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Review Article

Chemical characterization and health risks associated with e-cigarettes: A comprehensive review

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Abstract

The evolution of the cigarette industry took us from traditional to electronic cigarettes (e-cigs). These are electronic devices that produce nicotine-containing aerosols by heating a liquid (e-liquid) that contains the drug as well as other numerous compounds. Although designed to decrease the harmful effects of traditional cigarettes, little is known about the long-term health incidence of e-cigarettes. The chemical composition of e-liquids varies depending on their manufacturer, country of origin, and batches. Fundamentally, e-liquids contain glycerol, propylene glycol, water, and nicotine. However, a concerning number of toxic substances including heavy metals, nonmetals, pesticides, polycyclic aromatic hydrocarbons, volatile organic compounds, and many other molecules have been identified in them. A wide number of analytical techniques have been employed in the identification and quantitation of these chemicals in liquids as well as aerosols. This review will discuss the numerous chemical substances associated with the use of e-cigarettes, including the potential impact of these on human health. Additionally, this work will address the available analytical tools as well as promising technologies that can contribute to future toxicological characterization efforts. This review also covers some of the global regulatory policies including their challenges and loopholes.

Introduction

Smoking consists of inhaling aerosols produced by a combusted substance, typically dried and fermented tobacco leaves wrapped in thin paper that form a cylinder known as cigarettes [1]. Cigarettes have been described as "a drug administration system for the delivery of nicotine in an acceptable and attractive form" [2]. In 2020, the Statista Research Department estimated a total of 5.2 trillion cigarettes were consumed worldwide [3]. Although these numbers showed a decrease of 3.7% in comparison to the 5.4 trillion units consumed in 2019, the high demand for cigarettes translates into a highly competitive market. The traditional design involves the use of a filter, additives, paper, and dried tobacco leaves (Figure 1) [4]. To stand out from other brands, industries have opted to include various additive chemicals such as menthol, sugars, eucalyptol, and theobromine in their product [5-7]. These additives alter the natural flavor of tobacco and offer a more pleasurable experience to consumers. Some of the health risks associated with the practice of smoking are chronic obstructive lung diseases, asthma, cardiovascular diseases, and lung cancer [8,9].

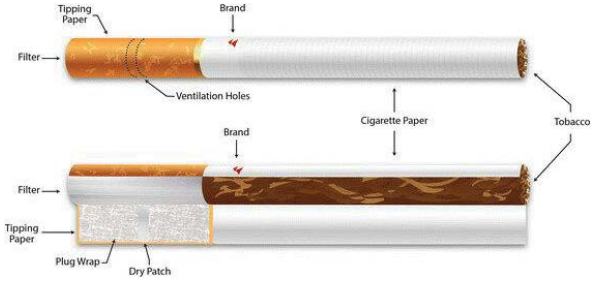

Figure 1: Components of a traditional cigarette [4].

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In 2003, Electronic Nicotine Delivery Systems (ENDS), also known as e-cigarettes, emerged [10]. ENDS are electronic devices used to produce a vaporized mixture of nicotine, flavoring agents, and propylene glycol that is inhaled by the users; an action which is known as "vaping".

E-cigarettes are rapidly displacing their traditional counterpart, especially in younger demographics. Some of the advantages offered by this electronic alternative include presentations with various flavors, varying options of nicotine percentages, and fewer combustion chemicals [11,12]. The primary e-cigarette design consists of a battery attached to an atomizing device and heater, followed by a cartridge that contains the nicotine solution (Figure 2) [13].

Examples of the different batteries used to power e-cigarettes are nickel-cadmium, lithium-ion, and lithium-manganese [14,15]. The production of aerosols in the atomizing device first begins with the transportation of liquid from the cartridge to the generator via multiple systems including pumps, a plunger, and thermal processes. Then, the liquid reaches the device's heating element, with varying temperature ranges based on the specific material properties and battery voltage. Last, the produced aerosol is inhaled by the consumer via an attached mouthpiece [14].

The nicotine-containing liquid, also known as e-liquid, contains a glycerin or propylene glycol base with various substances used to add flavors such as menthol, fruit, and traditional tobacco [16-19]. Research has demonstrated that nicotine exposure from e-cigarettes is influenced by the device characteristics and varying additives contained in the liquid [18]. Moreover, there is a significant range in the varying nicotine content of the liquids, contributing to nicotine dependence in the consumer [16].

Numerous analytical techniques have been applied to characterize both e-liquids and the aerosols they produce. Nicotine content could be determined using gas chromatography paired with a flame ionization detector (GC-FID). Through the utilization of gas chromatography coupled with mass spectrometry (GC-MS), the identification of propylene glycol, ethylene glycol, glycerol, and benzoic acid in e-liquids was determined. Then, through GC-MS in tandem mode (GC-MS-MS) it was made possible to identify the presence of pesticides and polycyclic aromatic hydrocarbons (PAHs). The quantification of carbonyl compounds was achieved by high-performance liquid chromatography with a diode array detector (HPLC-DAD). Finally, employing induced coupled plasma mass spectrometry was used in the characterization of trace elements found in e-liquids [20-22].

