

E-cigarettes and other tobacco and nicotine products: an update overview

Cigarrillos electrónicos y otros productos del tabaco y nicotina: una visión general actualizada

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Abstract

Smoking is a chronic, addictive, and relapsing disease that causes approximately 7 million deaths worldwide each year, representing a serious public health problem. Over the years, the tobacco industry has promoted alternatives to conventional tobacco, such as electronic cigarettes (ECs), heated tobacco products, and other tobacco products with and without nicotine. These products have been marketed as “harm reduction” or as an alternative to quitting smoking. However, scientific evidence has shown that the components of these devices are addictive and harmful to health, and there are no conclusive data indicating that they are safe and effective for smoking cessation. The toxicity of the components of ECs and other forms of smoking can produce serious health effects, regardless of whether they contain nicotine. Nicotine is a highly addictive substance that can lead to difficulties with attention, concentration, and learning, as well as behavioral changes and problems in family, school, and social settings. Furthermore, these new products can act as a gateway to the consumption of tobacco and other harmful substances.

Keywords: Smoking. Tobacco. Electronic cigarettes. Nicotine products. Addiction. Harm reduction.

Resumen

El tabaquismo es una enfermedad crónica, adictiva y recidivante que causa alrededor de 7 millones de muertes cada año a nivel mundial, lo cual representa un serio problema de salud pública. A lo largo de los años, la industria tabaquera ha promocionado formas de fumar distintas al tabaco convencional, tales como los cigarrillos electrónicos, el tabaco calentado, entre otros productos del tabaco con y sin nicotina. Estos productos han sido publicitados bajo la estrategia de “reducción de daños” o como una alternativa para dejar de fumar. Sin embargo, la evidencia científica ha demostrado que los componentes de estos dispositivos son adictivos y perjudiciales para la salud, y no existen datos concluyentes de que sean una herramienta segura y efectiva para dejar de fumar. La toxicidad de los componentes del cigarrillo electrónico y otras formas de fumar puede producir efectos graves en la salud, independientemente de que contengan o no nicotina. La nicotina es

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una sustancia altamente adictiva que puede condicionar dificultades en la atención, la concentración y el aprendizaje, así como cambios en el comportamiento y problemas en el entorno familiar, escolar y social. Además, estos nuevos productos pueden actuar como puerta de entrada al consumo de tabaco y otras sustancias nocivas.

Palabras clave: Tabaquismo. Tabaco. Cigarrillos electrónicos. Productos de nicotina. Adicción. Reducción de daños.

Introduction

According to Spanish Law 28/2005, of December 26, a nicotine delivery device, also known as an electronic cigarette (EC), e-cigarette, vape, or Electronic Nicotine Delivery System, is defined as “a product, or any of its components, including cartridges and the device without a cartridge, that can be used for the consumption of vapor containing nicotine through a mouthpiece.” These devices may be disposable, rechargeable through a refill container, or rechargeable with a single-use cartridge.¹

The first “smokeless and tobacco-free” cigarette was invented by the American Helbert A. Gilbert in 1963 and patented in 1965; however, it was not until 2003 that the Chinese pharmacist Hon Lik developed the EC as “an alternative to quit smoking.”² By 2007, e-cigarettes were available for online purchase, and since then their use has rapidly expanded worldwide.

The tobacco industry’s strategy to market these products is based on the concept of “harm reduction,” a true ambush in which hundreds of adolescents and young adults fall every day without considering the risks to which they are exposed. This review aims to explore the main aspects of ECs, the reasons underlying their addictive potential – particularly among younger populations – and the associated health risks based on current evidence.

