NCT
Neumología y Cirugía de Tórax
Vol. 81 - No. 2 / April-June 2022

Review
doi: 10.35366/108498

Pathophysiological effects of the E-cigarettes: a public health issue

Efectos fisiopatológicos del cigarro electrónico: un problema de salud pública

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ABSTRACT. Nowadays electronic nicotine delivery systems (ENDS) have become very popular among the general population, specifically among adolescents; however, the effect of these new devices on the health of consumers is not fully understood; also, it is unknown if it is a healthy alternative to replace combustion cigarettes or tobacco, or as a therapy to quit smoking. This review aims to clarify and update the pathophysiological effects of these new cigarettes so that the medical and scientific community can understand them, as well as to compare the damage to health generated by electronic nicotine delivery systems against that generated by the combustion cigarette. The alternative hypothesis was verified by observing that the consulted literature coincided in the concept that the consumption of the electronic cigarettes result in damage to the organism.

Keywords: vaping, tobacco, lung injury, e-liquid, ENAS, EVALI.

RESUMEN. Hoy en día los sistemas electrónicos de administración de nicotina (SEAN) comienzan a ser muy populares entre la población en general, en específico en los adolescentes; sin embargo, no se conocen totalmente los efectos de estos nuevos dispositivos en la salud de los consumidores, y se desconoce si es una alternativa saludable para reemplazar los cigarrillos de combustión o de tabaco, al igual que su uso como terapia para dejar de fumar. Esta revisión tiene como objetivo clarificar y actualizar los efectos fisiopatológicos de estos nuevos cigarros para que la comunidad médica y científica pueda entenderlos, así como comparar el daño a la salud que generan los sistemas electrónicos de administración de nicotina contra el que genera el cigarrillo de combustión. Se comprobó la hipótesis alterna al observar que las referencias que se ocuparon coincidían en el daño al organismo por el consumo del cigarro electrónico.

Palabras clave: vapeo, tabaco, lesión pulmonar, *e-liquid*, SEAN, EVALI.

INTRODUCTION

Electronic nicotine delivery systems (ENDS) are instruments used to aerolize substances without the use of a combustion process; after aerolization these substances are then inhaled.[1,2] The main components of an ENDS are: a rechargeable lithium battery, a vaporization chamber containing an atomizer and heating coil, and a cartridge in which the e-liquid product is stored.[1,2] When the device is turned on, the components of the e-liquid are aerosolized and then inhaled by the user, so the term «vaping» is incorrect because no vapor is generated; however, it is the simplified term that has been standardized to refer to the combustion process of the device. The substances contained in the liquid component of the ENDS generate certain elements that can be harmful to the body and that with their frequent inhalation could have serious consequences on the organism.[1,2]

Currently, the use of the electronic cigarette (EC) has increased as a «healthy alternative» to replace the traditional tobacco cigarette (TC) or as another way to consume nicotine or other substances.[3] However, this is a subject on which little information is available and whose veracity is not fully proven by the scientific community. Furthermore, its use as a replacement for TC has not been approved by the Food and Drug Administration (FDA) or the Center for Disease Control and Prevention (CDC). In fact, these agencies have reported that vaping as a healthy alternative is not recommended, since the health conditions it may cause have not been sufficiently studied.[4] In August 2019, cases of E-cigarette or Vaping Use-

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Received: XI-17-2021; accepted: VI-07-2022.

How to cite: Martínez-Larenas MV, Montañez-Aguirre ÁA, González-Valdelamar CA, Fraga-Duarte M, Cossío-Rodea G, Vera-López JC. Pathophysiological effects of the E-cigarettes: a public health issue. Neumol Cir Torax. 2022; 81 (2): 119-127. https://dx.doi.org/10.35366/108498

Associated Lung Injury (EVALI) were reported with deaths associated with its use, even though these are marketed as a safe and healthy strategy to quit smoking. According to several studies, it has been found that vaping used for the purpose of quitting smoking TC has only replaced it and the bad habit of smokers continues, therefore, it is not efficient as a measure to quit smoking.[5] Throughout these years, a notorious increase in its use has been observed in several population groups, in particularly in the youngest age group there has been an increase in its consumption, a population ranging from 18 to 24 years old.[6]

In addition, the *Instituto Nacional de Enfermedades Respiratorias Ismael Cosío Villegas* in Mexico City and other respiratory, cardiology and public health societies worldwide have issued an important alert to the general population about lung damage in vapers.[7] Taking into account these alerts and the increase in EC consumption, the pathophysiological mechanism of EC should be investigated to warn consumers of the possible damage they may present and to improve possible treatments for such damage.[7]

This review aims to find and clarify the possible pathophysiological effects of these new cigarettes so that the medical and scientific community can understand them, as well as the comparison between the health damage generated by the EC and the tobacco cigarette.