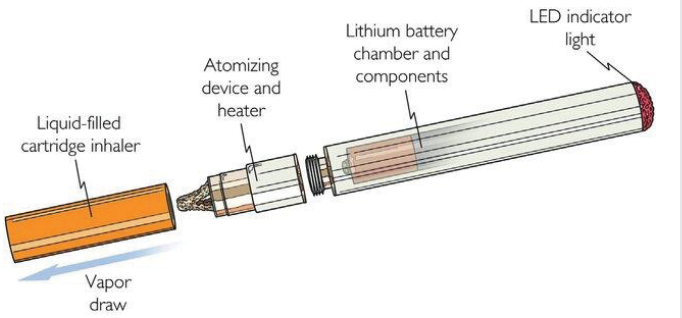

Figure 2: Components of an e-cigarette [12].

Considerable research has been done on the many health risks contributed to smoking cigarettes as well as the dual use of traditional, and e-cigarettes. However, few studies have found a relationship between the practice of vaping and associated health issues. To the best of our knowledge, the only significant finding was done by Judith Groner, who concluded that there is a link between pre-symptomatic cardiovascular dysfunction and the use of e-cigarettes [23]. Other works have expressed concerns about possible risks, for example, Tegin, et al. concluded that the use of e-cigarettes can lead to nicotine dependence and addiction [12]. Additionally, Marques, et al. expressed that stricter regulations are required for e-liquids, as many incidents of mislabeling have been detected [9].

This article reviews the toxic compounds associated with e-cigarettes, the challenges, and possible health risks that are associated with these molecules both in first and second-hand exposure. First, we discuss the organic and inorganic constituents found in e-cigarettes as well as the analytical methods that have been utilized so far in these determinations. Secondarily, we cover the health risks connected to toxic compound exposure and current regulations.

Toxic chemicals characterization of e-cigarettes

The chemical components of e-cigarettes can be divided into two main categories: toxic metals and organic matter. The latter can be subdivided into pesticides, PAHs, and carbonyl groups [20]. An estimated number of 98 hazardous chemicals were previously reported in the literature [24]. The source of these substances varies within the overall action of vaping. Zhao, et al. observed significant concentrations of Cd and Pb in e-liquids as well as elevated amounts of Cu and Ni in the produced aerosols [25]. A recent study showed higher levels of the toxic metals Cr, Cd, Pb, Ni, and Al in comparison to e-liquids after several days of use [26]. Recent studies by Jităreanu, et al. determined higher concentrations of heavy metals such as tin, chromium, copper, lead, and nickel in the used liquids [27,28]. These findings by Mulder, et al. suggest that metal lost by the heating coils may enter the aerosols [29]. Hence the presence of these toxic metals in the e-liquids. Other metals such as K, Ca, Ti, Cr, Mn, Fe, Zn, and the nonmetal Br have been recently identified in e-liquids [30,31]. A complete list of the metals and nonmetal species that have been identified in e-cigarettes along with the health risks suggested by the FDA is shown in Table 1.

A wide range of organic contaminants have been identified in the vaping system. Beauval, et al. detected acrolein, formaldehyde, and acetaldehyde in the dispenser and vapors produced by the e-cig [20]. Tobacco-specific nitrosamines (TSNAs) such as N'-nitrosonornicotine (NNN) and 4-(methylnitrosoamino)-1-(3-pyridyl)-1-butanone (NNK) have been previously characterized in the vapors of e-cigarettes [35]. Other relevant toxics are the PAHS

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anthracene, benzofluoranthenes, fluorene, naphthalene, and pyrene; potential carcinogens found in the vapors [36]. Schober, et al. also detected benzene and benzene derivatives 36. In Table 2, the presence of several classes of organic compounds is presented, along with their source within the vaping system.

Current analytical tools and challenges in the chemical characterization from e-cigarettes

Organic matter characterization: Various analytical techniques are required to comprehensively characterize electronic cigarettes, as shown in Figure 3. Examples of these tools are gas chromatography (GC) and liquid chromatography (LC) which are mostly used to characterize VOCs, carbonyls, and nicotine contained in the e-liquids [37]. These chromatographic methods coupled with mass spectrometry (MS) have shown greater experimental results in terms of detectability and compositional identification in both liquid and aerosol samples [38]. In 2016, Bansal, et al. recommended GC-MS as the most appropriate tool for the analysis of volatile organic compounds [39]. Furthermore, GC-MS has been able to characterize numerous components in both aerosols and smoke of e-cigs. Some examples of these include acetaldehyde, benzaldehyde, formaldehyde, glycerol, limonene, naphthalene, and N-Nitrosonornicotine (NNN) [40,41].