Demographic data in Spain

The consumption of ECs continues to increase progressively. According to the 2024 Survey on Alcohol and Drugs in Spain, 19% of the population aged 15-64 years has used ECs at least once in their lifetime, representing an increase of nearly 7% compared with 2022. Although the increase in prevalence has been observed in both men and women, it remains higher among men for “occasional use,” whereas for “recent use,” prevalence is higher among women.³

In addition, the 2025 Survey on Drug Use in Secondary Education in Spain found that 49.5% of students aged 14-18 years had used ECs at least once in their lifetime, reflecting a slight decrease of 5.1%

compared with 2023.⁴ Regarding sex differences, a higher prevalence was observed among female students.⁴

Main characteristics of ECs

ECs consist of three main components: a battery, an atomizer, and a cartridge. These components are assembled to form a device that may resemble a conventional cigarette. However, these devices have evolved over time, adopting increasingly attractive and sophisticated designs.⁵

Although designs vary, all ECs function similarly. The cartridge is filled with a liquid (e-liquid) that is heated by the atomizer, which, in turn, is powered by the battery (Fig. 1). The user inhales the substances contained in the device through a mouthpiece and subsequently exhales an aerosol resembling a light or dense vapor cloud.⁵⁻⁷

The development of ECs has progressed through several phases (Fig. 2): first-generation disposable “cig-a-likes” resembling conventional cigarettes; second-generation devices with refillable cartridges and a pen-like appearance; third-generation refillable “mods” with tank or box shapes; and fourth-generation “pod mods,” which may be prefilled or refillable and resemble USB devices – hence their designation as “vape pods” or “tobacco-USB.” These fourth-generation devices are typically small and lightweight, contain liquids with multiple flavors, and may deliver high doses of nicotine. Moreover, they have been designed to be highly appealing, particularly to attract younger populations, and have been extensively promoted by the tobacco industry.^{6,7}

Composition

The U.S. National Institutes of Health has identified up to 22 toxic substances associated with vaping, including nicotine, propylene glycol (PG), glycerin, heavy metals (such as chromium, zinc, and tin), and other chemicals.⁵ The health effects of these substances are detailed below.

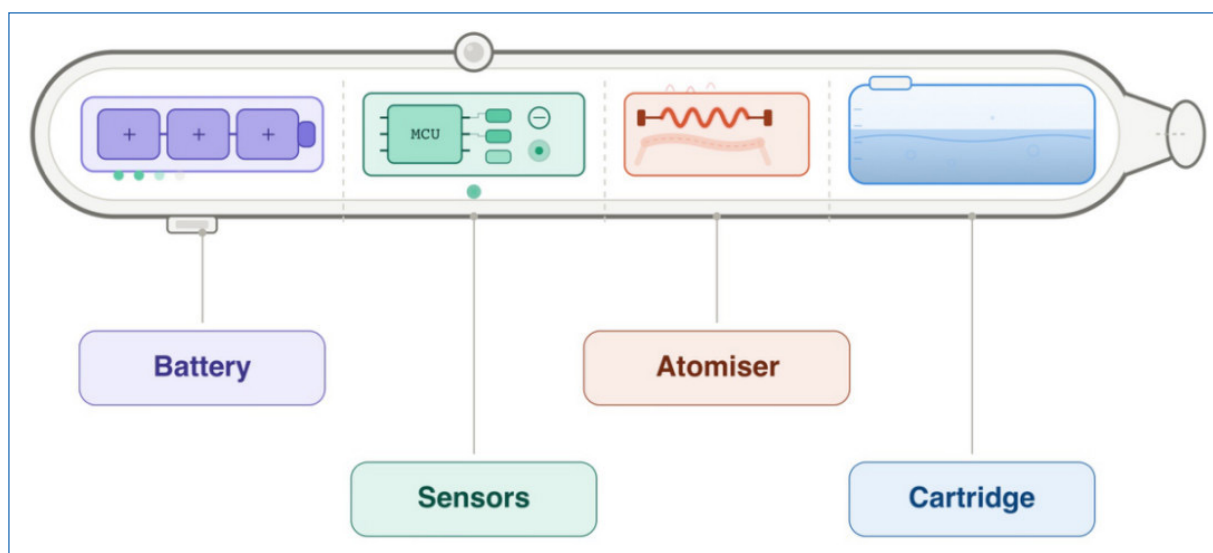


Figure 1. Main characteristics of ECs (modified from National Institute on Drug Abuse website⁵)