EPIDEMIOLOGY

The increase of EC is closely related to the popularity that this product has gained over the years in the general population. It was invented in China in 2003 and first introduced to the US market in 2007, since then it has experienced some success among smokers, non-smokers, pregnant women and even young people, therefore increasing the demand for this product and, consequently, its consumption, with a boom in sales starting in 2013. This clearly increased curiosity and the need for the scientific community to evaluate the safety of its consumption.[1]

It has been shown that the reasons for EC consumption and the pattern of consumption vary greatly depending on the age of the consumer. In the last decade, EC use among the US adult population has increased by 3.8%; of which 16% were cigarette smokers and 22% were former TC smokers.[1] On the other hand, the young population has had the largest increase in EC use, of which 5.3% of all users are middle school students and 16% are high school students.[1] EC use in this age-group is closely related to users' curiosity and the «appealing» flavors contained in e-liquids. The latter is alarming because nicotine exposure at these ages can interfere with brain development and impact academic performance, as well as increase susceptibility to addiction to nicotine or other drugs.[1]

According to the article *Epidemiology of electronic cigarettes: the arrival of JUUL* by Arroyo-Cózar,[6] in the National Health Interview Survey (NHIS) from 2014 to 2018 on «daily use» and «use on at least one occasion in the last month» of EC, it was observed that the prevalence rose markedly in the age-group of minors, with consumers having an approximate age of 18 to 24 years. Likewise, it refers that since 2014, the most consumed product by youth in the United States is EC.

On the other hand, in the context of the consumption of this product in Europe, a survey was conducted in 2017 among almost 28,000 individuals; the investigators reported that 84% had «never consumed EC»; this result differs with the 2015 survey, where this population was 87%.[6]

In the epidemiological notice issued by the National Epidemiological Surveillance Committee (CONAVE) on September 25, 2019, it warns of a possible association between severe lung disease and EC or vape use and presents the epidemiological situation in the United States and Mexico.[7] On September 19, 2019, 530 cases of lung injury and seven deaths were reported in 38 states in the United States, whose specific cause of lung injury was unknown, but it did show that all cases had a history of EC use. Among the 530 cases, 72% were males between the age group of 18 and 34 years. Of the cases, 16% were younger than 18 years and 17% were older than 35 years. These cases showed what is called a pattern of pneumonitis, which are: acute eosinophilic pneumonia, lipoid pneumonia, diffuse alveolar damage and acute respiratory distress syndrome, diffuse alveolar hemorrhage, hypersensitivity pneumonitis and giant cell interstitial pneumonitis.[7]

In Mexico, data obtained in the Tobacco Report of the National Survey on Drug, Alcohol and Tobacco Use (ENCODAT) 2016-2017 revealed that 5.9% of the population aged 12 to 65 years alluded to having ever tried EC. The prevalence of EC consumption in this same survey was 1.1%, resulting in a total of 975,000 Mexicans consumers of this product.[7]

Electronic cigarette components (EC)

The EC is an electronic device for administering nicotine or some other substance, which can be combined with nicotine or administered independently. It generates a mixture of aerosols of the substances contained in the e-liquid to be inhaled by the user.[1,8] Its designs have evolved over the years, creating different generations of this product; however, all models contain three main components: a power source, a vaporization chamber and a cartridge.[1,2] The power source is usually a rechargeable lithium battery *(Figures 1 and 2)* connected to the vaporization chamber where an atomizer is in contact with a heating coil,

which obtains its energy from the battery. The cartridge is the place where the e-liquid is stored and also has a communication with the vaporization chamber. When the user wants to use the device, he must press a button that makes the battery turn on the heating coil (some of them contain a led light that indicates that the device is on), converting the e-liquid components into aerosols, which will be inhaled into the lungs by the user through an attached mouthpiece.[1,2] The industry of this product has been evolving more and more, nowadays there are new EC models that allow to make the use of this device more personalized through a microprocessor, with the ability to modify the resistance, the voltage supplied to the heating coil (modifying the temperature that each user wants) and the desired amount of nicotine.[2]

