, including some known or suspected carcinogens. There is a large degree of variability in user exposure to these aerosol constituents across ENDS devices, e-liquids, and patterns of ENDS use.

HEALTH RISKS AND EFFECTS ON ENDS USERS

The literature regarding the effects of ENDS on the various body systems is sparse and marked by a lack of standardization in methods. Health risks are usually assessed using *in vitro* methods, and observation of short- and long-term exposure of animals and humans to ENDS aerosols. Based mainly on the levels and number of toxicants produced during the typical use of ENDS, it is very likely that ENDS aerosols are less toxic than cigarette smoke[113].

There has not yet been enough research, however, to quantify the relative risk of ENDS over combustible products. No specific figure about how much "safer" the use of these products is compared to smoking can be given any scientific credibility at this time. On the other hand, ENDS are unlikely to be harmless. There are already some indications that ENDS aerosols are not benign, especially with respect to body systems that are sensitive to various toxicant effects.

Effects of ENDS use on the respiratory system

In laboratory studies on the exposure of cultured cells to ENDS aerosols, the methods involve exploration of the air-liquid interface (ALI) or the solution of aerosol in the culture media[114]. To date, only one study has been published that used primary human airway epithelial cells, exposed to ENDS aerosol by the ALI method. The exposure did not result in cytotoxicity or decrease in epithelial barrier activity as assessed by transepithelial electrical resistance (TEER), in contrast to exposure to whole cigarette smoke, which had toxic effects[115].

Two studies using CL-1548 and A549 bronchial epithelial cell lines to evaluate cell viability and pro-inflammatory cytokine release concluded that ENDS aerosol was markedly less toxic than tobacco smoke[116,117]. In addition, study of the effect of ENDS and cigarette aerosol at different concentrations in the culture medium of cultured mouse fibroblast cells for 24 h, demonstrated that the ENDS aerosols were less toxic to cell viability than that of cigarettes[118]. In response to treatment with several e-liquids, human lung fibroblasts exhibited stress and morphological changes, and secreted high levels of interleukin (IL)-8, while in response to a cinnamon flavored e-liquid, they showed loss of cell viability and secreted increased IL-8[119]. In two studies using non-differentiated primary airway epithelial cells, exposure to ENDS aerosol resulted in reduced viability and increased oxidative stress[120,121]. In another study, exposure to ENDS aerosol of the airway epithelial tumor cell line NCIH292 caused increased production of IL-6 and IL-8[119].

In the immortalized bronchial epithelial cell line BEAS2B, an aqueous ENDS aerosol extract caused protein aggregation due to inhibition of autophagy, resulting in oxidative stress, apoptosis and senescence. This mechanism is believed to contribute to the development and progression of chronic obstructive pulmonary disease (COPD), which may be one of the adverse health effects of ENDS[122].

Normal human bronchial epithelial (NHBE) cells cultured at an air-liquid interface exposed to nicotine-containing ENDS aerosol showed impaired ciliary beat frequency, airway surface liquid volume, cystic fibrosis transmembrane regulator and ATP-stimulated K+ ion conductance and decreased expression of FOXJ1 and KCNMA1. Exposure of this cell culture to nicotine for 5 days increased the secretion of IL-6 and IL-8[123]. ENDS aerosol extract applied to human neutrophils caused an increase in the expression of CD11b and CD66b, and increased the

release of MMP-9 and CXCL8 and the activity of neutrophil elastase (NE) and MMP-9, and p38 MAPK activation. All of these effects may have an impact on various aspects of COPD pathophysiology[124].

A few studies have been conducted using whole animal exposure. The larynges of Wistar albino female rats exposed to aerosol produced from e-liquid containing nicotine (0.9% weight/volume) in an enclosed chamber for 1 hour per day for 4 weeks, showed no differences from those of non-exposed control animals in epithelial distribution, inflammation, hyperplasia, and metaplasia[125]. A study of 8-week old mice (wild type C57BL/6J), exposed to ENDS aerosol for 5h over 3 successive days, demonstrated increase in pro-inflammatory cytokines and decrease in glutathione, which is critical in maintaining cellular redox balance[119]. In another study, neonatal mice were exposed to aerosol generated from a specific ENDS (3.3V) for the first 10 days of life, while mice in the control group were exposed to room air. Those exposed to ENDS aerosol weighed 13.3% less and had moderately impaired lung growth measured on the 10th day of life on comparison to the controls[126].

Ova-albumin sensitized mice were submitted to 10week ENDS exposure consisting of intratracheal instillation of diluted cartridge solution containing 16 mg/ml nicotine. This treatment increased infiltration of inflammatory cells, including eosinophils, aggravated asthmatic airway inflammation and airway hyperresponsiveness, and stimulated the production of the cytokines IL4, IL-5 and IL-13 and OVA-specific IgE[127].

In another study, mice were exposed to inhaled e-liquids, either nicotine-containing or nicotine-free, for 1 hour daily for 4 months. Exposure to inhaled nicotine containing e-liquid triggered effects normally associated with the development of COPD, including cytokine expression, airway hyperreactivity and lung tissue destruction, while exposure to nicotine-free e-liquid had no apparent effect. The researchers concluded that inhaled nicotine contributes to airway and lung disease in addition to its addictive properties, and that their findings highlight the potential dangers of nicotine inhalation during ENDS use[128].

Clinical studies examining the effects of ENDS exposure on the human respiratory system are scarce and not standardized. Short-term ENDS use has been variously reported to be associated with normal spirometry-assessed lung function[129], increased airway resistance[130-132], increased impedance and overall peripheral airway resistance[132], and decreased specific airway conductance[131]. All of the above findings are similar to those seen with tobacco smoking.

In people using ENDS, two studies reported immediate reduction in exhaled nitric oxide (FeNO), similar to that produced by smoking[130,132], while another study reported increased FeNO[133].

In one study, the use of ENDS with >60% propylene glycol and 1 mg/mL nicotine did not produce acute impairment of lung function after active use or passive exposure[134], although in another, passive exposure to, but not active vaping of, one ENDS resulted in short-term lung obstruction, with reduced FEV1/FVC[129].

A study including both healthy volunteers and patients with asthma and COPD also showed that 10 min of vaping caused immediate significant airway obstruction[135], which is in contrast with a retrospective review finding objective and subjective improvements in asthma outcome[136]. In a 1-year randomized controlled trial of 300 smokers intending to quit cigarettes and receiving ENDS, long-term changes in spirometric indices and respiratory symptoms were evaluated prospectively. Spirometric data and complete information on respiratory symptoms were available from 130 and 145 participants, respectively. After 12, 24 and 52 weeks smoking phenotype classification (Quitters, Reducers, Failures) had no significant effect on spirometric indices (FEV1, FVC and FEV1/FVC) with the exception of FEF 25–75%, which significantly increased over the time in the Quitters (p= 0.034). The high prevalence of cough/phlegm (43.1%) and shortness of breath (34.8%) reported at base level was substantially reduced at subsequent follow-up visits among Quitters and Reducers[137]. Differences in device, liquid, and measurement times may explain the contradictory findings in the various clinical studies.

Effects of ENDS use on cardiovascular system

Laboratory studies examining the effects of ENDS aerosol on the cardiovascular system are very few. One study investigated the cytotoxic effect on cardiomyoblasts of 20 ENDS liquid samples with a wide range of nicotine concentrations[138]. The vapor tested was produced using commercially available ENDS devices. Cytotoxicity was detected in 4 samples, 3 of which 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, under similar experimental conditions, cigarette smoke was highly cytotoxic at all dilutions, with toxicity observed even when the extract was diluted to 12.5%.

Aerosols produced by ENDS with a 4.5-V battery resulted in reduced cell viability compared with the effects produced by ENDS with a 3.7-V battery[139].

In order to study the effects of ENDS on the development of the cardiac system, zebrafish were exposed to ENDS and tobacco cigarettes aerosols. Dose-dependent developmental defects were observed with both types of exposure, with severe heart malformation, pericardial edema and reduced cardiac function. Tobacco cigarettes were more toxic than ENDS at comparable nicotine concentrations. Using an *in vitro* model with human embryonic stem cells, both ENDS aerosol and cigarette smoke decreased expression of cardiac transcription factors in cardiac progenitor cells, suggesting a persistent delay in differentiation, and reduced expression of sarcomeric genes, such as MLC2v and MYL6 in definitive human cardiomyocytes. These results demonstrate harmful effects of ENDS aerosol on cardiac tissue, although less severe than those of cigarette smoke[140].

Studies in ENDS-naïve smokers demonstrated that short-term vaping resulted in an increase in heart rate[141-145], an elevation in diastolic blood pressure[142], and a decrease in oxygen saturation[144]. Other studies detected no effect on cardiac function[146-149], or blood pressure, but one reported an increase in oxygen saturation[148].

Effects of ENDS use on immune system

Several studies have shown that both nicotine and ENDS aerosol can have negative effects on the immune system. One recent study using rat, mouse and human lung epithelial cell lines showed dose-dependent deleterious effects of nicotine from exposure both to nicotine alone and to ENDS nicotine containing aerosol, including disruption of the lung endothelial lung barrier function, proinflammatory effects, and decreased cell proliferation. Nicotine-independent effects were also noted from exposure to ENDS solutions. In the same study, female mice were nebulized with nicotine containing ENDS aerosol or a saline control. Increased lung inflammation and oxidative stress were observed in the ENDS group under these experimental conditions, which the researchers reported to be due to the nicotine, acrolein, PG, and glycerol in the ENDS aerosol[150].

In a set of experiments using a mice model, ENDS aerosol exposure resulted not only in airway inflammation, but in impairment of the immune response to bacteria and viruses, and impaired bacterial phagocytosis. Exposure to ENDS aerosol also increased virus-caused morbidity and mortality under experimental conditions[151,152].

Superficial nasal scrape biopsies collected from non-smokers, cigarette smokers, and ENDS users were assessed for changes in immune gene expression profiles. Smoking cigarettes or vaping ENDS resulted in decreased expression of large number of immune-related genes. All genes with decreased expression in cigarette smokers (*n*=53) were also suppressed in e-cigarette users. Vaping ENDS was associated with suppression of a large number of unique genes (*n*=305), and the ENDS users showed greater suppression of the genes in common with those changed in cigarette smokers. This was particularly apparent for suppressed expression of transcription factors, such as EGR1, which was functionally associated with decreased expression of 5 target genes in cigarette smokers and 18 target genes in e-cigarette users. The researchers concluded that these data indicate that vaping ENDS is associated with decreased expression of a large number of immune-related genes, consistent with immune suppression at the level of the nasal mucosa. This study also showed that vaping ENDS does not reverse smoking-induced gene expression changes and may even result in immunomodulatory effects that go beyond those induced by smoking cigarettes alone[153].

Case reports on ENDS users

Additional information on ENDS health effects can be gained from case reports on individuals who present with symptoms attributed to ENDS use or exposure. One systematic review identified 26 case reports on 27 individuals who experienced negative health effects and 2 who reported a positive or improved outcome attributed to ENDS usage. The health effects attributed to ENDS use could be classified in three categories: systemic health effects (n=13), nicotine poisoning (n=12), and mechanical injury (n=2)[154].

Six case reports involved the respiratory system, with two cases of exogenous lipoid pneumonia[155,156], and one case each of bronchiolitis[157], acute eosinophilic pneumonia[158], pneumonia with bilateral pleural effusion[159], inhalation injury, and suspected acute hypersensitivity pneumonitis[160]. The gastrointestinal system was involved in three case reports. The specific diagnoses were relapsed ulcerative colitis (UC)[161], clinical remission of UC[162], and necrotizing enterocolitis in the developing gut of an infant[163]. Both adult patients (a male and female) had a history of UC and were previous smokers.

The two cases involving the cardiovascular system were diagnosed as paroxysmal atrial fibrillation and acute myocardial infarction[164,167]. One individual experienced

reversible cerebral vasoconstriction syndrome (RCVS)[166]. In addition, 2 cases of mechanical injury were reported, one of leg burns and the other of oral injuries caused by explosion of an ENDS device[167,168].

