ERJ Express. Published on November 21, 2018 as doi: 10.1183/13993003.01151-2018

EUROPEAN RESPIRATORY *journal*

FLAGSHIP SCIENTIFIC JOURNAL OF ERS

Early View

Task Force Report

Electronic Cigarettes – Task Force report from the European Respiratory Society

Robert Bals, Jeanette Boyd, Susanna Esposito, Robert Foronjy, Pieter S. Hiemstra, Carlos A. Jiménez-Ruiz, Paraskevi Katsaounou, Anne Lindberg, Carlos Metz, Wolfgang Schober, Avrum Spira, Francesco Blasi

Please cite this article as: Bals R, Boyd J, Esposito S, *et al*. Electronic Cigarettes - Task Force report from the European Respiratory Society. *Eur Respir J* 2018; in press (https://doi.org/10.1183/13993003.01151-2018).

Electronic Cigarettes –

Task Force report from the European Respiratory Society

Robert Bals [1], Jeanette Boyd [2], Susanna Esposito [3], Robert Foronjy [4], Pieter S. Hiemstra [5], Dr. Carlos A. Jiménez-Ruiz [6], Paraskevi Katsaounou [7], Anne Lindberg [8], Carlos Metz [1], Wolfgang Schober [9], Avrum Spira [10], Francesco Blasi [11]

[1] Department of Internal Medicine V – Pulmonology, Allergology and Critical Care Medicine, Saarland University, 66421 Homburg, Germany, robert.bals@uks.eu

[2] European Lung Foundation (ELF), Sheffield, United Kingdom jeanette.boyd@europeanlung.org

[3] Pediatric Clinic, Department of Surgical and Biomedical Sciences, Università degli Studi di Perugia, Perugia, Italy; email: susanna.esposito@unipg.it

[4] Pulmonary and Critical Care Medicine, SUNY Downstate Medical Center, 450 Clarkson Avenue, MSC 19, Brooklyn, New York 11203, robert.foronjy@downstate.edu

[5] Department of Pulmonology, Leiden University Medical Center, P.O. Box 9600, 2300 RC Leiden, The Netherlands. p.s.hiemstra@lumc.nl

[6] Smoking Cessation Service. Region of Madrid, Spain, victorina@ctv.es

[7] 1rst ICU Evangelismos Hospital, National Kapodistrian University of Athens, Greece, paraskevikatsaounou@gmail.com

[8] Department of Public Health and Clinical Medicine, Division of Medicine, Umeå University, Umeå, Sweden, anne.lindberg@umu.se

[9] Bavarian Health and Food Safety Authority, Department of Chemical Safety and Toxicology, Pfarrstrasse 3, 80538 Munich, Germany
wolfgang.schober@lgl.bayern.de

[10] Boston University School of Medicine, Boston, MA; aspira@bu.edu

[11] Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Internal Medicine Department, Respiratory Unit and Regional Adult Cystic Fibrosis Center, IRCCS Fondazione Cà Granda Ospedale Maggiore Policlinico, Milan, Italy

Corresponding author:

Prof. Dr. Dr. Robert Bals

Department of Internal Medicine V – Pulmonology, Allergology and Critical Care Medicine

Saarland University Medical Center

66421 Homburg, Germany

Tel. +49 6841 16 23600

Fax. +49 6841 16 23602

robert.bals@uks.eu

Abstract

There is a marked increase in the development and use of electronic nicotine delivery systems (ENDS) or electronic cigarettes (ECIGs). This statement covers electronic cigarettes (ECIGs), defined as “electrical devices that generate an aerosol from a liquid” and thus excludes devices that contain tobacco. Database searches identified published articles that were used to summarize the current knowledge on: the epidemiology of ECIG use; their ingredients and accompanied health effects; secondhand exposure; use of ECIGs for smoking cessation; behavioural aspects of ECIGs and social impact, *in vitro* and animal studies; and user perspectives.

ECIG aerosol contains potentially toxic chemicals. As compared to conventional cigarettes, these are fewer and generally in lower concentrations. Second-hand exposures to ECIG chemicals may represent a potential risk, especially to vulnerable populations. There is not enough scientific evidence to support that ECIGs are an aid to smoking cessation due to a lack of controlled trials, including those that compare ECIGs with licensed stop-smoking treatments. So far, there is conflicting data that use of ECIGs results in a renormalization of smoking behaviour or for the gateway hypothesis. Experiments in cell cultures and animal studies show that ECIGs can have multiple negative effects. The long-term effects of ECIGs use are unknown, and there is therefore no evidence that ECIGs are safer than tobacco in the long term. Negative health effects cannot, based on the current knowledge, be ruled out.

Short sentence of 120 characters

Electronic cigarettes are the objective of intense research with the goal to define the potential harmful effects for human health.

Introduction

Smoking of tobacco products is one of the major preventable risk factors for death related to cardiovascular, neoplastic, infectious and respiratory diseases. There has recently been a marked increase in the development and use of electronic nicotine delivery systems (ENDS) or electronic cigarettes (ECIGs). This statement covers electronic cigarettes (ECIGs), defined as “electrical devices that generate an aerosol from a liquid” and thus excludes devices that contain tobacco (such as heat-not-burn tobacco products). ECIGs contain nicotine, propylene glycol and/or glycerin, flavourings (>8000 different types available), water, alcohol and other substances, which are vapourized and delivered to the lungs. Analysis of published literature demonstrates that worldwide research activities on ECIGs has been and still is increasing [1].

An intense discussion is ongoing on the potential benefits and harms of the use of ECIGs. Related to the ERS’ view that “human lungs are made to breath clean air and any substance inhaled long term may be detrimental” many publications provide data on the toxicology and harm-causing effects of ECIGs. The discussion on ECIGs focuses on the questions whether changing from smoking of tobacco products to ECIGs could reduce harm. There is also a large number of publications that addresses this approach. The main issues analysed in this discussion are: a) health concerns related to exposure to ECIG constituents, including nicotine; b) risks coming from secondhand emissions; c) the role of ECIGs as a gateway, particularly to the young, both for tobacco smoking and nicotine dependence; and d) their potential role as a smoking cessation tool.

Recently, the Forum of International Respiratory Societies (FIRS) issued a position statement on ECIGs asking for more independent studies on the benefits and potential harms of ECIG use, and a prudent restriction of the usage of these products at least until their safety can be established [2].

As this scientific field is quite young, a potential bias might be introduced by active authors or groups that have published multiple papers in a specific direction. In addition, specific authors have a documented COI with the ECIG industry (relevant for references 39, 40, 52, 53, 91, 104, 105, 108, 109, 110, 153, 180, 185, 210, 211, 217, 218, 220, 247, 279, 282).

On this basis, the European Respiratory Society (ERS) has established a Task Force (TF) to collect, analyse and integrate the current knowledge on ECIGs, and to provide an evaluation of the subject for various stakeholders, including physicians, scientists, patients, users, and policy makers. The TF group was geographically balanced and experts of 10 different European and American countries were included. A potential conflict of interest, especially with the tobacco or ECIG industry, was evaluated by using the ICMJE form according to ERS guidelines. No such COI was identified.

Methods

The TF collected publications on research published in peer-reviewed journals and publicly available documents on ECIGs. Eligible studies were original papers with empirical data including:

- experimental studies, including preclinical studies (work on molecules cells, animals)
- observational studies (including case-control, cohort and cross-sectional studies)
- case reports and case series
- clinical trials using ECIGs
- systematic reviews with or without meta-analysis

Only studies in the English language published up until August 2016 were included (except two non-English papers). Later publications that were relevant were added as the report was finalized. If individual papers were not identified by the search strategy, experts of the TF could propose the inclusion of studies from other sources. The TF conducted literature searches in the National Library of Medicine's PubMed electronic database (MEDLINE, PubMed), Scopus, PsycInfo, and Embase. The database searches were performed by Carlos Metz and Robert Bals and all results were put in a reference management system (Mendeley team package). All other members of the TF were eligible to include references. Based on the database searches, a total number 2271 of publications was identified. The publications were allocated to eight working groups of the TF. The allocation was supervised by the two chairmen (RB, FB). The full-text publications were obtained and inserted into a web-based database system. The analysis and discussion of each topic area were performed both in face-to–face meetings and web-based conferences. During this process, we excluded documents (non-systematic reviews, small observational studies, commentaries) with 289 references included in the present publication.

For the identification of user-specific items, the work groups responsible for identifying and reviewing the literature for each chapter of the manuscript, were asked to identify specific articles that contained user perspectives particularly around their values (attitudes, beliefs and motivations) for using ECIGs. The aim being to complement the studies identified from the systematic review to provide further insight into user-centred values and preferences in relation to ECIG use. A total of 35 articles were identified. These articles were then passed to the European Lung Foundation (ELF) to review and analyse using thematic content analysis. Following review, 16 articles were selected by ELF as within the scope of the manuscript and having content relating to user values and preferences. A summary of the themes from the articles identified were written up by ELF to produce the user-focused section of the manuscript.

The initial draft of the manuscript was prepared by the co-chairs together with members of the working groups. The manuscript was reviewed, edited, and approved by all authors prior to submission. Despite the intense literature search, this paper is not a systematic review.

1. Epidemiology of ECIG use

ECIG use among teenagers and young adults

Several studies have shown that the awareness and use of ECIGs has been increasing in teenagers. Dual cigarette and ECIG use increased from 0.8% in February 2010 to 1.9% in June 2011 (p=0.03) in a US High School population and >80% of the ECIGs users also used cigarettes [3]. In Korea, 4,341 students from middle- and high school (mean age 14.0 and 16.5 years respectively) responded to a questionnaire in 2008; 10.2% had seen or heard of ECIGs, but only 0.5% had tried them [4].The Florida Youth Tobacco Survey (FYTS) was a self-completed, school-based paper survey that has been administered to a random sample (>12,000 students) of public middle- and high school students annually since 1998 in the state of Florida, US. In 2011, 6.0% of high school students had tried ECIGs, while in 2012 the proportion increased by 40% to 8.4%, the use of ECIGs within the past 30 days was 3.1 and 3.5%, respectively [5]. The U.S. Population Assessment of Tobacco and Health (PATH) Study, a nationally representative study conducted in 2013 and 2014, which included 13,651 youths between 12 and 17 years, found that 13.4% had ever used an ECIG, 3.1% of youth had used ECIGs in the past 30 days, and 0.2% used them daily [6]. Numerous other studies show similar results, which indicate that adolescents use or experiment with ECIGs [4, 7-14]. A number of studies investigated risk factors for ECIG use in teenagers and the educational and social levels of school forms were associated with ECIG use frequency [15]. A strong predictor of frequency of ECIG use is cigarette smoking. Most youths, who use ECIGs, are also cigarette smokers [16]. Among never-smokers who used ECIGs, most only use them 1-2 days per month, and many use nicotine-free ECIGs. The designation “nicotine-free” was based on information supplied by the manufacturers. Among cigarette smokers the frequency of past 30 day use of ECIGs is much higher. Other risk factors include family smoking behaviour [17] or current cigarette smoking [10, 18]. These studies indicate that ECIG use among teenagers and young adults has increased over the last few years [16, 19].

ECIG use among adults

A large number of studies show that the use and awareness of ECIGs has been increasing in adults over the last few years. In 2012, the prevalence of use was still low and ECIG use was associated with lower age and better education [20]. Larger studies are sparse and often compare results from several countries [21]. Data regarding ECIG use was collected in 2012 from 25 European countries, with the highest prevalence in Denmark (4.2%) and lowest in Portugal and Lithuania (0.6%) [22]. More recent data from 2017 from 28 EU member states indicated that since 2014, the proportion of those who have at least tried ECIGs has increased (12% in 2014 *versus* 15% in 2017). However, the proportion of adults currently using ECIGs appears to remain stable at 2% of the EU population [23]. Studies involving French college students revealed a prevalence of ever-use and current-use of ECIGs of 23.0% and 5.7% respectively, while prevalence of the combined use of conventional cigarettes and ECIGs was 14.5% [24]. Awareness was high and variable in a survey involving 10 countries [25]. In addition, a telephone survey in France showed similar data [26], as did related studies in other European countries [27]. There have been repeated surveys in the US comparing ECIGs use in 2010 and 2013 in study samples of 2,505 to 4,170 individuals. During this period, ever-use of ECIG increased among current and former cigarette smokers (9.8-36.5% and 2.5-9.6%, respectively), while it was remained on a similar level among never-smokers (1.3-1.2%) (8). Several studies showed increasing use and awareness of ECIGs, especially in countries where they can be legally obtained and companies have open market access [28-36]. The number of tobacco cigarettes smoked per day and high income was associated with ECIG use [30, 37]. Repeated cross-sectional surveys in the US during the years 2010, 2011, 2012 and 2013 included over 3,000 individuals aged 18 years and above in each sample. Both ever- and current-use of ECIGs increased, from 1.8% to 13.0% and 0.3% to 6.8% from 2010 to 2013, respectively. Current use of ECIGs, defined as any use within the past 30 days, was associated with smoking status; it was 30.3% among daily smokers, 5.4% among former smokers and 5.4% among never-smokers [34]. The PATH study, a nationally representative US study conducted in 2013 and 2014, that included 45,971 adults, reported ECIG use in 6.7% in the past 30 days and 1.2% daily [6]. Similar prevalence of ECIGs use has been found in patients with cancer [21, 38]. However, more regular use of ECIGs (weekly or daily) is seen almost exclusively in smokers [39, 40]. It is important to also note that 1.2% of never cigarette smokers reported having ever used an ECIG in the EU, which is approximately 29.3 million adults.

The most common reasons for using ECIGs is to quit or cut down tobacco usage based on the assumption that they are less harmful than other tobacco products but also that they can be used where smoking is prohibited [24, 41]. In addition, curiosity is a main factor for the use of ECIGs [42, 43]. Individuals with mental health conditions show a high prevalence of ECIG use [44-46]. It is also important to note that there is much discussion over how best monitor to the prevalence of ECIGs use [47, 48].

Conclusion

Taken together, the use of ECIGs has increased in the past decade both among adolescents and adults. Up to now, regular use of ECIGs is most common among individuals, who are current or former smokers.

2. In vitro and in vivo animal studies

A variety of *in vitro* and *in vivo* model systems have been used in the evaluation of effects of ECIGs. In many studies, effects of ECIGs were compared to those resulting from exposure to traditional tobacco cigarettes (TCIG). This section is focussed on effects of ECIG liquid and vapour, whereas effects of individual constituents such as nicotine are discussed in section 2 (Ingredients and health effects).

***In vitro* model studies on ECIGs**

Different models have been used to study the effect of ECIGs on a variety of cell types. These include studies focusing on the vapour generated by ECIGs, but also studies of E-liquids and individual constituents of ECIGs. Study designs show marked differences with regards to the exposure systems used, including the puffing regimen used.

Cytotoxicity to various cell lines, causing cell death, decreased cell proliferation and increased oxidative stress have been reported [49-51]. Studies using a variety of cell types showed that effects of ECIGs on cell death and changes in gene expression were markedly lower than TCIGs [52-58]. However, it has been documented that ECIGs do cause a variety of adverse cellular effects on a range of cell types. Airway epithelial cells are a principal target for inhaled ECIG vapour, and primary airway epithelial cells are increasingly used in cytotoxicity studies because they are thought to better represent the airway epithelium than the widely used continuous tumour or immortalized cell lines. An overview of the effects of ECIGs on such human primary airway epithelial cells is provided in table 1. The design of such studies differed markedly, and only two used exposure of cells differentiated at the air-liquid interface (ALI) to ECIG vapour [54, 59]. These studies are therefore discussed in detail. Both studies used the same commercially available culture model system using primary bronchial epithelial cells obtained from a single donor cultured and differentiated at the ALI (EpiAirway MatTek). A study from British American Tobacco [59] showed that exposure to ECIG vapour did not induce cytotoxicity or a decrease in epithelial barrier function, whereas TCIG smoke exposure caused marked effects on these parameters. Moses et al. [54] used a similar approach by exposing cells to aerosols generated by ECIGs (4 different ECIGs from one single manufacturer) or smoke generated by TCIGs (3R4F reference cigarettes; University of Kentucky) using a commercially available exposure system (Vitrocell). Whereas, in line with the study by Neilson, no overt cytotoxicity was noted with ECIGs (as compared to TCIGs), both ECIGs and TCIGs caused similar changes in gene expression. In particular, alterations in expression of genes related to xenobiotic metabolism, oxidative stress, DNA damage, apoptosis and cilia formation and function were noted. Whereas the magnitude of these changes was higher in TCIGs than in ECIGs, nicotine-containing ECIGs caused more profound changes than ECIGs that did not contain nicotine. The authors also noted remarkably similar changes in gene expression in airway epithelial cells derived from bronchial brushes of ECIG users and cultures exposed to ECIGs.

In addition to studies on primary lung epithelial cells, other studies used human immortalized or tumour lung epithelial cells to assess cytotoxic effects, and changes in gene expression or function induced by exposure to extracts of ECIG vapour or ECIG liquid, as shown in studies using A549 [49, 57, 58] and BEAS-2B cells [60]. In addition, effects of ECIGs on other cell types have been explored. Such studies showed cytotoxic and other adverse effects of (extracts from) ECIG vapour or E-liquid on human gingival and lung fibroblasts [49, 61], vascular smooth muscle cells [62], embryonic stem cells [63], neutrophils [64] and a macrophage cell line[65], as well as a myocardial cell line [52].