There are four generations of ECs on the market. The first generation are the so-called ciga like devices,[1] this type of EC is mainly composed of a cartridge, an atomizer and a low voltage battery (3.7 V); usually for users who are just starting to consume this type of product, most of these ECs are disposable.[1] The second generation of ECs are slightly different from the first, as they are quite a bit larger and contain a rechargeable tank for refilling with e-liquid with the flavoring of the user's choice; they also contain a battery that allows the user to adjust the voltage between high or low (3 to 6 V) during the inhalation of the aerosol.[1] The third generation differ only by the size of the battery; these are larger and have a higher voltage, up to 8 volts.[1] Finally, we have the most recent generation of this product, the fourth generation. These have a heating coil that maintains a resistance of less than 1 Ohm. In addition, they have temperature control devices that provide the user with the ability to modify the temperature and thus be able to inhale larger amounts of the aerolized components, which also leads to higher e-liquid consumption per inhalation.[1]

Now, e-liquid is a component that contains three main ingredients: the solvent (which can be vegetable glycerin and/or propylene glycol), various flavorings, and nicotine in various dosages.[2,9] Manufacturing labels are usually incomplete as to all the components that e-liquid contains; however, a large variation in chemicals can be detected in the aerosol resulting from the solvents and flavors used in the reaction.[2] These chemicals *(Figure 2)* that can be detected are carbonyl compounds such as formaldehyde, acetaldehyde, acetone and acrolein; volatile organic compounds such as benzene and toluene; tobacco-specific nitrosamines; particulate matter (suspended particles); and metals such as nickel, copper, zinc, tin and lead.[9] One of the great challenges currently faced in assessing the health effects of ECs is the high variability of the chemical components found in the aerosols produced (even within samples of the same product, differences have been observed);[9] this is due to the customization of ECs, which allows some components to be adjusted as mentioned above.[2] This has led to great confusion regarding whether these types of cigarettes are healthier than traditional tobacco cigarettes. Concentrations of these chemicals have been reported to be below those found in conventional cigarettes and below occupational safety standards, although this is not a consistent finding, so not all studies have had this result.[2]

Besides electronic nicotine delivery devices, there are also ECs used for the delivery of tetrahydrocannabinol (THC), a psychoactive component found in cannabis. The structural components of these devices are similar to those of ECs for nicotine delivery, but one of the main components that differentiates them is the vitamin E acetate used as a solvent.[10] This is one of the main components involved in the pathophysiology of lung injury associated with ENDS.

Adverse effects and attributed diseases

It should be taken into account that the effects of EC depend on several factors. According to the evidence investigators propose the following: the type of device, content of the liquid to convert to aerosol, user behavior and experience.[11] Still, both the long-term effects,[11] the rate of adverse effects (AE) and the impact to health are not well known.[12]

In a cross-sectional study conducted by Pénzes *et al.* in 2018, it was found that 44.6% of 65 Hungarian adults who are daily EC users reported AEs. The most common AEs in daily users were: dry mouth and pharynx, cough, burning

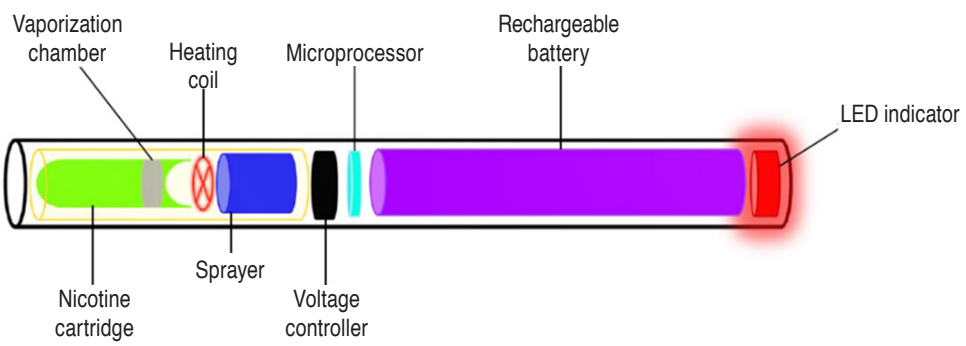

Figure 1:

Constitution and design of an electronic cigarette with microprocessor. Modified from: Qasim H, et al.[1]

