Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

HHS Public Access

Author manuscript

Crit Rev Toxicol. Author manuscript; available in PMC 2023 July 13.

Published in final edited form as:

Crit Rev Toxicol. 2022 March ; 52(3): 188–220. doi:10.1080/10408444.2022.2082918.

E-Cigarette Vaping Associated Acute Lung Injury (EVALI): State of science and future research needs

Antonella Marrocco[1], **Dilpreet Singh**[1], **David C. Christiani**[1], **Philip Demokritou**[1,2,*]

[1]Center for Nanotechnology and Nanotoxicology, T.H. Chan School of Public Health, Harvard University, 665 Huntington Ave., Boston, MA 02115, USA

[2]Environmental Occupational Health Sciences Institute, School of Public Health, Rutgers University, 170 Piscataway, NJ 08854, USA

Abstract

"E-Cigarette (e-cig) Vaping-Associated Acute Lung Injury" (EVALI) has been linked to vitamin-E-acetate (VEA) and Δ-9-tetrahydrocannabinol (THC), due to their presence in patients' e-cigs and biological samples. Lacking standardized methodologies for patients' data collection and comprehensive physicochemical/toxicological studies using real-world-vapor exposures, very little data are available, thus the underlying pathophysiological mechanism of EVALI is still unknown. This review aims to provide a comprehensive and critical appraisal of existing literature on clinical/epidemiological features and physicochemical-toxicological characterization of vaping emissions associated with EVALI. The literature review of 161 medical case reports revealed that the predominant demographic pattern was healthy white male, adolescent, or young adult, vaping illicit/informal THC-containing e-cigs. The main histopathologic pattern consisted of diffuse alveolar damage with bilateral ground-glass-opacities at chest radiograph/CT, and increased number of macrophages or neutrophils and foamy-macrophages in the bronchoalveolar lavage. The chemical analysis of THC/VEA e-cig vapors showed a chemical difference between THC/VEA and the single THC or VEA. The chemical characterization of vapors from counterfeit THC-based e-cigs or in-house-prepared e-liquids using either cannabidiol (CBD), VEA, or medium-chain triglycerides (MCT), identified many toxicants such as carbonyls, volatile organic compounds, terpenes, silicon compounds, hydrocarbons, heavy metals, pesticides and various industrial/manufacturing/automotive-related chemicals. There is very scarce published toxicological data on emissions from THC/VEA e-liquids. However, CBD, MCT, and VEA emissions exert varying degrees of cytotoxicity, inflammation, and lung damage, depending on puffing topography and cell line. Major knowledge gaps were identified, including the

[*]**Corresponding author:** Prof. Philip Demokritou, Department of Environmental Health, Center for Nanotechnology and Nanotoxicology, Harvard T.H. Chan School of Public Health, 665 Huntington Ave, Building 1, Room 1310, Boston, MA 02115, USA, Tel: +1 617 432 3481, pdemokri@hsph.harvard.edu.

Declaration of Interest

This review aims to provide a comprehensive and critical appraisal of existing literature on clinical/epidemiological features and physicochemical-toxicological characterization of vaping emissions associated with EVALI. The authors believe that highlighting the knowledge gaps in the current literature and the limitations in the e-cigs regulations is necessary for the development of new study designs and for the federal regulatory agencies in future decisions on the regulation of e-cigs or vaping products, to prevent future outbreaks.

This review was made possible by the T32 Grant No. HL007118 from NIH. The authors have not participated in and do not anticipate participation in any legal, regulatory, or advocacy proceedings related to the contents of the paper.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

need for more systematic-standardized epidemiological surveys; comprehensive physicochemical characterization of real-world e-cig emissions, and mechanistic studies linking emission properties to specific toxicological outcomes.

Keywords

EVALI; Vitamin E Acetate (VEA); Δ-9-tetrahydrocannabinol (THC); e-cigarettes; vaping; counterfeit cartridges; pneumonia; acute lung injury; acute respiratory distress syndrome (ARDS)

1 Introduction

The “E-cigarette (e-cig), or Vaping product use, associated Acute Lung Injury” (EVALI) outbreak started in the United States in July 2019, leading to 2807 hospitalizations, including 68 deaths, until February 18, 2020, when the Centers for Disease Control and Prevention (CDC) ended case reporting as SARS-Cov2 arose in the USA. The EVALI outbreak raised public health concerns about the health risks associated with vaping, especially among the young population (CDC 2020a).

The use of e-cigs in the USA has constantly and rapidly grown, since they became commercially available in the marketplace in 2007, among the general population, mainly young adults and middle and high school students.(Wang and Wu 2020; Wang L et al. 2020). Despite the slow decline registered in 2020 in terms of e-cigs’ sales and users, the number of current young consumers is still relatively high (3.6 million) (Wang TW et al. 2020), and the e-cig market continues to expand exponentially especially in North America, reaching a market value of 12.41 billion US dollars in 2019, and projected to reach 104.51 billion US dollars by 2028 (Research 2021). Some of the reasons that favored such exponential growth included the misconception that e-cigs are a healthier and safer alternative to conventional cigarettes (Gilbert 1965; CDC 2016). In addition, the extensive availability of more than 466 e-cig brands and 7700 flavors (2014 data) (Zhu et al. 2014; CDC 2016) and the recent introduction of Δ-9-tetrahydrocannabinol (D9THC) and cannabinoid (CBD) oils in the vape market further contributed to their increased marketability. Moreover, the lack of regulations and controls in manufacturing and commercialization allowed the tremendous expansion of the e-cig market (Gottlieb 2019).

There is a growing literature on the potential short- and long-term health effects associated with e-cigs and vaping, including mechanical injury, nicotine poisoning (Hua M. and Talbot 2016; Jonas AM and Raj 2020), and effects on the respiratory, cardiovascular system, and gastrointestinal systems (Darnell and Sofi; Hureaux et al. 2014; Thota and Latham 2014; Atkins and Drescher 2015; Modi et al. 2015; Moore et al. 2015; Ring Madsen et al. 2016). However, the recent EVALI outbreak posed even more serious questions about the health risks and safety of vaping.

To date, many medical case reports have been published, which highlighted the main features of the EVALI patients: a healthy white male, adolescent or young adult, predominantly vaping THC and vitamin E acetate (VEA) containing e-cigs, obtained from illicit sources (Blagev et al. 2019; Chatham-Stephens et al. 2019; Gaub et al. 2019; Ghinai

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

et al. 2019; Kalininskiy et al. 2019; Lewis et al. 2019; Lozier et al. 2019; Moritz et al. 2019; Navon et al. 2019; Perrine et al. 2019; Aberegg, Cirulis, et al. 2020; Adkins et al. 2020; Artunduaga et al. 2020; Blount et al. 2020; Chidambaram et al. 2020; Doukas et al. 2020; Ellington et al. 2020; Ghinai et al. 2020; Krishnasamy, Hallowell, Ko, Board, Hartnett, Salvatore, Danielson, Kite-Powell, Twentyman, Kim, Cyrus, Wallace, Melstrom, Haag, King, Briss, Jones, Pollack, Ellington, et al. 2020; Layden J. E. et al. 2020; Mikosz et al. 2020; Rao et al. 2020; Reagan-Steiner et al. 2020; Tanz et al. 2021). In addition, in a small percentage of cases, nicotine has also been linked to EVALI (Blount et al. 2020). The clinical signs and symptoms of EVALI are unspecific, similar to an acute viral infectious disease or other respiratory diseases characterized by diffuse alveolar damage and hypoxemia, therefore, the diagnosis is a process of elimination. As clearly stated from CDC, the main diagnostic criteria are: 1) history of e-cigs vaping in the 90 days before the onset of the symptoms; 2) signs of pulmonary infiltrates, such as opacities, on chest radiograph, or ground-glass opacities on chest-computed tomography (CT); 3) respiratory symptoms in absence of pulmonary infection or any alternative diagnosis for lung injury (CDC 2019).

Although the CDC investigations indicated that counterfeit THC/VEA containing e-cigs were strongly linked to the EVALI outbreak based on the presence of THC and VEA in patients' bronchoalveolar-lavage (BAL) (Blount et al. 2020), the presence of many more toxicants, including pesticides, oils, diluents, plasticizers in the illicit THC vaping products (Muthumalage, Friedman, et al. 2020; Ciolino, Falconer, et al. 2021; Lu SJ et al. 2021), and the decreased but not erased number of EVALI cases even after banning the VEA as well as illicit vaping products (Helfgott et al. 2022; Lim et al. 2022; Schaffer et al. 2022; Singh A 2022), increased the needs for a comprehensive physicochemical and toxicological properties of THC/VEA e-cig vapors.

While to date many efforts have been made to characterize physicochemically and toxicologically the nicotine-based e-cig vapors (Williams et al. 2013; Zhao et al. 2016; Zhao, Nelson, et al. 2018; Zhao, Zhang, et al. 2018; Hwang et al. 2020; Lee M-S and Christiani 2020), the literature regarding vapors emitted from THC/VEA-based e-liquids is very scarce, making it difficult for health risk assessors to perform risk assessment evaluations. To date, the majority of published studies focus on the physicochemical characterization (Meehan-Atrash et al. 2019; Duffy B et al. 2020; Jiang et al. 2020; Lanzarotta et al. 2020; Mikheev et al. 2020; Muthumalage, Friedman, et al. 2020; Wagner et al. 2020; Ciolino, Falconer, et al. 2021; Ciolino, Ranieri, et al. 2021; Duffy BC et al. 2021; Gonzalez-Jimenez et al. 2021; Guo et al. 2021; Kovach et al. 2021; Lu SJ et al. 2021; Lynch et al. 2021; Brosius et al. 2022; Marrocco et al. 2022; McGuigan et al. 2022; Mikheev and Ivanov 2022) or biological *in vivo/in vitro* assessment (Muthumalage and Rahman 2019; Bhat et al. 2020; Jiang et al. 2020; Matsumoto et al. 2020; Muthumalage, Lucas, et al. 2020a; Marrocco et al. 2022; Matsumoto et al. 2022) of e-liquids or vapors generated from a single e-liquid compound (i.e., THC or VEA or other additives). Despite the paucity of data, many lung irritants and toxicant chemicals have been identified in the vaping emissions, which can play crucial roles in the development of EVALI, such as carbonyls, alkyl alcohols, esters, carboxylic acids, short-chain alkanes, silicon compounds, hydrocarbons, volatile organic compounds (VOC), terpenes, reactive oxygen species (ROS)

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

and heavy metals, which have been found to exert varying degrees of cytotoxicity, alveolar epithelial damage and lung inflammation both *in vivo* and *in vitro*.

The complex chemistry of these chemicals depends on many variables, such as e-liquid composition, the device type (coil materials, heating power, operational voltage, temperature, etc.), and users puffing topography. The lack of regulations on manufacturing and commercialization allows for wide customizability of the devices that consequently drives the generation of a variety of chemical mixtures in the e-cig vapors, in which the toxic components can potentially exert a synergistic effect in the development of EVALI.

Moreover, the lack of standardized methodologies to generate e-cig emissions under "real-world" vaping conditions prevents the generation of reliable and generalizable physicochemical and toxicological characterization data, which are necessary to link specific properties of e-cig vapors to the etiopathogenesis of EVALI.

The current risk uncertainties related to EVALI are also hindered by the limited and inconsistent clinical data. Many pieces of information are often missing, improperly collected, or misreported, on the human behavior, clinical history, specimen collection, or analysis. The limited physicochemical and toxicological data based on "real world" vaping conditions also make it difficult to derive proper hazard characterization data and understand potential mechanistic pathways related to EVALI.

This review aims to provide a comprehensive and critical appraisal of the existing literature on the clinical and epidemiological aspects of EVALI, as well as the physicochemical and toxicological characterization of vaping emissions associated with the EVALI syndrome in order to identify current knowledge gaps and future research needs.

2 Methods.

Online searches were performed using, Science.gov (www.science.gov), PubMed, EMBASE, and Web of Science search engines with the search phrases: "electronic cigarette or vaping and associated lung Injury", "EVALI", "electronic cigarette and acute lung injury", "vaping and acute lung injury", "electronic cigarette and pneumonia", "vaping and pneumonia", "EVALI and vitamin E acetate", "EVALI and tetrahydrocannabinol", "electronic cigarette and vitamin E acetate", "vaping and vitamin E acetate", "electronic cigarette and tetrahydrocannabinol", "vaping and tetrahydrocannabinol", "electronic cigarette and acute respiratory distress syndrome", "vaping and acute respiratory distress syndrome". A literature search for regulations and policies related to electronic cigarettes was also performed. This search included the Food and Drug Administration (FDA), Centers for Disease Control and Prevention (CDC), Food and Drug Administration's Center for Tobacco Products (FDA-CTP), and the World Health Organization (WHO). For this review, only the papers that reported clinical case reports, physicochemical characterization of emissions generated from THC and VEA e-cigs, and *in vivo/in vitro* toxicological studies associated with the EVALI syndrome, as defined by the CDC, were included. All other studies evaluating the general health consequences of e-cigs, as well as toxicological and physicochemical characterization of emissions not directly associated with EVALI

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

syndrome, were excluded. The search was also restricted to peer-reviewed publications in English from the years 2019–2022.

3 Results and Discussion.

A total of 3903 peer-reviewed articles were identified and then screened for duplicates. It is worth noting that editorials, commentary, notes, conference papers, and perspective papers were excluded from the review. Finally, 186 peer-reviewed articles specifically related to EVALI, THC, and VEA were identified and reviewed. Among these articles, 161 were medical reports, including 85 clinical case reports, 59 clinical case series, 17 epidemiological reports, and 25 were research articles addressing the physicochemical (18 studies) and toxicological (7 studies) characterization of the e-cig liquids or vapors. In more detail:

3.1 Demographic pattern, prior medical history, and symptoms manifestation of EVALI patients.

The analysis of the patients from the 161 medical reports showed that the predominant demographic pattern of the EVALI patients is a healthy white male, adolescent, or young adult. In more detail, among the 15,748 cases reported and summarized in supplemental Table S1, 65% of patients were males, and 35% females (Figure 1A). 37% of 15,748 patients had an age between 18 and 24 years, followed by age 25–34 (26%), 13–17 (17%), 35–44 (16%), 45–64 (16%) and over 65 (4%) (Figure 1B). Non-Hispanic White adults (68%) were more likely than Hispanic (18%), Non-Hispanic black (14%), Non-Hispanic Asian (3%), or Native American (1%) to develop EVALI (Figure 1C) (Blagev et al. 2019; Chatham-Stephens et al. 2019; Gaub et al. 2019; Ghinai et al. 2019; Kalininskiy et al. 2019; Lewis et al. 2019; Lozier et al. 2019; Moritz et al. 2019; Navon et al. 2019; Perrine et al. 2019; Aberegg, Cirulis, et al. 2020; Adkins et al. 2020; Artunduaga et al. 2020; Chidambaram et al. 2020; Doukas et al. 2020; Ellington et al. 2020; Ghinai et al. 2020; Heinzerling et al. 2020; Krishnasamy, Hallowell, Ko, Board, Hartnett, Salvatore, Danielson, Kite-Powell, Twentyman, Kim, Cyrus, Wallace, Melstrom, Haag, King, Briss, Jones, Pollack, Ellington, et al. 2020; Layden J. E. et al. 2020; Mikosz et al. 2020; Rao et al. 2020; Reagan-Steiner et al. 2020; Hassoun et al. 2021; Kligerman et al. 2021; Sangani et al. 2021; Tanz et al. 2021; Helfgott et al. 2022; Podguski et al. 2022; Schaffer et al. 2022; Singh A 2022).

Interestingly, 17% of 15,748 patients were between 13 and 17 years of age, which may be related to the current spread of e-cigs among high school students (27.5%, 4.11 million, in 2019) and middle school students (10.5%, 1.24 million, in 2019) (Cullen et al. 2019). Despite the measures taken at the local, state, or federal level to moderate the epidemic of e-cigs among the younger population, including increasing the minimum age for purchase from 18 to 21 years (Congress 2019) and prohibition of attractive advertisements or packaging (FDA 2018), still, the number of middle or high school students currently vaping is not declining.

The case reports were also screened for pre-existing conditions. Even though the majority of EVALI patients were healthy or without any documented pre-existing condition (80% of

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

15,748 patients) (Figure 1D), from the records available, some patients reported suffering from “one or more” and “two or more” chronic conditions (Blagev et al. 2019; Gaub et al. 2019; Lewis et al. 2019; Ghinai et al. 2020; Mikosz et al. 2020). Specifically, among the patients that reported pre-existing conditions (n=3,171/15,748, 20%) the most common referred disorders included mental health diseases (n=1,205/3,171, 38%), of whom 30% (n=362/1,205) suffering from mental behavioral disorder, 26% (n=313/1,205) anxiety, 21% (n=253/1,205) depression, 17% (n=205/1,205) substance use disorder, and 6% (n=73/1,205) attention deficit hyperactivity disorder. In addition, among the 3,171 patients, 37% were former/current tobacco smokers, 37% were former/current marijuana smokers, and 31% reported chronic respiratory diseases (asthma, chronic obstructive pulmonary disease, obstructive sleep apnea) (Figure 1D) (Blagev et al. 2019; Chatham-Stephens et al. 2019; Gaub et al. 2019; Ghinai et al. 2019; Kalininskiy et al. 2019; Lewis et al. 2019; Lozier et al. 2019; Moritz et al. 2019; Navon et al. 2019; Perrine et al. 2019; Aberegg, Cirulis, et al. 2020; Adkins et al. 2020; Artunduaga et al. 2020; Chidambaram et al. 2020; Doukas et al. 2020; Ellington et al. 2020; Ghinai et al. 2020; Krishnasamy, Hallowell, Ko, Board, Hartnett, Salvatore, Danielson, Kite-Powell, Twentyman, Kim, Cyrus, Wallace, Melstrom, Haag, King, Briss, Jones, Pollack, Ellington, et al. 2020; Layden J. E. et al. 2020; Mikosz et al. 2020; Rao et al. 2020; Reagan-Steiner et al. 2020; Pitlick et al. 2021; Reddy et al. 2021; Regmi et al. 2021; Tanz et al. 2021; Schaffer et al. 2022). Other pre-existing syndromes referred to by EVALI patients were cardiovascular diseases (i.e. hypertension, heart failure, and congenital malformation), chronic pain, metabolic diseases (i.e. diabetes mellitus and obesity), gastrointestinal diseases (i.e. chronic liver diseases, gastroesophageal reflux, and inflammatory bowel diseases) (Figure 1D), allergies, immune suppression, chronic kidney diseases, and seizures/epilepsy (Supplemental Table S1) (Blagev et al. 2019; Chatham-Stephens et al. 2019; Gaub et al. 2019; Ghinai et al. 2019; Kalininskiy et al. 2019; Lewis et al. 2019; Lozier et al. 2019; Moritz et al. 2019; Navon et al. 2019; Perrine et al. 2019; Aberegg, Cirulis, et al. 2020; Adkins et al. 2020; Artunduaga et al. 2020; Chidambaram et al. 2020; Doukas et al. 2020; Ellington et al. 2020; Ghinai et al. 2020; Krishnasamy, Hallowell, Ko, Board, Hartnett, Salvatore, Danielson, Kite-Powell, Twentyman, Kim, Cyrus, Wallace, Melstrom, Haag, King, Briss, Jones, Pollack, Ellington, et al. 2020; Layden J. E. et al. 2020; Mikosz et al. 2020; Rao et al. 2020; Reagan-Steiner et al. 2020). The correlation between conventional cigarette smoke, chronic respiratory disease, such as asthma or chronic obstructive pulmonary disease (COPD), and EVALI is intuitive. Cigarette smoke affects almost every organ in the body, causing many diseases, including coronary heart disease, stroke, COPD, and lung cancer (CDC 2014). The underlying epithelial inflammatory status and lung damage due to the chemicals, irritants, and toxicants released in the cigarette smoke can sensitize the respiratory epithelium and induce a stronger response even against inhalants that are normally well-tolerated. In contrast, mental health and substance addiction have been underestimated in vapers and smokers (Patten 2021), and very few studies have examined the correlation between substance abuse/addiction and vaping (Young-Wolff et al. 2021), while none are available on the correlation with EVALI.

The initial EVALI manifestation, that drove the patients to the emergency department, was unspecific, but included respiratory, gastrointestinal, and constitutional symptoms (fever, weight loss, fatigue, etc.), resembling the general presentation of a relatively acute viral

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

disease (Figure 1E) (Blagev et al. 2019; Chatham-Stephens et al. 2019; Gaub et al. 2019; Ghinai et al. 2019; Kalininskiy et al. 2019; Lewis et al. 2019; Lozier et al. 2019; Moritz et al. 2019; Navon et al. 2019; Perrine et al. 2019; Aberegg, Cirulis, et al. 2020; Adkins et al. 2020; Artunduaga et al. 2020; Chidambaram et al. 2020; Doukas et al. 2020; Ellington et al. 2020; Ghinai et al. 2020; Heinzerling et al. 2020; Krishnasamy, Hallowell, Ko, Board, Hartnett, Salvatore, Danielson, Kite-Powell, Twentyman, Kim, Cyrus, Wallace, Melstrom, Haag, King, Briss, Jones, Pollack, Ellington, et al. 2020; Layden J. E. et al. 2020; Mikosz et al. 2020; Rao et al. 2020; Reagan-Steiner et al. 2020; Kligerman et al. 2021; Sangani et al. 2021; Tanz et al. 2021; Podguski et al. 2022; Schaffer et al. 2022; Singh A 2022). In particular, 95% of the 15,748 patients experienced respiratory symptoms, more frequently including dyspnea and cough (>80% of 15,748), accompanied by chest pain, hemoptysis, dyspnea on exertion, and/or wheezing. In addition, 80% of the 15,748 patients reported gastrointestinal symptoms, characterized primarily by emesis and nausea, followed by diarrhea, and abdominal pain. Lastly, 86% of the 15,748 patients manifested constitutional symptoms, including fever, fatigue, chills, weight loss, night sweats, headache, and myalgia (Supplemental Table S1) (Blagev et al. 2019; Chatham-Stephens et al. 2019; Gaub et al. 2019; Ghinai et al. 2019; Kalininskiy et al. 2019; Lewis et al. 2019; Lozier et al. 2019; Moritz et al. 2019; Navon et al. 2019; Perrine et al. 2019; Aberegg, Cirulis, et al. 2020; Adkins et al. 2020; Artunduaga et al. 2020; Chidambaram et al. 2020; Doukas et al. 2020; Ellington et al. 2020; Ghinai et al. 2020; Heinzerling et al. 2020; Krishnasamy, Hallowell, Ko, Board, Hartnett, Salvatore, Danielson, Kite-Powell, Twentyman, Kim, Cyrus, Wallace, Melstrom, Haag, King, Briss, Jones, Pollack, Ellington, et al. 2020; Layden J. E. et al. 2020; Mikosz et al. 2020; Rao et al. 2020; Reagan-Steiner et al. 2020; Kligerman et al. 2021; Sangani et al. 2021; Tanz et al. 2021; Helfgott et al. 2022; Podguski et al. 2022; Singh A 2022). The duration of symptoms before hospitalization was generally 20 days (range 1–240 days) (Supplemental Table S1) (Blagev et al. 2019; Chatham-Stephens et al. 2019; Gaub et al. 2019; Lewis et al. 2019; Adkins et al. 2020; Ghinai et al. 2020; Mikosz et al. 2020; Rao et al. 2020).

3.2 Clinical presentation: signs and symptoms of EVALI.

The 161 identified medical case reports present a complete clinical history of 1160 cases of EVALI. Their main findings are summarized in Tables 1–4 and Supplemental Table S1.

Table 1 provides a summary of the clinical presentation of the EVALI patients, at their first admission to the emergency department or urgent care facility.

The observed acute lung injury was associated with a heterogeneous pattern of clinical signs and symptoms, including temperature ≥38 °C, heart rate >100 beats/min, respiratory rate >20 breaths/min, oxygen saturation <95% on room air or with supplemental oxygen, leukocytosis with neutrophil predominance, increased inflammatory biomarkers [including erythrocyte sedimentation rate (ESR) >30 mm/hr, C-reactive protein (CRP)> 10 mg/l, procalcitonin >0.07 ng/ml, lactate dehydrogenase (LDH) >280 U/L and pro-BNP >125 pg/ml], and absence of bacterial, viral or fungal infection, or autoimmune disease (Table 1 and S1). Lung auscultation was positive for diffuse bibasilar crackles, wheezes, or rhonchi; when performed, the pulmonary function test revealed either an obstructive or a restrictive

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

pattern, while the arterial blood gas analysis was mostly diagnostic for a primary respiratory alkalosis, both documented only in a few patients. Interestingly, the urine toxicological screening was reported only in a small number of case reports, and it resulted often positive for cannabinoid use. (Table 1 and S1)

The heterogeneity of clinical signs and symptoms was reflected in the varying pathologic findings, at chest radiograph and CT, BAL, and lung biopsy (Tables 2–4 and S1). While chest radiographs and CT scan findings are variable in 929 EVALI patients, they showed a predominant pattern characterized by diffuse bilateral ground-glass opacity (71%, n=661), parenchymal consolidation (12%, n=111) bilateral parenchymal/nodular opacities (24%, n=228), bilateral interstitial infiltrates (19%, n=175), interlobular septal thickening (17%, n=158) and pleural/subpleural sparing (43%, n=399). Very few cases have been described showing bilateral pleural effusion (11%, n=106), pneumothorax (2%, n=20), pneumo-mediastinum (4%, n=38), mediastinal/hilar lymphadenopathy (16%, n=147), and pulmonary emboli (0%, n=3). (Table 2).

In a cohort of 304 patients (Table 3 and S1), bronchoscopy and collection of broncho-alveolar lavage fluid (BALF) showed the absence of any infectious agent (bacteria, virus, and fungi), fundamental for the exclusion of any other possible cause of disease. The cytological findings revealed a non-specific cellular pattern, characterized by increased total cell count with the predominance of neutrophils (38%, n=120), macrophages (22%, n=68), lymphocytes (3%, n=10), or eosinophils (2%, n=7), which was not revealing in the diagnosis of EVALI. The increased number of red and white blood cells was registered in 7% (n=21) and 7% (n=22) of patients respectively. In contrast, a more common finding in BAL of EVALI patients was the lipid-laden macrophages reported in 50% (n=158) of patients.

The presence of lipid-laden macrophages in the alveolar or interstitial spaces of vaping patients was first noted in a case of acute lung injury in 2012 (McCauley et al. 2012), and subsequently, it was commonly detected in the BAL of EVALI patients, which initially misguided the physicians toward the diagnosis of exogenous lipoid pneumonia, possibly correlated to the presence of VEA in the e-cigs. This finding was later found to be not specific to EVALI, since it was detected also in the BAL of healthy adult smokers, e-cig users, and never-smokers (Shields Peter G et al. 2020), and was not always consistent with histopathological or radiological evidence of exogenous lipoid pneumonia (Butt et al. 2019).

On 85 BALF samples out of 313, chemical analysis was also performed aimed at detecting the presence of a causative agent such as THC, VEA, nicotine, or metabolites. THC, VEA, and nicotine were detected in 70 (82%), 82 (96%), and 46 (54%) samples respectively. (Blount et al. 2019; Taylor et al. 2019; Blount et al. 2020); other chemicals were found in BALF and were probably associated with EVALI symptoms, like cannabinoid (CBD) oils, coconut oil, and terpenes, such as limonene (Blount et al. 2019; Taylor et al. 2019; Blount et al. 2020). (Table 3 and S1)

The cyto- and histo- pathological assessments through the trans-bronchial lung biopsy, summarized in Table 4 and S1, showed a variety of patterns including acute lung injury, diffuse alveolar damage, and organizing pneumonia in 21%, 25%, and 46% (total cases

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

n=249) respectively, accompanied by foamy macrophages in airspace in 76% of the 249 cases. The most common findings were type II pneumocytes hyperplasia, acute fibrinous pneumonitis with organization, fibrinous exudates in airspaces, interstitial chronic inflammation, respiratory bronchiolitis, lymphocytic infiltration, mild interstitial fibrosis, diffuse alveolar hemorrhage, and lipoid pneumonia.

To date, neither the bronchoscopy/BALF nor the lung biopsy is required for the diagnosis of EVALI, mostly because the main purpose of these exams is the exclusion of pulmonary infection or alternative cause of disease. In this regard, the chemical analysis of the BAL can be beneficial to detect chemical toxic compounds involved in the development of EVALI (Brosius et al. 2022). Many variables can negatively affect the result, such as the time window between the last use of e-cigs and bronchoscopy, variation in collection technique, and fluid dilution. Nevertheless, on a small number of samples (n=85) the chemical analysis of BALF was crucial to detect THC, VEA, and nicotine (82%, 96%, and 54% of samples respectively), even when any THC use was denied, as well as other chemicals probably related to EVALI, such as cannabinoid oils, coconut oil, and terpenes, such as limonene (Blount et al. 2019; Taylor et al. 2019; Blount et al. 2020). In addition, making the toxicological testing for cannabinoids routinely would be beneficial in reducing EVALI diagnosis delay, especially for those patients that hide this crucial information.

In summary, such differences in clinical and radiographic EVALI manifestation may be due to a variety of factors, including underlying conditions, individual host response to the inhaled substances, but most importantly, the diversity of toxic compounds inhaled, which are still difficult to determine, given the multitude of e-cig compositions and operating parameters of the cartridges prevalent among the vaping population.