Whereas many studies assessing effects of ECIGs have used cell death, epithelial barrier or changes in gene expression related to inflammation [49, 66] or oxidative stress [49, 54, 56, 60] as a read-out, fewer studies have explored the effect of ECIGs on tumour development and growth. This is highly relevant, since TCIG smoke has been shown to contain various carcinogens. Heating of ECIG liquid was found to result in the release of carcinogenic substances [67], and ECIG vapour, both with and without nicotine, was found to be cytotoxic and cause DNA strand breaks in keratinocyte and head and neck squamous cancer carcinoma cell lines [68].

In selected studies, the contribution of nicotine to the observed adverse effects was assessed. Those studies clearly showed that effects were not mediated only by nicotine in E-liquid or vapour [56, 57, 66, 68, 69]. Thousands of ECIG flavours are marketed, but little is known about their toxicity, especially following heating and inhalation. The contribution of such flavourings and of other constituents, including nicotine, is discussed in section 2, showing that more information is needed on the cytotoxic potential of ECIG flavours.

Limitations of in vitro studies. In vitro studies exploring effects of ECIGs frequently use non-differentiated, continuous cell lines, such as the A549 lung epithelial cell line. However, *in vitro* toxicology studies are increasingly using more advanced systems using primary epithelial cells that have been differentiated and are exposed at the air-liquid interface (Table 1). An important issue in such studies is the consideration of puffing regime, and of deposition efficiency; information on the latter is usually not available. It is therefore difficult to determine whether exposure conditions *in vitro* can be extrapolated to the situation in ECIG users.

	HAEC culture system	ECIG exposure	Effect	Reference
Type of analysis				
Metabolomics	ALI	liquid	Change (comparable to TCIG smoke condensate)	[70]
Transcriptomics	ALI	aerosol	Change (partly similar to whole TCIG smoke)	[54]
Observed changes				
Oxidative stress	ALI*	aerosol	Increase (mostly lower than with TCIG smoke)	[54, 56]
Ciliary function	ALI	aerosol	Decrease in gene expression	[54]
Cytotoxicity	ALI	aerosol	No toxicity	[54, 59]
	ALI*	aerosol	Decreased viability	[56]
Barrier function	ALI	aerosol	No effect on TEER	[54]

Table 1. Effects of ECIGs on human airway epithelial cells (HAEC). ALI: air-liquid interface; TEER: trans-epithelial electrical resistance. *Note: HAEC in [56] were exposed at the ALI, but not differentiated at the ALI.

Animal models

A limited number of animal studies have been used to investigate the effect of ECIGs on the lung and other organs. In a murine model of ovalbumin-based asthma, the application of diluted ECIG solution increased airway inflammation illustrated by an increase in eosinophils, levels of Th1-cytokines IL-4, IL-5 and IL-13, OVA-specific IgE, and airway hyperresponsiveness [71]. Four months exposure to inhaled nicotine-containing ECIG fluids triggered effects normally associated with the development of a COPD-like tissue damage in a nicotine-dependent manner [72]. A 7-month cigarette smoke inhalation study (industry sponsored) in C57BL/6 mice showed nicotine-dependent lung inflammation and emphysema after ECIG exposure that was however lower than that observed following exposure to smoke from conventional cigarettes [73]. Acute exposure to electronic and conventional cigarettes showed lower, but still measurable adverse effects of ECIGs with regard to barrier disruption and cytokine release [58].

Several studies investigated the effect of ECIG exposure on host defence. One study investigated the effect of exposure to ECIG vapour for 2 weeks, and showed an increased susceptibility to infection with influenza A and *Streptococcus pneumoniae* [74]. A 4-week exposure to ECIG vapour decreased macrophage and neutrophil antimicrobial function and increased susceptibility in a mouse pneumonia model [75]. Exposure of rats with a commercial ECIG device in whole-body mode showed induction of mutations and activation of carcinogen-bioactivating enzymes [76].

Extrapulmonary effects. Neonatal mice were exposed to ECIGs for the first 10 days of their life and were found to have modestly impaired lung growth, alveolar cell proliferation, and total body weight [77]. A whole-body exposure to cigarette smoke or ECIG vapour showed that nicotine-containing ECIG vapour induces addiction-related neurochemical, physiological and behavioural changes [78]. The offspring of the ECIG-vapour exposed mice showed significant behavioural alterations [79].

Systemic application of ECIG liquid in a rat model showed that E-liquid with or without nicotine leads to diminished sperm density and viability, and a decrease in testicular lactate dehydrogenase activity and testosterone level [80]. An identical experimental setup from the same research group also revealed decreased food and energy intake and a significant decrease in cholesterol and LDL levels [81], and alterations of the anti-oxidant defense and minor changes in renal function parameters [82]. Cardiac development was studied in zebrafish (*Danio rerio*) and in human embryonic stem cells (hESCs), and showed that ECIGs have a less detrimental effect in these outcomes as compared to conventional cigarettes [83]. Larva of *Caenorhabditis elegans* worms were exposed to ECIG liquids and this study showed that propylene glycol exposure is sufficient to induce an oxidative stress response in nematodes, while nicotine is not. Both propylene glycol and nicotine independently influence physiological measures of health and viability [84].

Conclusion

An increasing number of studies have used cell culture and animal models to investigate the effects of ECIGs. Most of these studies revealed adverse effects of ECIGs, although these were less pronounced than with TCIGs. ECIGs were found to affect cell viability in some but not all studies, but also in the absence of cytotoxic effects changes in oxidative stress, inflammatory mediator production and host defence against infection were noted. These studies focused on acute and subacute effects of ECIGs, and cell culture experiments cannot be used to show long-term effects. Notably nicotine and flavouring agents present in ECIG products are thought to contribute to their toxic effects. Caution is needed in extrapolating ECIG studies performed in cell culture or animals to human exposures. Aerosol exposure studies in cell culture and animals are technically difficult, and therefore some researchers used extracts of vapours. Other researchers focussed on E-liquids, which reflects a different exposure than that to inhalation of ECIG vapour. Whereas these *in vitro* and *in vivo* exposure studies raise concern regarding the use of ECIGs, conclusive answers will only be obtained with carefully conducted long-term studies in ECIG users.

3. Ingredients and health effects

ECIGs include a wide variety of battery-powered devices that heat a liquid, usually containing nicotine, to generate a vapour/aerosol that is inhaled [85]. Devices vary considerably in design, including the size of the device, battery power and characteristics of the liquid chamber, composition of the coil and of the wick. As discussed below, different devices can generate very different chemical exposures and most likely different levels of toxicity.

Constituents

E-liquid

The liquid (E-liquid) is generally comprised of propylene glycol (PG) and/or vegetable glycerin (VG), nicotine and flavourings. The concentrations of nicotine may vary widely, but typically are from 3 to 50 mg/ml, and some E-liquids are nicotine-free. The stated nicotine concentrations are not always accurate [86, 87]. A recent study of 27 US E-liquids with nominal nicotine concentrations of 6-22 mg/ml found that actual concentrations were 45-131% of the stated concentration, and that 67% had greater than 10% variance from stated values [87]. In most cases the measured concentrations are lower than that stated. Nicotine in E-liquids is extracted from tobacco, so the liquid may contain low levels of minor tobacco alkaloids and tobacco-specific nitrosamines (NNK, NNN), depending on the degree of purification [86]. The ratio of PG to VG differs between E-liquids, with many containing more PG than VG. Thousands of different E-liquid flavourings are available. Flavourings consist of complex mixtures of chemicals, and may include aldehydes (such as benzaldehyde in fruit flavours and cinnamaldehyde in cinnamon flavours), diacetyl, acetyl propionyl and acetoin (butter flavours) and alcohol [88-91]. The pH of E-liquids can vary widely from 6 to 9.8, depending on nicotine content (higher pH with higher nicotine content) and various flavourings [92].

Aerosol

When the ECIG is activated, a current is applied to the metal coils that surround the wick, which is saturated with E-liquid. The characteristics of the aerosol depend on the composition of the liquid, the heating temperature of the coil and wick, and an individual puffing pattern. ECIGs do not generate carbon monoxide or many other toxic chemicals produced by a burning cigarette. However, at high temperatures and with frequent puffing by a puffing machine, PG and VG undergo thermal degradation to form acetaldehyde, formaldehyde, acrolein and other potentially toxic carbonyls [93-95]. In some devices, heating of mixtures of PG, VG, benzoic acid and benzaldehyde generates benzene, a human carcinogen, which is present at lower levels than those in cigarette smoke [96]. Thermal degradation products can also be derived from the flavouring agents [97]. In general, the more powerful the battery, the higher the coil temperature, the more aerosol produced and the more potentially toxic thermal degradation products formed. The levels of formed carbonyls in ECIG aerosols are usually much lower than those generated by cigarettes, but with high voltage settings the concentration of carbonyls can be as high, or higher, than those produced from cigarettes. However, research on the generation of carbonyls and other thermal degradation products with high-voltage batteries and high temperatures have been conducted with smoking machines, and there is some evidence that ECIG users will rarely operate ECIG devices under these conditions due to the potentially adverse taste of the aerosol [67].

Heating of the coils and the wick, as well as solders, can also release metals into the aerosol, such as nickel and chromium (from nichrome coils), cadmium, manganese, lead, silver, tin and silicates [98]. While exposure to metals can be toxic, the levels of metals in the aerosol are generally quite low and the risk of toxicity is likely low. Metals in the aerosol may also be released as nanoparticles [99]. Heating of the liquids generates oxidizing chemicals, including reactive oxygen species. Levels of oxidants are reported to be orders of magnitude lower than those in cigarette smoke, but higher than that of air pollution [100]. However, oxidant generation has been reported for only a few products and use conditions.

The ECIG generates a vapour that rapidly condenses to an aerosol (particles suspended in a gas) when leaving the device. The particles exhibit a bimodal size distribution [99]. The larger particles appear to consist of liquid (primarily PG and VG), which vapourize quickly in the air or are absorbed quickly in the lung. Very fine particles (nanoparticles), thought to consist of semivolatile chemicals and possibly metals generated near the hot coil, are also generated and persist longer as particles than the larger liquid particles.

Health effects

This section contains data from studies with health effects as main outcome, also other section of the statement contain data on health effects of ECIGs. Only a few studies have addressed the effects of electronic cigarettes on ECIG users, often referred to as vapers. A human study showed (30 smokers vs. controls) that acute inhalation of ECIG vapour increased respiratory impedance and airway resistance but did not immediately impact forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC) [101]. Another study showed an acute effect of ECIGs on airway resistance, showing increasing of Raw in asthmatic smokers, healthy smokers and never smokers (ECIGs with and without nicotine) [102]. A separate study with 15 smokers and 15 controls found no effect of acute ECIG exposure on lung function as determined by FEV_1/FVC [103]. Two studies (one year prospective and retrospective evaluation) showed improvements in lung function and symptoms in smokers who switched to vaping [104, 105]. Of note, these studies contain small group sizes and some originate from the same group. Authors of the references 104, 105, 109, 110 reported COI with companies involved in ECIG manufacturing.

To date, human ECIGs studies have reported an acute increase in heart rate, likely secondary to the acute effects of nicotine exposure [106, 107]. An echocardiography study found that acute ECIG exposure did not impair myocardial relaxation in contrast to conventional cigarettes [108]. While ECIG use may acutely increase blood pressure, smokers with hypertension who reduced or quit smoking with ECIG use had a significant reduction in blood pressure within two small studies [109, 110].

Several studies of the acute cardiovascular effects of ECIGs have been reported. One study found that ECIG use acutely increased aortic stiffness, while another found no change in aortic stiffness [111, 112]. Endothelial function, assessed by flow-mediated dilation, was impaired by cigarette smoking and ECIG use, with ECIG use having a smaller effect [113]. The effects may be related to effects of nicotine, oxidative stress and/or particulates. ECIG use acutely increases circulating levels of endothelial progenitor cells (EPC), which may be evidence of endothelial injury, but can also be an acute nicotine effect [114]. However, in this study ECIG use did not increase microvesicles associated with activation of inflammation or platelet activation, which are major mechanisms of smoking-induced cardiovascular injury. Reduced heart rate variability was reported in a study of regular ECIG users [115]. While reduced heart rate variability is a predictor of future cardiovascular events, it is likely that this is a consequence of underlying disease, rather than acute changes in heart variability (reflecting sympathetic stimulation) being a determinant of future cardiovascular events. This study also reported increased levels of oxidized low-density lipoprotein (LDL), consistent with increased oxidative stress, but no effect on biomarkers of inflammation. Nothing is known about the long-term effects of chronic ECIG use on lung or cardiovascular function in humans.

Toxicity of constituents

Nicotine

Nicotine is an important constituent of ECIGs and therefore evaluation of its effects is discussed separately. While most adult consumers choose E-liquids that contain nicotine, many younger users may choose nicotine-free liquids [116]. In one study, ECIGs were found to release up to 93 µg of nicotine per puff as compared to 147 µg per puff for a conventional cigarette [117], but this may vary significantly between difference ECIG devices and liquids.

Effects of nicotine are mediated by nicotinic acetylcholine receptors (nAchR). Nicotinic receptors have been most intensely studied with respect to psychoactive effects or in neurological diseases, yet they are also widely expressed in a variety of cell types, including immune cells, epithelial, endothelial and adipocytes, and keratinocytes [118]. In the lung, nicotinic receptors are abundantly present in epithelial cells [119, 120]. The bronchiolar epithelium expresses the α3, α4, α5, α7, α9, β2 and β4 subunits of nAchRs [121-123]. This expression is most intense on the apical surface [124], where exposure to nicotine mainly occurs [125]. Moreover, activation of these receptors triggers protease expression [126], mucin production [127] and smooth muscle contraction [128, 129], which mediate airway obstruction [130, 131]. Increasing evidence indicates that the expression of these receptors, in particular α7nAchR, could play a pivotal role in the development of chronic obstructive pulmonary disease (COPD) [132]. The α7nAChR regulates epithelial cell proliferation [133], differentiation [124] and mediates intracellular Ca^{2+} influx [134], which activates protein kinase C (PKC) [135]. Nicotine-induced α7nAchR activation also decreases cystic fibrosis transmembrane receptor (CFTR) channel activity in the airway epithelium [132], thereby increasing mucus viscosity.

Consequences of nicotine inhalation. Nicotine promotes proliferation of airway smooth muscle [136, 137] and epithelial cells [138], which may contribute to small airway remodelling in COPD. Despite these findings, few studies have directly examined the impact of nicotine inhalation alone on emphysema in the adult lung. In elastase-treated rats, cigarette smoke from high-dose nicotine-containing cigarettes does induce more emphysematous changes than smoke from low-dose nicotine cigarettes [139]. Several animal studies have demonstrated that nicotine exposure by itself could induce pathogenic responses similar to those that occur in COPD. Intranasal administration of nicotine in mice resulted in impaired autophagy, enhanced oxidative stress and bronchial epithelial cell apoptosis [60, 140]. Thus, acute exposure to nicotine in mice induced lung processes that play a central role in the development of COPD in humans [141].

As noted previously, very few studies have evaluated how chronic nicotine inhalation impacts the development of lung disease. One recent study in mice examined the effects of a 4-month exposure to a nicotine-containing ECIG aerosol in mice. The study found that mice exposed to an ECIG aerosol containing nicotine developed airway hyperresponsiveness and histological changes consistent with emphysema, while mice exposed to the same aerosol without nicotine showed no pathological changes [72]. The emphysema that resulted from this exposure was similar to what has been reported in cigarette smoke-exposed mice [142]. The study also found that airborne exposure to nicotine impaired ion conductance and ciliary function, and increased cytokine release in normal human bronchial epithelial cells [72]. Aside from this inhalational study, it has also been shown that chronic intraperitoneal injection of nicotine induced emphysematous changes in A/J mice [143]. These studies provide early evidence implicating nicotine as a potential aetiological factor in the pathogenesis of COPD. It needs to be noted that the animals in these studies received high nicotine doses that may not correspond to human exposure. Further studies are needed to establish effects of nicotine on the human lung that may be relevant for obstructive lung diseases.

Nicotine also suppresses apoptosis in lung tumours through PKC activation [144]. Though it is not a carcinogen, nicotine promotes tumour proliferation [145] and chemotherapeutic resistance [146]. Some animal studies have implicated nicotine [147], but others found that nicotine had no impact on tumourigenesis [148, 149].

While animal studies suggest that nicotine may contribute to COPD and cancer, human epidemiological studies on smokeless tobacco users do not find evidence of such effects. Smokeless tobacco (snus) exposes the user to as much nicotine as cigarette smoking, but without exposing the user to toxic products of combustion and avoiding a topical exposure of the lung. In some countries like Sweden, snus use is common, especially in men. Swedish snus delivers high levels of nicotine with relatively low levels of carcinogenic nitrosamines. Swedish men have the lowest smoking prevalence and the lowest lung cancer and COPD rates of any European country [150]. Aside from pancreatic and oesophageal cancer, which are likely nitrosamine-mediated, there is no increased incidence in any other cancer compared to non-tobacco users in Sweden [151]. This suggests that nicotine, at least in an oral form without inhalation, is not a major cause of cancer or COPD in people. However, a study of survival in prostate cancer patients found that both cancer-related and total mortality was higher to a small but significant extent in either exclusive smoker or exclusive snus users [152].

