

## **ELECTRONIC CIGARETTE TOXICITY AND RISK FOR EVALI: AN INTEGRATIVE REVIEW**

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**Abstract:** Electronic cigarettes (EC) have emerged as an alternative to restricting the consumption of traditional cigarettes. Its composition has numerous substances such as nicotine, flavorings, flavorings and even tetrahydrocannabinol (THC), and the diversity of constituents is one of the reasons why its consumption becomes attractive among the population. However, the use of EC has been responsible for triggering cases of a pathology called electronic cigarette-induced lung injury (EVALI). Thus, the present work aims to discuss the toxicity of EC and its relationship with the development of EVALI. A qualitative approach was carried out in the form of integrative literature review, whose searches were carried out in the Pubmed, Periódicos Capes and VHL databases. It was found that one of the main substances related to EVALI is tocopheryl acetate (vitamin E), which when inhaled causes inflammatory responses and oxidative stress in cells. It is concluded with this review that the chemical substances used in EC have diversified toxic potential, causing from coughing or dyspnea, to the development of EVALI with potential lethality. However, studies on EC components and their relationship with EVALI are still limited and hampered by the lack of standardization in the association between constituents. Given the scarcity of studies that address the issue in question in Brazil, more studies are needed to elucidate the toxicity of substances contained in EC and its relationship with EVALI.

**Keywords:** *Vaping*, toxicity, lung injury.

## INTRODUCTION

The electronic cigarette (EC), a type of Electronic Smoking Device (ESD), popularly known as *vaping*, became popular among users, since due to the different functioning mechanism of the traditional cigarette, it was defended as less harmful to health (INCA, 2016).

Its structure is composed of a battery that, when heated, transforms the liquid contained in the container into an aerosol. Its composition may have varying amounts of nicotine and other substances, such as flavoring essences whose toxic properties are not fully elucidated (SALZMAN et al., 2019).

From a sanitary point of view, Brazil was one of the pioneers in the prohibition of DEFs through Resolution of the Collegiate Board of Directors (RDC) n° 46/2009 of the National Health Surveillance Agency, based on studies pointing out that the potential aid in smoking cessation is not was proven and the risk-benefit was not proven (BRAZIL, 2009; SILVA, 2019).

In addition, the dissemination of electronic cigarettes among young adults and adolescents has been posing a risk to public health, since the presentation with varied and pleasant aromas and flavors can mask the harm present in DEFs. In this scenario, the impacts of the use of these devices are evidenced in the associated pathologies that have been developing over the years, such as depression of the central nervous system, bronchitis and irritation of the respiratory tract. (BERTONI et al., 2021).

Among the reported diseases, EVALI, an acronym for E-cigarette or Vaping product use-Associated Lung Injury, was described in 2019 and stands out due to its lethal potential (KALININSKIY). et al., 2019; STEPHENS et al., 2019).

In addition, the treatment for EVALI is not yet elucidated, but most patients affected by the pathology require hospitalization. To help understand the cause of EVALI, the US Centers for Disease Control (CDC) concluded that tocopheryl acetate present in e-cigarettes was the main substance associated with the disease (LAYDEN et al., 2020; BLOUNT et al., 2020).

Therefore, the present study aimed to carry out an integrative literature review, having as

a guiding question the relationship between the toxicity of electronic cigarettes and the occurrence of the described EVALI, in order to clarify which substances are most associated with its development.

## **THEORETICAL REFERENCE EMERGENCE OF ELECTRONIC CIGARETTES**

For centuries tobacco was used in different ways, chewed, sniffed (snuff) and smoked in pipes and cigars. With the emergence of the industrial revolution, a large proportion of the industrialized cigarette was possible (BUTERI et al., 2022) followed by technological modernization, which brought new forms of smoking. The first DEF was developed in the United States in 1963 by Hebert A. Gilbert and, currently, there are forms of electronic cigarettes, heated tobacco cigarettes and electronic hookah (BRASIL, 2016).