Table 1: Inorganic constituents, concentration range, and their source within e-cigarettes. FDA classification.

Ionic species	Concentration (ppb)			
	Vapor / Aerosol [20,31,32]	Cartridge [33]	Atomizer [33]	FDA Classification [34]
Metals				
Aluminium (Al)	< 10-160	17.5-128	7.22-20.2	N/A
Arsenic (As)	< 0.23-11	-	-	CA, CT, RDT
Barium (Ba)	< 15-130	-	-	N/A
Beryllium (Be)	< 0.057-0.12	-	-	CA
Bismuth (Bi)	< 0.089-0.3	-	-	N/A
Cadmium (Cd)	< 0.02-1	0.267	<0.1	CA
Cobalt (Co)	< 0.089-0.9	-	-	CA, CT
Chromium (Cr)	< 2.1-43.9	17.4-217	<0.5 - 2.26	CA, RT, RDT
Copper (Cu)	< 5.2-51	42.0-543	<1 - 16.1	N/A
Iron (Fe)	< 53-3000	127-1,360	9.14-91.3	N/A
Mercury (Hg)	< 4-14	-	-	CA, RDT
Lithium (Li)	0.7- 9	-	-	N/A
Manganese (Mn)	< 1.6-9.56	13.0-93.9	<1 - 2.74	N/A
Molybdenum (Mo)	< 0.45-3	-	-	N/A
Nickel (Ni)	< 2.3-289	69.5-675	<1 - 42.1	CA, RT
Lead (Pb)	< 0.23-37.1	13.6-189	0.243-1.05	CA, CT, RDT
Antimony (Sb)	< 0.11-10	<0.1-2.57	<0.1-0.219	N/A
Selenium (Se)	44.6-4.6	-	-	N/A
Tin (Sn)	< 0.24-19.4	9.10-72.2	0.489-3.55	N/A
Thallium (Ti)	< 0.055-0.18	-	-	N/A
Vanadium (V)	< 0.4-0.64	-	-	N/A
Uranium (U)	< 0.21-0.7	-	-	CA, RT
Zinc (Zn)	< 62-809	152-1,540	6.74-23.0	N/A
Non metals				
Boron (B)	< 61; < 37-140	-	-	N/A

CA: Carcinogen; RT: Respiratory Toxicant; CT: Cardiovascular Toxicant; RDT: Reproductive or Developmental Toxicant; AD: Addictive

Table 2: Organic constituents, concentration range, and their source within e-cigarettes. FDA classification.

Organic Compounds	Concentration			
	ng/ml of heated liquid [20]	pg/ml of emission) [20]	µg/ 15 Puffs [33]	FDA Classification [34]
Pesticides				
Chlorpyrifos ethyl	< 20-66.3 (pg/ml)	< 0.09-0.30	-	N/A
a-endosulfan	-	< 0.09 -0.30	-	N/A
b-endolsulfan	-	< 0.1-0.60	-	N/A
cyhalothrin	-	< 0.09-0.30	-	N/A
cyphermethrin	-	< 0.38-0.19	-	N/A
Trifuralm	< 20-25.3 (pg/ml)	< 0.09-0.30	-	N/A
PAHs				
Acenaphthene	< 0.20-1.12	< 0.09-0.30	-	N/A
Acenaphthylene	< 0.02-0.05	< 0.09-0.37	-	N/A
Benzo[a]pyrene	< 0.02	< 0.09-0.30	-	CA
Benzo[b] fluoranthene	< 0.02-0.03	< 0.09-0.30	-	CA, CT
Benzo[ghi] perylene	< 0.05-0.07	< 0.09-0.30	-	N/A
Chrysene	< 0.02-0.03	< 0.09-0.30	-	CA, CT
Fluoranthene	< 0.05-0.09	< 0.19-0.60	-	CA, CT
Fluorene	< 0.20-0.57	< 0.19-0.60	-	N/A
Naphthalene	< 18.9-61.8	< 0.47-4.1	-	CA, RT
Phenanthrene	< 2.43-3.83	< 0.19-0.60	-	N/A
Benz[a] anthracene	-	< 0.09-0.30	-	CA, CT
dibenz[a,h] anthracene	-	< 0.19-0.60	-	CA
Indenol[1,2,3-cd] pyrene	-	< 0.19-0.60	-	CA
pyrene	-	< 0.19-0.60	-	N/A
Carbonyls				
Acetaldehyde	-	< 0.30-0.96 (ng/ml)	1.77-57.19	CA, RT, AD
acrolein	-	< 0.11-2.2 (ng/ml)	-	RT, CT
formaldehyde	-	< 0.37-1.48 (ng/ml)	0.32-0.53	
acetone	-	-	9.61-37.22	RT
propionaldehyde	-	-	0.28-9.52	RT, CT
crotonaldehyde	-	-	0.44-3.6	CA
methacrolein	-	-	1.02-4.8	N/A
Butyraldehyde	-	-	0.32	N/A
Valeraldehyde	-	-	0.21-0.45	N/A
Glyoxal	-	-	0.72-1.52	N/A
Methylgyozal	-	-	1.2-13.37	N/A