3.3 Vaping devices, e-liquids, and frequency of vaping by EVALI patients.

Among the 11,350 EVALI patients that disclosed information on vaping products and behavior, an average of 34% (n=3879) and 17% (n=54) patients reported exclusive use of THC- and nicotine-based e-cigs, respectively, while 51% (n=5742) patients reported using both THC and nicotine e-cigs (Figure 2A). Moreover, 2% (n=227) of patients reported exclusive CBD oil e-cigs, while 8% (n=851) reported using CBD and THC, 4% (n=397) reported using CBD and nicotine, and 10% (n=1078) reported using all three substances (THC, nicotine, and CBD) in e-cigs. (Blagev et al. 2019; Chatham-Stephens et al. 2019; Gaub et al. 2019; Ghinai et al. 2019; Layden Jennifer E. et al. 2019; Lewis et al. 2019; Lozier et al. 2019; Moritz et al. 2019; Navon et al. 2019; Perrine et al. 2019; Taylor et al. 2019; Adkins et al. 2020; Chidambaram et al. 2020; Ellington et al. 2020; Krishnasamy, Hallowell, Ko, Board, Hartnett, Salvatore, Danielson, Kite-Powell, Twentyman, Kim, Cyrus, Wallace, Melstrom, Haag, King, Briss, Jones, Pollack, Ellington, et al. 2020; Pray et al. 2020; Rao et al. 2020; Tanz et al. 2021) (Figure 2A). In addition to vaping, patients reported using combustible marijuana, combustible tobacco, or both. (Ghinai et al. 2019; Layden Jennifer E. et al. 2019; Lewis et al. 2019; Adkins et al. 2020) (Supplemental Table S1)

Very few papers described in more detail the length of use, type of device, brand, and source of e-cigs or e-liquids. With regard to the type of device used among the interviewed patients, irrespective of THC or nicotine e-liquids used, the majority used disposable type of

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

e-cigs (n=135/187, 72%), followed by reusable devices (n=63/187, 34%), reusable devices for wax or dry herbs (n= 41/187, 22%), vape rig (n=36/187, 20%), and pods for vaping salts (n=24/187, 13%).(Blagev et al. 2019; Ghinai et al. 2019; Perrine et al. 2019) (Figure 2B)

The frequency of THC vaping reported by EVALI patients is summarized in Figure 2C. 62% (n=1677/2727) reported daily vaping use, with 54% (n=1473/2727) of them reporting between 1–5 times/day, 43% (n=1182/2727) more than 5 times/day, and 24% (n=654/2727) more than 25 times/day. 25% (n=691/2727) reported vaping 2–3 times/week, 6% (n=164/2727) a few times per month, and 16% (n=427/2727) monthly or less (Figure 2C) (Blagev et al. 2019; Gaub et al. 2019; Ghinai et al. 2019; Lewis et al. 2019; Navon et al. 2019; Taylor et al. 2019; Adkins et al. 2020; Ellington et al. 2020; Pray et al. 2020; Rao et al. 2020). Regarding the duration of being an e-cig user, Baglev et al. reported that of the 23 patients examined, 43% vaped for less than 1-year, 17% vaped for 1–2 years, 26% vaped for 2–3 years, 13% vaped for ≥ 3 years. (Blagev et al. 2019) The duration of use was not correlated to the onset of symptoms. (Supplemental Table S1)

The most common brands of THC-containing devices used were Dank Vape, followed by Rove, Golden Gorilla, Smart Carts / Exotic Carts, Chronic Carts, and Cereal Carts. (Figure 2D). Interestingly, 81% (n=1439/1773) of them were obtained from informal sources, such as family or friend, illicit dealer, online, or out-of-state dispensary, but only 15% (n=271/1773) of THC products were purchased from formal sources, including dispensary, vape or smoke shop, pop-up shop, or grocery, drug, or convenience store. (Blagev et al. 2019; Gaub et al. 2019; Ghinai et al. 2019; Lewis et al. 2019; Navon et al. 2019; Adkins et al. 2020; Ellington et al. 2020; Pray et al. 2020; Rao et al. 2020) (Figure 2E)

Because, as mentioned before, 64% of 11,244 EVALI patients also reported the use of nicotine-containing e-liquids, the frequency of use, inhalation device, and source were investigated as well. Similarly to the THC users, 69%, of the 2100 nicotine users vaped daily, among whom 64% reported vaping frequency more than 5 times/day and 55% more than 25 times/day. (Supplemental Table S1). (Blagev et al. 2019; Gaub et al. 2019; Ghinai et al. 2019; Lewis et al. 2019; Navon et al. 2019; Taylor et al. 2019; Adkins et al. 2020; Ellington et al. 2020; Rao et al. 2020) The most common brands of nicotine-based devices were Juul, Njoy, and Smok, (Blagev et al. 2019; Gaub et al. 2019; Ghinai et al. 2019; Rao et al. 2020), more frequently (n=845/1280, 66%) purchased through formal sources (such as vape shops and convenience stores) than informal sources (n=341/1280, 27%) (online dealers, friends, out of state dispensary). (Ghinai et al. 2019; Lewis et al. 2019; Adkins et al. 2020; Ellington et al. 2020; Rao et al. 2020) (Supplemental Table S1).

Previous studies have highlighted the simultaneous increase of e-cigs and/or cannabis use and mental disorders such as depressive symptoms and suicidality in the young population, emphasizing the need for screening, prevention, and intervention strategies to help mitigate both substance abuse and mental health outcomes (Chadi et al. 2019). This issue is particularly relevant in those states where THC e-cigs are illegal for non-medical use, such as Utah or Minnesota, where the burden of EVALI reached the highest rate nationally (Lewis et al. 2019; Cole et al. 2021), which could be attributed to the high prevalence of illicit THC-cartridges (Arons et al. 2021).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

No major difference was found in the use of disposable and reusable e-cigs (72% vs 56% of 187, respectively); therefore, it was not possible to correlate the type of device utilized to the specific active ingredient (THC or nicotine). Nonetheless, the commercially available reusable CCell 510 thread cartridges were most commonly associated with EVALI patients, because of the higher suitability for a thick and viscous liquid, such as THC (Wagner et al. 2020), high rate of availability and reproducibility in the illicit market, and high customizability by the users and manufacturers. The latter aspect is particularly important because the inappropriate manipulation of cartridges and e-liquid compositions often evades oversight from the regulatory agencies and increases the likelihood of generating and inhaling toxic chemical vapors.

As clearly stated by the Centers for Disease Control and Prevention (CDC), much crucial information is missing due to the lack of a standardized data collection methodology, which generates an obvious inconsistency. The information on patients' demographics and vaping behavior was collected through anonymous surveys or telephone interviews taken from the patients or their families. The applied methodologies give space to a lot of intrinsic bias, such as selection bias, recall bias, response bias, and social desirability bias. In addition, the patients or their families were not always aware of the chemical substances contained in the cartridges, especially because the majority of vaping products were obtained from an illicit/informal source, leading to unreliable reporting. In addition, reporting potentially mislabeled cartridges leads to exposure's misclassification errors in epidemiological studies. For all these reasons, it is difficult to draw strong and generalizable conclusions about the factors responsible for the evolution of EVALI.

A more accurate characterization of the vaping history is needed, especially in the younger population, including start date, last use, and method of use (aerosol, dabbing or dripping), length and frequency of vaping, device type (refillable or disposable), product brand name, source of THC- or nicotine-containing products, relative composition of the e-liquid components, number of cartridges consumed per day and volume of e-liquids vaped per day. Current or former use of combustible tobacco or marijuana or other substance abuse should be included as well.

3.4 Physicochemical characterization of emissions from vaping.

The topic of physicochemical characterization of emissions from e-cigs has been widely studied since their release in the global market in 2007 and the complex chemistry of the emissions is well-documented (Margham et al. 2016; Zhao et al. 2016; Pourchez et al. 2018; Zhao, Nelson, et al. 2018; Zhao, Zhang, et al. 2018; El-Hellani et al. 2019; Erythropel et al. 2019; Omaiye et al. 2019; Strongin 2019; Jiang et al. 2020; Nicol et al. 2020). Of special note is the lack of regulations concerning manufacturing and commercialization of e-cig devices. As a result, a plethora of devices is available including widely customizable ones in terms of temperature, operational voltage, puffing duration, and e-liquid composition. This enormous variability makes it difficult to characterize the emissions physicochemically and toxicologically and to generalize or predict their potential health risks.

Furthermore, the available literature on the topic is limited to the physicochemical characterization of emissions from nicotine-based e-liquids, while very little is known for

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

the case of THC, VEA, or their combination-based e-liquids. We found only ten studies focusing on the characterization of real-world liquids or emissions from **counterfeit or patient-provided** cartridges (Table 5), and nine on the characterization of gas and particles released from **in-house prepared** e-cigs containing VEA or THC/VEA. (Table 6).

On a special note, the physical inspection of the patient-provided cartridges exhibited severe burn marks, probably due to the high operating voltage and the resulting high temperature of the e-liquid. Nickel and chromium heating coils were detected in all devices, along with other metals present in the filaments, battery contact, and ceramics. Other metals identified included Cu, Pb, Au, Fe, Zr, Si, Al, Na, K, Ni, Sn (Wagner et al. 2020; Gonzalez-Jimenez et al. 2021). Other substances also found were phosphorus (P), silicon-rich rubbers, or fluorinated microplastics. Their presence in the e-cig cartridges raises concerns in terms of potential chemicals released during the vaping phase (Wagner et al. 2020).

The first investigation on the chemical composition of e-liquids from 38 samples collected from the first 10 New York cases of EVALI showed that compared to the marijuana medical products, the illicit cartridges contained a low concentration of cannabinoids (50% vs 80–90% in marijuana medical products), along with an unusual ratio of Δ^9THC/Δ^8THC isomers, due to the high volume of the synthetic Δ^8THC. In addition, high concentrations of diluents, such as VEA (64% of samples - concentration range 16–58%) and MCT (41% of samples - concentration range 3–24%) were also detected. (Duffy B et al. 2020) This trend was confirmed by further and later investigation nationwide, that showed the presence of additional cannabinoids in the EVALI patient-provided cartridges as well as in the aerosol generated from them, such as cannabichromene (CBC), cannabidiol (CBD) cannabidivarin (CBDV), cannabidiolic acid (CBDA), cannabigerol (CBG), cannabigerolic acid (CBGA), cannabinol (CBN), tetrahydrocannabinolic acid (THCA) and tetrahydrocannabivarin (THCV) (Ciolino, Ranieri, et al. 2021; Duffy BC et al. 2021; Guo et al. 2021; Lu SJ et al. 2021). All the illicit/patient-ptovided cartridges were found to contain various concentration of VEA, MCT, polyethylene glycol used as diluents either in combination or alone. (Ciolino, Falconer, et al. 2021; Duffy BC et al. 2021; Guo et al. 2021; Lu SJ et al. 2021). The most common terpenes reported were caryophyllene, limonene, myrcene (Lu SJ et al. 2021) (Table 5).

Numerous chemicals were identified in the e-liquids contained in counterfeit cartridges used by EVALI patients, including pesticide residues (such as myclobutanil and piperonyl butoxide-d_9, bifenazate, bifenthrin), 2,2-dimethoxybutane, tetramethyl silicate, decane, methyl esters, ethyl esters, siloxanes, and acetates, as well as pine rosin acids, pine rosin derived methyl esters, dipropylene glycol dibenzoate isomers, and sucrose acetate isobutyrate compounds, (Muthumalage, Friedman, et al. 2020; Ciolino, Falconer, et al. 2021; Lu SJ et al. 2021) (Table 5).

Chemicals detected in the emissions generated from counterfeit cartridges included n-butane, benzene, xylene, pentene, ethanol, acetone, ethylbenzene and toluene, PCP-polycaprolactone/household constituents (e.g. methacrolein, acetaldehyde, crotonaldehyde, formaldehyde etc.), other toxic compounds (e.g. acrolein, pentadiene compounds, hexane compounds, methyl vinyl ketone, etc.), and elements such as Si, Cu, Ni, and Pb

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

(Muthumalage, Friedman, et al. 2020; Gonzalez-Jimenez et al. 2021; McGuigan et al. 2022) (Table 5).

The majority of the detected chemicals, such as hydrocarbons, silicon conjugates and derivates, and VOCs, are known to be respiratory irritants, depressants, and paralytic agents, which could potentially cause dyspnea, chest tightness, and pulmonary edema (common symptoms among EVALI patients) (FDA 2012; Muthumalage, Friedman, et al. 2020; McGuigan et al. 2022). These chemicals can also physically interact with phospholipids and surfactants, inducing chemical pneumonitis, and interstitial and alveolar alterations, such as alveolar-capillary membranes dysfunction, pulmonary edema, and surfactant alteration, representative of acute lung injury (McKee et al. 2015). In addition, the identification of solvents, such as n-butane, a gaseous petroleum compound used in the illicit cartridge to increase the amount of THC released and retained in the lung (Varlet et al. 2016; Muthumalage, Friedman, et al. 2020; Ahmed et al. 2021), could be accounted for the atypical/eosinophilic pneumonia, acute lung injury and pulmonary edema, as described in some EVALI cases (Anderson R. P. and Zechar K. 2019; Stephens et al. 2020; Ahmed et al. 2021).

FDA's preliminary lab analysis, dated February 12, 2020, reported that among the 1090 samples collected from vaping devices and products containing liquid, packaging, or other documentation, related to the EVALI patients, 511 (50%) contained THC, 50% of which were diluted with VEA, in a concentration between 23% and 88%, while 29% of them were diluted with MCT. Moreover, through the chemical analysis of 677 out of the 1090 samples, directly linked to 95 EVALI patients identified with CDC case numbers, it was determined that 73% patients were exposed to THC, and among them, 81% were also exposed to VEA, 32% to aliphatic esters (e.g. triglycerides), and 9% to polyethylene glycol. (FDA 2020c)

Based on the presence of VEA in BAL and the liquids of THC-based e-cigs from EVALI patients (Duffy B et al. 2020; FDA 2020b; Muthumalage, Friedman, et al. 2020), the federal agencies, CDC and FDA, declared in the early 2020 THC and VEA the two most presumable causative agents of EVALI, even in the absence of strong mechanistic hypothesis of disease. Since then, few studies have investigated the physical and chemical properties of particles and gaseous byproducts generated from THC and VEA pyrolysis, summarized in Table 6. Indeed, we found only three papers attempting the analysis of the aerosol generated from VEA, THC, and their mixtures, (Mikheev et al. 2020; Marrocco et al. 2022; Mikheev and Ivanov 2022), while nine papers investigated the chemical analysis of liquid and vapors generated from various combination of THC, VEA, Terpenes (Meehan-Atrash et al. 2019; Lanzarotta et al. 2020; Lynch et al. 2021; Mikheev and Ivanov 2022), and two addressed the physical and chemical analysis of aerosol emitted by pyrolysis of VEA alone (Mikheev et al. 2020; Kovach et al. 2021) or single diluents, either as liquid or vapor (Jiang et al. 2020).

The aerosol characterization showed that on average, the emitted particle number concentration in the vapors ranged from 10^6 to 10^8 particles/cm^3, while the count median diameter varied from 50 to 200 nm, depending upon the device type, heating power, and puffing topography. Interestingly, for the case of VEA 100%, as the flow rate or the voltage increased, the count median diameter decreased while the particle number

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

concentration increased (Mikheev et al. 2020; Marrocco et al. 2022; Mikheev and Ivanov 2022). The total number concentration, mean and modal aerosol size of particles generated from different combinations of D8THC/VEA/Terpenes varied also according to the e-liquid composition and voltages, but without any apparent specific trend. The released VOC and total PM mass concentration significantly rose with increasing e-liquid VEA concentration and operational voltages. Specifically, the concentration of VOCs increased linearly or exponentially with time, within a range between 0.173 and 24.5 ppm, while the total PM mass concentration ranged widely between 67 and 910 mg/m^3, with the bulk of PM mass distributed between the $PM_{0.1}$ and $PM_{0.1–2.5}$; in both cases, the higher number was reached by emissions from VEA 100% at 5V. (Marrocco et al. 2022) (Table 6) The only three studies addressing the physical properties of the particles emitted from the pyrolysis of e-liquids containing different concentrations of THC, VEA and Terpenes confirmed that the e-liquid composition, device type, heating power, and puffing topography influenced the aerosol particles' size and concentration (Mikheev et al. 2020; Marrocco et al. 2022). Although these studies represent a first attempt to clarify the possible link between the nanoparticles released from e-cigs and EVALI, they highlighted the concept that there is a significant difference between vapors generated from individual e-liquid components (ie, VEA 100%) and e-liquid mixture (ie, Δ8THC + VEA + Terp): the combination of VEA with THC and terpenes would certainly affect the physical characteristics of released particles (size and number concentration) and induce chemical heterogeneity in the released particles and gaseous byproducts.

Lanzarotta et al investigated the chemical properties of vapor generated from the combination THC/VEA (~50:50 w/w) from a CCell cartridge connected to a vaping device, operated at 3.7V, with a puff duration of 4 seconds and an interval between puffs of 30 seconds, sampled at flow rate 1.0 liter/min, mimicking the real-word exposure. The main finding of the study was that the THC/VEA liquids exhibit sufficient chemical differences compared to the individual THC and VEA controls, and the chemical spectrum generated from the pure VEA vapor exhibited a carbonyl peak, similar to THC/VEA, which was absent in the case of THC-only vapor spectrum. (Lanzarotta et al. 2020) A similar study was subsequently performed by Lynch et al. Starting from the same e-liquid composition (THC/VEA ~50:50 w/w) and puffing topography (puff duration 4 sec, interval 30s, flow 1L/min), they measured the coil temperature at increasing operational voltages, from 3.0 V to 4.5 or 5V, using 6 in-house prepared cartridges, as well as one black-market cartridge and 1 "authentic" cartridge containing D9THC from EVALI investigations (Lynch et al. 2021). Regardless of the type of cartridges, the following degradant products were identified in the emitted vapors: D9THC, VEA, 1-pristene, durohydroquinone monoacetate (DHQMA), 4-acetoxy-2,3,5trimethyl-6-methylene-2,4-cyclohexadienone (ATMMC). However, as intuitively expected, they also measured a voltage-dependent increase of the coil temperature during vaping: from a range of 217–300°C at 3.0 V to 415–476° C at 5.0 V for the in-house prepared cartridges, to 454–510°C at 5.5 V and 548–632°C at 6V for black-market and authentic cartridges. (Lynch et al. 2021) This temperature trend was further confirmed by Mikheev at al, who reported a coil temperature rise dependent on chemical liquids and temperature setting. Specifically, the authors used the "Kind Dream" vape pen, loaded with combination of THC 100%,

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

THC/VEA 50%/50% w/w or VEA 100% and operated at 2 different temperature settings, low (177°C) and high (221°C), following a puffing protocol of 5 sec puff, 60 sec interval for 8 puffs. Interestingly, they found that regardless of the e-liquid composition, when operated at low temperature (177°C), the coil temperature was stably below 250°C; increasing the operational temperature to 221°C led to a rise of coil temperature up to 500–550°C, that was faster in cartridges containing the higher concentration of VEA (50%−100%). (Mikheev and Ivanov 2022)

In order to characterize the production of VOCs and other harmful and potentially harmful constituents (HPHCs) from THC pyrolysis, Meehan-Atrash et al. investigated the chemical composition of vapors generated from dabbing pure THC or the synthetic distillate THC:terpenes 90:10 v/v, compared to the vapor generated from vaping the mixture THC/Terpenes 90:10 v/v using a CCell cartridge vaporizer, operated at 3 voltages, 3.2 V, 4.0 V, and 4.8 V, with 1 puff of 55 ml volume over 3 seconds. The adsorption/thermal desorption gas chromatography−mass spectrometry (ATD-GCMS) helped to selectively identify the following chemical species in the gas phase: methacrolein, benzene, xylenes, toluene, styrene, ethylbenzene, isoprene, other non-target hydrocarbons, and total VOCs. Interestingly, as shown also by Marrocco et al. (2022) the relative amount of each species, as well as the other hydrocarbons, and total VOCs, increased depending on e-liquid composition (THC vs THC/Terpenes) and the operating voltage (when compared among the three vaping voltage conditions) (Meehan-Atrash et al. 2019).

Jiang et al. studied the vaping emission products from commonly used liquid diluents, such as propylene glycol (PG), vegetable glycerin (VG), VEA, vitamin e (VE), MCT oil, squalane (SQL), and triethyl citrate (TEC). It is worth noting that this study does not represent the real-world human exposures (cartridges containing only diluents are not commercially available). However, it was confirmed that the chemical composition of aerosols is very different from their parent e-liquid, due to the formation of new by-products during the vaping process. The detected new products included carbonyls, alkyl alcohols, esters, carboxylic acids, and short-chain alkanes, likely resulting from thermal decomposition and oxidation of liquid diluents. In particular, VEA and VE released carbonyls, long-chain alcohols, and quinone-like products (Jiang et al. 2020).

From the analysis of the degradation products of VEA 100% or THC/VEA 50%/50% pyrolysis, several products were identified. In the vapors generated from VEA 100%, the most common by-products were 1-pristene, durohydroquinone monoacetate (DHQMA), duroquinone (DQ),, while 2,6,10,14-tetramethyl-1-pentadecene (TMPD) was not confirmed (Mikheev et al. 2020; Kovach et al. 2021); in addition, in vapor generated from combination of THC/VEA 50%/50%, but not in VEA 100%, 4-acetoxy-2,3,5trimethyl-6-methylene-2,4-cyclohexadienone (ATMMC) was also found (Lynch et al. 2021) (Table 6).

In summary, the main finding of the presented studies is that there is a substantial difference in the chemical composition and structure between the parent e-liquid and the generated vapors (Jiang et al. 2020; Mikheev et al. 2020), and between the vapors generated from a single e-cig constituent compared to the vapors from real-world e-liquid mixtures (Meehan-Atrash et al. 2019; Lanzarotta et al. 2020; Lynch et al. 2021; Marrocco et al. 2022; Mikheev

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

and Ivanov 2022). Although the process toward understanding the possible cause of EVALI starts with the identification of the e-liquids ingredients, it is not useful, besides being unrealistic, to rely only on the e-liquids' physicochemical properties aiming to clarify the mechanistic pathway of EVALI, since it is clear that the thermal degradation generates byproducts with substantial differences from the parental e-liquids, and increases the likelihood of having a mixture of toxic chemicals in the vapor, which can exert synergistic effects on the respiratory system, and potentially leading to the development of EVALI.

An interesting hypothesis on the causative agent of EVALI has been the possibility of the release of ketene from the thermal degradation of VEA. Ketene is a highly reactive and highly toxic molecule, produced by cleavage of the acetate group from the whole VEA molecule (Committee on Acute Exposure Guideline Level et al. ; National Institute for Occupational Safety and Health NIOSH 1994). Although very few and historic studies have documented that the minimum lethal in-air concentration of ketene is 200 ppm, causing death after single 10-min inhalation exposure in primates, and concentrations as low as 5 ppm can trigger severe alveolar damage and secondary cerebral anoxia 24 h after inhalation in humans and animals (Committee on Acute Exposure Guideline Level et al. ; Treon et al. 1949; National Institute for Occupational Safety and Health NIOSH 1994), to date, the role of ketene in the development of EVALI, its generation in the vaping process, and consequently its presence in the BAL are still unknown. Indeed, the chemical analysis of VEA and VE vaping emissions under real-world vaping conditions did not identify the presence of ketene (Mikheev et al. 2020; Wu and O'Shea 2020; Mikheev and Ivanov 2022). Recently, few studies have addressed the possibility to generate ketene in the vaping atmosphere, however many discrepancies have been characterized: 1) the difference between the VEA boiling point 220˚C, and the temperature at which e-cigs typically operate, 170°C, in a wet-through-wick condition (Chen W et al. 2018; Dibaji et al. 2018); 2) the high power (30W or 50W - 11.0 or 15.5 A, respectively) (Wu and O'Shea 2020) or high temperature (700°C-1000°C) (Narimani and da Silva 2020) of VEA pyrolysis necessary to generate ketene not comparable with the power and temperature of real-world e-cigs (3.6 V, 9.4 W, 2.5 A), at which ketene was not detectable in vaping emissions (Jiang et al. 2020). Nevertheless, Narimani et al revealed that such high temperatures could be reached in "dry-hits" conditions, i.e. in those devices where the temperature is not automatically adjusted based on the e-liquid level, and lower e-liquid levels increase the operating temperature (Narimani and da Silva 2020). This information is particularly important if related to the fact that THC counterfeit vaping cartridges from EVALI patients showed severe burn marks (extensive charred, blackened material on the inside and outside of the oil-soaked ceramics and insulation), distinctive signs of devices that were operating at very high internal temperatures (Jiang et al. 2020).

To better understand and predict the lung response to the e-cig emissions, it is of great importance to understand the chemical and physical properties of vapors, including both the gaseous and particulate phase, and their diffusion/deposition patterns in the various regions of the respiratory tract, that can help explain the distinctive health effects from such complex exposures. The lack of standardized methodologies and platforms to generate and characterize vaping emissions under real-world consumer vaping conditions prevents

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

the generation of reliable and generalizable physicochemical data, which are necessary to understand the etiopathogenesis of EVALI.

3.5 Toxicological studies related to EVALI

While the toxicological properties of aerosols emitted from nicotine-based e-cigs have been under investigation in the last decade, there is still a limited number of studies focusing on the *in vivo/in vitro* toxicity of vapors generated from THC/VEA e-cigs associated with EVALI syndrome. Indeed, very few studies have focused on the toxicity of aerosols emitted from the use of pure VEA or other diluents, while only one study has investigated the effect of THC/VEA pyrolysis byproducts (including both particles and vapors) on lung epithelial cells, thus highlighting a major knowledge gap preventing the understanding of the mechanistic pathways leading to EVALI.

Table 7 summarizes the most relevant studies published since 2019 focusing on the *in vitro/in vivo* toxicological characterization of the aerosols generated from e-liquids containing THC/VEA, CBD, and other common diluents, aiming to find a causative link to EVALI. Among them, five studies assessed the acute cytotoxic effect of counterfeit CBD or commonly used liquid diluents, including PG, VG, MCT, VEA, as either e-liquids or vapors, either *in vivo* (C57BL/6NCr mice) (Bhat et al. 2020; Matsumoto et al. 2020; Muthumalage, Lucas, et al. 2020a; Matsumoto et al. 2022) or *in vitro* (human bronchial epithelial cells, human monocytes, human lung fibroblasts cells, human primary AT-II cells) (Muthumalage and Rahman 2019; Bhat et al. 2020; Jiang et al. 2020; Matsumoto et al. 2020; Muthumalage, Lucas, et al. 2020a). Their findings revealed that the aerosols could induce a varying degree of cytotoxicity, barrier dysfunction, and inflammation *in vitro* and *in vivo* depending on e-liquid composition, puffing protocol, operational voltage, and cell lines. Acute (24 h) *in vitro* exposure of human bronchial epithelial cells (BEAS-2B or 16-HBE) or human monocytes cells (MM6) to aerosols generated from MCT, VEA or CBD, induced a substantial secretion of pro-inflammatory cytokines such as IL-6, IL-8, Eotaxin, MCP-1, CXCL1, and CXCL2, massive generation of reactive oxygen species (ROS), increased cytotoxicity and lactate dehydrogenase (LDH) release (Muthumalage and Rahman 2019; Jiang et al. 2020; Muthumalage, Lucas, et al. 2020a).

Mice challenged with VEA, MCT or CBD e-cig vapors from 3 to 15 or 28 days also exhibited increased inflammatory markers, such as IL-6, IL-8, Eotaxin, G-CSF, and MCP-3, and reduction of RANTES, IL-4, IL-17A, and IL-12p40, accompanied by the presence of VEA in the BAL (only in the VEA-treated mice), the disruption of alveolar-capillary barrier, progressive increase of BAL total fluid volume, total cell count (mono/macrophages and neutrophils), increased total protein (including albumin), presence of large vacuolated macrophages, decreased lung surfactant protein A or increased surfactant protein-D, and alteration of lipidomic profile (Bhat et al. 2020; Matsumoto et al. 2020; Muthumalage, Lucas, et al. 2020a; Matsumoto et al. 2022). The lung parenchymal alteration was represented by alveolar and parenchymal inflammation in a bronchiolocentric pattern with an increased number of monocytes and neutrophils, and large, foamy and vacuolated macrophages, also associated with alveolar septal thickening and pulmonary blood vessels

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

surrounded by lymphocyte-rich cell aggregates (Bhat et al. 2020; Matsumoto et al. 2022). (Table 7)

We found only one research study that systematically investigated the *in vitro* toxicity of aerosol generated from real-world combination of D8THC/VEA/Terpenes, operated at 2 different voltages (3.7 and 5V). Using 2 physiologically relevant cell lines, Calu 3 human lung epithelial cells and THP-1 human monocytes, Marrocco et al investigated the cytotoxic effect of 2 doses of the collected vapors, representative of 1 and 3 months vaping exposure. Overall, the aerosol generated from D8THC 36% + VEA 54% + Terpenes 10% was the most bioactive, on both cell lines, as demonstrated by the increased LDH release, increased ROS generation (only in THP-1), significant decrease in mitochondrial membrane potential, and increase in caspase 3 activation, and upregulation of a limited number of pro-inflammatory markers, while suppressing the majority of them. (Marrocco et al. 2022)

From the studies analyzed, while it is clear that the injury of the alveolar epithelium is crucial in the pathogenesis of EVALI, it is still difficult to delineate a precise cascade of events. The only one study, performed by Matsumoto et al, approaching the identification of the specific mechanistic pathway through the RNA sequencing on two VEA-exposed alveolar epithelial (AT-II) cells from a single donor, revealed that the VEA-induced severe inflammatory status was correlated to the enrichment in the IL-17, MAPK and TNF signaling pathways (Matsumoto et al. 2020).

A common feature between the *in vivo* toxicology studies and the clinical reports was the presence of lipid-laden macrophages in the airspace, which is a non-specific marker of EVALI. Yet, since lipid-laden macrophages were characterized in mice exposed to e-cig vapors generated from PG and VG regardless of the presence of nicotine or VEA as a result of the alteration of lipid homeostasis (Madison M. C. et al. 2019), as well as in lungs of individuals exposed to other chemicals and healthy smokers (Maddock et al. 2019; Christiani 2020; Jonas A 2020; Shields P. G. et al. 2020), it raises questions about the possible role of these macrophages on lung injury development and progression. The involvement of alveolar and interstitial macrophages is crucial both in the recognition, activation, and reaction against a foreign body or pathogenic factors at early stages (Higgins et al. 2008) and in the resolution of inflammation, regulation of fibro-proliferative response, and wound healing in the late stage of disease (Bellingan 2002; Gordon 2003; Huang X et al. 2018; Matsumoto et al. 2022).

The detection of ROS in MCT, VEA, and CBD e-cig vapors has also been demonstrated (Muthumalage and Rahman 2019; Muthumalage, Lucas, et al. 2020a; Marrocco et al. 2022). Previous studies have already identified the presence of ROS in conventional tobacco smoke and nicotine e-cig emissions (Goel et al. 2015; Lerner et al. 2015; Tierney et al. 2016; Zhao, Zhang, et al. 2018; Son et al. 2019), and their role as mediators both *in vivo* and *in vitro* of oxidative stress, cell death, DNA damage, and lung inflammation, underlying also the pathogenesis of chronic obstructive pulmonary disease and lung cancer (Anderson et al. 2016; Yu et al. 2016; Rouabhia et al. 2017). Even though the generation of ROS by pyrolysis of e-liquids cannot be directly accounted as a specific cause or marker of EVALI,

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

the simultaneous release of heavy metals and organic compounds in the e-liquid vapor can increase the generation of ROS, thus potentiating their dangerous health effects.

Even though these results highlight a certain correlation between the nature of vaping exposures (mainly VEA) and EVALI, major limitations still need to be addressed to understand the mechanistic pathophysiological pathway underlying EVALI.

The major limitation consist on the fact that among the available toxicological studies only one has tested the effect of vapors generated from combination D8THC/VEA/Terpenes on the human lung epithelial cells *in vitro*, and none has tested D9THC either *in vitro* or *in vivo*, which is mostly due to ongoing strict federal research restrictions on D9THC; moreover the majority of the studies focused on the cytotoxicity of pure VEA e-liquid or its vapor, which is unrealistic, and not representative of complex mixtures containing VEA. Although VEA serves mainly as a diluent of the active agent THC, the mixture of distinct chemicals in the combination THC/VEA vapor can exert synergistic effects on bioactivity and toxicity, which can further be modulated by the relative composition of ingredients and e-cig operating conditions. Moreover, there is no consistency in the puffing topography, cartridges' operational voltage, and vapor sampling method among the studies, as well as the dose ranges and time-points assessed for toxicity, leading to inconsistencies in the physicochemical characterization of vapors and incomparable biological endpoints between different studies. These issues prevent the generalizability of the data that could be used to explain the EVALI-related health effects observed in the general population. Finally, as mentioned before, *in vitro* or *in vivo* exposure to e-liquids obtained as-is does not help to understand if the aerosols generated from them during vaping will be harmful to the alveolar epithelial cells, because pyrolysis involves drastic changes in physicochemical properties during the transformation from the e-liquid to the vapor phase and thus they can have significantly different toxicological profiles.