Unlike conventional cigarettes, in DEF the release of nicotine does not depend on combustion to produce smoke, but on an electronic mechanism that produces steam, heating a liquid that contains propylene glycol, glycerol and additives such as nicotine. Thus, they were disseminated as a less harmful alternative to the use of conventional cigarettes and they were even attributed the function of helping to stop smoking (NUTT et al., 2014).

However, there are studies that show that e-cigarettes increase the risk of trying conventional cigarettes, in addition to increasing the frequency of smoking relapse among former smokers. From this perspective, there was a ban on the commercialization, import and advertising of all types of electronic smoking devices in Brazil, through RDC n° 46, of August 28, 2009 (BARUFALDI et al., 2020; BRASIL, 2009).

In the year 2022, Order Number 962/2022 was published by the Ministry of Justice and Public Security/National Consumer

Secretariat/Department of Consumer Protection and Defense, determining the definitive interruption of companies that still sell DEFs, under penalty of R\$ 5,000.00/day for non-compliance (BRASIL, 2022).

## **CLASSIFICATION OF ELECTRONIC SMOKING DEVICES**

Most electronic cigarettes are composed of an atomizer that heats and vaporizes the nicotine contained in a cartridge (KNORST et al., 2014). There are four generations of DEFs, shown in figure 1.

## **COMPOSITION AND TOXIC EFFECTS OF COMPONENTS**

The composition of electronic cigarettes is vast and non-standard. Table 1 shows the list of substances most commonly found in electronic cigarettes and their actions on the human body.

The liquid composition of the devices can have several possible variations, highlighting four main ones: Propylene glycol (PG), glycerin, flavorings and nicotine (optional). In addition to these constituents, they may contain cannabis-based products, including Tetrahydrocannabinol (THC), the psychoactive component of Cannabis sativa L. (marijuana) (TRABOULSI H, et al., 2020).

The products found in electronic cigarettes considered toxic are still being investigated, the main ones being tocopheryl acetate, propylene glycol, glycerin, nicotine, aldehydes and hydrocarbons. Inhalation of glycerol and propylene glycerol can compromise lipid homeostasis and immune defense, as they can alter gene expression in the innate immune system, causing tissue damage and inflammation, as heating transforms them into hydrocarbons (such as benzene, toluene) and aldehydes (formaldehyde), respectively (HAGER and SCHUURMANS MM, 2020; HUSSAIN S, et al., 2021).

	1st Generation	2nd Generation	3rd Generation	4th Generation	Vaporizer
Basic Components					
Characteristics	<p>They resemble traditional cigarettes;</p> <p>Small battery;</p> <p>Need for frequent recharges;</p> <p>small cartridge</p>	<p>Different shape and size, compared with traditional cigarette;</p> <p>Contains the tank to store liquids (stores more liquid);</p> <p>Medium-sized battery (less frequent charge);</p> <p>Manual control of blow duration and force.</p>	<p>High-capacity battery;</p> <p>Tank with greater storage of liquids;</p> <p>Coil to heat the liquid to the desired temperature;</p> <p>Ability to produce higher quality vapor for vaping power.</p>	<p>Replaceable liquid features;</p> <p>Uses USB battery charging.</p>	<p>Ability to heat plant material;</p> <p>Ability to heat wax/THC oil (400°C)</p>

Subtitle:

- Tank
- Coil
- voltage control

Figure 1 - Types of electronic cigarettes

Source: Adapted from STEFANIAK et al., 2021.

<b>Propylene glycol (heated)</b>	May cause eye irritation. High concentrations of aerosol can cause mild nasal and throat irritation as well as central nervous system depression.
<b>Glycerin (heated)</b>	Cytotoxic, carcinogenic, irritant, causing emphysema and dermatitis.
<b>Tocopheryl Acetate (Vitamin E)</b>	It causes injury to lung tissue by oxidative stress of cells and triggers inflammatory responses.
<b>Tetrahydrocannabinol</b>	It has psychotropic and hallucinogenic properties, capable of causing chemical dependence in users.
<b>Nicotine</b>	Hypertension, cardiorespiratory problems and dependence.
<b>aldehydes</b>	Dermatitis and eye irritation.
<b>Nitrosamines</b>	As stomach, esophageal and liver cancer, as well as teratogenic and mutagenic.
<b>Hydrocarbons</b>	Nausea, vomiting, central nervous system depression and death from respiratory or cardiac arrest.

