

Electronic Cigarettes: An Overview of Types, Content, Use and Legislation

Vakaki Chrysoula¹
Gkoulitou Evangelia¹
Pepelassi Eudoxie^{2*}

¹Private practice, Athens, Greece

²Department of Periodontology, School of Dentistry, National and Kapodistrian University of Athens, Greece

Abstract

Electronic cigarettes are electronic nicotine delivery systems which have gained wide popularity in recent years. Their increasing demand led to the production of a vast variety of devices, differing in design and vaporization model. Electronic liquids are vaporized in each “puff” and contain a plethora of substances, some of which have been proved safe, others carcinogenic, while the safety of many needs further investigation to be validated. Despite the lack of sufficient evidence on their effects on human health, their use has expanded among people of different ages and smoking experiences. Interestingly, never-smokers vapers are more frequently adolescents or young adults, rather than adults. Some of the most common reasons of vaping are the management of withdrawal symptoms after smoking cessation, evasion of smoke-free policies and the belief that e-cigarettes are less harmful than conventional cigarettes. However, the effectiveness of vaping’s aid in smoking cessation and its safety has not been proved yet. Moreover, regulations on e-cigarettes production, storage, sale, use and marketing are scarce and mostly non-uniform and therefore render their control challenging. This article aims to overview the types, content, use and legislation of e-cigarettes.

Keywords

E-smoking; E-cigarette; Vaping; Components; Cessation; Adolescents; Youth; Legislation

Introduction

The electronic nicotine-delivery device was developed and patented in 2003 by the Ruyan Group (Holdings), limited at first in Beijing, China. After their launch on the European and American market in 2006, electronic cigarettes (e-cigarettes or e-cigs or ECs) expanded worldwide [1]. WHO Study Group on Tobacco Product Regulation categorized ECs as electronic nicotine delivery systems (ENDS), where tobacco is not necessary for their operation [2]. The heating element of these devices vaporizes a small amount of a liquid in every ‘puff’. In this format, an aerosol/vapor (up to 24-100 mg), instead of smoke is inhaled [3,4]. Since there is no disease they treat, electronic liquids (e-liquids, e-juices) cannot be considered as medications or food products in any country [5].

According to an evidence review by Public Health England, e-cigarettes are 95% less harmful than smoking [6]. However, due to the lack of standardized manufacturing protocol, contamination of e-liquids with cancer-inducing substances is possible [7-10]. Moreover, there is no regulation for the storage of these products and therefore, the oxidation of nicotine in open containers is possible, leading to the unintentional presence of degradation products [11].

The purpose of the present study was to thoroughly review the types and content of e-cigarettes, the reasons to use them and the relative legislation.

Design

In general, there are two types of e-cigarettes, depending on whether combustion is conducted. In the most popular model vaporization is achieved *via* heating or vibration [12,13] and not combustion. The main subtypes of this model are: disposable “cigalike,” rechargeable “cigalike,” and rechargeable vaporizers (tank or open systems) [14] (Figure 1). Variations in design affect how the product is used [15], as well as its safety profile [16]. The uniform features include a cartridge that contains a solution, a tube used by the user when inhaling the vapor, and a battery powered part called the atomizer that absorbs and heats the solution at a low temperature (up to 160°C, depending on the model) [17]. In some products, the cartridge and the atomizer are combined to create a single part called the cartomizer. The battery-powered microprocessor turns on the red-orange light (LED: Light Emitting Diode) on the tip of the device, providing the appearance of a burning cigarette [18] (Figure 2). Design and whether the tip color changes during inhalation differ among products. In the other type of e-cigarettes, tobacco is used but its combustion takes place

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*Corresponding author:

Pepelassi Eudoxie
Department of Periodontology
School of Dentistry
National and Kapodistrian University of Athens, Athens, Greece
Tel: (+30) 210-7461223, 7461203
E-mail: epepela@dent.uoa.gr

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at a lower temperature. The combustion temperature of tobacco in conventional cigarettes is approximately 750-1000°C [19], while in this type of e-cigarettes called “heat-not-burn Tobacco Products” is 350°C [20].

Composition of e-liquid

According to the American E-liquid Manufacturing Standards Association (AEMSA), liquids manufactured before 2013 were of lower accuracy, whereas the purity, consistency and accuracy of nicotine content have been drastically ameliorated in newest products [21]. The main substances contained in e-liquids are: nicotine, glycerol, propylene glycol, ethylene glycol, 1,3-propanediol, 1,2-propanediol, thujone, ethyl vanillin [2,22,23] and flavorings [5] (Figure 3). For flavoring many compounds are added in the liquid, such as aldehydes (formaldehyde, acetaldehyde, acrolein, crotonaldehyde, benzaldehyde) [5], nitrosamines (nitrosonornicotine, 4-(nitroso methyl-amino)-1-(3-pyridyl)-butanone and nitrosoanatabins) [20], acetone [24], terpenic molecules [5], vanillin and ethyl vanillin, maltol and ethyl maltol, benzyl alcohol, ethyl butyrate and and ethyl acerate [25].

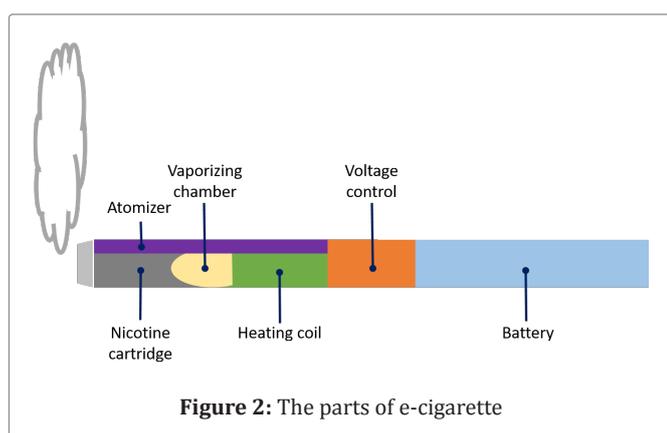
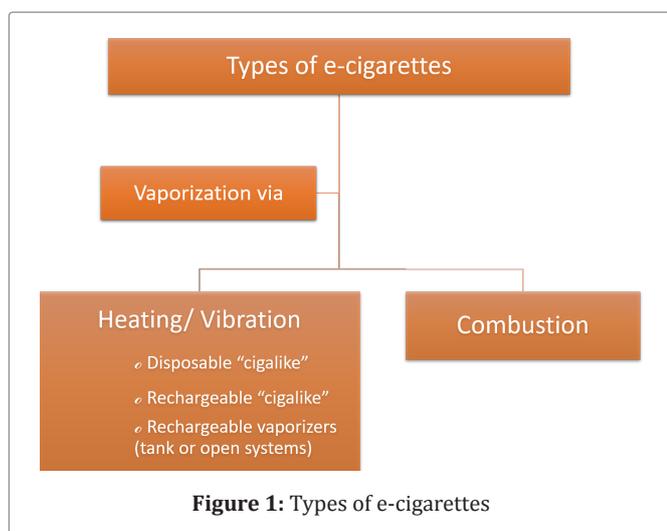
The amounts of nicotine contained in the cartridge vary widely with a mean range of 0 to 87.2 mg/ml in most e-liquids [26], though mislabeling is frequently found [22]. The presence or not of nicotine as well as the amount of nicotine intake is selected by the user in e-cigarette [20]. When the propylene glycol in e-liquid is heated and aerosolized, it is converted to propylene oxide, which is considered to be a potent carcinogen in humans [27]. Average ethylene glycol exposure can also exceed the minimal risk level of Agency for Toxic Substances and Disease Registry [28]. It should be noted that ethylene glycol (in contrast to propylene glycol) is not recognized as safe by the U.S. Food and Drug Administration [2]. Ethylene glycol and diethylene glycol can be found as contaminants in a variety of products, although not considered as food and pharmaceutical ingredients, and therefore