Neumol Cir Torax. 2022; 81 (2): 119-127

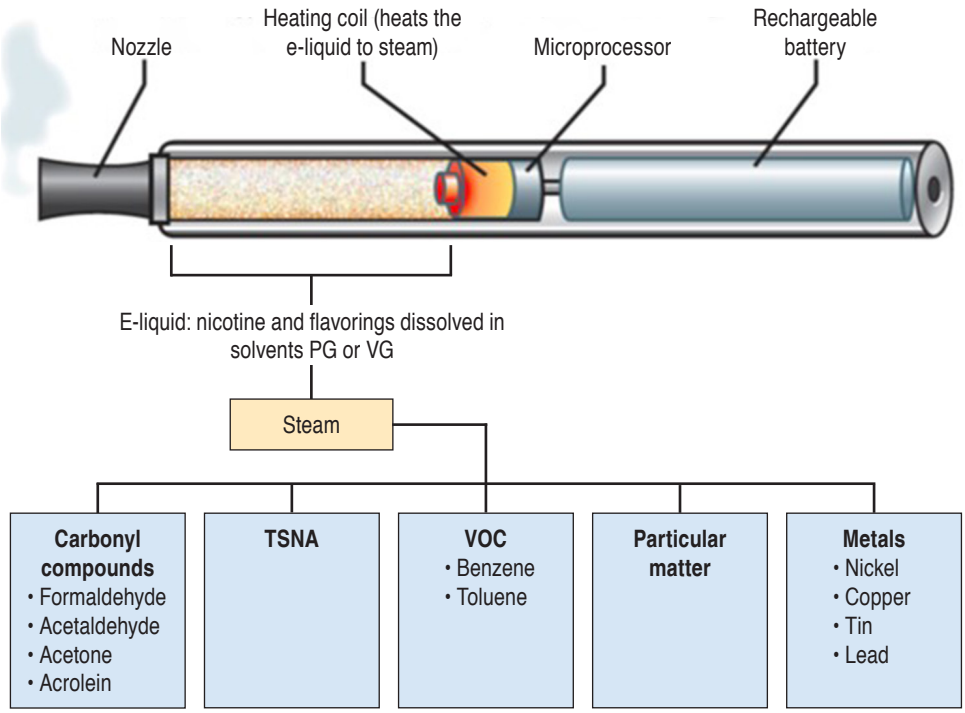

Figure 2:

Composition and design of an electronic cigarette. The electronic cigarette is made up of three main components: power source, vaporization chamber and a cartridge. By heating the e-liquid its substances are aerolized and subsequently inhaled by the user. Modified from: Sood AK, Kesic MJ, Hernandez ML. Electronic cigarettes: One size does not fit all. J Allergy Clin Immunol. 2018;141(6):1973-1982.
PG = propylene glycol.
VG = vegetable glycerin.
TSNA = tobacco-specific nitrosamines.
VOC = volatile organic compounds.

sensation in mouth, lips and pharynx, and headache. In contrast, former users reported a variety of other AEs such as: palpitations, breathing problems, dizziness, decreased taste and drowsiness.[12]

EVALI. An entity has been recognized in the medical literature associated with EC use, EVALI.[4,13,14] The CDC established the epidemiologic surveillance definition of this lesion as «cases of patients who have used e-cigarette and vaporizer products 90 days prior to symptom onset, with pulmonary infiltrates on imaging studies and not attributed to any other entity (either pulmonary infection or other likely diagnosis)».[4]

An investigation conducted in Illinois and Wisconsin revealed that 98 patients exhibited a clinical picture that included respiratory, gastrointestinal, and constitutive manifestations. The most common symptoms were shortness of breath (85%), cough (85%), chest pain (52%), nausea (66%), vomiting (61%), diarrhea (44%), abdominal pain (44%) and subjective fever (84%). Similarly, 83% of cases were found to have leukocytosis (> 11,000 leukocytes/mm^3) with a predominance of neutrophils > 80%.[14] On chest X-ray and CT scan the most common pattern found was ground glass infiltrates with predominance in the lower lobes.[14,15]

Another review found that pathological anatomy showed nonspecific histological changes with patterns of other identities of acute lung injury such as fibrinous pneumonia, diffuse alveolar damage, and organizing pneumonia. The only histopathological finding in all cases was the presence of foamy macrophages and vacuolated pneumocytes.[16]

Myocardial infarction (MI) and other cardiovascular diseases. A cross-sectional study in the United States in 2020 revealed that EC use is associated with MI, although this depended on the user's history. Similarly, current users were found to have an association with one MI event during their lifetime.[17] In the Pénzes study, 46.9% of current users mentioned that they had experienced a MI compared with 35.2% of the ex-users. On the other hand, exclusive EC users reported more MIs than combustion cigarette users, 63.1 vs. 38.6%.[12] In mice, EC has been shown to have effects on hemostasis and to increase the risk of thrombogenic events,[18] although more research is needed.