CA: Carcinogen; RT: Respiratory Toxicant; CT: Cardiovascular Toxicant; RDT: Reproductive or Developmental Toxicant; AD: Addictive

Gas chromatography with a flame ionization detector (GC-FID) has been applied for the analyses of nicotine and artificial flavors in liquids and aerosols [42]. Moreover, this method allowed the study of solvents and volatile compounds found in the e-liquids [43]. Liquid chromatography high-performance mass spectrometry (LC-HRMS) has been employed in the complete study of the e-liquids as well as the aerosol generated by the devices. This technique was able to identify tributylphosphine oxide and caffeine in the aerosols and liquids, whose presence was unknown until then [20,44]. Furthermore, hazardous chemicals including polycyclic aromatic hydrocarbons (PAH), pesticides, and carbonyl compounds as well as commonly e-liquids components such as

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propylene glycol, glycerol, and nicotine have been previously identified by LC-MS [20].

Other compounds of interest such as volatile organic compounds, carbonyls, tobacco-specific nitrosamines (TSNAs), and polycyclic aromatic hydrocarbons (PAHs) can be studied by selected ion flow tube mass spectrometry (SIFT-MS) [39,46]. A promising tool in the study of the organic matter in these samples is nuclear magnetic resonance spectroscopy (NMR). Hahn, et al. concluded that NMR is a quick alternative to HPLC and GC that provides information about the composition of e-liquids [47]. The protocols available for the study of organic compounds may hinder the complete characterization of the organics present in the vapors and aerosols of e-cigarettes. The use of untargeted analysis techniques may aid in this promising research field.

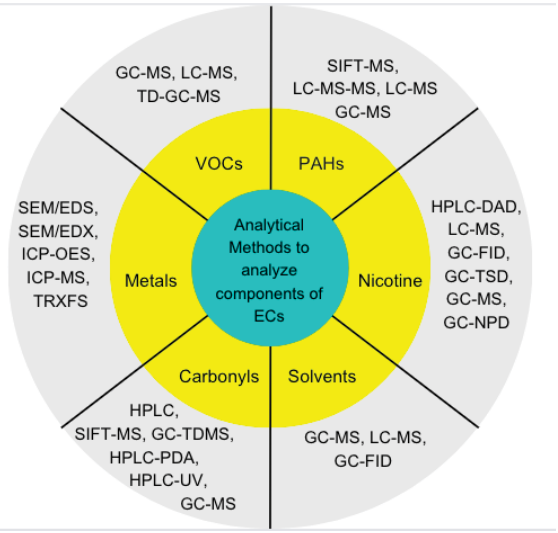

Figure 3: Schematic of the different chemicals associated with e-cigarettes and the respective analytical techniques that are used for analyte detection and quantitation [39,45].

Inorganic components identification: On the other hand, the detection and quantitation of heavy metals relies on the use of inductively coupled plasma (ICP) optical emission spectroscopy (ICP-OES) and ICP-MS [26,38,39,48]. Another technique utilized in the characterization of metals in e-liquids is X-ray fluorescence spectrometry [30,31]. Similarly, total reflection X-ray fluorescence spectrometry (TRXFS) has been employed for heavy metals characterization in e-liquids, demonstrating short analysis time, and simultaneous multi-element determination [45]. Additional methods for metal analysis are scanning electron microscopy coupled to an energy dispersive spectrometer (SEM-EDS) as well as SEM with an energy-dispersive X-ray detector (EDX) [38]. These are non-destructive promising technologies for the study of metals in the device. For instance, in 2020, Mulder used SEM to study the metal loss from the heating coils in the e-cig [29].

First and second-hand exposure to E-cigarettes

Electronic cigarettes are still young in the aspect of development, characterization, and of the substances produced inside. Little is known about their negative health impact and the corresponding health issues caused by their use [20]. The use of ENDS is believed to be less harmful in terms of human health than traditional cigarettes [49]. The World Health Organization (WHO) expressed that e-liquid consumption may be related to an increased risk of cancer, pulmonary and cancer disease. Additionally, the WHO stated that second-hand smokers are exposed to toxic chemicals and nicotine [50]. In Figure 4, several of the potential effects of e-cigarettes

