ARTICLE
https://doi.org/10.22239/2317-269X.02292

Lung injury caused by excessive use of electronic cigarettes: toxicants involved and pathophysiological mechanisms

Lesão pulmonar induzida pelo uso excessivo de cigarros eletrônicos: toxicantes envolvidos e mecanismos fisiopatológicos

Cáren Caroline Andrade Travassos[I]

Karla Frida Torres Flister[II,*]

ABSTRACT

Introduction: Electronic cigarettes were introduced to the market for assisting in smoking cessation. However, this alternative is related to the development of Lung Injury Associated with the Use of Electronic Cigarettes and Vaporizers (EVALI), especially in the young population. In this context, it is necessary to understand the mechanisms of lung injury produced by the use of electronic cigarettes in order to establish the true risks of long-term exposure to these vapors. **Objective:** To elucidate the pathophysiological mechanisms of EVALI. **Method:** Integrative literature review based on the PRISMA method and search in the LILACs, PubMed, and EMBASE databases, from 2003 to 2023 and free access experimental and epidemiological research in full, with an approach to the pathogenesis of EVALI, were selected. **Results:** The different constituents present in electronic cigarettes are involved in the development of EVALI as they age through different mechanisms, such as: changes in the structure and functions of the lung surfactant; accumulation of oil droplets in mucus, and alteration of the structure, function, and chemotaxis of cells that make up innate immunity, such as neutrophils and macrophages. **Conclusions:** Electronic cigarettes induce EVALI through different mechanisms due to the complexity of the composition of substances present in vapors. Clarifying the mechanisms of lung injury is pertinent for regulatory agencies to apply more stringent measures to electronic cigarettes in order to reduce the impact of exposure and cases of morbidity and mortality among young people and adults.

KEYWORDS: Eletronic Cigarette; EVALI; Lung Injury

[I] Universidade Federal do Maranhão (UFMA), São Luís, MA, Brasil

[II] Departamento de Farmácia, Universidade Federal do Maranhão (UFMA), São Luís, MA, Brasil

* **E-mail:** karla.flister@ufma.br

Received: Dec 29, 2023
Approved: May 22, 2024

How to cite: Travassos CCA, Flister KFT. Lung injury caused by excessive use of electronic cigarettes: toxicants involved and pathophysiological mechanisms. Vigil Sanit Debate, Rio de Janeiro, 2024, v.12: e02292. https://doi.org/10.22239/2317-269X.02292

RESUMO

Introdução: Os cigarros eletrônicos, que foram introduzidos no mercado com a finalidade de auxiliar na cessação do tabagismo, está relacionado ao desenvolvimento da lesão pulmonar associada ao uso de cigarros eletrônicos e vaporizadores (Evali), principalmente na população jovem. Neste contexto, é imprescindível entender os mecanismos de lesão pulmonar produzidos pelo uso de cigarros eletrônicos, a fim de estabelecer os verdadeiros riscos da exposição a longo prazo a esses vapores. **Objetivo:** Elucidação dos mecanismos fisiopatológicos da Evali. **Método:** Revisão de literatura integrativa baseada no método PRISMA e busca nas bases de dados LILACS, PubMed, Embase, no período de 2003 a 2023. Foram selecionadas pesquisas experimentais e epidemiológicas de livre acesso na íntegra com abordagem na patogênese da Evali. **Resultados:** Os diferentes constituintes presentes no cigarro eletrônico estão envolvidos no desenvolvimento da Evali, visto que agem por diversos mecanismos, como: modificação na estrutura e funções do surfactante pulmonar, acúmulo de gotículas de óleo no muco e modificação da estrutura, função e quimiotaxia de células que compõem a imunidade inata, como os neutrófilos e macrófagos. **Conclusões:** O cigarro eletrônico induz a Evali por diferentes mecanismos em virtude da complexidade da composição de substâncias presentes nos

vapores. O esclarecimento acerca dos mecanismos de lesão pulmonar é pertinente para nortear as agências regulatórias na aplicação de medidas mais rigorosas aos cigarros eletrônicos, a fim de reduzir os impactos da exposição e dos casos de morbimortalidade entre os jovens e adultos.