One case report was of a positive health effect associated with ENDS use in a male patient with a previous history of idiopathic neutrophilia and smoking. After 6 months of ENDS use and smoking cessation, the patient experienced a reversal of idiopathic neutrophilia, at which time his condition returned to baseline/normal white blood count[169].

In a small uncontrolled study, 18 daily ENDS users with mild to moderate asthma were monitored prospectively for one year. With reduction in tobacco consumption, significant, stable improvement in respiratory symptoms, lung function, AHR and ACQ, were observed in 16 ENDS users, but no significant changes in exacerbation rates were reported. Similar findings were found in the dual users.

A recently published study reported persisting long term benefits of smoking abstinence and reduction in asthmatic smokers who switched to e-cigarettes[170].

An exploratory search among US federal agencies, the scientific literature and news media outlets identified 92 episodes of overheating, fire or explosion of ENDS devices since 2009[171], of which 45 (49%) injured 47 people, and 67 (73%) involved damage of property other than the product itself. The reporting rate peaked at an average of 6 reports per month in late 2013 with a smaller peak of 3 to 4 reports per month in the second quarter of 2015. The 47 injured individuals included 34 users, 5 non-users and 8 of unclear user status. The injuries included chemical (n=4) and thermal burns (n=33), smoke inhalation (n=4), fractured neck vertebrae (n=2), fractured palate and finger (n=1), loss, displacement or damage of one or more teeth (n=3), lacerations (n=5), bruising (n=1), psychological distress (n=3), sensory disturbances (n=3), nicotine overdose (n=1) and oral discoloration (n=1).

The media have reported over 100 ENDS fire or explosion events in the UK. Two deaths have been recorded, while 19 cases were of episodes resembling those in the USA [172,173].

In summary, ENDS use is associated with its own set of health effects that need to be better characterized and understood. Data from case reports and small uncontrolled studies show that ENDS use can be accompanied by negative and also, but less frequently, positive health effects, usually in individuals who quit smoking conventional cigarettes. Health is reported to be affected by ENDS use in both adults and children (non-users).

OTHER HEALTH EFFECTS RELATED TO NICOTINE

Nicotine and case reports

Oral ingestion and dermal, inhalation and ocular exposure were the primary routes of exposure reported. Compared to cigarette exposure calls, ENDS exposure calls were more likely to report an adverse event, most commonly related to nicotine toxicity, including vomiting, nausea, and eye irritation. Symptoms ranged from mild to moderate and appeared to be related to acute nicotine toxicity. Relevant case reports from emergency departments presented similar findings in exposed children[174-176].

Nicotine and fetal through adolescent development

Because the health effects of combusted tobacco products are so devastating, and medicinal nicotine products approved for smoking cessation pose far fewer health risks than smoking, the effects of nicotine itself are often regarded as being of minor importance. Human and animal data, however, demonstrate that nicotine exposure during periods of developmental vulnerability (fetal through adolescent stages) has multiple adverse health consequences, including impaired fetal brain and lung development, and altered development of cerebral cortex and hippocampus in adolescents[177].

There is ample evidence that prenatal, early postnatal, and adolescent brain maturation is physiologically regulated by acetylcholine (ACh), via activation of nicotine acetylcholine receptors (nAChRs). Consistent with a dynamic developmental role for acetylcholine, exogenous nicotine, which is an Ach agonist, produces marked and unique long-term deficits in developing structures by interfering with the cholinergic regulatory processes. The diverse functional consequences of nicotine are highly dependent on the timing of exposure[178].

Prenatal nicotine exposure produces autonomic deficits, and alters developing catecholamine systems, with particular vulnerability of the dopamine system. The nicotine-induced deficits may be related to problems later in life, such as behavioral disorders, including attention deficit hyperactivity disorders (ADHD), cognitive impairment, anxiety, and vulnerability to nicotine and to substance abuse during childhood and adolescence[179,180].

The effects of nicotine on the fetus are not limited to the nervous system. Exposure to prenatal tobacco smoke affects offspring lung development, including reduced respiratory compliance, forced expiratory flow, and tidal breathing ratio in infants, and impaired lung function with

reduced expiratory flow rates in school-aged children[181].

Early postnatal nicotine exposure in rodents, (or third trimester exposure in humans), appears to preferentially interfere with cortical development, with human newborns and children exhibiting long-lasting defects in auditory cognitive processing[182]. Finally, exposure to nicotine during adolescence may preferentially interfere with limbic circuitry, producing enhanced vulnerability to addiction to nicotine and other stimulant drugs, increased impulsivity, and mood disorders[183]. Overall, the evidence is sufficient to caution children and adolescents, pregnant women, and women of reproductive age against ENDS use, because of the potential for fetal and adolescent nicotine exposure to have long-term adverse consequences for brain development[180].

Nicotine and cancer

The potential carcinogenic effects of nicotine *per se* at levels found in users of nicotine delivery products has been addressed in a number of studies. Overall, taking both human and animal studies into consideration, there appears to be inadequate evidence to conclude that nicotine *per se* does or does not cause or modulate carcinogenesis in humans[181], as stated in the recent US Surgeon General's 2014 report on the health consequences of nicotine exposure[184].

Studies, using various cell line models, suggest that nAChRs contribute to the development and progression of types of cancer directly induced by nicotine and its derived carcinogenic nitrosamines[185,186].

Deregulation of nAChRs is observed in many cancers, and genome-wide association studies (GWAS) indicate that single nucleotide polymorphisms (SNPs) of nAChRs are associated with risk of lung cancer and of nicotine addiction. For example, SNPs of the gene cluster 15q25, which contains CHRNA3, CHRNA5, CHRNB4, are associated with an increased risk of lung cancer and COPD, but also nicotine dependence[187].

Several cellular and molecular studies on nAChRs indicate that chronic exposure to nicotine or nicotine derived carcinogenic nitrosamines upregulates α7-nAChR and α9nAChR and desensitizes the heteromeric $\alpha 4\beta 2$nAChR, activating oncogenic pathways, promoting tumor angiogenesis and inhibiting drug induced apoptosis in multiple types of cancer[186].

CHRNA3, CHRNA5, CHRNB4 genes have been found to be necessary for the viability of small cell lung carcinoma (SCLC), the most aggressive type of lung cancer. It was shown that SCLC cell viability is promoted by nicotine and was inhibited by an α3β4-selective antagonist, α-conotoxin AuIB. This suggests a mechanism whereby signaling via α3/α5/β4-containing nAChRs promotes lung carcinogenesis[188]. This is in line with previous findings showing that nicotine promotes tumor growth in various *in vivo* models[189,190].

Clinical trials have revealed epidermal growth factor receptor tyrosine kinase inhibitor (EGFR-TKI) as the most promising therapeutic agent (e.g., erlotinib, gefitinib) in non SCLC (NSCLC)[191,192]. Smoking (nicotine) exposure has been shown to have a negative effect on EGFR-TKI therapy in lung cancers[193]. Several studies showed that exposure to nicotine increases EGFR expression in lung cells by activating survival pathways[194,195].

Based on the above findings, it was hypothesized that interaction between nicotine and nAChRs may contribute to the process that generates resistance to EGFR-TKI. The EGFR system appears to interact with the nAChR system in NSCLC cell lines; for example, the α1 nAChR subunit mediates resistance to EGFR-TKI therapy, induced by chronic nicotine exposure, through activation of the ERK and Akt (Ser-473) pathways[196].

Long-term smoking is major risk factor for a variety of other cancers, including those of the gastrointestinal (GI) tract. Many endogenous and environmental factors, including nicotine, trigger carcinogenic mechanisms in the GI[197]. The cellular and molecular pathways activated by nicotine mimic physiological and environmental carcinogenesis in cancers throughout the GI tract, potentiating cancer growth and/or inducing the formation of cancer[198], via several carcinogenic mechanisms. Chronic nicotine exposure causes an increase in α7-nAChR and a decrease in $\alpha 4\beta 2$-nAChR expression. While the α7-nAChR promotes cancer through increased catecholamine production, the $\alpha 4\beta 2$-nAChR suppresses the development of cancer via GABA inhibition of β-adrenergic signaling[199]. In addition, nicotine induces the synthesis of hormones and cytokines important for the growth, metastasis, and invasion of cancer. This is exemplified by VEGF, which mediates the growth of cancer arising in nearly all GI organs, and the pro-inflammatory cytokine COX-2, most known for its role in the development of gastric cancer[200]. Nicotine and its derivatives may activate mitogenic pathways such as the MAPKs, either directly, or through signal-transduction by cholinergic signaling[201].

Dependence

Nicotine is a psychomotor stimulant that can lead to dependence. Numerous studies have determined that

traditional cigarettes and other tobacco products cause nicotine dependence. Since ENDS, also, can deliver various amounts of nicotine, it is very possible that dependence is induced by their use. While many instruments have been designed for estimating nicotine dependence in smokers, only one dependence questionnaire has been specifically developed to evaluate ENDS use.

Nicotine abuse liability and dependence are closely related to rapid nicotine absorption rates and exposure[202]. The speed of nicotine delivery to the blood may be slower for ENDS than for tobacco cigarettes, but is certainly similar to or faster than that for nicotine medications[97,203-205]. Because the addictiveness of a nicotine-delivery device is in part determined by the speed of drug delivery to the brain[206], the differences across devices suggest that some ENDS may be less addictive than tobacco cigarettes, but as addictive as nicotine medications, or more. Nicotine delivering ant-smoking aids range from being not at all (patch) to not very addictive (gum, lozenge)[207]. This hypothesis is partially supported by data showing that the abuse liability of ENDS is less than that of tobacco cigarettes, in both inexperienced[208] and experienced ENDS users[209,210].

Self-reporting from cross-sectional studies and internet and mail surveys has been used to assess dependence levels in users of ENDS, electronic non-nicotine delivery systems (ENNDS), gums and tobacco cigarettes, and in dual ENDS and tobacco cigarettes users. Three instruments are commonly used to assess dependence in tobacco cigarettes users, the Fagerström Test for Nicotine Dependence (FTND)[211], the Nicotine Dependence Syndrome Scale (NDSS)[212], and the Cigarette Dependence Scale (CDS)[213]. Modified versions of the above instruments have also been used to measure dependence in non-smokers. Dependence ratings were slightly higher in users of ENDS than of ENNDS. In former smokers, long-term (>3 months) users of ENDS were less dependent than long-term users of nicotine gum. In dual users, dependence on ENDS was generally lower than dependence on tobacco cigarettes.

Long-term ENDS users may be more addicted than short-term users, and the new ENDS models may be more addictive than older models. Nicotine dependence was examined in 111 subjects who had completely substituted traditional smoking with ENDS use for at least 1 month (mean 8 months). The subjects were included in the study irrespective of the type of ENDS used or the nicotine level. According to the answers to the first FTND question, scored from 0-3, the median dependence scores were 2 for both cigarettes (range 2–3) and ENDS (range 1–2). Using a 100-point visual analogue scale, the dependence scores were 59 (range 49–66) for ENDS users and 83 (range 77–89) for cigarette smoking, demonstrating lower dependence for ENDS[214].

Dependence on ENDS and on tobacco cigarettes was assessed using the recently developed Penn State (PS) Electronic Cigarette Dependence Index and its 10-item cigarette equivalent, with a score range of 0-20[215]. A total of 3,609 former cigarette smokers who switched to ENDS, were included in the study. The mean scores on the PS Cigarette Dependence Index were significantly higher than the mean scores on the PS Electronic Cigarette Dependence Index (14.5 vs. 8.1, $p < 0.0001$). Those who had used ENDS longer and those who were using more advanced ENDS devices, had higher dependence scores. Those using zero nicotine liquid had significantly lower dependence scores than those using 1–12 mg/ml, who scored significantly lower than those using 13 or greater mg/ml nicotine liquid ($p < 0.003$). In summary, the current ENDS users reported being less dependent on ENDS than they had been on cigarettes before they switched to ENDS. Their dependence appeared to vary by product characteristics, liquid nicotine concentration and length of ENDS use.