The level of nicotine generated by ECIGs depends on the device and amount of nicotine in the liquid. The first-generation cigarette-like devices delivered low levels, while the more advanced devices can deliver levels similar to cigarettes [153-155]. Cotinine levels in regular vapers have been reported to be similar to those of smokers, suggesting comparable levels of nicotine exposure [156, 157]. Of note, users of high-battery voltage, advanced devices with low nicotine content liquids have similar cotinine levels to users of lower voltage devices with much higher nicotine content, reflecting titration of desired nicotine levels in the body [156].

The primary pharmacological effect of nicotine is sympathetic neural stimulation [158]. Such actions could contribute to acute cardiovascular events and accelerated atherosclerosis. Epidemiological studies of Swedish snus users who, as noted above, are exposed to nicotine without combustion products, find no increase in overall rate of myocardial infarction or stroke, and no evidence of accelerated atherosclerosis based on carotid intima thickness, but do find a small but significant increased mortality after myocardial infarction [159]. One study found that in the two years after myocardial infarction, the mortality in snus users who continued to use snus was substantially higher than that of those who quit snus [160]. The presence of confounding cannot be excluded in this retrospective study. Overall, based on studies of Swedish snus users, who are exposed to high levels of nicotine without combustion products, and studies of long-term users of nicotine medications, nicotine appears to have little cardiovascular toxicity in healthy individuals, but may pose some risk in those with underlying cardiovascular disease [159-164]. It should be noted that no data exit on a direct comparison of ECIGs, conventional cigarettes and snus, and that the role of the route of exposure is unknown. Nicotine has adverse reproductive effects, including a foetal neuroteratogenicity, impaired foetal lung development and complications of pregnancy, including premature birth, low birth weight and pre-eclampsia, and possibly impaired wound healing [165, 166]. Minor tobacco alkaloids have nicotine-like activity and tobacco-specific nitrosamines are carcinogenic. These substances may be present in ECIG vapour, but at lower levels as compared to conventional cigarettes.

Propylene glycol and vegetable glycerine

PG and VG are common food additives, and PG has been used as a diluent in parenteral medications and in some medicinal inhalers. PG is also used to produce fog in theatrical productions and in that context has been reported to produce respiratory irritation [167]. Animal studies of the inhalational toxicity of PG have reported relatively few adverse effects [168]. As noted previously, there is temperature-dependent thermal degradations of PG and VG with formation of potentially toxic aldehydes including acetaldehyde, formaldehyde and acrolein. Such aldehydes in adequate concentration can be irritants, can be carcinogenic and can contribute to cardiovascular and pulmonary toxicity [169, 170]. Generally, concentrations of these aldehydes n ECIG aerosol are much lower than those in cigarette smoke, but can be quite high under conditions of high heating coil temperature devices or during “dry puffing”, i.e. when the liquid overheats and the wick dries out. Whether users will actually use devices that generate high levels of aldehydes, including “dry puffs”, has been questioned because the resultant aerosol is harsh and unpleasant tasting. Human exposure studies of urine metabolites of acrolein, a thermal degradation product of PG and VG, find levels much lower than those of smokers and similar to those of non-smokers, suggesting that actual exposure levels are low [171-174].

Oxidizing chemicals

Oxidizing chemicals can damage cell membranes, produce endothelial dysfunction and inflammation, promote atherogenesis and activate thrombogenesis. Oxidizing chemicals are thought to be the major contributors to cardiovascular disease in smokers [175, 176]. Reported levels of oxidants in ECIG aerosol are much lower than those generated by cigarettes [100]. However as noted previously relatively few different ECIG devices have been tested so the range of exposure levels is unknown.

Particles and metals

Particle exposure from cigarettes and from air pollution is associated with increased incidence of cardiovascular disease [177]. Particles have irritant and oxidant effects as described above, and can also affect cardiac autonomic function. However, the composition of ECIG particles is quite different from that of particles generated by combustion of organic materials. The latter are much more complex and include solid carbonaceous materials. Nanoparticles are of concern because they are more persistent, and some nanoparticles are known to cross capillaries in the lung and enter the systemic circulation. The hazards posed by nanoparticles generated by ECIGs are ,at this time, unknown.

Metals are released from heating coils and possibly from other components of the device [98, 178, 179]. Metals such as cadmium, nickel and chromium in high concentrations are carcinogenic and can cause cardiovascular and/or pulmonary disease. Levels of metals in ECIG aerosols are typically lower than those from cigarettes. Larger metal particles have been found in some liquids, and such particles could potentially cause pulmonary toxicity [178]. The chemical composition of the vapour phase, which is likely different from the one of the liquid phase, has still not been studied in depth.

Flavorants.

Several flavour constituents are of toxicological concern. Benzaldehyde and cinnamaldehyde are irritants and are cytotoxic, and are of concern for chronic respiratory effects [89, 90]. Diacetyl, acetyl propionyl and acetoin have been associated with pulmonary inflammation and injury, including bronchiolitis obliterans [88, 180, 181]. Diacetyl is an example of a flavouring substance that has been approved and is safe when ingested, but has established adverse health effects upon inhalation. Diacetyl was found to be present in a substantial proportion of sweet-flavoured ECIG liquids [91], in levels that are however much lower than those in cigarette smoke (over 6,700 micrograms per day, [182]). There is evidence that some flavoring chemicals undergo thermal degradation, which could also be a source of other toxic organic chemicals [97].

Due to the large number of available flavourings, a detailed toxicological evaluation of each component is not available, leaving the health effects of many ECIG flavourings largely unknown.

Human health effects

There have been few systematic studies of the health effects of ECIG use. Health effect studies are difficult to design because most ECIG users are either past or current cigarette smokers. Short-term, experimental use of ECIGs has been shown to have acute effects on airways physiology and respiratory symptoms in COPD smokers, asthmatic smokers, "healthy" smokers and healthy never-smokers [102]. Common adverse effects include throat irritation and cough [183]. Experimental studies on the effect of ECIGs on heart rate and blood pressure are discussed above (section "health effects"). *In vitro* platelet activation has been reported after exposure to ECIG extracts, similar to effects of tobacco smoke extract [184]. However, another study examined microvesicle release *in vivo* after ECIG use and found no evidence of markers of activation of leukocytes (reflecting inflammation) or platelet activation [114]. In a small cross-sectional study, low density lipoprotein (LDL) oxidizability was increased in ECIG users when compared to non-users, consistent with elevated oxidant stress, but there were no differences in C-reactive protein or fibrinogen levels, markers of inflammation [115]. Acute pulmonary effects have included increased dynamic airway compliance, which could be a result of lung irritation. Various studies in which cigarette smokers have switched to vaping exclusively or who vaped and smoked fewer cigarettes per day have reported benefits consistent with harm reduction. After switching, smokers with hypertension had lower blood pressure [109, 110], those with asthma and COPD had improved pulmonary function and symptoms [105, 185], and smokers without COPD demonstrated improved pulmonary small airway flow [104]. In contrast, another study showed that acute use of ECIGs in smokers with or without asthma results in cough and decreased lung function [102]. Smokers who switched to vaping reported a reduction in upper respiratory tract infections [186], but the finding is based on an on-line survey of vapers and needs to be interpreted with caution. In contrast, one study has reported an association between ECIG use in adolescents and chronic bronchitis symptoms, although there was no association when controlling for smoking status [187]. One case of atrial fibrillation associated with ECIG use has been reported [188].

Nicotine in high concentrations is extremely toxic and potentially fatal. A number of cases of nicotine toxicity and some deaths in children who ingested nicotine-containing e-liquids have been reported [189]. Poison centers have received numerous calls about nicotine toxicity from e-liquids, including inhalation, dermal exposure, and ingestion [190, 191]. Cases of exploding ECIG batteries, some associated with serious burns, have also been reported [192].

Conclusion

ECIG aerosol contains a number of potentially toxic chemicals. The composition and, most likely the toxicity of ECIG aerosol varies considerably across devices and liquids. Experimental human studies demonstrate acute cardiovascular effects consistent with stimulant effects of nicotine, but there is a lack of studies evaluating the long-term effects of ECIGs. Evidence that ECIGs use actually cause disease in users is lacking, but the products have not been in use long enough to observe possible chronic disease associations. Most ECIG users are former and current smokers, making causation difficult to establish. As compared to conventional cigarettes, the chemicals found in the vapour are fewer and generally in much lower concentrations. A few studies with limited numbers of participants suggest short-term harm reduction in smokers with COPD, who have completely switched to the use of ECIGs or who smoke fewer cigarettes per day. In this area, numerous publications have been published from only few group of authors, which might introduce the possibility of research subjectivity. Due to the lack of long-term studies, no conclusions are available on the long-term effects of switching.

4. Secondhand exposure

Unlike tobacco cigarettes, ECIGs do not produce side-stream emissions, and therefore bystanders are only exposed to chemicals that are exhaled by vapers into the indoor environment [193]. Most of the pollutants that occur in ECIG aerosols are retained in the respiratory tract of the user, but a fraction of the toxicants in exhaled vapour may also impact non-users through secondhand exposures. Several studies have confirmed the presence of harmful substances in passive vapour during ECIG use, including nicotine [194], fine and ultrafine particles [195-198], polycyclic aromatic hydrocarbons (PAH) [196, 199], metals (e.g. Ni, Zn, Ag) [200], reactive oxygen species (ROS) [49] and volatile organic compounds (VOC) [196, 197, 201]. Soule et al. recently showed that ECIG use can generate fine particles ($PM_{2.5}$) in high concentrations during natural use conditions in indoor environments (average mean: 607.12 $\mu g/m^3$) [202]. A study monitoring fine particle air concentrations in homes of low-income families identified no air pollution from vaping (while conventional cigarettes, use of candles etc. did contribute to indoor air pollution) [203]. This effect is caused by the evapouration of the liquid particles in the lung of the user and also in the environment after exhalation. Depending on exposure conditions (e.g. room size, number of vapers), bystanders of ECIG users may experience irritation of the throat, nose and eyes when a number of people vape in close proximity. Nicotine analysis in oral fluids of nonusers exposed to ECIG aerosols also confirmed passive uptake of nicotine during vaping activity [204], although at much lower levels as compared to passive exposure to conventional cigarettes [205, 206]. The amount of nicotine exhaled by ECIG users into the indoor environment varies greatly and depends on the device and nicotine concentration in the E-liquid. First-generation ECIG devices deliver less nicotine than late-generation devices, whereas more advanced devices with larger liquid reservoirs and higher voltage batteries produce larger amounts of aerosol and can deliver as much nicotine as a tobacco cigarette to users in the mainstream vapour [106, 153, 207]. Currently there are no studies that analyze the nicotine exposure to bystanders during the use of third-generation devices (mods) or tank models in small indoor environments (e.g. passenger compartments of cars). Nicotine released from ECIGs can also stick to various surfaces [208] and may contribute to passive exposure by subsequent desorption from surfaces to indoor air [209], but whether this could result in levels that could pose any risks is not known.

Conclusion

The harm potential of secondhand exposure to ECIG aerosols is currently not known. Potential health risks for bystanders are strongly dependent on the individual exposure conditions, such as the composition of the E-liquids used, the vaping topography of the ECIG users, the number of vapers, the dimensions of the room, the amount of ventilation, and the duration of exposure. While it is highly likely that involuntary indoor exposure to ECIG chemicals is much less hazardous than exposure to secondhand cigarette smoke, it is possible that such exposure could present a potential health risk, especially to vulnerable populations, including children, pregnant women, and people with cardiovascular or respiratory impairments. More research is needed in order to allow for a solid risk assessment.

5. ECIGs as a tool for smoking cessation

The effects of ECIGs on smoking cessation can be examined in two different ways. One approach examines the effects of ECIGs as part of a smoking cessation treatment in which they are provided pro-actively by healthcare professionals. The other is to assess effects of ECIG use by smokers who purchase them as consumer products. The general view and use of ECIGs as a quitting tool varies between different countries.

Regarding effects of vaping in the treatment context, only three randomised studies addressed this issue [210-213], and the available evidence is much weaker than the evidence available for licensed stop-smoking medications. A Cochrane meta-analysis [214] of two trials that used early ECIG models with poor nicotine delivery but provided long-term outcomes, found evidence that ECIGs help smokers quit compared with placebo ECIGs, with one trial showing the same (low) effect for ECIGs and for the nicotine patch [212]. The small number of trials, low event rates and wide confidence intervals around the estimates mean that the confidence in the result is rated 'low' by GRADE classification of the quality of evidence, but the uncertainty concerns the size rather than the direction of the effect. This is because there are over 100 randomized trials of nicotine replacement treatments (NRT) that show that a provision of an alternative source of nicotine helps smokers quit [215]. The third randomised controlled trial (RCT) only had a 2-months outcome and so was not included in the meta-analysis, but it showed a significant effect of a more advanced ECIG product [213].

Five intervention studies provided smokers with ECIGs and followed them up for at least 6 months [210, 216-219]. All reported good abstinence rates (36 – 40 %) or reduction of cigarette consumption (50 – 80 %), some in populations that are normally hard-to-reach, such as smokers not wanting to quit [218] and schizophrenic patients [210, 220]. The outcomes of this last group of studies are difficult to interpret because of the absence of control groups or small group sizes. In addition, several of these publications originated by the same group. A recent "pragmatic trial" applying different protocols for smoking cessation in a cohort of 6131 smokers found no significant effect of ECIGs as compared to the usual care group [221]. At the present time, the evidence for licensed stop-smoking medications is stronger. Authors of the references 210, 211, 217, 218, 220 reported COI with companies involves in ECIG manufacturing.

Regarding effects of vaping on smoking cessation on the population level, extrapolated data from the cross-sectional survey of EU citizens in 2015 (Eurobarometer survey data) suggest that an estimated 6.1 million people in Europe report that ECIGs helped them to stop smoking [39]. Some would have stopped anyway, with other methods or unaided, but analyses of trends in quitting outcomes and ECIG impact in the England suggest a net benefit [222, 223]. The most recent Eurobarometer data show that among ex-smokers in Europe, 7% had quit with the help of licensed stop-smoking medications and 6% quit with help of ECIGs [23]. Of note, the Eurobarometer data are a collection of surveys and often not analysed in detail. The most recent UK survey estimates (population forecast based on prevalence) that there are currently 1.5 million ex-smokers in Great Britain alone who switched completely to vaping (http://ash.org.uk/download/use-of-e-cigarettes-among-adults-in-great-britain-2017). The rise in vaping experimentation among the youth is considered alarming by some authorities [224], but in France, UK and USA where data on smoking and vaping exist, the rise in vaping has been accompanied by a decline rather than an increase in smoking prevalence, particularly among young people [225-227]. The increase in ECIG use among US adult smokers has been associated with a statistically significant increase in the smoking cessation rate at the population level [228]. Compared to smokers who did not use ECIGs, those who did use ECIGs were more likely to have tried to quit (40.1 *versus* 65.1%) and more likely to have successfully quit (4.8 *versus* 8.2 %).

These results could have been confounded by factors such as increased education, population awareness and other traditional tobacco control factors, and on-going monitoring is needed.

Two reports provided quit rates in smokers who used different quitting methods at their last serious quit attempt [229, 230]. In both cases, quit rates with ECIGs were significantly higher than quit rates with other methods. This needs to be interpreted cautiously because treatments were self-selected.

Finally, several studies recruited smokers who had never tried ECIGs and smokers who did but continued to smoke; and reported their smoking status at a later stage. A systematic review and meta-analysis of a number of studies that have examined the association between ECIG use and smoking cessation reported that ECIG use was associated overall with a significant 28% decrease in smoking cessation in the general population [231]. Other researchers have commented that the findings may be artefactual due to many of the studies excluding vapers who had successfully stopped smoking from the sample at baseline [232]. A meta-analysis on ECIGs and smoking cessation in real-world and clinical settings showed that ECIGs use is associated with significantly less quitting among smokers [231]. The results of these meta-analyses come to opposite conclusions from the more recent U.S. longitudinal study finding that ECIG use increases the likelihood of stopping smoking, as discussed above [228]. Data from a prospective US cohort (1284 random sample of smokers) showed no increased cessation rates [233].

More data on the effectiveness of ECIGs as a quitting tool on the population level will emerge when comparisons of trends in smoking prevalence and cigarette sales in countries that allow and countries that ban ECIGs become available.

Conclusion

On the population level, a number of smokers claim to have successfully stopped smoking using ECIGs and in two cohorts of smokers attempting to quit with different methods, while other studies showed no effect. Observational studies have obvious limitations and cannot rule out effects of self-selection. Controlled studies are needed to compare the putative effectiveness of ECIGs to the proven effectiveness of other cessation interventions to substantiate these uncontrolled observations. In the treatment context, only a few relevant studies have been published so far. Early models of ECIGs have shown a limited although significant long-term efficacy in two RCTs and a more advanced ECIG type showed a significant short-term effect. In contrast, another study comparing different cessation approached found no significant effect of ECIGs. The evidence is limited and further studies are needed, especially studies that compare ECIGs with licensed stop-smoking treatments.

6. Behavioural aspects and social impacts of ECIGs

This section deals with the evidence regarding potential consequences of ECIG use, i.e. with the impact of ECIGs on the social perception of smoking and with the potential interplay of ECIG use and tobacco use. The central question with regards to the social perception of smoking was whether ECIG use in public places leads to renormalization of tobacco smoking. Central questions concerning the interplay between ECIGs and tobacco use were: 1) whether ECIG use deters smoking cessation, 2) whether and why ECIG users continue using conventional cigarettes (dual use), which would not necessarily be associated with reduced health risks, and 3) whether ECIGs act as a gateway to smoking initiation for youths.