PALAVRAS-CHAVE: Cigarro Eletrônico; Evali; Lesão Pulmonar

INTRODUCTION

The worldwide fight against smoking began with the signing of the first global health treaty at the World Health Organization (WHO) Framework Convention with the proposal to reduce the demand for nicotine-based products by increasing taxes, incorporating health warning labels, and banning advertising that encourages their use[1]. These measures have contributed to a global reduction in smoking, although it still affects a large proportion of the world's population[2].

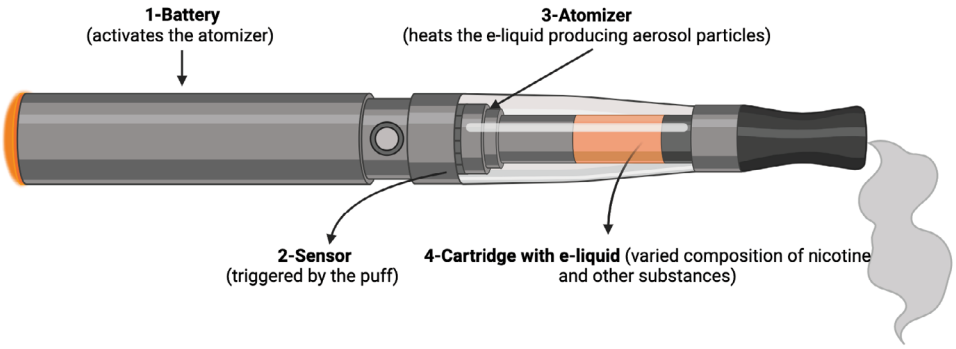
Smoking is a chronic disorder caused by nicotine dependence and conditioned behaviors, which is among the top three risk factors in terms of Disability Adjusted Life Year, associated with the development of multimorbidities, and is also considered a global health problem[2]. In Brazil, during 2019, according to analyses carried out by Wanderlei-Flores et al., the highest burden of deaths attributable to smoking was due to cardiometabolic diseases (41.4%), followed by respiratory diseases (34%) and cancer (24.6%)[3], which killed more than 160,000 people in 2020[4].

Nicotine is the substance responsible for addiction in smoking, as it shares the same neurological basis for addiction as other types of drugs of abuse[5]. There are around 7,000 chemicals in cigarette smoke, 93 of which are harmful and potentially harmful according to the Food and Drug Administration (FDA), including: cadmium, lead, acrolein, acetaldehyde, benzene, ammonia, carbon monoxide, 1,3-butandiene, and tobacco-specific nitrosamines[6]. In this context, e-cigarettes were introduced to the market in 2004 to aid smoking cessation and with the justification that they were harmless to health, even in the absence of clinical studies proving such benefits[7]. In Brazil, their sale is prohibited by the National Health Surveillance Agency by RDC No. 46 of August 28, 2009[8], but they are easily purchased on websites and their use is widespread among adolescents, bringing unexpected health risks to this population[9].

E-cigarettes have evolved since their creation, and today there are four generations of them on the market with a basic structure (Figure 1). The first generation resembles conventional cigarettes in shape and size and is disposable and non-refillable. The second generation has rechargeable batteries and cartridges. The third-generation devices have a kind of tank for storing nicotine or other drugs. The latest generation has a pre-filled or refillable cartridge, which contains e-liquid that can be heated to a desired temperature, producing more vapor[10].

The basic functional components of an electronic cigarette are: a battery, a wick, and a heating coil responsible for aerolizing the e-liquid to release the vapor, which can contain various components, such as: psychoactive substances (nicotine or Δ^9 -THC), diluents - propylene glycol (PG), vegetable glycerin (VG), or vitamin E -, and flavoring agents, for inhalation. Although the act of inhaling these compounds is colloquially called vaping, this term is misleading, as it is actually a superheated complex aerosol of semi-liquid particulate material, and not a gaseous vapor that the user absorbs, which is linked to lung damage[11].