maximum residual limits are allowed. These limits (1 mg/g according to FDA and 620 µg/g according to the US Pharmacopeial Convention in 2007) [29,30] were not exceeded in a study where multiple samples were tested. For daily e-cigarette users, the average exposure to ethylene glycol and 1,2 propanediol is not safe [22]. Ethanol (beverage alcohol) is often found in food and other products and has also been detected in e-liquids in a concentration of 0.4%, which should be mentioned on the label. Hydrocarbons, in high concentrations, have been detected in e-liquids as flavor intensifiers [5]. In addition, heavy metal nanoparticles (i.e. Sn, Ag, Fe, Ni, Al, Cr) have been detected in e-cigarettes, which might be attributed to oxidation of the heating coil [31].

The exact flavoring compounds used are not always mentioned on the label [25]. Aldehydes belong to the ‘primary irritants’ of the respiratory mucosa [32]. Formaldehyde is prohibited in food, though it might be present originating from various sources, such as raw materials of poor quality, the use of natural flavorings extracts or thermal degradation [5]. The same applies for acetaldehyde, which is approved for use in food, and for acrolein and crotonaldehyde, which are considered toxic contaminants [33,34]. Though, it has been suggested that formaldehyde might derive from exhalation, rather than from the e-cigarettes [35]. Formaldehyde and acetaldehyde are some of the carcinogens found in electronic cigarettes [7]. In a study carried out on a high-voltage battery powered “tank-style” system, e-cigarette users were found to be exposed to more formaldehyde [16]. Inhalation rates of benzaldehyde exceeded twice the limits suggested in an *in-vitro* study [25]. Other aldehydes (propionaldehyde, butyraldehyde, isovaleraldehyde and hexaldehyde), all of which are authorized for use as food flavorings, have not been detected in levels higher than those recommended [25].

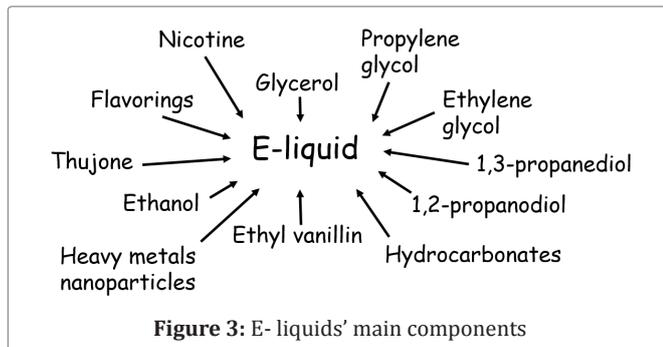
Acetone has been found in quantities higher than the authorized maximum food limits [24]. Nevertheless, it should be mentioned that the e-liquids are not perceived as food products. Again, these substances may result from the contamination of raw materials, possibly through inadequate purification [5]. Nitrosamines, 1,3-butadiene and 2-methyl-1,3-dioxane are compounds with well-established carcinogenicity [36] and they should not be present in e-liquids at any concentration [37]. However, nitrosonornicotine (NNN), 4-(nitroso-methyl-amino)-1-(3-pyridyl)-butanone (NNK) and nitrosoanatabins (NAT) among the nitrosamines specific to tobacco, known for their carcinogenic properties have been detected in the content of e-cigarettes [7]. In general, carcinogen levels of e-cigarettes were found to be 9-450 times lower than that of tobacco products [38]. Terpenic molecules are often detected in flavoring agents. These molecules have a relatively low oral toxicity, however, they might be harmful in high concentrations [5].

Menthol is one of the most common e-cigarette flavors, which has a masking effect on the bitter taste of cigarette smoke [39] and a cooling, pain-relieving and slightly numbing effect [40]. Menthol increases the chances to develop nicotine addiction, which is attributed to desensitization to nicotine and to tolerance to nicotine increase [41].



E-cigarette use

E-cigarette use expands quickly worldwide [42]. Certain factors have been associated with e-cigarette use, such as smoking experience and age. Several studies demonstrated that ENDS are most common among current or recent former smokers [14,43-45]. The daily ENDS use was higher among recent former smokers [14]. The dual use was really common, with most of e-cigarette users smoking conventional cigarettes as well [45]. Though, the overall daily ENDS use was rare [46]. Age is another factor strongly associated with e-cigarette use with the highest prevalence for youth aged 15-19 and young adults aged 20-24 [45,47]. Interestingly, the majority of young e-cigarette users are never-smokers [45]. Gender has also been associated as influential factor, with males being more prominent in e-cig use [46]. However, this association is not strong and it seems to be influenced by other correlates, such as social and legalistic [45,48].



It seems that e-cigarette users prefer sweet and tobacco flavors, since the most common e-cigarette flavors used are fruit, menthol, tobacco and candy [49]. The e-smoking behavior varies between women and men. For women it is highly influenced by sensory aspects of smoking, whereas for men by nicotine dosing [50].

Due to lack of manufacturing and utilization standards, e-cigarettes can easily be misused. Interestingly, many users are unaware of the brand they use, which may be explained by the use of refillable 'tank' systems. Branding of the refillable liquids ('e-juice') is much less prominent—and sometimes largely absent—compared to disposable e-cigarettes [46]. Moreover, these electronic devices are used for the enjoyment of illicit substances. Marijuana is mostly used in liquid form or in the form of wax. It is perfect for users since there is no characteristic odor that occurs when smoking marijuana. This way, unimpeded by police or similar services, illegal drugs can be used or smuggled [51].