HEALTH RISKS OF PASSIVE EXPOSURE TO ENDS AEROSOL

Passive exposure to combustible cigarette smoke, also called secondhand smoke or environmental tobacco smoke, has been extensively researched, and is recognized to be hazardous to health[216]. Passive exposure to ENDS aerosol, also called secondhand aerosol (SHA), has not been well studied because ENDS are relatively new. Unlike traditional cigarettes, ENDS produce no secondary or side-stream emissions; therefore, passive exposure consists only of what the ENDS user exhales. Passive exposure to ENDS is of concern, however, because of its potential adverse health effects for people who are involuntarily exposed.

A review was recently made of 16 studies with varying designs that investigated the potential adverse health effects of passive exposure to ENDS aerosols[216]. The majority of the studies concluded that passive exposure to ENDS aerosol may pose a health risk142, [200-210], although 4 detected no apparent risk to bystanders[211-215].

It is of note that those studies undertaken by tobacco employees or funded by the National Vapers Club con-

cluded that there is no apparent risk to bystanders from ENDS use.

Examination of the ENDS aerosol in comparison with background levels showed, variously, that ENDS aerosol contains elevated levels of nicotine[142,225,229,232] PM19[142,223,225,226,228] glycerine[225,229] propylene glycol[225,230], formaldehyde and acetaldehyde[225], PAHs and metals[230]. These studies demonstrate that ENDS aerosol can contain harmful chemicals and thus have an impact on indoor air quality.

When examining the relative impact from passive exposure to ENDS aerosol, and combustible cigarette smoke, it is apparent that ENDS aerosol contains much lower levels of most of the substances measured[142,223-226,229,232]. The exceptions are nickel and silver, which were found to be higher in ENDS aerosols than in cigarette smoke[228].

Nicotine has been shown to produce adverse health effects from both short-term and long-term exposure[224]. A recent review examined the effect of nicotine on the developing human, and concluded that nicotine exposure during vulnerable periods of brain and lung development, such as the fetal period, childhood and adolescence, can have detrimental effects[233]. Epidemiological evidence has demonstrated adverse health effects from short-term and long-term exposure to inhaled particulate matter (PM), even at very low concentrations[234]. Adverse health effects detected from exposure to PM 2.5 include an increase in cardiovascular and respiratory diseases, and in mortality from all causes[235].

A WHO-commissioned review concluded that the levels of some metals, such as nickel and chromium, are higher in second hand aerosol (SHA) from ENDS than in second hand smoke (SHS) and certainly higher than in background air. Compared to air background levels, PM 1.0 and PM 2.5 in SHA are respectively 14-40 times, and 6-86 times higher. In addition, nicotine in SHA has been found 10-115 times higher than in background air levels, acetaldehyde 2-8 times higher, and formaldehyde about 20% higher. Apart from heavy metals, most compounds are generally found at lower concentrations than those in SHS[236].

At present, the magnitude of the health risks from the content of ENDS aerosols that are higher than background levels of these compounds and elements is unknown, but as ENDS aerosol has been shown to contain harmful constituents, passive exposure to ENDS aerosol has the potential for adverse health effects. While some authors argue that exposure to SHA is unlikely to be a significant health risk[237], they concede that SHA may be deleterious to bystanders with respiratory conditions[238]. Overall, it is reasonable to assume that the increased concentration of toxicants from SHA over background levels poses an increased risk for the health of all bystanders[239], and the possibility of adverse effects of chronic exposure to SHA, especially of infants and children in residential settings, is of particular concern.

ENDS AS AN AID TO SMOKING CESSATION

The evidence for the effectiveness of ENDS as a method for quitting or reducing tobacco smoking is limited and of low quality. Some studies have found a significant relationship between ENDS use and increased success of smoking cessation, while many others have found no association.

The effectiveness of ENDS when used to aid smoking cessation compared with over-the-counter nicotine replacement therapy (NRT) and with unaided quitting was studied in representative survey. The study included 5,863 adults who had smoked within the previous 12 months and made at least one attempt to quit during that period with either an e-cigarette only (n=464), NRT bought over-the-counter only (n=1,922) or no aid in their most recent quit attempt (n=3,477). Among smokers who attempted to stop without professional support, those who used ENDS were more likely to report continued abstinence than those who used a licensed NRT product bought over-the-counter (adjusted odds ratio, aOR 1.63, 95% CI 1.17–2.27) or no aid to cessation (aOR 1.61, 95% CI 1.19–2.18)[240].

A prospective study recorded sustained smoking abstinence at 12 and 24 months from tobacco smoking. At 12 months, it was found that abstinence was more likely among the people who enrolled as ENDS users (n=343) than in those who enrolled as smokers (n=643), (aOR 5.19, 95% CI 3.35–8.02) but that people who both used ENDS and smoked (n=319) were not more likely to quit. Of the 43 smokers who at baseline started to use ENDS, 34 (80%) were abstinent from tobacco smoking[241].

At 24 months, 61.1% of the ENDS users (n=229), 23.1% of tobacco-only smokers (n=480) and 26.0% of dual users (n=223) achieved tobacco abstinence ($p<0.001$). The proportion of participants who achieved complete abstinence i.e., who were using neither tobacco cigarettes nor e-cigarettes) did not significantly differ by baseline use group: ENDS users 18.8%, tobacco smokers 17.5% and dual users, 14.3%, (all $p>0.05$). Multivariate analysis showed that tobacco smoking abstinence was significantly more

likely among ENDS users (adjusted OR 5.56, 95% CI 3.89 to 7.95), p<0.001), while dual use of ENDS and tobacco cigarettes did not encourage quitting tobacco or ENDS[242].

In a representative sample of 695 smokers from the US, ENDS users classified as intensive users (used ENDS daily for at least 1 month) were much more likely than nonusers/triers (used ENDS at most once or twice) to have quit smoking at 1–2 years of follow-up (aOR 6.07, 95%CI 1.11–33.18). Intermittent users (used ENDS regularly, but not daily for >1 month) were not more likely to quit smoking (aOR 0.31, 95% CI 0.04–2.80)[243].

More recent studies have explored explicitly the association between the type of ENDS, and quitting smoking. Among 1,643 smokers surveyed in the UK, 36% reported any use of ENDS at 12-month follow-up. Compared with non-ENDS triers, only daily users of a G2 or later product were more likely to be abstinent from tobacco at the follow-up (OR 2.69, 95% CI 1.48–4.89). Non-daily use of G2 ENDS and any use of G1 ENDS were associated with either no increase or less likelihood of cessation[244].

A scientific review of 4 longitudinal studies and 1 cross-sectional study, with a combined population of 16,626 on ENDS efficacy as a smoking cessation aid, random-effects meta-analysis yielded a pooled OR of 0.61 (95% CI 0.50-0.75), indicating that ENDS use in the real world is associated with significantly lower odds of quitting smoking cigarettes[245].

Systematic review of 38 relevant studies showed that the odds of quitting cigarettes were 28% lower in those who used ENDS than in those who did not use ENDS (OR 0.72, 95%CI 0.57-0.91). Association of ENDS use with quitting did not significantly differ between studies of all smokers using ENDS (irrespective of interest in quitting cigarettes) and studies of only smokers interested in cigarette cessation (OR 0.63, 95% CI 0.45-0.86 vs OR 0.86, 95% CI 0.60-1.23; p=0.94). Other study characteristics (design, population, comparison group, control variables, time of exposure assessment, biochemical verification of abstinence, and definition of ENDS use) showed no association with the overall effect size (p≥0·77 in all cases)[246].

In another recent review on ENDS efficacy as an aid to smoking cessation or reduction and/or in reducing withdrawal symptoms and cravings, 62 references were evaluated[247]. In with the GRADE system, the quality of the evidence in support of ENDS effectiveness in helping smokers quit was assessed as very low to low, and the evidence on smoking reduction was assessed as very low to moderate.

A small amount of evidence suggested that G2 ENDS may be more effective than G1 devices in helping smokers to quit or smoke less. Most of the studies found that ENDS, especially G2 devices, could alleviate smoking withdrawal symptoms and cravings in the laboratory setting, which could be explained by the increased control over aerosol production and nicotine delivery by the newer generations of ENDS compared to G1 models.[248]

Recent Cochrane systemic reviews of ENDS for smoking cessation[250] identified only two randomized clinical trials (RCT)[251,252], with a combined sample size of 662, that compared G1 ENDS delivering nicotine, with placebo (non-nicotine) ENDS and nicotine patches. Participants using an ENDS with nicotine were more likely to have abstained from smoking for at least 6 months than those using placebo ENDS (placebo 4% v ENDS 9%, RR 2.29, 95% CI 1.05 to 4.96, GRADE: low). The one study that compared ENDS with nicotine patch (n=584) found no significant difference in 6-month abstinence rate, but the CI does not rule out a clinically important difference (RR 1.26, 95% CI 0.68 to 2.34, GRADE: very low).

The overall quit rates in the study comparing ENDS with NRT were much lower than would be expected for a clinical trial (>90% of participants failed to quit at 6 months)[250]. This could be explained by a range of factors including the limited behavioral support received by the participants. A combination of behavioral support and medication to stop smoking generates better chances of quitting than minimal support, with some evidence of a dose–response effect for treatment intensity[252]. It has been found that using NRT over the counter with no support was no more effective than trying quitting without a pharmaceutical aid[253].

Overall, the evidence for the effectiveness of ENDS as a method for quitting tobacco smoking is limited, with very few relevant well-designed studies, and does not allow conclusions to be reached.

ABILITY OF ENDS TO INITIATE YOUNG PEOPLE IN NICOTINE USE AND SMOKING

There is great concern about avoiding nicotine initiation in non-smokers and particularly in youth and young adults. This is referred to as the gateway effect, which is related to two circumstances, firstly, the possibility that children, adolescents and young people, who are non-smokers, will initiate nicotine use with ENDS at a rate greater than that to be expected in the absence of ENDS, and secondly, the possibility that once addicted

to nicotine through ENDS, these individuals will switch to cigarette smoking. The data from the last half decade highlights the fact that simultaneous use of conventional cigarettes is the most common behavior among young ENDS users, but at the same time, studies have shown that about 10%–30% of ENDS users may have never smoked a conventional cigarette[254].

WHO commissioned a review of the data on the prevalence and trends of ENDS use among people of 20 years of age or less. This review identified 27 studies that used probability sampling, from very few countries, of which 6, with a total of 91,051 participants, were included. The trend data show two groups of countries. In one, the prevalence of ENDS use is low and is not increasing significantly; in the other, which includes the largest market in the world (the USA), the prevalence is increasing rapidly. There is considerable debate about whether in these countries the increase in ENDS use among young non-smokers is a precursor to smoking[236].

In two nationally representative studies in the USA, the potential risk of nicotine naïve adolescents and young adults aged 18-29 years old who experiment with ENDS to transit to combustible tobacco was examined. The data suggest that among middle and high school students, having ever used ENDS was correlated with intention to smoke combustible tobacco cigarettes (adjusted OR 1.70, 95% CI 1.24–2.32) and ever use ENDS was associated with being open to cigarette smoking (adjusted OR = 2.4, 95% CI 1.7-3.3)[255,257].

In addition, a longitudinal cohort study evaluated 694 participants aged 16 to 26 years who were never cigarette smokers and who were attitudinally non-susceptible to smoking cigarettes. At 1-year follow up, the primary fully adjusted model revealed that baseline ENDS use was independently associated with progression to smoking (aOR, 8.3, 95% CI, 1.2–58.6). It is of note that estimates were based on only 16 never ENDS users at initial evaluation[258].

Four studies have been published on the longitudinal association between ENDS use and subsequent igarette use among adolescents. The first study was on 2,630 minor students with a mean age of 14.1 years and no history of combustible tobacco product use at initial evaluation. At 12 months, those who reported ever use of ENDS had 1.75 times the odds (95% CI: 1.10–2.77) as never users of reporting subsequent use of cigarettes and 2.73 times the odds (95% CI: 2.00–3.73) of reporting use of any combustible tobacco product, after adjustment for several potentially confounding characteristics at study entry[259].