In the absence of strong and reliable data on the mechanism of toxicity of THC/VEA vapor, to date many hypotheses on the pathogenesis of EVALI have been proposed, mostly correlating to the presence of VEA, such as the longer residence of un-hydrolyzed VEA in the lung airspace, due to the absence of pancreatic carboxyl ester hydrolase and cholesteryl ester hydrolase. (Hybertson et al. 1998; Jensen et al. 1999; Hybertson et al. 2005; Desmarchelier et al. 2013; Lee H 2020) Moreover, the hydrophobic nanoparticles potentially generated by VEA aerosolization could reach the alveoli surface and directly interact with the lipid monolayer or the liquid crystalline phase of the pulmonary surfactant (Lee H 2020; Mikheev et al. 2020), leading to increased surface tension (Blount et al. 2020; DiPasquale et al. 2020), impairment of alveolar-capillary function of gas exchange (DiPasquale et al. 2020), and respiratory compression-expansion cycling (Lee H 2020), consequently inducing acute lung injury.

As mentioned before, the role of ketene in the development of EVALI has also been supposed. The acute respiratory distress syndrome manifested by acute occupational intoxication with a mixture of ketene and crotonaldehyde, consisting in respiratory failure and ground-glass opacities presented 12 hours post-5-minutes exposure (Huang J-F et al. 2013; Attfield et al. 2020), was consistent with the small number of young EVALI patients

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

who developed life-threatening symptoms literally within hours after initial constitutional, respiratory, and gastrointestinal symptoms (Layden J. E. et al. 2020). However, this hypothesis was not supported by the *in vivo* acute exposure of mice to the aerosol generated by pure VEA under real-world vaping conditions (Bhat et al. 2020; Matsumoto et al. 2020). Besides these speculations, the exclusive correlation between EVALI and VEA has failed to be proven (Kleinman et al. 2020), while many other toxicants contained in THC-based aerosol (for example, silica and silicon-derivates) are already known to react with alveolar surfactant and induce respiratory failure due to alveolar damage (McKee et al. 2015; Christiani 2020).

Other authors have considered that either inhalation of a single chemical contained in the e-cig vapor, such as diacetyl, chlorine, VEA, can be directly cytotoxic to certain lung cells, leading to cellular necrosis, neutrophilic inflammation, collateral damage, or inhalation of the base ingredients of e-liquids (PG and VG) from the e-cigs vapor can alter the physiologic state of the immune system, making the lung sensitive to any other inhalants that are normally well tolerated (Alexander et al. 2020).

However, it is also reasonable to speculate that the mixture of chemicals and particles released in the THC/VEA e-cigs vapors can exert a synergistic and direct cytotoxic effect on the alveolar epithelial cells, inducing cells membrane damages, cellular necrosis, and impairment of the alveolar-capillary barrier leading to increased permeability, pulmonary edema, and recruitment of inflammatory cells. In alternative, it is also possible that alveolar macrophages can recognize and engulf the particles and give rise to the cytokine storm and ROS generation, which induces a strong pro-inflammatory phenotype, leading to cytotoxicity in the alveolar epithelial cells, impairment of the alveolar-capillary barrier, and in turn acute lung injury pattern.

Given the multitude of unanswered questions, further and more comprehensive molecular biology and toxicological studies are needed to investigate the mechanism of immune response to vapors generated from THC/VEA e-cigs and the resulting acute, sub-acute, and chronic health effects.

Besides the cytokine/chemokine profile assessment, previous studies on nicotine e-cig exposure have also focused on the membrane pattern recognition receptors and cellular protein expression. For example, Singh et al described alteration of proteins related to cellular processes including cell adhesion, cell migration, membrane trafficking, cell communication, apoptosis, and transcriptional regulation. In particular, they illustrated an overexpression of TLR-4 (toll-like receptor 4) and cytosolic receptor NOD-1 (nucleotide-binding oligomerization domain-containing protein-1), and a lipid raft-associated protein caveolin-1, which governed the amplified downstream signaling cascade, leading to the inflammatory response to the nicotine e-cig vapors *in vitro* (Singh DP et al. 2021). If it is clear that EVALI is driven by a severe alveolar pro-inflammatory status, the precise cytokines/chemokine profile is still unknown, and many inconsistencies are reported in the literature. Therefore, a more systematic proteomic approach can help elucidate the trigger event, and subsequently the signaling cascade leading to the diffuse and massive alveolar damage.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

In addition to the protein profile, transcriptomic RNA-sequencing analysis would be of great help in elucidating the alteration in the expression of key genes involved in the pathogenesis of EVALI, as already tentatively shown for the VEA treated cells by Matsumoto et al (Matsumoto et al. 2020). Previous investigation on the effect of nicotine e-cigs vapors on gene expression and subsequent molecular pathways of vapers' oral epithelium have shown a significant number of aberrantly expressed transcripts, mostly related to regulatory non-coding RNAs associated with the development of cancer (Tommasi et al. 2019). More importantly, Park et al reported significant transcriptomic changes in pathways related to downregulation of ciliogenesis, leading to a decreased number of ciliated cells, downregulation of new protein synthesis, and upregulation of inflammatory response, in normal human bronchial epithelial cells treated with nicotine e-cigs vapors which can ultimately impair the immune response against foreign bodies and pathogens (Park H-R et al. 2019; Park HR et al. 2021).

A preliminary study on the lipidomic profile alteration induced by pure VEA or counterfeit CBD e-cig vapors in mice was proposed by Muthumalage et al. They reported an increased level of leukotrienes in mice, and increased hydroxyeicosatetraenoic acids (HETEs) in plasma of e-cigs users, both of which are implicated in oxidative stress and inflammatory response in lungs (Muthumalage, Lucas, et al. 2020a). Many studies have reported the dysregulation of lung lipid homeostasis in response to e-cigs vapors (Madison Matthew C et al. 2020; Singh DP et al. 2021), however, Moshensky et al. reported that mice exposed to nicotine e-cigs vapors for 1 h daily for 12 days exhibited changes in circulating metabolites depending on the type of device, e-liquid composition, puffing protocol, operational voltage and temperature (Moshensky et al. 2021). This study is particularly relevant because it supports the need for a systematic and standardized vapor generation and sampling methodology and also highlights the need for studies addressing the potential health effects of real-world THC/VEA and nicotine e-cigs vapors.

A comprehensive genomic, proteomic and metabolomic approach would help to elucidate crucial processes of lung inflammation, cell damage, and death, aiming to understand the mechanistic pathways underlying EVALI.

3.6 Regulations

E-cigs and their components and parts have been under the jurisdiction of the Food and Drug Administration since May 2016 (Register 2016), when they were classified under the definition of "tobacco products", and consequently subjected to the Tobacco Control Act provisions, addressing advertising/promotion, child safety, health warning labeling, restriction of marketing and sales to youth (of minimum age), and reporting/notification. In more detail, the regulation includes 1. Enforcement action against adulterated and misbranded products; 2. Disclosure of ingredient listing, including Harmful and Potentially Harmful Constituents (HPHCs); 3. Registration of manufacturers and product listings; 4. Restrictions on sale and distribution of products with mislabeled risk description; 5. Prohibition on sales or distribution of free samples; 6. Premarket review of tobacco products. In addition, the FDA established 3 further restrictions, concerning the minimum age of

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

purchase, the health warning labeling on packages and advertisements, and the prohibition on vending machine distribution.

In 2018, in an attempt to mitigate the expansion of youth sales, the FDA began to regulate e-liquid packaging to make them less appealing to minors. (FDA 2018) Following the FDA provision, on December 20, 2019, a federal law raised the federal minimum legal sales age for all tobacco products, including e-cigarettes, from 18 to 21 across the United States. (Congress 2019) The legislation was passed in all 50 states on December 31, 2020. (CDC 2020b)

In conjunction with all the efforts taken to limit and constrain the spread of e-cigs especially among the young population, in September 2019, the President of the United States announced his plan to clear the market of unauthorized, non-tobacco-flavored e-cigs products. (FDA 2020a), which was finalized in January 2020 by the FDA through the enforcement of the policy on unauthorized flavored cartridge-based e-cigarettes that appealed to children, including fruit and mint flavorings. (FDA 2020b) It is also worth mentioning that although flavors were not found to be correlated to the development of EVALI, the flavor contribution to the vapor toxicity has been already recognized, and correlated either to the presence of toxic ingredients in the parent e-liquid, or the release of toxic chemicals after vaporization (Behar et al. 2014; Clapp et al. 2017; Hua My et al. 2019; Rowell et al. 2020; Salam et al. 2020).

Subsequently, in December 2019, due to the EVALI outbreak, the FDA and Drug Enforcement Administration (DEA) started a law enforcement response against the sales of illicit THC-containing products, and the elimination of VEA from vaping products (FDA 2019; Krishnasamy, Hallowell, Ko, Board, Hartnett, Salvatore, Danielson, Kite-Powell, Twentyman, Kim, Cyrus, Wallace, Melstrom, Haag, King, Briss, Jones, Pollack, Ellington 2020).

In February 2020, the U.S. House of Representatives approved the “Protecting American Lungs and Reversing the Youth Tobacco Epidemic Act”, to prohibit all flavored tobacco products, among the other restrictions.

In addition to the federal measures, state governors have enacted measures to prevent the escalation of EVALI cases. For example, in 2019 many states like Washington and Colorado banned the use of vitamin E acetate in vaping products, while the State of Oregon only issued a recommendation for cannabis retailers to carefully review their vaping products for potential safety concerns. The Governor of Massachusetts declared a public health emergency in September 2019 due to the increased number of vaping-related illnesses and deaths, with a moratorium on vaping produced, and two months later, in November 2019, the Massachusetts House Bill No. 4196 (“An act Modernizing Tobacco control”) imposed a 75% excise tax on nicotine-containing vaping products, temporary banning all flavors and flavored products from the market, except in licensed smoking bars starting on June 1, 2020 (Massachusetts 2019). Similarly, the Governor of New York State prohibited the sale of flavored e-cigs and e-liquids (NewYorkState 2020), while the Governor of California

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

proposed a 12.5% increase in excise taxes on e-cigs (Senate Bill No.395 signed in October 2021 (California 2021).

It is also important to highlight that until 2019, only 7 states had legalized cannabis and THC-containing products for recreational use, while only medical marijuana was allowed in 26 States, and the remaining 18 states prohibited all cannabis use. (Wing et al. 2020) Many pitfalls are strictly correlated to the legalization of cannabis. While some studies have speculated a higher incidence of EVALi in the States where THC is prohibited (Wing et al. 2020), the legalization of cannabis has led to an expansion of the uncontaminated and un-adulterated THC products in the legal market, as well as of contaminated e-liquids and counterfeit cartridges both in the states where the THC-e-cigs are prohibited and in more liberal states, due to the trafficking across the States. (Cirulis et al. 2020; Wing et al. 2020; Hall et al. 2021b, 2021a) Although more accurate surveys, data reports and new study designs design are necessary to confirm these hypotheses, the Governments should put into policies that discourage illicit trade market, and estabilish laws to protect the THC-users rather than just banning THC products. To date, in fact, there are very limited existing policies, regulations, and standards at the local, state, and federal level that address permissible or recommended volumes and/or concentrations of ingredients (including nicotine, THC, flavors, and diluents) and safety/hygiene parameters of e-liquids and cartridges (e.g., standardization and quality control for liquids and vaporizers, disclosure of ingredients in liquids).

4 Conclusions and the way forward

“E-cigs, or vaping, associated acute lung injury” is characterized by an acute inflammatory process of the lungs that disrupts the lung endothelial and epithelial barriers (alveolar-capillary membrane damage), leading to increased permeability, excessive transudation of fluid, recruitment of neutrophils and monocytes in the alveoli, and release of pro-inflammatory cytokines (Johnson and Matthay 2010). This acute inflammation, which results in collapse of alveoli and severe impairment of gas exchange, has been presumably attributed in the e-cig or vaping product users to the presence of THC and VEA in the e-liquids, due to their detection in the majority of patients’ biological samples and vaping products. However, scant, non-standardized and inconclusive studies have been performed to assess the physical-chemical and toxicological properties of vaping aerosols and to delineate the possible pathophysiological mechanisms leading to acute lung injury. Consequently, big knowledge gaps still exist at multiple levels, such that the mechanistic pathway(s) that lead to respiratory failure in e-cig users are still unknown.

The very few vaping atmospheres examined in the current literature are not always representative of the real-world e-cigs aerosols, thus are not comparable. Subsequently, the *in vivo*/*in vitro* toxicological studies performed are based on variable experimental approaches, due to the lack of standardized methodologies to generate and characterize controlled real-world e-cigs aerosols. In the absence of sufficient reliable data on the physico-chemical and toxicological properties of THC/VEA aerosol, it is therefore difficult to draw specific conclusions on the etiopathogenesis of EVALI.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

More studies are warranted to fill in the existing gaps: a comprehensive analytical assessment of the VOC, hydrocarbons, ROS, elements, and other organic constituents of the THC/VEA emissions, along with an extensive physicochemical characterization of the aerosol particulates, and exhaustive *in vitro/in vivo* toxicological investigations, through a multi-omics approach, would help to delineate the cascade of events leading to the acute lung injury, to detect pathognomonic signs or biomarkers of disease, and also characterize long-term cardiopulmonary consequences of the EVALI patients and asymptomatic users. Such a multi-disciplinary approach would also help the federal regulatory agencies in future decisions on the regulation of e-cigs or vaping products.

Besides the prompt law enforcement response to the illicit products, and the elimination of VEA from vaping products (FDA 2019; Krishnasamy, Hallowell, Ko, Board, Hartnett, Salvatore, Danielson, Kite-Powell, Twentyman, Kim, Cyrus, Wallace, Melstrom, Haag, King, Briss, Jones, Pollack, Ellington 2020), which helped to dampen the EVALI outbreak, to date, no other measure has been taken to prevent future outbreaks. Indeed, the possibility of a resurgence of the EVALI crisis may still resurface given the lack of measures against the use of illicit or widely customizable e-cigs products. In addition to dismantling the illicit market and increasing the minimum age from 18 to 21 years old, there are still more actions that need to be taken. For example, the prohibition of flavoring sales should be applied also to the disposable and large cartridges, as well as pods, flavored with tobacco or menthol. Moreover, limiting the parameters easily customizable by the user, such as e-liquid ingredient proportions, voltage, and temperature, can greatly help toward the prevention of a future EVALI epidemic or other accidental health hazards. In addition, the identification of released harmful chemical compounds in the e-cig vapors and available information on their individual toxicological dose parameters (such as lethal dose, lethal concentration, no/lowest-observed adverse effect level) can be a useful tool for risk assessors and legislators to implement e-cig restrictions based on evidence of toxicity.

Human epidemiological studies, based on standardized and more comprehensive surveys or interviews along with regular follow-ups and clinical testing, could also be beneficial in gathering pertinent information on the e-cigs or vaping product use (such as type of device, source, brand, composition, operating conditions) and vapers' behavioral patterns (such as frequency of use), and linking them to any observed pulmonary abnormalities to prevent future outbreaks.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgment

The authors gratefully acknowledge all the past and present members of the Center for Nanotechnology and Nanotoxicology, Harvard T.H. Chan School of Public Health, including Jeff Rawson Ph.D., Postdoctoral Fellow from Prof. George M. Whitesides Laboratory, Department of Chemistry and Chemical Biology, Harvard University, for helpful discussions and comments; Professor Dhimiter Bello, Department of Public Health, UMass Lowell, and Professor Ilias Kavouras, Environmental, Occupational, and Geospatial Health Sciences, CUNY Graduate School of Public Health and Health Policy, for the internal review of the manuscript; the Editor in Chief and the anonymous peer-reviewers selected by the editor for their suggestions and comments that helped to improve the quality of this manuscript.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

References

Abeles M, Popofsky S, Wen A, Valsamis C, Webb A, Halaby C, Pirzada M. 2020. Vaping-associated lung injury caused by inhalation of cannabis oil [case report]. Pediatr Pulmonol. 55(1):226–228. eng. [PubMed: 31746559]

Aberegg SK, Cirulis MM, Maddock SD, Freeman A, Keenan LM, Pirozzi CS, Raman SM, Schroeder J, Mann H, Callahan SJ. 2020. Clinical, Bronchoscopic, and Imaging Findings of e-Cigarette, or Vaping, Product Use-Associated Lung Injury Among Patients Treated at an Academic Medical Center [case series]. JAMA Netw Open. 3(11):e2019176. eng. [PubMed: 33156346]

Aberegg SK, Maddock SD, Blagev DP, Callahan SJ. 2020. Diagnosis of EVALI: General Approach and the Role of Bronchoscopy [review]. Chest. 158(2):820–827. [PubMed: 32092322]

Acharya S, Ali SI, Anwar S, Glaser A. 2020. DO NOT FALL to the VAPE TRAP! [case report]. Respir Med Case Rep. 31:101165. eng. [PubMed: 32685366]

Adhikari R, Koritala T, Gotur R, Malayala SV, Jain NK. 2021. EVALI - E-Cigarette or Vaping Product Use-Associated Lung Injury: A Case Report [case report]. Cureus. 13(2):e13541. eng. [PubMed: 33815967]

Adhikari R, Manduva D, Malayala SV, Singh R, Jain NK, Deepika K, Koritala T. 2021. A Rare Case of Vaping-Induced Spontaneous Pneumomediastinum [case report]. Cureus. 13(8):e17166. eng. [PubMed: 34532191]

Adkins SH, Anderson KN, Goodman AB, Twentyman E, Danielson ML, Kimball A, Click ES, Ko JY, Evans ME, Weissman DN et al. 2020. Demographics, Substance Use Behaviors, and Clinical Characteristics of Adolescents With e-Cigarette, or Vaping, Product Use-Associated Lung Injury (EVALI) in the United States in 2019 [epidemiology survey]. JAMA Pediatr. 174(7):e200756. eng. [PubMed: 32421164]

Aftab G, Ahmad M, Frenia D. 2019. Vaping-associated Lung Injury [case report]. Cureus. 11(11):e6216. eng. [PubMed: 31890417]

Ahmad M, Aftab G, Rehman S, Frenia D. 2020. Long-term Impact of E-cigarette and Vaping Product Use-associated Lung Injury on Diffusing Capacity for Carbon Monoxide Values: A Case Series [case series]. Cureus. 12(2):e7002. eng. [PubMed: 32206466]

Ahmed A, Shapiro D, Su J, Nelson LP. 2021. Vaping Cannabis Butane Hash Oil Leads to Severe Acute Respiratory Distress Syndrome-A Case of EVALI in a Teenager With Hypertrophic Cardiomyopathy [case report]. J Intensive Care Med. 36(5):617–621. [PubMed: 32686568]

Al-Abdouh A, Phillips E, Allison MG. 2020. E-Cigarette or Vaping Product Use-Associated Lung Injury: A Severe Case That Responded to Corticosteroid Treatment [case report]. Cureus. 12(11):e11544. eng. [PubMed: 33365213]

Al-Hamdani M, Hopkins DB, Hardardottir A, Davidson M. 2021. Perceptions and Experiences of Vaping Among Youth and Young Adult E-Cigarette Users: Considering Age, Gender, and Tobacco Use [epidemiology]. J Adolesc Health. 68(4):787–793. [PubMed: 32943292]

Aldy K, Cao DJ, McGetrick M, Willcutts D, Verbeck G, De Silva I, Hsu S. 2020. Severe E-Cigarette, or Vaping, Product Use Associated Lung Injury Requiring Venovenous Extracorporeal Membrane Oxygenation [case report]. Pediatr Crit Care Med. 21(4):385–388. eng. [PubMed: 32150124]

Alexander LEC, Bellinghausen AL, Eakin MN. 2020. What are the mechanisms underlying vaping-induced lung injury? The Journal of clinical investigation. 130(6):2754–2756. [PubMed: 32391805]

Ali M, Khan K, Buch M, Ramos-Ramirez M, Sharma M, Patel S, Choudhury S, Anjum H, Khan A, Surani S. 2020. A Case Series of Vaping-Induced Lung Injury in a Community Hospital Setting [case series]. Case Rep Pulmonol. 2020:9631916. eng. [PubMed: 32082682]

Alqahtani A, Ammari Z, Ramahi A, Said Ahmed TS, Klada E. 2019. Cannabis Smoking-induced Diffuse Alveolar Hemorrhage [case series]. Cureus. 11(7):e5089. eng. [PubMed: 31511809]

Alzghoul BN, Innabi A, Mukhtar F, Jantz MA. 2020. Rapid Resolution of Severe Vaping-induced Acute Lipoid Pneumonia after Corticosteroid Treatment [case report]. Am J Respir Crit Care Med. 202(2):e32–e33. [PubMed: 32142357]

Amin AA, Haught E, Mousattat Y. 2020. Do Not Huff, Puff, or Vape That Stuff: Interstitial Airspace Disease in a Teenager [case report]. Case Rep Pediatr. 2020:8822362. eng. [PubMed: 33343957]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Anderson C, Majeste A, Hanus J, Wang S. 2016. E-cigarette aerosol exposure induces reactive oxygen species, DNA damage, and cell death in vascular endothelial cells. Toxicological Sciences. 154(2):332–340. [PubMed: 27613717]

Anderson RP, Zechar K. 2019. Lung injury from inhaling butane hash oil mimics pneumonia. Respir Med Case Rep. 26:171–173. eng. [PubMed: 30671339]

Anderson RP, Zechar K. 2019. Lung injury from inhaling butane hash oil mimics pneumonia [case report]. Respiratory medicine case reports. 26:171–173. [PubMed: 30671339]

Ansari-Gilani K, Petraszko AM, Teba CV, Reeves AR, Gupta A, Gupta A, Ramaiya NH, Gilkeson RC. 2020. E-cigarette use related lung disease, review of clinical and imaging findings in 3 cases [case report]. Heart Lung. 49(2):139–143. eng. [PubMed: 32008808]

Aokage T, Tsukahara K, Fukuda Y, Tokioka F, Taniguchi A, Naito H, Nakao A. 2019. Heat-not-burn cigarettes induce fulminant acute eosinophilic pneumonia requiring extracorporeal membrane oxygenation [case report]. Respiratory medicine case reports. 26:87–90. [PubMed: 30560050]

Arons MM, Barnes SR, Cheng R, Whittle K, Elsholz C, Bui D, Gilley S, Maldonado A, LaCross N, Sage K et al. 2021. Examining the temporality of vitamin E acetate in illicit THC-containing e-cigarette, or vaping, products from a public health and law enforcement response to EVALI - Utah, 2018–2020 [policy]. Int J Drug Policy. 88:103026. eng. [PubMed: 33246266]

Arter ZL, Wiggins A, Hudspath C, Kisling A, Hostler DC, Hostler JM. 2019. Acute eosinophilic pneumonia following electronic cigarette use [case report]. Respir Med Case Rep. 27:100825. [PubMed: 30963023]

Artunduaga M, Rao D, Friedman J, Kwon JK, Pfeifer CM, Dettori A, Winant AJ, Lee EY. 2020. Pediatric Chest Radiographic and CT Findings of Electronic Cigarette or Vaping Product Use-associated Lung Injury (EVALI) [case series]. Radiology. 295(2):430–438. [PubMed: 32125258]

Atkins G, Drescher F. 2015. Acute Inhalational Lung Injury Related to the Use of Electronic Nicotine Delivery System (ENDS). CHEST. 148(4):83A.

Attfield KR, Chen W, Cummings KJ, Jacob P 3rd, O'Shea DF, Wagner J, Wang P, Fowles J. 2020. Potential of Ethenone (Ketene) to Contribute to Electronic Cigarette, or Vaping, Product Use-associated Lung Injury [chemical]. Am J Respir Crit Care Med. 202(8):1187–1189. [PubMed: 32551843]

Ayoub M, Quamme M, Abdel-Reheem AK, Lwin P. 2021. COVID or Not COVID? A Great Mimicker Behind the Smoke Screen [case report]. Cureus. 13(11):e19480. eng. [PubMed: 34912621]

Baumann B, Churg A, Aboulhosn K. 2020. Vaping-associated lung injury causing organizing pneumonia: A case report [case report]. British Columbia Medical Journal. 62(8):268–271.

Baxter RD, Vaquera K, George TJ. 2020. Extracorporeal Membrane Oxygenation Support for Vaping-Induced Acute Lung Injury [case report]. Ann Thorac Surg. 110(3):e193–e194. eng. [PubMed: 32114044]

Behar R, Davis B, Wang Y, Bahl V, Lin S, Talbot P. 2014. Identification of toxicants in cinnamon-flavored electronic cigarette refill fluids. Toxicology in vitro. 28(2):198–208. [PubMed: 24516877]

Bellingan GJ. 2002. The pulmonary physician in critical care * 6: The pathogenesis of ALI/ARDS. Thorax. 57(6):540–546. [PubMed: 12037231]

Bharat A, Jain N, Sheikh B, Jeelani HM, Shayuk M. 2020. Vaping-Induced Lung Injury: An Uncharted Territory [case report]. Cureus. 12(7):e8970. eng. [PubMed: 32766012]

Bhat TA, Kalathil SG, Bogner PN, Blount BC, Goniewicz ML, Thanavala YM. 2020. An Animal Model of Inhaled Vitamin E Acetate and EVALI-like Lung Injury [research in vivo]. N Engl J Med. 382(12):1175–1177. [PubMed: 32101656]

Billa R, Tigges C, Vijayakumar N, Radke J, Pedati C, Weiner R, McCabe D. 2020. E-Cigarette, or Vaping, Product Use Associated Lung Injury (EVALI) with Acute Respiratory Failure in Three Adolescent Patients: a Clinical Timeline, Treatment, and Product Analysis [case series]. J Med Toxicol. 16(3):248–254. [PubMed: 32193828]

Blagev DP, Harris D, Dunn AC, Guidry DW, Grissom CK, Lanspa MJ. 2019. Clinical presentation, treatment, and short-term outcomes of lung injury associated with e-cigarettes or vaping: a prospective observational cohort study [case series]. Lancet. 394(10214):2073–2083. English. [PubMed: 31711629]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Blount BC, Karwowski MP, Morel-Espinosa M, Rees J, Sosnoff C, Cowan E, Gardner M, Wang L, Valentin-Blasini L, Silva L et al. 2019. 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 [case report]. MMWR Morb Mortal Wkly Rep. 68(45):1040–1041. eng. [PubMed: 31725707]

Blount BC, Karwowski MP, Shields PG, Morel-Espinosa M, Valentin-Blasini L, Gardner M, Braselton M, Brosius CR, Caron KT, Chambers D et al. 2020. Vitamin E Acetate in Bronchoalveolar-Lavage Fluid Associated with EVALI [case series]. N Engl J Med. 382(8):697–705. [PubMed: 31860793]

Bolona E, Felix M, Vanegas E, Vera Paz C, Cherrez-Ojeda I. 2020. A Case of Vaping-associated Pulmonary Illness in South America: Highlighting the Need for Awareness and Surveillance Programs in the Region [case report]. Am J Respir Crit Care Med. 201(6):733–735. eng. [PubMed: 31810372]

Bozkanat KM, Rao DR, Lieu TJ, Rivera-Sanchez YM. 2020. The perfect storm: A case of COVID-19 infection in an adolescent patient with EVALI [case report]. Respir Med Case Rep. 31:101306. English. [PubMed: 33251101]

Brosius CR, Caron KT, Sosnoff CS, Blount BC, Wang L. 2022. Rapid Development and Validation of a Liquid Chromatography-Tandem Mass Spectrometry Method to Measure Cannabinoids in Bronchoalveolar-Lavage Fluid of Patients with e-Cigarette, or Vaping, Product Use-Associated Lung Injury [chemical analysis]. ACS Omega. 7(1):443–452. eng. [PubMed: 35036713]

Butt YM, Smith ML, Tazelaar HD, Vaszar LT, Swanson KL, Cecchini MJ, Boland JM, Bois MC, Boyum JH, Froemming AT et al. 2019. Pathology of Vaping-Associated Lung Injury [Case series]. N Engl J Med. 381(18):1780–1781. [PubMed: 31577870]

California TSo. 2021. SB-395 Excise tax: electronic cigarettes: Health Careers Opportunity Grant Program: Small and Rural Hospital Relief Program.(2021–2022) https://leginfo.legislature.ca.gov/faces/billTextClient.xhtml?bill_id=202120220SB395.

Carroll BJ, Kim M, Hemyari A, Thakrar P, Kump TE, Wade T, De Vela G, Hall J, Diaz CD, D'Andrea LA. 2020. Impaired lung function following e-cigarette or vaping product use associated lung injury in the first cohort of hospitalized adolescents [case series]. Pediatr Pulmonol. 55(7):1712–1718. eng. [PubMed: 32320538]

Casanova GS, Amaro R, Soler N, Sanchez M, Badia JR, Barbera JA, Agusti A. 2020. An imported case of e-cigarette or vaping associated lung injury in Barcelona [case report]. Eur Respir J. 55(2). eng.

CDC. 2014. The Health Consequences of Smoking—50 Years of Progress: A Report of the Surgeon General. Atlanta: U.S. Department of Health and Human Services, Centers for Disease Control and Prevention, National Center for Chronic Disease Prevention and Health Promotion, Office on Smoking and Health, 2014

CDC. 2016. E-cigarette use among youth and young adults: a report of the Surgeon General. Atlanta, GA US Department of Health and Human Services [book].

CDC. 2019. Centers for Disease Control and Prevention. For state, local, territorial, and tribal health departments. Electronic cigarettes. Smoking & tobacco use. 2019 Lung Injury Surveillance Primary Case Definition (CDC) – September 18, 2019

CDC. 2020a. Centers for Disease Control and Prevention. Outbreak of Lung Injury Associated with the Use of E-Cigarette, or Vaping, Products. Page last reviewed: November 27, 2020.

CDC. 2020b. State Tobacco Activities Tracking and Evaluation (STATE) System, STATE System E-Cigarette Fact Sheet, at https://www.cdc.gov/statesystem/factsheets/ecigarette/ECigarette.html#state-legislative-activity.