The most common reasons vapers use e-cigarettes

- Management of tobacco withdrawal symptoms [14,52] by the efficient delivery of nicotine [53,54] and imitation of the physical experience of smoking [55,56] and therefore aid for smoking reduction/cessation [14,43,46], preventing relapse [14,52].
- Evasion of smoke-free policies [46] or avoiding people disturbance with secondhand smoke [14].
- The perception that e-cigarettes are less harmful or less toxic than conventional cigarettes [14,52,57,58,59] and other non-combustible tobacco products [59]. This perception is shaped by many factors, such as:
 - Aggressive media marketing: The majority of current smokers report learning about e-cigarettes by advertisements on television [59,60], YouTube [61] and websites [13,21,62], where their safe use is overstressed [59,63]. Nonetheless, certain websites outline the health risks of smokeless tobacco, misleading people into believing that harm reduction is not possible by switching from smoked to smokeless products [64].
 - E-cigarettes' novelty: The technological innovativeness, that e-cigarettes may represent, is really appealing, especially among youth [65]. Moreover, the innovative status might reinforce their positive characteristics. Users believe novel e-cigarettes are less harmful compared to conventional cigarettes [66].
 - Manufacturers' misleading concept: Certain manufacturers of e-liquids claim that the flavoring chemicals they use are all 'food grade', and/or 'generally recognized as safe' (GRAS). However, GRAS certification by the Flavor Extracts Manufacturers Association (FEMA) relates only to ingestion, not inhalation [25].
 - Gender: Women believe that e-cigarettes are more likely to cause health problems, as smoking-related cancer [67], than men, who believe they are more invulnerable [68].
 - Race: Non-hispanic whites perceived themselves at lower risk of experiencing or dying from tobacco-related health problems than some other racial and ethnic minorities [69].
- Easy access and convenience [14,57, 58,70]
- Lower cost than conventional cigarettes [14,52]

- Curiosity [14,43]
- Social reasons, such as peer influence [14,46]
- Opportunity of personalization [15,71] through the wide variety of available flavors [14,72]
- Their stylish design [43], making them more aesthetically pleasing [57,58]

E-smoking and Cessation

Most ex-smokers report not using smoking cessation aids [73]. E-cigarette appears as a promising cessation aid, since it addresses both the pharmacological and the sensorimotor aspects of smoking, leading to higher users' satisfaction [74,75]. It was reported that one in every ten ex-smokers have used e-cigarettes in their attempt to quit [56,73]. In EU, the percentage of e-cigarettes experimentation as cessation aid doubled from 2012 to 2014 [73]. However, there are various trends in using e-cigarettes as cessation aid among EU member countries, which might be attributed to differences in regulatory approaches regarding vaping [76,77], the cost of cessation aids and whether and in what extent this is covered by the public healthcare system [73]. Observational studies on the use of ENDS in terms of reason, time, type, decreasing nicotine content and cigarette smoking reduction, suggest that ENDS can be helpful in the cessation process [14,78]. However, highly dependent smokers were found to continue smoking or relapse in a short time, while no differences in satisfaction according to the use of e-cigarettes with or without nicotine were found [11].

The factors reported to relate to the use of e-cigarettes as cessation aid include the age [56,73], socioeconomic status [73], previous use of cessation aids [56] and ethnicity [56]. Younger smokers (aged 15-24) are more likely to use e-cigarettes for quitting smoking than older ones (aged 55+) [56,73]. Higher socioeconomic status was associated with lower likelihood of e-cigarette use in quitting attempt [73]. In a study, conducted in the multicultural population of Hawaii, native Hawaiians were significantly less likely to have used e-cigs for cessation aid compared to Whites [56].

Self-reported Data of e-cig users

Former smokers, who are currently vapers, report e-smoking as less addictive than conventional smoking [52,72,79,80]. The beliefs about the efficiency of e-cigarettes in smoking cessation vary. In a cross-sectional study among EU population, half of the participants reported that e-cigarettes were not helpful in smoking cessation, and in some cases their use enhanced smoking, while a fifth of the participants reported that they helped them reduce smoking. Almost 15% reported that e-cigarettes helped them to quit completely, but among respondents who explicitly reported having experimented with e-cigarettes for quitting, 23.5% reported themselves as successful quitters. Though, 13.1% reported that they quit for a small period of time, but then relapsed [73].

An interesting category of e-cig users is dual users. In a wide, cross-sectional survey dual users reported cutting cigarette consumption by half (from 23.3 to 11.7 cigarettes per day) after e-cigarettes use initiation. Moreover, among daily dual users, the majority rated their current dependence on e-cigarettes as "weaker" than their dependence on cigarettes. Furthermore, dual users were also less dependent on e-cigarettes than former smokers [52].

Scientific Evidence on e-cig dependence

Plasma nicotine concentration (PNC) as well as the speed of nicotine delivery to the blood - and therefore to the brain - partly determine the addictiveness of tobacco products [81]. It seems that PNC with vaping does not exceed PNC with smoking. PNC with vaping might in certain cases approximate PNC values with smoking and it might approximate or exceed PNC values found with other nicotine replacement agents [75,82-86]. The speed of nicotine delivery to the blood seems to be faster for conventional cigarettes than for e-cigarettes, but it approaches or exceeds that of other nicotine replacement agents [83,85-88]. The nicotine patch is

not addictive and the nicotine gum or lozenge is not very addictive [89-91]. The speed of nicotine delivery to the blood varies among the different types of ENDS [14]. It seems that END products may induce lower dependence than cigarettes, but are not completely unable of inducing satisfaction and dependence, especially for second-generation ENDS (e.g. tank devices) [14]. Moreover, nicotine dependence is affected by previous smoking experience, as well as previous smoking duration [80]. Therefore, some vapers might be already dependent on nicotine when they start vaping, and most of them report that they vape to avoid relapsing [52].

Summarizing the possible role of e-cigarettes in smoking cessation, there is evidence that e-cigarettes help in the attempt of smoking cessation, though this is not thoroughly documented yet. The existing studies vary in type and design, not allowing to have comparable data [11]. Carefully-designed, wide, cohort studies on e-cigarettes do not exist. Success and failure in quitting cigarette smoking with the use of e-cigarettes has not been reliably assessed yet [92]. Data are insufficient to draw safe conclusions on the effectiveness of e-cigarettes in smoking cessation. Therefore, carefully-designed with shared protocols, wide, cohort studies should be conducted, in order evidence of greater value to be obtained.

Since neither the effectiveness of e-cigarettes for smoking cessation, nor their potentially harmful health effects have not been proved yet, the replacement of conventional cigarettes with e-cigarettes cannot be recommended [41].

E-smoking and Adolescents

From 2011 to 2015, the use of cigarette during the past month declined among adolescents of both sexes (with the exception of intense smoking), while the e-cigarette use rose sharply [93], becoming the most prevalent type of tobacco consumption by U.S. youth [94-98]. One in every six U.S. high school seniors reported using e-cigarettes during the past month [99]. The average adolescent e-cigarette users' profile has changed over the years. Male gender and previous tobacco products use are no longer strongly associated with adolescent e-cigarette users [63,100-106]. On the contrary, teenagers with no past month tobacco experience are more likely to initiate vaping [93]. Therefore, it seems that both smoking has been partially replaced by vaping and vaping expanded among adolescents who would not otherwise smoke tobacco [93]. Moreover, e-cigarette users have reported much higher intentions to smoke cigarettes than never users of e-cigarettes. This trend suggests that e-cigarettes might be a gateway to nicotine dependence and dual use with cigarettes or other tobacco products [63]. However, there are indications that the rate of increase among youth seems to decrease after 2015 [14].