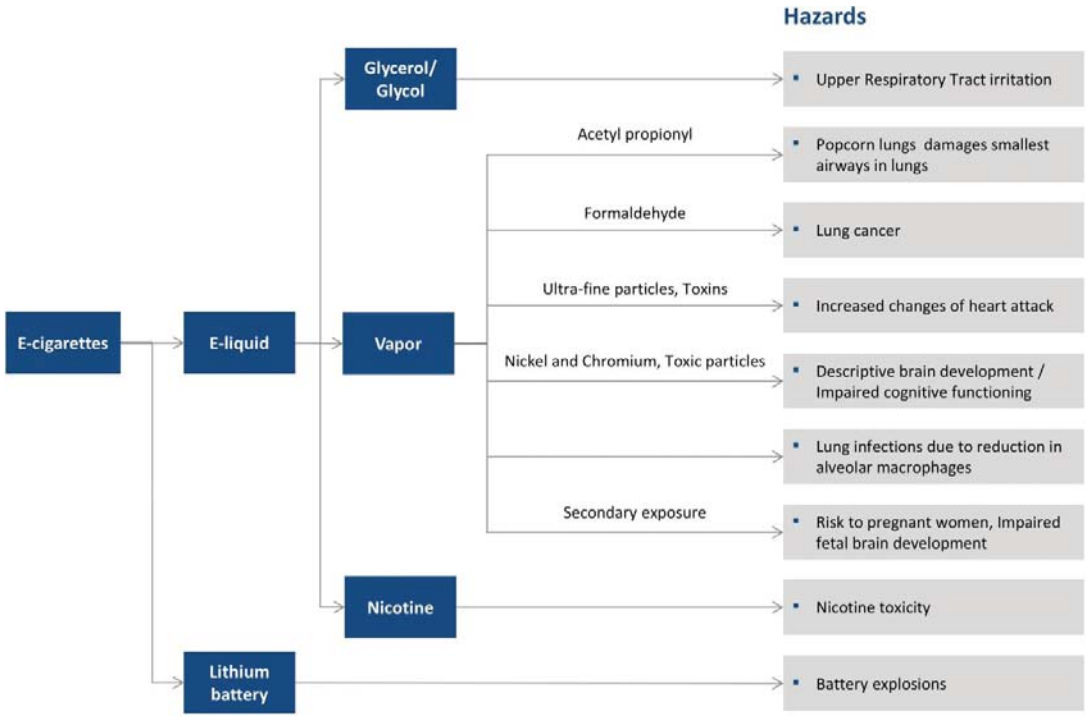

Figure 4: Health risks associated with the use of e-cigarettes. Extracted from Sapru, et al. [49].

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on health are shown, which are determined by various and ranging factors such as particulate size, climate conditions, battery voltage, vaping pattern, type of vaping instrument, age, gender, and health status [49,51-53].

Previous studies concluded that there is no change in the lung health of e-cigarette users [54]. A different study attributed an improvement in respiratory functions of smokers who switch from traditional to electronic cigarettes [55]. However, recent studies have associated exposure to e-cig aerosols with a number of cardiac as well as pulmonary pathologies [56,57]. In 2019, Son, et al. concluded that exposure to the hydroxyl radicals formed when vaping may increase the risk of asthma and chronic obstructive pulmonary disease, a progressive inflammatory response of the airways (COPD) [58,59]. Especially in those with vegetable glycerin e-liquids. Further studies suggested that the vapors generated by e-cigarettes increased the tolerance and inflammatory potential of pathogenic bacteria similar to the smoke of traditional cigarettes [60]. Studies suggest that passive smokers are at risk of respiratory tract irritation and palpitations [61]. However, Further studies are required regarding the direct effect of vapor exposure and bystanders as the main interaction is mediated by quickly evaporating nanoparticles [53]. In Table 3, the findings of several studies regarding the connection of smoking exposure with respiratory and cardiac health are presented.

Other concerns include oral health and the levels of toxic metals in biological fluids. In 2020, Zhao et. al. found similar levels of metals and metalloids in biosamples from e-cigs users as those who used traditional cigarettes and cigars [25]. On the other hand, shifts in the oral microbiota of vapers with the colonization of microbial biofilms have been observed [65]. Additionally, microbial toxins have been identified in e-liquids [66]. Exposure to certain levels of endotoxins may trigger inflammation, reduced lung function, and asthma [67-69]. The increased risk of cancer by vapers has also been suggested. Previous studies have identified several molecules belonging to the TSNAs family, which are known to be carcinogenic [39,70]. In a recent study, carcinogenic biomarkers have been detected in the urine of e-cigarette users. These molecules are believed to have a link to bladder cancer [71].

Current legislation: Challenges and future perspectives

The legislative landscape surrounding e-cigarettes has been the subject of intense debate and evolution across the world. E-cigarettes have gained popularity as an alternative to traditional tobacco products, leading to a diverse array of regulations aiming to balance public health concerns with harm reduction for users. The rapid proliferation of the availability of ENDS in many countries often results in a delayed approach to e-cigarette legislation and the struggle to find a balance between

Table 3: Summary of findings in various studies on the health effects of first and secondhand exposure to e-cigarettes. Modified from Li, et al. [62]. The clinical indicators nitric oxide (NO) and carbon monoxide (CO) measure airway inflammation and smoking habits respectively [63,64].