The second study, which was also among adolescents (n=1,136, mean age 14.7 years), found similar results: ENDS users had 2.87 times the odds (95% CI 2.03–4.05) of initiating combustible cigarette use between baseline and follow-up 1 year later as never users, after adjustment for age, gender, ethnicity, parental education, parental support, and rebelliousness[260].

In the third study, the risk of smoking initiation associated with ENDS use in the transition to adulthood was prospectively evaluated in 298 young students (mean age 17.4 years). During the 16-month (average) follow-up, >40% of ENDS users at baseline initiated cigarette use, 6.17 times the odds (95% CI 3.30–11.6) of initiating cigarettes as never ENDS users. The association remained statistically significant after adjustment for use of other combustible tobacco products at study entry and for social environmental factors. The associations was stronger in adolescents with no intention of smoking at initial evaluation[261].

The fourth study, with a sample of 4,100 high school students in Los Angeles, found that ENDS use was prospectively associated with an increased risk of combustible tobacco use initiation during early adolescence. The association was consistent across unadjusted (OR 4.27, 95% CI 3.19 - 5.71) and adjusted models (OR 2.73, 95% CI 2.00 - 373), multiple tobacco product outcomes, and various sensitivity analyses. Supplementary analysis showed that adolescents who ever (vs. never) smoked at baseline were more likely to initiate ENDS use during the follow-up period. These results raise the possibility that the association between ENDS use and combustible tobacco use initiation may be bi-directional[262].

Studies examining the relationship between ENDS use and openness to smoke, defined as the lack of a firm intention not to smoke, are extremely rare. In such a study on a representative sample of young adults in the US (n=4,310) who had never established cigarette smoking behavior, 7.9% had tried ENDS. Ever tried ENDS was positively associated with openness to smoking, compared with never tried ENDS, after adjusting for several factors, i.e., sex, age group, race/ethnicity, educational attainment and experimentation with conventional cigarettes, (adjusted odds ratio, aOR = 2.4)[260].

Taken together all the findings from prospective studies on adolescent and young adult populations, suggest that ENDS use is a clear and consistent indicator of the likelihood of subsequent initiation of cigarette and other combustible tobacco product use, at ages spanning from early adolescence through emerging adulthood. It is not clear, however, whether the association of ENDS use with

smoking is because ENDS use leads to smoking, or because young ENDS users and smokers share similar social and behavioral characteristics that render them susceptible to the use of nicotine[236].

Future longitudinal research is needed to elucidate tobacco use behavior over time and to provide additional insight on the relationship between ENDS use and conventional cigarette use among young adult populations.

EPILOGUE

The prevalence of ENDS use has increased rapidly in the past few years. ENDS are being promoted as safer than conventional cigarettes, and as effective aids to quitting, and to reducing the adverse health effects related to smoking. Scientific research to date is inconclusive, as the possible short- and long-term risks and benefits of ENDS have not yet been thoroughly investigated.

The precautionary principal (PP) originated as a link between "uncertain scientific information and a political responsibility… [in order] to prevent damage to human health"[258]. The PP encourages planning, precaution, and prevention. In addition, it calls for common sense when science is uncertain or absent (i.e., if a product appears to be negatively affecting the environment or individuals, use should be diminished or cease while the alternatives are explored). In an effort to prevent another nicotine crisis, PP may be utilized in order to increase protection of the population and to minimize the risk from ENDS use[263].

REFERENCES

1. Abrams DB. Promise and peril of e-cigarettes: can disruptive technology make cigarettes obsolete? JAMA 2014;311:135–6.
2. Maziak W. Harm reduction at the crossroads: the case of ecigarettes. Am J Prev Med 20 14;47:505–7.
3. Bareham D, Ahmadi K, Elie M, Jones AW. E-cigarettes: controversies within the controversy. Lancet Respir Med, Published online October 12, 2016. http://dx.doi.org/10.101 6S2213-2600(16)30312-5
4. Agaku IT, King BA, Husten CG, et al; Centers for Disease Control and Prevention (2014) Tobacco product use among adults–United States, 2012-2013. Morb Mortal Wkly Rep 2014; 63:542–7.
5. McMillen RC, Gottlieb MA, Shaefer RM, Winickoff JP, Klein JD. Trends in electronic cigarette use among U.S. adults: use is increasing in both smokers and nonsmokers. Nicotine Tob Res 2015;17:1195-202.
6. Electronic cigarette use among adults: United States, 2014. NCHS Data Brief No. 217, October 2015.
7. Attitudes of Europeans towards tobacco. Eurobarometer 385 (77.1), European Commission, 2012. Attitudes of Europeans towards tobacco and electronic cigarettes. Eurobarometer 429 (82.4). European Commission 2015.
8. Filippidis FT, Laverty AA, Gerovasili V, Vardavas CI. Two-year trends and predictors of e-cigarette use in 27 European Union member states. Tob Control 2016; 0:1–7. doi:10.1136/tobaccocontrol-2015-052771.
9. Farsalinos KE, Poulas K, Voudris V, Le Houezec J. Electronic cigarette use in the European Union: analysis of a representative sample of 27 460 Europeans from 28 countries. Addiction. 2016 Jun 24. doi: 10.1111/add.13506.
10. Breland A, Soule E, Lopez A, Ramôa C, El-Hellani A, Eissenberg T. Electronic cigarettes: what are they and what do they do? Ann NY Acad Sci 2016; 1–26.
11. Dutra LM, Glantz SA. Electronic cigarettes and conventional cigarette use among U.S. adolescents: a cross-sectional study. JAMA Pediatr 2014;168:610-7.
12. Singh T, Arrazola RA, Corey CG, et al. Tobacco use among middle and high school students — United States, 2011–2015. MMWR Morb Mortal Wkly Rep 2016;65:361-7.
13. Jeon C, Jung KJ, Kimm H, et al. E-cigarettes, conventional cigarettes, and dual use in Korean adolescents and university students: Prevalence and risk factors. Drug Alcohol Depend 2016;168:99-103. doi: 10.1016/j.drugalcdep.2016.08.636.
14. Breland A, Soule E, Lopez A, Ramôa C, El-Hellani A, Eissenberg T. Electronic cigarettes: what are they and what do they do? Ann NY Acad Sci 2016;1–26.
15. Adkison SE, O'Connor RJ, Bansal-Travers M, et al. Electronic nicotine delivery systems: International tobacco control four-country survey. American Journal of Preventive Medicine, 2013;44:207–15.
16. Dawkins L, Turner J, Roberts A, Soar K. 'Vaping' profiles and preferences: An online survey of electronic cigarette users. Addiction 2013;108:1115–25.
17. Dockrell M, Morison R, Bauld L, McNeill A. E-cigarettes: Prevalence andattitudes in Great Britain. Nicotine and Tobacco Research, 2013, http://dx.doi.org/10).
18. Etter JF, Bullen C. Electronic cigarette: Users profile, utilization, satisfaction and perceived efficacy. Addiction 2011;106:2017–28.
19. Goniewicz ML, Lingas EO, Hajek P. Patterns of electronic cigarette use and user beliefs about their safety and benefits: An Internet survey. Drug and Alcohol Review 2013,32:133–40.
20. Richardson A, Pearson J, Xiao H, Stalgaitis C, Vallone D. Prevalence, harm perceptions, and reasons for using noncombustible tobacco products among current and former smokers. American Journal of Public Health 2014;104:1437–44.
21. Zhu SH, Gamst A, Lee M, Cummins S, Yin L, Zore L. The use and perception of electronic cigarettes and snus among the U.S. population. PLOSONE (2013). 8(10), e79332).
22. Pepper JK, Ribisl, Emery SL, Brewer NT. Reasons for Starting and Stopping Electronic Cigarette Use. Int J Environ Res Public Health 2014;11:10345-61; doi:10.3390/ijerph111010345
23. Hummel K, Hoving C, Nagelhout GE, et al. Prevalence and reasons for use of electronic cigarettes among smokers: findings from the International Tobacco Control (ITC) Netherlands survey. Int J Drug Policy 2015;26:601-8.

24. Soule EK, Rosas SR, Nasim A. Reasons for electronic cigarette use beyond cigarette smoking cessation: a concept mapping approach. Addict Behav 2016;56:41–50.
25. Soule EK, Lopez AA, Guy MC, Cobb CO. Reasons for using flavored liquids among electronic cigarette users: A concept mapping study. Drug Alcohol Depend (2016), http://dx.doi.org/10.1016/j.drugalcdep.2016.07.007
26. Piñeiro B, Correa JB, Simmons VN, et al. Meltzer LR, Brandona TH. Gender differences in use and expectancies of e-cigarettes: Online survey results. Addictive Behaviors 2016;52:91–7.
27. Kong G, Morean ME, Cavallo DA, Camenga DR, Krishnan-Sarin S. Reasons for electronic cigarette experimentation and discontinuation among adolescents and young adults. Nicotine Tob Res 2015;17:847–54.
28. Saddleson ML, Kozlowski LT, Giovino GA, et al. Enjoyment and other reasons for electroniccigarette use: results from college students in New York. Addict Behav 2016;54:33–9.
29. Ambrose BK, Day HR, Rostron B, et al. Flavored tobacco product use among us youth aged 12–17 years, 2013–2014. JAMA 2015;314:1871–3.
30. Margolis KA, Nguyen AB, Slavit WI, King BA. E-cigarette curiosity among U.S. middle and high school students: Findings from the 2014 national youth tobacco survey. Preventive Medicine (2016), doi: 10.1016/j.ypmed.2016.05.001
31. Patrick ME, Miech RA, Carlier C, O'Malley PM, Johnston LD, Schulenberg JE. Self-reported reasons for vaping among 8th, 10th, and 12th graders in the US: Nationally-representative results Drug and Alcohol Dependence 2016;165:275–8.
32. Zhu S, Sun J, Bonnevie E, et al. Four hundred and sixty brands of e-cigarettes and counting: implications for product regulation. Tobacco Control 2014;23(suppl 3):iii3-iii9.
33. Czoli C, Goniewicz M, Islam T, Kotnowski K, Hammond D. Consumer preferences for electronic cigarettes: results from a discrete choice experiment. Tobacco Control 2015;25(e1):e30-e36.
34. Ford A, MacKintosh A, Bauld L, Moodie C, Hastings G. Adolescents' responses to the promotion and flavouring of e-cigarettes. International Journal of Public Health 2015;61:215-24.
35. Vasiljevic M, Petrescu D, Marteau T. Impact of advertisements promoting candy-like flavoured e-cigarettes on appeal of tobacco smoking among children: an experimental study. Tobacco Control 2016; http//:tobaccocontrol-2015-052593.
36. Lovato C, Watts A, Stead L. Impact of tobacco advertising and promotion on increasing adolescent smoking behaviours. Cochrane Database Syst Rev 2011(10)
37. Portnoy D, Wu C, Tworek C, Chen J, Borek N. Youth curiosity about cigarettes, smokeless tobacco, and cigars Prevalence and associations with advertising. Am J Prev Med 2014;47:S76-S86.
38. Ganz O, Cantrell J, Moon-Howard J, Aidala A, Kirchner T, Vallone D. Electronic cigarette advertising at the point-of-sale: a gap in tobacco control research. Tobacco Control 2014;24(e1):e110-e112.
39. Huang J, Kornfield R, Szczypka G, Emery S. A cross-sectional examination of marketing of electronic cigarettes on Twitter. Tobacco Control 2014;23(suppl 3):iii26-iii30.
40. Luo C, Zheng X, Zeng DD, Leischow S. Portrayal of electronic cigarettes on YouTube. Public Health 2014;14:1028.
41. Cobb N, Brookover J, Cobb C. Forensic analysis of online marketing for electronic nicotine delivery systems. Tobacco Control 2015;24:128-31.
42. Cantrell J, Emelle B, Ganz O, Hair E, Vallone D. Rapid increase in e-cigarette advertising spending as Altria's MarkTen enters the marketplace. Tobacco Control 2015;25(e1):e16-e18.
43. Kornfield R, Huang J, Vera L, Emery S. Rapidly increasing promotional expenditures for e-cigarettes. Tobacco Control 2014; 24:110-11.
44. Kim AE, Arnold KY, Makarenko O. E-cigarette advertising expenditures in the U.S. 2011-2012. Am J Prev Med 2014;46:409-12.
45. Sebastian M. E-cig marketing budgets growing by over 100% year over year. Ad Age.2014. http://adage.com/article/media/ecig-companies-spent-60-million-adsyear/292641/.Accessed 7/14/2015.
46. Duke J, Lee Y, Kim A, Watson K. Exposure to electronic cigarette television advertisements among youth and young adults. Pediatrics 2014;134:e29-e3628.
47. E-Cigs. Stanford research into the impact of tobacco industry. http://tobacco.stanford.edu/tobacco_main/ecigs.php
48. Grana R, Ling P. "Smoking Revolution". American Journal of Preventive Medicine 2014;46:395-403.
49. Richardson A, Ganz O, Vallone D. Tobacco on the web: surveillance and characterization of online tobacco and e-cigarette advertising. Tobacco Control 2014;24:341-7.
50. Singh T, Marynak K, Arrazola R, Cox S, Rolle I, King B. Vital Signs: Exposure to Electronic Cigarette Advertising Among Middle School and High School Students — United States, 2014. MMWR Morbidity and Mortality Weekly Report 2016;64:1403-8.
51. Ramamurthi D, Fadadu R, Jackler R. Electronic cigarette marketers manipulate antitobacco advertisements to promote vaping. Tob Control 2016;25:720-722. E-Cigs. Stanford research into the impact of tobacco industry. http://tobacco.stanford.edu/tobacco_main/ecigs.php
52. Trumbo C, Kim S. The effect of electronic cigarette advertising on intended use among college students. Addict Behav 2015;46:77-81.
53. Mantey DS, Cooper MR, Clendennen SL, Pasch KE, Perry CL. E-cigarette marketing exposure is associated with e-cigarette use among US youth. Journal of Adolescent Health 2016; 58: 686e690
54. FDA's New Regulations for E-Cigarettes, Cigars, and All Other Tobacco Products. Consumer Health Information www.fda.gov/consume
55. European Parliament and European Council of the European Union. Directive of the European Parliament and of the Council on the Approximation of the Laws, Regulations, and Administrative Provisions of the Member States concerning the manufacture, presentation and sale of tobacco and related products. Pe-Cons No/Yy - 2012/0366 (Cod). February 26, 2014. http://www.europarl.europa.eu/sides/getDoc.do?type=REPORT&reference=A7-2013- 0276&format=XML&language=EN. Accessed March 25, 2014.
56. Grana R, Benowitz N, Glantz SA. E-cigarettes: a scientific review. Circulation 2014;129:1972–86.