Considering the frequency of the past-month e-cigarette use, the majority of young users vape experimentally (use for 1-2 days during the past month) [14,107,108]. The use of cannabis in adolescents was associated with smoking of conventional tobacco and smoking of e-cigarettes [107]. Interestingly, the prevalence of several school- and substance-related risk behaviors (e.g. use of other tobacco products, alcohol use, drunkenness, oral tobacco, snuff, sleeping pills or unprescribed tranquilizers, sniffed glue, marijuana, amphetamine) was significantly higher among e-cigarette users compared to non-users [93,108]. A noteworthy tiered risk gradient, regarding the frequency and intensity, for engaging risk behaviors was observed, with the daily and the dual e-cigarette users having the highest risk while the experimental e-cigarette users and non-users having the lowest risk [108,109]. Among adolescents, the exposure to nicotine is greater for dual (e-cigarettes and cigarettes) users than single either e-cigarettes or cigarettes users, since dual users seem to vapor more frequently than single e-cigarette users and smoke similarly to daily cigarette smokers. Moreover, dual adolescent users are more prone to use nicotine in their e-liquid, while many of them report to be unaware of the e-liquid nicotine concentration [110,111].

Concerning Greece, where the prevalence of smoking is high, in 2012 around 40% of the smokers were 15 years or older and they

reported daily smoking [112-114]. Approximately one in every five of 11-15 years old students report ever e-cigarette use, with almost 8% solely being vapers, equal between the sexes. Regarding e-cigarettes, over a third of ever smokers and just over half of the current smokers, the majority of whom were males, report vaping. The majority of daily and heavy tobacco smokers have used e-cigarettes, while below 1% of 11-15 years old students report current smoking of both conventional and e-cigarettes (dual current smokers) [107].

Causes

The main causes for e-smoking during adolescence are as it follows. **Marketing:** Among teens that never used e-cigarettes, advertisement seems to create positive attitudes toward e-cigarettes and intentions for e-cigarettes experimentation [115,116]. This greater influence is mainly attributed to the wide variety of e-liquids' flavors, since younger smokers prefer unique and exotic flavors [117], which make smoking appear healthier and more acceptable [118,119,120].

E-smoking's perceived harmfulness: E-cigarettes are perceived as less harmful and less addictive than conventional cigarettes by many students [48,95,99], especially among vapers [120], while some students are uncertain about the health risks of e-cigarettes [121]. Interestingly, in a survey conducted among Greek students, males did not consider e-smoking as harmful [107].

Wide availability [122]

Easy access [122]

Curiosity: The majority of young vapers report no intention to maintain e-cigarettes use in the next year [48].

Family and peer influence: Students report getting their information about e-smoking from peers, family and school, along with advertisements [121]. Those whose peers have tried e-cigarettes are more prone to experiment with e-cigarette, while almost one in every 10 students, whose parents or siblings had used e-cigarettes, reported e-cig use [48]. Moreover, having peers who use tobacco is a strong independent influential factor for smoking of both conventional tobacco and e-cigarettes in adolescence [107].

Regulation: Lack of age verification on on-line e-cigarettes' purchasing make adolescents have access to that market [123].

Cessation: Some students report that e-cigarettes could help in smoking cessation. Though, among e-cigarette users a limited percentage reported using them for smoking cessation [48]. Nevertheless, there is contradicting evidence on the role of e-cigarettes in the smoking cessation process, with some studies indicating a helpful role [124] and others showing no significant association between experimentation with e-cigarettes and the intention to quit conventional smoking [48].

The major reasons for e-cig cessation are loss of interest, perceiving e-cigarettes as not cool and health concerns, confirming the above mentioned causes [115].

Therefore, the popularity of e-cigarettes among youth and adolescents raises concerns, as they may present a possible gateway to future smoking [13,100,125,126] or that their use may preserve nicotine addiction [65]. However, there is a lack of long-term data on past month use of both e-cigarettes and other tobacco products from adolescence into adulthood [93]. Educating adolescents on the risks of the e-cigarette use and legislate strict and specific regulations on e-cigarette use might reduce the possible harm to young people [48]. It is important to restrict flavors and TV/internet marketing [127], educate teens on the health risks and change social norms [128] by targeting the lack of sufficient knowledge teens may have on e-cigarettes [115].

Legislation

Legislation on ENDS varies widely among countries and states. There is no shared and adequate regulation about e-cigarettes design, manufacturing and utilization among nations (Table 1).

	Regulation production	Regulation sales	Regulation on use	Regulation on advertisement
U.S.A	Implemented standards	Banned under the age of 18	No uniform legislation	Restrictions, especially for food, candy, beverage shaped products
Europe	No uniform and inadequate legislation	No uniform and inadequate legislation	No uniform and inadequate legislation	No uniform and inadequate legislation
Greece	Implemented standards	Banned under the age of 18 (only for nicotine-containing cartridges)	Prohibited use in public venues	Banned marketing via internet, press, television, radio and promoting events

Table 1: Legislation regarding e-cigarettes in U.S.A., Europe and Greece

Europe: Until 2013, in the majority of European countries, e-cigarettes were not considered either as tobacco products or as medical agents and they were legally controlled only by the national Consumer Protection Act that controls exclusively technical issues of products. In 2013, in the European countries, in addition to the decision on banning menthol containing cigarettes, harmonization of the legislation concerning e-cigarettes and their advertising restriction [129] were proposed. The European Parliament, in February 2014, implemented nicotine concentration of 20 mg/mL as the borderline concentration for tobacco products. Products with a higher concentration or devices which are utilized for therapeutic purposes can be considered medicinal agents. This directive forbids e-cigarettes' advertising and sets requirements on packaging, labelling and purity of the ingredients [130]. Moreover, refillable cartridges are allowed if their volume does not exceed 2 mL. Nevertheless, if at least three country members assess that they are potentially dangerous, they might be banned by the European Commission [51]. However, e-cigarettes are not mentioned as tobacco products in various current laws, and therefore are not subject to stricter regulations [51]. Furthermore, despite the new EU regulations, laws on e-cigarettes use, sale, marketing, production and taxation vary among EU members [131]. For example, in Belgium the minimum age for e-cigarettes' purchase is 16 and not 18, while e-cigarettes are taxed only in Italy, Latvia, Poland, Portugal, England, Scotland, Wales.

As for Greece, since 2008, sales of e-cigarettes are prohibited for people under 18 years old (only for nicotine-containing cartridges) (LAW NUMBER 3730, FIRST ISSUE 262/23.12.2008). In 2016, a new law banned e-cigarette marketing *via* internet, press, television and radio, as well as events promoting e-smoking. Moreover, specific standards for manufacturing, packaging and selling of e-cig and e-liquid products were implemented, while vaping in indoor public places, along with conventional smoking, was prohibited (LAW NUMBER 4419, FIRST ISSUE 174/20.09.2016).

U.S.A.: Prior to 2016, there was a great legislative variety among the states of America. The majority of regulations referred to youth, as it is easier to target a specific group of population rather than the customers as a whole [132]. In August of 2016, the FDA banned access to minors, as well as their sale in all-ages vending machines [133]. Some local and state laws set the age of 21 as the legal age for e-cigarettes purchase [134]. Regulations also applied to the marketing of e-cigarettes [135], while certain issues, such as composition, product features and health risks, as well their appeal to youth and non-users are frequently revised since 2016 [133]. Since May 2018, the FDA began to charge e-liquid products with packaging resembling food, candy or beverage as being misbranded and using false advertising, which is illegal [136]. Regarding the use of e-cigarettes in public places, in many US states and cities comprehensive smoke-free laws apply for conventional, as well as electronic smoking. Although some state laws permit vaping in bars and restaurants, while prohibiting e-cigarettes in other indoor venues [137].