Cedano J, Sah A, Cedeno-Mendoza R, Fish H, Remolina C. 2020. Confirmed E-cigarette or vaping product use associated lung injury (EVALI) with lung biopsy; A case report and literature review [case report]. Respir Med Case Rep. 30:101122. [PubMed: 32577363]

Chadi N, Li G, Cerda N, Weitzman ER. 2019. Depressive symptoms and suicidality in adolescents using e-cigarettes and marijuana: A secondary data analysis from the Youth Risk Behavior Survey. Journal of addiction medicine. 13(5):362–365. [PubMed: 30688723]

Chapman R, Tweed CD, Moonsie I. 2020. Lung injury from e-cigarette use: a foul and pestilent congregation of vapours [case report]. BMJ Case Rep. 13(11). eng.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Chatham-Stephens K, Roguski K, Jang Y, Cho P, Jatlaoui TC, Kabbani S, Glidden E, Ussery EN, Trivers KF, Evans ME et al. 2019. Characteristics of Hospitalized and Nonhospitalized Patients in a Nationwide Outbreak of E-cigarette, or Vaping, Product Use-Associated Lung Injury - United States, November 2019 [MMWR REPORT]. MMWR Morb Mortal Wkly Rep. 68(46):1076–1080. eng. [PubMed: 31751326]

Chawla H, Weiler T. 2020. E-cigarette or Vaping Product Use-Associated Lung Injury Presenting as Sub-Acute Hypoxemia Without Increased Work of Breathing [case report]. Cureus. 12(8):e9855. [PubMed: 32963897]

Chen J, English S, Ogilvie JA, Siu MKM, Tammara A, Haas CJ. 2020. All up in smoke: vaping-associated lung injury [case series]. J Community Hosp Intern Med Perspect. 10(6):571–578. eng. [PubMed: 33194132]

Chen W, Wang P, Ito K, Fowles J, Shusterman D, Jaques PA, Kumagai K. 2018. Measurement of heating coil temperature for e-cigarettes with a “top-coil” clearomizer. PLoS One. 13(4):e0195925. eng. [PubMed: 29672571]

Chidambaram AG, Dennis RA, Biko DM, Hook M, Allen J, Rapp JB. 2020. Clinical and radiological characteristics of e-cigarette or vaping product use associated lung injury [case series]. Emerg Radiol. 27(5):495–501. eng. [PubMed: 32462343]

Choe J, Chen P, Falk JA, Nguyen L, Ng D, Parimon T, Ghandehari S. 2020. A Case Series of Vaping-Associated Lung Injury Requiring Mechanical Ventilation [case series]. Crit Care Explor. 2(1):e0079. eng. [PubMed: 32166299]

Christiani DC. 2020. Vaping-Induced Acute Lung Injury [letter]. N Engl J Med. 382(10):960–962. [PubMed: 31491071]

Ciolino LA, Falconer TM, Ranieri TL, Brueggemeyer JL, Taylor AM, Mohrhaus AS. 2021. EVALI Vaping Liquids Part 2: Mass Spectrometric Identification of Diluents and Additives [chemical analysis]. Front Chem. 9:746480. eng. [PubMed: 34760870]

Ciolino LA, Ranieri TL, Brueggemeyer JL, Taylor AM, Mohrhaus AS. 2021. EVALI Vaping Liquids Part 1: GC-MS Cannabinoids Profiles and Identification of Unnatural THC Isomers [chemical analysis]. Front Chem. 9:746479. eng. [PubMed: 34631667]

Cirulis MM, Callahan SJ, Aberegg SK. 2020. Marijuana Legislation and Electronic Cigarette– or Vaping–Associated Lung Injury: A Historical Perspective. JAMA Network Open. 3(4):e202238–e202238. [PubMed: 32250430]

Clapp PW, Pawlak EA, Lackey JT, Keating JE, Reeber SL, Glish GL, Jaspers I. 2017. Flavored e-cigarette liquids and cinnamaldehyde impair respiratory innate immune cell function. American Journal of Physiology-Lung Cellular and Molecular Physiology. 313(2):L278–L292. [PubMed: 28495856]

Cole C, Wiens T, Taylor J, Danila R, D’Heilly P, Margetta J, Bye M, Mumm E, Schwerzler L, Makhtal R et al. 2021. Vaping, lung injury, and mental health Minnesota 2018–2019 [case reports]. Minn Med. 104(3):41–43. eng. [PubMed: 34413546]

Colesar MT, McCollum DJ. 2020. E-Cigarette or Vaping Product Use-Associated Lung Injury (EVALI) in an Active Duty Service Member [case report]. Mil Med.

Committee on Acute Exposure Guideline Level, Committee on Toxicology, Board on Environmental Studies and Toxicology, Division on Earth and Life Studies, National Research Council. Acute Exposure Guideline Levels for Selected Airborne Chemicals: Volume 16. Washington (DC): National Academies Press (US); 2014 Mar 21. 6, Ketene. [BOOK].

Congress t. 2019. S.1258 - Tobacco to 21 Act, at https://www.congress.gov/bill/116th-congress/senate-bill/1258/text.

Conuel EJ, Chieng HC, Fantauzzi J, Pokhrel K, Goldman C, Smith TC, Tiwari A, Chopra A, Judson MA. 2020. Cannabinoid Oil Vaping-Associated Lung Injury and its Radiographic Appearance [case series]. Am J Med. 133(7):865–867. eng. [PubMed: 31751528]

Cruz-Vidal DA, Mull ES, Taveras J, Shell R, Hunt GW, Fowler B, Wallihan R, Erdem G. 2021. EVALI versus MIS-C, one more overlapping diagnosis to consider [case series]. Pediatr Pulmonol. 56(9):2918–2924. eng. [PubMed: 34219413]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Cullen KA, Gentzke AS, Sawdey MD, Chang JT, Anic GM, Wang TW, Creamer MR, Jamal A, Ambrose BK, King BA. 2019. E-cigarette use among youth in the United States, 2019. Jama. 322(21):2095–2103. [PubMed: 31688912]

Darnell RT, Sofi U. Vapor Lung: Bronchiolitis Obliterans Organizing Pneumonia (BOOP) in Patient with E-Cigarette Use. D22 REDUCING HARMS OF TOBACCO USE. p. A6513–A6513.

Davidson K, Brancato A, Heetderks P, Mansour W, Matheis E, Nario M, Rajagopalan S, Underhill B, Wininger J, Fox D. 2019. Outbreak of Electronic-Cigarette-Associated Acute Lipoid Pneumonia - North Carolina, July-August 2019 [MMWR report]. MMWR Morb Mortal Wkly Rep. 68(36):784–786. eng. [PubMed: 31513559]

DeCarli K, Arabiat M, Ward C, Levinson A, Carino G. 2020. A Case of Vaping-Associated Lung Injury in Rhode Island [case report]. R I Med J (2013). 103(1):38–41. eng.

Deliwala S, Sundus S, Haykal T, Theophilus N, Bachuwa G. 2020. E-cigarette, or Vaping, Product Use-associated Lung Injury (EVALI): Acute Lung Illness within Hours of Switching from Traditional to E-cigarettes [case report]. Cureus. 12(4):e7513. [PubMed: 32373415]

Derespina KR, Kaushik S, Mitchell W, Gorstein S, Ushay HM, Medar SS. 2020. E-cigarette or Vaping-Associated Acute Lung Injury and Hemophagocytic Lymphohistiocytosis [case report]. Pediatrics. 146(4).

Desmarchelier C, Tourniaire F, Preveraud DP, Samson-Kremser C, Crenon I, Rosilio V, Borel P. 2013. The distribution and relative hydrolysis of tocopheryl acetate in the different matrices coexisting in the lumen of the small intestine during digestion could explain its low bioavailability. Mol Nutr Food Res. 57(7):1237–1245. eng. [PubMed: 23520193]

Dibaji SAR, Guha S, Arab A, Murray BT, Myers MR. 2018. Accuracy of commercial electronic nicotine delivery systems (ENDS) temperature control technology [research]. PLoS One. 13(11):e0206937. eng. [PubMed: 30395592]

Dicpinigaitis PV, Trachuk P, Fakier F, Teka M, Suhrland MJ. 2020. Vaping-Associated Acute Respiratory Failure Due to Acute Lipoid Pneumonia [Case report]. Lung. 198(1):31–33. [PubMed: 31583455]

DiPasquale M, Gbadamosi O, Nguyen MHL, Castillo SR, Rickeard BW, Kelley EG, Nagao M, Marquardt D. 2020. A Mechanical Mechanism for Vitamin E Acetate in E-cigarette/Vaping-Associated Lung Injury [research tox]. Chem Res Toxicol. 33(9):2432–2440. [PubMed: 32842741]

Doukas SG, Kavali L, Menon RS, Izotov BN, Bukhari A. 2020. E-cigarette or vaping induced lung injury: A case series and literature review [case series]. Toxicol Rep. 7:1381–1386. [PubMed: 33102141]

Duffy B, Li L, Lu S, Durocher L, Dittmar M, Delaney-Baldwin E, Panawennage D, LeMaster D, Navarette K, Spink D. 2020. Analysis of Cannabinoid-Containing Fluids in Illicit Vaping Cartridges Recovered from Pulmonary Injury Patients: Identification of Vitamin E Acetate as a Major Diluent [research toxic chemical analysis]. Toxics. 8(1). eng.

Duffy BC, Li L, Lu S, Dittmar MA, Delaney-Baldwin EM, Durocher LA, Spink DC. 2021. Chemotyping of Delta8-THC-Containing e-Liquids Analyzed during the 2019–2020 New York State EVALI Investigation [chemical analysis]. J Anal Toxicol. eng.

Edmonds PJ, Copeland C, Conger A, Richmond BW. 2020. Vaping-induced diffuse alveolar hemorrhage [case report]. Respir Med Case Rep. 29:100996. [PubMed: 31956478]

El-Hellani A, Al-Moussawi S, El-Hage R, Talih S, Salman R, Shihadeh A, Saliba NA. 2019. Carbon Monoxide and Small Hydrocarbon Emissions from Sub-ohm Electronic Cigarettes [research tox]. Chem Res Toxicol. 32(2):312–317. eng. [PubMed: 30656934]

El Chebib H, McArthur K, Gorbonosov M, Domachowske JB. 2020. Anaerobic Necrotizing Pneumonia: Another Potential Life-threatening Complication of Vaping? [case report]. Pediatrics. 145(4). eng.

Ellington S, Salvatore PP, Ko J, Danielson M, Kim L, Cyrus A, Wallace M, Board A, Krishnasamy V, King BA et al. 2020. Update: Product, Substance-Use, and Demographic Characteristics of Hospitalized Patients in a Nationwide Outbreak of E-cigarette, or Vaping, Product Use-Associated Lung Injury - United States, August 2019-January 2020 [MMWR REPORT]. MMWR Morb Mortal Wkly Rep. 69(2):44–49. eng. [PubMed: 31945038]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Erythropel HC, Davis LM, de Winter TM, Jordt SE, Anastas PT, O'Malley SS, Krishnan-Sarin S, Zimmerman JB. 2019. Flavorant-Solvent Reaction Products and Menthol in JUUL E-Cigarettes and Aerosol [aerosol chemistry]. Am J Prev Med. 57(3):425–427. eng. [PubMed: 31358341]

Essa A, Macaraeg J, Jagan N, Kwon D, Randhawa S, Kruse M, Thomas S, Velagapudi M, Horne J, Narechania S et al. 2020. Review of Cases of E-Cigarette or Vaping Product Use-Associated Lung Injury (EVALI) and Brief Review of the Literature [case series]. Case Rep Pulmonol. 2020:1090629. [PubMed: 32607271]

Fan T, DuBose L, Wayne C, Sisniega C. 2020. E-cigarette, or Vaping, Associated Lung and Hepatic Injury [CASE REPORT]. J Pediatr Gastroenterol Nutr. 71(3):e98–e100. [PubMed: 32304558]

Farooq U, Anwar M, Alcantar D, Amine M, Colon Hidalgo D. 2020. Gastroenteritis and Miliary Lung Opacities: An Interesting Combination of Findings [case report]. Cureus. 12(6):e8848. eng. [PubMed: 32754390]

Fathima S, Zhang H. 2020. Histologic patterns of lung injury in patients using e-cigarettes [case series]. Proc (Bayl Univ Med Cent). 33(4):619–620. [PubMed: 33100546]

FDA. 2012. Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke: Established List; Office of the Federal Register: Washington, DC, USA,.

FDA. 2018. FTC take action against companies misleading kids with e-liquids that resemble children's juice boxes, candy and cookies [press release].

FDA. 2019. FDA, DEA seize 44 websites advertising sale of illicit THC vaping cartridges to US consumers as part of Operation Vapor Lock. FDA. from https://www.fda.gov/news-events/press-announcements/fda-dea-seize-44-websites-advertising-sale-illicit-thc-vaping-cartridges-us-consumers-part-operation.

FDA. 2020a. Commissioner of the Trump Administration Combating Epidemic of Youth E-Cigarette Use with Plan to Clear Market of Unauthorized, Non-TobaccoFlavored E-Cigarette Products. . https://www.fda.gov/news-events/press-announcements/trumpadministration-combating-epidemic-youth-e-cigarette-use-plan-clearmarket-unauthorized-non.

FDA. 2020b. FDA finalizes enforcement policy on unauthorized flavored cartridge-based ecigarettes that appeal to children, including fruit and mint [press release].

FDA. 2020c. Lung Illnesses Associated with Use of Vaping Products. .

Fedt A, Bhattarai S, Oelstrom MJ. 2020. Vaping-Associated Lung Injury: A New Cause of Acute Respiratory Failure [case report]. J Adolesc Health. 66(6):754–757. eng. [PubMed: 32473722]

Freathy S, Kondapalli N, Patlolla S, Mora A, Trimmer C. 2020. Acute lung injury secondary to e-cigarettes or vaping [case report]. Proc (Bayl Univ Med Cent). 33(2):227–228. eng. [PubMed: 32313466]

Fryman C, Lou B, Weber AG, Steinberg HN, Khanijo S, Iakovou A, Makaryus MR. 2020. Acute Respiratory Failure Associated With Vaping [case series]. Chest. 157(3):e63–e68. eng. [PubMed: 32145818]

Galo J, Celli D, Gross D, Holt G, Campos M. 2020. A presentation of E-Cigarette vaping associated lung injury (EVALI) caused by THC-Containing electronic smoking device [case report]. Respir Med Case Rep. 31:101154. [PubMed: 32690998]

Ganne N, Palraj R, Husted E, Shah I. 2021. E-cigarette or vaping product use-associated lung injury (EVALI) masquerading as COVID-19 [case report]. BMJ Case Rep. 14(7). eng.

Gaub KL, Hallyburton S, Samanic C, Paddack D, Clark CR, Pence S, Brown JA, Hawkins E. 2019. Patient Characteristics and Product Use Behaviors Among Persons with E-cigarette, or Vaping, Product Use-Associated Lung Injury - Indiana, June October 2019 [MMWR report]. MMWR Morb Mortal Wkly Rep. 68(49):1139–1141. eng. [PubMed: 31830007]

Gay B, Field Z, Patel S, Alvarez RM, Nasser W, Madruga M, Carlan SJ. 2020. Vaping-Induced Lung Injury: A Case of Lipoid Pneumonia Associated with E-Cigarettes Containing Cannabis [case report]. Case Rep Pulmonol. 2020:7151834. eng. [PubMed: 32309002]

Ghinai I, Navon L, Gunn JKL, Duca LM, Brister S, Love S, Brink R, Fajardo G, Johnson J, Saathoff-Huber L et al. 2020. Characteristics of Persons Who Report Using Only Nicotine-Containing Products Among Interviewed Patients with E-cigarette, or Vaping, Product Use-Associated Lung Injury - Illinois, August-December 2019 [MMWR report]. MMWR Morb Mortal Wkly Rep. 69(3):84–89. eng. [PubMed: 31971930]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Ghinai I, Pray IW, Navon L, O'Laughlin K, Saathoff-Huber L, Hoots B, Kimball A, Tenforde MW, Chevinsky JR, Layer M et al. 2019. E-cigarette Product Use, or Vaping, Among Persons with Associated Lung Injury - Illinois and Wisconsin, April-September 2019 [MMWR report]. MMWR Morb Mortal Wkly Rep. 68(39):865–869. [PubMed: 31581166]

Gilbert A, inventor; Brown & Williamson Collection, assignee. 1965. U.S. Patent No. 3,200,819. Smokeless Non-Tobacco Cigarette.

Girvin F, Naidich D. 2020. CT features of electronic-cigarette or vaping-associated lung injury (EVALI); our experience during the recent outbreak [case series]. BJR Case Rep. 6(3):20200027. [PubMed: 32922848]

Goel R, Durand E, Trushin N, Prokopczyk B, Foulds J, Elias RJ, Richie JP Jr. 2015. Highly reactive free radicals in electronic cigarette aerosols. Chemical research in toxicology. 28(9):1675–1677. [PubMed: 26244921]

Gonzalez-Jimenez N, Gray N, Pappas RS, Halstead M, Lewis E, Valentin-Blasini L, Watson C, Blount B. 2021. Analysis of Toxic Metals in Aerosols from Devices Associated with Electronic Cigarette, or Vaping, Product Use Associated Lung Injury [chemical analysis]. Toxics. 9(10). eng.

Gordon S 2003. Alternative activation of macrophages. Nat Rev Immunol. 3(1):23–35. [PubMed: 12511873]

Gottlieb MA. 2019. Regulation of e-cigarettes in the United States and its role in a youth epidemic. Children. 6(3):40. [PubMed: 30836677]

Griffiths A, Rauzi A, Stadheim K, Wheeler W. 2020. Lung Injury Associated with E-Cigarette or Vaping Product Use [case report]. Pediatr Ann. 49(2):e93–e98. eng. [PubMed: 32045489]

Guo W, Vrdoljak G, Liao VC, Moezzi B. 2021. Major Constituents of Cannabis Vape Oil Liquid, Vapor and Aerosol in California Vape Oil Cartridge Samples [chemical analysis]. Front Chem. 9:694905. eng. [PubMed: 34368078]

Gutsche J, Pasternak R, Campbell D, Schili JL, Boyle PJ, Tilney P. 2020. A 19-Year-Old Man With Vaping-Associated Lung Injury [case report]. Air Med J. 39(1):6–8. eng. [PubMed: 32044072]

Hall W, Gartner C, Bonevski B. 2021a. The EVALI outbreak makes a strong case for better regulation of all vaporizer products [commentary]. Addiction. 116(5):999. English. [PubMed: 33594753]

Hall W, Gartner C, Bonevski B. 2021b. Lessons from the public health responses to the US outbreak of vaping-related lung injury [commentary]. Addiction. 116(5):985–993. eng. [PubMed: 32364274]

Hallowell RW, Feldman MB, Little BP, Leaf RSK, Hariri LP. 2019. Case 38–2019: A 20-Year-Old Man with Dyspnea and Abnormalities on Chest Imaging [case report]. New England Journal of Medicine. 381(24):2353–2363. [PubMed: 31826344]

Harada HA, Liu J, Shortell JD, Beesley SJ. 2021. A 20-Year-Old Man with e-Cigarette or Vaping Product Use-Associated Lung Injury (EVALI) and Thrombotic Coagulopathy [Case report]. Am J Case Rep. 22(1):e929915. English. [PubMed: 33854029]

Hassoun A, Brady K, Arefi R, Trifonova I, Tsirilakis K. 2021. Vaping-Associated Lung Injury During COVID-19 Multisystem Inflammatory Syndrome Outbreak [Case Report]. J Emerg Med. 60(4):524–530. English. [PubMed: 33483200]

Heinzerling A, Armatas C, Karmarkar E, Attfield K, Guo W, Wang Y, Vrdoljak G, Moezzi B, Xu D, Wagner J et al. 2020. Severe Lung Injury Associated With Use of e-Cigarette, or Vaping, Products-California, 2019 [review]. JAMA Intern Med. 180(6):861–869. eng. [PubMed: 32142111]

Helfgott D, Capozzoli G, Madray J, Baig A, Uppaluri L, Gaur S, Simon M, Amorosa J, Ramagopal M. 2022. E-cigarette or vaping product use associated lung injury (EVALI) in the time of COVID-19: A clinical dilemma. Pediatr Pulmonol. 57(3):623–630. eng. [PubMed: 34964550]

Higgins DM, Sanchez-Campillo J, Rosas-Taraco AG, Higgins JR, Lee EJ, Orme IM, Gonzalez-Juarrero M. 2008. Relative levels of M-CSF and GM-CSF influence the specific generation of macrophage populations during infection with Mycobacterium tuberculosis. J Immunol. 180(7):4892–4900. [PubMed: 18354213]

Hilton R, Summer R, Roman J, Sundaram B, George G. 2020. E-cigarettes and Vaping Associated Lung Injury: A Case Series and Brief Review [case series]. Am J Med Sci. 359(3):137–139. eng. [PubMed: 32089155]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Hoshina Y 2021. E-cigarette or vaping product use-associated lung injury: A great COVID-19 mimicker in young adult [case report]. Clin Case Rep. 9(10):e05016. eng. [PubMed: 34721869]

Hua M, Omaiye EE, Luo W, McWhirter KJ, Pankow JF, Talbot P. 2019. Identification of cytotoxic flavor chemicals in top-selling electronic cigarette refill fluids. Scientific reports. 9(1):1–15. [PubMed: 30626917]

Hua M, Talbot P. 2016. Potential health effects of electronic cigarettes: A systematic review of case reports [review]. Prev Med Rep. 4:169–178. [PubMed: 27413679]

Huang J-F, Zhu D-M, Ma J-F, Zhong M 2013. Acute respiratory distress syndrome due to exposure to high-concentration mixture of ethenone and crotonaldehyde. Toxicology and Industrial Health. 31(7):585–587. [PubMed: 23448861]

Huang X, Xiu H, Zhang S, Zhang G. 2018. The Role of Macrophages in the Pathogenesis of ALI/ARDS. Mediators Inflamm. 2018:1264913. [PubMed: 29950923]

Hureaux J, Drouet M, Urban T. 2014. A case report of subacute bronchial toxicity induced by an electronic cigarette. Thorax. 69(6):596–597. [PubMed: 24436327]

Hwang JH, Ryu DH, Park I, Park SW. 2020. Cigarette or E-Cigarette Use as Strong Risk Factors for Heated Tobacco Product Use among Korean Adolescents. Int J Environ Res Public Health. 17(19).

Hybertson BM, Chung JH, Fini MA, Lee YM, Allard JD, Hansen BN, Cho OJ, Shibao GN, Repine JE. 2005. Aerosol-administered alpha-tocopherol attenuates lung inflammation in rats given lipopolysaccharide intratracheally [research in vivo]. Exp Lung Res. 31(3):283–294. eng. [PubMed: 15962709]

Hybertson BM, Kitlowski RP, Jepson EK, Repine JE. 1998. Supercritical fluid-aerosolized vitamin E pretreatment decreases leak in isolated oxidant-perfused rat lungs. J Appl Physiol (1985). 84(1):263–268. eng. [PubMed: 9451645]

Isakov KMM, Legasto AC, Hossain R, Verzosa Weisman S, Toy D, Groner LK, Feibusch A, Escalon JG. 2021. A Case-Based Review of Vaping-Induced Injury-Pulmonary Toxicity and Beyond [case series]. Curr Probl Diagn Radiol. 50(3):401–409. eng. [PubMed: 32703539]

Ismail AS, Imaduddeen T, Ibrahim WH. 2021. Electronic Cigarette or Vaping Product Use-Associated Lung Injury in a Previously Healthy Young Male [case report]. Cureus. 13(9):e18269. eng. [PubMed: 34722048]

Israel AK, Velez MJ, Staicu SA, Ambrosini R, McGraw M, Agrawal T. 2020. A Unique Case of Secondary Pulmonary Alveolar Proteinosis after E-Cigarette, or Vaping, Product Use-associated Lung Injury [case report]. Am J Respir Crit Care Med. 202(6):890–893. eng. [PubMed: 32392077]

Jankharia B, Rajan S, Angirish B. 2020. Vaping associated lung injury (EVALI) as an organizing pneumonia pattern- A case report [Case report]. Lung India. 37(6):533–535. English. [PubMed: 33154217]

Jensen SK, Engberg RM, Hedemann MS. 1999. All-rac-alpha-tocopherol acetate is a better vitamin E source than all-rac-alpha-tocopherol succinate for broilers. J Nutr. 129(7):1355–1360. [PubMed: 10395598]

Jiang H, Ahmed CMS, Martin TJ, Canchola A, Oswald IWH, Garcia JA, Chen JY, Koby KA, Buchanan AJ, Zhao Z et al. 2020. Chemical and Toxicological Characterization of Vaping Emission Products from Commonly Used Vape Juice Diluents [research tox]. Chem Res Toxicol. 33(8):2157–2163. eng. [PubMed: 32618192]

Johnson ER, Matthay MA. 2010. Acute lung injury: epidemiology, pathogenesis, and treatment [review]. J Aerosol Med Pulm Drug Deliv. 23(4):243–252. eng. [PubMed: 20073554]

Jonas A 2020. Lipid-Laden alveolar macrophages and vaping: Lessons from EVALI [commentary]. EBioMedicine. 60:103010. [PubMed: 32971470]

Jonas AM, Raj R. 2020. Vaping-Related Acute Parenchymal Lung Injury: A Systematic Review [review]. Chest. 158(4):1555–1565. eng. [PubMed: 32442559]

Kalantary A, Abdelazeem B, Shams N, Pratiti R, Al-Sanouri I. 2021. Coagulopathy and Acute Respiratory Distress Syndrome: Dual Complications of E-Cigarette-Associated Lung Injury [case report]. Cureus. 13(2):e13531. eng. [PubMed: 33786238]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Kalininskiy A, Bach CT, Nacca NE, Ginsberg G, Marraffa J, Navarette KA, McGraw MD, Croft DP. 2019. E-cigarette, or vaping, product use associated lung injury (EVALI): case series and diagnostic approach [case series]. Lancet Respir Med. 7(12):1017–1026. eng. [PubMed: 31711871]

Kaous M, Xian J, Rongo D, McDonald M, Ocasionez D, Mathew R, Estrada YMRM, Patel B, Cherian SV, Jani PP. 2020. Clinical, radiology, pathologic patterns and outcomes of vaping related pulmonary injury in a single institution; A case series [case series]. Respir Med. 173:106153. [PubMed: 33017782]

Kass AP, Overbeek DL, Chiel LE, Boyer EW, Casey AMH. 2020. Case series: Adolescent victims of the vaping public health crisis with pulmonary complications [case series]. Pediatr Pulmonol. 55(5):1224–1236. eng. [PubMed: 32168438]

Khan A, Parlette K, Kuntz HM. 2021. E-cigarettes and Vaping, Product-use Associated Lung Injury: A Case Series of Adolescents [case series]. Clin Pract Cases Emerg Med. 5(1):11–16. eng. [PubMed: 33560943]

Kinney WH, Beckstrom C, Snyder T, Judiscak P, Miller P, Marett J, Pessetto A, Scherbak D. 2020. Electronic-Cigarette or Vaping Associated Lung Injury (EVALI) [case report]. Applied Radiology. 49(2):42–44.

Kleinman MT, Arechavala RJ, Herman D, Shi J, Hasen I, Ting A, Dai W, Carreno J, Chavez J, Zhao L et al. 2020. E-cigarette or Vaping Product Use-Associated Lung Injury Produced in an Animal Model From Electronic Cigarette Vapor Exposure Without Tetrahydrocannabinol or Vitamin E Oil [research in vitro]. J Am Heart Assoc. 9(18):e017368. [PubMed: 32896206]

Kligerman SJ, Kay FU, Raptis CA, Henry TS, Sechrist JW, Walker CM, Vargas D, Filev PD, Chung MS, Digumarthy SR et al. 2021. CT Findings and Patterns of e-Cigarette or Vaping Product Use-Associated Lung Injury: A Multicenter Cohort of 160 Cases [report]. Chest. 160(4):1492–1511. English. [PubMed: 33957099]

Kooragayalu S, El-Zarif S, Jariwala S. 2020. Vaping Associated Pulmonary Injury (VAPI) with superimposed Mycoplasma pneumoniae infection [case report]. Respir Med Case Rep. 29:100997. [PubMed: 32042584]

Kovach AL, Carter RR, Thornburg JW, Wiethe R, Fennell TR, Wiley JL. 2021. Thermal Degradants Identified from the Vaping of Vitamin E Acetate [chemical analysis]. J Anal Toxicol. eng.

Krishnan S, Thind GS, Soliman M, Tolle L, Mireles-Cabodevila E, Adi A, Anandamurthy B, Bribriesco A, Yun J. 2021. A case of vaping-induced acute respiratory distress syndrome requiring extracorporeal life support [case report]. Perfusion. 36(3):308–310. eng. [PubMed: 32650708]

Krishnasamy VP, Hallowell BD, Ko JY, Board A, Hartnett KP, Salvatore PP, Danielson M, Kite-Powell A, Twentyman E, Kim L et al. 2020. Update: Characteristics of a Nationwide Outbreak of E-cigarette, or Vaping, Product Use-Associated Lung Injury - United States, August 2019-January 2020 [Article]. MMWR Morbidity and mortality weekly report. 69(3):90–94. English. [PubMed: 31971931]

Krishnasamy VP, Hallowell BD, Ko JY, Board A, Hartnett KP, Salvatore PP, Danielson M, Kite-Powell A, Twentyman E, Kim L et al. 2020. Update: Characteristics of a Nationwide Outbreak of E-cigarette, or Vaping, Product Use-Associated Lung Injury - United States, August 2019-January 2020 [MMWR report]. MMWR Morb Mortal Wkly Rep. 69(3):90–94. eng. [PubMed: 31971931]

Kupelian C, Kim A, Vijayan V. 2021. E-cigarette or Vaping Product Use-Associated Lung Injury Complicated by Pulmonary Aspergillosis [case report]. Cureus. 13(12):e20075. eng. [PubMed: 34987937]

Landman ST, Dhaliwal I, Mackenzie CA, Martinu T, Steele A, Bosma KJ. 2019. Life-threatening bronchiolitis related to electronic cigarette use in a Canadian youth [case report]. CMAJ. 191(48):E1321–E1331. eng. [PubMed: 31753841]

Lanzarotta A, Falconer TM, Flurer R, Wilson RA. 2020. Hydrogen Bonding between Tetrahydrocannabinol and Vitamin E Acetate in Unvaped, Aerosolized, and Condensed Aerosol e-Liquids [research tox]. Anal Chem. 92(3):2374–2378. eng. [PubMed: 31951379]

Layden JE, Ghinai I, Pray I, Kimball A, Layer M, Tenforde M, Navon L, Hoots B, Salvatore PP, Elderbrook M et al. 2019. Pulmonary Illness Related to E-Cigarette Use in Illinois and Wisconsin — Preliminary Report [case series]. New England Journal of Medicine.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Layden JE, Ghinai I, Pray I, Kimball A, Layer M, Tenforde MW, Navon L, Hoots B, Salvatore PP, Elderbrook M et al. 2020. Pulmonary Illness Related to E-Cigarette Use in Illinois and Wisconsin - Final Report [case report]. N Engl J Med. 382(10):903–916. [PubMed: 31491072]

Lee H 2020. Vitamin E acetate as linactant in the pathophysiology of EVALI [Commentary]. Med Hypotheses. 144:110182. eng. [PubMed: 33254504]

Lee M-S, Christiani DC. 2020. Microbial toxins in nicotine vaping liquids. American journal of respiratory and critical care medicine. 201(6):741–743. [PubMed: 31816248]

Lerner CA, Sundar IK, Yao H, Gerloff J, Ossip DJ, McIntosh S, Robinson R, Rahman I. 2015. Vapors produced by electronic cigarettes and e-juices with flavorings induce toxicity, oxidative stress, and inflammatory response in lung epithelial cells and in mouse lung. PloS one. 10(2):e0116732. [PubMed: 25658421]

Lewis N, McCaffrey K, Sage K, Cheng CJ, Green J, Goldstein L, Campbell H, Ferrell D, Malan N, LaCross N et al. 2019. E-cigarette Use, or Vaping, Practices and Characteristics Among Persons with Associated Lung Injury - Utah, April-October 2019 [MMWR report]. MMWR Morb Mortal Wkly Rep. 68(42):953–956. eng. [PubMed: 31647788]

Lilley J, Kravitz S, Haynes Z, Church T, McKay S, Mertz A. 2021. E-cigarette, or vaping, product use associated lung injury and the risks and benefits of a thorough infectious work-up [case report]. Respir Med Case Rep. 33:101465. eng. [PubMed: 34401301]

Lim W, Suhail M, Diaz K. 2022. A Case of E-cigarette or Vaping Product Use-Associated Lung Injury Mimicking Miliary Tuberculosis. Cureus. 14(2):e22406. eng. [PubMed: 35345753]

Lozier MJ, Wallace B, Anderson K, Ellington S, Jones CM, Rose D, Baldwin G, King BA, Briss P, Mikosz CA et al. 2019. Update: Demographic, Product, and Substance-Use Characteristics of Hospitalized Patients in a Nationwide Outbreak of E-cigarette, or Vaping, Product Use-Associated Lung Injuries - United States, December 2019 [MMWR REPORT]. Mmwr-Morbidity and Mortality Weekly Report. 68(49):1142–1148. [PubMed: 31830008]

Lu MA, Jabre NA, Mogayzel PJ Jr. 2020. Vaping-related Lung Injury in an Adolescent [case report]. Am J Respir Crit Care Med. 201(4):481–482. eng. [PubMed: 31904992]

Lu SJ, Li L, Duffy BC, Dittmar MA, Durocher LA, Panawennage D, Delaney-Baldwin ER, Spink DC. 2021. Investigation of Vaping Fluids Recovered From New York State E-Cigarette or Vaping Product Use-Associated Lung Injury Patients [chemical analysis]. Front Chem. 9:748935. eng. [PubMed: 34778204]

Lynch J, Lorenz L, Brueggemeyer JL, Lanzarotta A, Falconer TM, Wilson RA. 2021. Simultaneous Temperature Measurements and Aerosol Collection During Vaping for the Analysis of Delta(9)-Tetrahydrocannabinol and Vitamin E Acetate Mixtures in Ceramic Coil Style Cartridges [aerosol chemical analysis]. Front Chem. 9:734793. eng. [PubMed: 34434923]

Macedonia TV, Krefft SD, Rose CS. 2020. Persistent Severe Fixed Airways Obstruction in a High-Dosing E-cigarette User [case report]. J Gen Intern Med. 35(1):345–349. eng. [PubMed: 31705470]

MacMurdo M, Lin C, Saeedan MB, Doxtader EE, Mukhopadhyay S, Arrossi V, Reynolds J, Ghosh S, Choi H. 2020. e-Cigarette or Vaping Product Use-Associated Lung Injury: Clinical, Radiologic, and Pathologic Findings of 15 Cases [case series]. Chest. 157(6):e181–e187. eng. [PubMed: 32505323]

Maddock SD, Cirulis MM, Callahan SJ, Keenan LM, Pirozzi CS, Raman SM, Aberegg SK. 2019. Pulmonary Lipid-Laden Macrophages and Vaping [case series]. N Engl J Med. 381(15):1488–1489. eng. [PubMed: 31491073]

Madison MC, Landers CT, Gu B-H, Chang C-Y, Tung H-Y, You R, Hong MJ, Baghaei N, Song L-Z, Porter P. 2020. Electronic cigarettes disrupt lung lipid homeostasis and innate immunity independent of nicotine. The Journal of clinical investigation. 129(10):4290–4304.