Lung cancer. EC theoretically has an oncogenic effect because several of the components of vape liquids contain proven human carcinogens, most notably formaldehyde, heavy metals, and nitrosamines. However, there is no research that has been done to confirm this in humans.[19]

Physiopathology

The main causes of the damage generated by ECs are the materials they contain, ranging from flavorings and tobacco to carcinogenic substances such as n-nitrosonornicotine and nitrosamine ketone (substances derived from nicotine). ECs containing heavy metals have also been found in e-liquid, and although not all ECs use the same materials, their unmeasured consumption generates lung damage at best (EVALI) as well as neurological and cardiovascular conditions at worst.[1]

Causes and symptoms of EVALI. Patients with EVALI have presented with a variety of symptoms including: breathlessness, fever, coughing, vomiting, diarrhea, headache, dizziness, and pain after use of vaping devices. Symptoms are generally consistent with chemical pneumonitis, they may appear and worsen suddenly.

In spite of the fact that it is known that EVALI is caused by the use of EC or some other vaping device that provokes biochemical, cellular and molecular changes in the pulmonary epithelium, giving rise to the appearance of this disease, the exact etiology is unknown.[20] Several hypotheses have been generated trying to explain the etiology of this alteration, the most accepted seems to be related to the materials used in vaping products, from the combustion mechanisms they use to the chemical products they contain, among them, the one that seems to be most related is the use of vitamin E acetate, which is a chemical product with a sticky and oily texture, used as a component for the elaboration of ECs containing THC, which when inhaled adheres to lung tissue.[20]

In a study that analyzed bronchoalveolar lavage from healthy patients and patients with or likely to have EVALI, it was reported that 25 patients were confirmed with EVALI and 26 patients with probable EVALI.[20] Of these patients, bronchoalveolar lavage identified vitamin E acetate in the bronchoalveolar fluid obtained in 48 of 51 patients, 94% of the cases. When compared with bronchoalveolar fluid from healthy patients, it was reported that the bronchoalveolar fluid obtained from the healthy comparison group did not show traces of vitamin E acetate.[20]

The role of vitamin E acetate in lung injury. Vitamin E acetate possesses a structure showing a long aliphatic chain that appears to be able to penetrate the surfactant layer to align the molecule in parallel with the surfactant phospholipids.[21] Several biochemical properties of vitamin E acetate have been proposed that may be responsible for the occurrence of EVALI, which are:

1. Role as an inducer of the crystalline to gel-liquid phase transition: phosphatidylcholine appears to undergo a transition from gel to a crystalline liquid phase. This transition to a crystalline liquid phase allows the surfactant to lose the ability to maintain the lung surface tension necessary for ventilatory mechanisms to occur in the lung, making this situation the main mechanism of respiratory dysfunction by vitamin E acetate.
2. Acts as an inducer of exogenous lipoid pneumonia: in the biological system vitamin E acetate has the characteristic of having a lipid droplet deposition. It has been shown that one of the most prominent features of lung biopsies from patients with EVALI is the observation of intraalveolar lipid-laden macrophages, which may be evidence of vitamin E acetate accumulation.
3. It is a modulator of the DGK-PKC pathway: vitamin E acetate may antagonize the catalytic activity of PKCα K, as studies indicate that the substance is able to compete with diacylglycerol (DAG) for its binding site on PKCα.[22] For this reason, vitamin E acetate could play an analogous anti-inflammatory role in the pulmonary system, interfering with the normal inflammatory response of the lung to irritant compounds such as dust or even components present in the EC itself.[22]
4. It can behave as a pregnane X receptor (PXR) agonist: when administered to the biological system, vitamin E is transformed into a large number of bioactive metabolites, most notably PXR agonists, which function as a transcription factor of cytochrome P450 monooxygenase genes. If vitamin E acetate behaves as a PXR agonist, a transcriptional activator of cytochrome P450 genes could contribute to the pathogenesis of EVALI where there is a large increase in cytochrome P450 activity.

These biochemical properties of vitamin E acetate may explain the participation of this compound in the pathophysiogenesis of EVALI. It is of utmost importance to think of vitamin E acetate as the main compound responsible for the pathophysiogenesis of EVALI because of the strong relationship between the presence of this compound in bronchoalveolar fluid with the presence of EVALI, which is 94%.[20]

Although vitamin E acetate is the chemical component that has the strongest relationship with lung damage, it is not present in all ECs, so the pulmonary pathophysiology in these cases is associated more with the other chemicals contained in the EC. The main ones are the flavorings and the processes used to generate the vapor that is inhaled, since these can contribute to the accumulation of heavy metals derived from this process. An example of the contribution of chemical products (in addition to vitamin E acetate), as stated above, are the flavorings, since[23] several flavors in the vapor extract of the EC were shown to have a cytotoxic effect on the airway epithelium, causing alterations in the conformation of the airways and, therefore, problems in gas exchange. Variations were reported to exist among different brands.[23] In addition, exposure to EC vapor induces oxidative stress in the respiratory epithelium. Nicotine and flavorings mostly contained in the liquid of EC cartridges have a synergistic effect on the induction of oxidative stress genes,[24] so these products, may contribute to the pathophysiology of lung damage caused by EC.