Conclusion

Electronic nicotine delivery systems were initially launched, in order to aid smoking cessation. However, their current utilization is multifaceted and expands among people with different age

groups and smoking experiences. Due to lack of uniform and in some countries/states inadequate regulations regarding their design, manufacturing, sale, use and marketing, their misuse, as well as their contamination with degradation products is frequent. Especially, adolescents have an easy access to these devices, mainly through internet, and therefore are exposed to the potential hazards of vaping and nicotine exposure. Hence, stricter and comprehensive laws are required, until the e-cigarette effects on human health, as well as their effectiveness on smoking cessation are revealed.

Author Contributions

All authors contributed equally to study design, data collection, paper preparation and figures and tables design.

References

1. Yamin CK, Bitton A, Bates DW. E-cigarettes: a rapidly growing Internet phenomenon. *Ann Intern Med.* 2010 Nov;153(9):607-609.
2. FDA. Brief in Opposition to Motion for Preliminary Injunction, USA. Food and Drug Administration, USA 2009.
3. Jorenby DE, Smith SS, Fiore MC, Baker TB. Nicotine levels, withdrawal symptoms, and smoking reduction success in real world use: A comparison of cigarette smokers and dual users of both cigarettes and E-cigarettes. *Drug Alcohol Depend.* 2017 Jan;170:93-101.
4. Ruhe M, Haller-Stevenson E, Roulston K, Jourdan M. Strengthening the capacity of local health departments to reduce exposure to electronic nicotine delivery systems. *J Public Health Manag Pract.* 2017;23(1):93-94.
5. Varlet V, Farsalinos K, Augsburger M, Thomas A, Etter JF. Toxicity assessment of refill liquids for electronic cigarettes. *Int J Environ Res Public Health.* 2015 Apr;12(5):4796-4815.
6. McNeill A, Brose LS, Calder R, Hitchman SC, Hajek P, et al. E-cigarettes: an evidence update. A report commissioned by Public Health England. *Public Health England.* 2015;111.
7. Kim HJ, Shin HS. Determination of tobacco-specific nitrosamines in replacement liquids of electronic cigarettes by liquid chromatography-tandem mass spectrometry. *J Chromatogr A.* 2013 May;1291:48-55.
8. Goniewicz ML, Kuma T, Gawron M, Knysak J, Kosmider L. Nicotine levels in electronic cigarettes. *Nicotine Tob Res.* 2013 Jan;15(1):158-166.
9. Chen IL. FDA summary of adverse events on electronic cigarettes. *Nicotine Tob Res.* 2013 Feb;15(2):615-616.
10. Etter JF, Zäther E, Svensson S. Analysis of refill liquids for electronic cigarettes. *Addiction.* 2013 Sep;108(9):1671-1679.
11. Martinez RE, Dhawan S, Sumner W, Williams BJ. On-Line Chemical Composition Analysis of Refillable Electronic Cigarette Aerosol-Measurement of Nicotine and Nicotyrine. *Nicotine Tob Res.* 2015 Oct;17(10):1263-1269.
12. Wollscheid KA, Kremzner ME. Electronic cigarettes: safety concerns and regulatory issues. *Am J Health Syst Pharm.* 2009 Oct;66(19):1740-1742.
13. Grana RA, Ling PM. "Smoking revolution": a content analysis of electronic cigarette retail websites. *Am J Prev Med.* 2014 Apr;46(4):395-403.