57. FCTC. Conference of the parties to the WHO framework convention on tobacco control. FCTC/COP/6/10, 21 July 2014.
58. Breland A, Soule E, Lopez A, Ramôa C, El-Hellani A, Eissenberg T. Electronic cigarettes: what are they and what do they do? Ann NY Acad Sci 2016; 1–26.
59. The truth about: electronic nicotine delivery systems. December 2015. truthinitiative.org
60. Trehy ML, Ye W, Hadwiger ME, et al. Analysis of electronic cigarette cartridges, refill solutions, and smoke for nicotine and nicotine related impurities. J Liquid Chromatogr Related Technol 2011;34:1442–58.
61. Kubica P, Wasik AK, Wasik A, Namiesnik J. "Dilute & Shoot" approach for rapid determination of trace amounts of nicotine in zero-level e-liquids by reversed phase liquid chromatography and hydrophilic interactions liquid chromatography coupled with tandem mass spectrometry electrospray ionization. J Chromatogr 2013;1289:13–8.
62. Kim HJ, Shin HS. Determination of tobacco-specific nitrosamines in replacement liquids of electronic cigarettes by liquid chromatography–tandem mass spectrometry. J Chromatogr 2013;1291:48–55.
63. Laugesen M, Thornley S, McRobbie H, Bullen C. The results of independent chemical and microbiological analysis. Christchurch, New Zealand: Health New Zealand; 2008. How safe is an e-cigarette?
64. Lisko JG, Tran H, Stanfill SB, Blount BC, Watson CH. Chemical composition and evaluation of nicotine, tobacco alkaloids, pH, and selected flavors in e-cigarette cartridges and refill solutions. Nicotine Tob Res 2015;17:1270-8.
65. Varlet V, Farsalinos K, Augsburger M, Thomas A, Etter JF. Toxicity assessment of refill liquids for electronic cigarettes. Int J Environ Res Public Health 2015;12:4796-815.
66. Goniewicz ML, 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. doi: 10.1111/add.12410. Epub 2013 Dec 18.
67. Pagano T, DiFrancesco AG, Smith SB, et al. Determination of Nicotine Content and Delivery in Disposable Electronic Cigarettes Available in the United States by Gas Chromatography-Mass Spectrometry. Nicotine Tob Res 2016;18:700-7. doi:10.1093/ntr/ntv120. Epub 2015 Jun 4.
68. Abramovitz A, McQueen A, Martinez RE, Williams BJ, Sumner W. Electronic cigarettes: The nicotyrine hypothesis. Med Hypotheses 2015;85:305-10. doi:10.1016/j.mehy.2015.06.002. Epub 2015 Jun 9.
69. Zhang Y, Sumner W, Chen DR. In vitro particle size distributions in electronic and conventional cigarette aerosols suggest comparable deposition patterns. Nicotine Tob Res 2013;15:501-8.
70. Kosmider L, Sobczak A, Fik M, et al. Carbonyl compounds in electronic cigarette vapors: effects of nicotine solvent and battery output voltage. Nicotine Tob Res 2014;16:1319-26.
71. Etter JF, Bullen C, Flouris AD, Laugesen M, Eissenberg T. Electronic nicotine delivery systems: a research agenda. Tob Control 2011;20:243-8.
72. Lerner CA, Sundar IK, Yao H, et al. Vapors produced by electronic cigarettes and e-juices with flavorings induce toxicity, oxidative stress, and inflammatory response in lung epithelial cells and in mouse lung. PLoS One 2015;10:e0116732.
73. Talih S, Balhas Z, Eissenberg T, et al. Effects of user puff topography, device voltage, and liquid nicotine concentration on electronic cigarette nicotine yield: measurements and model predictions. Nicotine Tob Res 2015;17:150-7.
74. Hajek P, Goniewicz ML, Phillips A, Myers Smith K, West O, McRobbie H. Nicotine intake from electronic cigarettes on initial use and after 4 weeks of regular use. Nicotine Tob Res 2015;17:175-9. doi: 10.1093/ntr/ntu153. Epub 2014 Aug 13.
75. Goniewicz ML, Kuma T, Gawron M, et al. Nicotine levels in electronic cigarettes. Nicotine Tob Res 2013;15:158–66.
76. Westenberger BJ. Evaluation of e-cigarettes FDA. 2009. http://www.fda.gov/ downloads/drugs/Scienceresearch/UCM173250.pdf (accessed 12 Sept 2013).
77. McAuley TR, Hopke PK, Zhao J, et al. Comparison of the effects of e-cigarette vapor and cigarette smoke on indoor air quality. Inhal Toxicol 2013;24:850–7.
78. Pellegrino RM, Tinghino B, Mangiaracina G, et al. Electronic cigarettes: an evaluation of exposure to chemicals and fine particulate matter (PM). Ann Ig 2012;24:279–88.
79. Farsalinos KE, Romagna G, Tsiapras D, et al. Evaluation of electronic cigarette use (vaping) topography and estimation of liquid consumption: implications for research protocol standards definition and for public health authorities' regulation. Int JEnviron Res Public Health 2013;10:2500–14.
80. Yan XY, D'Ruiz CDD. Effects of using electronic cigarettes on nicotine delivery and cardiovascular function in comparison with regular cigarettes. Reg Tox and Pharm 2015;71:24–34.
81. Farsalinos KE, Spyrou A, Tsimopoulou K, Stefopoulos C, Romagna G, Voudris V. Nicotine absorption from electronic cigarette use: comparison between first and new-generation devices. Sci Rep 2014;4:4133.
82. Vansickel AR, Eissenberg T. Electronic cigarettes: effective nicotine delivery after acute administration. Nicotine Tob Res 2013;15:267–70.
83. Ramôa AP, Hiler MM, Spindle TR, et al. Electronic cigarette nicotine delivery can exceed that of combustible cigarettes: a preliminary report. Tob Control doi:10.1136/tobaccocontrol-2015-052447
84. Wagener TL, Floyd EL, Stepanov I, et al. Have combustible cigarettes met their match? The nicotine delivery profiles and harmful constituent exposures of second-generation and third-generation electronic cigarette users. Tob Control. 2016 Oct 11. pii: tobaccocontrol-2016-053041. doi: 10.1136/tobaccocontrol-2016-053041. [Epub ahead of print]
85. Balhas Z, Talih S, Eissenberg T, Salman R, Karaoghlanian N, Shihadeh A. Effects of user puff topography and device characteristics on electronic cigarette nicotine yield. Presented at the 20th Annual Meeting of the Society for Research on Nicotine and Tobacco (SRNT), February 5–8, 2014, Seattle, WA. 2014; POS4-57.
86. Paschke T, Scherer G, Heller WD. Effects of ingredients on cigarette smoke composition and biological activity: A literature