Table 1 – Main substances found in electronic cigarettes and their main effects.

Source: Adapted from BRAZIL, 2016.

Tocopherol acetate can be harmful to pulmonary surfactant function, causing respiratory disorders due to the inability to break large molecules, it can accumulate in the vacuoles of alveolar macrophages, triggering an inflammatory response and acute lung injury. Such mechanisms are being associated with the development of EVALI. Furthermore, the toxicity of the association of these compounds is not elucidated, it is believed that it can be potentiated by the high temperatures reached by DEFs (BELOK SH, et al., 2020).

## **E-CIGARETTE-INDUCED LUNG INJURY**

In recent years, cases of lung injury attributed to the use of electronic cigarettes by *Center for Disease Control and Prevention* – CDC. This lung lesion has been described as EVALI, with a nonspecific diagnosis, characterized by cough, chest pain and tiredness, in addition to general and gastrointestinal symptoms such as diarrhea and vomiting (SMITH et al., 2020).

Among the compounds present in electronic cigarettes, tocopheryl acetate (vitamin E) stands out. It is believed to be one of the most toxic substances present in DEFs, as it can cause lung tissue damage through oxidative stress (WINNICKA, 2020; HOLT AK, POKLIS, PEACE, 2021).

EVALI is a disease of difficult detection, being easily confused with other respiratory diseases and is not yet fully established by the scientific community. Thus, the Brazilian Society of Pulmonology and Tisiology - SBPT guides the adoption of the diagnostic and classification criteria described in Table 2:

Jonas et al. (2020) interviewed 155 e-cigarette users, of whom 81% had dyspnea, 74% cough, 84% fever, and 63% gastrointestinal symptoms. Patients who presented EVALI were young people of median age, 19 to 35 years old, and mostly male (77%).

The substances present in electronic cigarettes were THC (91%), nicotine (70%) and cannabidiol (8%). Regarding deaths due to the use of these cigarettes, a survey was carried out in 2019 reporting 68 deaths among 2,807 users with lung tissue injuries (JONAS et al., 2020).

## **METHODOLOGY**

This is an integrative review outlined by the guiding question: “What is the relationship between electronic cigarette toxicity and the development of Pulmonary Injury - EVALI?”.

The studies included in the sample were searched in the following databases: U.S. National Library of Medicine (PubMed), Capes Periodicals and Virtual Health Library (BVS). The Descriptors in Health Sciences/ Medical Subjective Headings (DeCS/MeSH) were used: “Vaping”, “Toxicity”, “Lung Injury”, using Boolean operators AND and OR.

The inclusion criteria adopted were: works available in their entirety; in Portuguese, English or Spanish; published in the last 7 years. For exclusion, literature reviews, duplicate articles and incomplete texts were considered. The selected articles were analyzed for their potential to participate in the study, evaluating their titles and abstracts to meet the research question, as shown in Figure 2.

## **RESULTS AND DISCUSSION**

The final sample consisted of eight articles in a foreign language, since no studies were found in Portuguese that met the inclusion criteria. Table 2 presents the pre-selected articles to reach the objectives.

From the analysis of the studies, it was found that one of the main triggering substances for lung injury caused by electronic cigarettes is vitamin E acetate (alpha-tocopherol VEA), used as an additive to dissolve oils (mineral, coconut, limonene and especially tetrahydrocannabinol (THC)

<b>Confirmed</b>	<b>likely</b>
Use of electronic cigarettes in the 90 days prior to the onset of symptoms;	Use of electronic cigarettes in the 90 days prior to the onset of symptoms;
Pulmonary infiltrate on chest X-ray or ground-glass opacities on chest computed tomography;	Pulmonary infiltrate on chest X-ray or ground-glass opacities on chest computed tomography;
Absence of pulmonary virus infection;	Virus infection was identified;
Absence of an alternative plausible diagnosis (eg, cardiac, rheumatologic, or neoplastic process).	Minimum criteria to exclude infection were not performed, but infection is not thought to be the sole cause of lung injury.
-	Absence of an alternative plausible diagnosis (eg, cardiac, rheumatologic, or neoplastic process).