14. Glasser AM, Collins L, Pearson JL, Abudayyeh H, Niaura RS, et al. Overview of Electronic Nicotine Delivery Systems: A Systematic Review. *Am J Prev Med.* 2017 Feb;52(2):e33-e66.
15. Brown CJ, Cheng JM. Electronic cigarettes: product characterisation and design considerations. *Tob Control.* 2014 May;23 Suppl 2:ii4-ii10.
16. Kosmider L, Sobczak A, Fik M, Knysak J, Zaciera M, et al. Carbonyl compounds in electronic cigarette vapors: effects of nicotine solvent and battery output voltage. *Nicotine Tob Res.* 2014 Oct;16(10):1319-1326.
17. Annice Underwood. Poster 5-11, Society for Research on Nicotine and Tobacco, Dublin, 2009.
18. WHO. Tobacco Fact Sheet. World Health Organization, Geneva, 2018.
19. Baker RR. Smoke generation inside a burning cigarette: Modifying combustion to develop cigarettes that may be less hazardous to health. *Prog Energy Combust Sci.* 2006;32(4):373-385.
20. Nayir E, Karacabey B, Kirca O, Ozdogan M. Electronic cigarette (e-cigarette). *J Oncol Sci.* 2016;2(1):16-20.
21. Polosa R, Rodu B, Caponnetto P, Maglia M, Raciti C. A fresh look at tobacco harm reduction: the case for the electronic cigarette. *Harm Reduct J.* 2013 Oct;10:19.
22. Hahn J, Monakhova YB, Hengen Y, Kohl-Himmelseher M, Schüssler J, et al. Electronic cigarettes: overview of chemical composition and exposure estimation. *Tob Induc Dis.* 2014;12(1):23.
23. McAuley TR, Hopke PK, Zhao J, Babaian S. Comparison of the effects of e-cigarette vapor and cigarette smoke on indoor air quality. *Inhal Toxicol.* 2012;24(12):850-857.
24. EU Commission. Report EUR 14482 EN Food Science and techniques. In: Reports of the Scientific Committee for Food, Twenty-Ninth Series. EU Commission, Brussels, Belgium. 1992;1-37.
25. Tierney PA, Karpinski CD, Brown JE, Luo W, Pankow JF. Flavour chemicals in electronic cigarette fluids. *Tobacco control.* 2016;25(1):10-15.
26. NASEM. Public health consequences of e-cigarettes. National Academies of Sciences, Engineering, and Medicine. 2018.
27. WHO. Framework Convention on Tobacco Control, England. World Health Organization. 2013.
28. Agency for Toxic Substances and Disease Registry, USA, 2010.
29. FDA. Guidance for industry. In Testing of Glycerin for Diethylene Glycol, USA. Food and Drug Administration. 2007.
30. The United States Pharmacopeial Convention. (467) Residual solvents. *harmacopeial Forum.* 2007;33(3):1-4.
31. 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. 2013;8(3):e57987.
32. William PL, James RC, Roberts SM. Principles of toxicology: environmental and industrial applications. John Wiley & Sons. 2014:346.
33. Van Andel I, Sleijffers A, Schenk E. Adverse Health Effects of Cigarette Smoke: Aldehydes. RIVM Report 340603002: Bilthoven. 2006;1-65.
34. EPA. Ambient Water Quality Criteria for Acrolein. United States Environmental Protection Agency. 1980.
35. Schripp T, Markewitz D, Uhde E, Salthammer T. Does e-cigarette consumption cause passive vaping? *Indoor air.* 2013;23(1):25-31.
36. IARC. N'-nitrosornicotine and 4-(methylnitrosamino)-1-(3pyridyl)-1-butanone. *Iarc Monogr. Eval. Carcinog Risks Hum.* 2012;100:319-331.
37. Stepanov I, Jensen J, Hatsukami D, Hecht S. Tobacco-specific nitrosamines in new tobacco products. *Nicotine Tob Res.* 2006;8(2):309-313.
38. Goniewicz ML, Knysak J, Gawron M, Kosmider L, Sobczak A, et al. Levels of selected carcinogens and toxicants in vapour from electronic cigarettes. *Tob Control.* 2014 Mar;23(2):133-139.
39. Squier CA, Mantz MJ, Wertz PW. Effect of menthol on the penetration of tobacco carcinogens and nicotine across porcine oral mucosa ex vivo. *Nicotine Tob Res.* 2010 Jul;12(7):763-767.
40. Ahijevych K, Garrett BE. Menthol pharmacology and its potential impact on cigarette smoking behavior. *Nicotine Tob Res.* 2004 Feb;6 Suppl 1:S17-S28.
41. Willershhausen I, Wolf T, Weyer V, Sader R, Ghanaati S, et al. Influence of E-smoking liquids on human periodontal ligament fibroblasts. *Head Face Med.* 2014 Sep;10:39.
42. Czoli CD, Hammond D, White CM. Electronic cigarettes in Canada: prevalence of use and perceptions among youth and young adults. *Can J Public Health.* 2014 Feb;105(2):e97-e102.
43. Jiang N, Chen J, Wang MP, McGhee SM, Kwong AC, et al. Electronic cigarette awareness and use among adults in Hong Kong. *Addict Behav.* 2016 Jan;52:34-38.
44. Alawsi F, Nour R, Prabhu S. Are e-cigarettes a gateway to smoking or a pathway to quitting? *Br Dent J.* 2015 Aug;219(3):111-115.
45. Reid JL, Rynard VL, Czoli CD, Hammond D. Who is using e-cigarettes in Canada? Nationally representative data on the prevalence of e-cigarette use among Canadians. *Prev Med.* 2015 Dec;81:180-183.
46. Shiplo S, Czoli CD, Hammond D. E-cigarette use in Canada: prevalence and patterns of use in a regulated market. *BMJ Open.* 2015 Aug;5(8):e007971.
47. Adkison SE, O'Connor RJ, Bansal-Travers M, Hyland A, Borland R, et al. Electronic nicotine delivery systems: international tobacco control four-country survey. *Am J Prev Med.* 2013 Mar;44(3):207-215.
48. Awan KH. Experimentation and correlates of electronic nicotine delivery system (electronic cigarettes) among university students - A cross sectional study. *Saudi Dent J.* 2016 Apr;28(2):91-95.
49. Dawkins L, Turner J, Roberts A, Soar K. 'Vaping' profiles and preferences: an online survey of electronic cigarette users. *Addiction.* 2013 Jun;108(6):1115-1125.
50. Perkins KA, Fonte C, Meeker J, White W, Wilson A. The discriminative stimulus and reinforcing effects of nicotine in humans following nicotine pretreatment. *Behav Pharmacol.* 2001 Feb;12(1):35-44.
51. Jovanovic M, Mihajlo M. Regulatory issues surrounding audit of electronic cigarette charge composition. *Front Psychiatry.* 2015;6:133.
52. Etter JF, Eissenberg T. Dependence levels in users of electronic cigarettes, nicotine gums and tobacco cigarettes. *Drug Alcohol Depend.* 2015;147:68-75.
53. Vansickel AR, Cobb CO, Weaver MF. A clinical laboratory model for evaluating the acute effects of electronic "cigarettes": nicotine delivery profile and cardiovascular and subjective effects. *Cancer Epidemiol Biomarkers Prev.* 2010;19(8):1945-1953.
54. Eissenberg T. Electronic nicotine delivery devices: ineffective nicotine delivery and craving suppression after acute administration. *Tob Control.* 2010;19(1):87-88.
55. Barbeau AM, Burda J, Siegel M. Perceived efficacy of e-cigarettes versus nicotine replacement therapy among successful e-cigarette users: A qualitative approach. *Addict Sci Clin Pract.* 2013;8(1):5.
56. Pokhrel P, Fegan P, Little MA, Kawamoto CT, Herzog TA. Smokers who try e-cigarettes to quit smoking: findings from a multiethnic study in Hawaii. *American journal of public health.* 2013;103(9):e57-e62.
57. Cardenas VM, Breen PJ, Compadre CM, Delongchamp RR, Barone CP, et al. The smoking habits of the family influence the uptake of e-cigarettes in US children. *Ann Epidemiol.* 2015;25(1):60-62.
58. Peters RJ Jr, Meshack A, Lin MT, Hill M, Abughosh S. The social norms and beliefs of teenage male electronic cigarette use. *J Ethn Subst Abuse.* 2013;12(4):300-307.
59. Pepper JK, Emery SL, Ribisl KM, Brewer NT. How do U.S. adults find out about electronic cigarettes? Implications for public health messages. *Nicotine Tob Res.* 2014;16(8):1140-1144.

