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Cannabis vaping: existing and emerging modalities, chemistry, and pulmonary toxicology

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Abstract

The outbreak of e-cigarette or vaping product use-associated lung injury (EVALI) has been cause for concern to the medical community, particularly given that this novel illness has coincided with the COVID-19 pandemic, another cause of severe pulmonary illness. Though cannabis e-cigarettes tainted with vitamin E acetate were primarily associated with EVALI, acute lung injuries stemming from cannabis inhalation were reported in the literature prior to 2019, and it has been suggested that cannabis components or additives other than vitamin E acetate may be responsible. Despite these concerning issues, novel cannabis vaporizer ingredients continue to arise, such as Δ^8-tetrahydrocannabinol, Δ^{10}-tetrahydrocannabinol, hexahydrocannabinol, and cannabichromene. In order to address cannabis e-cigarette safety and vaping in an effective manner, we provide a comprehensive knowledge of latest products, delivery modes, and ingredients. This perspective highlights the types of cannabis vaping modalities common to the United States cannabis market, with special attention to cartridge type cannabis e-cigarettes toxicology and their involvement in the EVALI outbreak in particular acute lung injurious responses. Novel ingredient chemistry, origins, and legal statuses are reviewed, as well as the toxicology of known cannabis e-cigarette aerosol components.

Keywords

Cannabis; THC; vaping; e-cigarettes; lung; inflammation; EVALI

Introduction

Vaping cannabis and tobacco has rapidly expanded over the past decade, and though concern by the medical community has existed from the outset,[1, 2] the perceived innocuity of cannabis due to this plant's extensively reported medical uses painted cannabis vaping as a useful harm reduction strategy for medical cannabis users.[3–5] However, the 68 deaths and 2,807 hospitalizations recorded by the Centers for Disease Control (CDC) until February 2020 due to the outbreak of EVALI[6] were the wakeup call needed to realize that, despite

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its public image of harmlessness, cannabis vaping can indeed cause injury and mortality. Despite the fact that tobacco and cannabis are frequently co-used, EVALI was associated largely with cannabis vaping, as 82% of patients reported the use of e-cigarettes containing Δ^9-tetrahydrocannabinol (Δ^9-THC), 33% reported using only Δ^9-THC e-cigarettes, and 14% reported using only electronic nicotine delivery systems (ENDS).[7] Extensive media coverage during the outbreak, which peaked in September 2019,[7] put cannabis vaping into focus, and states with legalized recreational and medical cannabis markets responded by banning potentially harmful ingredients.[8–10] Researchers also responded by studying the *in vitro* and *in vivo* impacts of cannabis vaporizer adulterants on the respiratory system,[11–13] but for the major and often only ingredients in cannabis vaporizers, cannabinoids and terpenes,[14, 15] a dearth of toxicological data exists on how they may negatively impact the aerodigestive tract.

23.7% of US 12th graders reported lifetime use of any cannabis vaping in 2019, and 3.5% reporting near-daily use.[16] One study indicates that this practice is associated with increased bronchitis and allergic rhinitis symptoms, such as wheeze or shortness of breath in young adults, even after adjusting for ENDS use and smoking.[17] Stay-at-home orders during the COVID-19 pandemic have led to a significant increase in cannabis sales in US states with legal recreational markets.[18] Given these concerning trends, toxicological research must stay on top of this practice in order to prevent not only another EVALI outbreak, but long term pulmonary illness amongst the increasingly growing population of young users. This review will outline the existing research deficits in the field of cannabis vaping, with a focus on the cannabis e-cigarettes (CECs), the vaping modality associated with EVALI. Types and compositions of CECs are reviewed, as well as the known inhalation toxicology of cannabinoids, terpenes, and volatile organic compounds.