Madison MC, Landers CT, Gu BH, Chang CY, Tung HY, You R, Hong MJ, Baghaei N, Song LZ, Porter P et al. 2019. Electronic cigarettes disrupt lung lipid homeostasis and innate immunity independent of nicotine [research in vitro]. J Clin Invest. 129(10):4290–4304. eng. [PubMed: 31483291]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Margham J, McAdam K, Forster M, Liu C, Wright C, Mariner D, Proctor C. 2016. Chemical Composition of Aerosol from an E-Cigarette: A Quantitative Comparison with Cigarette Smoke [research tox]. Chem Res Toxicol. 29(10):1662–1678. eng. [PubMed: 27641760]

Marliere C, De Greef J, Gohy S, Hoton D, Wallemacq P, Jacquet LM, Belkhir L. 2020. Fatal e-cigarette or vaping associated lung injury (EVALI): a first case report in Europe [case report]. Eur Respir J. 56(1). eng.

Marrocco A, Singh D, Christiani DC, Demokritou P. 2022. E-cigarette (E-cig) liquid composition and operational voltage define the in vitro toxicity of Delta8Tetrahydrocannabinol/Vitamin E Acetate (Delta8THC/VEA) e-cig aerosols [research in vitro]. Toxicol Sci.

Massachusetts Co. 2019. Bill H.4196, 191st (2019–2020). An Act modernizing tobacco control. https://malegislature.gov/Bills/191/H4196. (H4196).

Matsumoto S, Fang X, Traber MG, Jones KD, Langelier C, Hayakawa Serpa P, Calfee CS, Matthay MA, Gotts JE. 2020. Dose-Dependent Pulmonary Toxicity of Aerosolized Vitamin E Acetate [research tox]. Am J Respir Cell Mol Biol. 63(6):748–757. [PubMed: 32822237]

Matsumoto S, Traber MG, Leonard SW, Choi J, Fang X, Maishan M, Wick KD, Jones KD, Calfee CS, Gotts JE et al. 2022. Aerosolized Vitamin E Acetate Causes Oxidative Injury in Mice and in Alveolar Macrophages. Am J Physiol Lung Cell Mol Physiol. eng.

Matta P, Hamati JN, Unno HL, Fox MD. 2020. E-cigarette or Vaping Product Use-Associated Lung Injury (EVALI) Without Respiratory Symptoms [case report]. Pediatrics. 145(5).

McCauley L, Markin C, Hosmer D. 2012. An unexpected consequence of electronic cigarette use. Chest. 141(4):1110. [PubMed: 22474155]

McGuigan M, Chapman G, Lewis E, Watson CH, Blount BC, Valentin-Blasini L. 2022. High-Performance Liquid Chromatography-Tandem Mass Spectrometry Analysis of Carbonyl Emissions from E-Cigarette, or Vaping, Products [chemical analysis]. ACS Omega. 7(9):7655–7661. eng. [PubMed: 35284728]

McKee RH, Adenuga MD, Carrillo JC. 2015. Characterization of the toxicological hazards of hydrocarbon solvents. Crit Rev Toxicol. 45(4):273–365. eng. [PubMed: 25868376]

Meehan-Atrash J, Luo W, McWhirter KJ, Strongin RM. 2019. Aerosol Gas-Phase Components from Cannabis E-Cigarettes and Dabbing: Mechanistic Insight and Quantitative Risk Analysis. ACS Omega. 4(14):16111–16120. [PubMed: 31592479]

Messina MD, Levin TL, Conrad LA, Bidiwala A. 2020. Vaping associated lung injury: A potentially life-threatening epidemic in US youth [case series]. Pediatr Pulmonol. 55(7):1705–1711. eng. [PubMed: 32251551]

Mikheev VB, Ivanov A. 2022. Analysis of the Aerosol Generated from Tetrahydrocannabinol, Vitamin E Acetate, and Their Mixtures. Toxics. 10(2). eng.

Mikheev VB, Klupinski TP, Ivanov A, Lucas EA, Strozier ED, Fix C. 2020. Particle Size Distribution and Chemical Composition of the Aerosolized Vitamin E Acetate [research NP]. Aerosol Sci Technol. 54(9):993–998. [PubMed: 33132476]

Mikosz CA, Danielson M, Anderson KN, Pollack LA, Currie DW, Njai R, Evans ME, Goodman AB, Twentyman E, Wiltz JL et al. 2020. Characteristics of Patients Experiencing Rehospitalization or Death After Hospital Discharge in a Nationwide Outbreak of E-cigarette, or Vaping, Product Use-Associated Lung Injury - United States, 2019 [MMWR report]. MMWR Morb Mortal Wkly Rep. 68(5152):1183–1188. eng. [PubMed: 31895917]

Miskoff JA, Chaudhri M. 2020. E-cigarette or Vaping Product Use-associated Lung Injury: A Case of an Adult Female Leading to Hospitalization [case report]. Cureus. 12(1):e6765. eng. [PubMed: 32140332]

Modi S, Sangani R, Alhajhusain A. 2015. Acute Lipoid Pneumonia Secondary to E-Cigarettes Use: An Unlikely Replacement for Cigarettes. Chest. 148(4):382A. [PubMed: 25569856]

Moore K, Young Ii H, Ryan MF. 2015. Bilateral Pneumonia and Pleural Effusions Subsequent to Electronic Cigarette Use [case report]. Open Journal of Emergency Medicine. 03(03):18–22.

Moritz ED, Zapata LB, Lekiachvili A, Glidden E, Annor FB, Werner AK, Ussery EN, Hughes MM, Kimball A, DeSisto CL et al. 2019. Update: Characteristics of Patients in a National Outbreak of E-cigarette, or Vaping, Product Use-Associated Lung Injuries - United States, October 2019 [MMWR report]. MMWR Morb Mortal Wkly Rep. 68(43):985–989. eng. [PubMed: 31671085]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Moshensky A, Du M, Shin J, Advani I, Gunge D, Mathew D, Alkolla R, Du A, Javier C, Ma L. 2021. Vaping-induced metabolomic signatures in the circulation of mice are driven by device type, e-liquid, exposure duration and sex. ERJ Open Research. 7(3).

Mughal MS, Dalmacion DLV, Mirza HM, Kaur IP, Dela Cruz MA, Kramer VE. 2020. E-cigarette or vaping product use associated lung injury, (EVALI) - A diagnosis of exclusion [case report]. Respir Med Case Rep. 31:101174. [PubMed: 32775191]

Mukhopadhyay S, Mehrad M, Dammert P, Arrossi AV, Sarda R, Brenner DS, Maldonado F, Choi H, Ghobrial M. 2020. Lung Biopsy Findings in Severe Pulmonary Illness Associated With E-Cigarette Use (Vaping) [case series]. Am J Clin Pathol. 153(1):30–39. eng. [PubMed: 31621873]

Mull ES, Erdem G, Nicol K, Adler B, Shell R. 2020. Eosinophilic Pneumonia and Lymphadenopathy Associated With Vaping and Tetrahydrocannabinol Use [case report]. Pediatrics. 145(4).

Mull ES, Shell R, Adler B, Holtzlander M. 2020. Bronchiectasis associated with electronic cigarette use: A case series [case series]. Pediatr Pulmonol. 55(12):3443–3449. [PubMed: 32902877]

Munagala R, Ullah A, Sharma C, Bhatt AN, Keshavamurthy J. 2021. Smoky Diagnosis: Importance of Patient History in Vaping Associated Lung Injury [case report]. Cureus. 13(11):e19596. eng. [PubMed: 34926065]

Muthumalage T, Friedman MR, McGraw MD, Ginsberg G, Friedman AE, Rahman I. 2020. Chemical Constituents Involved in E-Cigarette, or Vaping Product Use-Associated Lung Injury (EVALI) [research tox]. Toxics. 8(2).

Muthumalage T, Lucas JH, Wang Q, Lamb T, McGraw MD, Rahman I. 2020a. Pulmonary Toxicity and Inflammatory Response of E-Cigarette Vape Cartridges Containing Medium-Chain Triglycerides Oil and Vitamin E Acetate: Implications in the Pathogenesis of EVALI [research in vitro]. Toxics. 8(3).

Muthumalage T, Lucas JH, Wang Q, Lamb T, McGraw MD, Rahman I. 2020b. Pulmonary toxicity and inflammatory response of e-cigarettes containing medium-chain triglyceride oil and vitamin E acetate: Implications in the pathogenesis of EVALI but independent of SARS-COV-2 COVID-19 related proteins. bioRxiv. eng.

Muthumalage T, Rahman I. 2019. Cannabidiol differentially regulates basal and LPS-induced inflammatory responses in macrophages, lung epithelial cells, and fibroblasts [research in vitro]. Toxicol Appl Pharmacol. 382:114713. eng. [PubMed: 31437494]

Narimani M, da Silva G. 2020. Does ‘Dry Hit’ vaping of vitamin E acetate contribute to EVALI? Simulating toxic ketene formation during e-cigarette use [research tox]. PLoS One. 15(9):e0238140. [PubMed: 32881943]

National Institute for Occupational Safety and Health NIOSH. 1994. Ketene.

Navon L, Jones CM, Ghinai I, King BA, Briss PA, Hacker KA, Layden JE. 2019. Risk Factors for E-Cigarette, or Vaping, Product Use-Associated Lung Injury (EVALI) Among Adults Who Use E-Cigarette, or Vaping, Products - Illinois, July-October 2019 [MMWR report]. MMWR Morb Mortal Wkly Rep. 68(45):1034–1039. eng. [PubMed: 31725708]

NewYorkState. 2020. New York State Department of Health. Comprehensive Tobacco Control Policy, https://health.ny.gov/press/releases/2020/2020-05-18_fl_nicotine_vapor_products_ban.htm.

Nicol J, Fraser R, Walker L, Liu C, Murphy J, Proctor CJ. 2020. Comprehensive Chemical Characterization of the Aerosol Emissions of a Vaping Product Based on a New Technology [research tox]. Chem Res Toxicol. 33(3):789–799. eng. [PubMed: 32122129]

O’Carroll O, Sharma K, Fabre A, Murphy DJ, Keane MP, McCarthy C. 2020. Vaping-associated lung injury [case report]. Thorax. 75(8):706–707. eng. [PubMed: 32414864]

Ocampo-Gonzalez FA, Park JW. 2020. Cytologic features of vaping-induced lung injury: A case report [case report]. Diagn Cytopathol. 48(2):174–176. eng. [PubMed: 31714032]

Odish MF, Bellinghausen A, Golts E, Owens RL. 2020. E-cigarette, or vaping, product use-associated lung injury (EVALI) treated with veno-venous extracorporeal membrane oxygenation (VV-ECMO) and ultra-protective ventilator settings [case report]. BMJ Case Rep. 13(7).

Omaiye EE, McWhirter KJ, Luo W, Pankow JF, Talbot P. 2019. High-Nicotine Electronic Cigarette Products: Toxicity of JUUL Fluids and Aerosols Correlates Strongly with Nicotine and Some Flavor Chemical Concentrations [research tox]. Chem Res Toxicol. 32(6):1058–1069. eng. [PubMed: 30896936]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Pajak A, Bascoy S, Li JC, Benninghoff M, Deitchman A. 2020. E-cigarette or Vaping Product Use Associated Lung Injury Among Three Young Adults: A Retrospective Case Series From Delaware [cases series]. Cureus. 12(10):e11031. eng. [PubMed: 33224641]

Panse PM, Feller FF, Butt YM, Smith ML, Larsen BT, Tazelaar HD, Harvin HJ, Gotway MB. 2020. Radiologic and Pathologic Correlation in EVALI [case series]. AJR Am J Roentgenol. 215(5):1057–1064. [PubMed: 32877245]

Park H-R, O'Sullivan M, Vallarino J, Shumyatcher M, Himes BE, Park J-A, Christiani DC, Allen J, Lu Q. 2019. Transcriptomic response of primary human airway epithelial cells to flavoring chemicals in electronic cigarettes. Scientific reports. 9(1):1–11. [PubMed: 30626917]

Park HR, Vallarino J, O'Sullivan M, Wirth C, Panganiban RA, Webb G, Shumyatcher M, Himes BE, Park JA, Christiani DC et al. 2021. Electronic cigarette smoke reduces ribosomal protein gene expression to impair protein synthesis in primary human airway epithelial cells [researh in vitro]. Sci Rep. 11(1):17517. [PubMed: 34471210]

Patel VN, Rouse M, Brown C, Pandya S. 2020. Ground Glass Opacities Observed in a 26-Year-Old Coronavirus Disease 2019 (COVID-19) Rule-Out Patient With a History of Vape Use [case report]. Cureus. 12(9):e10302. [PubMed: 33052265]

Patten SB. 2021. Vaping and Mental Health [commentary]. J Can Acad Child Adolesc Psychiatry. 30(1):3–5. [PubMed: 33552167]

Perrenoud A, Vetos D, Wabwire G. 2020. Vaping-induced lung injury in a 21-year-old woman [case report]. BMJ Case Rep. 13(11). eng.

Perrine CG, Pickens CM, Boehmer TK, King BA, Jones CM, DeSisto CL, Duca LM, Lekiachvili A, Kenemer B, Shamout M et al. 2019. Characteristics of a Multistate Outbreak of Lung Injury Associated with E-cigarette Use, or Vaping - United States, 2019. MMWR Morb Mortal Wkly Rep. 68(39):860–864. eng. [PubMed: 31581168]

Phung B, Lam A. 2020. Pediatric Acute Respiratory Distress Syndrome and Hypersensitivity Pneumonitis Related to E-cigarette Vaping [case report]. J Pediatr Intensive Care. 9(2):128–134. [PubMed: 32351768]

Pitlick MM, Lang DK, Meehan AM, McCoy CP. 2021. EVALI: A Mimicker of COVID-19 [case report]. Mayo Clin Proc Innov Qual Outcomes. 5(3):682–687. English. [PubMed: 33817560]

Podguski S, Kaur G, Muthumalage T, McGraw MD, Rahman I. 2022. Noninvasive systemic biomarkers of e-cigarette or vaping use-associated lung injury: a pilot study. ERJ Open Res. 8(2). eng.

Poschenrieder F, Rotter M, Gschwendtner A, Hamer OW. 2020. E-cigarette-induced lung disease: from acute to chronic [case report]. Lancet. 396(10250):564. [PubMed: 32828188]

Pourchez J, Parisse S, Sarry G, Perinel-Ragey S, Vergnon J-M, Clotagatide A, Prévôt N. 2018. Impact of power level and refill liquid composition on the aerosol output and particle size distribution generated by a new-generation e-cigarette device [research NP]. Aerosol Science and Technology. 52(4):359–369.

Pray IW, Atti SK, Tomasallo C, Meiman JG. 2020. E-cigarette, or Vaping, Product Use-Associated Lung Injury Among Clusters of Patients Reporting Shared Product Use - Wisconsin, 2019 [MMWR report]. MMWR Morb Mortal Wkly Rep. 69(9):236–240. eng. [PubMed: 32134907]

Priemer DS, Gravenmier C, Batouli A, Hooper JE. 2020. Overview of Pathologic Findings of Vaping in the Context of an Autopsy Patient With Chronic Injury [case report]. Arch Pathol Lab Med. 144(11):1408–1413. eng. [PubMed: 32383974]

Puebla Neira D, Tambra S, Bhasin V, Nawgiri R, Duarte AG. 2020. Discordant bilateral bronchoalveolar lavage findings in a patient with acute eosinophilic pneumonia associated with counterfeit tetrahydrocannabinol oil vaping [case report]. Respir Med Case Rep. 29:101015. eng. [PubMed: 32071854]

Qarajeh R, Kitchen J. 2020. THC Vaping-Induced Acute Respiratory Distress Syndrome [case report commentary]. Am J Med. 133(4):e147–e148. [PubMed: 31794698]

Rao DR, Maple KL, Dettori A, Afolabi F, Francis JKR, Artunduaga M, Lieu TJ, Aldy K, Cao DJ, Hsu S et al. 2020. Clinical Features of E-cigarette, or Vaping, Product Use-Associated Lung Injury in Teenagers [case series]. Pediatrics. 146(1). eng.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Reagan-Steiner S, Gary J, Matkovic E, Ritter JM, Shieh WJ, Martines RB, Werner AK, Lynfield R, Holzbauer S, Bullock H et al. 2020. Pathological findings in suspected cases of e-cigarette, or vaping, product use-associated lung injury (EVALI): a case series [case series]. Lancet Respir Med. 8(12):1219–1232. [PubMed: 32763198]

Reddy A, Jenssen BP, Chidambaram A, Yehya N, Lindell RB. 2021. Characterizing e-cigarette vaping-associated lung injury in the pediatric intensive care unit [case report]. Pediatr Pulmonol. 56(1):162–170. [PubMed: 32970368]

Register F 2016. Deeming Tobacco Products To Be Subject to the Federal Food, Drug, and Cosmetic Act, as Amended by the Family Smoking Prevention and Tobacco Control Act; Restrictions on the Sale and Distribution of Tobacco Products and Required Warning Statements for Tobacco Products; Final Rule. 21 CFR Parts 1100, 1140, and 1143 81(90).

Regmi MR, Tandan N, Parajuli P, Maini R, Lara Garcia OE, Jagtap P, Kulkarni A. 2021. Extracorporeal membranous oxygenation for a severe case of vaping associated lung injury. Pulmonology. 27(1):69–70. eng. [PubMed: 32507701]

Research GV. 2021. E-cigarette And Vape Market Growth & Trends, Available online: https://www.grandviewresearch.com/press-release/global-e-cigarette-vaping-market# (updated May 2021).

Ring Madsen L, Vinther Krarup NH, Bergmann TK, Baerentzen S, Neghabat S, Duval L, Knudsen ST. 2016. A Cancer That Went Up in Smoke: Pulmonary Reaction to e-Cigarettes Imitating Metastatic Cancer [article]. Chest. 149(3):e65–67. [PubMed: 26965975]

Rodriguez JA, Roa AA, Lemos-Ramirez JC. 2020. E-Cigarette or Vaping Product Use-Associated Lung Injury (EVALI) Mimicking COVID-19 Disease [case report]. Case Rep Pulmonol. 2020:8821289. English. [PubMed: 33204563]

Roman S, Millet C, Geris S, Manickam R, Mechineni A. 2021. Crazy vaping and crazy-paving, a case of E-Cigarette/Vaping-Associated Lung Injury (EVALI) with chest CT showing crazy-paving pattern. Radiol Case Rep. 16(11):3208–3212. eng. [PubMed: 34484520]

Ronald AA, Defta D, Wright J, Rothstein B. 2020. Extensive Pneumorrhachis Associated with Vaping-Induced Lung Injury [case report]. World Neurosurg. 140:308–311. eng. [PubMed: 32473332]

Rouabhia M, Park HJ, Semlali A, Zakrzewski A, Chmielewski W, Chakir J. 2017. E-cigarette vapor induces an apoptotic response in human gingival epithelial cells through the caspase-3 pathway. Journal of cellular physiology. 232(6):1539–1547. [PubMed: 27808425]

Rowell TR, Keating JE, Zorn BT, Glish GL, Shears SB, Tarran R. 2020. Flavored e-liquids increase cytoplasmic Ca(2+) levels in airway epithelia. Am J Physiol Lung Cell Mol Physiol. 318(2):L226–L241. [PubMed: 31693394]

Sacci P, Au A, Hutchinson M. 2020. E-cigarette or vaping product use-associated lung injury (EVALI) characterized by pulmonary ultrasound [case report]. J Am Coll Emerg Physicians Open. 1(5):1101–1103. eng. [PubMed: 33145564]

Sakla NM, Gattu R, Singh G, Sadler M. 2020. Vaping-associated acute respiratory distress syndrome [case report]. Emerg Radiol. 27(1):103–106. eng. [PubMed: 31820270]

Salam S, Saliba NA, Shihadeh A, Eissenberg T, El-Hellani A. 2020. Flavor-toxicant correlation in e-cigarettes: a meta-analysis [review]. Chemical research in toxicology. 33(12):2932–2938. [PubMed: 33185445]

Salzman GA, Alqawasma M, Asad H. 2019. Vaping Associated Lung Injury (EVALI): An Explosive United States Epidemic [case report]. Mo Med. 116(6):492–496. [PubMed: 31911735]

Sangani R, Rojas E, Forte M, Zulfikar R, Prince N, Tasoglou A, Goldsmith T, Casuccio G, Boyd J, Olfert IM et al. 2021. Electronic Cigarettes and Vaping-Associated Lung Injury (EVALI): A Rural Appalachian Experience [case report]. Hosp Pract (1995). 49(2):79–87. [PubMed: 33136442]

Schaffer S, Strang A, Saul D, Krishnan V, Chidekel A. 2022. Adolescent E-cigarette or Vaping Use-Associated Lung Injury in the Delaware Valley: A Review of Hospital-Based Presentation, Management, and Outcomes. Cureus. 14(2):e21988. eng. [PubMed: 35282521]

Sharma M, Anjum H, Bulathsinghala CP, Buch M, Suran SR. 2019. A Case Report of Secondary Spontaneous Pneumothorax Induced by Vape [case report]. Cureus. 11(11).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Shields PG, Song M-A, Freudenheim JL, Brasky TM, McElroy JP, Reisinger SA, Weng DY, Ren R, Eissenberg T, Wewers MD. 2020. Lipid laden macrophages and electronic cigarettes in healthy adults. EBioMedicine. 60:102982. [PubMed: 32919101]

Shields PG, Song MA, Freudenheim JL, Brasky TM, McElroy JP, Reisinger SA, Weng DY, Ren R, Eissenberg T, Wewers MD et al. 2020. Lipid laden macrophages and electronic cigarettes in healthy adults [case series]. EBioMedicine. 60:102982. [PubMed: 32919101]

Singh A 2022. Adolescent e-cigarette or vaping product use-associated lung injury: A case series and review of the literature. Pediatr Pulmonol. 57(4):1076–1084. eng. [PubMed: 35072351]

Singh A, Tan Q, Saccone NM, Lindner DH. 2020. A Case of Vaping TCH Oil Leading to Vaping Associated Pulmonary Injury: Our Approach to Its Diagnosis, Management, and Recommendations [case report]. Case Rep Pulmonol. 2020:6138083. eng. [PubMed: 31976113]

Singh DP, Begum R, Kaur G, Bagam P, Kambiranda D, Singh R, Batra S. 2021. E-cig vapor condensate alters proteome and lipid profiles of membrane rafts: impact on inflammatory responses in A549 cells [research in vitro/in vivo]. Cell Biol Toxicol. 37(5):773–793. [PubMed: 33469865]

Smith E, Cherian R, McGillen B. 2020. A Case of E-cigarette, or Vaping, Product Use-Associated Lung Injury (EVALI) in a Previously Healthy Patient: Case Report and Literature Review [case report]. J Gen Intern Med. 35(9):2767–2770. [PubMed: 32440996]

Son Y, Mishin V, Laskin JD, Mainelis G, Wackowski OA, Delnevo C, Schwander S, Khlystov A, Samburova V, Meng Q. 2019. Hydroxyl radicals in e-cigarette vapor and e-vapor oxidative potentials under different vaping patterns. Chemical research in toxicology. 32(6):1087–1095. [PubMed: 30977360]

Stephens D, Patel JK, Angelo D, Frunzi J. 2020. Cannabis Butane Hash Oil Dabbing Induced Lung Injury Mimicking Atypical Pneumonia [case report]. Cureus. 12(2):e7033. eng. [PubMed: 32211266]

Strongin RM. 2019. E-Cigarette Chemistry and Analytical Detection [aerosol chemistry]. Annu Rev Anal Chem (Palo Alto Calif). 12(1):23–39. [PubMed: 30848928]

Tanz LJ, Christensen A, Knuth KB, Hoffman MN, Dandeneau D, Koehler K, Moore Z, Herndon S, Davidson K, Fleischauer A. 2021. Characteristics of an Outbreak of E-cigarette, or Vaping, Product Use-Associated Lung Injury-North Carolina, 2019 [report]. N C Med J. 82(6):384–392. eng. [PubMed: 34750211]

Taylor J, Wiens T, Peterson J, Saravia S, Lunda M, Hanson K, Wogen M, D'Heilly P, Margetta J, Bye M et al. 2019. Characteristics of E-cigarette, or Vaping, Products Used by Patients with Associated Lung Injury and Products Seized by Law Enforcement - Minnesota, 2018 and 2019 [MMWR REPORT]. MMWR Morb Mortal Wkly Rep. 68(47):1096–1100. eng. [PubMed: 31774740]

Temas D, Meyer A. 2020. E-Cigarette- and Vaping-Related Lung Injury (EVALI) at a Regional Hospital System in South Carolina [case series]. Case Rep Pulmonol. 2020:5370606. [PubMed: 32509369]

Thakrar PD, Boyd KP, Swanson CP, Wideburg E, Kumbhar SS. 2020. E-cigarette, or vaping, product use-associated lung injury in adolescents: a review of imaging features [case series]. Pediatr Radiol. 50(3):338–344. eng. [PubMed: 31897566]

Thota D, Latham E. 2014. Case report of electronic cigarettes possibly associated with eosinophilic pneumonitis in a previously healthy active-duty sailor [case report]. J Emerg Med. 47(1):15–17. eng. [PubMed: 24462024]

Tierney PA, Karpinski CD, Brown JE, Luo W, Pankow JF. 2016. Flavour chemicals in electronic cigarette fluids. Tobacco control. 25(e1):e10–e15. [PubMed: 25877377]

Tommasi S, Caliri AW, Caceres A, Moreno DE, Li M, Chen Y, Siegmund KD, Besaratinia A. 2019. Deregulation of biologically significant genes and associated molecular pathways in the oral epithelium of electronic cigarette users. International journal of molecular sciences. 20(3):738. [PubMed: 30744164]

Treon JF, Sigmon HE, et al. 1949. Physiologic response of animals exposed to air-borne ketene. J Ind Hyg Toxicol. 31(4):209–219. [PubMed: 18153385]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Triantafyllou GA, Tiberio PJ, Zou RH, Lamberty PE, Lynch MJ, Kreit JW, Gladwin MT, Morris A, Chiarchiaro J. 2019. Vaping-associated Acute Lung Injury: A Case Series [case series]. Am J Respir Crit Care Med. 200(11):1430–1431. eng. [PubMed: 31574235]

Varlet V, Concha-Lozano N, Berthet A, Plateel G, Favrat B, De Cesare M, Lauer E, Augsburger M, Thomas A, Giroud C. 2016. Drug vaping applied to cannabis: Is "Cannavaping" a therapeutic alternative to marijuana? [chemical analysis]. Sci Rep. 6:25599. eng. [PubMed: 27228348]

Vilanilam GK, Purushothaman R, Baskaran NP, Vohra I, Raghavan S, Bean B, Sajovitz L. 2021. Imaging in Vaping-associated Lung Injury: Beyond the Haze [case series]. J Addict Med. 15(3):258–260. [PubMed: 33021553]

Villeneuve T, Prevot G, Le Borgne A, Colombat M, Collot S, Ruiz S, Lanot T, Brouchet L, Rabeau A, Noel-Savina E et al. 2020. Diffuse alveolar haemorrhage secondary to e-cigarette "vaping" associated lung injury (EVALI) in a young European consumer [case report]. Eur Respir J. 56(1). eng.

Wagner J, Chen W, Vrdoljak G. 2020. Vaping cartridge heating element compositions and evidence of high temperatures [research tox]. PLoS One. 15(10):e0240613. [PubMed: 33075091]

Wang G, Wu L. 2020. Healthy People 2020: Social Determinants of Cigarette Smoking and Electronic Cigarette Smoking among Youth in the United States 2010–2018. Int J Environ Res Public Health. 17(20).