60. Zhu SH, Gamst A, Lee M, Cummins S, Yin L, et al. The use and perception of electronic cigarettes and snus among the U.S. population. *PLoS One*. 2013;8(10):e79332.
61. Paek HJ, Kim S, Hove T, Huh JY. Reduced harm or another gateway to smoking? Source, message, and information characteristics of e-cigarette videos on YouTube. *J Health Commun*. 2014;19(5):545-560.
62. Cobb NK, Brookover J, Cobb CO. Forensic analysis of online marketing for electronic nicotine delivery systems. *Tobacco Control*. 2015;24(2):128-131.
63. Couch ET, Chaffee BW, Gansky SA, Walsh MM. The changing tobacco landscape: What dental professionals need to know. *J Am Dent Assoc*. 2016;147(7):561-569.
64. Phillips CV, Wang C, Guenzel B. You might as well smoke; the misleading and harmful public message about smokeless tobacco. *BMC Public Health*. 2005;5(1):31.
65. Cobb NK, Abrams DB. E-cigarette or drug-delivery device? Regulating novel nicotine products. *N Engl J Med*. 2011;365(3):193-195.
66. Rogers EM. *Diffusion of innovations*, 5th edition. Free Press, New York, USA. 2003.
67. Oncken CA, Litt MD, McLaughlin LD, Burki NA. Nicotine concentrations with electronic cigarette use: effects of sex and flavor. *Nicotine Tob Res*. 2015;17(4):473-478.
68. Courtenay WH. *Dying to be men: Psychosocial, environmental, and biobehavioral directions in promoting the health of men and boys*. Routledge, New York. 2011.
69. ACS. *Cancer facts & figures 2013*. American Cancer Society. 2013.
70. Degenhardt L, Dierker L, Chiu WT, Medina-Mora ME, Neumark Y, et al. Evaluating the drug use "gateway" theory using cross-national data: consistency and associations of the order of initiation of drug use among participants in the WHO World Mental Health Surveys. *Drug Alcohol Depend*. 2010;108(1-2):84-97.
71. McQueen A, Tower S, Sumner W. Interviews with "vapers": Implications for future research with electronic cigarettes. *Nicotine Tob Res*. 2011;13(9):860-867.
72. Farsalinos KE, Romagna G, Tsiapras D, Kyrzopoulos S, Spyrou A, et al. Impact of flavour variability on electronic cigarette use experience: An internet survey. *Int J Environ Res Public Health*. 2013;10(12):7272-7282.
73. Filippidis FT, Laverty AA, Vardavas CI. Experimentation with e-cigarettes as a smoking cessation aid: a cross-sectional study in 28 European Union member states. *BMJ open*. 2016;6(10):e012084.
74. Hajek P. E-cigarettes: a vulnerable promise. *Addiction*. 2012;107(9):1549-1555.
75. Etter JF, Bullen C. Electronic cigarette: users profile, utilization, satisfaction and perceived efficacy. *Addiction*. 2011;106(11):2017-2028.
76. Filippidis FT, Laverty AA, Gerovasili V, Vardavas CI. Two-year trends and predictors of e-cigarette use in 27 European Union member states. *Tob Control*. 2017 Jan;26(1):98-104.
77. 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. *Tob Control*. 2015 Sep;24(5):442-448.
78. Lechner WV, Tackett AP, Grant DM, Tahirkheli NN, Driskill LM, et al. Effects of duration of electronic cigarette use. *Nicotine Tob Res*. 2015 Feb;17(2):180-185.
79. Goniewicz ML, Lingas EO, Hajek P. Patterns of electronic cigarette use and user beliefs about their safety and benefits: an internet survey. *Drug Alcohol Rev*. 2013 Mar;32(2):133-140.
80. Foulds J, Veldheer S, Yingst J, Hrabovsky S, Wilson SJ, et al. Development of a questionnaire for assessing dependence on electronic cigarettes among a large sample of ex-smoking E-cigarette users. *Nicotine Tob Res*. 2015 Feb;17(2):186-192.
81. Le Houezec J. Role of nicotine pharmacokinetics in nicotine addiction and nicotine replacement therapy: a review. *Int J Tuberc Lung Dis*. 2003 Sep;7(9):811-819.
82. Vansickel AR, Eissenberg T. Electronic cigarettes: effective nicotine delivery after acute administration. *Nicotine Tob Res*. 2013 Jan;15(1):267-270.
83. Dawkins L, Corcoran O. Acute electronic cigarette use: nicotine delivery and subjective effects in regular users. *Psychopharmacology (Berl)*. 2014 Jan;231(2):401-407.
84. Etter JF. Levels of saliva cotinine in electronic cigarette users. *Addiction*. 2014 May;109(5):825-829.
85. Nides MA, Leischow SJ, Bhattar M, Simmons M. Nicotine blood levels and short-term smoking reduction with an electronic nicotine delivery system. *Am J Health Behav*. 2014 Mar;38(2):265-274.
86. Spindle TR, Breland AB, Karaoghlanian NV, Shihadeh AL, Eissenberg T. Preliminary results of an examination of electronic cigarette user puff topography: the effect of a mouthpiece-based topography measurement device on plasma nicotine and subjective effects. *Nicotine Tob Res*. 2015 Feb;17(2):142-149.
87. Choi JH, Dresler CM, Norton MR, Strahs KR. Pharmacokinetics of a nicotine polacrilex lozenge. *Nicotine Tob Res*. 2003 Oct;5(5):635-644.
88. Bullen C, McRobbie H, Thornley S, Glover M, Lin R, et al. Effect of an electronic nicotine delivery device (e cigarette) on desire to smoke and withdrawal, user preferences and nicotine delivery: randomised cross-over trial. *Tob Control*. 2010 Apr;19(2):98-103.
89. Hughes JR. Dependence potential and abuse liability of nicotine replacement therapies. *Biomed Pharmacother*. 1989;43(1):11-17.
90. Henningfield JE. Nicotine medications for smoking cessation. *N Engl J Med*. 1995;333(18):1196-1203.
91. Shiffman S, Hughes JR, Di Marino ME, Sweeney CT. Patterns of over-the-counter nicotine gum use: persistent use and concurrent smoking. *Addiction*. 2003 Dec;98(12):1747-1753.
92. El Dib R, Suzumura EA, Akl EA, Gomaa H, Agarwal A, et al. Electronic nicotine delivery systems and/or electronic non-nicotine delivery systems for tobacco smoking cessation or reduction: a systematic review and meta-analysis. *BMJ Open*. 2017 Feb;7(2):e012680.
93. Chaffee BW, Couch ET, Gansky SA. Trends in characteristics and multi-product use among adolescents who use electronic cigarettes, United States 2011-2015. *PLoS One*. 2017 May;12(5):e0177073.
94. Arrazola RA, Singh T, Corey CG, Husten CG, Neff LJ, et al. Tobacco use among middle and high school students - United States, 2011-2014. *MMWR Morb Mortal Wkly Rep*. 2015;64(14):381-385.
95. Pu J, Zhang X. Exposure to advertising and perception, interest, and use of e-cigarettes among adolescents: findings from the US National Youth Tobacco Survey. *Perspect Public Health*. 2017 Nov;137(6):322-325.
96. Schneider S, Diehl K. Vaping as a Catalyst for Smoking? An Initial Model on the Initiation of Electronic Cigarette Use and the Transition to Tobacco Smoking Among Adolescents. *Nicotine Tob Res*. 2016 May;18(5):647-653.
97. Cobb CO, Villani AC, Graham AL, Pearson JL, Glasser AM, et al. Markov modeling to estimate the population impact of emerging tobacco products: A proof-of-concept study. *Tob Regul Sci*. 2015;1(2):129-141.
98. Benowitz NL. Emerging nicotine delivery products. Implications for public health. *Ann Am Thorac Soc*. 2014 Feb;11(2):231-235.
99. Johnston LD, Miech RA, O'Malley PM, Bachman JG, Schulenberg JE, et al. *Monitoring the Future. National Survey Results on Drug Use: 1975-2017: Overview, Key Findings on Adolescent Drug Use*. Ann Arbor: Institute for Social Research, The University of Michigan. 2017.
100. Bunnell RE, Agaku IT, Arrazola RA, Apelberg BJ, Caraballo RS, et al. Intentions to smoke cigarettes among never-smoking US middle and high school electronic cigarette users: National Youth Tobacco Survey, 2011-2013. *Nicotine Tob Res*. 2015 Feb;17(2):228-235.