Effect of ECIGs on renormalization of smoking

Only two articles directly or indirectly investigated whether ECIGs might lead to a renormalization of smoking. One experimental study in US-Americans studied reactions to depictions of vaping in ECIG commercials and found an increase in the urge to smoke in current cigarette smokers, and a lower intention to continue abstaining from smoking in former smokers, indicating that visual depictions of vaping might increase cigarette consumption and smoking rates [234]. A cross-sectional study in US-American adolescents reported an association between a social environment favourable to ECIG use and susceptibility to cigarette use independent of respondents' own ECIG use, suggesting that an increase in ECIG use might be followed by an increase in cigarette use in adolescents through mechanisms of social normalization [235].

Does ECIG use deter smoking cessation?

As noted previously, a meta-analysis of a number of different types of studies has reported that ECIG use is associated with a decreased likelihood of smoking cessation [231]. However, some methodologic concerns about the studies and analysis have been raised [232]. Several studies indicated that the intention to quit smoking is one of the main reasons reported by adults for initiating ECIG use [42, 236-239]. Studies also show that ECIG use is associated with quit intentions [36, 240] and that ECIG users are more likely to have unsuccessfully tried to quit smoking in the past [241, 242]. Indeed, those who use ECIGs to quit smoking are more likely to reduce or quit tobacco use [36, 238], and longer duration of ECIG use has been shown to go along with decreases in daily consumption of cigarettes [243]. Regularity of use seems to be critical as well. Daily use is associated with increased likelihood of quitting, while intermittent use has been associated with a reduced likelihood of quitting [244, 245]. Certain use characteristics and expectancies seem to moderate behavioural changes, as one cross-sectional study found positive ECIG expectancies among users to be associated with a greater likelihood of having quit smoking [238], and one longitudinal study indicated that smokers who found ECIGs more satisfying were more likely to reduce or quit smoking [246]. Product characteristics may also be important; one study for example found the number of flavours used to be independently associated with smoking cessation [247]. The interplay between smoking and ECIG use might however be different among young adults, as two studies reported that ECIG use among college students appears to be motivated by enjoyment rather than by the desire to quit smoking [248, 249]. A recent study based on representative population surveys found that ECIG use is associated with increased quit attempts and increased quitting success on the population level [228].

Does ECIG use go along with smoking (dual use)?

Several cross-sectional studies have investigated correlates of dual use, i.e. concomitant use of ECIG and tobacco cigarettes, reporting very different prevalence of dual use. The combination of ECIGs and cigarettes was less common than other dual tobacco product use (such as cigarettes + filtered cigars and cigarettes + waterpipe) among young US-Americans in a survey from 2010/2011 [250]. The PATH study conducted in the U.S. in 2013 and 2014 however found that 37.4% of adults and 43% of youth used multiple nicotine products, the most common combination being cigarettes and ECIGs [6]. Other surveys have showed comparably high prevalence of dual use, with more than half of all ECIG users concomitantly smoking cigarettes in a survey among youths in the US [251] and in a survey among youths in Poland [252]. A German study reported a dual use prevalence of approximately 50% [253]. A large worldwide online survey among adults however revealed dual use among roughly one fifth of ECIG users [247], and a similar prevalence was found in a US-American online survey among adults [238]. Correlates of use were quite inconsistent. The dual users among US-youths generally had a higher prevalence of current tobacco product use and lower harm perceptions for these products [251]. The findings of the Polish study suggested that adolescent dual users are more addicted to nicotine in view of their smoking behaviour (e.g. time to first cigarette, smoking intensity) [252], a finding supported by a study from Germany, in which adult dual users had significantly higher scores in the Fagerström test for nicotine dependence [253]. The previously mentioned large worldwide online survey among adult ECIG users indicated that dual use was associated with higher risk perceptions about ECIGs and less frequent ECIG use [247]. This is supported by the results of the US-American online survey, which showed dual use being associated with negative expectancies about ECIGs, such as ECIGs being addictive, physically irritating and less satisfying [238]. Dual users in another US-American study described ECIGs as less harmful and addictive, but less enjoyable than tobacco cigarettes [236]. A study of ECIG use among stable smokers showed that these dual users possess characteristics that are associated with difficulty in achieving smoking cessation [242], which is also supported by a German study in which dual users had lower self-efficacy for abstinence, lower quit intention and higher craving than those using only ECIGs [253].

ECIGs as a potential gateway to smoking

Quite a few studies have investigated whether ECIG use is associated with the later use of more harmful tobacco products, such as cigarettes; most of them were conducted in the USA or the UK. Several mostly cross-sectional studies found higher susceptibility to trying cigarettes among adolescent or young adult ECIG users who had never smoked cigarettes [235, 254-258], while others found tobacco use to be a predictor of intention to use ECIGs [259, 260]. Several cross-sectional studies found an association between ECIG use and smoking [260-266]. One study suggested that ECIG use leads to tobacco smoking [261], while others instead indicate that tobacco use is a risk factor for ECIG use [260, 262, 263, 266]. One study did not support an association between ECIG and cigarette use [267]. In longitudinal studies, and in a meta-analysis of many of the studies, ECIG users were more likely to try cigarettes than non-users of ECIGs [235, 256, 268-270]. A recent meta-analysis on longitudinal studies on the initial use of ECIGs and subsequent cigarette smoking found that ECIG use was associated with greater risk for subsequent cigarette smoking initiation and past 30-day cigarette smoking [271]. Also a meta-analysis on ECIG use and intention to cigarette smoking among never-smoking adolescents and young adults showed that previous ECIG use was associated with increased smoking intention [272]. While this might be considered as evidence supporting the gateway hypothesis, it is also possible that these studies did not sufficiently control for other characteristics confounding the association, such as common liability factors influencing the susceptibility to experiment with substances, including alcohol, cannabis and other tobacco products [273]. Such an alternative explanation is supported by studies finding associations between ECIG use and use of other legal and illegal substances in general [262, 264, 265, 274], and by studies demonstrating that cigarette and ECIG users share common risk factors, such as peer smoking, parent smoking and higher sensation-seeking [18, 275, 276].

Conclusion

Regarding the question of renormalization of smoking through ECIGs, there is still limited evidence due to a lack of studies. No evidence was found for the view that ECIGs might deter smoking cessation, but only a few studies were available on this matter. The available studies rather suggest that smokers often use ECIGs to aid in smoking cessation, at least among adults. The inconsistency in characteristics correlated with dual use suggests that a diverse group of smokers and ECIG users is gathered in this category: those who want to quit smoking with ECIGs and for whom dual use represents a transition phase; those who fail to quit smoking completely; and those who, for a variety of reasons, do not want to switch to ECIG completely. For the gateway hypothesis, there is not enough methodologically strong data to draw definite conclusions. While most longitudinal studies find a strong association between adolescent ECIG use and the likelihood of later cigarettes smoking, their designs and methodological shortcomings do not prove a gateway effect as opposed to a common liability to substance use. Likely alternative explanations supported by the literature, are that shared risk factors (such as parent smoking, peer smoking, other drug use and sensation-seeking) make these adolescents generally more inclined to experiment with substances. Furthermore, there are no data on the question on duration of cigarette smoking in those who initiated tobacco with

ECIGs. To conclude, the leading questions concerning the undesirable consequences of ECIG use could not be answered unequivocally, as the evidence base thus far is still insufficient. More longitudinal and methodologically sound studies are needed to understand potential long-term behavioural impacts of ECIG use, and a continuous monitoring of the potential societal and public health effects of increasing ECIG use seems justified. Recent data show that there is sufficient evidence to conclude on ECIGs as gateway to smoking initiation in children.

7. ECIG user perspectives

Studies within the wider empirical literature review that contained user perspectives were identified by the work groups reviewing the literature. Of these, 16 studies [253, 277-286], incorporating views on attitudes, beliefs and motivations relating to ECIGs, were reviewed using thematic content analysis. All of these studies used focus groups, questionnaires, surveys or interviews as their central methodology, with views taken from a wide range of participants, including current smokers, former smokers, ECIG ever-users and dual users, and across varied age groups, from school age children to adults.

Benefits

In the studies analysed, the main benefits of ECIGs versus traditional tobacco cigarettes expressed by users included: being a healthier option, being a useful aid when trying to reduce or quit smoking, receiving a more positive reaction from friends and family, a lack of odour and the added flexibility of being able use them in places where smoking is banned or unacceptable. In one retrospective survey [279], participants also reported improvements in pre-existing respiratory symptoms (including asthma and chronic obstructive lung disease).

Side effects

Participants in two studies [279, 287] revealed common side effects such as dryness of the mouth and throat [183].

Reasons for starting and stopping

One of the main reasons for trying ECIGs described across four studies [43, 277, 288, 289] was curiosity, particularly for young adults where experimentation levels were higher than for older users. For older users, as well as current and ex-smokers, the potential for ECIGs to help reduce or quit traditional tobacco products was one of the main reasons given in several studies [42, 43, 281-283, 285, 287, 290].

Other frequently expressed reasons for trying and using ECIGs included: the attraction of the flavour options and the approval of family and friends who saw them as an improvement on traditional cigarettes. Some users also saw them as a recreational product, with young people in one study specifically viewing them as part of the ever-growing technological culture in their daily lives [284].

Three studies [42, 43, 291] explored the reasons behind users stopping using ECIGs, which included loss of interest, health concerns and the perception that they were not fashionable. According to recent 2017 Eurobarometer data, 55% of respondents think that ECIGs are harmful to the health of their users [23].

Lack of information

In three studies [278, 284, 288], users expressed low levels of knowledge about ECIGs, including their ingredients and long-term effects. There were also some individual concerns expressed about monitoring, regulation and safety.

Areas for further research

Areas indicated in these studies for further research in the view of the users included: the motivations of young people and their experimental behaviour with ECIGs; the extent to which flavours and nicotine content contribute to initiation and regular use; exploration of the social norms surrounding ECIGs; the possible role/potential as a harm reduction or cessation tool among adult smokers; and to understand the context and nature of use among the next generation, as this may be quite different from use among current teenagers.

Conclusions

The scientific field of ECIGs is complex and grows quickly. In parallel, new products to replace conventional cigarettes and current ECIGs are continuously being developed by the industry. Therefore, whereas the literature review within this statement is a snapshot at the present time, it does highlight several important issues regarding the use of ECIGs. The main conclusions of this statement are:

- The use of ECIGs has increased in the last years in adults and adolescents. In adults and especially in adolescents regular use of ECIGs is largely limited to current or ex-smokers.
- ECIG aerosol contains potentially toxic chemicals. There is a lack of data on their long-term effects and thus the toxicity of ECIGs remains to be determined. Therefore, at the present time it cannot be concluded that long-term use of ECIGs is safer than that of tobacco products.
- Secondhand exposure to ECIG chemicals may represent a potential risk, especially to vulnerable populations. There are a limited number of studies on secondhand exposures to ECIGs, and they do not provide sufficient evidence enough to exclude a potential risk.
- The use of ECIGs as a smoking cessation tool is insufficiently supported by controlled clinical trials. In the treatment context, only a few relevant studies of early ECIG types have been published so far. They show a small positive effect, but further studies are needed to evaluate the usefulness of current ECIG products as cessation tools. There is lack of evidence that ECIGs are an aid to smoking cessation and there is also a lack of studies that compare ECIG as smoking cessation tool to other approaches to smoking cessation.

- So far, there is not sufficient data to exclude that use of ECIGs results in a renormalization of smoking or for the gateway hypothesis in adults. Recent data show that there is sufficient evidence to conclude on ECIGs as gateway to smoking initiation in children.
- Experiments in cell cultures and animal studies show that ECIGs can have multiple negative effects, but less than conventional cigarettes or other tobacco products. One main shortcoming of the available information on ECIGs is the absence of any long-term data on active and passive exposure. This also implies that it is not possible to exclude that new risks may emerge from ECIG use.

These conclusions are in line with the recently published “Electronic Cigarettes: A position statement of the Forum of International Respiratory Societies” (https://www.firsnet.org) underling the fact that “health risks of electronic cigarettes have not been adequately studied” and thus “potential benefits to an individual smoker should be weighed against harm to the population of increased social acceptability of smoking and use of nicotine”. The task force members identified several areas for future independent research that are summarized in table 2. In line with the European Respiratory Society statement that “human lungs are made to breath clean air and any substance inhaled long term may be detrimental” [Bush et al. Electronic cigarettes for smoking cessation BMJ 2018;360: j5543] and on the basis of the literature analysis, the task force suggests a cautious use and application of ECIGs to avoid potential health problems or dangers. The area of ECIGs and novel inhaled devices remains a challenging and interesting field for healthcare providers, politicians and numerous other stakeholders. More independent and well-controlled studies are needed.

Table 2. Areas of future research

Epidemiology	• Provide long-term cohort data on risk for disease development, including lung, cardiovascular and infectious disease in ECIG users • Provide long-term data on risk for lung, cardiovascular and infectious disease in ECIG users who switched to vaping compared to those who continue to smoke • Compare trends in cigarette sales, smoking prevalence and, later on, in disease development (e.g. cancer and CVD morbidity), in countries that allow and countries that restrict vaping • Compare between different countries ECIG use pattern among adolescents, analysing differences in type of ECIGs that are used, risk factors for their use and long-term impact on cigarette smoking • Studies on the gateway hypothesis and normalization of smoking • Studies that assess risk of ECIGs for secondhand exposures
Clinical studies	• Conduct RCTs that compare the effectiveness of ECIGs with that of other stop-smoking interventions • Conduct RCTs on combination of ECIGs with licenced therapies for smoking cessation • Further characterisation of flavouring toxicology during exposure • Characterisation of secondhand exposures in different settings

Basic research	• Better assessment of actual exposure and deposition in models of ECIG exposure • Long-term studies (including time-course studies) to assess effects of prolonged ECIG use • Identification of molecular pattern to identify risks for disease development • More detailed analysis of components and ECIG design and effects of conditions of use on generation of potentially toxic thermal degradation products • Additional studies which characterise the health effects and toxicology of ECIG flavourings, particularly those that have not previously been studied

Literature

Reference List

1. Zyoud SeH, Al-Jabi SW, Sweileh WM. Worldwide research productivity in the field of electronic cigarette: a bibliometric analysis. *BMC public health* 2014: 14: 667.
2. Schraufnagel DE, Blasi F, Drummond MB, Lam DC, Latif E, Rosen MJ, Sansores R, Van Zyl-Smit R, Forum of International Respiratory S. Electronic cigarettes. A position statement of the forum of international respiratory societies. *Am J Respir Crit Care Med* 2014: 190(6): 611-618.
3. Camenga DR, Delmerico J, Kong G, Cavallo D, Hyland A, Cummings KM, Krishnan-Sarin S. Trends in use of electronic nicotine delivery systems by adolescents. *Addictive behaviors* 2014: 39: 338-340.
4. Cho JH, Shin E, Moon S-S. Electronic-cigarette smoking experience among adolescents. *The Journal of adolescent health : official publication of the Society for Adolescent Medicine* 2011: 49: 542-546.
5. Barnett TE, Soule EK, Forrest JR, Porter L, Tomar SL. Adolescent Electronic Cigarette Use: Associations With Conventional Cigarette and Hookah Smoking. *American journal of preventive medicine* 2015: 49: 199-206.
6. Kasza KA, Ambrose BK, Conway KP, Borek N, Taylor K, Goniewicz ML, Cummings KM, Sharma E, Pearson JL, Green VR, Kaufman AR, Bansal-Travers M, Travers MJ, Kwan J, Tworek C, Cheng YC, Yang L, Pharris-Ciurej N, van Bemmel DM, Backinger CL, Compton WM, Hyland AJ. Tobacco-Product Use by Adults and Youths in the United States in 2013 and 2014. *N Engl J Med* 2017: 376(4): 342-353.
7. White J, Li J, Newcombe R, Walton D. Tripling use of electronic cigarettes among New Zealand adolescents between 2012 and 2014. *The Journal of adolescent health : official publication of the Society for Adolescent Medicine* 2015: 56: 522-528.
8. Caraballo RS, Jamal A, Nguyen KH, Kuiper NM, Arrazola RA. Electronic Nicotine Delivery System Use Among U.S. Adults, 2014. *American journal of preventive medicine* 2016: 50: 226-229.
9. Czoli CD, Hammond D, Reid JL, Cole AG, Leatherdale ST. Use of Conventional and Alternative Tobacco and Nicotine Products Among a Sample of Canadian Youth. *The Journal of adolescent health : official publication of the Society for Adolescent Medicine* 2015: 57: 123-125.
10. Dutra LM, Glantz SA. Electronic cigarettes and conventional cigarette use among U.S. adolescents: a cross-sectional study. *JAMA pediatrics* 2014: 168: 610-617.
11. Eastwood B, Dockrell MJ, Arnott D, Britton J, Cheeseman H, Jarvis MJ, McNeill A. Electronic cigarette use in young people in Great Britain 2013-2014. *Public Health* 2015: 129(9): 1150-1156.
12. Gilreath TD, Leventhal A, Barrington-Trimis JL, Unger JB, Cruz TB, Berhane K, Huh J, Urman R, Wang K, Howland S, Pentz MA, Chou CP, McConnell R. Patterns of Alternative Tobacco Product Use: Emergence of Hookah and E-cigarettes as Preferred Products Amongst Youth. *J Adolesc Health* 2016: 58(2): 181-185.