In September 2019, in the United States, the Centers for Disease Control and Prevention (CDC) warned of the growing number of cases of lung damage associated with the use of electronic cigarettes by young people, with global repercussions. This new nosological entity was then called lung injury associated with the



Source: Prepared by the authors, 2023.

Figure 1. Basic structure of electronic cigarettes.

use of electronic cigarettes and vaporizers (EVALI). In the population exposed to the use of these devices, a broad spectrum of lung diseases has been identified, characterized by four different types of damage: acute eosinophilic pneumonia, diffuse alveolar damage, organizational pneumonia, and lipoid pneumonia. Therefore, such diversity suggests different mechanisms of lung damage[12].

EVALI usually presents as an acute or sub-acute respiratory illness with non-specific symptoms, including shortness of breath, cough, chest pain, and/or hemoptysis. They also present with gastrointestinal problems (nausea, vomiting, and/or diarrhea) and/or constitutional symptoms (fever, chills, fatigue, and/or weight loss) that develop over days to weeks with no specific laboratory findings. Confirmed cases of EVALI are defined as the onset of pulmonary infiltrates on chest X-ray or computed tomography (CT) scan that occur within 90 days of e-cigarette use. The diagnostic criteria suggested for EVALI refer only to acute cases of respiratory disease due to e-cigarette use and do not address chronic respiratory diseases or other diseases that may be induced or aggravated by use. Due to the lack of knowledge of its pathophysiological mechanisms, current treatment involves systemic corticosteroid therapy, but its efficacy has yet to be proven[13].

Thus, electronic cigarettes (e-cigarettes) are a threat to the health of young people due to their accessibility, the attractiveness of the different designs of these devices and the omission of manufacturers about their real constituents, claiming that they are safe and less harmful than conventional cigarettes[14,15]. Therefore, it is essential to elucidate the pathophysiological mechanisms of EVALI resulting from the use of electronic cigarettes, establishing the true risks of long-term exposure to these aerosols, helping regulatory agencies to create public risk management policies.

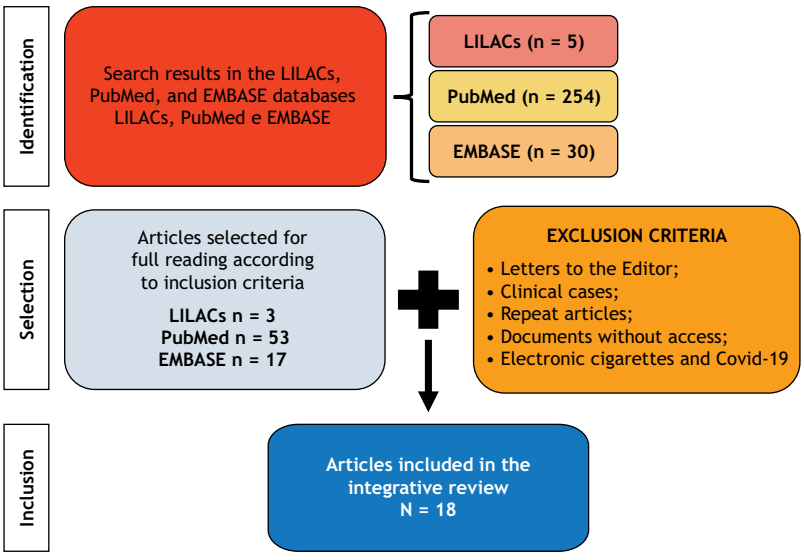
METHOD

This study is a literature review based on the Principal Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) method. Firstly, a search was carried out for relevant studies on the mechanisms of lung injury caused by electronic cigarette use in the LILACS, PubMed, and Embase databases using the following descriptors: ("E-Cigarette Vapor") AND ("Lung Injury") OR ("E-Cigarette or Vaping Product Use-Associated Lung Injury").