Cannabis vaping use modes

Before this discussion may begin, it is important to understand what exactly is a CEC and how the terminology surrounding vaping for cannabis is used, as at least three distinct practices may be referred to as “cannabis vaping.” Of the three vaping modalities, cannabis flower vaping (Figure 1a) was the earliest to surface, first documented in the literature in 2001[19] two years before the patent for the ENDS device was issued.[20] Cannabis flower vaporizers are handheld or tabletop devices that pass hot air over milled cannabis to produce an aerosol.[21, 22] 2.9% of US 16–19 year-olds reported past 30-day flower vaping.[23] Dabbing, another popular method for cannabis consumption first reported in 2014,[24] consists of flash vaporization of cannabis wax/shatter/oil on a heated surface connected to a water pipe (Figure 1b).[15, 25] 4.2% of 16–19 year-olds reported past 30-day consumption of cannabis products (wax/shatter/oil)[23] that are typically consumed by dabbing.[26, 27] A third type of cannabis vaping is by use of the CEC (Figure 1c), which were first reported in 2011.[2] Mimicking ENDS, CECs use a resistively-heated coil to vaporize cannabis oil contained in a small cartridge.[14, 15] While cannabis flower vaping and dabbing often require extensive paraphernalia and connoisseur-level knowledge, CECs are portable, disposable, easily concealed and easy to use, making them readily accessible by novices including youth.[28–30] 4.2% of 16–19 year-olds reported past 30-day cannabis oil consumption.[23]

Cannabis extract types and physical properties

Cannabis extracts can vary greatly based on the methodology employed and the intended consumption mode. Of the three vaping modalities, dabbing and CEC vaping exclusively use some form of cannabis extract/oil. Figure 2 displays the most common extraction and processing methods used for producing cannabis extracts used for CEC vaping and dabbing. CEC compositions are described further below in Table 2.

Cannabinoids are biosynthesized as acids and contain an aryl carboxyl moiety at the 2-position of the resorcinol ring.[31] Extracts that have not undergone decarboxylation (heating to 100+ °C[32]) contain acid cannabinoids such as Δ^9-tetrahydrocannabinolic acid (Δ^9-THCA) and cannabidiolic acid (CBDA), and are solids or thick, sappy oils at room temperature, making them readily amenable for dabbing as they are easily handled with small spoons/spatulas for administration onto the dabbing nail.[33] Vacuum distilled cannabis extract amended with terpenes/flavorants and superfluid extract (SFE) are the most amenable extracts/oils for CEC vaping given that these contain decarboxylated, or neutral Δ^9-THC, which is a viscous liquid at room temperature.[33] In the case of distillate cannabis oil, added terpenes serve not only to reduce viscosity further, but as added flavors.[33] A sufficiently low viscosity of the vape liquid/oil is necessary for the CEC vaporizer to function given these devices reliance on wicking to deliver the vape liquid/oil to the atomizer from the cartridge reservoir.[33]

It is known that the aerosolization temperature in an ENDS is controlled by the boiling point of the propylene glycol (PG)/glycerol (GL) system.[34] The normal boiling points of Δ^9-THC and CBD (Table 1) were recently predicted via equations of state calculated by measuring vapor pressures using porous layered open tubular cryoadsorption.[35] The diversity of ingredients and co-extracted components make it difficult to determine an exact aerosolization temperature, however, recent analysis of gas phase degradation products of a simplified system that recreates distillate cannabis oil has shown that CEC vaping of Δ^9-THC added with increasing levels of β-myrcene (an abundant cannabis terpene) is correlated with reaction products associated with lowered aerosolization temperatures.[14] A recent analysis that measured temperatures occurring at the atomizer using a thermocouple when vaping 1:1 Δ^9-THC:vitamin E acetate (VEA) indicates that reaction temperatures in this system increase with each sequential puff, and may exceed 400 °C.[36] Further work to characterize cannabis extract/oil boiling points will aid the description of chemical degradation and oxidation reactions that occur during aerosolization.