101. Corey C, Wang B, Johnson SE, Apelberg B, Husten C, et al. Cancer-Related News from the CDC: Electronic Cigarette Use Among Middle and High School Students. *Oncology Times*. 2013;35(19):36.
102. Dutra LM, Glantz SA. Electronic cigarettes and conventional cigarette use among U.S. adolescents: a cross-sectional study. *JAMA Pediatr*. 2014 Jul;168(7):610-617.
103. Huang LL, Kowitz SD, Sutfin EL, Patel T, Ranney LM, et al. Electronic Cigarette Use Among High School Students and Its Association With Cigarette Use And Smoking Cessation, North Carolina Youth Tobacco Surveys, 2011 and 2013. *Prev Chronic Dis*. 2016 Aug;13:E103.
104. Hughes K, Bellis MA, Hardcastle KA, McHale P, Bennett A, et al. Associations between e-cigarette access and smoking and drinking behaviours in teenagers. *BMC Public Health*. 2015 Mar;15:244.
105. Leventhal AM, Strong DR, Kirkpatrick MG, Unger JB, Sussman S, et al. Association of Electronic Cigarette Use With Initiation of Combustible Tobacco Product Smoking in Early Adolescence. *JAMA*. 2015 Aug;314(7):700-707.
106. Primack BA, Soneji S, Stoolmiller M, Fine MJ, Sargent JD, et al. Progression to Traditional Cigarette Smoking After Electronic Cigarette Use Among US Adolescents and Young Adults. *JAMA Pediatr*. 2015 Nov;169(11):1018-1023.
107. Fotiou A, Kanavou E, Stavrou M, Richardson C, Kokkevi A. Prevalence and correlates of electronic cigarette use among adolescents in Greece: a preliminary cross-sectional analysis of nationwide survey data. *Addict Behav*. 2015 Dec;51:88-92.
108. McCabe SE, West BT, Veliz P, Boyd CJ. E-cigarette Use, Cigarette Smoking, Dual Use, and Problem Behaviors Among U.S. Adolescents: Results From a National Survey. *J Adolesc Health*. 2017 Aug;61(2):155-162.
109. 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. *J Adolesc Health*. 2015 Nov;57(5):562-564.
110. Miech R, Patrick ME, O'Malley PM, Johnston LD. What are kids vaping? Results from a national survey of US adolescents. *Tob Control*. 2017 Jul;26(4):386-391.
111. Morean ME, Kong G, Cavallo DA, Camenga DR, Krishnan-Sarin S. Nicotine concentration of e-cigarettes used by adolescents. *Drug Alcohol Depend*. 2016;167:224-227.
112. Filippidis FT, Vardavas CI, Loukopoulou A, Behrakis P, Connolly GN, et al. Prevalence and determinants of tobacco use among adults in Greece: 4 year trends. *Eur J Public Health*. 2013 Oct;23(5):772-776.
113. Ng M, Freeman MK, Fleming TD, Robinson M, Dwyer-Lindgren L, et al. Smoking prevalence and cigarette consumption in 187 countries, 1980-2012. *JAMA*. 2014 Jan;311(2):183-192.
114. OECD/European Union. *Health at a glance: Europe 2014*. OECD Publishing, Paris. 2014.
115. Modesto-Lowe V, Alvarado C. E-cigs . . . Are They Cool? Talking to Teens About E-Cigarettes. *Clin Pediatr (Phila)*. 2017 Sep;56(10):947-952.
116. Vasiljevic M, Petrescu DC, Marteau TM. Impact of advertisements promoting candy-like flavoured e-cigarettes on appeal of tobacco smoking among children: an experimental study. *Tob Control*. 2016 Dec;25(e2):e107-e112.
117. Brown, Williamson. *Taste Segmentation Study Final Report*, May 1984, Bates No. 538003902-538003933.
118. Morris P. *New flavors qualitative research insights*, October 1992. Bates No. 2023163698-2023163710.
119. WHO. *The scientific basis of tobacco product regulation: a WHO Study Group on Tobacco Product Regulation Report*; No. 945. World Health Organization. 2007.
120. Cooper M, Harrell MB, Pérez A, Delk J, Perry CL. Flavorings and Perceived Harm and Addictiveness of E-cigarettes among Youth. *Tob Regul Sci*. 2016 Jul;2(3):278-289.
121. Roditis ML, Halpern-Felsher B. Adolescents' Perceptions of Risks and Benefits of Conventional Cigarettes, E-cigarettes, and Marijuana: A Qualitative Analysis. *J Adolesc Health*. 2015 Aug;57(2):179-185.
122. Wasowicz A, Feleszko W, Goniewicz ML. E-Cigarette use among children and young people: the need for regulation. *Expert Rev Respir Med*. 2015 Oct;9(5):507-509.
123. Williams RS, Derrick J, Ribisl KM. Electronic cigarette sales to minors via the internet. *JAMA Pediatr*. 2015 Mar;169(3):e1563.
124. Kong G, Morean ME, Cavallo DA, Camenga DR, Krishnan-Sarin S. Reasons for Electronic Cigarette Experimentation and Discontinuation Among Adolescents and Young Adults. *Nicotine Tob Res*. 2015 Jul;17(7):847-854.
125. Wills TA, Sargent JD, Knight R, Pagano I, Gibbons FX. E-cigarette use and willingness to smoke: a sample of adolescent non-smokers. *Tob Control*. 2016 Apr;25(e1):e52-e59.
126. Gmel G, Baggio S, Mohler-Kuo M, Daepfen JB, Studer J. E-cigarette use in young Swiss men: is vaping an effective way of reducing or quitting smoking? *Swiss Med Wkly*. 2016 Jan;146:w14271.
127. Duke JC, Allen JA, Eggers ME, Nonnemaker J, Farrelly MC. Exploring Differences in Youth Perceptions of the Effectiveness of Electronic Cigarette Television Advertisements. *Send to Nicotine Tob Res*. 2016 May;18(5):1382-1386.
128. Camenga DR, Cavallo DA, Kong G, Morean ME, Connell CM, et al. Adolescents' and Young Adults' Perceptions of Electronic Cigarettes for Smoking Cessation: A Focus Group Study. *Nicotine Tob Res*. 2015 Oct;17(10):1235-1241.
129. EU. *Proposal for a directive of the European Parliament and of the Council on the approximation of the laws, regulations and administrative provisions of the member states concerning the manufacture, presentation and sale of tobacco and related products*. European Union. 2012.
130. EU. *Directive of the European Parliament and of the Council on the Approximation of the Laws, Regulations, and Administrative Provisions of the Member States Concerning the Manufacture, Presentation and Sale of Tobacco and Related Products*. Pe-Cons No/Yy - 2012/0366 (Cod), Brussels, 2014.
131. *Global Tobacco Control. E-cigarette Policy Scan*. Institute for Global Tobacco Control, USA.
132. Tremblay MC, Pluye P, Gore G, Granikov V, Filion KB, et al. Regulation profiles of e-cigarettes in the United States: a critical review with qualitative synthesis. *BMC Med*. 2015 Jun;13:130.
133. FDA. *FDA's New Regulations for E-Cigarettes, Cigars, and All Other Tobacco Products*. US Department of Health and Human Services. US Food and Drug Administration. 2016.
134. Morean ME, Kong G, Cavallo DA, Camenga DR, Krishnan-Sarin S. Nicotine concentration of e-cigarettes used by adolescents. *Drug Alcohol Depend*. 2016 Oct;167:224-227.
135. FDA. *Regulation of Electronic Nicotine Delivery Systems and E-Liquids*. FDA Center for Tobacco Products. 2018.
136. FDA. *2018 Warning Letters*. Food and Drug Administration, USA. 2018.
137. ANRF. *States and Municipalities with Laws Regulating Use of Electronic Cigarettes*. American Nonsmokers' Rights Foundation, USA. 2018.