Wang KY, Jadhav SP, Yenduri NJS, Lee SA, Farber HJ, Guillerman RP. 2020. E-cigarette or vaping product use-associated lung injury in the pediatric population: imaging features at presentation and short-term follow-up [case series]. Pediatr Radiol. 50(9):1231–1239. eng. [PubMed: 32495177]

Wang L, Chen J, Ho SY, Leung LT, Wang MP, Lam TH. 2020. Exposure to e-cigarette advertising, attitudes, and use susceptibility in adolescents who had never used e-cigarettes or cigarettes. BMC Public Health. 20(1):1349. [PubMed: 32887586]

Wang TW, Neff LJ, Park-Lee E, Ren C, Cullen KA, King BA. 2020. E-cigarette Use Among Middle and High School Students - United States, 2020. MMWR Morb Mortal Wkly Rep. 69(37):1310–1312. [PubMed: 32941408]

Wekon-Kemeni C, Santhanam P, Halani P, Bradford L, Loughlin CE. 2021. A Gut Feeling: Abdominal Symptoms as an Initial Presentation of EVALI. Pediatrics. 147(1). eng.

Werner AK, Koumans EH, Chatham-Stephens K, Salvatore PP, Armatas C, Byers P, Clark CR, Ghinai I, Holzbauer SM, Navarette KA et al. 2020. Hospitalizations and Deaths Associated with EVALI [case series]. N Engl J Med. 382(17):1589–1598. [PubMed: 32320569]

Wilhite R, Patel T, Karle E, Shankar S, Krvavac A. 2019. Diffuse Alveolar Hemorrhage: An Uncommon Manifestation of Vaping-associated Lung Injury [case report]. Cureus. 11(12):e6519. eng. [PubMed: 32025438]

Williams M, Villarreal A, Bozhilov K, Lin S, Talbot P. 2013. Metal and silicate particles including nanoparticles are present in electronic cigarette cartomizer fluid and aerosol. PloS one. 8(3):e57987. [PubMed: 23526962]

Wing C, Bradford AC, Carroll AE, Hollingsworth A. 2020. Association of State Marijuana Legalization Policies for Medical and Recreational Use With Vaping-Associated Lung Disease. JAMA network open. 3(4):e202187–e202187. eng. [PubMed: 32250431]

Wolf M, Richards J. 2020. Acute Eosinophilic Pneumonia Due to Vaping-Associated Lung Injury [case report]. J Crit Care Med (Targu Mures). 6(4):259–262. eng. [PubMed: 33200099]

Works K, Stack L. 2020. E-cigarette or vaping product-use-associated lung injury (EVALI): A case report of a pneumonia mimic with severe leukocytosis and weight loss [case report]. J Am Coll Emerg Physicians Open. 1(1):46–48. [PubMed: 33000013]

Wu D, O'Shea DF. 2020. Potential for release of pulmonary toxic ketene from vaping pyrolysis of vitamin E acetate [research tox]. Proc Natl Acad Sci U S A. 117(12):6349–6355. eng. [PubMed: 32156732]

Youmans AJ, Harwood J. 2020. Gross and Histopathological Findings in the First Reported Vaping-Induced Lung Injury Death in the United States [case report]. Am J Forensic Med Pathol. 41(1):1–4. eng. [PubMed: 31977349]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Young-Wolff KC, Adams SR, Sterling SA, Tan AS, Salloum RG, Torre K, Carter-Harris L, Prochaska JJ. 2021. Nicotine and cannabis vaping among adolescents in treatment for substance use disorders [report]. Journal of Substance Abuse Treatment. 125:108304. [PubMed: 34016296]

Yu V, Rahimy M, Korrapati A, Xuan Y, Zou AE, Krishnan AR, Tsui T, Aguilera JA, Advani S, Alexander LEC. 2016. Electronic cigarettes induce DNA strand breaks and cell death independently of nicotine in cell lines. Oral oncology. 52:58–65. [PubMed: 26547127]

Zhao J, Nelson J, Dada O, Pyrgiotakis G, Kavouras IG, Demokritou P. 2018. Assessing electronic cigarette emissions: linking physico-chemical properties to product brand, e-liquid flavoring additives, operational voltage and user puffing patterns. Inhal Toxicol. 30(2):78–88. eng. [PubMed: 29564955]

Zhao J, Pyrgiotakis G, Demokritou P. 2016. Development and characterization of electronic-cigarette exposure generation system (Ecig-EGS) for the physico-chemical and toxicological assessment of electronic cigarette emissions. Inhal Toxicol. 28(14):658–669. eng. [PubMed: 27829296]

Zhao J, Zhang Y, Sisler JD, Shaffer J, Leonard SS, Morris AM, Qian Y, Bello D, Demokritou P. 2018. Assessment of reactive oxygen species generated by electronic cigarettes using acellular and cellular approaches. J Hazard Mater. 344:549–557. eng. [PubMed: 29102637]

Zhu SH, Sun JY, Bonnevie E, Cummins SE, Gamst A, Yin L, Lee M. 2014. Four hundred and sixty brands of e-cigarettes and counting: implications for product regulation. Tob Control. 23 Suppl 3(Suppl 3):iii3–9. eng. [PubMed: 24935895]

Zou RH, Tiberio PJ, Triantafyllou GA, Lamberty PE, Lynch MJ, Kreit JW, McVerry BJ, Gladwin MT, Morris A, Chiarchiaro J et al. 2020. Clinical Characterization of E-Cigarette, or Vaping, Product Use-associated Lung Injury in 36 Patients in Pittsburgh, Pennsylvania [case series]. Am J Respir Crit Care Med. 201(10):1303–1306. eng. [PubMed: 32023422]

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

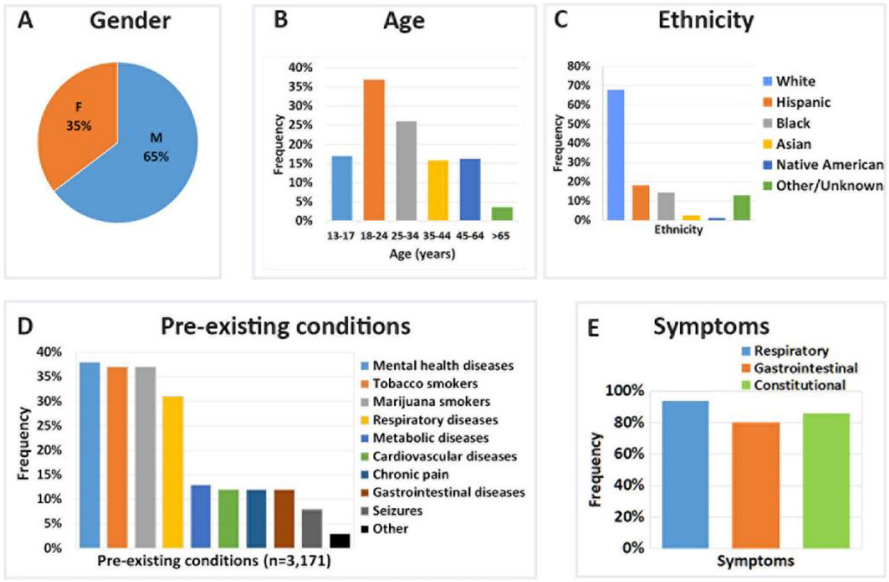


Figure 1.

Summary of the demographic, medical history and clinical symptoms at presentation in emergency department observed in EVALI patients (n=15,748 unless otherwise specified).

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

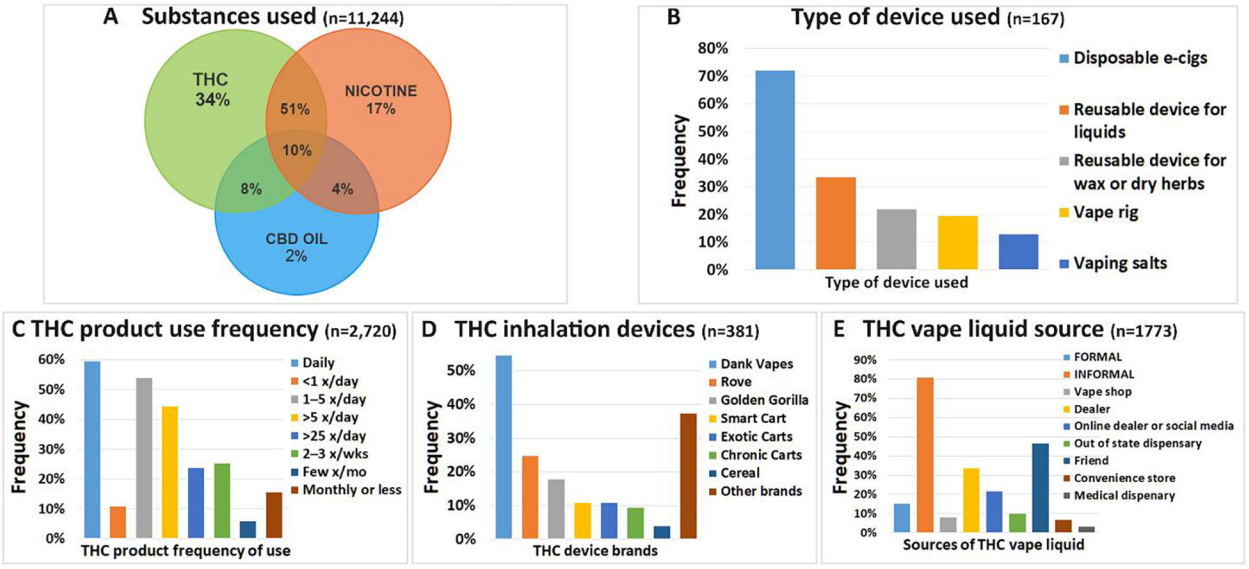


Figure 2.

Relative frequencies of different vaping substances; e-cig device types, brand names and sources; and vaping behavioral patterns of EVALI patients.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 1.

Results from the physical examination and biological specimen testing of EVALI patients.

Findings	References
Physical exam	
Diffuse bibasilar crackles	(Arter et al. 2019; Landman et al. 2019; Salzman et al. 2019; Sharma et al. 2019; Abeles et al. 2020; Al-Abdouh et al. 2020; Casanova et al. 2020; Chen J et al. 2020; Derespina et al. 2020; El Chebib et al. 2020; Essa et al. 2020; Freathy et al. 2020; Gay et al. 2020; Israel et al. 2020; Kinney et al. 2020; Miskoff and Chaudhri 2020; Mughal et al. 2020; Phung and Lam 2020; Puebla Neira et al. 2020; Stephens et al. 2020; Thakrar et al. 2020; Villeneuve et al. 2020; Wolf and Richards 2020; Ayoub et al. 2021; Hoshina 2021; Ismail et al. 2021; Kalantary et al. 2021; Munagala et al. 2021; Regmi et al. 2021)
Bilateral wheezes	(Anderson Ryan P and Zechar Katie 2019; Salzman et al. 2019; Ali et al. 2020; Bolona et al. 2020; Colesar and McCollum 2020; Mull, Erdem, et al. 2020; Sacci et al. 2020; Stephens et al. 2020; Temas and Meyer 2020; Thakrar et al. 2020; Ayoub et al. 2021; Ganne et al. 2021; Ismail et al. 2021; Kalantary et al. 2021; Khan et al. 2021; Singh A 2022)
Rhonchi, use of accessory muscles and diminished but clear breath sounds bilaterally at the bases	(Aftab et al. 2019; Alqahtani et al. 2019; Anderson Ryan P and Zechar Katie 2019; Wilhite et al. 2019; Alzghoul et al. 2020; Bharat et al. 2020; Chapman et al. 2020; DeCarli et al. 2020; El Chebib et al. 2020; Gay et al. 2020; Jankharia et al. 2020; Mull, Erdem, et al. 2020; Ocampo-Gonzalez and Park 2020; Phung and Lam 2020; Stephens et al. 2020; Temas and Meyer 2020; Thakrar et al. 2020; Wolf and Richards 2020; Ganne et al. 2021; Roman et al. 2021; Vilanilam et al. 2021)
Fever Temperature ≥38 °C	(Arter et al. 2019; Blagev et al. 2019; Kalininskiy et al. 2019; Landman et al. 2019; Layden Jennifer E. et al. 2019; Aberegg, Maddock, et al. 2020; Ali et al. 2020; Bharat et al. 2020; Billa et al. 2020; Bolona et al. 2020; Casanova et al. 2020; Chen J et al. 2020; Choe et al. 2020; Colesar and McCollum 2020; Dicpinigaitis et al. 2020; Doukas et al. 2020; El Chebib et al. 2020; Freathy et al. 2020; Fryman et al. 2020; Galo et al. 2020; Ghinai et al. 2020; Heinzerling et al. 2020; Kooragayalu et al. 2020; Matta et al. 2020; Mughal et al. 2020; Ocampo-Gonzalez and Park 2020; Pajak et al. 2020; Perrenoud et al. 2020; Phung and Lam 2020; Puebla Neira et al. 2020; Rao et al. 2020; Rodriguez et al. 2020; Ronald et al. 2020; Sakla et al. 2020; Singh A et al. 2020; Smith et al. 2020; Temas and Meyer 2020; Werner et al. 2020; Zou et al. 2020; Adhikari, Koritala, et al. 2021; Ayoub et al. 2021; Cruz-Vidal et al. 2021; Harada et al. 2021; Hassoun et al. 2021; Kalantary et al. 2021; Munagala et al. 2021; Pitlick et al. 2021; Reddy et al. 2021; Tanz et al. 2021; Vilanilam et al. 2021)
Tachycardia Heart rate >100 beats per minute	(Alqahtani et al. 2019; Anderson Ryan P and Zechar Katie 2019; Aokage et al. 2019; Arter et al. 2019; Blagev et al. 2019; Kalininskiy et al. 2019; Landman et al. 2019; Layden Jennifer E. et al. 2019; Wilhite et al. 2019; Acharya et al. 2020; Al-Abdouh et al. 2020; Aldy et al. 2020; Ansari-Gilani et al. 2020; Bharat et al. 2020; Billa et al. 2020; Casanova et al. 2020; Chawla and Weiler 2020; Chen J et al. 2020; Choe et al. 2020; Colesar and McCollum 2020; DeCarli et al. 2020; Deliwala et al. 2020; Doukas et al. 2020; Edmonds et al. 2020; El Chebib et al. 2020; Freathy et al. 2020; Israel et al. 2020; Kooragayalu et al. 2020; Matta et al. 2020; Mughal et al. 2020; Ocampo-Gonzalez and Park 2020; Pajak et al. 2020; Perrenoud et al. 2020; Phung and Lam 2020; Puebla Neira et al. 2020; Rao et al. 2020; Rodriguez et al. 2020; Ronald et al. 2020; Singh A et al. 2020; Smith et al. 2020; Stephens et al. 2020; Temas and Meyer 2020; Werner et al. 2020; Works and Stack 2020; Adhikari, Koritala, et al. 2021; Ahmed et al. 2021; Cruz-Vidal et al. 2021; Ganne et al. 2021; Harada et al. 2021; Hassoun et al. 2021; Hoshina 2021; Ismail et al. 2021; Kalantary et al. 2021; Khan et al. 2021; Krishnan et al. 2021; Kupelian et al. 2021; Munagala et al. 2021; Pitlick et al. 2021; Tanz et al. 2021; Vilanilam et al. 2021; Wekon-Kemeni et al. 2021; Lim et al. 2022)
Tachypnea respiratory rate >20 breaths per minute	(Aftab et al. 2019; Alqahtani et al. 2019; Anderson Ryan P and Zechar Katie 2019; Aokage et al. 2019; Arter et al. 2019; Blagev et al. 2019; Davidson et al. 2019; Kalininskiy et al. 2019; Layden Jennifer E. et al. 2019; Abeles et al. 2020; Acharya et al. 2020; Al-Abdouh et al. 2020; Aldy et al. 2020; Ansari-Gilani et al. 2020; Bharat et al. 2020; Billa et al. 2020; Casanova et al. 2020; Cedano et al. 2020; Chapman et al. 2020; Chen J et al. 2020; Colesar and McCollum 2020; DeCarli et al. 2020; Deliwala et al. 2020; Derespina et al. 2020; Doukas et al. 2020); Duffy B et al. (2020); (Edmonds et al. 2020; El Chebib et al. 2020; Fedt et al. 2020; Freathy et al. 2020; Gay et al. 2020; Israel et al. 2020); Jiang et al. (2020); (Kooragayalu et al. 2020; Lu MA et al. 2020; Mughal et al. 2020; Mull, Erdem, et al. 2020; Ocampo-Gonzalez and Park 2020; Perrenoud et al. 2020; Phung and Lam 2020; Priemer et al. 2020; Puebla Neira et al. 2020; Rao et al. 2020; Rodriguez et al. 2020; Ronald et al. 2020; Sacci et al. 2020; Sakla et al. 2020; Singh A et al. 2020; Smith et al. 2020; Thakrar et al. 2020; Villeneuve et al. 2020; Adhikari, Koritala, et al. 2021; Ahmed et al. 2021; Cruz-Vidal et al. 2021; Ganne et al. 2021; Harada et al. 2021; Hassoun et al. 2021; Hoshina 2021; Ismail et al. 2021; Kalantary et al. 2021; Khan et al. 2021; Kupelian et al. 2021; Munagala et al. 2021; Pitlick et al. 2021; Tanz et al. 2021; Singh A 2022)
High blood pressure (BP)> 120/80 mmHg	(Alqahtani et al. 2019; Ali et al. 2020; Ansari-Gilani et al. 2020; Bolona et al. 2020; Choe et al. 2020; Deliwala et al. 2020; Doukas et al. 2020; Patel et al. 2020; Rao et al. 2020; Rodriguez et al. 2020; Singh A et al. 2020; Ayoub et al. 2021; Harada et al. 2021; Hassoun et al. 2021; Kalantary et al. 2021; Krishnan et al. 2021; Kupelian et al. 2021; Roman et al. 2021; Vilanilam et al. 2021; Wekon-Kemeni et al. 2021)
White Blood Cells (WBC) count > 11000/mm^3 with neutrophils predominance (>60%)	(Aftab et al. 2019; Alqahtani et al. 2019; Anderson Ryan P and Zechar Katie 2019; Aokage et al. 2019; Arter et al. 2019; Blagev et al. 2019; Davidson et al. 2019; Kalininskiy et al. 2019; Landman et al. 2019; Layden Jennifer E. et al. 2019; Maddock et al. 2019; Salzman et al. 2019; Sharma et al. 2019; Triantafyllou et al. 2019; Wilhite et al. 2019; Abeles et al. 2020; Aberegg, Cirulis, et al. 2020; Aberegg, Maddock, et al. 2020; Ahmad et al. 2020; Al-Abdouh et al. 2020; Aldy et al. 2020; Ali et al. 2020; Amin et al. 2020; Ansari-Gilani et al. 2020; Bharat et al. 2020; Bozkanat et al. 2020; Carroll et al. 2020; Casanova et al. 2020; Chawla and Weiler 2020;

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Findings	References
	Chen J et al. 2020; Choe et al. 2020; Colesar and McCollum 2020; DeCarli et al. 2020; Deliwala et al. 2020; Dicpinigaitis et al. 2020; Doukas et al. 2020; Edmonds et al. 2020; El Chebib et al. 2020; Essa et al. 2020; Fedt et al. 2020; Gay et al. 2020; Girvin and Naidich 2020; Israel et al. 2020; Kass et al. 2020; Kinney et al. 2020; Kooragayalu et al. 2020; Marliere et al. 2020; Matta et al. 2020; Messina et al. 2020); Mikheev et al. (2020); (Mughal et al. 2020; Mukhopadhyay et al. 2020; Pajak et al. 2020; Perrenoud et al. 2020; Phung and Lam 2020; Priemer et al. 2020; Puebla Neira et al. 2020; Rao et al. 2020; Rodriguez et al. 2020; Sakla et al. 2020; Singh A et al. 2020; Smith et al. 2020; Stephens et al. 2020; Temas and Meyer 2020; Thakrar et al. 2020; Wolf and Richards 2020; Works and Stack 2020; Zou et al. 2020; Adhikari, Koritala, et al. 2021; Ahmed et al. 2021; Hassoun et al. 2021; Isakov et al. 2021; Ismail et al. 2021; Kalantary et al. 2021; Krishnan et al. 2021; Kupelian et al. 2021; Munagala et al. 2021; Reddy et al. 2021; Regmi et al. 2021; Roman et al. 2021; Tanz et al. 2021; Vilanilam et al. 2021; Wekon-Kemeni et al. 2021; Helfgott et al. 2022; Lim et al. 2022; Podguski et al. 2022; Singh A 2022)
Inflammatory markers elevated: Erythrocyte sedimentation rate ESR >30 mm/hr, C reactive protein CRP> 10 mg/l Procalcitonin >0.07 ng/ml LDH >280 U/L Pro-BNP >125 pg/mL	(Aokage et al. 2019; Blagev et al. 2019; Kalininskiy et al. 2019; Maddock et al. 2019; Triantafyllou et al. 2019; Wilhite et al. 2019; Abeles et al. 2020; Aberegg, Cirulis, et al. 2020; Al-Abdouh et al. 2020; Alzghoul et al. 2020; Amin et al. 2020; Bharat et al. 2020; Bolona et al. 2020; Bozkanat et al. 2020; Carroll et al. 2020; Casanova et al. 2020; Cedano et al. 2020; Chawla and Weiler 2020; Chen J et al. 2020; Choe et al. 2020; DeCarli et al. 2020; Derespina et al. 2020; Doukas et al. 2020; Essa et al. 2020; Fedt et al. 2020; Fryman et al. 2020; Galo et al. 2020; Girvin and Naidich 2020; Heinzerling et al. 2020; Israel et al. 2020; Kass et al. 2020; Kinney et al. 2020; Kooragayalu et al. 2020; Marliere et al. 2020; Matta et al. 2020; Messina et al. 2020; Mughal et al. 2020; Mukhopadhyay et al. 2020; O'Carroll et al. 2020; Pajak et al. 2020; Phung and Lam 2020; Puebla Neira et al. 2020; Rao et al. 2020; Rodriguez et al. 2020; Singh A et al. 2020; Smith et al. 2020; Temas and Meyer 2020; Thakrar et al. 2020; Works and Stack 2020; Adhikari, Koritala, et al. 2021; Ahmed et al. 2021; Ayoub et al. 2021; Cruz-Vidal et al. 2021; Ganne et al. 2021; Harada et al. 2021; Hassoun et al. 2021; Ismail et al. 2021; Krishnan et al. 2021; Pitlick et al. 2021; Wekon-Kemeni et al. 2021; Helfgott et al. 2022; Podguski et al. 2022; Schaffer et al. 2022; Singh A 2022)
Oxygen saturation <95% on room air or with supplemental oxygen	(Aftab et al. 2019; Alqahtani et al. 2019; Aokage et al. 2019; Arter et al. 2019; Blagev et al. 2019; Kalininskiy et al. 2019; Landman et al. 2019; Layden Jennifer E. et al. 2019; Salzman et al. 2019; Sharma et al. 2019; Wilhite et al. 2019; Abeles et al. 2020; Al-Abdouh et al. 2020; Ali et al. 2020; Amin et al. 2020; Billa et al. 2020; Bolona et al. 2020; Cedano et al. 2020; Chapman et al. 2020; Chawla and Weiler 2020; Choe et al. 2020; DeCarli et al. 2020; Derespina et al. 2020; Dicpinigaitis et al. 2020; Doukas et al. 2020; El Chebib et al. 2020; Essa et al. 2020; Farooq et al. 2020; Fedt et al. 2020; Fryman et al. 2020; Galo et al. 2020; Gay et al. 2020; Kaous et al. 2020; Kinney et al. 2020; Kooragayalu et al. 2020; Lu MA et al. 2020; MacMurdo et al. 2020; Mughal et al. 2020; Mull, Erdem, et al. 2020; Mull, Shell, et al. 2020; Ocampo-Gonzalez and Park 2020; Odish et al. 2020; Pajak et al. 2020; Phung and Lam 2020; Priemer et al. 2020; Puebla Neira et al. 2020; Qarajeh and Kitchen 2020; Rao et al. 2020; Rodriguez et al. 2020; Sacci et al. 2020; Sakla et al. 2020; Singh A et al. 2020; Stephens et al. 2020; Temas and Meyer 2020; Thakrar et al. 2020; Villeneuve et al. 2020; Wolf and Richards 2020; Zou et al. 2020; Krishnan et al. 2021) (Aberegg, Cirulis, et al. 2020; Ansari-Gilani et al. 2020; Bharat et al. 2020; Heinzerling et al. 2020; Israel et al. 2020; Adhikari, Koritala, et al. 2021; Ahmed et al. 2021; Ayoub et al. 2021; Cruz-Vidal et al. 2021; Ganne et al. 2021; Harada et al. 2021; Ismail et al. 2021; Kalantary et al. 2021; Kupelian et al. 2021; Pitlick et al. 2021; Reddy et al. 2021; Regmi et al. 2021; Roman et al. 2021; Tanz et al. 2021)
Blood Gas Analysis (BGA): Primary respiratory alkalosis: pH≥ 7.45, PaCO2 < 35 mmHg. Normal range BGA: pH 7.35–7.45, pCO2 35–45 mmHg, pO2 80–100 mmHg, and HCO3 22–26 mMol/L.	(Alqahtani et al. 2019; Anderson Ryan P and Zechar Katie 2019; Landman et al. 2019; Salzman et al. 2019; Sharma et al. 2019; Acharya et al. 2020; Aldy et al. 2020; Ali et al. 2020; Casanova et al. 2020; Fryman et al. 2020; Gay et al. 2020; Kass et al. 2020; Mull, Shell, et al. 2020; Perrenoud et al. 2020; Puebla Neira et al. 2020; Temas and Meyer 2020; Werner et al. 2020; Adhikari, Koritala, et al. 2021; Ahmed et al. 2021; Reddy et al. 2021)
Infectious diseases screening (bacteria, virus, fungi, mycobacters) = negative **Rheumatological and vasculitis serologic evaluation (**ANA, ANCA, GBM-Ab, cryoglobulins, APA, RF, anti-CCPA, anti-MPO-Ab, anti-dsDNA, Anti-RNP) = negative.	(Aftab et al. 2019; Alqahtani et al. 2019; Anderson Ryan P and Zechar Katie 2019; Blagev et al. 2019; Butt et al. 2019; Hallowell et al. 2019; Kalininskiy et al. 2019; Layden Jennifer E. et al. 2019; Maddock et al. 2019; Salzman et al. 2019; Wilhite et al. 2019; Abeles et al. 2020; Aberegg, Cirulis, et al. 2020; Acharya et al. 2020; Ahmad et al. 2020; Al-Abdouh et al. 2020; Alzghoul et al. 2020; Baumann et al. 2020; Baxter et al. 2020; Bharat et al. 2020; Billa et al. 2020; Carroll et al. 2020; Casanova et al. 2020; Cedano et al. 2020; Chawla and Weiler 2020; Colesar and McCollum 2020; DeCarli et al. 2020; Deliwala et al. 2020; Doukas et al. 2020; Edmonds et al. 2020; Fryman et al. 2020; Galo et al. 2020; Girvin and Naidich 2020; Kass et al. 2020; Kinney et al. 2020; Kooragayalu et al. 2020; Macedonia et al. 2020; Mughal et al. 2020; Mull, Shell, et al. 2020; Pajak et al. 2020; Perrenoud et al. 2020; Poschenrieder et al. 2020; Priemer et al. 2020; Puebla Neira et al. 2020; Qarajeh and Kitchen 2020; Rao et al. 2020; Singh A et al. 2020; Temas and Meyer 2020; Ayoub et al. 2021; Cruz-Vidal et al. 2021; Ganne et al. 2021; Hassoun et al. 2021; Hoshina 2021; Ismail et al. 2021; Kalantary et al. 2021; Khan et al. 2021; Kupelian et al. 2021; Lilley et al. 2021; Pitlick et al. 2021; Reddy et al. 2021; Regmi et al. 2021; Roman et al. 2021; Wekon-Kemeni et al. 2021; Helfgott et al. 2022; Schaffer et al. 2022)
Pulmonary function test abnormal Restrictive or obstructive pattern	(Carroll et al. 2020; Jankharia et al. 2020; Macedonia et al. 2020; Matta et al. 2020; Messina et al. 2020; Rao et al. 2020; Thakrar et al. 2020; Zou et al. 2020; Hassoun et al. 2021; Schaffer et al. 2022)

Findings	References
Urine toxicological screening positive for cannabinoids	(Alqahtani et al. 2019; Kalininskiy et al. 2019; Wilhite et al. 2019; Aberegg, Cirulis, et al. 2020; Al-Abdouh et al. 2020; Blount et al. 2020; Bozkanat et al. 2020; DeCarli et al. 2020; Deliwala et al. 2020; Dicpinigaitis et al. 2020; Doukas et al. 2020; Fryman et al. 2020; Kass et al. 2020; Kinney et al. 2020; Kooragayalu et al. 2020; Lu MA et al. 2020; MacMurdo et al. 2020; Matta et al. 2020; Mull, Erdem, et al. 2020; Odish et al. 2020; Pajak et al. 2020; Perrenoud et al. 2020; Rao et al. 2020; Rodriguez et al. 2020; Sacci et al. 2020; Shields P. G. et al. 2020; Singh A et al. 2020; Temas and Meyer 2020; Werner et al. 2020; Harada et al. 2021; Hassoun et al. 2021; Hoshina 2021; Reddy et al. 2021; Sangani et al. 2021; Wekon-Kemeni et al. 2021)

Abbreviations: ANA antinuclear antibodies, ANCA Antineutrophil cytoplasmic antibody, GBM-Ab Anti–glomerular basement membrane antibodies, APA anti-phospholipid antibodies, RF rheumatoid factor anti–CCPA Cyclic citrullinated peptide antibodies, anti MPO-Ab Myeloperoxidase-antibodies, anti-dsDNA Anti-double stranded DNA, Anti-RNP anti ribonucleoprotein.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 2

Summary of the imaging characteristics of EVALI patients: Chest radiographs and CT.