Then, after reading and analysis by two researchers, the following inclusion criteria were used: the year of publication of the articles - between 2003 (when e-cigarettes first appeared) and 2023 - and the language - Portuguese, English, and Spanish - and articles that addressed the pathogenesis of EVALI. The exclusion criteria selected for the search were letters to the editor, repeated articles, documents without access, and articles relating the use of electronic cigarettes and COVID-19. In the event of a discrepancy, a third researcher was recruited to review the quality of the information according to the inclusion and exclusion criteria (Figure 2).

Lung tissue is responsible for gas exchange in the body and has an important cellular defense network against particles and pathogens. Airway homeostasis is maintained through different physiological mechanisms, such as mucociliary clearance and phagocytosis of invading particles. When type I and type II alveolar cells are exposed to aerosols from the vaporization of electronic cigarettes, macrophages (AMs) and polymorphonuclear leukocytes (PMNs) are recruited to defend the pulmonary system, as they are part of innate immunity[16].

However, exposure to electronic cigarette vapors (EVE), which have a complex composition of substances, produces important changes in the immune system, as it alters the fluidity of the



Source: Prepared by the authors, 2023.

Figure 2. Flowchart of the identification and selection of articles based on the PRISMA method.

neutrophil cell membrane, inhibits their chemotaxis process and the production of extracellular traps that play an important role in the defense process promoted by these cells. In addition, exposure to EVE also inhibits the production of reactive oxygen species (ROS) mediated by these cells, consequently interfering with the antimicrobial defense system of the alveoli[17]. Therefore, lung tissue becomes susceptible to damage and injury due to alterations in the tissue defense process mediated by immune system cells.

Electronic cigarettes also contain psychoactive compounds such as nicotine and tetrahydrocannabinol (Δ^9 -THC), which are involved in triggering EVALI. Experiments on animal models have shown that electronic devices containing nicotine trigger airway hyperreactivity and impair ciliary movement[18]. Δ^9 -THC acts mainly by modulating the response of the pulmonary immune system, as its vaporization has the ability to suppress cell chemotaxis, nitric oxide production, secretion of tumor necrosis factor-α, phagocytic activity, and induces the expression of inflammatory cytokines, contributing to a reduction in pulmonary immune defense. It also promotes the direct oxidation of phosphatidylcholines and the consequent rupture of pulmonary surfactant, resulting in tissue damage and respiratory distress[19].

Other important components of electronic cigarettes that can contribute to the occurrence of EVALI are the diluents of psychoactive compounds present in the formulations, such as PG and VG contained in nicotine-based formulations, and vitamin E acetate (VEA), contained in electronic cigarettes with Δ -THC[920]. In bronchoalveolar lavage from patients hospitalized with EVALI, the presence of VEA was found[21]. This finding has contributed to the development of several studies in experimental and *in vitro* models to understand the pathophysiological mechanisms of this compound in the development of EVALI.

Vitamin E is found in various foods and dietary supplements and is considered safe to take according to the FDA[12]. However, its vaporization in electronic cigarettes generates VEA, which has been associated with various pulmonary damages[11]. Vitamin E has a rigid double ring (chroman) with the ability to insert itself and cause a disturbance in the phosphatidylcholine bilayer that makes up the pulmonary surfactant, by reversing the gel phase to the crystalline phase, which exponentially increases its surface fluidity, thus altering the cycle of pulmonary compression and decompression, resulting in extensive hypoxemia and respiratory discomfort. Another specific finding of VEA exposure is the formation of lipid-laden intra-alveolar AMs which are related to the development of lipoid pneumonia[22].

Still on the subject of mechanisms involving VEA, there is a reduction in the process of spherocytosis of alveolar AMs. The impaired morphological and functional functions of AMs lead to the accumulation of apoptotic neutrophils with the intensification and activation of a pro-inflammatory cascade. Therefore, the alteration of the homeostasis processes of AMs due to the use of electronic cigarettes with VEA is capable of promoting the installation of a pulmonary inflammatory condition associated with systemic oxidative stress observed both in experimental models and in patients with EVALI[23]. Manna et al. also observed in experimental models that exposure to VEA vapor promotes an increase in the mucus production rate of goblet cells and the formation of insoluble oil droplets in the pulmonary mucus capable of triggering an inflammatory response similar to that observed in EVALI[24].