Cannabis e-cigarette compositions

Type 1: Δ^9-THC; terpenes/ flavorants

Type 1 CECs are highly available in states with recreational and/or medical cannabis programs, but may be diverted to black markets in illegal states by producers or third parties.[46] Due to the highly restricted legal status of drug-type cannabis (i.e. cannabis containing >0.3% Δ^9-THC), academic researchers are not able to access products for sale in dispensaries in states with recreational and/or medicinal cannabis programs, even those with licenses issued by the Drug Enforcement Agency (DEA). Specialized channels through

the Department of Justice exist to allow access to products seized by law enforcement for research, though this is a rare occurrence, and does not necessarily guarantee access to the aforementioned dispensary products.

Type 2: Δ^8-THC, Δ^{10}-THC, HHC; terpenes/ flavorants; cutting agents/viscosity modifiers

Hemp-derived cannabidiol (CBD) for vaping in CECs rapidly proliferated after the 2018 Agriculture Improvement Act (the "Farm Bill") effectively legalized hemp and its derivatives at the federal level.[47] After concerns that hemp producers were synthesizing Δ^9-THC from hemp-derived CBD (Figure 3), the DEA published an interim final rule in August, 2020 to clarify that the legal definition of "tetrahydrocannabinols" does not include any compound derived from hemp, and that "marijuana extract" is limited to any formulation containing >0.3% Δ^9-THC.[48] This theoretically left open the possibility of selling hemp-derived cannabinoids other than Δ^9-THC, an opportunity that was capitalized on to market Δ^8-tetrahydrocannabinol (Δ^8-THC). Δ^8-THC is a Δ^9-THC thermal isomerization artefact that occurs *in situ* on storage and heating[49] and is approximately half as psychoactive as Δ^9-THC.[50] Δ^8-THC for ingestion and vaping currently is sold through the existing hemp marketing network, both online and brick-and-mortar, that operates independently of the traditional recreational and medical cannabis markets.[51] Even before this DEA's interim final rule, Duffy *et al.* (2020) reported that several EVALI-associated CEC oils contained unnatural levels of Δ^8-THC, and it was speculated this may be manufacturing artefact, deliberately purified from drug-type cannabis, or manufactured from hemp using a synthetic process.[52]

CBD conversion to tetrahydrocannabinols by acid catalysis (Figure 3) was reported in the literature as early as 1940 by Adams *et al.*,[53] and at least one patent has been issued for this process.[54] The ring closing reaction to Δ^9-THC is accompanied by the double bond isomerization to Δ^8-THC which also occurs under acid catalysis,[55] and generation of the latter may be favored by longer reaction times. The use of CBD as a substrate for the synthesis of other cannabinoids has been recently reviewed[56] and additional products that may result from these processes have been described.[57, 58] Crude online guides exist for this synthesis,[59] and it has been suggested that some Δ^8-THC CEC manufacturers do not include a post-reaction purification step, potentially resulting in traces of sulfuric acid, hydrochloric acid, trifluoroacetic acid or *p*-toluenesulfonic acid.[60] One analysis by the US Cannabis Council found that a majority of CEC products tested contained Δ^9-THC concentrations far in excess of the 0.3% Δ^9-THC required to not meet the DEA's definition "marijuana extract," and were also contaminated with residual solvents and heavy metals.[51] Several states have blocked the sale of Δ^8-THC,[61] and members of the medical community have expressed alarm over the lack of safety data and regulations that has allowed the sale of products with packaging and flavors that may entice consumption by minors.[62] These vaporizers may be flavored with terpenes to recreate the scent of cannabis, but may also include non-cannabis flavors including menthol, fruit, etc.