13. Krishnan-Sarin S, Morean ME, Camenga DR, Cavallo DA, Kong G. E-cigarette Use Among High School and Middle School Adolescents in Connecticut. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco* 2015: 17: 810-818.
14. Lee YO, Hebert CJ, Nonnemaker JM, Kim AE. Youth tobacco product use in the United States. *Pediatrics* 2015: 135: 409-415.
15. Corsi DJ, Lippert AM. An examination of the shift in school-level clustering of US adolescent electronic cigarette use and its multilevel correlates, 2011-2013. *Health & place* 2016: 38: 30-38.
16. Warner KE. Frequency of E-Cigarette Use and Cigarette Smoking by American Students in 2014. *American journal of preventive medicine* 2016: 51: 179-184.
17. Cardenas VM, Breen PJ, Compadre CM, Delongchamp RR, Barone CP, Phillips MM, Wheeler JG. The smoking habits of the family influence the uptake of e-cigarettes in US children. *Annals of Epidemiology* 2015: 25: 60-62.
18. Hanewinkel R, Isensee B. Risk factors for e-cigarette, conventional cigarette, and dual use in German adolescents: a cohort study. *Preventive medicine* 2015: 74: 59-62.
19. Bauld L, MacKintosh AM, Ford A, McNeill A. E-Cigarette Uptake Amongst UK Youth: Experimentation, but Little or No Regular Use in Nonsmokers. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco* 2016: 18(1): 102-103.
20. Ooms GI, Bosdriesz JR, Portrait FR, Kunst AE. Sociodemographic Differences in the Use of Electronic Nicotine Delivery Systems in the European Union. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco* 2016: 18(5): 724-729.
21. Vardavas CI, Filippidis FT, Agaku IT. Determinants and prevalence of e-cigarette use throughout the European Union: a secondary analysis of 26 566 youth and adults from 27 Countries. *Tobacco control* 2015: 24(5): 442-448.
22. Agaku IT, Filippidis FT, Vardavas CI, Odukoya OO, Awopegba AJ, Ayo-Yusuf OA, Connolly GN. Poly-tobacco use among adults in 44 countries during 2008-2012: evidence for an integrative and comprehensive approach in tobacco control. *Drug and alcohol dependence* 2014: 139: 60-70.
23. Commission E. Special Eurobarometer 458: Attitudes of Europeans towards tobacco and electronic cigarettes 2017 [cited; Available from: https://data.europa.eu/euodp/en/data/dataset/S2146_87_1_458_ENG
24. Tavolacci MP, Vasiliu A, Romo L, Kotbagi G, Kern L, Ladner J. Patterns of electronic cigarette use in current and ever users among college students in France: a cross-sectional study. *BMJ Open* 2016: 6(5): e011344.
25. Gravely S, Fong GT, Cummings KM, Yan M, Quah ACK, Borland R, Yong H-H, Hitchman SC, McNeill A, Hammond D, Thrasher JF, Willemsen MC, Seo HG, Jiang Y, Cavalcante T, Perez C, Omar M, Hummel K. Awareness, trial, and current use of electronic cigarettes in 10 countries: Findings from the ITC project. *International journal of environmental research and public health* 2014: 11: 11691-11704.
26. Andler R, Guignard R, Wilquin JL, Beck F, Richard JB, Nguyen-Thanh V. Electronic cigarette use in France in 2014. *Int J Public Health* 2016: 61(2): 159-165.
27. Babineau K, Taylor K, Clancy L. Electronic Cigarette Use among Irish Youth: A Cross Sectional Study of Prevalence and Associated Factors. *PloS one* 2015: 10(5): e0126419.
28. Adkison SE, O'Connor RJ, Bansal-Travers M, Hyland A, Borland R, Yong HH, Cummings KM, McNeill A, Thrasher JF, Hammond D, Fong GT. Electronic nicotine

delivery systems: international tobacco control four-country survey. *American journal of preventive medicine* 2013: 44(3): 207-215.
29. Allem J-P, Forster M, Neiberger A, Unger JB. Characteristics of emerging adulthood and e-cigarette use: Findings from a pilot study. *Addictive behaviors* 2015: 50: 40-44.
30. Brown J, West R, Beard E, Michie S, Shahab L, McNeill A. Prevalence and characteristics of e-cigarette users in Great Britain: Findings from a general population survey of smokers. *Addictive behaviors* 2014: 39: 1120-1125.
31. Dockrell M, Morrison R, Bauld L, McNeill A. E-cigarettes: prevalence and attitudes in Great Britain. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco* 2013: 15: 1737-1744.
32. Douptcheva N, Gmel G, Studer J, Deline S, Etter J-F. Use of electronic cigarettes among young Swiss men. *Journal of epidemiology and community health* 2013: 67: 1075-1076.
33. King BA, Patel R, Nguyen KH, Dube SR. Trends in awareness and use of electronic cigarettes among US adults, 2010-2013. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco* 2015: 17: 219-227.
34. McMillen RC, Gottlieb MA, Shaefer RMW, Winickoff JP, Klein JD. Trends in Electronic Cigarette Use Among U.S. Adults: Use is Increasing in Both Smokers and Nonsmokers. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco* 2015: 17: 1195-1202.
35. Weaver SR, Majeed BA, Pechacek TF, Nyman AL, Gregory KR, Eriksen MP. Use of electronic nicotine delivery systems and other tobacco products among USA adults, 2014: results from a national survey. *International journal of public health* 2015.
36. Rutten LJF, Blake KD, Agunwamba AA, Grana RA, Wilson PM, Ebbert JO, Okamoto J, Leischow SJ. Use of E-Cigarettes Among Current Smokers: Associations Among Reasons for Use, Quit Intentions, and Current Tobacco Use. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco* 2015: 17: 1228-1234.
37. Adkison SE, O'Connor RJ, Bansal-Travers M, Hyland A, Borland R, Yong H-H, Cummings KM, McNeill A, Thrasher JF, Hammond D, Fong GT. Electronic Nicotine Delivery Systems. *American journal of preventive medicine* 2013: 44: 207-215.
38. Borderud SP, Li Y, Burkhalter JE, Sheffer CE, Ostroff JS. Electronic cigarette use among patients with cancer: characteristics of electronic cigarette users and their smoking cessation outcomes. *Cancer* 2014: 120: 3527-3535.
39. 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 (Abingdon, England)* 2016.
40. Filippidis FT, Gerovasili V, Laverty AA. Commentary on Farsalinos et al. (2016): Electronic cigarette use in the European Union: analysis of a representative sample of 27 460 Europeans from 28 countries. *Addiction* 2017: 112(3): 544-545.
41. Laverty AA, Vardavas CI, Filippidis FT. Design and marketing features influencing choice of e-cigarettes and tobacco in the EU. *European journal of public health* 2016: 26(5): 838-841.
42. Pepper JK, Ribisl KM, Emery SL, Brewer NT. Reasons for starting and stopping electronic cigarette use. *International journal of environmental research and public health* 2014: 11: 10345-10361.
43. Kong G, Morean ME, Cavallo DA, Camenga DR, Krishnan-Sarin S. Reasons for Electronic Cigarette Experimentation and Discontinuation Among Adolescents and Young Adults. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco* 2015: 17: 847-854.

44. Cummins SE, Zhu SH, Tedeschi GJ, Gamst AC, Myers MG. Use of e-cigarettes by individuals with mental health conditions. *Tobacco control* 2014: 23 Suppl 3: iii48-53.
45. Prochaska JJ, Grana RA. E-cigarette use among smokers with serious mental illness. *PloS one* 2014: 9: e113013.
46. Lee YO, Hebert CJ, Nonnemaker JM, Kim AE. Multiple tobacco product use among adults in the United States: cigarettes, cigars, electronic cigarettes, hookah, smokeless tobacco, and snus. *Preventive medicine* 2014: 62: 14-19.
47. Amato MS, Boyle RG, Levy D. How to define e-cigarette prevalence? Finding clues in the use frequency distribution. *Tobacco control* 2016: 25(e1): e24-29.
48. Giovenco DP, Lewis MJ, Delnevo CD. Factors associated with e-cigarette use: a national population survey of current and former smokers. *American journal of preventive medicine* 2014: 47: 476-480.
49. Lerner CA, Sundar IK, Yao H, Gerloff J, Ossip DJ, McIntosh S, Robinson R, Rahman I. 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(2): e0116732.
50. Hiemstra PS, Bals R. Basic science of electronic cigarettes: assessment in cell culture and in vivo models. *Respir Res* 2016: 17(1): 127.
51. Schweitzer KS, Chen SX, Law S, Van Demark M, Poirier C, Justice MJ, Hubbard WC, Kim ES, Lai X, Wang M, Kranz WD, Carroll CJ, Ray BD, Bittman R, Goodpaster J, Petrache I. Endothelial disruptive proinflammatory effects of nicotine and e-cigarette vapor exposures. *Am J Physiol Lung Cell Mol Physiol* 2015: 309(2): L175-187.
52. Farsalinos KE, Romagna G, Allifranchini E, Ripamonti E, Bocchietto E, Todeschi S, Tsiapras D, Kyrzopoulos S, Voudris V. Comparison of the cytotoxic potential of cigarette smoke and electronic cigarette vapour extract on cultured myocardial cells. *International journal of environmental research and public health* 2013: 10: 5146-5162.
53. 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(6): 354-361.
54. Moses E, Wang T, Corbett S, Jackson GR, Drizik E, Perdomo C, Perdomo C, Kleerup E, Brooks D, O'Connor G, Dubinett S, Hayden P, Lenburg ME, Spira A. Molecular Impact of Electronic Cigarette Aerosol Exposure in Human Bronchial Epithelium. *Toxicol Sci* 2017: 155(1): 248-257.
55. Misra M, Leverette RD, Cooper BT, Bennett MB, Brown SE. Comparative in vitro toxicity profile of electronic and tobacco cigarettes, smokeless tobacco and nicotine replacement therapy products: e-liquids, extracts and collected aerosols. *International journal of environmental research and public health* 2014: 11: 11325-11347.
56. 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. *International journal of environmental research and public health* 2015: 12(4): 3915-3925.
57. Cervellati F, Muresan XM, Sticozzi C, Gambari R, Montagner G, Forman HJ, Torricelli C, Maioli E, Valacchi G. Comparative effects between electronic and cigarette smoke in human keratinocytes and epithelial lung cells. *Toxicology in vitro : an international journal published in association with BIBRA* 2014: 28(5): 999-1005.
58. Husari A, Shihadeh A, Talih S, Hashem Y, El Sabban M, Zaatari G. Acute Exposure to Electronic and Combustible Cigarette Aerosols: Effects in an Animal Model and in Human Alveolar Cells. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco* 2016: 18(5): 613-619.

59. 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. *Toxicology in vitro : an international journal published in association with BIBRA* 2015: 29(7): 1952-1962.
60. Shivalingappa PC, Hole R, Westphal CV, Vij N. Airway Exposure to E-Cigarette Vapors Impairs Autophagy and Induces Aggresome Formation. *Antioxid Redox Signal* 2015.
61. Sancilio S, Gallorini M, Cataldi A, di Giacomo V. Cytotoxicity and apoptosis induction by e-cigarette fluids in human gingival fibroblasts. *Clin Oral Investig* 2016: 20(3): 477-483.
62. Yoshiyama S, Chen Z, Okagaki T, Kohama K, Nasu-Kawaharada R, Izumi T, Ohshima N, Nagai T, Nakamura A. Nicotine exposure alters human vascular smooth muscle cell phenotype from a contractile to a synthetic type. *Atherosclerosis* 2014: 237(2): 464-470.
63. Bahl V, Lin S, Xu N, Davis B, Wang YH, Talbot P. Comparison of electronic cigarette refill fluid cytotoxicity using embryonic and adult models. *Reprod Toxicol* 2012: 34(4): 529-537.
64. Higham A, Rattray NJ, Dewhurst JA, Trivedi DK, Fowler SJ, Goodacre R, Singh D. Electronic cigarette exposure triggers neutrophil inflammatory responses. *Respir Res* 2016: 17(1): 56.
65. Rubenstein DA, Hom S, Ghebrehiwet B, Yin W. Tobacco and e-cigarette products initiate Kupffer cell inflammatory responses. *Mol Immunol* 2015: 67(2 Pt B): 652-660.
66. Wu Q, Jiang D, Minor M, Chu HW. Electronic Cigarette Liquid Increases Inflammation and Virus Infection in Primary Human Airway Epithelial Cells. *PloS one* 2014: 9(9): e108342.
67. Kosmider L, Sobczak A, Fik M, Knysak J, Zaciera M, Kurek J, Goniewicz ML. Carbonyl compounds in electronic cigarette vapors: effects of nicotine solvent and battery output voltage. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco* 2014: 16(10): 1319-1326.
68. Yu V, Rahimy M, Korrapati A, Xuan Y, Zou AE, Krishnan AR, Tsui T, Aguilera JA, Advani S, Crotty Alexander LE, Brumund KT, Wang-Rodriguez J, Ongkeko WM. Electronic cigarettes induce DNA strand breaks and cell death independently of nicotine in cell lines. *Oral Oncol* 2016: 52: 58-65.
69. Sancilio S, Gallorini M, Cataldi A, di Giacomo V. Cytotoxicity and apoptosis induction by e-cigarette fluids in human gingival fibroblasts. *Clinical oral investigations* 2015.
70. Aug A, Altraja S, Kilk K, Porosk R, Soomets U, Altraja A. E-Cigarette Affects the Metabolome of Primary Normal Human Bronchial Epithelial Cells. *PloS one* 2015: 10(11): e0142053.
71. Lim HB, Kim SH. Inhallation of e-Cigarette Cartridge Solution Aggravates Allergen-induced Airway Inflammation and Hyper-responsiveness in Mice. *Toxicological research* 2014: 30(1): 13-18.
72. Garcia-Arcos I, Geraghty P, Baumlin N, Campos M, Dabo AJ, Jundi B, Cummins N, Eden E, Grosche A, Salathe M, Foronjy R. Chronic electronic cigarette exposure in mice induces features of COPD in a nicotine-dependent manner. *Thorax* 2016.
73. Phillips B, Veljkovic E, Peck MJ, Buettner A, Elamin A, Guedj E, Vuillaume G, Ivanov NV, Martin F, Boue S, Schlage WK, Schneider T, Titz B, Talikka M, Vanscheeuwijck P, Hoeng J, Peitsch MC. A 7-month cigarette smoke inhalation study in C57BL/6 mice demonstrates reduced lung inflammation and emphysema following smoking cessation or aerosol exposure from a prototypic modified risk tobacco product. *Food Chem Toxicol* 2015: 80: 328-345.

74. Sussan TE, Gajghate S, Thimmulappa RK, Ma J, Kim JH, Sudini K, Consolini N, Cormier SA, Lomnicki S, Hasan F, Pekosz A, Biswal S. Exposure to electronic cigarettes impairs pulmonary anti-bacterial and anti-viral defenses in a mouse model. *PloS one* 2015: 10(2): e0116861.
75. Hwang JH, Lyes M, Sladewski K, Enany S, McEachern E, Mathew DP, Das S, Moshensky A, Bapat S, Pride DT, Ongkeko WM, Crotty Alexander LE. Electronic cigarette inhalation alters innate immunity and airway cytokines while increasing the virulence of colonizing bacteria. *J Mol Med (Berl)* 2016.
76. Canistro D, Vivarelli F, Cirillo S, Babot Marquillas C, Buschini A, Lazzaretti M, Marchi L, Cardenia V, Rodriguez-Estrada MT, Lodovici M, Cipriani C, Lorenzini A, Croco E, Marchionni S, Franchi P, Lucarini M, Longo V, Della Croce CM, Vornoli A, Colacci A, Vaccari M, Sapone A, Paolini M. E-cigarettes induce toxicological effects that can raise the cancer risk. *Sci Rep* 2017: 7(1): 2028.
77. McGrath-Morrow SA, Hayashi M, Aherrera A, Lopez A, Malinina A, Collaco JM, Neptune E, Klein JD, Winickoff JP, Breysse P, Lazarus P, Chen G. The effects of electronic cigarette emissions on systemic cotinine levels, weight and postnatal lung growth in neonatal mice. *PloS one* 2015: 10(2): e0118344.
78. Ponzoni L, Moretti M, Sala M, Fasoli F, Mucchietto V, Lucini V, Cannazza G, Gallesi G, Castellana CN, Clementi F, Zoli M, Gotti C, Braida D. Different physiological and behavioural effects of e-cigarette vapour and cigarette smoke in mice. *Eur Neuropsychopharmacol* 2015.
79. Smith D, Aherrera A, Lopez A, Neptune E, Winickoff JP, Klein JD, Chen G, Lazarus P, Collaco JM, McGrath-Morrow SA. Adult Behavior in Male Mice Exposed to E-Cigarette Nicotine Vapors during Late Prenatal and Early Postnatal Life. *PloS one* 2015: 10(9): e0137953.
80. El Golli N, Rahali D, Jrad-Lamine A, Dallagi Y, Jallouli M, Bdiri Y, Ba N, Lebret M, Rosa JP, El May M, El Fazaa S. Impact of electronic-cigarette refill liquid on rat testis. *Toxicol Mech Methods* 2016: 26(6): 427-434.
81. El Golli N, Dkhili H, Dallagi Y, Rahali D, Lasram M, Bini-Dhouib I, Lebret M, Rosa J-P, El Fazaa S, Asmi MA-E. Comparison between electronic cigarette refill liquid and nicotine on metabolic parameters in rats. *Life sciences* 2016: 146: 131-138.
82. Golli NE, Jrad-Lamine A, Neffati H, Dkhili H, Rahali D, Dallagi Y, El May MV, El Fazaa S. Impact of e-cigarette refill liquid exposure on rat kidney. *Regul Toxicol Pharmacol* 2016: 77: 109-116.
83. 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: 10: e0126259.
84. Panitz D, Swamy H, Nehrke K. A C. elegans model of electronic cigarette use: Physiological effects of e-liquids in nematodes. *BMC pharmacology & toxicology* 2015: 16: 32.
85. Brown JE, Luo W, Isabelle LM, Pankow JF. Candy flavorings in tobacco. *The New England journal of medicine* 2014: 370: 2250-2252.
86. 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 & tobacco research : official journal of the Society for Research on Nicotine and Tobacco* 2015: 17: 1270-1278.
87. Peace MR, Baird TR, Smith N, Wolf CE, Poklis JL, Poklis A. Concentration of Nicotine and Glycols in 27 Electronic Cigarette Formulations. *Journal of analytical toxicology* 2016: 40: 403-407.