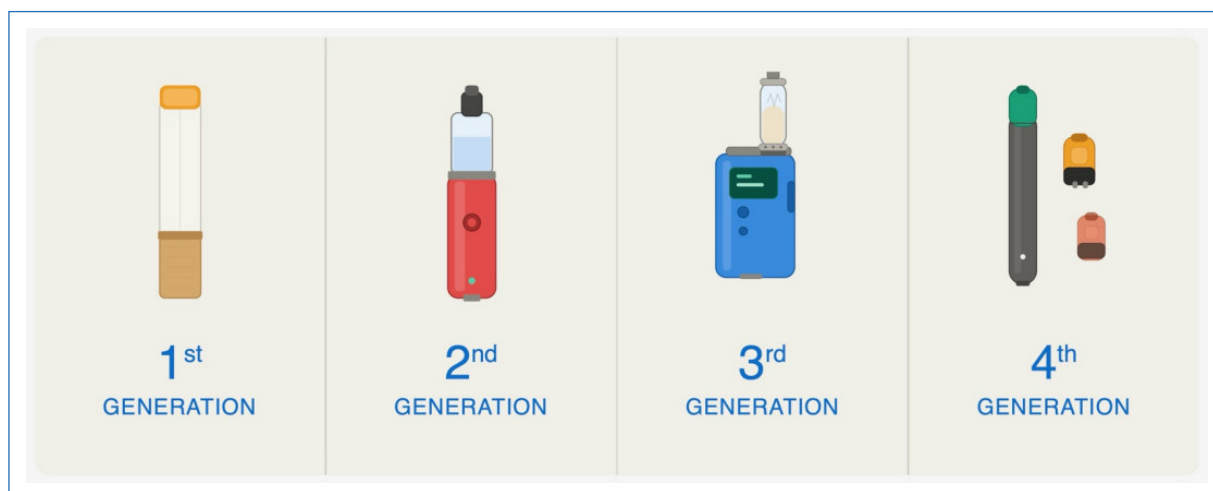


Figure 2. ECs evolution (modified from National Institute on Drug Abuse website⁵).

Nicotine

Nicotine is a highly addictive substance that can affect brain development, especially in adolescents. It plays a fundamental role in cognition, mood, and behavior.⁸

Nicotine binds to heterogeneous nicotinic acetylcholine receptors (nAChRs) in the brain, which are also present at neuromuscular junctions and lymphatic ganglia. Binding allows sodium and calcium influx, stimulating dopamine release. Dopamine is responsible for the pleasurable effects of nicotine and plays a central role in addiction. In addition to dopamine, receptor activation triggers the release of glutamate, γ -aminobutyric

acid, serotonin, norepinephrine, acetylcholine, and endorphins. Glutamate release has been associated with memory and learning through its role in synaptic plasticity. The release of these neurotransmitters reverses withdrawal symptoms, improves performance, and enhances mood. Sustained nicotine consumption induces neuroadaptation by increasing the number of nAChRs and desensitizing receptors to the agonist.⁸⁻¹⁰

The most used nicotine salt in EC liquids is nicotine pyruvate, formed from pyruvic acid and freebase nicotine, such as PureNic99+. This nicotine salt is smoother, less irritating, and more efficiently absorbed than nicotine from conventional cigarettes.¹¹

According to Royal Decree-Law 17/2017 of November 17, disposable cartridges and refillable tanks must contain a maximum of 2 mL and refill liquid containers a maximum of 10 mL. Liquids must not exceed 20 mg/mL of nicotine.¹² A disposable EC is estimated to deliver between 400 and 700 puffs, depending on user consumption patterns.

PG and glycerin

ECs use humectants such as PG and glycerol (commonly known as vegetable glycerine [VG]), which are the most common vaporization solvents.¹³

PG (also known as 1,2-dihydroxypropane, 1,2-propanediol, methyl glycol, or trimethyl glycol) is a transparent, colorless, nearly odorless, and tasteless liquid widely used in the chemical, food, and pharmaceutical industries. It is used as a humectant to absorb excess water and maintain moisture in medications, cosmetics, and food products, as well as a solvent for food colorings and flavorings and in the paint and plastic industries. It is also used to create artificial smoke or fog in firefighter training and theatrical productions.^{5,13}