Impact of vaporizers on the cardiovascular system. The impact that vaporizers will have on the cardiovascular system is directly proportional to various factors, both of the vaporizer and the liquid they contain.[1] It has been shown that vaporizers that handle higher voltages will produce a

higher concentration of aerosols of the elements contained in the e-liquid when vaporized.[25] Another factor to evaluate is the percentage of each substance in each liquid as well as the materials it is made of, as is the case with flavorings, glycerin or propylene glycol, and nicotine.[1] It is important to emphasize that the EC, unlike the conventional cigarette, does not generate a total combustion of the materials it contains, which is extremely important because this was the main advantage or characteristic with which these products were initially sold.[1] However, it has been proven that the aerosol that can be generated can be equally or more harmful to the body and especially to the cardiovascular system than if a conventional cigarette were smoked.

According to the American Heart Association,[1] it is mentioned that although the concentrations of various toxic materials are lower than those of conventional cigarettes, they can still cause significant damage to the cardiovascular system. This may vary according to the studies taken into account, since the results vary according to the wide variety of vaporizers, nicotine concentration, vaping techniques and the experiences of each user. So to understand the damage caused by ECs, we must know the damage caused individually by each element contained in the liquid.[1]

Nicotine. It is probably one of the major components of the solution contained in the EC and all products used for smoking in general. In this same article it is reported that many times the companies that manufacture these solutions do not label them correctly, since some brands specify that their products do not contain nicotine, but when examined, small amounts can be found.[1] It is important to mention that nicotine is a psychoactive substance, which has a high affinity to nicotinic cholinergic receptors, having an activating action at the beginning and later a blocking action. In general, the action at the cerebral level is that of central stimulation, resulting from an increase in the release of several neurotransmitters. However, it also causes an increase in the plasma concentration of adrenocorticotropic hormone (ACTH), activating the adrenal medulla and releasing noradrenaline and adrenaline, which cause the cardiovascular effects of nicotine.

First generation vaporizers have reported a low delivery of nicotine levels to the human body compared to the latest generation devices, where higher concentrations have been reported. This is due to the fact that in the new ECs, both voltage and temperature can be altered to generate more or less aerosol. One of the characteristics that stands out in JUUL devices with respect to the others is their high nicotine concentrations. Qasim et al. explain the risks that nicotine has on the human body when delivered by a conventional cigarette. Although there are not many studies that explain the damage of ECs directly on the cardiovascular system, there is one study that concluded that after five minutes of using different types of ECs, both heart rate and nicotine concentration in plasma are increased, while there are other studies that show the opposite.[1] On the other hand there is a lot of interesting data regarding people who do not smoke but who are exposed to the aerosol generated by the EC. Evidence shows that this is an important source of nicotine exposure.[25] Passive vaping has also become an issue of relevance due to the fact that concentrations of formaldehyde higher than the permitted limit have been documented in environments where vaping is allowed, creating a harmful environment for those who do not consume it.

Carbonyl compounds. Another important component of ECs are carbonyl compounds that are the result of the degradation of propylene glycol and glycerol that are used as solvents in vaporizer liquids.[25] It is important to know that these compounds are found in greater quantities in ECs than in conventional cigarettes and they are quite harmful. They can alter the heart rate by increasing it through the sympathetic nervous system, raise blood pressure, as well as muscle contractility. An association with cardiac oxidative stress and cell damage in this organ has also been seen. Another result showed an increase in the number of circulating platelets which is important to take into account in cases of thrombosis.[25]

Acrolein is another carbonyl that generates excessive toxicity increases systolic and diastolic pressure. An imbalance of this carbonyl can lead to increased risk of arrhythmia in rats,[25] due to the formation of an acrolein protein adduct, induction of oxidative stress and dysregulation of proinflammatory cytokines, as well as inhibition of cardioprotective signaling.[1] Finally, it can lead to vascular injury by impairing vascular repair capacity, risk of thrombosis and atherosclerosis due to endothelial dysfunction, dyslipidemia and platelet activation.[1]