Table 2 - EVALI diagnostic and classifying criteria (CDC)

Source: JONAS et al., 2020.

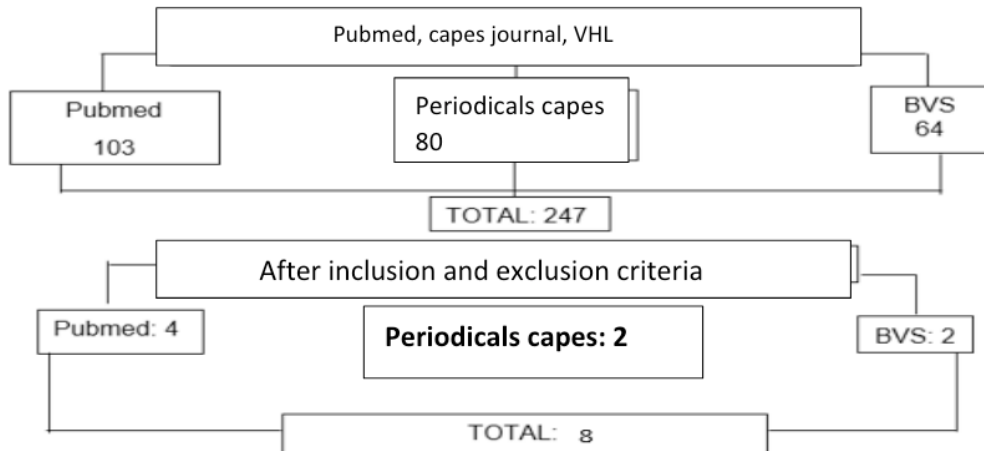


Figure 2. Schematic representation of the choice of articles.

Source: Author himself, 2022.

Data base	Title	Objective	Author and year of publication
Pubmed	Pulmonary Toxicity and the Pathophysiology of Electronic Cigarette, or Product <i>Vaping</i> , Associated Lung Injury Use.	Discuss the recent reports of EVALI, etiology, as well as the mechanisms underlying the pulmonary pathophysiology related to e-cigarette toxicity.	CHAND, Hitendra S. et al., 2020.
	Vape cartridge heating element composition and evidence of high temperatures.	Identify the substances present within vaping, elucidating the risks for EVALI.	WAGNER J, CHEN W, VRDOLJAK G., 2020.
	A retrospective analysis of chemical constituents in regulated and unregulated e-cigarette liquids.	Address the main substances that cause EVALI.	HOLT AK, POKLIS JL, Peace MR, 2021.
	Analysis of Toxic Metals in Aerosols from Devices Associated with Electronic Cigarettes, or Vaping, Lung Injury Associated with Product Use.	To analyze toxic metals present in DEFs and associations with EVALI.	GONZALEZ-JIMENEZ N. et. al, 2021.
Virtual Health Library	Cardiopulmonary Consequences of Vaping in Adolescents: A Scientific Statement from the American Heart Association.	Provide information on cardiopulmonary consequences of e-cigarettes in adolescents, guide therapeutic and preventive strategies, and inform about risks.	WOLD et al., 2022.
	E-cigarette, or vaping, lung injury associated with product use among patient groups reporting shared product use – Wisconsin, 2019.	Interview electronic cigarette users, perform laboratory analysis of bronchoalveolar lavage fluid (BAL).	PRAY et al., 2020.
Capes Journals	Pulmonary Toxicity and Inflammatory Response of Vape Cartridges Containing Medium Chain Triglycerides Oil and Vitamin E Acetate: Implications in the Pathogenesis of EVALI	To study pulmonary toxicity and inflammatory response associated with EVALI.	MUTHUMALAGE. et. al, 2020.
	Fundamentals of vaping-associated lung injury leading to severe respiratory distress	Demonstrate lung injuries caused by the use of DEFs.	ESQUER, CAROLINA, et. al, 2022

Table 2 - Articles selected for the integrative review and its objective

Source: Own author, 2022.

or as a thickening agent, when inhaled it causes inflammatory responses and cellular oxidative stress (CHAND et al., 2020).