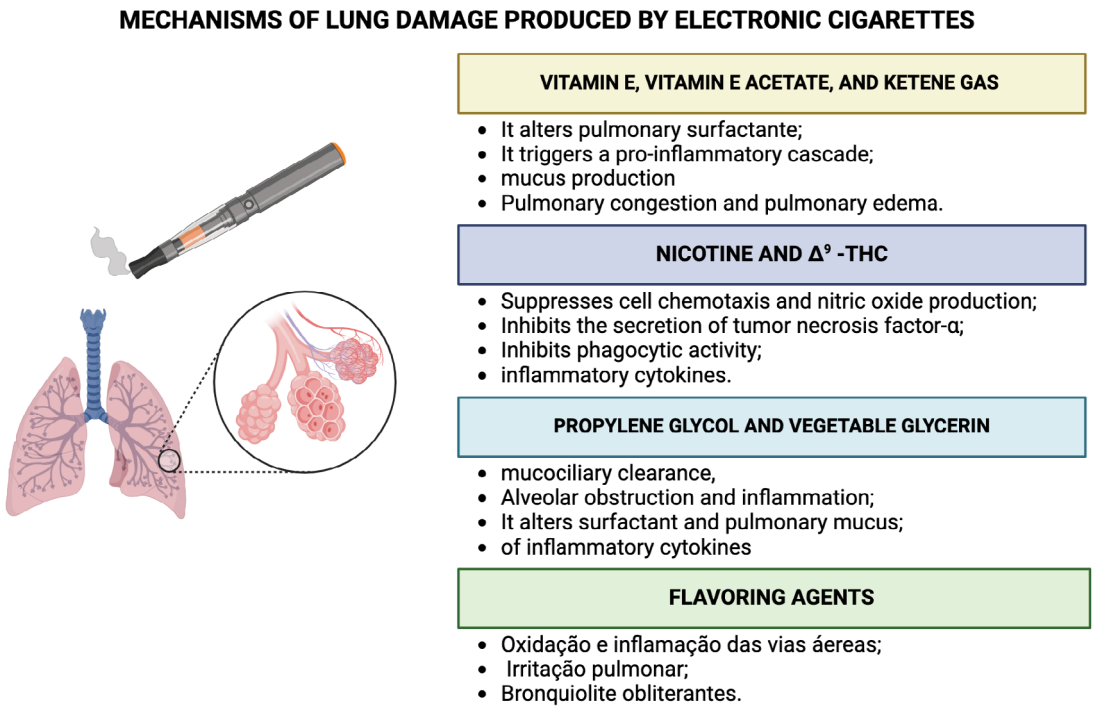
Furthermore, when the VEA is subjected to excessive pyrolysis by vaporization, it degrades into ketene gas, which also seems to be involved in the pathogenesis of EVALI[13,25]. Ketene is formed under the conditions of dry-hits, which are devices that do not adjust their operating temperature according to the level of e-liquid, resulting in overheating and the production of ketene gas. This situation recurs in counterfeit tetrahydrocannabinol e-cigarettes, whose internal materials are found burnt[26]. Exposure to concentrations of 12 ppm of ketene gas promotes acute pulmonary congestion and alveolar edema, which can contribute to the development of EVALI[27].

PG and VG also play a role in the lung damage induced by the use of electronic cigarettes. Due to their hygroscopic properties, PG and VG dehydrate the liquid on the surface of the airways, which triggers a decrease in mucociliary clearance, causing alveolar obstruction and inflammation. In addition, PG and VG induce hyperosmotic stress, since they do not cross biological membranes, and can induce the expression and secretion of pro-inflammatory cytokines capable of producing bronchoconstriction. Together, these effects can also disrupt mucus/surfactant rheological properties, increase surface tension and result in small airway collapse and disturb gas exchange[28].