Findings	References
Lesions, pattern and distributions	
Bilateral ground-glass opacities	(Alqahtani et al. 2019; Aokage et al. 2019; Arter et al. 2019; Blagev et al. 2019; Butt et al. 2019; Davidson et al. 2019; Hallowell et al. 2019; Kalininskiy et al. 2019; Layden Jennifer E. et al. 2019; Maddock et al. 2019; Salzman et al. 2019; Sharma et al. 2019; Triantafyllou et al. 2019; Wilhite et al. 2019; Abeles et al. 2020; Acharya et al. 2020; Ahmad et al. 2020; Al-Abdouh et al. 2020; Aldy et al. 2020; Ali et al. 2020; Alzghoul et al. 2020; Amin et al. 2020; Ansari-Gilani et al. 2020; Artunduaga et al. 2020; Baumann et al. 2020; Bharat et al. 2020; Billa et al. 2020; Bolona et al. 2020; Bozkanat et al. 2020; Carroll et al. 2020; Casanova et al. 2020; Cedano et al. 2020; Chen J et al. 2020; Chidambaram et al. 2020; Colesar and McCollum 2020; Conuel et al. 2020; DeCarli et al. 2020; Deliwala et al. 2020; Derespina et al. 2020; Dicpinigaitis et al. 2020; Doukas et al. 2020; Edmonds et al. 2020; Essa et al. 2020; Freathy et al. 2020; Fryman et al. 2020; Galo et al. 2020; Gay et al. 2020; Girvin and Naidich 2020; Griffiths et al. 2020; Gutsche et al. 2020; Heinzerling et al. 2020; Israel et al. 2020; Jankharia et al. 2020; Kass et al. 2020; Kinney et al. 2020; Kooragayalu et al. 2020; Lu MA et al. 2020; Macedonia et al. 2020; MacMurdo et al. 2020; Matta et al. 2020; Messina et al. 2020; Miskoff and Chaudhri 2020; Mughal et al. 2020; Mukhopadhyay et al. 2020; Mull, Erdem, et al. 2020; O'Carroll et al. 2020; Ocampo-Gonzalez and Park 2020; Odish et al. 2020; Pajak et al. 2020; Panse et al. 2020; Patel et al. 2020; Perrenoud et al. 2020; Phung and Lam 2020; Priemer et al. 2020; Puebla Neira et al. 2020; Qarajeh and Kitchen 2020; Rao et al. 2020; Reagan-Steiner et al. 2020; Sakla et al. 2020; Singh A et al. 2020; Smith et al. 2020; Stephens et al. 2020; Temas and Meyer 2020; Thakrar et al. 2020; Villeneuve et al. 2020; Wang KY et al. 2020; Werner et al. 2020; Wolf and Richards 2020; Works and Stack 2020; Zou et al. 2020; Ayoub et al. 2021; Cruz-Vidal et al. 2021; Ganne et al. 2021; Harada et al. 2021; Hassoun et al. 2021; Hoshina 2021; Isakov et al. 2021; Ismail et al. 2021; Kalantary et al. 2021; Khan et al. 2021; Kligerman et al. 2021; Krishnan et al. 2021; Kupelian et al. 2021; Lilley et al. 2021; Munagala et al. 2021; Pitlick et al. 2021; Reddy et al. 2021; Regmi et al. 2021; Sangani et al. 2021; Vilanilam et al. 2021; Wekon-Kemeni et al. 2021; Helfgott et al. 2022; Lim et al. 2022; Schaffer et al. 2022; Singh A 2022)
Bibasilar parenchymal consolidation	(Aftab et al. 2019; Aokage et al. 2019; Arter et al. 2019; Butt et al. 2019; Hallowell et al. 2019; Maddock et al. 2019; Triantafyllou et al. 2019; Al-Abdouh et al. 2020; Ansari-Gilani et al. 2020; Artunduaga et al. 2020; Baumann et al. 2020; Bharat et al. 2020); Bhat et al. (2020); (Casanova et al. 2020; Chapman et al. 2020; Chidambaram et al. 2020; Conuel et al. 2020; Dicpinigaitis et al. 2020; Fedt et al. 2020; Fryman et al. 2020; Gay et al. 2020; Girvin and Naidich 2020; Kass et al. 2020; MacMurdo et al. 2020; Mukhopadhyay et al. 2020; Pajak et al. 2020; Panse et al. 2020; Poschenrieder et al. 2020; Reagan-Steiner et al. 2020; Smith et al. 2020; Temas and Meyer 2020; Villeneuve et al. 2020; Wang KY et al. 2020; Werner et al. 2020; Wolf and Richards 2020; Works and Stack 2020; Hassoun et al. 2021; Hoshina 2021; Isakov et al. 2021; Khan et al. 2021; Kligerman et al. 2021; Lilley et al. 2021; Sangani et al. 2021; Vilanilam et al. 2021; Helfgott et al. 2022; Schaffer et al. 2022)
Bilateral pleural effusions	(Kalininskiy et al. 2019; Layden Jennifer E. et al. 2019; Artunduaga et al. 2020; Carroll et al. 2020; Casanova et al. 2020; Colesar and McCollum 2020; El Chebib et al. 2020; Girvin and Naidich 2020; Kass et al. 2020); Lanzarotta et al. (2020); (Messina et al. 2020; Panse et al. 2020; Temas and Meyer 2020; Thakrar et al. 2020; Wang KY et al. 2020; Ayoub et al. 2021; Ismail et al. 2021; Khan et al. 2021; Kligerman et al. 2021; Kupelian et al. 2021; Lilley et al. 2021; Reddy et al. 2021; Tanz et al. 2021; Vilanilam et al. 2021; Helfgott et al. 2022)
Bilateral opacities	(Aftab et al. 2019; Alqahtani et al. 2019; Arter et al. 2019; Butt et al. 2019; Hallowell et al. 2019; Layden Jennifer E. et al. 2019; Maddock et al. 2019; Salzman et al. 2019; Triantafyllou et al. 2019; Abeles et al. 2020; Aberegg, Cirulis, et al. 2020; Ahmad et al. 2020; Al-Abdouh et al. 2020; Ali et al. 2020; Amin et al. 2020; Baumann et al. 2020; Bharat et al. 2020; Billa et al. 2020; Bozkanat et al. 2020; Carroll et al. 2020; Cedano et al. 2020; Chapman et al. 2020; Chawla and Weiler 2020; Chen J et al. 2020; Chidambaram et al. 2020; Derespina et al. 2020; Doukas et al. 2020; Essa et al. 2020; Fedt et al. 2020; Girvin and Naidich 2020; Gutsche et al. 2020; Israel et al. 2020; Jankharia et al. 2020; Kaous et al. 2020; Kass et al. 2020; Kinney et al. 2020; Kooragayalu et al. 2020; Messina et al. 2020; O'Carroll et al. 2020; Pajak et al. 2020; Phung and Lam 2020; Puebla Neira et al. 2020; Qarajeh and Kitchen 2020; Reagan-Steiner et al. 2020; Ronald et al. 2020; Sakla et al. 2020; Thakrar et al. 2020; Wang KY et al. 2020; Werner et al. 2020; Wolf and Richards 2020; Works and Stack 2020; Ahmed et al. 2021; Cruz-Vidal et al. 2021; Ganne et al. 2021; Harada et al. 2021; Isakov et al. 2021; Khan et al. 2021; Lilley et al. 2021; Munagala et al. 2021; Pitlick et al. 2021; Regmi et al. 2021; Vilanilam et al. 2021; Wekon-Kemeni et al. 2021; Helfgott et al. 2022)
Bilateral pulmonary interstitial infiltrates	(Alqahtani et al. 2019; Anderson Ryan P and Zechar Katie 2019; Butt et al. 2019; Layden Jennifer E. et al. 2019; Ali et al. 2020; Alzghoul et al. 2020; Baxter et al. 2020; Bharat et al. 2020; Casanova et al. 2020; Chawla and Weiler 2020; Chen J et al. 2020; Colesar and McCollum 2020; El Chebib et al. 2020; Fan et al. 2020; Farooq et al. 2020; Heinzerling et al. 2020; Hilton et al. 2020; MacMurdo et al. 2020; Marliere et al. 2020; Messina et al. 2020; Phung and Lam 2020; Reagan-Steiner et al. 2020; Rodriguez et al. 2020; Ronald et al. 2020; Singh A et al. 2020; Temas and Meyer 2020; Werner et al. 2020; Youmans and Harwood 2020; Adhikari, Koritala, et al. 2021; Ahmed et al. 2021; Cruz-Vidal et al. 2021; Ganne et al. 2021; Ismail et al. 2021; Kalantary et al. 2021; Munagala et al. 2021; Pitlick et al. 2021; Reddy et al. 2021; Roman et al. 2021; Vilanilam et al. 2021)
Interlobular septal thickening	(Triantafyllou et al. 2019; Aberegg, Cirulis, et al. 2020; Aldy et al. 2020; Artunduaga et al. 2020; Carroll et al. 2020; Chen J et al. 2020; Chidambaram et al. 2020; Dicpinigaitis et al. 2020; Doukas et al. 2020; Essa et al. 2020; Gay et al. 2020; Girvin and Naidich 2020; Griffiths et al. 2020; Israel et al. 2020; Kass et al. 2020; Lu MA et al. 2020; MacMurdo et al. 2020; Marliere et al. 2020; Matta et al. 2020; Messina et al. 2020; Mull, Erdem, et al. 2020; Ocampo-Gonzalez and Park 2020; Pajak et al. 2020; Panse et al. 2020; Perrenoud et al. 2020; Phung and Lam 2020;

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Findings	References
	Qarajeh and Kitchen 2020; Rao et al. 2020; Sakla et al. 2020; Smith et al. 2020; Thakrar et al. 2020; Wang KY et al. 2020; Works and Stack 2020; Ayoub et al. 2021; Cruz-Vidal et al. 2021; Harada et al. 2021; Hassoun et al. 2021; Isakov et al. 2021; Khan et al. 2021; Kligerman et al. 2021; Krishnan et al. 2021; Lilley et al. 2021; Munagala et al. 2021; Pitlick et al. 2021; Roman et al. 2021; Wekon-Kemeni et al. 2021; Schaffer et al. 2022)
Pleural / Subpleural sparing	(Kalininskiy et al. 2019; Landman et al. 2019; Layden Jennifer E. et al. 2019; Triantafyllou et al. 2019; Aberegg, Cirulis, et al. 2020; Artunduaga et al. 2020; Bharat et al. 2020; Carroll et al. 2020; Chidambaram et al. 2020; Conuel et al. 2020; Essa et al. 2020; Fryman et al. 2020; Girvin and Naidich 2020; Griffiths et al. 2020; Heinzerling et al. 2020; Israel et al. 2020; Kaous et al. 2020; MacMurdo et al. 2020; Matta et al. 2020; Messina et al. 2020; Mughal et al. 2020; O'Carroll et al. 2020; Pajak et al. 2020; Panse et al. 2020; Smith et al. 2020; Temas and Meyer 2020; Thakrar et al. 2020; Wang KY et al. 2020; Works and Stack 2020; Ayoub et al. 2021; Cruz-Vidal et al. 2021; Harada et al. 2021; Isakov et al. 2021; Kalantary et al. 2021; Khan et al. 2021; Kligerman et al. 2021; Krishnan et al. 2021; Lilley et al. 2021; Roman et al. 2021; Sangani et al. 2021; Schaffer et al. 2022)
Fibrotic features	(Kalininskiy et al. 2019; Khan et al. 2021; Roman et al. 2021; Singh A 2022)
Pneumo-thorax	(Butt et al. 2019; Triantafyllou et al. 2019; Ali et al. 2020; Gutsche et al. 2020; Panse et al. 2020; Ronald et al. 2020; Khan et al. 2021; Munagala et al. 2021; Reddy et al. 2021; Tanz et al. 2021)
Pneumo-mediastinum	(Layden Jennifer E. et al. 2019; Triantafyllou et al. 2019; Aldy et al. 2020; Artunduaga et al. 2020; Chidambaram et al. 2020; Essa et al. 2020; Messina et al. 2020; Panse et al. 2020; Rao et al. 2020; Ronald et al. 2020; Adhikari, Manduva, et al. 2021; Isakov et al. 2021; Khan et al. 2021; Kligerman et al. 2021; Reddy et al. 2021; Tanz et al. 2021; Schaffer et al. 2022; Singh A 2022)
Pulmonary emboli	(Wilhite et al. 2019; Artunduaga et al. 2020; Harada et al. 2021)
Mediastinal/hilar lymphadenopathy	(Kalininskiy et al. 2019; Ahmad et al. 2020; Carroll et al. 2020; Derespina et al. 2020; Essa et al. 2020; Fan et al. 2020; Galo et al. 2020; Girvin and Naidich 2020; Messina et al. 2020; Panse et al. 2020; Reagan-Steiner et al. 2020; Temas and Meyer 2020; Thakrar et al. 2020; Wang KY et al. 2020; Kalantary et al. 2021; Kligerman et al. 2021; Lim et al. 2022; Singh A 2022)
Reverse halo sign	(Chidambaram et al. 2020; Isakov et al. 2021)

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 3

Summary of the biochemical analyses of bronchoalveolar lavage (BAL) samples collected from EVALI patients.

Findings	References
Macrophages predominance	(Blagev et al. 2019; Butt et al. 2019; Kalininskiy et al. 2019; Maddock et al. 2019; Triantafyllou et al. 2019; Aberegg, Cirulis, et al. 2020; Baumann et al. 2020; Conuel et al. 2020; DeCarli et al. 2020; Essa et al. 2020; Fryman et al. 2020; Kaous et al. 2020; Kass et al. 2020; Marliere et al. 2020; Mughal et al. 2020; Mukhopadhyay et al. 2020; O'Carroll et al. 2020; Youmans and Harwood 2020; Lilley et al. 2021; Pitlick et al. 2021; Sangani et al. 2021)
Eosinophil predominance	(Arter et al. 2019; Blagev et al. 2019; Phung and Lam 2020)
Neutrophil predominance	(Aftab et al. 2019; Aokage et al. 2019; Blagev et al. 2019; Butt et al. 2019; Davidson et al. 2019; Landman et al. 2019; Layden Jennifer E. et al. 2019; Maddock et al. 2019; Abeles et al. 2020; Ahmad et al. 2020; Alzghoul et al. 2020; Bharat et al. 2020; Carroll et al. 2020; Choe et al. 2020; Conuel et al. 2020; Essa et al. 2020; Fryman et al. 2020; Griffiths et al. 2020; Kaous et al. 2020; Kass et al. 2020; Kooragayalu et al. 2020; Odish et al. 2020; Perrenoud et al. 2020; Puebla Neira et al. 2020; Rao et al. 2020; Singh A et al. 2020; Temas and Meyer 2020; Thakrar et al. 2020; Villeneuve et al. 2020; Works and Stack 2020; Al-Hamdani et al. 2021; Krishnan et al. 2021)
Lymphocytic Predominance	(Butt et al. 2019; Davidson et al. 2019; Sharma et al. 2019; Ali et al. 2020; Alzghoul et al. 2020; Casanova et al. 2020; Fryman et al. 2020; Hilton et al. 2020; Poschenrieder et al. 2020)
Diffuse alveolar hemorrhage	(Alqahtani et al. 2019; Fryman et al. 2020; Villeneuve et al. 2020)
Organizing pneumonia (activate type 2 pneumocytes)	(Ansari-Gilani et al. 2020; Essa et al. 2020; Fryman et al. 2020; Gay et al. 2020; Mughal et al. 2020; Poschenrieder et al. 2020; Cruz-Vidal et al. 2021; Lilley et al. 2021; Munagala et al. 2021; Roman et al. 2021)
Lipid laden macrophages/ foamy macrophages	(Aftab et al. 2019; Alqahtani et al. 2019; Blagev et al. 2019; Butt et al. 2019; Davidson et al. 2019; Kalininskiy et al. 2019; Layden Jennifer E. et al. 2019; Maddock et al. 2019; Abeles et al. 2020; Aberegg, Cirulis, et al. 2020; Ahmad et al. 2020; Alzghoul et al. 2020; Carroll et al. 2020; Casanova et al. 2020; Chidambaram et al. 2020; Choe et al. 2020; Colesar and McCollum 2020; Conuel et al. 2020; Derespina et al. 2020; Dicpinigaitis et al. 2020; Freathy et al. 2020; Galo et al. 2020; Gay et al. 2020; Girvin and Naidich 2020; Griffiths et al. 2020; Israel et al. 2020; Kaous et al. 2020; Kass et al. 2020; Kinney et al. 2020; Kooragayalu et al. 2020; Messina et al. 2020; Mukhopadhyay et al. 2020; O'Carroll et al. 2020; Ocampo-Gonzalez and Park 2020; Poschenrieder et al. 2020; Shields P. G. et al. 2020; Thakrar et al. 2020; Wolf and Richards 2020; Harada et al. 2021; Kupelian et al. 2021; Lilley et al. 2021; Munagala et al. 2021; Pitlick et al. 2021; Sangani et al. 2021)
RBC	(Alqahtani et al. 2019; Blagev et al. 2019; Wilhite et al. 2019; Ali et al. 2020; Carroll et al. 2020; Derespina et al. 2020; Edmonds et al. 2020; Griffiths et al. 2020; Mull, Shell, et al. 2020; Temas and Meyer 2020; Villeneuve et al. 2020; Ahmed et al. 2021; Kupelian et al. 2021)
WBC	(Alqahtani et al. 2019; Blagev et al. 2019; Triantafyllou et al. 2019; Ali et al. 2020; Temas and Meyer 2020; Villeneuve et al. 2020; Ahmed et al. 2021; Ismail et al. 2021; Krishnan et al. 2021)
BACTERIA VIRUS FUNGI NEGATIVE	(Alqahtani et al. 2019; Arter et al. 2019; Blagev et al. 2019; Kalininskiy et al. 2019; Landman et al. 2019; Maddock et al. 2019; Sharma et al. 2019; Abeles et al. 2020; Ahmad et al. 2020; Al-Abdouh et al. 2020; Aldy et al. 2020; Ali et al. 2020; Alzghoul et al. 2020; Baumann et al. 2020; Baxter et al. 2020; Carroll et al. 2020; Casanova et al. 2020; Chapman et al. 2020; Chawla and Weiler 2020; Chen J et al. 2020; Chidambaram et al. 2020; Choe et al. 2020; DeCarli et al. 2020; Derespina et al. 2020; Dicpinigaitis et al. 2020; Farooq et al. 2020; Freathy et al. 2020; Fryman et al. 2020; Galo et al. 2020; Griffiths et al. 2020; Kass et al. 2020; Mull, Shell, et al. 2020; Ocampo-Gonzalez and Park 2020; Odish et al. 2020; Phung and Lam 2020; Poschenrieder et al. 2020; Puebla Neira et al. 2020; Rao et al. 2020; Smith et al. 2020; Temas and Meyer 2020; Wolf and Richards 2020; Works and Stack 2020; Ahmed et al. 2021; Krishnan et al. 2021; Vilanilam et al. 2021)
Fibrin exudates within airspace	(Essa et al. 2020; Fryman et al. 2020; Kinney et al. 2020)
VEA	(Blount et al. 2019; Taylor et al. 2019; Blount et al. 2020)
THC OR METABOLITES	(Blount et al. 2019; Blount et al. 2020)
NICOTINE	(Blount et al. 2019; Blount et al. 2020)

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 4

Summary of histo-pathology patterns from transbronchial lung biopsy of EVALI patients.

Findings	References
Respiratory bronchiolitis	(Butt et al. 2019; Layden Jennifer E. et al. 2019; Macedonia et al. 2020)
Organizing pneumonia	(Butt et al. 2019; Layden Jennifer E. et al. 2019; Ansari-Gilani et al. 2020; Baumann et al. 2020; Cedano et al. 2020; Fathima and Zhang 2020; Lu MA et al. 2020; MacMurdo et al. 2020; Mukhopadhyay et al. 2020; Panse et al. 2020; Reagan-Steiner et al. 2020; Youmans and Harwood 2020; Cruz-Vidal et al. 2021; Lilley et al. 2021; Munagala et al. 2021; Regmi et al. 2021)
Mild interstitial fibrosis	(Baumann et al. 2020; Kaous et al. 2020; Priemer et al. 2020)
Alveolar fibrosis	
Acute lung injury	(Fathima and Zhang 2020; Freathy et al. 2020; MacMurdo et al. 2020; Mukhopadhyay et al. 2020; Panse et al. 2020; Reagan-Steiner et al. 2020)
Lipoid pneumonia	(Freathy et al. 2020)
Acute fibrinous pneumonitis with organization	(Butt et al. 2019; Panse et al. 2020; Reagan-Steiner et al. 2020)
Diffuse alveolar damage	(Butt et al. 2019; Layden Jennifer E. et al. 2019; Griffiths et al. 2020; MacMurdo et al. 2020; Marliere et al. 2020; Messina et al. 2020; Mukhopadhyay et al. 2020; Panse et al. 2020; Priemer et al. 2020; Reagan-Steiner et al. 2020; Werner et al. 2020; Youmans and Harwood 2020)
Diffuse alveolar hemorrhage	(Hallowell et al. 2019; Kaous et al. 2020; Youmans and Harwood 2020)
Fibrinous pleuritic	(Hallowell et al. 2019)
Granulomatous inflammation	(Hallowell et al. 2019; Layden Jennifer E. et al. 2019; MacMurdo et al. 2020)
Neutrophils and eosinophils	(Hallowell et al. 2019)
Lymphocytic infiltration	(Kaous et al. 2020; Macedonia et al. 2020; Mukhopadhyay et al. 2020)
Foamy Macrophages in airspace	(Layden Jennifer E. et al. 2019; Baumann et al. 2020; Fathima and Zhang 2020; Freathy et al. 2020; Griffiths et al. 2020; Macedonia et al. 2020; Messina et al. 2020; Mukhopadhyay et al. 2020; Panse et al. 2020; Priemer et al. 2020; Reagan-Steiner et al. 2020; Werner et al. 2020; Youmans and Harwood 2020)
Fibrinous exudates in airspaces	(Fathima and Zhang 2020; Mukhopadhyay et al. 2020; Panse et al. 2020; Youmans and Harwood 2020)
Interstitial chronic inflammation	(Baumann et al. 2020; Fathima and Zhang 2020; Mukhopadhyay et al. 2020; Panse et al. 2020; Priemer et al. 2020)
No evidence of exogenous lipoid pneumonia	(Mukhopadhyay et al. 2020)
Acid-Fast Bacilli and Grocott-Gomori's methenamine silver stain (GMS) negative	(Mukhopadhyay et al. 2020)
Type II pneumocytes hyperplasia	(Fathima and Zhang 2020; Griffiths et al. 2020; Kaous et al. 2020; Panse et al. 2020; Youmans and Harwood 2020)
Focal acute inflammation in airspaces	(Landman et al. 2019; Layden Jennifer E. et al. 2019; Mukhopadhyay et al. 2020)

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 5

Summary of chemical analysis of counterfeit or **patient-provided** cartridges used by EVALI patients

Author	Method	Results
(Muthumalage, Friedman, et al. 2020)	• Chemical analysis of rinses or e-cigs liquids collected from: **1.** Counterfeit or patient-provided e-cig vaping cartridges (n = 38), **2.** CBD-containing e-cig vaping cartridges (n = 4) **3.** Medical-grade (positive) e-cig vaping cartridges • Gas chromatography (GC) and mass spectrometry (MS). • Chemical analysis of aerosols from e-cig vaping cartridges sampled in 1L vacuum bottles, for 10 minutes with 10 puffs each. – Elemental Analysis of cartridge liquids	• Commonly present constituents in all cartridges: majority were terpenes, silicon compounds. Other compounds included flavors, additives, cannabinoids, plasticizer/ polycaprolactone/ drugs/ manufacturing, humectants/ oil/ plant components, vitamins, and conjugates, miscellaneous. • Chemicals unique to e-cig counterfeit: 2,2-dimethoxybutane, tetramethyl silicate, decane, methyl esters, ethyl esters, siloxanes, acetates, and α-tocopherol/vitamin E acetate (VEA). • Vapor phase constituents in counterfeit cartridge: terpenes, majority were manufacturing/ pesticides/automotive/industrial active and inert agents and solvents. Others: PCP-polycaprolactone/ household, miscellaneous. • Most abundant elements In counterfeit cartridges: Si, Cu, Ni, and Pb (up to 600 ppm)
(Wagner et al. 2020)	• Characterization of 6 THC vape cartridges and 2 nicotine e-cigarette devices. • Among the THC cartridges, 2 were used by EVALI patients in 2019, 2 were unused and filled. 2 THC unused and empty cartridges, and 2 nicotine devices were used as comparison/control. • Extraction of liquid for chemical analysis.	• Cartridges from EVALI patients exhibited severe burn marks, due to the high operating temperature. • The combination of ceramics, metals and high temperatures in newer THC cartridges is consistent with conditions hypothesized to produce VEA reactions during vaping. • Analysis of metals present in filaments and battery contact: Ni and Cr (all devices); Cu, Pb, Au, Sn, Fe, Zr, silicon-rich rubbers, or fluorinated microplastics. The ceramics in the CCell cartridges contained Si, and various amount of Al, Na, K, P. • Metals Ni, Cr, Zn, Cu, Pb, Au, and Sn can also be inhaled when heated at high temperatures.
(Duffy B et al. 2020)	• Analyses of 38 samples from the first 10 New York cases of EVALI • GC-MS Untargeted Analysis • LC-HRMS/MS Untargeted Analysis	• VEA contained in 23/38 samples, concentration range 16–57% • MCT present in 14/38 cartridges, concentration 2–24% • Synthetic cannabinoids and opioids not present • Fungicide myclobutanil: 22/36, 61% - concentration range 0.28– 28.30 μg/g • Pesticide piperonyl butoxide- d9 (PBO-d9): 19/36, 53% -concentration range 0.54– 24.1 μg/g. • Most common chemicals found in 6 commercially available cannabis oil diluent and thickener: D) VEA, Squalane, MCT oil, triethyl citrate (minor), T) bisabolol, isophytol (minor)
(Duffy BC et al. 2021)	• Analysis of 175 cartridges submitted to the Wadsworth Center of the New York State Department of Health (NYSDOH) by medical practitioners and	• 28 cartridges were found to contain THC, of whom 7 clusters contained a similar cannabinoids ratio.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Author	Method	Results
	poison control centers across New York State as part of the statewide 2019–2020 EVALI investigation • HPLC for cannabinoids • For untargeted analysis GC-MS and LC-HRMS	• THC mass from 15–54%. • D9THC concentration range 90.4–2%, D8THC concentration range 98–9.6%. • All the cartridges were diluted with VEA (11), VEA + MCT (11), MCT (4), VEA+MCT+PEG (1), None (1). • Additional cannabinoids: cannabichromene (CBC), cannabidiol (CBD) cannabidivarin (CBDV), cannabidiolic acid (CBDA), cannabigerol (CBG), cannabigerolic acid (CBGA), cannabinol (CBN), tetrahydrocannabinolic acid (THCA) and tetrahydrocannabivarin (THCV). • Clusters were also similar for point of origin in the New York area (manufacturing sources)
(Guo et al. 2021)	• 12 cannabis vape cartridges obtained through the California state surveillance program from September 2018 to December 2019 • Nontargeted GC-MS for cannabis cartridge vape oil • Headspace GC-MS Screen for Cannabis Vape Oil Vapor • SPME GC-MS Screen for Cannabis Vape Oil Aerosol (aerosol was generated from 5 puffs ranged from 15–31 mg) • LIMITATIONS: **1.** vacuum flow used to generate aerosol different from inhaling by a person's breath. **2.** SPME fiber used can only absorb limited amount of volatile and semivolatile compounds. **3.** exact vape temperature cannot be measured, and it can be different as used by consumers; **4.** the same vape device with the same voltage was used which may be different from consumers that use various vape devices with different voltage settings. **5.** various constituents and additives were not accurately quantified in this study.	• Terpenes, terpenoids, flavor, fragrance, cannabinoids, additives were investigated in liquid, vapor, aerosol. • **LIQUIDS**. Flavor names and cannabinoids were mislabeled on the packages. • TERPENES: Found around 60 chemicals, concentration <1–7%. Major terpenes found were consistent with the ones found in Cannabis plants. • CANNABINOIDS: Most common D9THC (concentration 4.5–70%) CBN (1–20%), CBT, CBG, THCV, CBC, D10THC, Cannabifuran. D8THC (>30%) • In samples containing lower cannabinoids, VEA was >30%, MCT 25–39%, PEG 2–15%. • **VAPOR.** When vape oil samples were heated at 200°C : • TERPENES: Increased number of terpenes released (>100), Concentration 60% • CANNABINOIDS: most common CBT, CBN, D9THC (concentration 15%), CBC, D8THC, CBV, THCV. • VEA, PEG, MCT were much lower concentration in vapor: VEA and MCT in vapors were found <7%. • **AEROSOL.** Inconsistency in aerosol generation between cartridges, and between puffs from the same cartridge. • TERPENES. >100 terpenes and natural extract were found in aerosols, >75% total peak area. • CANNABINOIDS. Most common D9THC (concentration 27–63%), CBN, CBC, CBG, THVC, CBT, D10THC, minor cannabinoids were also found. Lower amount compared to oil. • VEA, MCT, PGE were found concentration similar to vapor. Ketene was not found.
(Ciolino, Ranieri, et al. 2021)	• Around 300 cartridges received from the Forensic Chemistry Center, US Food and Drug Administration, in Cincinnati Ohio in 2019–2020. • Chemical analysis of e-liquids for **unnatural THC isomers**: Fourier transform infrared (FT-IR) and	• Compounds found in 214 samples: – D9THC up to 80% w/w (frequently >50% w/w) (38 samples). – D8THC (58 samples) – Major levels of d6a,10aTHC/d10THC isomers (26 samples), – Minor levels of the d6a, 10aTHC/d10THC isomers (138 samples)

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Author	Method	Results
	Raman spectroscopy, HPLC-DAD, GC-MS, LC-HRMS, and DART-HRMS.	– CBD, CBN, CBG, CBC, and varinol cannabinoids (d9THCV and CBDV • Compounds found in 299 samples: – D9THC and THCA (18 samples) – CBD or CBN (few samples) • Other compounds : – D6a,10aTHC, 6aR,9R-D10THC, 6aR,9S-D10THC, exoTHC. • Different THC isomer patterns represent different processes to produce high THC source materials
(Ciolino, Falconer, et al. 2021)	• Around 300 cartridges received from the Forensic Chemistry Center, US Food and Drug Administration, in Cincinnati Ohio in 2019–2020, half associated with EVALI patients, other obtained in the US through independent investigations. • Chemical analysis of **additives** in THC based e-liquids: GC-MS, LC-HRMS, DART-HRMS	• Compounds found: – VEA (50–60% samples), No additives (20% samples), MCT oils (30% samples), PEGs (5% samples), other (20% samples). – Terpenes (85% of samples) – Single component: vitamin E acetate (alpha-tocopherol acetate), triethyl citrate, trioctanoin, or squalane. – Multiple components (in 60 samples): MCT oils, PEG oligomers, pine rosin acids, pine rosin derived methyl esters, dipropylene glycol dibenzoate (DPG dibenzoate) isomers, and sucrose acetate isobutyrate (SAIB) compounds. – Most frequent combination: VEA+MCT – Less frequent combinations: MCT + SAIB, MCT + PEG, MCT + pine rosin acids, and VEA + DPG dibenzoate. – A few vaping liquids contained VEA + MCT oil + SAIB.
(GGonzalez-Jimenez et al. 2021)	• E-**liquid**: 50 cartridges from 2019 EVALI patients, collected from federal and state partners, both nicotine and THC. • **Device:** Jupiter CCELL® Liquid6 510 Thread Cartridge glass tank system with unknown voltage • **Puff topography:** Puff duration 3 s, interval 30 s, puff volume 55 mL, collected 15 puffs. • **Chemical analysis:** triple quadrupole inductively coupled plasma mass spectrometry (QQQ-ICP-MS) for analysis of aluminum, chromium, iron, cobalt, nickel, copper, cadmium, tin, barium, lead.	• Results reported pr 10 puffs. • For most samples, the metal concentration were <LOD. • 5 samples reported levels fir toxic metals: – Cu= concentr range 15.4, 73.15, 447 ng/10 puffs (nicotine samples); 16.1 ng/10 puffs (THC sample) – Ni= 15.5, 36 ng/10 puffs (nicotine samples) – Sn= 4.77, 202.7 ng/10 puffs (nicotine samples) – Pb= 6.71 ng/10 puffs (nicotine samples) • 39 samples THC (+), CBD (+), THC+CBD (+) • 11 samples Nicotine (+)
(Lu SJ et al. 2021)	• Analysis of 284 vaping products from 83 EVALI patients to the Wadsworth Center of the New York State Department of Health (NYSDOH) or by medical	• Cannabinoids only n=39 cases (47%) • Both Cannabinoids and nicotine n=24 cases (28.9%)