The authors detected vitamin E acetate in bronchoalveolar lavage of several cases of EVALI, highlighting the possibility that inhalation/vaporization of AEV or oxidant derivatives may interfere with pulmonary physiological functions, interacting with phospholipids and surfactants in the epithelial lining fluid.

Also nicotine-based products identified as causing EVALI. It is concerned about the other chemical components of electronic cigarettes, as there is a deficiency in the regulation of such substances and knowledge about the toxicity they present when inhaled by the mechanism of DEFs release. Histopathological reports showed darkened lungs, suggesting that aromatic/volatile hydrocarbons, including terpenes (diluent) and oils, are involved in the process. Acrolein, 1,3-butadiene, benzene, toluene, propylene and reactive aldehydes are formed by heating these compounds to 260°C (the temperature of most vapings) (WAGNER; CHEN; VRDOLJAK, 2020).

WAGNER; CHEN; VRDOLJAK (2020) address that toxic compounds may be related to the content of the cigarette itself at high temperature, raising the hypothesis that vitamin E acetate can produce toxic ketone (ethenone) at elevated temperatures. As chemical reactions are catalyzed on the surfaces of ceramics or metals such as nickel (Ni) or cobalt (Co), any of these materials within the DEFs can potentiate these reactions. Furthermore, the presence of THC combined with ceramics, metals and high temperatures in THC cartridges may be strongly related to EVALI cases.

In the HOLT study; POKLIS; PEACE (2021) identified 350 chemical constituents among which nicotine, caffeine, menthol and vitamin E, olivetol and cannabinoids were

the main ones. These are believed to be the main substances potentially causing EVALI and warned about the lack of information on chemical interactions between the components.

GONZALEZ et al., (2021) investigated the concentration of metals in electronic cigarettes, finding Al, Cr, Fe, Co, Ni, Cu, Cd, Sn, Ba and Pb. In addition, considerable levels of nicotine were found. They highlighted that these constituents may be related to the development of Lung Injury, as they can cause oxidative stress to lung cells.

WOLD et al. (2022) report that to increase the attractiveness of EC, many manufacturers usually add compounds capable of modifying the flavor in their cartridges. In addition, the lack of regulation of substances contained in DEFs encourages the idea that electronic cigarettes are less harmful than traditional cigarettes (PRAY et al., 2020).

MUTHUMALAGE. et. al, (2020) showed that counterfeit ECs are more toxic. Furthermore, when studying the plasma of users already with EVALI, a compound called hydroxyeicosatetraenoic acid was identified, responsible for pulmonary obstruction. The study concluded that acute exposure to specific EC cartridges induces in vitro cytotoxicity, barrier dysfunction and inflammation.

ESQUER, CAROLINA, et. al, (2022) report cases of profound pathological changes in the upper airways, lung tissue architecture and cellular structure after 9 weeks of exposure to electronic cigarettes. Marked histological changes include increased parenchymal tissue density, cellular infiltrates proximal to the airways, alveolar rarefaction, increased collagen deposition, and bronchial thickening with disruption of elastin fibers.

## CONCLUSION

The spread of electronic cigarettes has brought an alert to health regulatory bodies,



resulting in a ban on their use. However, its use has not ceased and reaches different audiences, mainly adolescents and young people. The lack of knowledge about the toxicity of substances present in DEFs contributes to the spread of the use of devices as a less harmful alternative when compared to traditional cigarettes.

However, after reports of cases of EVALI, toluene acetate (vitamin E) was pointed out as the main cause of lung injury. Although it is not the only substance, it is associated with most hospitalizations and deaths related to the pathology. In addition to it, metals and nicotine can also contribute to the development of the clinical picture.

Therefore, there is an evident association between the use of electronic cigarettes and lesions in lung tissue, requiring regulation and supervision of DEFs, as well as the inclusion of labeling with health warning, description of ingredients and, public awareness of the scratches.

It is hoped that this article will contribute to the access to information on e-cigarette toxicity and the risk for EVALI. It is suggested that the topic be further explored until the elucidation of all components of electronic cigarettes and their toxicity, relating them to EVALI.

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