Benowitz concluded that the cardiovascular risk that ECs can produce are more likely to occur in patients with a history of cardiovascular disease.[25] To consider an EC as a risk factor for cardiovascular problems, the toxicity of each element, the levels of exposure to them, mechanisms and above all more studies on the subject should be evaluated there is no direct empirical evidence that ECs can cause cardiovascular disease or that they are a risk factor as cigarettes are; probably they do impose some degree of risk, but at a lower level than the former.[25]

Impact of electronic cigarettes on the nervous system. The effect of vaporizers on the nervous system, as well as on the cardiovascular system, has been a topic for which there is not much research and very few articles discuss vaporizers. An article published by Ruszkiewicz explains the effects of e-liquid in both gaseous and liquid states.[26] The first article reviewed by Nguyen et al. involved exposing pregnant prepartum and postpartum rats to vaporizer-

generated aerosol, where they found a deficit in the short-term memory of the offspring, as well as less anxiety and hyperactivity.[26,27] This was due to the effects of nicotine on the nervous system, while the reduction in anxiety was seen in groups exposed to both nicotine and non-nicotine aerosols. Another meaningful change is that the exposure to non-nicotine aerosols promotes gene methylation and affects histone acetyltransferases causing changes in genes related to neurological activity.[26]

Prenatal nicotine neurotoxicity generates an imbalance in cholinergic transmission, resulting in significant behavioral changes as well as perinatal death.[26] On the other hand, solvents such as glycerol and glycerin do not show a risk to the nervous system unless a significantly overdosed. In this case only damage to the peripheral nervous system has been demonstrated.[26]

Tobacco versus vaping comparison

«Vaping» (electronic cigarette smoking) is a practice that has become very common among adolescents and adults, so it is necessary to know the health implications and compare it with traditional cigarettes. This section will review the common and differentiating components of EC versus TC as well as their effects on the lungs.

As previously mentioned, ECs are composed of the following parts: a lithium battery and a vaporization chamber (atomizer and heating coil and a refillable cartridge for liquid).[28] It is important to remember that e-liquid is made up of propylene glycol, vegetable glycerol, nicotine, among other substances. The TC consists mainly of a tobacco column, a filter and a paper with adhesive covering them.

Regarding the different pulmonary damage caused by both products, studies in murine C57BL/6 strain have shown that the substances that make up the e-liquid are responsible for the toxic effects seen in pulmonary fibroblasts. It was also observed that direct exposure of primary bronchial epithelial cells to EC vapor containing glycerol/propylene and glycol induced oxidative stress, although with less intensity than that induced by TC.

As for e-liquid containing nicotine, it was found that when nicotine was added, the effects already present were aggravated. When e-liquid contained both nicotine and flavoring in a three-day exposure to EC vapor, IL-6 and IL-1β interleukins were increased compared to solutions without flavoring.

In both flavored and nicotine-free EC vapor and TC, elevations were found in the methacholine response, which is a parasympathetic bronchoconstrictor that serves as a marker for determining bronchial hyperresponsiveness. Also in the study by Glynos et al.[28] measurements of mucin production were compared, and it was shown that after a three-day exposure there was an increase in Muc5ac levels in the airways with both EC vapor and TC. This study highlights that lung resistance, elasticity and distensibility were only affected by EC vapor. Thus, CE vapor causes lung inflammation, changes in respiratory mechanics and physiology, and when flavoring is added, these effects are aggravated.

Social impact

The invention of CE dates back to 1963, but it was patented in 2003 by a Chinese pharmacist. The popularity of EC started worldwide in 2009 and 2010, mainly because it was promoted as a novel product and as a useful and pleasant alternative for those who wanted to reduce their tobacco consumption. Companies promote these products as an alternative for tobacco users to quit their addiction. Furthermore, this began to attract the attention of young people who were anxious to start smoking, but were held back by fear of tobacco and nicotine.[29] However, this has not been sufficient reason to allow the free sale of these products in many countries. Due to several studies, in addition to the fact that it is still a tobacco-related product, some countries decided to ban its sale, such as the United States, Canada and Australia. Another important fact is that the World Health Organization (WHO), although it was the first to make reference to the use of these products, did not declare whether there were harmful effects, which gave companies a window of opportunity to sell freely.[30] The popularity of these products is also due to the fact that they make them attractive by adding artificial flavorings (e-liquids) and their eye-catching and fun designs. Having a better smell than tobacco, depending on the flavoring, has been found to be an important factor for people in deciding to try EC or switch from tobacco to EC.