overview. Beiträge zur Tabakforschung International/Contributions to Tobacco Research 2002;20:107–247.
87. Hopke PK, Zhao J, Babaian S. Comparison of the effects of e-cigarette vapor and cigarette smoke on indoor air quality. Inhal Toxicol 2012;24:850-7.
88. Counts ME, Morton MJ, Laffoon SW, Cox RH, Lipowicz PJ. Smoke composition and predicting relationships for international commercial cigarettes smoked with three machine-smoking conditions. Regulatory Toxicology and Pharmacology 2005;41:185–227.
89. Hua M, Yip H, Talbot P. Mining data on usage of electronic nicotine delivery systems (ENDS) from YouTube videos. Tob Control 2013;22:103–6.
90. Spindle TR, Breland AB, Karaoghlanian NV, Shihadeh AL, Eissenberg T. Preliminary results of an examination of electronic cigarette user puff topography: the effect of a mouthpiecebased topography measurement device on plasma nicotine and subjective effects. Nicotine Tob Res 2015;17:142-9.
91. Bullen C, McRobbie H, Thornley S, et al. Effect of an electronic nicotine delivery device (e cigarette) on desire to smoke and withdrawal, user preferences and nicotine delivery: randomised cross-over trial. Tob Control 2010;19:98–103.
92. Eissenberg T. Electronic nicotine delivery devices: Ineffective nicotine delivery and craving suppression after acute administration. Tob Control 2010;19:87–8.
93. Vansickel AR, Cobb CO, Weaver MF, et al. 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.
94. Vansickel AR, Weaver MF, Eissenberg T. Clinical laboratory assessment of the abuse liability of an electronic cigarette. Addiction 2012;107:1493–500.
95. Etter JF, Bullen C. Saliva cotinine levels in users of electronic cigarettes. Eur Respir J 2011;38:1219.
96. Vansickel AR, Eissenberg T. Electronic cigarettes: Effective nicotine delivery after acute administration. Nicotine Tob Res 2013;15:267–70.
97. Dawkins L, Corcoran O. Acute electronic cigarette use: nicotine delivery and subjective effects in regular users. Psychopharmacology (Berl) 2014;231:401–7.
98. Geiss O, Bianchi I, Barahona F, Barrero Moreno J. Characterisation of mainstream and passive vapours emitted by selected electronic cigarettes. Int J Hyg Environ Health 2015;218:169-80.
99. Goniewicz ML, Knysak J, Gawron M, et al. Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. Tob Control 2014;23:133-9.
100. Farsalinos KE, Voudris V, Poulas K. Are metals emitted from electronic cigarettes a reason for health concern? A risk assessment analysis of currently available literature. Int J Environ Res Public Health 2015;12:5215-32.
101. Williams M, Villarreal A, Bozhilov K, Lin S, Talbot P. Metal and silicate particles including nanoparticles are present in electronic cigarette cartomizer fluid and aerosol. PLoS One 2013;8:e57987.
102. Lerner CA, Sundar IK, Watson RM, et al. Environmental health hazards of e-cigarettes and their components: oxidants and copper in e-cigarette aerosols. Environ Pollut 2015;198:100-7.
103. Visser W, Geraets L, Klerx W, et al. The health risks of using e-cigarettes. [Internet]. Bilthoven The Netherlands: National Institute for Public Health and the Environment; 2015. Available from: http://www.rivm.nl/bibliotheek/rapporten/2015-0144.pdf.
104. Counts ME, Morton MJ, Laffoon SW, Cox RH, Lipowicz PJ. Smoke composition and predicting relationships for international commercial cigarettes smoked with three machine smoking conditions. Regulatory Toxicology and Pharmacology 2005;41:185–227.
105. Kosmider L, Sobczak A, Fik M, et al. Carbonyl compounds in electronic cigarette vapors: effects of nicotine solvent and battery output voltage. Nicotine Tob Res 2014;16:1319-26.
106. Integrated Risk Information System (IRIS) [Internet]. Research Triangle Park (NC): U.S. Environmental Protection Agency; [Last Revision Date 20081028; cited 2015 Apr]. Summary on Chromium (VI) (18540-29-9); substance 0144. http://www.epa.gov/iris/subst/0144.htm.
107. Geiser M, Kreyling WG. Deposition and biokinetics of inhaled nanoparticles. Part Fibre Toxicol 2010;20;7(2). doi: 10.1186/1743-8977-7-2.
108. International Commission on Radiologic Protection (ICRP). Human respiratory model for radiological protection. Ann ICRP 1994;24:1-300.
109. Fuoco FC, Buonanno G, Stabile L, Vigo P. Influential parameters on particle concentration and size distribution in the mainstream of e-cigarettes. Environ Pollut 2014;184:523–9.
110. Ingebrethsen BJ, Cole SK, Alderman SL. Electronic cigarette aerosol particle size distribution measurements. Inhal Toxicol 2012;24:976–84.
111. Zhang Y, Sumner W, Chen DR. In vitro particle size distributions in electronic and conventional cigarette aerosols suggest comparable deposition patterns. Nicotine Tob Res 2013;15:501–8.
112. Mikheev VB, Brinkman MC, Granville CA, Gordon SM, Clark PI. Real-time measurement of electronic cigarette aerosol size distribution and metals content analysis. Nicotine & Tobacco Research Advance Access published May 4, 2016.
113. McNeill A, Brose L, Calder R, Hitchman S, Hajek P, McRobbie H. E-cigarettes: an evidence update A report commissioned by Public Health England. 2015. Available from: https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/457102/Ecigarettes_an_evidence_update_A_report_commissioned_by_Public_Health_England_FINAL.pdf).
114. Hiemstra PS, Bals R. Basic science of electronic cigarettes: assessment in cell culture and in vivo models. Respiratory Research 2016;17:127, pp 1-5.
115. Neilson L, Mankus C, Thorne D, Jackson G, DeBay J, Meredith C. Development of an in vitro cytotoxicity model for aerosol exposure using 3D reconstructed human airway tissue; application for assessment of e-cigarette aerosol. Toxicol In Vitro 2015;29:1952–62.
116. Scheffler S, Dieken H, Krischenowski O, Aufderheide M. Cytotoxic Evaluation of e-Liquid Aerosol using Different Lung-Derived

Cell Models. Int J Environ Res Public Health 2015;12:12466–74.
117. Cervellati F, Muresan XM, Sticozzi C, et al. Comparative effects between electronic and cigarette smoke in human keratinocytes and epithelial lung cells. Toxicol In Vitro 2014;28:999–1005.
118. Romagna G, Allifranchini E, Bocchietto E, Todeschi S, Esposito M, Farsalinos KE. Cytotoxicity evaluation of electronic cigarette vapor extract on cultured mammalian fibroblasts (ClearStream-LIFE): comparison with tobacco cigarette smoke extract. Inhal Toxicol 2013;25:354-61.
119. Lerner CA, Sundar IK, Yao H, et al. Vapors produced by electronic cigarettes and e-juices with flavorings induce toxicity, oxidative stress and inflammatory response in lung epithelial cells and in mouse lung. PLoS One 2015; 6,10:e0116732.
120. Scheffler S, Dieken H, Krischenowski O, Aufderheide M. Cytotoxic Evaluation of e-Liquid Aerosol using Different Lung-Derived Cell Models. Int J Environ Res Public Health 2015;12:12466–74.
121. Scheffler S, Dieken H, Krischenowski O, Forster C, Branscheid D, Aufderheide M. Evaluation of E-cigarette liquid vapor and mainstream cigarette smoke after direct exposure of primary human bronchial epithelial cells. Int J Environ Res Public Health 2015;12:3915–25.
122. Shivalingappa PC, Hole R, Westphal CV, Vij N. Airway Exposure to E-Cigarette Vapors Impairs Autophagy and Induces Aggresome Formation. Antioxid Redox Signal 2015;24:186–204.
123. Garcia-Arcos I, Geraghty P, Baumlin N, et al. Chronic electronic cigarette exposure in mice induces features of COPD in a nicotine-dependent manner. Thorax 2016; 24. pii: thoraxjnl-2015-208039. doi: 10.1136/thoraxjnl-2015-208039.
124. Rattray NJW, Dewhurst JA, Trivedi DK, et al. Electronic cigarette exposure triggers neutrophil inflammatory responses Respiratory Research 2016;17:56.
125. Salturk Z, Çakır Ç, Sünnetçi G, et al. Effects of Electronic Nicotine Delivery System on Larynx: Experimental Study. J Voice 2015;29:560-3.
126. McGrath-Morrow SA, Hayashi M, Aherrera A, et al. The effects of electronic cigarette emissions on systemic cotinine levels, weight and postnatal lung growth in neonatal mice. PLoS One 2015;10:e0118344.
127. Lim HB, Kim SH. Inhallation of e-Cigarette Cartridge Solution Aggravates Allergen-induced Airway Inflammation and Hyperresponsiveness in Mice. Toxicol Res 2014;30:13-8.
128. Garcia-Arcos I, Geraghty P, Baumlin N, et al. Chronic electronic cigarette exposure in mice induces features of COPD in a nicotine-dependent manner. Thorax 2016; 0:1–11.
129. Chorti M, Poulianiti K, Jamurtas A, et al. Effects of active and passive electronic and tobacco cigarette smoking on lung function. Toxicol Lett 2012; 211S, 43 (Abstracts/Ref Type:Abstract).
130. Marini S, Buonanno G, Stabile L, Ficco G. Short-term effects of electronic and tobacco cigarettes on exhaled nitric oxide. Toxicol Appl Pharmacol 2014;278:9–15.
131. Palamidas A, Gennimata SA, Kaltsakas G, et al. Acute effect of an e-cigarette with and without nicotine on lung function. Tobacco Induced Diseases Conference: 11th Annual Conference of the International Society for the Prevention of Tobacco Induced Diseases, ISPTID 2013 Athens Greece Conference Start: 20131209 Conference End: 20131211 Conference Publication: (var pagings), p. 12.
132. Vardavas CI, Anagnostopoulos N, Kougias M, Evangelopoulou V, Connolly GN, Behrakis PK. Short-term pulmonary effects of using an electronic cigarette: impact on respiratory flow resistance, impedance, and exhaled nitric oxide. Chest 2012;141:1400–6.
133. Schober W, Szendrei K, Matzen W, et al. Use of electronic cigarettes (e-cigarettes)impairs indoor air quality and increases FeNO levels of e-cigarette consumers. Int J Hyg Environ Health 217:628–37.
134. Flouris AD, Chorti MS, Poulianiti KP, et al. Acute impact of active and passive electronic cigarette smoking on serum cotinine and lung function. Inhal Toxicol 2013;25:91–101.
135. Gennimata SA, Palamidas A, Kaltsakas G, et al. Acute effect of e-cigarette on pulmonary function in healthy subjects and smokers. European Respiratory Society 2014. Thematic Poster Session: Tobacco Dependence and Respiratory Disease (Ref Type: Abstract).
136. Polosa R, Morjaria J, Caponnetto P, et al. Effect of smoking abstinence and reduction in asthmatic smokers switching to electronic cigarettes: evidence for harm reversal. Int J Environ Res Public Health 2014;11:4965–77.
137. Cibella F, Campagna D, Caponnetto P, et al. Lung function and respiratory symptoms in a randomized smoking cessation trial of electronic cigarettes. Clin Sci (Lond) 2016;130:1929-37.
138. Farsalinos K, Tsiapras D, Kyrzopoulos S, Savvopoulou M, Voutris V. Acute effects of using an electronic nicotine-delivery device (e-cigarette) on myocardial function: comparison with the effects of regular cigarettes. BMC Cardiovascular Disorders 2014;14:78. DOI: 10.1186/1471-2261-14-78.
139. Farsalinos KE, Romagna G, Allifranchini E, et al. Comparison of the cytotoxic potential of cigarette smoke and electronic cigarette vapour extract on cultured myocardial cells. Int J Environ Res Public Health 2013;10:5146-62.
140. Palpant NJ, Hofsteen P, Pabon L, Reinecke H, Murry CE. Cardiac development in zebrafish and human embryonic stem cells is inhibited by exposure to tobacco cigarettes and e-cigarettes. PLOS ONE 2015; DOI:10.1371/journal.pone.0126259.
141. Battista, L, Di IM, Tancredi M, et al. Cardiovascular effects of electronic cigarettes. Circulation Conference: American Heart Association 2013 Scientific Sessions and Resuscitation Science Symposium Dallas, TX, 2013;128(22 suppl. 1):26.
142. Czogala J, Goniewicz ML, Fidelus B, Zielinska-Danch W, Travers MJ, Sobczak A. Secondhand exposure to vapors from electronic cigarettes. Nicotine Tob Res 2014;16:655–62.
143. Tsikrika S, Vakali S, Gennimata SA, et al. Short term use of an e-cig: influence on clinical symptoms, vital signs and eCO levels. Tobacco Induced Diseases Conference: 11th Annual Conference of the International Society for the Prevention of Tobacco Induced Diseases, ISPTID 2013 Athens Greece Conference Start: 20131209 Conference End: 20131211 Conference Publication: (var pagings), 2014 p. 12.
144. Vakali S, Tsikrika S, Gennimata SA, et al. E-cigarette acute effect on symptoms and airway inflammation: comparison of nicotine