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Author	Method	Results
	practitioners and poison control centers across New York State as part of the statewide 2019–2020 EVALI investigation • HPLC for cannabinoids • For untargeted analysis GC-MS, LC-HRMS/MS, for targeted analysys HPLC for cannabidiolic acid (CBDA), cannabigerolic acid (CBGA), cannabigerol (CBG), cannabidiol (CBD), tetrahydrocannabivarin (THCV), cannabinol (CBN), Δ9tetrahydrocannabinol (Δ9-THC), Δ8-tetrahydrocannabinol (Δ8THC), cannabichromene (CBC), cannabidivarin (CBDV), and Δ9-tetrahydrocannabinolic acid-A (THCA). • Untargeted analysis for pesticides: UHPLC coupled with a a quadrupole-orbitrap mass spectrometer (QE-Orbitrap-MS);	• Nicotine only n=20 cases (24.1%) • 202 cannabis vaping products were illicit or black-market products and contained:

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Author	Method	Results
		• Diluents identified in 185 vaping liquids: – Δ9-THC n=194 range 1.1–88.7% – CBG n=102 range 1.2–5.3% – CBN n=86 range 1.1–16.9% – Δ8-THC n=29 range 1.9–88.8% – CBD n=25 range 0.8–44.9% – THCA n=17 range 1.9–87.9% – CBC n=11 range 1.2–2.6% – THCV n=1 range 2.3% – CBDA n=1 range 4% – CBDV – CBGA ND

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Author	Method	Results
		<table><tr><td>No diluents 17 samples, 12 cases VEA only 107 samples, 51 cases MCT only 42 samples, 18 cases PEG only 8 samples 4 cases Castor oil 2 samples 2 cases</td><td>VEA+MCT 19 samples, 8 cases VEA+PEG 4 samples 3 cases MCT+PEG 1 sample 1 cases VEA+MCT+PEG 2 samples 1 case</td></tr></table> • VEA/THC ratio 0.07–5.33, average 1.35 • VEA concentration 37.0 ± 15.4 mass%, range 2.0–67.8. • 159/202 THC vaping products contained pesticides and pesticides metabolites, including: Myclobutanil (101 samples), piperonyl butoxide (75), bifenazate (59), bifenthrin (38), trifloxytrobin (29), metalaxyl (25), tecubonazole (19), malathion (11), propamocarb (10, etoxazole (9), triticonazole (6), boscalid (5), propiconazole (3). • Diluents: Terpenes: Caryophyllene (8/9 samples), limonene (7/9 samples), myrcene (5/9 samples), etc. • 82 NICOTINE samples were also tested: – Additive: Benzoic Acid – Carriers: Glycerin, Propylene glycol, Benzyl alcohol – Flavors: Triacetin, Vanillin, Levomenthol, menthol, Triethyl Citrate, Ethyl maltol – Cooling agents: WS-3, WS-23
(McGuigan et al. 2022)	• E-**liquid/device**: 77 e-cig/vaping products collected from 37 EvAll patients. • **Puff topography:** 55 mL puff volume, 3 s puff duration, 30 s puff interval, square puff profile, operated at the higher voltage (max 4 V). 15 puffs collected for each product • **Chemical analysis:** HPLC-MS aerosol carbonyl content.	• CDC EVALI 45 samples were examined: 34 containing THC, 10 containing nicotine, (nicotine, CBD and THC), 1 containing no appreciable amount of THC, nicotine or CBD. • Carbonyls detected: – Acetaldehyde (89% of samples) = range 0.0856–5.59 ug/15 puffs = ND-0.373 ug/puff – Acrolein (71% of samples) = range 0.00646–1.05 ug/15 puffs = ND-0.070 ug/puff – Crotonaldehyde (87% of samples) = range 0.00168–0.108 ug/15 puffs = ND-0.00720 ug/puff – Formaldehyde (42% of samples) = range 0.0533–12.6 ug/15 puffs = ND-0.840 ug/puff • 34 THC samples= Acetaldehyde 0.0856– 2.58 ug in 29 samples Acrolein 0.00646– 1.05 ug in 25 samples Crotonaldehyde 0.00213– 0.108 ug in 33 samples Formaldehyde 0.0533– 12.6 ug in 8 samples • 10 Nicotine samples= Acetaldehyde 0.301– 5.59 ug in 10 samples Acrolein 0.0383– 0.805 ug in 7 samples

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Author	Method	Results
		Crotonaldehyde 0.00168– 0.00549 ug in 6 samples Formaldehyde 0.930– 5.00 ug in 10 samples • 1 No THC, No Nicotine samples= Acetaldehyde 0.414 ug in 1 sample Acrolein N/A Crotonaldehyde N/A Formaldehyde 2.22 ug in 1 sample

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

–	Δ9-THC n=194 range 1.1–88.7%	–	THCA n=17 range 1.9–87.9%
–	CBG n=102 range 1.2–5.3%	–	CBC n=11 range 1.2–2.6%
–	CBN n=86 range 1.1–16.9%	–	THCV n=1 range 2.3%
–	Δ8-THC n=29 range 1.9–88.8%	–	CBDA n=1 range 4%
–	CBD n=25 range 0.8–44.9%	–	CBDV – CBGA ND

No diluents 17 samples, 12 cases VEA only 107 samples, 51 cases MCT only 42 samples, 18 cases PEG only 8 samples 4 cases Castor oil 2 samples 2 cases	VEA+MCT 19 samples, 8 cases VEA+PEG 4 samples 3 cases MCT+PEG 1 sample 1 cases VEA+MCT+PEG 2 samples 1 case

Author Manuscript
Author Manuscript
Author Manuscript
Author Manuscript

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 6

Summary of physicochemical characterization of vapor/aerosol generated from **in-house prepared** e-cigs containing THC and/or VEA.

Author	Method	Results
(Mikheev et al. 2020),	• **E-liquid: VEA** 100%. • **Device**: 4 vaping pens (Kind Dab, Kind Discreet, Kind Mist, and Joyetech eVic) • **Puff topography**: duration 5 sec, interval 60 sec, flow rate of 20 or 40 ml/s (1.2 or 2.4 liter/min), low and high voltage for each device. • **Aerosol size distribution characterization**: Differential Mobility Spectrometer (DMS500) in combination with the Smoking Cycle Simulator (SCS) • **Chemical analysis**: two-dimensional gas-chromatography–time-of-flight mass-spectrometry (GC×GC-TOFMS)	**Aerosol size distribution characterization**: • Particle number concentration = 10^7 – 10^8 particles/cm^3. • Count median diameter = 50 to 200 nm • Mass median aerodynamic diameter average = 370 nm. • Aerosol size is dependent upon the device type, heating power, and puffing topography. **Chemical analysis** of intermediate of VEA degradation not conclusive. **Identified vaping emission product** (not confirmed with standards): 1-pristene, durohydroquinone monoacetate (DHQMA), and duroquinone (DQ). No direct evidence for ATMMC, DQM, and ketene.
(Jiang et al. 2020)	• **E-liquids**: Propylene glycol (PG), vegetable glycerin (VG), vitamin E acetate (VEA), Vitamin E (VE), medium-chain triglyceride (MCT) oil, squalane (SQL), triethyl citrate (TEC). • **Device**: vape pen connected to a CCell cartridge • **Puff topography:**duration 4 sec, interval 60 sec. Total puffs collected 10. Flow rate 0.18 liter/min operated at 3.6 V. • **Chemical analysis** of liquid diluents and vapors using mass spectrometry analysis.	• Significant changes in chemical composition between e-liquid and vapor. • Toxic byproducts formed during the vaping process likely resulting from thermal decomposition and oxidation of liquid diluents. **Identified vaping emission product**: • PG and VG → Carbonyls; alkyl alcohols • MCT OIL and SQL→ Short-chain esters, short-chain carbonyls, short-chain alkanes, alkyl alcohols • VE and VEA→ carbonyls, long-chain alcohol, quinone-like products • TEC→ small esters, carboxylic acids.
(Lanzarotta et al. 2020)	• **E-liquids**: Combination of Δ-9-THC/VEA (~50:50 w/w), vs THC or VEA (100% controls) • **Device:** CCell cartridge connected to a vaping device • **Puff topography:** duration 4 sec, interval 30 sec, flow rate 1 liter/min, operating voltage 3.7 V. • **Chemical analysis** of e-liquids and vapors: 1) Infrared spectra collected on a Nicolet 8700 FT-IR spectrometer, 2) Direct analysis in real-time ionization coupled to a high-resolution mass spectrometer (DART-HRMS)	• The liquid form of THC/VEA exhibits sufficient differences compared to the individual THC and VEA controls. – No carbonyl peak observed in the THC control spectrum. – VEA control spectrum exhibited a carbonyl peak at 169.760 ppm. – THC/VEA pre-vape mixture and THC/VEA post-vape condensate spectra exhibited a carbonyl peak downfield at 169.775 ppm
(Meehan-Atrash et al. 2019)	• **E-liquids**: pure THC, synthetic distillate (SND) THC/Terpenes 90:10 (v/v) • **Dabbing Device**: Jibtronix Corp. Errlectric Concentration Station • **Dabbing protocol**: single dab of 11 ± 2.5 mg of either THC or SND, Temp 370 °C (pure THC or SND) • **Vaping device**: CCell TH2 oil cartridge	• **Identified vaping emission product**: methacrolein, benzene, xylenes, toluene, styrene, ethylbenzene, isoprene, other nontarget hydrocarbons, and total VOCs. • Release of each component, other hydrocarbons, and total VOC increased in a voltage-dependent manner

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Author	Method	Results
	• **Puff topography**: 3 voltages 3.2 V, 4.0V, and 4.8V, 1 puff, duration 3 sec, 55 uL puff volume, 1.4–1.5 Ω. • **Chemical analysis** of aerosol gas phase ATD-GCMS	
(Lynch et al. 2021)	• **E-liquids**: THC/VEA 50/50 (w/w), • **Vaping Device**: six 510 threaded vaping cartridges ceramic coil connected to Eleaf iStick 30W, + 1 black-market ceramic coil cartridge and 1 authentic cartridge containing D9THC from EVALI investigation • **Puff topography**: puff duration 4 sec, interval 30s, flow 1L/min, 3 puffs/ voltage, voltage started at 3.0 V and increased by 0.5 V up to 4.5 or 5 V. Black-market cartridge 1.5 Ω resistance and voltage of 3.7 V. • **Temperature measurement:** Type-K thermocouple probe • **Chemical analysis:** GC/MS, GC/FT-IR/MS, and LC-APCI-HRMS/MS	• **Temperature:** clear difference within the cartridges depending on the distance from the center of the cartridge. • **Temperature increase was voltage dependent:** ranges of 217–300° C at 3.0 V and 415–476° C at 5.0 V, 454–510°C at 5.5 V, 548–632°C at 6V (illegal and authentic) • **Identified vaping emission product:** D9THC, VEA, 1-pristene, durohydroquinone monoacetate (DHQMA), 4-acetoxy-2,3,5trimethyl-6-methylene-2,4-cyclohexadienone (ATMMC)
(Kovach et al. 2021)	• **E-liquids**: VEA 100%, • **Vaping Device**: V8 X-Baby M2 atomizers using 0.25ohm, 40W, 3 V; Exxus EX6 1.6ohm ceramic oil cartridges 12W, 4 V. Smoking machine Bordwaldy LX 5.1 • **Puff topography**: puff duration 3 sec, interval 30s, puff volume 55ml, for 50 puffs approximately. • **Chemical analysis:** aerosol collected on Cambridge Filter Pads; GC-HRMS for durohydroquinone (DHQ), duroquinone (DQ), 2,6,10,14-tetramethyl-1-pentadecene (TMPD)	• DQ and TMPD are 2 major thermal degradants of aerosolized VEA. • Third major degradant is similar to DQ. (maybe ethyl-DQ).
(Mikheev and Ivanov 2022)	• **E-liquid:** VEA 100%, THC 100%, THC/VEA 20%/80%, THC/VEA 50%/ 50%, THC/VEA 80%/20%. • **Device**: Kind Dream (dab-type ceramic with two horizontally positioned coils) • **Puff topography**: duration 5 sec, interval 60 sec, flow rate of 20 or 40 ml/s (1.2 or 2.4 liter/min), low and high voltage for each device. Temperatures: low 177°C, high 221°C. Number of puffs collected = 8. • **Aerosol size distribution characterization**: Differential Mobility Spectrometer (DMS500) in combination with the Smoking Cycle Simulator (SCS) • **Chemical analysis**: two-dimensional gas-chromatography–time-of-flight mass-spectrometry (GC×GC-TOFMS)	**Temperature measurement depends on chemical liquids and temperature setting.** • **THC 100% at 177C and 221C=** temperature <250°C • **THC/VEA 50/50 at 177C=** temperature <250°C • **THC/VEA 50/50 at 221C=** temperature increased up to 500C toward the ends of the 8 puffs. • **VEA 100% at 117C =** temperature <250C • **VEA 100% at 221C =** temperature increased puff to puff reaching platau shortly at 500–555 **Aerosol size distribution characterization:** • **CMD =** range 73–186 nm, geometrical SD 1.6 – 1.8 • **PNC** = ~2×10^7 to ~1×10^8 particles/cm3, increase flow resulted in increased PNC. No influence of eliquid composition or heating power. • **VEA 100% =** smallest particle size: average 118 nm at 20 ml/s, and 84 nm at 40 ml/s. No influence of heating power.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Author	Method	Results
		• **Chemical analysis:** no evidence of chemical reaction between THC and VEA.
(Marrocco et al. 2022)	**E-liquids:** • D8THC +VEA+ Terpene (80%+ 0% +20%) 3.7 V (63% + 27% +10%) 3.7 – 5 V (36% + 54% +10%) 3.7 – 5 V (0%+100% + 0%) 3.7 – 5 V • Nic + PG + VG + Menthol (2% + 48% + 50% +0%) 3.7 V (5% + 45% + 50% +0%) 3.7 V (5% + 43% + 50% +2%) 3.7 – 5 V • **Device**: CCell cartridge 510 thread (1ml) for THC e-liquids, KangerTech refillable cartridges T3S series clear cartomizer 1.8ohm for nicotine e-liquids • **Puff topography**: duration 4 sec, interval 30 sec, flow rate of 1 l/min, puff volume 55 ml. • **Aerosol size distribution characterization**: scanning mobility particle sizer spectrometer (NanoScan SMPS), aerodynamic particle sizer spectrometer (APS), CO and CO2 (Q-Trak Indoor Air Quality (IAQ) Monitor), volatile organic compound (tVOC) (photo-ionization detector sensor (TG-502 probe), Time-integrated mass-size distribution (Harvard Compact Cascade Impactor)	• **D8THC/VEA** – nano-PNC (4.7–8.6) × 10^6 particles/cm^3, MPD 115–212 nm – micro-PNC 3,364– 7,865 particles/cm^3, APD 1.25–1.43 μm. – tVOC range 0.173–24.5 ppm depending on VEA concentration and operational voltage – average CO2 level 650–925 ppm, CO 10 ppm (VEA 27%) and 46 ppm (VEA 100%) – total PM mass concentration 67–910 mg/m^3, depending on VEA concentration and operational voltage (highest PM mass concentration for VEA 100% 5V). • **NICOTINE** – nano-PNC (5.2–9.2) × 10^6 particles/cm^3, mean-MPD 110–125 nm. – micro-PNC 4,052–7,048 particles/cm^3, mean-APD 1.25–1.31 μm. – tVOC range 0.044–0.707 ppm depending on menthol concentration – CO2 average ~900 ppm, CO not detectable. – total PM mass concentration 240–668 mg/m^3, depending on menthol concentration and operational voltage

Crit Rev Toxicol. Author manuscript; available in PMC 2023 July 13.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

Table 7

Summary of the *in vivo/in vitro* toxicological experiments conducted on various e-liquids or the generated aerosols/vapors.

AUTHOR	Cell/Animal model	EXPOSURE	FINDINGS:	COMMENT:
(Muthumalage, Lucas, et al. 2020b)	• Bronchial epithelial cells (BEAS-2B) • Monocytes, Mono-Mac-6 cells (MM6) • Epithelial cells (16-HBE)	Aerosols generated from: • MCT oil 0.25% *v/v* • VEA 0.025% (*w/v*) or 50 μM for MM6 • VEA 50% *w/v* in MCT for BEAS-2B • Cannabidiol/Counterfeit vape Cartridge (CBD) 0.25% Operated voltages: 3.8V 70 mL puffs ×10 minutes in air-liquid interface. Time-point 24 hours	• Cellular and acellular ROS generation increased by MCT and VEA more than CBD. • CBD aerosol caused the greatest cytotoxicity in BEAS-2B cells (34% cell death), while CBD liquid in MM6 (98% cell death) • IL-6 and IL-8 secretion increased by CBD in BEAS-2B, and by VEA in MM6. • VEA, CBD and MCT had the same effect on barrier dysfunction. • MM6 lipid-laden index: MCT 56.7, CBD 30.8, VEA 1.2, Control 3.4	• Acute exposure to VEA and CBD induce *in vitro* cytotoxicity, barrier dysfunction, and inflammation. • *In vivo* mouse exposure induces acute inflammation with elevated pro-inflammatory markers. • Both VEA and CBD may have caused acute respiratory distress inducing eosinophilic pneumonia. • Prolonged exposure to VEA and CBD may cause significant lung damage, which is involved in the pathogenesis of EVALI.
	• C57BL/6 mice, M and F, 4 months old	• MCT oil • VEA 50% w/v in MCT, • VEA 1.06 M 6 Cartridges 70 ml puff, 2 puff/min, for 1 h/day × 3 consecutive days	• Mouse arterial oxygen saturation: AIR 96%, MCT 92%, VEA 94%, and CBD 95% • BALF total cells, neutrophils and CD4 lymphocytes increased by CBD • CBD and VEA increased IL-6, EOTAXIN, G-CSF. • CBD and MCT decreased MCP-1, RANTES, IL4. • CBD/CVC, VEA and MCT decreased IL-17A, IL-12p40. • VEA decreased lung surfactant protein A (SP-A) • VEA and CBD altered the lipidomic profile altered by in BALF.	
			VOCs release: CBD =20.03 ppm, MCT= 10.33 ppm, VEA= 9.67 ppm.	
	Human Plasma	E-cig users vs non-smokers	• E-cig users had less TXB2, AA, and Acetic Acid and increased levels of 5HETE, 11HERE, 12HETE, and 17OHDHA in their plasma compared to non-smokers	

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

AUTHOR	Cell/Animal model	EXPOSURE	FINDINGS:	COMMENT:
(Muthumalage and Rahman 2019)	• Human monocytic cell line (U937) • Normal primary human bronchial epithelial cells (NHBE) cells (CC-2540) • Human bronchial epithelial cells (BEAS-2B) • Human lung fibroblasts cells (HFL-1)	• 1. CBD liquid 10.6 μM, 21.2 μM, 31.8 μM, or 42.4 μM. • 2. CBD aerosol (1000 mg) • 3. Dexamethasone (DEX) 10 Mm + CBD 10.6 μM • 4. (Lipopolisaccharide) LPS 1 μg/ml +CBD liquid 10.6 μM • 5. TNF-α + CBD liquid 10.6 μM • **ALI: Propylene glycol/Vegetable glycerin (50:50)** or **CBD aerosol**: 51 mL volume, 2 puffs/min, 2 L/min flow for 30 minutes. Heating temperature of the e-liquid 230 °C with a 0.55 Ω atomizer. • **LPS** 1 μg/ mL or 10 μg/mL.	• CBD liquid decreased cell viability in U937 (any dose), HFL-1 (42.4 μM), and BEAS-2b (31.8 μM). • CBD liquid 10.6 μM differently altered the secretion of inflammatory cytokines among the cell lines: dose-dependent increase of IL-8 and dose-dependent decrease of MCP-1/CCL2 in U937- BEAS-2B - HFL-1. NHBE is not affected. • BEAS-2B exposed to CBD vapor: elevated Eotaxin, MCP-1, CXCL1, CXCL2, IL-8, and IL-6 levels compared to PG/VG. • DEX reduced CBD-mediated inflammation in U937. • CBD attenuated the LPS-induced release of IL-8, MCP-1, CCL3, CCL4, and TNF-α, CXCL2, IL-33, IL-6, and RANTES in U937. • CBD reduced the TNFa-induced release of CXCL1, G-CSF, and IL-6 levels, and increased CXCL2, IL-8, GM-CSF in NHBE • In BEAS-2B, CBD decreased the TNFa-induced release of MCP-1, CXCL-1, IL-6, G-CSF, and GM-CSF. DEX reduced the TNFa-induced release of CXCL1, CXCL2, IL-6, IL-8, and GM-CSF. CBD + DEX significantly reduce almost all cytokines except IL-8.	• *In-vitro* cell exposure to CBD induces a varying degree of toxicity depending on the cell type. Monocytes and fibroblasts were particularly prone to cell death and damage by exposure to CBD. • Cells treated with CBD showed increased IL-8 response, hallmark of acute inflammation, recruitment, and activation of naïve inflammatory cells. • CBD liquids, as well as aerosols, generated significant amounts of acellular/cellular ROS (potential cause of oxidative stress), and mitochondrial ROS (potential mitochondrial dysfunction).
	• Mouse macrophage RAW 264.7		• **Cellular and mitochondrial ROS** generation were higher with CBD at 21.2 μM and 42.4 μM respectively. CBD liquids (350 mg and 550 mg by Green Roads) and aerosol (Green Roads 100 mg) induced a dose-dependent increasing generation of **acellular ROS.** • **CBD liquid** significantly elevated G-CSF, GM-CSF, IFN-γ, IL-1a, IL-6, IL-27, I-TAC, M-CSF, MCP-1, RANTES, and TNF-α., and decreased eotaxin, IL-1ra, and IL-2. • **CBD liquid** 21.2 μM inhibited NF-κB activity and decreased MCP-1/	

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

AUTHOR	Cell/Animal model	EXPOSURE	FINDINGS:	COMMENT:
			CCL2 cytokine in LPS-activated 10 μg/mL macrophages. • **CBD liquid** upregulated MCP1 protein even after LPS inhibition	
(Bhat et al. 2020)	• 3 groups of C57BL/6NCr mice n=10 (5 males and 5 females) 6 weeks old. • Animals were sacrificed 16 h after the last exposure.	• VEA, PG:VG, or fresh air • Mice exposed for 5 hr/day, 5 days/ week for 2 weeks • Puff Protocol: 10 puffs (3 sec each) every 15 sec, volume 55 ml. Interval between clusters 7.5 min (total 240 puffs/day). 4.8V	• VEA levels in BAL fluid: only in VEA exposed mice (5×10^3 ng/ml) • ALBUMIN levels in BAL fluid: in VEA exposed mice 1.5×10^5ng/ml, in AIR and PG: VG $<5.0\times10^4$ ng/ml. • CD45+ CELLS in Lung: in VEA exposed mice 1.5×10^5 ng/ml, AIR $<5.0\times10^5$ ng/ml, PG:VG $>5.0\times10^5$ ng/ml. • Lipid-laden macrophages are often in clusters only in BAL from VEA-exposed mice.	Limitation of the study: • No exposure to THC or THC/VEA. • No chemical evaluation of aerosol to evaluate by-products of VEA.
(Jiang et al. 2020)	Human bronchial epithelial cells (BEAS-2B)	• PG, VG, MCT, SQL, VE, VEA, TEC e-liquid, or 100 puffs/15ml (LHC-9 medium) vaping emission samples for 48h. • CCell cartridge (510 thread, 0.5 mL, TH205, 1.4 Ω) 3.6 V 9.25W • Puff topography: duration 4 sec, interval 60 sec, volume 12 ml, flow rate 0.18 liter/mi.	• Cells exposed for 48 hours to a higher concentration of vapor showed higher cell death compared to liquid exposure, except for TEC (cell death similarly increased with both TEC liquid and vapor). • LDH released from cells exposed to MCT oil and TEC did not differ much between e-liquid and vaping emissions. • PG and VG **e-liquid** induced a higher LDH release compared to vaping emission. • SQL, VE, and VEA **vaping emission** increased the LDH release compared to e-liquid; however, VE induced a stronger cytotoxic effect.	• vaping topography does not mimic the real vaping scenarios. • The liquid diluents were studied individually in an isolated system. • Only the acute cytotoxic effects of vaping emissions from commonly used liquid diluents were examined • Collection efficiency of impinger 80% for aerosols.
(Matsumoto et al. 2020)	C57BL6 mice Human primary AT-II cells (from 1 single adult human lung donor)	• **VEA 100%** aerosolized with a ShenZen aerosolizer, 1.5 V ceramic coil, using a Gram Universal Vaping Machine, at 9.4 W. • Puff volume 80 ml, duration 4 sec. • Mice exposed for 1 hour twice daily for 6 or 15 days	VEA aerosol 1-hour × 2/day for 6 or 15 days: • Progressive increase in excess extravascular lung water, BAL total protein, and SP-D (surfactant protein-D). 15 days of VEA exposure: • BAL fluid and cells analysis: increased total BAL cell count	• micece exposed to VEA develop diffuse acute lung injury. • Surfactant-producing human AT-II cells are directly injured by VEA aerosol. • Lack of: THC experiments due to

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

AUTHOR	Cell/Animal model	EXPOSURE	FINDINGS:	COMMENT:
		• **JUUL** (VG:PG 30:70) + Nicotine 5% • 10 puffs initially injected over 1 minute, followed by 110 puffs over 1 hour. • To generate ketene in that study, a metal coil was operated at 30 W or 50 W (11.0 or 15.5 A, respectively) • VEA aerosol for 20 – 120 min/day for 3 days in humans	(mono/macrophages and neutrophils), presence of large vacuolated macrophages, and Increased release of inflammatory cytokines (IL-8, MCP-3). • Histological analysis: monocytic and neutrophilic alveolar and interstitial inflammation in a bronchiolocentric pattern with increased large, foamy, and vacuolated macrophages in the airspaces, in association with a dense inflammatory infiltrate affecting the alveolar septa. Pulmonary blood vessels are frequently surrounded by lymphocyte-rich cell aggregates, with progression between 6 and 15 days of VEA exposure. • Human AT-II exposed to VEA aerosol: Dose-dependent cell death, LDH release, and TUNEL staining; increased chemokines release from monocyte and neutrophil; punctate cytoplasmic staining with Oil Red O; Dose-dependent increase in VEA and a-TP. • JUUL aerosol: Well tolerated in mice and humans.	ongoing strict federal research restrictions; aerosol VEA byproducts measurement; assessment of potential synergistic toxicity between VEA and nicotine-containing aerosols.
(Marrocco et al. 2022)	Human lung epithelial cell line (Calu-3) Human peripheral blood monocytes (THP-1)	**E-liquids:** • D8THC +VEA+ Terpene (80%+ 0% +20%) 3.7 V (63% + 27% +10%) 3.7 – 5 V (36% + 54% +10%) 3.7 – 5 V (0%+ 100% + 0%) 3.7 – 5 V • Nic + PG + VG + Menthol (2% + 48% + 50% +0%)3.7 V (5% + 45% + 50% +0%)3.7 V (5% + 43% + 50% +2%)3.7–5V 2 doses: 85 – 257 puffs/m^2 (1–3 months), 24 h • **Device**: CCell cartridge 510 thread (1ml) for THC e-liquids, KangerTech refillable cartridges T3S series clear cartomizer 1.8ohm for nicotine e-liquids	**Cell viability** • **VEA 54% 5V and Nic 5% +Menthol 2% 5V at a higher dose** increased the LDH release and decreased the metabolic activity of Calu 3 epithelial cells. • **VEA 54% 3.7–5V and all nicotine both doses=** dose-dependent diminution on the metabolic activity of THP-1. **ROS** • **VEA 100% 3.7% low dose** increased ROS generation in Calu-3 cells. • **VEA 54% and All Nicotine both doses** increased ROS generation in THP-1 cells. **Apoptosis** • **VEA 27% 5V and 54% 3.7 – 5V high dose and all nicotine higher**	• aerosol generated from THC 36% +VEA 54% + Terp 10% and Nicotine 5% +Menthol 2% increased a limited number of pro-inflammatory cytokines and suppressed the majority of them while inducing a higher level of cytotoxicity. • Possible dysregulation of the immune response, which is possible in the context of EVALI.

Author Manuscript Author Manuscript Author Manuscript Author Manuscript

AUTHOR	Cell/Animal model	EXPOSURE	FINDINGS:	COMMENT:
		• **Puff topography**: duration 4 sec, interval 30 sec, the flow rate of 1 l/min, puff volume 55 ml	**dose** significantly decreased the mitochondrial membrane potential in Calu-3 • **VEA 54%, VEA 100%, Nicotine 3.7 – 5 V high dose** increased caspase 3 activation in Calu-3 **Inflammatory response** • Cytokine release was overall suppressed by THC or nicotine treatment. • **VEA 54% 3.7 – 5 V** upregulated FGF-2, G-CSF, IL-1a, IL-1RA, IL-18, M-CSF, PDGF AB/BB, and downregulated GRO-a, IL-4, IL-22, MDC, RANTES, TNF-b, VEGF-A. • **-NIC 5%+Menthol 2%** increased FGF-2, IL-1α, IL-1RA, IL-18, and M-CSF. G-CSF, GM-CSF, IL-8, MCP-1, PDGF-AB/BB, IL-15, TGF-a, and inhibited IL-6.	
(Matsumoto et al. 2022)	C57BL6 mice Primary human alveolar macrophages from adult human lungs	• **VEA 100%** aerosolized with a ShenZen aerosolizer, 1.5 V ceramic coil, using a Gram Universal Vaping Machine, at 9.4 W. • Puff volume 80 ml, duration 4 sec, • 1 puff was injected into the chamber every 30 seconds for 1 hour twice daily for up to 28 days. • Mice sacrificed either 12 hours or 6 days after the last exposure. • Some mice were intranasally treated with 400 FFU influenza Puerto Rico/8/34 (PR8) or PBS control 12 hours after the last exposure, then sacrificed 7 days after the inoculation. • AM exposed to VEA aerosol for 1 hour daily for 3 consecutive days	• BAL: increased protein concentration, macrophage/monocyte counts, vacuolization of macrophages, MCP3, KC, IL-6 starting at day 15 of exposure. • Lung Histology: mixed acute and chronic inflammation in the distal bronchioles, diffuse foamy macrophages, and neutrophil infiltration in thickened septa. Increased Angiopoietin-2 (ARDS), ICAM1, and MMP8 (sepsis). Presence of VE, and VEQ in the airspace. Dose-dependent increase of plasma MDA. • After 6 days from exposure: persistent lung edema; decreased BAL protein, total cells, and neutrophils, smaller macrophages, constant number, lower cytokines. • VEA cytotoxic on alveolar macrophages in vitro, increased vacuolization after a 3-day exposure.	• VEA exposure induces systemic inflammation and increased susceptibility to viral infection in mice. • VEA aerosol is phagocytosed by alveolar cells, then hydrolyzed to free tocopherol, likely resulting in oxidative stress in mice. • VEA aerosol is cytotoxic to primary human alveolar macrophages, impairs efferocytotic function, and induces AM chemokine release.