VG interacts with the lipids that make up pulmonary surfactant, altering the position of the phosphatidylcholine chains by replacing the water molecules in the solvation layer and concentrating in the interfacial region in a thin layer over the lipid phase, thus altering the stability of pulmonary surfactant[29]. In addition, inhalation of these diluents increases serum levels of Clara cell protein 16 (CC16), an inflammatory marker of lung epithelial injury[28].

The flavoring agents contained in the e-liquid may have contributed to EVALI. Among the flavoring agents are 2,3 pentanedione, acetoin, menthol and cinnamaldehyde, which have an oxidative and inflammatory effect on the airways, benzaldehyde, furfural and 5-hydroxyfurfural, which have been shown to cause irritation of the upper respiratory tract, while vanillin has an inflammatory and irritating effect on the respiratory tract[30].

Flavoring agents are added to electronic cigarettes to attract young people and mask the perceived risks of their use[11]. 2,3-butanedione (BD) is an a-diketone found in nature that gives butter its characteristic flavor and is an important constituent of artificial flavors. BD is widely used as a food additive, and its consumption in food is not associated with adverse health effects[31]. This substance has been found in vape e-liquids along with its dicetone analog, 2,3-pentanedione. This product has known pulmonary toxicity, triggering bronchiolitis obliterans or "popcorn lung"[11].



Source: Prepared by the authors, 2023.

Figure 3. Summary of the mechanisms of lung damage triggered by the constituents of electronic cigarettes.

The mechanisms of lung damage caused by electronic cigarettes involve a set of actions triggered by the different components contained in these devices which can generate changes in the structure and functions of pulmonary surfactant, which consequently promotes alveolar collapse and the accumulation of oil droplets, modifying the structure, function, and chemotaxis of cells that make up innate immunity, such as neutrophils and AMs (Figure 3). More studies are needed to elucidate precisely the mechanisms of lung damage caused by the constituents of electronic cigarettes, under what conditions this occurs and to establish the real risks of long-term exposure to the vapors of these electronic devices.

CONCLUSIONS

Thus, there is evidence that the vaporization of electronic cigarette components, such as psychoactive substances (nicotine and tetrahydrocannabinol), diluents (vitamin E/VEA/ketene gas; polyethylene glycol and VG), and various flavoring agents, are related to the pathogenesis of EVALI. It is therefore important to understand the different mechanisms of lung damage caused by the use of electronic cigarettes in order to guide regulatory agencies in controlling, restricting, and possibly maintaining the ban on such devices on the Brazilian market, so as to protect the health of young people and adults.

REFERENCES

1. Hiilamo H, Glantz S. Global implementation of tobacco demand reduction measures specified in framework convention on tobacco control. Nicotine Amp Tob Res. 18;24(4):503-10. https://doi.org/10.1093/ntr/ntab216
2. Santoro A, Tomino C, Prinzi G, Lamonaca P, Cardaci V, Fini M et al. Tobacco smoking: risk to develop addiction, chronic obstructive pulmonary disease, and lung cancer. Rec Pat Anti-Cancer Drug Disc. 2019;14(1):39-52. https://doi.org/10.2174/1574892814666190102122848
3. Wanderlei-Flores B, Rey-Brandariz J, Corrêa PCRP, Ruano-Ravina A, Guerra-Tort C, Candal-Pedreira C et al. Smoking-attributable mortality by sex in the 27 brazilian federal units: 2019. Public Health. 2024;229:24-32. https://doi.org/10.1016/j.puhe.2024.01.016
4. Instituto Nacional de Câncer – INCA. Dados e números do tabagismo. Observatório da Política Nacional de Controle do Tabaco. 19 out 2022[acesso 8 dez 2023]. Disponível em: https://www.gov.br/inca/pt-br/assuntos/gestor-e-profissional-de-saude/observatorio-da-politica-nacional-de-controle-do-tabaco/dados-e-numeros-do-tabagismo
5. Pupulim AF, Sarris AB, Fernandes LG, Nakamura MC, Camargo TV, Paula JB. Mecanismos de dependência química no tabagismo: revisão da literatura. Rev Médica UFPR. 2015;2(2):74-8. https://doi.org/10.5380/rmu.v2i2.42122