with a non-nicotine cigarette. Tobacco Induced Diseases Conference: 11th Annual Conference of the International Society for the Prevention of Tobacco Induced Diseases, ISPTID 2013 Athens Greece. Conference Start: 20131209 Conference End: 20131211 Conference Publication: (var pagings), 2014; p. 12.
145. Vansickel AR, Weaver MF, Eissenberg T. Clinical laboratory assessment of the abuse liability of an electronic cigarette. Addiction 2012;107:1493–500.
146. Farsalinos K, Tsiapras D, Kyrzopoulos S, et al. Acute effects of using an electronic nicotine-delivery device (e-cigarette) on myocardial function: comparison with the effects of regular cigarettes. Eur Heart J 2012;33(Abstract Supplement):
147. Eissenberg T. Electronic nicotine delivery devices: ineffective nicotine delivery and craving suppression after acute administration. Tob Control 2010;19:87–8.
148. Van Staden SR, Groenewald M, Engelbrecht R, Becker PJ, Hazelhurst LT. Carboxyhaemoglobin levels, health and lifestyle perceptions in smokers converting from tobacco cigarettes to electronic cigarettes. S Afr Med J 2013;103:865–8.
149. Vansickel AR, Cobb CO, Weaver MF, Eissenberg TE. A clinical laboratory model for evaluating the acute effects of electronic "cigarettes": nicotine delivery profile and cardiovascular and subjective effects. Cancer Epidemiol Biomarkers Prev 2010;19:1945–53.
150. Schweitzer KS, Chen SX, Law S, et al. Endothelial disruptive proinflammatory effects of nicotine and e-cigarette vapor exposures. Am J Physiol Lung Cell Mol Physiol 2015;309:L175–87.
151. Sussan TE, Gajghate S, Thimmulappa RK, et al. Exposure to electronic cigarettes impairs pulmonary anti-bacterial and antiviral defenses in a mouse model. PLoS One 10: e0116861, 2015.
152. Hwang JH, Lyes M, Sladewski K, et al. Electronic cigarette inhalation alters innate immunity and airway cytokines while increasing the virulence of colonizing bacteria. J Mol Med (Berl) 2016;94:667–79.
153. Martin EM, Clapp PW, Rebuli ME, et al. E-cigarette use results in suppression of immune and inflammatory-response genes in nasal epithelial cells similar to cigarette smoke. Am J Physiol Lung Cell Mol Physiol 2016;311:L135–44.
154. Hua M, Talbot P. Potential health effects of electronic cigarettes: A systematic review of case reports. Preventive Medicine Reports 2016, 4:169-78.
155. McCauley L, Markin C, Hosmer D. An unexpected consequence of electronic cigarette use. Chest 2012;141:1110–3.
156. Modi S, Sangani R, Alhajhusain A. Acute lipoid pneumonia secondary to e-cigarettes use: an unlikely replacement for cigarettes. Chest 2015;148:382A.
157. Hureaux J, Drouet M, Urban T. A case report of subacute bronchial toxicity induced by an electronic cigarette. Thorax 2014;69:596–7.
158. Thota D, Latham E. Case report of electronic cigarettes possibly associated with eosinophilic pneumonitis in a previously healthy active-duty sailor. J Emerg Med 2014;47:15–7.
159. Moore K, Young H, Ryan M. Bilateral pneumonia and pleural effusions subsequent to electronic cigarette use. Open J Emerg Med 2015;(3):18–22.
160. Atkins G, Drescher F. Acute Inhalational Lung Injury Related to the Use of Electronic Nicotine Delivery System (ENDS). Chest 2015; 148 (4_MeetingAbstracts), 83A.
161. Camus M, Gallois G, Marteau P. Ulcerative colitis and electronic cigarette: what's the matter? Am J Gastroenterol 2014;109:608–9.
162. Lee S, Taleban, Targan S, Melmed G. E-cigarettes as salvage therapy for medically refractory ulcerative colitis. Infammatory Bowel Diseases. Conference: Advances in Inflammatory Bowel Diseases, Crohn's and Colitis Foundation's National Clinical and Research Conference Hollywood, FL United States, 2013. Conference Start: 20131212 Conference End: 20131214.
163. Gillen S, Saltzman D, 2014. Antenatal exposure to e-cigarette vapor as a possible etiology to total colonic necrotizing enterocolititis: a case report. J Pediatr Surg Case Rep 2014;2:536–7.
164. Monroy AE, Hommel E, Smith ST, Raji M. Paroxysmal atrial fibrillation following electronic cigarette use in an elderly woman. Clin Geriatr 2012;20:28–32.
165. Kivrak T, Sunbul M, Durmus E, Dervisova R, Sari I, Yesildag O. Acute myocardial infarction due to liquid nicotine in a young man. Ther Adv Cardiovasc Dis 2014;8:32–4.
166. Vannier S, Ronziere T, Ferre JC, Lassalle V, Verin M. Reversible cerebral vasoconstriction syndrome triggered by an electronic cigarette: case report. Eur J Neurol 2015;22:64–5.
167. Jablow LM, Sexton RJ. Spontaneous electronic cigarette explosion: a case report. Amer J Med Case Rep 2015;3:93–4.
168. Rogér JM, Abayon M, Elad S, Kolokythas A. Oral trauma and tooth avulsion following explosion of e-cigarette. J Oral Maxillofac Surg. http://dx.doi.org/10. 1016/j.joms.2015.12.017.
169. Farsalinos KE, Romagna G. Chronic idiopathic neutrophilia in a smoker, relieved after smoking cessation with the use of electronic cigarette: a case report. Clin Med Insights Case Rep 2013;6:15–21.
170. Polosa R, Morjaria JB, Caponnetto P, et al. Discov Med 2016;21:99-108.
171. Donnelly L, PA. E-cigarettes linked to more than 100 fires. The Telegraph 3 November 2014. http://www.telegraph.co.uk/ health/healthnews/11203884/E-cigarettes-linked-to-morethan-100-fires. html (accessed 13 Nov 2014).
172. Chesterfield: E-cigarette linked to fatal care home blaze. Derbyshire Times 7 July 2013; Updated 7 November 2013. http://www.derbyshiretimes.co.uk/news/grassroots/chesterfielde-cigarette-linked-to-fatal-care-home-blaze-1-6225619 (accessed 5 Aug 2014).
173. Man killed as e-cigarette explodes, Merseyside fire service says. BBC News 8 August 2014. http://www.bbc.com/news/uk-england-merseyside-28701515 (accessed 11 Aug 2014).
174. Chatham-Stephens K, Law R, Taylor E, et al. Centers for Disease Control and Prevention (CDC). MMWR Morb Mortal Wkly Rep 2014; 4, 63:292-3.
175. Vakkalanka JP, Hardison LS Jr, Holstege CP. Epidemiological trends in electronic cigarette exposures reported to U.S. Poison Centers. Clin Toxicol (Phila) 2014;52:542-8.
176. Gill N, Sangha G, Poonai N, Lim RE. Cigarette liquid nicotine ingestion in a child: Case report and discussion. CJEM

2015;17:699-703.
177. England LJ, Bunnell RE, Pechacek TF, Tong VT, McAfee TA. Nicotine and the developing human: a neglected element in the electronic cigarette debate. Am J Prev Med 2015;49:286-93.
178. Dwyer JB, McQuown SC, Leslie FM. The dynamic effects of nicotine on the developing brain. Pharmacol Ther 2009; 122:125-39.
179. Kutlu M, Gould T. Nicotine modulation of fear memories and anxiety: Implications for learning and anxiety disorders. Biochemical Pharmacology 2015;97:498-511.
180. Yuan M, Cross S, Loughlin S, Leslie F. Nicotine and the adolescent brain. J Physiol 2015;593:3397-412.
181. The health consequences of smoking — 50 years of progress: a report of the Surgeon General. Atlanta: Centers for Disease Control and Prevention, 2014.
182. Hall F, Der-Avakian A, Gould T, Markou A, Shoaib M, Young J. Negative affective states and cognitive impairments in nicotine dependence. Neuroscience & Biobehavioral Reviews 2015;58:168-85.
183. Dwyer JB, McQuown SC, Leslie FM. The dynamic effects of nicotine on the developing brain. Pharmacol Ther 2009;122:125-39.
184. Haussmanna H-J and Fariss MW. Comprehensive review of epidemiological and animal studies on the potential carcinogenic effects of nicotine per se. Critical Reviews in Toxicology 2016; 46:701–34.
185. US Department of Health and Human Services. The health consequences of smoking – 50 years of progress. A report of the Surgeon General 2014.
186. Hung RJ, McKay JD, Gaborieau V, et al. A susceptibility locus for lung cancer maps to nicotinic acetylcholine receptor subunit genes on 15q25. Nature 2008;452:633–7. doi:10.1038/nature06885.
187. Zhao Y. The oncogenic functions of nicotinic acetylcholine receptors. J Oncol 2016;2016:9650481. doi: 10.1155/2016/9650481. Epub 2016 Feb 14.
188. Amos CI, Wu X, Broderick P, et al. Genome-wide associations can of tag SNPs identifies a susceptibility locus for lung cancer at 15q25. Nat Genet 2008; 40:616–22. doi: 10.1038/ng.109.
189. Improgo MR, Soll LG, Tapper AR, Gardner PD. Nicotinic acetylcholine receptors mediate lung cancer growth. Front Physiol 2013;17:251. doi: 10.3389/fphys.2013.00251. eCollection 2013.
190. Davis R, Rizwani W, Banerjee S, et al. Nicotine promotes tumor growth and metastasis in mouse models of lung cancer. PLoS ONE 2009;4:e7524. doi:10.1371/journal.pone.0007524
191. Al-Wadei HA, Al-Wadei MH, Ullah MF, Schuller HM. Gammaamino butyric acid inhibits the nicotine-imposed stimulatory challenge in xenograft models of non-small cell lung carcinoma. Curr Cancer Drug Targets 2012;12:97–106.
192. Ciardiello F, Tortora G. Drug therapy: EGFR antagonists in cancer treatment. N Engl J Med 2008;358:1160–74.
193. Heist RS, Christiani D. EGFR-targeted therapies in lung cancer: predictors of response and toxicity. Pharmacogenomics 2009;10:59–68.
194. Miller VA, Kris MG, Shah N, et al. Bronchioloalveolar pathologic subtype and smoking history predict sensitivity to gefitinib in advanced nonsmall-cell lung cancer. J Clin Oncol 2004;22:1103–9.
195. Carlisle DL, Liu X, Hopkins TM, et al. Nicotine activates cellsignaling pathways through muscle-type and neuronal nicotinic acetylcholine receptors in non-small cell lung cancer cells. Pulm Pharmacol Ther 2007;20:629–41.
196. Nakayama H, Numakawa T, Ikeuchi T. Nicotine-induced phosphorylation of Akt through epidermal growth factor receptor and Src in PC12h cells. Journal of Neurochemistry 2002;83:1372–9.
197. Wang S, Takayama K, Tanaka K, et al. Nicotine induces resistance to epidermal growth factor receptor tyrosine kinase inhibitor by α1 nicotinic acetylcholine receptor-mediated activation in PC9 cells. J Thorac Oncol 2013;8:719-25.
198. Tun MJ, Henley SJ, Calle EE. Tobacco use and cancer: an epidemiologic perspective for geneticists. Oncogene 2002;21:7307–25.
199. Jensen K, Afroze S, Munshi K, Guerrier M, Glaser SS. Mechanisms for nicotine in the development and progression of gastrointestinal cancers. Transl Gastrointest Cancer 2012;1:81–7.
200. Schuller HM. Is cancer triggered by altered signaling of nicotinic acetylcholine receptors? Nat Rev Cancer 2009;9:195–205.
201. Shin VY, Cho CH. Nicotine and gastric cancer. Alcohol 2005; 35:259–64.
202. Chowdhury P, Udupa KB. Nicotine as a mitogenic stimulus for pancreatic acinar cell proliferation World J Gastroenterol 2006;12:7428–32.
203. Henningfield JE, Keenan RM. Nicotine delivery kinetics and abuse liability. J Consult Clin Psychol 1993;61:743–50.
204. Nides MA, Leischow S, Bhatter M, Simmons M. Nicotine blood levels and short-term smoking reduction with an electronic nicotine delivery system. American Journal of Health Behavior 2014;38:265–74.
205. Spindle TR, Breland AB, Karaoghlanian NV, Shihadeh AL, Eissenberg T. Preliminary results of an examination of electronic cigarette user puff topography: The effect of a mouthpiece-based topography measurement device on plasma nicotine and subjective effects. Nicotine Tob Res 2015;17:142-9.
206. Henningfield JE. Nicotine medications for smoking cessation. N Engl J Med 1995;333:1196–203.
207. Le Houezec J. Role of nicotine pharmacokinetics in nicotine addiction and nicotine replacement therapy: a review. Int J Tuberc Lung Dis 2003;7:811–9.
208. Shiffman S, Hughes JR, Di Marino ME, Sweeney CT. Patterns of over-the-counter nicotine gum use: persistent use and concurrent smoking. Addiction 2003;98:1747–53.
209. Vansickel AR, Weaver MF, Eissenberg T. Clinical laboratory assessment of the abuse liability of an electronic cigarette. Addiction 2012;107:1493–500.
210. Farsalinos K, Romagna G, Tsiapras D, Kyrzopoulos S, Voudris V. Evaluating nicotine levels selection and patterns of electronic cigarette use in a group of "Vapers" who had achieved complete substitution of smoking. Subst Abuse 2013;7:139–46.
211. Goniewicz ML, Lingas EO, Hajek P. Patterns of electronic cigarette use and user beliefs about their safety and benefits: An Internet survey. Drug and Alcohol Review 2013;32:133–40.