CECs containing Δ^{10}-THC are also available, and at least one online source suggests this synthesis uses Δ^9-THC as a starting material,[63] though the cited chemical literature indicates that both Δ^9-THC and Δ^8-THC may be isomerized to Δ^{10}-THC under

strongly basic conditions (Figure 3).[64] Hexahydrocannabinol (HHC), a hydrogenated tetrahydrocannabinol, also has limited commercial availability but may continue to expand.[65]

Type 3: CBD, CBC, CBL, and CBT, terpenes/ flavorants

Advances in hemp extraction technologies have allowed the proliferation of Type 3 CECs which are non-psychoactive. These are often advertised as CBD vaporizers, though other cannabinoids are included for which additional health claims are made, such as cannabichromene (CBC), cannabicylol (CBL), cannabicitran (CBT), etc. While Δ^9-THC and Δ^8-THC are viscous oils at room temperature[38] allowing them to be formulated as the sole cannabinoid in a CEC, pure CBD is a solid[39] and requires the addition of other compounds to lower its melting temperature and prevent crystallization in the cartridge. These may also be formulated as hemp extracts with sufficiently high contents of terpenes and other plant lipids/waxes to prevent CBD crystallization, and may also include viscosity modifiers such as PG.

Type 4: Δ^9-THC, CBD; terpenes/ flavorants; cutting agents/viscosity modifiers

The existence of Type 4 CECs was brought to the public's attention primarily due to the EVALI outbreak. Initial chemical analyses of vaporizer cartridges from affected individuals by the New York State Department of Health showed EVALI was largely associated with counterfeit or black market CECs containing elevated levels of VEA, which was subsequently confirmed by The Food and Drug Administration.[66] Subsequent publications identified a variety of adulterants including squalene, phytol, medium chain triglyceride oil, etc.[52, 67] Identification of VEA in all the bronchoalveolar lavage (BAL) fluids of a convenience sample of 29 EVALI patients prompted the CDC to identify this substance as a potential causative agent, though the organization was not able to rule the potential for other contributing factors.[68] It has been speculated that the rapid decrease is EVALI patients is due to the discontinuation of VEA specifically as a cutting agent,[7] and though some compounds have been banned from use in certain states[9, 10, 69] (Table 2), it is not known how common cutting agents continue to be in legal, medical, or black market CECs.

Type 5: CBD; flavorants; PG, GL

Type 5 CECs are a combination of cannabis and ENDS formulation techniques. Propylene glycol (PG) and glycerol (GL) are the two most commonly used solvents in ENDS,[70] and CBD is moderately soluble in the least polar of the two, PG. Such products were first reported by Peace *et al.* (2016)[71] and have more recently been used in toxicological studies (*vide infra*). While Types 1–4 are often formulated using terpenes as their primary flavorant source in a manner that seeks to replicate the flavor/scent of cannabis flower, Type 5 CEC liquids may be formulated with any combination of the diverse flavorant molecules used in ENDS including, but not limited to, menthol, tobacco, fruit, beverages, candy, and caramel.

Pulmonary toxicology of CEC aerosol components: cannabinoids

Inhaled cannabis smoke, a well-studied consumption modality, produces a measurable Δ^9-THC content in plasma within seconds and peaks in 9–10 minutes.[72, 73] Δ^9-THC