The people most interested in acquiring and consuming ECs are under-age children, adolescents, and people seeking to quit smoking. Several studies have been conducted to gather information about early consumption and its relationship to the onset of tobacco addiction; one study found that adolescents in middle school or early high school who had already consumed ECs were up to seven times more likely to start using TCs, which was found when they were interviewed half a year later.[31] In contrast, students who had already tried TC showed no interest in starting to consume EC. This study, as well as other similar studies, suggests that there is a relationship between starting to consume EC at an early age and smoking.[32] As to whether it really helps to quit smoking, the FDA today has not accepted EC as an aid for people who wish to quit smoking, as it does not meet the necessary requirements stipulated by the organization. In addition, there is still not enough research on the safety of these products as a tool. A study in Europe showed that

the use of EC is not beneficial for smoking cessation; in this research more than 800 people were interviewed who were interested in quitting smoking and who currently use EC as an alternative, of these, only 9% (72 people) reported having quit smoking when asked one year later.[30]

For its part, the management of ECs in Mexico has undergone several changes. At the beginning, the government, through the General Law for Tobacco Control in its article 16, prohibited the sale of ECs: «to trade, sell, distribute, exhibit, promote or produce any object that is not a tobacco product, that contains any of the elements of the brand or any type of design or auditory signal that identifies it with tobacco products».[33] This law was drafted in 2008, its last modification was two years later, but it is still in force. Likewise, the Federal Commission for the Protection against Sanitary Risks (COFEPRIS) at the time supported these declarations by stating that these products «do not have a sanitary registration». The above is called into question because on October 19 of this year, the Supreme Court declared unconstitutional the prohibition that had been discussed just a few days before regarding the commercialization of ECs and other related products. The proclamation went directly to the aforementioned Article 16.[34,35] While declaring something unconstitutional does not mean that it is law, it does open the possibility that in the future there may be changes in the law.

The facts indicate that due to the premise that the majority of the population considers ECs to be less harmful than conventional cigarettes, they continue to be consumed. Today, in many countries where their sale is prohibited, they are readily available to the general public, the only requirement being that the person can afford the product rather than demanding that they are of legal age.

DISCUSSION

The impact that these products have had on a cultural level since their appearance and popularity a little more than 10 years ago until today is still observed in a greater tendency in adolescents and young adults. Their popularity lies in several aspects that depend mainly on the age group, as people decide to try EC or change the TC, either because of popularity or because it is sold as an alternative to quit smoking, which, thanks to several studies and the FDA itself, has been shown not to be the case.

The purpose of this review is to guide the reader to learn more about the functioning of EC, as well as its possible repercussions in order to provide the necessary knowledge and make a decision as to whether or not to continue using EC. Because EC is a recent product, the pathophysiological mechanisms have not yet been fully established, but it is known that the impact on the homeostasis of EC users can vary greatly depending on the history and habits of the user as well as the composition of the EC.[11] It is important to conduct further research on pathophysiology to understand and prevent the pathologies that EC may generate in the future with its chronic use, as this may be triggering a public health problem, especially in young people.[29]

Due to the attributed manifestations that include life-threatening diseases, such as cardiovascular diseases, EVALI and lung cancer,[1,17,19,20] research will help to establish certain quality controls on the chemical products used for their manufacture, seeking to avoid the appearance of these pathologies, as well as to identify which materials tend to affect the organism the most and which are common in the majority of EC.

CONCLUSION

Evidence indicates that EC consumption can produce adverse effects to serious health consequences such as pulmonary, cardiovascular and even neurological damage.[11,12] Although the pathophysiology of these alterations is not fully understood, it is mainly associated with the chemical components that constitute the EC.[1] It is worth mentioning that the damage that can be caused by EC is multifactorial and includes: type of device, content of the liquid to be converted into aerosol, user behavior and experience. Even combinations can be made in the CE with nicotine, THC and other chemicals. Due to the high variability offered by the customization in product use, it is not possible to establish a specific harm from EC.[11]

Currently, there is still much controversy and uncertainty regarding the harmful effects of EC. The assumptions made by the EC industries that this product is less harmful compared to TC or that it is a healthy alternative are not correct or are not entirely true.[33]

It is important to continue doing research, especially comparative studies between TC and EC in more species to be able to determine with more specificity the differences in lung damage caused by consumption of EC versus smoking TC. It is also urgent to regulate e-liquids because due to the boom in their popularity, many liquids of different composition have been manufactured in the market that need to be analyzed and regulated.

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Conflict of interests: the authors declare that they have no conflict of interests.