212. Heatherton TF, Kozlowski LT, Frecker RC, Fagerström K-O. The fagerström test for nicotine dependence: a revision of the Fagerström Tolerance Questionnaire. Br J Addic 1991;86:1119–112
213. Shiffman S, Waters AJ, Hickcox M. The Nicotine Dependence Syndrome Scale: A multidimensional measure of nicotine dependence. Nicotine and Tobacco Research 2004;6:3217-348.
214. Etter JF, Le Houezec J, Perneger TV. A self-administered questionnaire to measure dependence on cigarettes: the cigarette dependence scale. Neuropsychopharmacology 2003;28:359-70.
215. Farsalinos KE, Spyrou A, Tsimopoulou K, Stefopoulos C, Romagna G, Voudris V. Nicotine adsorption from electronic cigarette use Q comarison between first and new-gemeration devices. Sci Rep 2014;4:4133.
216. Foulds J, Veldheer S, Yingst J, et al. Development of a questionnaire to assess dependence on electronic cigarettes in a large sample of ex-smoking e-cig users. Nicotine Tob Res 2015;186–92.
217. Publications and Reports of the Surgeon General. The health consequences of involuntary exposure to tobacco smoke: a report of the Surgeon General. Atlanta, GA: US Department of Health and Human Services, Centers for Disease Control and Prevention, Coordinating Center for Health Promotion, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health; 2006 [cited 2016 Mar 1]. Available from: www. surgeongeneral.gov/library/reports/secondhandsmoke/fullreport.pdf12.
218. Hess IMR, Lachireddya K, Capona A. A systematic review of the health risks from passive exposure to electronic cigarette vapour. Public Health Res Pract 2016;26:1-9:e2621617.
219. Ballbè M, Martínez-Sánchez JM, Sureda X, et al. Cigarettes vs. e-cigarettes: passive exposure at home measured by means of airborne marker and biomarkers. Environ Res 2014;135:76–80.
220. Flouris AD, Chorti MS, Poulianiti KP, et al. Acute impact of active and passive electronic cigarette smoking on serum cotinine and lung function. Inhal Toxicol 2013;25:91–101.
221. McGrath-Morrow SA, Hayashi M, Aherrera A, et al. The effects of electronic cigarette emissions on systemic cotinine levels, weight and postnatal lung growth in neonatal mice. PLoS ONE 2015;10:e0118344.
222. Ruprecht AA, De Marco C, Pozzi P, et al. Comparison between particulate matter and ultrafine particle emission by electronic and normal cigarettes in real-life conditions. Tumori 2014;100:e24–7.
223. Saffari A, Daher N, Ruprecht A, et al. Particulate metals and organic compounds from electronic and tobacco-containing cigarettes: comparison of emission rates and secondhand exposure. Environ Sc Process Impacts 2014;16:2259–67.
224. Schober W, Szendrei K, Matzen W, et al. Use of electronic cigarettes (e-cigarettes) impairs indoor air quality and increases FeNO levels of e-cigarette consumers. Int J Hyg Environ Health 2014;217:628–37.
225. Schripp T, Markewitz D, Uhde E, Salthammer T. Does e-cigarette consumption cause passive vaping? Indoor Air 2013;23:25–3127, 29, and four concluded that their investigation showed no risk to bystanders.
226. Geiss O, Bianchi I, Barahona F, Barrero-Moreno J. Characterisation of mainstream and passive vapours emitted Schripp T, Markewitz D, Uhde E, Salthammer T. Does e-cigarette consumption cause by selected electronic cigarettes. Int J Hyg Environ Health 2015;218:169–80. Cross Ref
227. Pellegrino RM, Tinghino B, Mangiaracina G, et al. Electronic cigarettes: an evaluation of exposure to chemicals and fine particulate matter (PM). Ann Ig 2012;24:279–88.
228. Long GA. Comparison of select analytes in exhaled aerosol from e-cigarettes with exhaled smoke from a conventional cigarette and exhaled breaths. Int J Environ Res Public Health 2014;11:11177–91.
229. O'Connell G, Colard S, Cahours X, Pritchard J. An assessment of indoor air quality before, during and after unrestricted use of e-cigarettes in a small room. Int J Environ Res Public Health 2015;12:4889.
230. Colard S, Connell G, Verron T, Cahours X, Pritchard J. Electronic cigarettes and indoor air quality: a simple approach to modeling potential bystander exposures to nicotine. Int J Env Res Public Health 2014;12:282–99. CrossRef | PubMed
231. McAuley TR, Hopke PK, Zhao J, Babaian S. Comparison of the effects of e-cigarette vapor and cigarette smoke on indoor air quality. Inhal Toxicol 2012;24:850–7. CrossRef | PubMed
232. Office of the Surgeon General. The health consequences of smoking – 50 years of progress: a report of the Surgeon General. Rockville, MD: US Department of Health and Human Services, Public Health Service; 2014 [cited 2016 Mar 1]. Available from: www.surgeongeneral.gov/library/reports/50years-of-progress/full-report.pdf
233. England LJ, Bunnell RE, Pechacek TF, Tong VT, McAfee TA. Nicotine and the developing human: a neglected element in the electronic cigarette debate. Am J Prev Med 2015;49:286–93.
234. HEI review panel on ultrafine particles. Understanding the health effects of ambient ultrafine particles. HEI Perspectives 3. Boston, MA: Health Effects Institute; 2013 [cited 2016 Mar 1]. Available from: pubs.healtheffects. org/getfile.php?u=893
235. Pope CA 3rd, Dockery DW. Health effects of fine particulate air pollution: lines that connect. J Air Waste Manag Assoc 2006;56:709–42.
236. United States Environmental Protection Agency. Final Report: Integrated science assessment for particulate matter. Washington, DC: United States Environmental Protection Agency; 2009 [cited 2016 Mar 23]. Available from: cfpub.epa.gov/ncea/risk/recordisplay.cfm?deid=216546 (FCTC/COP/7/11, Electronic Nicotine Delivery Systems and Electronic Non-Nicotine Delivery Systems (ENDS/ENNDS), report by WHO, 2016)
237. Royal College of Physicians. Nicotine without smoke: Tobacco harm reduction [Internet]. Rcplondon.ac.uk. 2016 [cited 31 July 2016]. Available from: https://www.rcplondon.ac.uk/file/3563/download?token=uV0R0Twz
238. Public Health England. Use of e-cigarettes in public places and workplaces. London, England: Public Health England; 2016.
239. Unger J. E-Cigarettes: Introducing New Complexities and Controversies to the Field of Nicotine and Tobacco Research. Nicotine & Tobacco Research 2015;17:1185-6.

240. Brown J, Beard E, Kotz D, Michie S, West R. Real-world effectiveness of e-cigarettes when used to aid smoking cessation: a cross-sectional population study. Addiction 2014;109:1531–40.
241. Manzoli L, Flacco ME, Fiore M, et al. Electronic cigarettes efficacy and safety at 12 months: cohort study. PLoS One 2015;10:e0129443.
242. Manzoli L, Flacco ME, Ferrante M, et al, the ISLESE Working Group. Cohort study of electronic cigarette use: effectiveness and safety at 24 months. Tob Control 2016; 0:1–9.
243. Biener L, Hargraves JL. A longitudinal study of electronic cigarette use in a population-based sample of adult smokers: association with smoking cessation and motivation to quit. Nicotine Tob Res 2015;17:127–33.
244. Brose LS, Hitchman SC, Brown J, West R, McNeill A. Is the use of electronic cigarettes while smoking associated with smoking cessation attempts, cessation and reduced cigarette consumption? A survey with a 1-year follow-up. Addiction 2015;110:1160–8.
245. Grana R, Benowitz N, Glantz SA. E-cigarettes: a scientific review. Circulation 2014;129:1972–86.
246. Kalkhoran S, Glantz S. E-cigarettes and smoking cessation in real-world and clinical settings: a systematic review and meta-analysis. The Lancet Respiratory Medicine 2016;4:116-28.
247. Malas M, van der Temple J, Schwartz R, et al. Electronic cigarettes for smoking cessation: a systematic review. Nicotine Tob Res 2016;18:1926-36.
248. Wagener TL, Floyd EL, Stepanov I, et al. Have combustible cigarettes met their match? The nicotine delivery profiles and harmful constituent exposures of second-generation and third-generation electronic cigarette users. Tob Control 2016 Oct 11. pii: tobaccocontrol-2016-053041. doi: 10.1136/tobaccocontrol-2016-053041. [Epub ahead of print]
249. Hartmann-Boyce J, McRobbie H, Bullen C, Begh R, Stead LF, Hajek P. Electronic cigarettes for smoking cessation. Cochrane Database Syst Rev 2016, 9;CD010216.
250. Bullen C, Howe C, Laugesen M, et al. Electronic trial. Lancet 2013;382:1629–37.
251. Caponnetto P, Campagna D, Cibella F, 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.
252. Stead LF, Lancaster T. Combined pharmacotherapy and behavioural interventions for smoking cessation. Cochrane Database Syst Rev 2012;10:CD008286.
253. Kotz D, Brown J, West R. 'Real-world' effectiveness of smoking cessation treatments: a population study. Addiction 2014;109:491–9.
254. Shiplo S, Czoli CD, Hammond D. E-cigarette use in Canada: prevalence and patterns of use in a regulated market. BMJ Open 2015;5:e007971.
255. Notes from the field: electronic cigarette use among middle and high school students – United States, 2011–2012. MMWR Morb Mortal Wkly Rep 2013;62:729–30.
256. Bunnell RE, Agaku IE, Arrazola RA, et al. Intentions to smoke cigarettes among never-smoking US middle and high school electronic cigarette users: National Youth Tobacco Survey, 2011–2013. Nicotine & Tobacco Research, 2015;228–30.
257. Coleman BN, Apelberg BJ, Ambrose BK, et al. Association Between Electronic Cigarette Use and Openness to Cigarette Smoking Among US Young Adults. Nicotine & Tobacco Research, 2015;212–8.
258. Primack BA, Soneji S, Stoolmiller M, Fine MJ, Sargent JD. Progression to traditional cigarette smoking after electronic cigarette use among US adolescents and young adults. JAMA Pediatrics 2015;169:1018–23.
259. Leventhal A, Strong D, Kirkpatrick M, et al. Association of Electronic Cigarette Use With Initiation of Combustible Tobacco Product Smoking in Early Adolescence. JAMA 2015;314:700-7.
260. Wills T, Knight R, Sargent J, Gibbons F, Pagano I, Williams R. Longitudinal study of e-cigarette use and onset of cigarette smoking among high school students in Hawaii. Tobacco Control 2016; :tobaccocontrol-2015-052705.
261. Barrington-Trimis J, Urman R, Berhane K, et al. E-Cigarettes and Future Cigarette Use. Pediatrics 2016;138(1):e 20160379 2016.
262. O'Riordan T, Cameron J. Interpreting the Precautionary Principle. London: Earthscan Publications Limited 2004; p. 315.
263. Bush AM, Holsinger JW Jr, Prybil LD. Employing the Precautionary Principle to evaluate the use of e-cigarettes. Frontiers in Public Health 2016; 4: article 5.