PG has been associated with dryness and irritation of the respiratory tract, bronchial hyperreactivity,¹⁴ and even cases of lipid pneumonia.^{15,16}

Carbonyl compounds

Formaldehyde, acetaldehyde, acrolein, and glyoxal are carbonyl compounds commonly found in EC aerosols and may be potentially harmful to health. These compounds are incidentally generated by oxidation of the e-liquid when it contacts the heated nichrome coil. Their composition and concentration vary depending on the type of e-liquid and battery voltage.¹⁶

Jensen et al.¹⁷ demonstrated, using techniques such as nuclear magnetic resonance spectroscopy, that hemiacetals containing formaldehyde—a group 1 carcinogen according to the International Agency for Research on Cancer—can be formed during vaping.^{16,17} Acetaldehyde is classified as a possible human carcinogen (Group 2B),¹⁶ while acrolein causes nasal irritation and is associated with pulmonary epithelial damage.¹⁶

Heavy metals

Several studies have shown that EC aerosols may contain significant amounts of toxic metals such as lead, mercury, and cadmium. These metals are released from metallic components of EC devices, including

heating coils and solder joints, which can leach metals into the liquid and aerosol during vaping.^{7,18,19}

Heavy metals are recognized environmental toxins that pose significant health risks. Over time, they may accumulate in the body, leading to adverse health effects, including neurotoxicity, nephrotoxicity, and carcinogenicity.^{7,18}

Yang and Lee¹⁸ examined serum concentrations of heavy metals (lead, mercury, and cadmium) among EC users in the Korean population. Participants were divided into non-smokers, EC users, and conventional smokers. Both EC users and conventional smokers showed higher mean concentrations of these metals compared with non-smokers. EC users had serum lead levels 10.0% higher than non-smokers, while conventional smokers showed a 5.4% increase. Mercury levels were 13.7% higher in EC users than in non-smokers, with no significant difference between conventional smokers and non-smokers. Cadmium levels were 61.4% higher in EC users, exceeding the 37.0% increase observed in conventional smokers.

Nitrosamines

Several studies have detected tobacco-specific nitrosamines (TSNAs) in vaping liquids. TSNAs are highly potent carcinogens due to their ability to form DNA adducts, inhibit tumor suppressor genes, and activate oncogenes.¹⁹

A systematic review and meta-analysis identified TSNAs, volatile organic compounds (VOCs), N'-nitrosonornicotine, 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, and polycyclic aromatic hydrocarbons in the chemical profiles of 15 studies. Although wide variability in chemical composition was reported—likely due to the lack of standardized protocols and heterogeneity of devices and liquids evaluated—these findings raise significant concerns.¹³

Flavorings and aromatizers

Flavorings used in vaping liquids are often marketed as “safe” because they are approved for ingestion. However, the respiratory and digestive systems are fundamentally different and exhibit significantly different toxicological susceptibilities.²⁰

Diacetyl and acetyl propionyl are artificial flavoring agents used to impart a buttery flavor to popcorn. Although approved for ingestion, excessive inhalation exposure has been associated with an increased risk of bronchiolitis obliterans.^{13,20} Compounds such as

2,5-dimethylpyrazine and vanillin have been linked to altered physiological responses in airway epithelial cells.²⁰ Among flavors, cinnamon and menthol/mint may increase cellular necrosis, while sweet, fruity, and citrus flavors have been associated with oxidative stress.¹³

The flavoring profile of vaping liquids plays a key role in airway dysfunction by increasing bronchial epithelial cell apoptosis, causing phagocytic dysfunction of alveolar macrophages, and altering airway cytokine responses.²¹

“Nicotine-free” products

Although some EC liquids are marketed as “nicotine-free,” “without nicotine,” or “zero nicotine,” several researchers have detected the presence of nicotine in many of these products.²²

Chivers et al.²³ evaluated the chemical composition of a range of liquids available in Australia, focusing on nicotine and other potentially harmful compounds. Ten “nicotine-free” liquids of various brands and flavors were quantitatively analyzed using gas chromatography–mass spectrometry. Nicotine was detected in six of the 10 liquids analyzed: three contained concentrations comparable to so-called “low nicotine” ECs available on the market (1.3, 1.4, and 2.9 mg/mL, respectively).