Smokers/nonsmokers study subjects (n)	Exposure duration (min)	Health effect indicator	Findings
Respiratory and cardiovascular effects in active e-cig users			
15	30	Lung function, exhaled CO, exhaled NO	No difference before and after e-cig use
20	5	Lung function, exhaled CO, exhaled NO	Reduction in lung function post-use
16	10	Exhaled NO	No difference before and after e-cig use
30	5	Lung function, exhaled NO, airway resistance	Increased airway resistance and decreased exhaled NO post-use
25	5	Exhaled NO	Increased exhaled NO post-use
9	120	Exhaled CO and exhaled NO	Increased exhaled NO post-use
30	15	Cough reflex sensitivity	Inhibited cough reflex sensitivity post-use
28	N/A	Airway proteome	Changes in protein profile in lungs
15	30	Blood count	No difference before and after e-cig use
16	10	Endothelial function biomarkers	Increased endothelial progenitor cell counts post-use
15	30	Oxidative stress biomarker	No difference before and after e-cig use
33	30	Heart rate variability, blood pressure, oxidative stress, inflammation	Shift in cardiac autonomic balance post-use
40	N/A	Endothelial function biomarkers and oxidative stress biomarkers	Increase in oxidative stress biomarkers and decrease in endothelial function biomarkers
10	3	Oxidative stress biomarker and inflammation	Increase in oxidative stress biomarkers and inflammation post-use
42	1.6 years	Heart rate variability, blood pressure, oxidative stress, inflammation	Shift in cardiac autonomic balance and increase in oxidative stress post-use
Respiratory and cardiovascular effects in passive e-cig users			
15	60	Lung function, exhaled CO, exhaled NO	No difference before and after the exposure
40	30	Lung function, exhaled CO, exhaled NO, and airway resistance	Increased air resistance and decrease in exhaled NO post-exposure
15	60	Complete blood count	No difference before and after the exposure
15	60	Oxidative stress biomarker	No difference before and after the exposure

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caution and adaptation. Efforts to implement and maintain regulation are often complicated by the varying names and brands under which e-cigarettes are sold [72]. Internationally, several nations have taken a more comprehensive approach by treating e-cigarettes as traditional tobacco products or medical devices, subjecting them to parallel regulations. This includes taxation, health warnings, and public usage restrictions, which are all similar to rules established for combustible cigarettes [73]. Such measures are often rooted in the precautionary principle, as limited long-term research exists regarding the health effects of e-cigarettes.

The global nature of this debate has led to varying degrees of regulation and enforcement. In countries like the United States, regulations have fluctuated over the years, with FDA regulations imposing tighter controls on e-cigarette sales, flavors, and marketing to address youth usage [74]. These FDA regulations directly affect privately owned establishments that sell e-cigarette products. For example, prohibiting shops from offering free samples of nicotine-containing liquids, required health warnings on packaging and advertisements, and the cessation of youth-targeted advertising campaigns [75]. The World Health Organization's report on nicotine delivery systems examined legislation regarding the topic in 98 countries; 70 countries classify and regulate e-cigarettes uniquely as vaping products, 57 as tobacco products on the same level as classic combustible cigarettes, 18 as consumer products/devices, and 4 as poisons or hazardous substances due to their lack of medicinal purpose [73]. Table 4 below shows different regulatory approaches and classifications of END products in countries that enforce their marketing and distribution.

Challenges in e-cigarette regulations continue to evolve rapidly as governments look for the balance between safeguarding public health and supporting adult smokers seeking alternatives. Complexity arises when considering the potential of e-cigarettes as harm-reduction tools for current smokers seeking to quit. Advocates argue that these devices could play a pivotal role in reducing smoking-related diseases. Consequentially, some jurisdictions have adopted a more lenient stance, differentiating between e-cigarettes and traditional tobacco products. These areas often allow for easier access to e-cigarettes, and even encourage their use among smokers looking to transition as well as opening up loopholes in regulation [77].

Loopholes in legislation

Many current regulatory efforts are not immune to vulnerabilities and gaps that can be exploited by e-cigarette manufacturers, marketers, and users. The wide variety of flavors, creative naming, and brands available can attract young users, despite efforts to restrict marketing towards minors. Manufacturers utilize these tactics to bypass legislation against specific flavor bans [78]. While certain flavors are banned, variations under different names are introduced, actively undermining the intention to reduce youth appeal [79]. The common perception of reduced harm associated with flavored e-cigarettes is a common trend amongst young adult users regardless of the prevalence of risk-posing chemicals in the liquid. While current FDA legislation imposes flavor bans on tank and cartridge-based ENDS except for menthol and tobacco flavorings, disposable e-cigarettes (which are the most popular amongst youth users) have no flavor regulation due to FDA gray areas in the defining of a cartridge [80].

Table 4: 2016 Global policies for e-cigarettes. Extracted from Kennedy, et al. 2017 [76].