88. Barrington-Trimis JL, Samet JM, McConnell R. Flavorings in electronic cigarettes: an unrecognized respiratory health hazard? *JAMA* 2014: 312: 2493-2494.
89. Behar RZ, Davis B, Wang Y, Bahl V, Lin S, Talbot P. Identification of toxicants in cinnamon-flavored electronic cigarette refill fluids. *Toxicology in vitro : an international journal published in association with BIBRA* 2014: 28(2): 198-208.
90. Kosmider L, Sobczak A, Prokopowicz A, Kurek J, Zaciera M, Knysak J, Smith D, Goniewicz ML. Cherry-flavoured electronic cigarettes expose users to the inhalation irritant, benzaldehyde. *Thorax* 2016: 71(4): 376-377.
91. Farsalinos KE, Kistler KA, Gillman G, Voudris V. Evaluation of electronic cigarette liquids and aerosol for the presence of selected inhalation toxins. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco* 2015: 17(2): 168-174.
92. El-Hellani A, El-Hage R, Baalbaki R, Salman R, Talih S, Shihadeh A, Saliba NA. Free-Base and Protonated Nicotine in Electronic Cigarette Liquids and Aerosols. *Chemical research in toxicology* 2015: 28: 1532-1537.
93. Jensen RP, Luo W, Pankow JF, Strongin RM, Peyton DH. Hidden formaldehyde in e-cigarette aerosols. *N Engl J Med* 2015: 372(4): 392-394.
94. Sleiman M, Logue JM, Montesinos VN, Russell ML, Litter MI, Gundel LA, Destaillats H. Emissions from Electronic Cigarettes: Key Parameters Affecting the Release of Harmful Chemicals. *Environmental science & technology* 2016.
95. Uchiyama S, Ohta K, Inaba Y, Kunugita N. Determination of carbonyl compounds generated from the E-cigarette using coupled silica cartridges impregnated with hydroquinone and 2,4-dinitrophenylhydrazine, followed by high-performance liquid chromatography. *Analytical sciences : the international journal of the Japan Society for Analytical Chemistry* 2013: 29(12): 1219-1222.
96. Pankow JF, Kim K, McWhirter KJ, Luo W, Escobedo JO, Strongin RM, Duell AK, Peyton DH. Benzene formation in electronic cigarettes. *PloS one* 2017: 12(3): e0173055.
97. Khlystov A, Samburova V. Flavoring Compounds Dominate Toxic Aldehyde Production during E-Cigarette Vaping. *Environmental Science & Technology* 2016: 50: 13080-13085.
98. Goniewicz ML, Knysak J, Gawron M, Kosmider L, Sobczak A, Kurek J, Prokopowicz A, Jablonska-Czapla M, Rosik-Dulewska C, Havel C, Jacob P, 3rd, Benowitz N. Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. *Tobacco control* 2014: 23(2): 133-139.
99. 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 : official journal of the Society for Research on Nicotine and Tobacco* 2016.
100. Goel R, Durand E, Trushin N, Prokopczyk B, Foulds J, Elias RJ, Richie JP. Highly Reactive Free Radicals in Electronic Cigarette Aerosols. *Chemical Research in Toxicology* 2015: 28: 1675-1677.
101. 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: 1400-1406.
102. Palamidas A, Tsikrika S, Katsaounou P, Vakali S, Gennimata S-A, kaltsakas G, Gratziou C, Koulouris N. Acute effects of short term use of e-cigarettes on airways physiology and respiratory symptoms in smokers with and without airways obstructive diseases and in healthy non smokers. *Tobacco Prevention & Cessation* 2017: 3(March).

103. Flouris AD, Chorti MS, Poulianiti KP, Jamurtas AZ, Kostikas K, Tzatzarakis MN, Wallace Hayes A, Tsatsakis AM, Koutedakis Y. Acute impact of active and passive electronic cigarette smoking on serum cotinine and lung function. *Inhalation toxicology* 2013: 25: 91-101.
104. Cibella F, Campagna D, Caponnetto P, Amaradio MD, Caruso M, Russo C, Cockcroft DW, Polosa R. Lung function and respiratory symptoms in a randomized smoking cessation trial of electronic cigarettes. *Clin Sci (Lond)* 2016: 130(21): 1929-1937.
105. Polosa R, Morjaria JB, Caponnetto P, Prosperini U, Russo C, Pennisi A, Bruno CM. Evidence for harm reduction in COPD smokers who switch to electronic cigarettes. *Respir Res* 2016: 17(1): 166.
106. 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 epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* 2010: 19: 1945-1953.
107. Vansickel AR, Eissenberg T. Electronic cigarettes: effective nicotine delivery after acute administration. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco* 2013: 15: 267-270.
108. Farsalinos KE, Tsiapras D, Kyrzopoulos S, Savvopoulou M, Voudris V. Acute effects of using an electronic nicotine-delivery device (electronic cigarette) on myocardial function: comparison with the effects of regular cigarettes. *BMC cardiovascular disorders* 2014: 14: 78.
109. Polosa R, Morjaria JB, Caponnetto P, Battaglia E, Russo C, Ciampi C, Adams G, Bruno CM. Blood Pressure Control in Smokers with Arterial Hypertension Who Switched to Electronic Cigarettes. *International journal of environmental research and public health* 2016: 13(11).
110. Farsalinos K, Cibella F, Caponnetto P, Campagna D, Morjaria JB, Battaglia E, Caruso M, Russo C, Polosa R. Effect of continuous smoking reduction and abstinence on blood pressure and heart rate in smokers switching to electronic cigarettes. *Internal and emergency medicine* 2016: 1-10.
111. Vlachopoulos C, Ioakeimidis N, Abdelrasoul M, Terentes-Printzios D, Georgakopoulos C, Pietri P, Stefanadis C, Tousoulis D. Electronic Cigarette Smoking Increases Aortic Stiffness and Blood Pressure in Young Smokers. *J Am Coll Cardiol* 2016: 67(23): 2802-2803.
112. Szołtysek-Bołdys I, Sobczak A, Zielińska-Danch W, Bartoń A, Koszowski B, Kośmider L. Influence of inhaled nicotine source on arterial stiffness. *Przegląd lekarski* 2014: 71: 572-575.
113. Carnevale R, Sciarretta S, Violi F, Nocella C, Loffredo L, Perri L, Peruzzi M, Marullo AG, De Falco E, Chimenti I, Valenti V, Biondi-Zoccai G, Frati G. Acute impact of tobacco versus electronic cigarette smoking on oxidative stress and vascular function. *Chest* 2016.
114. Antoniewicz L, Bosson JA, Kuhl J, Abdel-Halim SM, Kiessling A, Mobarrez F, Lundback M. Electronic cigarettes increase endothelial progenitor cells in the blood of healthy volunteers. *Atherosclerosis* 2016: 255: 179-185.
115. Moheimani RS, Bhetraratana M, Yin F, Peters KM, Gornbein J, Araujo JA, Middlekauff HR. Increased Cardiac Sympathetic Activity and Oxidative Stress in Habitual Electronic Cigarette Users: Implications for Cardiovascular Risk. *JAMA cardiology* 2017.
116. Miech RA, O'Malley PM, Johnston LD, Patrick ME. E-Cigarettes and the Drug Use Patterns of Adolescents. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco* 2016: 18(5): 654-659.

117. Laugesen M. Nicotine and toxicant yield ratings of electronic cigarette brands in New Zealand. *The New Zealand medical journal* 2015: 128: 77-82.
118. Filippini P, Cesario A, Fini M, Locatelli F, Rutella S. The Yin and Yang of non-neuronal alpha7-nicotinic receptors in inflammation and autoimmunity. *Curr Drug Targets* 2012: 13(5): 644-655.
119. Jiang Y, Dai A, Zhou Y, Peng G, Hu G, Li B, Sham JS, Ran P. Nicotine elevated intracellular Ca(2)(+) in rat airway smooth muscle cells via activating and up-regulating alpha7-nicotinic acetylcholine receptor. *Cell Physiol Biochem* 2014: 33(2): 389-401.
120. Wilk JB, Shrine NR, Loehr LR, Zhao JH, Manichaikul A, Lopez LM, Smith AV, Heckbert SR, Smolonska J, Tang W, Loth DW, Curjuric I, Hui J, Cho MH, Latourelle JC, Henry AP, Aldrich M, Bakke P, Beaty TH, Bentley AR, Borecki IB, Brusselle GG, Burkart KM, Chen TH, Couper D, Crapo JD, Davies G, Dupuis J, Franceschini N, Gulsvik A, Hancock DB, Harris TB, Hofman A, Imboden M, James AL, Khaw KT, Lahousse L, Launer LJ, Litonjua A, Liu Y, Lohman KK, Lomas DA, Lumley T, Marciante KD, McArdle WL, Meibohm B, Morrison AC, Musk AW, Myers RH, North KE, Postma DS, Psaty BM, Rich SS, Rivadeneira F, Rochat T, Rotter JI, Soler Artigas M, Starr JM, Uitterlinden AG, Wareham NJ, Wijmenga C, Zanen P, Province MA, Silverman EK, Deary IJ, Palmer LJ, Cassano PA, Gudnason V, Barr RG, Loos RJ, Strachan DP, London SJ, Boezen HM, Probst-Hensch N, Gharib SA, Hall IP, O'Connor GT, Tobin MD, Stricker BH. Genome-wide association studies identify CHRNA5/3 and HTR4 in the development of airflow obstruction. *Am J Respir Crit Care Med* 2012: 186(7): 622-632.
121. Zia S, Ndoye A, Nguyen VT, Grando SA. Nicotine enhances expression of the alpha 3, alpha 4, alpha 5, and alpha 7 nicotinic receptors modulating calcium metabolism and regulating adhesion and motility of respiratory epithelial cells. *Res Commun Mol Pathol Pharmacol* 1997: 97(3): 243-262.
122. Maus AD, Pereira EF, Karachunski PI, Horton RM, Navaneetham D, Macklin K, Cortes WS, Albuquerque EX, Conti-Fine BM. Human and rodent bronchial epithelial cells express functional nicotinic acetylcholine receptors. *Mol Pharmacol* 1998: 54(5): 779-788.
123. Carlisle DL, Hopkins TM, Gaither-Davis A, Silhanek MJ, Luketich JD, Christie NA, Siegfried JM. Nicotine signals through muscle-type and neuronal nicotinic acetylcholine receptors in both human bronchial epithelial cells and airway fibroblasts. *Respir Res* 2004: 5: 27.
124. Maouche K, Polette M, Jolly T, Medjber K, Cloez-Tayarani I, Changeux JP, Burlet H, Terryn C, Coraux C, Zahm JM, Birembaut P, Tournier JM. {alpha}7 nicotinic acetylcholine receptor regulates airway epithelium differentiation by controlling basal cell proliferation. *Am J Pathol* 2009: 175(5): 1868-1882.
125. Proskocil BJ, Sekhon HS, Jia Y, Savchenko V, Blakely RD, Lindstrom J, Spindel ER. Acetylcholine is an autocrine or paracrine hormone synthesized and secreted by airway bronchial epithelial cells. *Endocrinology* 2004: 145(5): 2498-2506.
126. Li ZZ, Dai QY. Pathogenesis of abdominal aortic aneurysms: role of nicotine and nicotinic acetylcholine receptors. *Mediators Inflamm* 2012: 2012: 103120.
127. Fu XW, Wood K, Spindel ER. Prenatal nicotine exposure increases GABA signaling and mucin expression in airway epithelium. *Am J Respir Cell Mol Biol* 2011: 44(2): 222-229.
128. Hahn HL, Lang M, Bleicher S, Zwerenz S, Rausch C. Nicotine-induced airway smooth muscle contraction: neural mechanisms involving the airway epithelium. Functional and histologic studies in vitro. *Clin Investig* 1992: 70(3-4): 252-262.
129. Takayanagi I, Kizawa Y, Sone H. Action of nicotine on guinea-pig isolated bronchial smooth muscle preparation. *Gen Pharmacol* 1984: 15(4): 349-352.

130. Boucherat O, Boczkowski J, Jeannotte L, Delacourt C. Cellular and molecular mechanisms of goblet cell metaplasia in the respiratory airways. *Exp Lung Res* 2013: 39(4-5): 207-216.
131. Barnes PJ. Cellular and molecular mechanisms of chronic obstructive pulmonary disease. *Clin Chest Med* 2014: 35(1): 71-86.
132. Maouche K, Medjber K, Zahm JM, Delavoie F, Terryn C, Coraux C, Pons S, Cloez-Tayarani I, Maskos U, Birembaut P, Tournier JM. Contribution of alpha7 nicotinic receptor to airway epithelium dysfunction under nicotine exposure. *Proc Natl Acad Sci U S A* 2013: 110(10): 4099-4104.
133. Paleari L, Catassi A, Ciarlo M, Cavalieri Z, Bruzzo C, Servent D, Cesario A, Chessa L, Cilli M, Piccardi F, Granone P, Russo P. Role of alpha7-nicotinic acetylcholine receptor in human non-small cell lung cancer proliferation. *Cell Prolif* 2008: 41(6): 936-959.
134. Seguela P, Wadiche J, Dineley-Miller K, Dani JA, Patrick JW. Molecular cloning, functional properties, and distribution of rat brain alpha 7: a nicotinic cation channel highly permeable to calcium. *J Neurosci* 1993: 13(2): 596-604.
135. Boncoeur E, Bouvet GF, Migneault F, Tardif V, Ferraro P, Radzioch D, de Sanctis JB, Eidelman D, Govindaraju K, Dagenais A, Berthiaume Y. Induction of nitric oxide synthase expression by lipopolysaccharide is mediated by calcium-dependent PKCalpha-beta1 in alveolar epithelial cells. *Am J Physiol Lung Cell Mol Physiol* 2013: 305(2): L175-184.
136. He F, Li B, Zhao Z, Zhou Y, Hu G, Zou W, Hong W, Zou Y, Jiang C, Zhao D, Ran P. The pro-proliferative effects of nicotine and its underlying mechanism on rat airway smooth muscle cells. *PloS one* 2014: 9(4): e93508.
137. Pera T, Gosens R, Lesterhuis AH, Sami R, van der Toorn M, Zaagsma J, Meurs H. Cigarette smoke and lipopolysaccharide induce a proliferative airway smooth muscle phenotype. *Respir Res* 2010: 11: 48.
138. Grozio A, Catassi A, Cavalieri Z, Paleari L, Cesario A, Russo P. Nicotine, lung and cancer. *Anticancer Agents Med Chem* 2007: 7(4): 461-466.
139. Diamond L, Kimmel EC, Lai YL, Winsett DW. Augmentation of elastase-induced emphysema by cigarette smoke. Effects of reduced nicotine content. *Am Rev Respir Dis* 1988: 138(5): 1201-1206.
140. Bodas M, Van Westphal C, Carpenter-Thompson R, K Mohanty D, Vij N. Nicotine exposure induces bronchial epithelial cell apoptosis and senescence via ROS mediated autophagy-impairment. *Free radical biology & medicine* 2016: 97: 441-453.
141. Segura-Valdez L, Pardo A, Gaxiola M, Uhal BD, Becerril C, Selman M. Upregulation of gelatinases A and B, collagenases 1 and 2, and increased parenchymal cell death in COPD. *Chest* 2000: 117(3): 684-694.
142. Geraghty P, Hardigan A, Foronjy RF. Cigarette smoke activates the proto-oncogene c-src to promote airway inflammation and lung tissue destruction. *Am J Respir Cell Mol Biol* 2014: 50(3): 559-570.
143. Iskandar AR, Liu C, Smith DE, Hu KQ, Choi SW, Ausman LM, Wang XD. beta-cryptoxanthin restores nicotine-reduced lung SIRT1 to normal levels and inhibits nicotine-promoted lung tumorigenesis and emphysema in A/J mice. *Cancer Prev Res (Phila)* 2013: 6(4): 309-320.
144. Nishioka T, Guo J, Yamamoto D, Chen L, Huppi P, Chen CY. Nicotine, through upregulating pro-survival signaling, cooperates with NNK to promote transformation. *J Cell Biochem* 2010: 109(1): 152-161.
145. Hanaki T, Horikoshi Y, Nakaso K, Nakasone M, Kitagawa Y, Amisaki M, Arai Y, Tokuyasu N, Sakamoto T, Honjo S, Saito H, Ikeguchi M, Yamashita K, Ohno S, Matsura T.