Numerous studies have revealed measurable levels of nicotine in nicotine-free electronic liquids, raising concerns about the lack of quality control standards. Notably, some brands do not specify units when indicating nicotine levels. For example, labels may include “20 mg” or “20,” which could refer either to total nicotine content per cartridge or to a concentration of 20 mg/mL. Other brands use qualitative descriptors (“low,” “medium,” or “high”).²²

Recently, the tobacco industry has incorporated alternatives to nicotine in the composition of some ECs. These include nicotine analogues – synthetic substances with chemical structures similar to nicotine. The most used nicotine analogue is 6-methyl nicotine (6-MN), a rapidly absorbed, highly potent, and strongly addictive compound. 6-MN may be more harmful than nicotine, with a lower lethal dose and greater toxicity to bronchial epithelial cells compared with conventional nicotine.²⁴

Another nicotine substitute used in ECs is nicotinamide, a form of Vitamin B3 with sedative effects. Thermal degradation of nicotinamide produces potentially toxic compounds during inhalation, which may negatively affect health.²⁴

It is important to note that addiction mechanisms may also be activated by non-nicotine substances such as

thickeners and colorants present in ECs, as they stimulate oropharyngeal nerve endings. Likewise, flavorings and aromatizers stimulate gustatory and olfactory nerve endings, contributing to increased dopamine release in the nucleus accumbens (NAcc).¹¹

Reasons underlying ECs addiction

ECs possess addictive potential regardless of the nicotine concentration in their liquids, as they generate pleasurable sensations. Experiencing pleasure during certain behaviors motivates their repetition, a phenomenon with a clear scientific basis.

In 1954, researchers James Olds and Peter Milner²⁵ implanted electrodes in rodent models to stimulate a brain region known as the motivation and reward (reinforcement) system. During the experiment, rats repeatedly pressed a lever to self-stimulate through the electrode – up to 2,000 times/h – ignoring vital stimuli such as eating or drinking and even enduring painful electric shocks. Based on these observations, Olds and Milner concluded that pleasure strongly reinforces behavior.

Pleasurable sensations are regulated by several systems, the most important being the mesolimbic dopaminergic system, also known as the motivation and reward system. This system consists of dopaminergic neurones located in the ventral tegmental area, projecting to the NAcc and amygdala through the mesolimbic pathway and to the prefrontal cortex (PFC) through the mesocortical pathway. Dopamine acts on D1 and D2 receptors in these regions.²⁵

The mesolimbic dopaminergic system is activated by substances such as nicotine, which has strong addictive potential by promoting increased dopamine release and reinforcing consumption-related behaviors. Reducing or discontinuing consumption leads to withdrawal symptoms.²⁶

Early initiation of tobacco use increases the risk of stronger nicotine addiction. Furthermore, nicotine exposure in adolescents may act as a gateway to tobacco and other substance use.^{27,28}

As previously mentioned, so-called “nicotine-free” ECs may also induce addiction, as the inhalation mechanism itself, stimulation of oropharyngeal nerve endings, and behavioral and environmental cues play a crucial role in the development and maintenance of dependence.¹¹ Sensations associated with EC use – such as smell, taste, throat irritation, warmth, or cooling of the airways – generate satisfaction, pleasure, and craving.²⁹ In addition, olfactory, gustatory, and visual stimuli produced by vapor clouds, as well as device

handling and repetitive rituals (hand-to-mouth behavior), act as reinforcers of consumption.^{11,29,30}

Adolescent vulnerability

Adolescence is characterized by significant functional and anatomical changes essential for nervous system maturation and specialization.³¹ It is a transitional period marked by hormonal, psychosocial, and neuronal changes, associated with the development of social, emotional, and cognitive skills, as well as increased vulnerability to stress and risk-taking behaviors.³² The adolescent brain is still maturing and is particularly susceptible to the harmful effects of drugs of abuse, including tobacco and nicotine products.^{31,32}