Country	Regulatory approach(es)	Product classification(s)	Regulatory domain(s)
Argentina	Decree; existing law; ruling	ENDS, tobacco	Advertising/promotion, distribution, importation, sale, vape-free (implicit)
Australia	Existing law; statement	Poison, consumer good	Advertising/promotion, importation, sale
Austria	Amended law; existing law; new law	Tobacco-related products, medicinal, medical devices, consumer good	Advertising/promotion/sponsorship, child safety, health warning labelling, ingredients/flavours, nicotine volume/concentration, reporting/notification, safety/hygiene, sale, vape-free
Bahrain	Existing law; decision	ENDS, tobacco	Advertising/promotion, sale, vape-free
Belgium	Existing law	Medicinal, consumer good	Advertising/promotion, distribution, importation, manufacture, sale, vape-free
Brazil	Decree; resolution	E-cigarette, tobacco	Advertising/promotion, distribution, importation, sale, vape-free (implicit)
Brunei Darussalam	Existing law	Tobacco (imitation), poison	Importation, sale, vape-free (implicit)
Cambodia	Circular	E-cigarette	Importation, sale, vape-free
Canada	Existing law; notice	Drug, consumer good	Advertising/promotion, importation, manufacture, sale
Chile	Resolution	Medicinal	Unclear
Colombia	Existing law	Tobacco (imitation)	Advertising/promotion, manufacture, sale, vape-free
Costa Rica	Decree; existing law	ENDS, tobacco (derivative)	Advertising/promotion, minimum age, sale, vape-free
Croatia	Existing law	Consumer goods, chemical products, tobacco (imitation)	Advertising/promotion
Czech Republic	Existing law	Medicinal, tobacco (imitation), consumer good, hazardous substance	Advertising/promotion, manufacture, minimum age, sale

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Denmark	Existing law; new law	E-cigarette, medicinal	Advertising/promotion/sponsorship, health warning labelling, ingredients/flavours, minimum age, nicotine volume/concentration, reporting/notification, sale, vape-free
Ecuador	Decree; existing law	ENDS, tobacco (derivative)	Advertising/promotion, minimum age, sale, vape-free
Estonia	New law	Tobacco-related product, E-cigarette	Advertising/promotion/sponsorship, minimum age, nicotine volume/concentration, sale
Fiji	Amended law/decree	E-cigarette	Advertising/promotion, distribution, importation, manufacture, minimum age, sale, vape-free
Finland	New law	Medicinal, tobacco (imitation/substitute), tobacco-related product, e-cigarette	Advertising/promotion/sponsorship, child safety, health warning labelling, importation, ingredients/flavours, minimum age, nicotine volume/concentration, reporting/notification, safety/hygiene, sale, vape-free
France	Amended law; decree; existing law	Medicinal, e-cigarette, consumer good	Advertising/promotion, child safety, ingredients/flavours, nicotine volume/concentration, safety/hygiene, sale
Germany	New law	Tobacco-related products, e-cigarettes, consumer good	Advertising/promotion/sponsorship, child safety, health warning labelling, ingredients/flavours, minimum age, nicotine volume/concentration, reporting/notification, safety/hygiene, sale, vape-free
Greece	Amended law	E-cigarette	Advertising/promotion, distribution, manufacture, sale, vape-free
Honduras	Decree; existing law	Tobacco (derivative)	Advertising/promotion, minimum age, vape-free
Hungary	Amended law	Consumer good	Advertising/promotion, distribution, importation, sale
Iceland	Existing law	Medicinal, consumer product	Advertising/promotion, distribution, manufacture, importation, sale
Ireland	Existing law; new law	E-cigarette, medicinal, consumer good	Advertising/promotion/sponsorship, child safety, health warning labelling, ingredients/flavours, nicotine volume/concentration, reporting/notification, safety/hygiene, sale
Italy	Amended law/ordinance; decree	Tobacco-related products, e-cigarette	Advertising/promotion/sponsorship, child safety, health warning labelling, ingredients/flavours, minimum age, nicotine volume/concentration, reporting/notification, safety and hygiene, tax
Jamaica	Amended law; existing law	ENDS, medicinal	Distribution, importation, manufacture, sale, vape-free
Japan	Existing law; statement	Medicinal	Advertising/promotion, distribution, importation, sale
Jordan	Official letter	E-cigarette	Advertising/promotion, importation, manufacture, sale, vape-free
Kuwait	Decision	E-cigarette	Distribution, sale
Latvia	New law	Tobacco-related products, E-cigarette	Advertising/promotion/sponsorship, child safety, health warning labelling, ingredients/flavours, nicotine volume/concentration, reporting/notification, safety/hygiene, sale, tax
Lebanon	Decision	E-cigarette	Distribution, importation, sale
Lithuania	New law	Tobacco-related products, e-cigarette	Minimum age, advertising/promotion/sponsorship, child safety, health warning labelling, ingredients/flavours, nicotine volume/concentration, reporting/notification, safety/hygiene, sale, vape-free
Malaysia	Existing law	Poison, electrical appliance	Distribution, importation, minimum age, sale
Malta	Legal notice	Tobacco-related products, e-cigarette	Advertising/promotion/sponsorship, child safety, health warning labelling, ingredients/flavours, nicotine volume/concentration, reporting/notification, safety/hygiene, sale, vape-free
Mauritius	Existing law	Tobacco (imitation)	Distribution, sale
Mexico	Existing law	Tobacco (imitation)	Advertising/promotion, distribution, manufacture, sale
Nepal	Notification	ENDS	Advertising/promotion, vape-free
Netherlands	Existing law; decree; order	E-cigarettes, medicine, tobacco-related products, consumer good	Advertising/promotion/sponsorship, child-safety, health warning labelling, ingredients/flavours, minimum age, nicotine volume/concentration, reporting/notification, safety and hygiene, sale
New Zealand	Existing law	Medicinal, tobacco, consumer good	Advertising/promotion, distribution, importation, sale
Nicaragua	Existing law	Tobacco (imitation)	Importation, manufacture, sale
Norway	Existing law	Medicinal, tobacco surrogate, e-cigarette	Advertising/promotion, importation, minimum age, sale
Oman	Decision	E-cigarette	Distribution, sale
Panama	Decree	ENDS, tobacco (imitation)	Advertising/promotion, distribution, importation, sale, vape-free
Philippines	Order	Medicinal, medical device	Child-safety, sale, vape-free
Poland	New law	Chemical mixture, Consumer good	Unclear