plasma concentrations after the first inhalation of a 3.55% Δ^9-THC cannabis cigarette have been reported at 18±12 ng/mL,[73] and ~150 ng/mL after consuming a cigarette with ~34 mg Δ^9-THC. Lipophilic cannabinoids are protein bound in plasma and efficiently penetrate vascularized tissues, such as lung, liver, and muscle. leading a rapid concentration decrease in plasma.[72] Δ^9-THC is metabolized by hepatic cytochrome P450 enzymes to the active 11-hydroxy-Δ^9-tetrahydrocannabinol (11-OH-Δ^9-THC) with a concentration maximum in tandem with its parent molecule.[72, 73] This metabolite more easily penetrates the blood-brain-barrier than its parent and is thought to contribute significantly to its impacts on the central nervous system.[72] A further oxidized metabolite, 11-nor-carboxy-Δ^9-tetrahydrocannabinol (Δ^9-THCCOOH), peaks within an hour of smoking and has a long time course of detection in plasma.[73] Bioavailability of Δ^9-THC has been recently determined to be 14% in a naturalistic population pharmacokinetic study of regular cannabis smokers, and given the known high bioavailability of components of inhaled aerosols, it is estimated that chemical degradation due to combustion and sidestream smoke losses account for the majority of the transfer losses. The bioavailability of cannabinoids in CEC aerosols has not been studied in humans, but a recent chemical analysis of CEC aerosol components determined a Δ^9-THC yield of 50–90% and 3–5 mg/puff depending on device parameters, suggesting that this format may afford aerosols of higher Δ^9-THC concentrations.[14] Both cannabis and tobacco smoking has been shown to induce CYP1A1 and CYP1A2 leading to more efficient clearance of drugs, such as theophylline and chlorpromazine, though it is postulated that polycyclic aromatic hydrocarbons present in cannabis smoke tar induce these enzymes by activating the aromatic hydrocarbon receptor in a similar manner to that seen in tobacco smoke.[74] However, the interactions of the above two metabolites in aerosol is not known.

Cannabinoids have been shown to modulate lung immune response *in vitro* and *in vivo*. Cannabinoid receptors 1 and 2 (CB_1R and CB_2R) are both present in human lungs, though CB_1Rs show higher expression than CB_2Rs.[75] Expression of both receptors with higher levels of CB_2R is observed in both resident alveolar macrophages (AMs) and monocyte-derived macrophages, though CB_2Rs in the latter are non-functional.[76] Δ^9-THC (a CB_1R and CB_2R partial agonist) was shown to suppress chemotaxis and negatively impact bronchial epithelial cell energetics in a CB_2R-dependent manner *in vitro*,[77, 78] and CB_1R agonism by CP55,940 in a murine model induced the expression of inflammatory cytokines and oxidized phosphatidylcholines, which was postulated to result in lung surfactant disruption.[79] Δ^9-THC has been shown to downregulate nitric oxide production[80] and tumor necrosis factor-α secretion,[81] and impair phagocytic activity in murine macrophages.[82] In human cannabis smokers, but not tobacco smokers, AMs capability to ingest and kill *Staphylococcus aureus* is impaired, suggesting a reduced host defense response in the presence of Δ^9-THC.[83] Incidentally, an impaired host defense response was offered as an explanation for the 6 day delay in reaction to BHO dabbing that caused an acute lung injury as described in a case report by McMahon *et al.* (2016).[84]

Conversely, cannabinoids have been shown to possess anti-inflammatory capabilities in lipopolysaccharide-induced (LPS) murine models of lung inflammation.[85] Ribeiro *et al.* (2012) showed CBD attenuation of LPS-induced inflammation was reversed by prior adenosine-2A receptor antagonism, suggestive of CB_2-A2A receptor heteromers which

warrant further investigation.[86] Muthumalage & Rahman (2019) also showed that CBD vaporized in PG attenuates the LPS-induced inflammatory response in bronchial epithelial cells, but is pro-inflammatory in absence of LPS, and acts to override the anti-inflammatory effect of dexamethasone (steroid) when used in combination.[87] Notwithstanding, Leigh & Goniewicz (2020a) and Leigh & Goniewicz (2020b) demonstrate that CBD vaporized with PG is more cytotoxic to bronchial epithelial cells than PG vaporized alone, and leads to the release of higher levels of inflammatory biomarkers than PG alone.[88, 89]