6. U.S. Food and Drug Administration - FDA. Chemicals in every puff of cigarette smoke. Chemicals in Every Puff of Cigarette Smoke. 6 mar 2020[acesso 7 abr 2024]. Disponível em: https://www.fda.gov/tobacco-products/products-ingredients-components/chemicals-every-puff-cigarette-smoke
7. Tzortzi A, Kapetanstrataki M, Evangelopoulou V, Behrakis P. A systematic literature review of e-cigarette-related illness and injury: not just for the respirologist. Int J Environ Res Public Health. 2020;17(7):1-27. https://doi.org/10.3390/ijerph17072248
8. Agência Nacional da Vigilância Sanitária – Anvisa. Resolução RDC Nº 46, de 28 de agosto de 2009. Proíbe a comercialização, a importação e a propaganda de quaisquer dispositivos eletrônicos para fumar, conhecidos como cigarro eletrônico. Diário Oficial União. 31 ago 2009.
9. Knorst MM, Benedetto IG, Hoffmeister MC, Gazzana MB. The electronic cigarette: the new cigarette of the 21st century? J Bras Pneumol. 2014;40(5):564-72. https://doi.org/10.1590/s1806-37132014000500013
10. Silva IMC, Lopes PH, Silveira BB, Melo LD, Santos JA, Ferreira EB, Guerra EM et al. Dispositivos eletrônicos para fumar: aliados ou adversários ao tabagismo? Concilium. 2022;22(4):757-68. https://doi.org/10.53660/clm-358-358
11. Cao DJ, Aldy K, Hsu S, McGetrick M, Verbeck G, Silva I et al. Review of health consequences of electronic cigarettes and the outbreak of electronic cigarette, or vaping, product use-associated lung injury. J Med Toxicol. 2020;16(3):295-310. https://doi.org/10.1007/s13181-020-00772-w
12. Bello SS. Daño pulmonar asociado al uso de cigarrillos electrónicos- vapeadores. Rev Chil Enfermedades Respir. 2020;36(2):115-21. https://doi.org/10.4067/s0717-73482020000200115
13. Rebuli ME, Rose JJ, Noël A, Croft DP, Benowitz NL, Cohen AH et al. The e-cigarette or vaping product use–associated lung injury epidemic: pathogenesis, management, and future directions: an official american thoracic society workshop report. Ann Am Thorac Soc. 2023;20(1):1-17. https://doi.org/10.1513/annalsats.202209-796st
14. Urrutia-Pereira M, Solé D. Cigarros eletrônicos: esses ilustres desconhecidos. Arq Asma Alerg Imunol. 2018;2(3):309-14. https://doi.org/10.5935/2526-5393.20180038
15. Pinheiro AC, Borges YJ. Dispositivos eletrônicos para fumar e suas ameaças à saúde: uma revisão de literatura. Braz J Dev. 2023;9(1):3839-49. https://doi.org/10.34117/bjdv9n1-264
16. Lopes AJ, Noronha A, Mafort T. Mecanismos de defesa do aparelho respiratório. Rev Hosp Univ Pedro Ernesto. 2014;9(2):10-6.
17. Corriden R, Moshensky A, Bojanowski C, Meier A, Chien J, Nelson RK et al. E-cigarette use increases susceptibility to bacterial infection by impairment of human neutrophil chemotaxis, phagocytosis and NET formation. Faseb J. 2020;34(S1):1. https://doi.org/10.1096/fasebj.2020.34.s1.07371
18. Garcia-Arcos I, Geraghty P, Baumlin N, Campos M, Dabo AJ, Jundi B et al. Chronic electronic cigarette exposure in mice induces features of COPD in a nicotine-dependent manner. Thorax. 2016;71(12):1119-29. https://doi.org/10.1136/thoraxjnl-2015-208039
19. Meehan-Atrash J, Rahman I. Cannabis vaping: existing and emerging modalities, chemistry, and pulmonary toxicology. Chem Res Toxicol. 2021;34(10):2169-79. https://doi.org/10.1021/acs.chemrestox.1c00290