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Portugal	Existing law	E-cigarette	Advertising/promotion/sponsorship, child safety, health warning labelling, ingredients/flavours, minimum age, nicotine volume/ concentration, reporting/notification, safety/hygiene, sale, tax, vape-free
Qatar	Circular; decision	E-cigarette	Advertising/promotion, distribution, importation, sale
Republic of Korea	Amended Law; existing law	Tobacco, consumer good	Advertising/promotion, health warning labelling, minimum age, tax, vape-free
Saudi Arabia	Decision	E-cigarette	Advertising/promotion, sale
Seychelles	Existing law	Tobacco (imitation)	Advertising/promotion, distribution, importation, manufacture, sale
Singapore	Existing law	Tobacco (imitation)	Distribution, importation, sale
Slovakia	Amended law	Tobacco/tobacco-free product intended to be smoked	Advertising/promotion, minimum age, vape-free
South Africa	Ruling	Medicinal	Sale
Spain	Amended law	ENDS	Advertising/promotion, minimum age, vape-free
Suriname	New law	ENDS	Distribution, importation, sale
Switzerland	Existing law; statement	E-cigarettes, consumer good	Importation, sale
Thailand	Existing law; notification; order	'Modern' medicinal, tobacco (imitation), e-cigarette	Importation, manufacture, sale
Togo	New law	Tobacco (derivative)	Advertising/promotion, minimum age, tax, vape-free
Turkey	Amended law; circular; notice	Tobacco, e-cigarette	Sale, advertising/promotion, importation, vape-free
Ukraine	Amended Law	E-cigarette	Sale, vape-free
United Arab Emirates	Decision	E-cigarette	Advertising/promotion, importation, sale
UK	Existing law; new law; statement	E-cigarette, medicinal, consumer good	Advertising/promotion/sponsorship, child safety, health warning labelling, ingredients/flavours, minimum age, nicotine volume/ concentration, reporting/notification, safety and hygiene, tax
USA	New law	Tobacco product	Advertising/promotion, child-safety, health warning labelling, minimum age, reporting/notification
Uruguay	Amendment/decree	Electronic smoking device	Advertising/promotion, importation, sale, trademarks
Venezuela	Alert, existing law	Medicinal, tobacco (derivative), consumer good	Advertising/promotion, sale, vape-free
Vietnam	Existing law	Tobacco	Advertising/promotion, minimum age, vape-free

Conclusion

The health risks associated with the use of e-cigarettes are still unclear. Although chemicals have been detected in e-cigs as well as their aerosols, current evidence is not enough to support whether there will be a long-term effect on human health. There is a lot of work to be done regarding the chemical characterization of the wide range of organic and inorganic pollutants that may be present. Comprehensive studies dissecting the toxicity contributions of each component of the device should be considered. Moreover, untargeted analysis of VOCs and unknown organic molecules by LC-MS as well as GC-MS might be the right path to further understanding the toxicological risks of "vaping." Clinical studies should include the effects of exposure to e-cigs by bystanders, as active regulations are considerably tolerant regarding the commercialization and use of e-cigarettes. Furthermore, global measures should be considered as regulatory policies vary significantly by country. While the U.S. prohibits the sale of flavored e-liquids for cartridge-based devices, countries like the Dominican Republic have no regulation whatsoever on the matter.

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