Muthumalage *et al.* (2020) represents the only available literature that studied the toxicological impact of CECs other than Type 5.[11] In this case, EVALI-associated "counterfeit" CEC cartridges generated increased levels of reactive oxygen species in bronchial epithelial cells as compared to control at levels similar to cells exposed to VEA though lower than MCT oil, but significantly increased levels of inflammatory biomarkers interleukin-6 and −8 as compared to control, MCT oil, or VEA. EVALI CECs, MCT oil, and VEA all significantly induced epithelial barrier dysfunction. Both the EVALI CECs and MCT oil induced LLM formation *in vitro*, though curiously, VEA did not induce LLM significantly as compared to control. *In vivo*, aerosol exposure to the EVALI CEC aerosols increased total cell counts in mouse BAL fluids, with a more than fivefold increase in neutrophils, and nearly sevenfold increase in T-helper cells. Murine lung homogenates also showed lower levels of surfactant-associated proteins after EVALI CEC exposure and increased levels of leukotrienes. Together, these results indicate that EVALI CECs may induce cytotoxicity, barrier dysfunction, and inflammation associated with acute lung injuries, but also add to the complexity associated with the toxicological impacts of inhaling an aerosol with multiple and unknown components.

Of the CECs available to consumers as displayed in Table 2, toxicological studies only exist for Types 4 and 5. Far more common in states with recreational and/or medical marijuana programs are Type 1 CECs, and Types 2 and 3 ostensibly share more similarities with these given that they contain cannabinoids at levels as high as 90 %.[14, 15] Though Δ^9-THC toxicology is relatively well understood, aerosols from Type 1 CECs contain approximately double the Δ^9-THC content of cannabis smoke (7000–9000 ppm[14] vs. 2400–4000 ppm[90]), and it is not known what effects elevated Δ^9-THC concentrations have on the respiratory tract. Furthermore, no inhalation toxicology data exists for Δ^8-THC, Δ^{10}-THC, HHC, CBC, CBL, and CBT, and scant physicochemical characterization and commercial availability represent a significant hindrance to their evaluation. Inhalation models (mouse/cells) and human studies are lacking to understand the role of THC and CBD based products on lung and cardiovascular injuries.

Given the high use of novel vaporizer products among adolescents, the impacts of their use on development are a pressing concern. There are mixed findings with regards to early onset chronic cannabis use, and while a 2015 longitudinal study of youth cannabis users found that it may not be a predictor for later physical or mental health issues,[91] a 2019 longitudinal study found evidence that increased cannabis potency increases risk for development of a cannabis use disorder.[92] It is not yet known how exposure to novel cannabis vaporizer products may impact the development of adolescents who use them.

Pulmonary toxicology of CEC aerosol components: terpenes, volatile organic compounds, and metals

Toxicological impacts of terpene inhalation have been studied in the context of environmental exposure from indoor and outdoor ambient air, using primarily concentrations <100 ppm.[93] Type 1–4 CECs may contain 10–20% terpenes by weight in the cannabis oil resulting in aerosols with 2500–5000 ppm total terpenes.[14] Even at concentrations orders of magnitude lower than those seen in CECs, terpenes have been shown to induce sensory irritation, airflow limitation, and inflammatory responses *in vivo*.[93] One analysis that assessed free radicals generated by flavored ENDS by electron paramagnetic resonance and lipid peroxidation *in vitro* found that the terpenes linalool, dipentene (i.e. racemic limonene), and citral were the most radical-generating molecules of all the flavorants identified.[94] Terpenes easily auto-oxidize to form hydroperoxide species that are known to generate C-centered radicals which are potent sensitizers associated with allergic contact dermatitis.[95–97] Though terpene auto-oxidation is a spontaneous process, the formation of terpene hydroperoxides at elevated temperatures and in physicochemical environments similar to nicotine or cannabis vaping has not been studied.