20. Belok SH, Parikh R, Bernardo J, Kathuria H. E-cigarette, or vaping, product use-associated lung injury: a review. Pneumonia. 2020;12(1):1-8. https://doi.org/10.1186/s41479-020-00075-2
21. Blount BC, Karwowski MP, Morel-Espinosa M, Rees J, Sosnoff C, Cowan E et al. Evaluation of bronchoalveolar lavage fluid from patients in an outbreak of e-cigarette, or vaping, product use-associated lung injury: 10 states, August–October 2019. MMWR Morb Mortal Wkly Rep. 2019;68(45):1040-1. https://doi.org/10.15585/mmwr.mm6845e2
22. Lee H. Vitamin E acetate as linactant in the pathophysiology of EVALI. Med Hypoth. 2020;144:1-8. https://doi.org/10.1016/j.mehy.2020.110182
23. Matsumoto S, Traber MG, Leonard SW, Choi J, Fang X, Maishan M et al. Aerosolized vitamin E acetate causes oxidative injury in mice and in alveolar macrophages. Am J Physiol Lung Cell Mol Physiol. 2022;322(6):1-13. https://doi.org/10.1152/ajplung.00482.2021
24. Manna VJ, Dwyer S, Pizutelli V, Caradonna SJ. Utilizing primary human airway mucociliary tissue cultures to model ramifications of chronic E-cigarette usage. Toxicol Vitr. 2023;94:1-8. https://doi.org/10.1016/j.tiv.2023.105725
25. Wu D, O'Shea DF. Potential for release of pulmonary toxic ketene from vaping pyrolysis of vitamin E acetate. Proc National Acad Sci. 2020;117(12):6349-55. https://doi.org/10.1073/pnas.1920925117
26. Marrocco A, Singh D, Christiani DC, Demokritou P. E-cigarette vaping associated acute lung injury (EVALI): state of science and future research needs. Crit Rev Toxicol. 2022;52(3):1-33. https://doi.org/10.1080/10408444.2022.2082918
27. Attfield KR, Chen W, Cummings KJ, Jacob P, O'Shea DF, Wagner J et al. Potential of ethenone (Ketene) to contribute to electronic cigarette, or vaping, product use–associated lung injury. Am J Respir Crit Care Med. 2020;202(8):1187-9. https://doi.org/10.1164/rccm.202003-0654le
28. Chaumont M, van de Borne P, Bernard A, Van Muylem A, Deprez G, Ullmo J et al. Fourth generation e-cigarette vaping induces transient lung inflammation and gas exchange disturbances: results from two randomized clinical trials. Am J Physiol Lung Cell Mol Physiol. 2019;316(5):L705-19. https://doi.org/10.1152/ajplung.00492.2018

29. Hayeck N, Zoghzoghi C, Karam E, Salman R, Karaoghlanian N, Shihadeh A et al. Carrier solvents of electronic nicotine delivery systems alter pulmonary surfactant. Chem Res Toxicol. 2021;34(6):1572-7. https://doi.org/10.1021/acs.chemrestox.0c00528

30. Theron AJ, Feldman C, Richards GA, Tintinger GR, Anderson R. Electronic cigarettes: where to from here? J Thorac Dis. 2019;11(12):5572-85. https://doi.org/10.21037/jtd.2019.11.82

31. Morgan DL, Jokinen MP, Johnson CL, Price HC, Gwinn WM, Bousquet RW et al. Chemical reactivity and respiratory toxicity of the α-diketone flavoring agents. Toxicol Pathol. 2016;44(5):763-83. https://doi.org/10.1177/0192623316638962

Authors' Contribution

Travassos CCA, Flister KFT - Conception, planning (study design), acquisition, analysis, data interpretation, and writing of the paper. All the authors approved the final version of the paper.

Conflict of Interest

The authors inform that there is no potential conflict of interest with peers and institutions, political or financial, in this study.