Nicotine enhances the malignant potential of human pancreatic cancer cells via activation of atypical protein kinase C. *Biochimica et biophysica acta* 2016.
146. Czyzykowski R, Polowinczak-Przybylek J, Potemski P. Nicotine-induced resistance of non-small cell lung cancer to treatment--possible mechanisms. *Postepy Hig Med Dosw (Online)* 2016: 70: 186-193.
147. Hao J, Shi FD, Abdelwahab M, Shi SX, Simard A, Whiteaker P, Lukas R, Zhou Q. Nicotinic receptor beta2 determines NK cell-dependent metastasis in a murine model of metastatic lung cancer. *PloS one* 2013: 8(2): e57495.
148. Murphy SE, von Weymarn LB, Schutten MM, Kassie F, Modiano JF. Chronic nicotine consumption does not influence 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone-induced lung tumorigenesis. *Cancer Prev Res (Phila)* 2011: 4(11): 1752-1760.
149. Maier CR, Hollander MC, Hobbs EA, Dogan I, Linnoila RI, Dennis PA. Nicotine does not enhance tumorigenesis in mutant K-ras-driven mouse models of lung cancer. *Cancer Prev Res (Phila)* 2011: 4(11): 1743-1751.
150. Foulds J, Ramstrom L, Burke M, Fagerstrom K. Effect of smokeless tobacco (snus) on smoking and public health in Sweden. *Tobacco control* 2003: 12(4): 349-359.
151. Luo J, Ye W, Zendehdel K, Adami J, Adami HO, Boffetta P, Nyren O. Oral use of Swedish moist snuff (snus) and risk for cancer of the mouth, lung, and pancreas in male construction workers: a retrospective cohort study. *Lancet* 2007: 369(9578): 2015-2020.
152. Wilson KM, Markt SC, Fang F, Nordenvall C, Rider JR, Ye W, Adami HO, Stattin P, Nyren O, Mucci LA. Snus use, smoking and survival among prostate cancer patients. *Int J Cancer* 2016: 139(12): 2753-2759.
153. 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. *Scientific reports* 2014: 4: 4133.
154. Hajek P, Przulj D, Phillips A, Anderson R, McRobbie H. Nicotine delivery to users from cigarettes and from different types of e-cigarettes. *Psychopharmacology (Berl)* 2017: 234(5): 773-779.
155. Talih S, Balhas Z, Eissenberg T, Salman R, Karaoghlanian N, El Hellani A, Baalbaki R, Saliba N, Shihadeh A. Effects of user puff topography, device voltage, and liquid nicotine concentration on electronic cigarette nicotine yield: measurements and model predictions. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco* 2015: 17: 150-157.
156. Wagener TL, Floyd EL, Stepanov I, Driskill LM, Frank SG, Meier E, Leavens EL, Tackett AP, Molina N, Queimado L. Have combustible cigarettes met their match? The nicotine delivery profiles and harmful constituent exposures of second-generation and third-generation electronic cigarette users. *Tobacco control* 2016(0): 1-6.
157. Etter J-F. Levels of saliva cotinine in electronic cigarette users. *Addiction (Abingdon, England)* 2014: 109: 825-829.
158. Benowitz NL, Burbank AD. Cardiovascular toxicity of nicotine: Implications for electronic cigarette use. *Trends in cardiovascular medicine* 2016: 26: 515-523.
159. Arefalk G, Hambraeus K, Lind L, Michaelsson K, Lindahl B, Sundstrom J. Discontinuation of smokeless tobacco and mortality risk after myocardial infarction. *Circulation* 2014: 130(4): 325-332.
160. Hansson J, Galanti MR, Hergens MP, Fredlund P, Ahlbom A, Alfredsson L, Bellocco R, Eriksson M, Hallqvist J, Hedblad B, Jansson JH, Nilsson P, Pedersen N, Trolle Lagerros Y, Ostergren PO, Magnusson C. Use of snus and acute myocardial infarction: pooled analysis of eight prospective observational studies. *European journal of epidemiology* 2012: 27(10): 771-779.

161. Joseph AM, Norman SM, Ferry LH, Prochazka AV, Westman EC, Steele BG, Sherman SE, Cleveland M, Antonuccio DO, Hartman N, McGovern PG. The safety of transdermal nicotine as an aid to smoking cessation in patients with cardiac disease. *N Engl J Med* 1996: 335(24): 1792-1798.
162. Meine TJ, Patel MR, Washam JB, Pappas PA, Jollis JG. Safety and effectiveness of transdermal nicotine patch in smokers admitted with acute coronary syndromes. *Am J Cardiol* 2005: 95(8): 976-978.
163. Mills EJ, Thorlund K, Eapen S, Wu P, Prochaska JJ. Cardiovascular events associated with smoking cessation pharmacotherapies: a network meta-analysis. *Circulation* 2014: 129(1): 28-41.
164. Wallenfeldt K, Hulthe J, Bokemark L, Wikstrand J, Fagerberg B. Carotid and femoral atherosclerosis, cardiovascular risk factors and C-reactive protein in relation to smokeless tobacco use or smoking in 58-year-old men. *Journal of internal medicine* 2001: 250(6): 492-501.
165. England LJ, Aagaard K, Bloch M, Conway K, Cosgrove K, Grana R, Gould TJ, Hatsukami D, Jensen F, Kandel D, Lanphear B, Leslie F, Pauly JR, Neiderhiser J, Rubinstein M, Slotkin TA, Spindel E, Stroud L, Wakschlag L. Developmental toxicity of nicotine: A transdisciplinary synthesis and implications for emerging tobacco products. *Neuroscience and biobehavioral reviews* 2017: 72: 176-189.
166. Rau AS, Reinikovaite V, Schmidt EP, Taraseviciene-Stewart L, Deleyiannis FW. Electronic Cigarettes Are as Toxic to Skin Flap Survival as Tobacco Cigarettes. *Annals of plastic surgery* 2017.
167. Callahan-Lyon P. Electronic cigarettes: human health effects. *Tobacco control* 2014: 23 Suppl 2: ii36-40.
168. Montharu J, Le Guellec S, Kittel B, Rabemampianina Y, Guillemain J, Gauthier F, Diot P, de Monte M. Evaluation of lung tolerance of ethanol, propylene glycol, and sorbitan monooleate as solvents in medical aerosols. *Journal of aerosol medicine and pulmonary drug delivery* 2010: 23(1): 41-46.
169. Fowles J, Dybing E. Application of toxicological risk assessment principles to the chemical constituents of cigarette smoke. *Tobacco control* 2003: 12(4): 424-430.
170. Haussmann HJ. Use of hazard indices for a theoretical evaluation of cigarette smoke composition. *Chem Res Toxicol* 2012: 25(4): 794-810.
171. Goniewicz ML, Gawron M, Smith DM, Peng M, Jacob P, 3rd, Benowitz NL. Exposure to Nicotine and Selected Toxicants in Cigarette Smokers Who Switched to Electronic Cigarettes: A Longitudinal Within-Subjects Observational Study. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco* 2016: 00(00): 1-8.
172. McRobbie H, Phillips A, Goniewicz ML, Smith KM, Knight-West O, Przulj D, Hajek P. Effects of Switching to Electronic Cigarettes with and without Concurrent Smoking on Exposure to Nicotine, Carbon Monoxide, and Acrolein. *Cancer prevention research (Philadelphia, Pa)* 2015: 8: 873-878.
173. Hecht SS, Carmella SG, Kotandeniya D, Pillsbury ME, Chen M, Ransom BWS, Vogel RI, Thompson E, Murphy SE, Hatsukami DK. Evaluation of toxicant and carcinogen metabolites in the urine of e-cigarette users versus cigarette smokers. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco* 2015: 17: 704-709.
174. Shahab L, Goniewicz ML, Blount BC, Brown J, McNeill A, Alwis KU, Feng J, Wang L, West R. Nicotine, Carcinogen, and Toxin Exposure in Long-Term E-Cigarette and Nicotine Replacement Therapy Users: A Cross-sectional Study. *Annals of internal medicine* 2017.

175. Messner B, Bernhard D. Smoking and cardiovascular disease: mechanisms of endothelial dysfunction and early atherogenesis. *Arterioscler Thromb Vasc Biol* 2014: 34(3): 509-515.
176. Csordas A, Bernhard D. The biology behind the atherothrombotic effects of cigarette smoke. *Nat Rev Cardiol* 2013: 10(4): 219-230.
177. Brook RD, Rajagopalan S, Pope CA, 3rd, Brook JR, Bhatnagar A, Diez-Roux AV, Holguin F, Hong Y, Luepker RV, Mittleman MA, Peters A, Siscovick D, Smith SC, Jr., Whitsel L, Kaufman JD. Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association. *Circulation* 2010: 121(21): 2331-2378.
178. 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.
179. Hess CA, Olmedo P, Navas-Acien A, Goessler W, Cohen JE, Rule AM. E-cigarettes as a source of toxic and potentially carcinogenic metals. *Environ Res* 2017: 152: 221-225.
180. Farsalinos KE, Gillman G, Poulas K, Voudris V. Tobacco-Specific Nitrosamines in Electronic Cigarettes: Comparison between Liquid and Aerosol Levels. *International journal of environmental research and public health* 2015: 12: 9046-9053.
181. Allen JG, Flanigan SS, LeBlanc M, Vallarino J, MacNaughton P, Stewart JH, Christiani DC. Flavoring Chemicals in E-Cigarettes: Diacetyl, 2,3-Pentanedione, and Acetoin in a Sample of 51 Products, Including Fruit-, Candy-, and Cocktail-Flavored E-Cigarettes. *Environ Health Perspect* 2016: 124(6): 733-739.
182. Fujioka K, Shibamoto T. Determination of toxic carbonyl compounds in cigarette smoke. *Environ Toxicol* 2006: 21(1): 47-54.
183. Chen IL. FDA summary of adverse events on electronic cigarettes. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco* 2013: 15(2): 615-616.
184. Hom S, Chen L, Wang T, Ghebrehiwet B, Yin W, Rubenstein DA. Platelet activation, adhesion, inflammation, and aggregation potential are altered in the presence of electronic cigarette extracts of variable nicotine concentrations. *Platelets* 2016: 27(7): 694-702.
185. Polosa R, Morjaria J, Caponnetto P, Caruso M, Strano S, Battaglia E, Russo C. Effect of smoking abstinence and reduction in asthmatic smokers switching to electronic cigarettes: evidence for harm reversal. *International journal of environmental research and public health* 2014: 11: 4965-4977.
186. Astrid Miler J, Mayer B. Changes in the Frequency of Airway Infections in Smokers Who Switched To Vaping: Results of an Online Survey. *Journal of Addiction Research & Therapy* 2016: 7(4).
187. McConnell R, Barrington-Trimis JL, Wang K, Urman R, Hong H, Unger J, Samet J, Leventhal A, Berhane K. Electronic-cigarette Use and Respiratory Symptoms in Adolescents. *Am J Respir Crit Care Med* 2016.
188. Monroy AE, Hommel E, Smith ST, Raji M. Paroxysmal atrial fibrillation following electronic cigarette use in an elderly woman. *Clinical Geriatrics* 2012: 20: 28-32.
189. Kim JW, Baum CR. Liquid Nicotine Toxicity. *Pediatric emergency care* 2015: 31(7): 517-521; quiz 522-514.
190. Vakkalanka JP, Hardison LS, Holstege CP. Epidemiological trends in electronic cigarette exposures reported to U.S. Poison Centers. *Clinical toxicology (Philadelphia, Pa)* 2014: 52: 542-548.
191. Vardavas CB, P. Study on the identification of potential risks to public health associated with the use of refillable electronic cigarettes and development of technical specifications for refill mechanism. 2016.

192. Jiwani AZ, Williams JF, Rizzo JA, Chung KK, King BT, Cancio LC. Thermal injury patterns associated with electronic cigarettes. *International journal of burns and trauma* 2017: 7(1): 1-5.
193. Fromme H, Schober W. Waterpipes and e-cigarettes: Impact of alternative smoking techniques on indoor air quality and health. *Atmospheric Environment* 2015: 106: 429-441.
194. Czogala J, Goniewicz ML, Fidelus B, Zielinska-Danch W, Travers MJ, Sobczak A. Secondhand exposure to vapors from electronic cigarettes. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco* 2014: 16: 655-662.
195. Geiss O, Bianchi I, Barahona F, Barrero-Moreno J. Characterisation of mainstream and passive vapours emitted by selected electronic cigarettes. *International journal of hygiene and environmental health* 2015: 218: 169-180.
196. Schober W, Szendrei K, Matzen W, Osiander-Fuchs H, Heitmann D, Schettgen T, Jorres RA, Fromme H. Use of electronic cigarettes (e-cigarettes) impairs indoor air quality and increases FeNO levels of e-cigarette consumers. *International journal of hygiene and environmental health* 2014: 217(6): 628-637.
197. Schripp T, Markewitz D, Uhde E, Salthammer T. Does e-cigarette consumption cause passive vaping? *Indoor air* 2013: 23: 25-31.
198. Melstrom P, Koszowski B, Thanner MH, Hoh E, King B, Bunnell R, McAfee T. Measuring PM2.5, Ultrafine Particles, Air Nicotine and Wipe Samples Following the Use of Electronic Cigarettes. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco* 2017.
199. McAuley TR, Hopke PK, Zhao J, Babaian S. Comparison of the effects of e-cigarette vapor and cigarette smoke on indoor air quality. *Inhalation toxicology* 2012: 24: 850-857.
200. Saffari A, Daher N, Ruprecht A, De Marco C, Pozzi P, Boffi R, Hamad SH, Shafer MM, Schauer JJ, Westerdahl D, Sioutas C. Particulate metals and organic compounds from electronic and tobacco-containing cigarettes: comparison of emission rates and secondhand exposure. *Environmental science Processes & impacts* 2014: 16: 2259-2267.
201. Marco E, Grimalt JO. A rapid method for the chromatographic analysis of volatile organic compounds in exhaled breath of tobacco cigarette and electronic cigarette smokers. *Journal of chromatography A* 2015: 1410: 51-59.
202. Soule EK, Maloney SF, Spindle TR, Rudy AK, Hiler MM, Cobb CO. Electronic cigarette use and indoor air quality in a natural setting. *Tobacco control* 2017: 26(1): 109-112.
203. Klepeis NE, Bellettiere J, Hughes SC, Nguyen B, Berardi V, Liles S, Obayashi S, Hofstetter CR, Blumberg E, Hovell MF. Fine particles in homes of predominantly low-income families with children and smokers: Key physical and behavioral determinants to inform indoor-air-quality interventions. *PloS one* 2017: 12(5): e0177718.
204. Gallart-Mateu D, Elbal L, Armenta S, de la Guardia M. Passive exposure to nicotine from e-cigarettes. *Talanta* 2016: 152: 329-334.
205. Jarvis MJ, Russell MA, Feyerabend C, Eiser JR, Morgan M, Gammage P, Gray EM. Passive exposure to tobacco smoke: saliva cotinine concentrations in a representative population sample of non-smoking schoolchildren. *Br Med J (Clin Res Ed)* 1985: 291(6500): 927-929.
206. Jarvis MJ, Feyerabend C, Bryant A, Hedges B, Primatesta P. Passive smoking in the home: plasma cotinine concentrations in non-smokers with smoking partners. *Tobacco control* 2001: 10(4): 368-374.
207. St Helen G, Havel C, Dempsey DA, Jacob P, 3rd, Benowitz NL. Nicotine delivery, retention and pharmacokinetics from various electronic cigarettes. *Addiction* 2016: 111(3): 535-544.