During this stage, the brain is highly sensitive to novel experiences, with experience-dependent plasticity occurring predominantly in the PFC, the region responsible for executive control and decision-making. Structural changes include prolonged reorganization of grey and white matter and associated neurochemical systems. There is a significant reduction in gray matter volume and density in the PFC, parietal cortex, and basal ganglia – regions critical for executive function, sensory processing, and motivation – along with increased myelination and axonal diameter, resulting in more efficient impulse transmission. These changes are uneven, and this imbalance between subcortical emotional/reward systems and cortical executive control systems is believed to underlie increased risk-taking behaviors during adolescence.³²

Sociocultural factors also play a major role in the initiation and maintenance of use (Table 1).^{30,33} Peer pressure, sense of belonging, and social validation facilitate access to these products, particularly among younger populations. In addition, there is a low perception of disease risk, as many users believe that health risks are much lower than those associated with conventional smoking.^{5,27,32,33}

Importantly, the use of these electronic devices may facilitate initiation into tobacco smoking and other addictive substances, acting as a “gateway.”^{27,32,33}

Adverse health effects

Scientific reports from medical societies and relevant health institutions indicate that toxic substances present in EC vapor contribute to cardiovascular, pulmonary, neoplastic, infectious, and other diseases (Table 2).^{33,34}

Table 1. Factors facilitating electronic cigarette use among adolescents and young people

Low perception of disease risk
Sense of control over consumption
Social factors: peer pressure, group use, and social validation
Misleading advertising (social media and retail outlets)
Highly attractive devices (design, colors, flavors, and aromas)
Easy access

Adapted from de Higes Martinez EB et al.²⁷

Table 2. Effects of ECs on different organ systems

Nervous system	Impaired concentration and attention Delayed neurobehavioral development Disruption of blood–brain barrier integrity Vascular inflammation Hearing impairment
Oral cavity	Dryness or pain of tongue, mouth, and throat Oral lesions and ulcers Gingivitis and periodontal disease
Respiratory system	Impaired gas exchange at the alveolar-capillary membrane Immune dysfunction, inflammation, and oxidative stress Increased viral infections
Cardiovascular system	Increased blood pressure Acute endothelial dysfunction Oxidative stress
Digestive system	Nausea, vomiting, abdominal pain, and diarrhea Altered gastrointestinal motility Intestinal mucosal inflammation Elevated liver enzymes Promotes liver injury and induces hepatic steatosis
Genitourinary system	Albuminuria and hyperuricemia Inflammation and fibrosis Oxidative stress Reduced spermatogenesis Impaired embryonic implantation
Immune system	Immunosuppressive effects Increased pro-inflammatory cytokines Greater susceptibility to infections
Endocrine system	Impaired male and female reproductive health Altered breast milk production and composition
Musculoskeletal system	Osteotoxic Muscle damage Increased risk of osteoporosis

Adapted from Ali N et al.³⁴

Early-onset symptoms

The most common early-onset symptoms include ocular and pharyngeal irritation, irritative cough, dyspnea, chest pain, palpitations, headache, dizziness, and nausea.^{34,35}

Cardiovascular effects

A recent systematic review and meta-analysis highlighted several important findings regarding the impact of exposure to ECs on cardiovascular health.^{34,36} Sympathomimetic effects: increased heart rate and blood pressure, increased myocardial workload and oxygen demand, acute endothelial cell dysfunction, and increased oxidative stress. Clinical studies conducted in tobacco users who consumed conventional cigarettes under controlled conditions and nicotine-containing ECs showed an acute increase in the biomarkers CD40 and P-selectin, reflecting enhanced platelet aggregation.³⁷

Respiratory effects

Large-scale studies based on epidemiological surveillance have demonstrated that EC users may develop asthma-like respiratory symptoms due to fibrotic narrowing of the small airways.³⁸ Constrictive bronchiolitis, also known as bronchiolitis obliterans, is a pathological entity associated with the inhalation of chemical vapors that results in chronic injury to the small airways.³⁹

In 2019, in the United States, the e-cigarette or vaping-associated lung injury (EVALI) syndrome was officially recognized. EVALI is an acute and severe clinical syndrome characterized by cough, dyspnea, and constitutional symptoms.³⁴ Radiographic and histopathological findings associated with EVALI are consistent with a pattern of acute lung injury. These findings are nonspecific; therefore, it is essential to rule out pulmonary involvement due to medications, inhaled irritants, gastric acid aspiration, and viral infections, among others. Consequently, diagnosis should be based on a thorough medical history, an appropriate clinical context, and the exclusion of other etiological conditions with similar presentations. Treatment requires complete cessation of vaping and implementation of supportive care measures. Systemic corticosteroid therapy may be beneficial.^{37,38}

Beyond EVALI, it has been hypothesized that individuals who vape may be at risk of developing chronic

small airway disease due to recurrent and continuous injury to the distal regions of the bronchial tree.³⁹

Although relatively little is known about the long-term effects of ECs, published studies to date warn of potential health consequences of vaping, some of which may be irreversible.

Neoplastic pathology

ECs contain chemical substances that have been closely associated with cancer development, including formaldehyde, acrolein, heavy metals, and VOCs.⁴²⁻⁴⁴ A systematic review revealed that exposure to EC aerosols may induce oxidative stress, cellular apoptosis, DNA damage, genotoxicity, and tumor growth, potentially increasing the risk of lung cancer development or progression of other cancers.⁴³

Although nicotine itself is not carcinogenic, its degradation products can cause permanent mutations in tumor suppressor genes. Nicotine also influences cancer progression by acting on nAChRs, which promote cell proliferation, inhibit apoptosis, induce epithelial-mesenchymal transition, and stimulate angiogenesis.^{44,45}

Several studies indicate that ECs play an important role in cancer progression and metastasis by influencing antitumor immunity and the expression of cancer-related genes. Arias-Badia et al.^{44,46} used murine models to demonstrate that PG, VG, and nicotine dysregulate the immune system and promote metastatic formation. The researchers exposed murine colon adenocarcinoma MC38 cells to PG and VG, with or without nicotine, generating three groups: MC38 cells exposed to PG/VG with nicotine, MC38 cells exposed to PG/VG alone, and non-exposed MC38 cells. Using a scratch assay in each group, the authors found that both PG and VG amplified cell migration independently of nicotine, thereby promoting *in vitro* cellular proliferation.⁴⁶

Infectious pathology

Continuous exposure of the airways to EC chemicals may induce long-term inflammatory changes that increase susceptibility to infections.³³ Several preclinical models have evaluated the direct effects of EC exposure on innate immunity, the first line of defense against invading pathogens. Murine models exposed to EC aerosols developed mucus abnormalities, epithelial barrier disruption, impaired phagocytosis, and increased systemic inflammatory markers. These alterations have been shown to enhance bacterial and fungal

adhesion, as well as the virulence of common respiratory pathogens such as influenza virus, *Staphylococcus aureus*, and *Streptococcus pneumoniae*.⁴⁷

A study conducted by Sharma et al. demonstrated that repeated exposure to EC aerosols disrupted the intestinal epithelial barrier, increased susceptibility of the intestinal lining to bacterial infections, and triggered intestinal inflammation.⁴⁸

Conclusion

ECs have been promoted by the tobacco industry as less harmful products than conventional tobacco and are therefore perceived as suitable tools for tobacco harm reduction. However, there is no conclusive evidence demonstrating that ECs are harmless or safe. The message must be clear and explicit: ECs and new forms of tobacco and nicotine are harmful to health. Consequently, it is urgently necessary to implement strict legal measures regulating the sale, use, and advertising of ECs, heated tobacco, and other tobacco and nicotine products, with the aim of reducing their prevalence—especially among the most vulnerable populations.

Authors' contributions

R. Mirambeaux-Villalona wrote the paper, and it was sent to the rest of the authors. The contributions of these authors were discussed, approved, and added to the paper.

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Conflicts of interest

None.

Ethical considerations

Protection of human subjects and animals. The authors declare that no experiments on humans or animals were performed for this research.

Confidentiality, informed consent, and ethical approval. This study does not involve personal patient data, medical records, or biological samples, and does not require ethical approval. SAGER guidelines do not apply.

Declaration on the use of artificial intelligence.

The authors declare that AI was used to translate the document into British English and to design the included figures.

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