208. Goniewicz ML, Lee L. Electronic cigarettes are a source of thirdhand exposure to nicotine. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco* 2015: 17: 256-258.
209. Destaillats H, Singer BC, Lee SK, Gundel LA. Effect of ozone on nicotine desorption from model surfaces: evidence for heterogeneous chemistry. *Environ Sci Technol* 2006: 40(6): 1799-1805.
210. Polosa R, Caponnetto P, Morjaria JB, Papale G, Campagna D, Russo C. Effect of an electronic nicotine delivery device (e-Cigarette) on smoking reduction and cessation: a prospective 6-month pilot study. *BMC public health* 2011: 11: 786.
211. Caponnetto P, Campagna D, Cibella F, Morjaria JB, Caruso M, Russo C, Polosa R. EffiCiency and Safety of an eLectronic cigAreTte (ECLAT) as tobacco cigarettes substitute: a prospective 12-month randomized control design study. *PloS one* 2013: 8(6): e66317.
212. Bullen C, Howe C, Laugesen M, McRobbie H, Parag V, Williman J, Walker N. Electronic cigarettes for smoking cessation: a randomised controlled trial. *Lancet* 2013: 382(9905): 1629-1637.
213. Adriaens K, Van Gucht D, Declerck P, Baeyens F. Effectiveness of the electronic cigarette: An eight-week Flemish study with six-month follow-up on smoking reduction, craving and experienced benefits and complaints. *International journal of environmental research and public health* 2014: 11: 11220-11248.
214. 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.
215. Stead LF, Perera R, Bullen C, Mant D, Hartmann-Boyce J, Cahill K, Lancaster T. Nicotine replacement therapy for smoking cessation. *Cochrane Database Syst Rev* 2012: 11: CD000146.
216. Pacifici R, Pichini S, Graziano S, Pellegrini M, Massaro G, Beatrice F. Successful Nicotine Intake in Medical Assisted Use of E-Cigarettes: A Pilot Study. *International journal of environmental research and public health* 2015: 12: 7638-7646.
217. Polosa R, Caponnetto P, Maglia M, Morjaria JB, Russo C. Success rates with nicotine personal vaporizers: a prospective 6-month pilot study of smokers not intending to quit. *BMC public health* 2014: 14: 1159.
218. Polosa R, Caponnetto P, Cibella F, Le-Houezec J. Quit and smoking reduction rates in vape shop consumers: a prospective 12-month survey. *International journal of environmental research and public health* 2015: 12: 3428-3438.
219. Hajek P, Corbin L, Ladmore D, Spearing E. Adding e-cigarettes to specialist stop-smoking treatment: City of London pilot project. *J Addict Res Ther* 2015: 6: 2.
220. Caponnetto P, Auditore R, Russo C, Cappello GC, Polosa R. Impact of an electronic cigarette on smoking reduction and cessation in schizophrenic smokers: a prospective 12-month pilot study. *International journal of environmental research and public health* 2013: 10(2): 446-461.
221. Halpern SD, Harhay MO, Saulsgiver K, Brophy C, Troxel AB, Volpp KG. A Pragmatic Trial of E-Cigarettes, Incentives, and Drugs for Smoking Cessation. *N Engl J Med* 2018: 378(24): 2302-2310.
222. Beard E, West R, Michie S, Brown J. Association between electronic cigarette use and changes in quit attempts, success of quit attempts, use of smoking cessation pharmacotherapy, and use of stop smoking services in England: time series analysis of population trends. *BMJ* 2016: 354: i4645.
223. West R, Shahab L, Brown J. Estimating the population impact of e-cigarettes on smoking cessation in England. *Addiction* 2016: 111(6): 1118-1119.
224. E-Cigarette Use Among Youth and Young Adults: A Report of the Surgeon General. Atlanta, GA: U.S. Department of Health and Human Services; 2016.

225. Dautzenberg B, de Souza Moura M-A, Rieu N, Dautzenberg M-D, Birkui P. [The e-cigarette disrupts other consumptions in Parisian teenagers (2012-2014)]. *Revue des maladies respiratoires* 2015.
226. Statistics on Smoking: England 2015: Health and Social Care Information Centre; 2015.
227. L J, P OM, J B, J S, R M. Monitoring the Future national survey results on drug use, 1975–2015: Ann Arbor: Institute for Social Research, The University of Michigan; 2016.
228. Zhu SH, Zhuang YL, Wong S, Cummins SE, Tedeschi GJ. E-cigarette use and associated changes in population smoking cessation: evidence from US current population surveys. *BMJ* 2017: 358: j3262.
229. 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(9): 1531-1540.
230. Statistics on NHS Stop Smoking Services: England, April 2015 to March 2016: NHS Digital; 2016.
231. Kalkhoran S, Glantz SA. E-cigarettes and smoking cessation in real-world and clinical settings: a systematic review and meta-analysis. *The Lancet Respiratory medicine* 2016: 4(2): 116-128.
232. Nicotine without smoke: Tobacco harm reduction. London, England: Royal College of Physicians; 2016.
233. Weaver SR, Huang J, Pechacek TF, Heath JW, Ashley DL, Eriksen MP. Are electronic nicotine delivery systems helping cigarette smokers quit? Evidence from a prospective cohort study of U.S. adult smokers, 2015-2016. *PloS one* 2018: 13(7): e0198047.
234. Maloney EK, Cappella JN. Does Vaping in E-Cigarette Advertisements Affect Tobacco Smoking Urge, Intentions, and Perceptions in Daily, Intermittent, and Former Smokers? *Health communication* 2016: 31: 129-138.
235. Barrington-Trimis JL, Berhane K, Unger JB, Cruz TB, Urman R, Chou CP, Howland S, Wang K, Pentz MA, Gilreath TD, Huh J, Leventhal AM, Samet JM, McConnell R. The E-cigarette Social Environment, E-cigarette Use, and Susceptibility to Cigarette Smoking. *The Journal of adolescent health : official publication of the Society for Adolescent Medicine* 2016: 59: 75-80.
236. Rass O, Pacek LR, Johnson PS, Johnson MW. Characterizing use patterns and perceptions of relative harm in dual users of electronic and tobacco cigarettes. *Experimental and clinical psychopharmacology* 2015: 23: 494-503.
237. Schmidt L, Reidmohr A, Harwell TS, Helgerson SD. Prevalence and reasons for initiating use of electronic cigarettes among adults in Montana, 2013. *Preventing chronic disease* 2014: 11: E204.
238. Harrell PT, Simmons VN, Piñeiro B, Correa JB, Menzie NS, Meltzer LR, Unrod M, Brandon TH. E-cigarettes and expectancies: why do some users keep smoking? *Addiction (Abingdon, England)* 2015: 110: 1833-1843.
239. Piñeiro B, Correa JB, Simmons VN, Harrell PT, Menzie NS, Unrod M, Meltzer LR, Brandon TH. Gender differences in use and expectancies of e-cigarettes: Online survey results. *Addictive behaviors* 2016: 52: 91-97.
240. Gallus S, Lugo A, Pacifici R, Pichini S, Colombo P, Garattini S, La Vecchia C. E-cigarette awareness, use, and harm perceptions in Italy: a national representative survey. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco* 2014: 16(12): 1541-1548.
241. Brown-Johnson CG, Popova L. Exploring Smoking Stigma, Alternative Tobacco Product Use, & Quit Attempts. *Health Behav Policy Rev* 2016: 3(1): 13-20.

242. Pulvers K, Hayes RB, Scheuermann TS, Romero DR, Emami AS, Resnicow K, Olendzki E, Person SD, Ahluwalia JS. Tobacco Use, Quitting Behavior, and Health Characteristics Among Current Electronic Cigarette Users in a National Tri-Ethnic Adult Stable Smoker Sample. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco* 2015: 17: 1085-1095.
243. Lechner WV, Tackett AP, Grant DM, Tahirkheli NN, Driskill LM, Wagener TL. Effects of duration of electronic cigarette use. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco* 2015: 17: 180-185.
244. Hitchman SC, Brose LS, Brown J, Robson D, McNeill A. Associations Between E-Cigarette Type, Frequency of Use, and Quitting Smoking: Findings From a Longitudinal Online Panel Survey in Great Britain. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco* 2015: 17: 1187-1194.
245. Biener L, Hargraves JL. A longitudinal study of electronic cigarette use among a population-based sample of adult smokers: association with smoking cessation and motivation to quit. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco* 2015: 17: 127-133.
246. Grace RC, Kivell BM, Laugesen M. Estimating cross-price elasticity of e-cigarettes using a simulated demand procedure. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco* 2015: 17: 592-598.
247. Farsalinos KE, Romagna G, Voudris V. Factors associated with dual use of tobacco and electronic cigarettes: A case control study. *The International journal on drug policy* 2015: 26: 595-600.
248. Sutfin EL, McCoy TP, Morrell HER, Hoeppner BB, Wolfson M. Electronic cigarette use by college students. *Drug and alcohol dependence* 2013: 131: 214-221.
249. Saddleson ML, Kozlowski LT, Giovino GA, Goniewicz ML, Mahoney MC, Homish GG, Arora A. Enjoyment and other reasons for electronic cigarette use: Results from college students in New York. *Addictive behaviors* 2016: 54: 33-39.
250. Soneji S, Sargent J, Tanski S. Multiple tobacco product use among US adolescents and young adults. *Tobacco control* 2016: 25(2): 174-180.
251. Cooper M, Case KR, Loukas A, Creamer MR, Perry CL. E-cigarette Dual Users, Exclusive Users and Perceptions of Tobacco Products. *Am J Health Behav* 2016: 40(1): 108-116.
252. Goniewicz ML, Leigh NJ, Gawron M, Nadolska J, Balwicki L, McGuire C, Sobczak A. Dual use of electronic and tobacco cigarettes among adolescents: a cross-sectional study in Poland. *International journal of public health* 2015.
253. Ruther T, Wissen F, Linhardt A, Aichert DS, Pogarell O, de Vries H. Electronic Cigarettes-Attitudes and Use in Germany. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco* 2015.
254. Coleman BN, Apelberg BJ, Ambrose BK, Green KM, Choiniere CJ, Bunnell R, King BA. Association between electronic cigarette use and openness to cigarette smoking among US young adults. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco* 2015: 17: 212-218.
255. Moore GF, Littlecott HJ, Moore L, Ahmed N, Holliday J. E-cigarette use and intentions to smoke among 10-11-year-old never-smokers in Wales. *Tobacco control* 2016: 25(2): 147-152.
256. 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: 1018-1023.
257. Wills TA, Sargent JD, Knight R, Pagano I, Gibbons FX. E-cigarette use and willingness to smoke: a sample of adolescent non-smokers. *Tobacco control* 2015.

258. Best C, Haseen F, Currie D, Ozakinci G, MacKintosh AM, Stead M, Eadie D, MacGregor A, Pearce J, Amos A, Frank J, Haw S. Relationship between trying an electronic cigarette and subsequent cigarette experimentation in Scottish adolescents: a cohort study. *Tobacco control* 2017.
259. Trumbo CW, Harper R. Use and perception of electronic cigarettes among college students. *Journal of American college health : J of ACH* 2013: 61: 149-155.
260. Best C, van der Sluijs W, Haseen F, Eadie D, Stead M, MacKintosh AM, Pearce J, Tisch C, MacGregor A, Amos A, Miller M, Frank J, Haw S. Does exposure to cigarette brands increase the likelihood of adolescent e-cigarette use? A cross-sectional study. *BMJ Open* 2016: 6(2): e008734.
261. Cardenas VM, Evans VL, Balamurugan A, Faramawi MF, Delongchamp RR, Wheeler JG. Use of electronic nicotine delivery systems and recent initiation of smoking among US youth. *Int J Public Health* 2016: 61(2): 237-241.
262. Hughes K, Bellis MA, Hardcastle KA, McHale P, Bennett A, Ireland R, Pike K. Associations between e-cigarette access and smoking and drinking behaviours in teenagers. *BMC public health* 2015: 15: 244.
263. Kinnunen JM, Ollila H, El-Amin SE-T, Pere LA, Lindfors PL, Rimpela AH. Awareness and determinants of electronic cigarette use among Finnish adolescents in 2013: a population-based study. *Tobacco control* 2015: 24: e264-270.
264. Lessard J, Henrie J, Livingston JA, Leonard KE, Colder CR, Eiden RD. Correlates of ever having used electronic cigarettes among older adolescent children of alcoholic fathers. *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco* 2014: 16: 1656-1660.
265. Saddleson ML, Kozlowski LT, Giovino GA, Hawk LW, Murphy JM, MacLean MG, Goniewicz ML, Homish GG, Wrotniak BH, Mahoney MC. Risky behaviors, e-cigarette use and susceptibility of use among college students. *Drug and alcohol dependence* 2015: 149: 25-30.
266. Stenger N, Chailleux E. [Survey on the use of electronic cigarettes and tobacco among children in middle and high school]. *Revue des maladies respiratoires* 2015.
267. Meier EM, Tackett AP, Miller MB, Grant DM, Wagener TL. Which nicotine products are gateways to regular use? First-tried tobacco and current use in college students. *American journal of preventive medicine* 2015: 48: S86-93.
268. Sutfin EL, Reboussin BA, Debinski B, Wagoner KG, Spangler J, Wolfson M. The Impact of Trying Electronic Cigarettes on Cigarette Smoking by College Students: A Prospective Analysis. *American journal of public health* 2015: 105: e83-89.
269. Leventhal AM, Strong DR, Kirkpatrick MG, Unger JB, Sussman S, Riggs NR, Stone MD, Khoddam R, Samet JM, Audrain-McGovern J. Association of Electronic Cigarette Use With Initiation of Combustible Tobacco Product Smoking in Early Adolescence. *JAMA* 2015: 314: 700.
270. Barrington-Trimis JL, Urman R, Berhane K, Unger JB, Cruz TB, Pentz MA, Samet JM, Leventhal AM, McConnell R. E-Cigarettes and Future Cigarette Use. *Pediatrics* 2016: 138.
271. Soneji S, Barrington-Trimis JL, Wills TA, Leventhal AM, Unger JB, Gibson LA, Yang J, Primack BA, Andrews JA, Miech RA, Spindle TR, Dick DM, Eissenberg T, Hornik RC, Dang R, Sargent JD. Association Between Initial Use of e-Cigarettes and Subsequent Cigarette Smoking Among Adolescents and Young Adults: A Systematic Review and Meta-analysis. *JAMA Pediatr* 2017: 171(8): 788-797.
272. Zhong J, Cao S, Gong W, Fei F, Wang M. Electronic Cigarettes Use and Intention to Cigarette Smoking among Never-Smoking Adolescents and Young Adults: A Meta-Analysis. *International journal of environmental research and public health* 2016: 13(5).

273. Etter JF. Gateway effects and electronic cigarettes. *Addiction* 2017.
274. Kristjansson AL, Mann MJ, Sigfusdottir ID. Licit and Illicit Substance Use by Adolescent E-Cigarette Users Compared with Conventional Cigarette Smokers, Dual Users, and Nonusers. *The Journal of adolescent health : official publication of the Society for Adolescent Medicine* 2015: 57: 562-564.
275. Hampson SE, Andrews JA, Severson HH, Barckley M. Prospective Predictors of Novel Tobacco and Nicotine Product Use in Emerging Adulthood. *The Journal of adolescent health : official publication of the Society for Adolescent Medicine* 2015: 57: 186-191.
276. Pentz MA, Shin H, Riggs N, Unger JB, Collison KL, Chou C-P. Parent, peer, and executive function relationships to early adolescent e-cigarette use: a substance use pathway? *Addictive behaviors* 2015: 42: 73-78.
277. Biener L, Song E, Sutfin EL, Spangler J, Wolfson M. Electronic Cigarette Trial and Use among Young Adults: Reasons for Trial and Cessation of Vaping. *International journal of environmental research and public health* 2015: 12: 16019-16026.
278. Coleman BN, Johnson SE, Tessman GK, Tworek C, Alexander J, Dickinson DM, Rath J, Green KM. "It's not smoke. It's not tar. It's not 4000 chemicals. Case closed": Exploring attitudes, beliefs, and perceived social norms of e-cigarette use among adult users. *Drug and alcohol dependence* 2015.
279. Farsalinos KE, Romagna G, Tsiapras D, Kyrzopoulos S, Voudris V. Characteristics, perceived side effects and benefits of electronic cigarette use: a worldwide survey of more than 19,000 consumers. *International journal of environmental research and public health* 2014: 11: 4356-4373.
280. Harrell PT, Marquinez NS, Correa JB, Meltzer LR, Unrod M, Sutton SK, Simmons VN, Brandon TH. Expectancies for cigarettes, e-cigarettes, and nicotine replacement therapies among e-cigarette users (aka vapers). *Nicotine & tobacco research : official journal of the Society for Research on Nicotine and Tobacco* 2015: 17: 193-200.
281. Hendricks PS, Cases MG, Thorne CB, Cheong J, Harrington KF, Kohler CL, Bailey WC. Hospitalized smokers' expectancies for electronic cigarettes versus tobacco cigarettes. *Addictive behaviors* 2015: 41: 106-111.
282. Farsalinos KE, Romagna G, Tsiapras D, Kyrzopoulos S, Spyrou A, Voudris V. Impact of flavour variability on electronic cigarette use experience: an internet survey. *International journal of environmental research and public health* 2013: 10: 7272-7282.
283. 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: 133-140.
284. McDonald EA, Ling PM. One of several 'toys' for smoking: young adult experiences with electronic cigarettes in New York City. *Tobacco control* 2015: 24: 588-593.
285. Pokhrel P, Herzog TA, Muranaka N, Fagan P. Young adult e-cigarette users' reasons for liking and not liking e-cigarettes: A qualitative study. *Psychology & health* 2015: 30: 1450-1469.
286. Rooke C, Cunningham-Burley S, Amos A. Smokers' and ex-smokers' understanding of electronic cigarettes: a qualitative study. *Tobacco control* 2015.
287. Etter J-F. Electronic cigarettes: a survey of users. *BMC public health* 2010: 10: 231.
288. Etter JF. Electronic cigarettes: a survey of users. *BMC public health* 2010: 10: 231.
289. Nadasan V, Foley KL, Penzes M, Paulik E, Mihaicuta S, Abram Z, Balint J, Urban R. Use of electronic cigarettes and alternative tobacco products among Romanian adolescents. *International journal of public health* 2016.
290. Filippidis FT, Laverty AA, Gerovasili V, Vardavas CI. Two-year trends and predictors of e-cigarette use in 27 European Union member states. *Tobacco control* 2017: 26(1): 98-104.

291. Berg CJ. Preferred flavors and reasons for e-cigarette use and discontinued use among never, current, and former smokers. *Int J Public Health* 2016: 61(2): 225-236.