Wolkoff *et al.* (2008) demonstrated that airway irritation initiated by limonene-O_3 reaction product aerosols is primarily due to gaseous products such as formaldehyde.[98] While mice exposed to these aerosols displayed evidence of sensory irritation, mice exposed to the aerosols with prior removal of gaseous products with a denuder were indistinguishable from room air.[98] Gaseous volatile organic compounds (VOCs) that are thermal degradation products of cannabis terpenes and Δ^9-THC have been recently characterized.[14, 15, 25] VOCs emitted by Δ^9-THC share considerable overlap with those emitted by terpenes common in cannabis (Figure 4) due to the terpene backbone on Δ^9-THC, which is responsible for 22±6% of its VOC emissions.[33] Known carcinogens such as benzene, xylenes, isoprene, 1,3-butadiene etc., and potent respiratory tract irritants such as methyl vinyl ketone, methacrolein, butanal, etc. are present.[14, 15, 25] Carbonyls present in CEC aerosols may produce significant harm when inhaled, as photochemical oxidation products of isoprene and 1,3-butadiene (methacrolein, methyl vinyl ketone, and formaldehyde) have been shown to cause cytotoxicity and inflammation in human lung cells *in vitro*.[99] In addition to these known toxicants, many other molecules exist in high abundance that are not toxicologically characterized. For example, conjugated dienes are potent sensitizers for allergic contact dermatitis because they are metabolically oxidized to epoxides which in turn cause sensitization by covalently attaching to endogenous nucleophiles, such as cysteine residues,[100] but their impact on lung tissue has not been studied. Gas phase epoxides and conjugated dienes have been detected, but other terpene epoxides shown to be sensitizers[101, 102] may also exist in the particle phase.

Heavy metals as contaminants in CECs and other cannabis products are also cause for concern, as at least one case report exists wherein a patient suffered from giant cell interstitial pneumonia that was attributed to cobalt exposure from a CEC.[103] An analytical method for determining levels of heavy metals in such aerosols has been recently published, and spike/recovery experiments also demonstrated that heavy metal can transfer to the

aerosol in CECs and standard cannabis smoking.[104] Generation of heavy metals especially during vaping due to devices can not be rules out.

Etiology and causes of EVALI

Prior to outbreak of EVALI, cannabis vaping-associated acute lung injuries (ALIs) were reported several times in the literature. McMahon *et al.* (2016) described a severe acute pneumonitis in a 19 year old male from dabbing butane hash oil (BHO, a common cannabis extract).[84] BAL revealed elevated levels of lymphocytes and eosinophils, but lacked any evidence of bacterial, fungal, or viral infection.[84] It was suggested that some impurity may have caused a chemical injury leading to acute hypersensitivity pneumonitis.[84] He *et al.* (2017) reported a 54 year old male regular consumer of cannabis e-cigarettes that developed dyspnea and low O_2 saturation.[105] Computed tomography (CT) showed extensive airspace opacification and bronchoscopy indicated alveolar hemorrhage with leukocyte infiltration.[105] Though the patient reported vaping supercritical CO_2-extracted cannabis oil in an e-cigarette, the authors suspected the cannabis oil may have been contaminated with the nicotine e-cigarette solvents GL and PG.[105] Anderson and Zechar (2019) detailed a case of severe pneumonitis in an 18 year old female associated with dabbing BHO.[106] BAL was not performed, but lung CT showed bilateral patchy infiltrates, and blood workup showed leukocytosis, with no evidence of microbiological infection.[106] The acute lung injury was attributed to harmful degradation products (or chemical interactions upon vaping) that form due to high heat during the dabbing process.[106]

The EVALI outbreak began as a gradual increase in patients reporting severe respiratory distress associated with vaping starting approximately in June of 2019, and cases quickly increased through August, peaked in mid-September, after which they gradually decreased until February 2020 when the CDC discontinued monitoring.[7] EVALI patients reported a rapid onset of acute and severe respiratory distress after using e-cigarette products, with 82% of patients reporting the use of e-cigarettes containing Δ^9-THC.[7] Patients present with an airway-centered acute lung injury with severe bronchiolitis accompanied by mucosal edema and desquamation of bronchial epithelium.[107] LLM, unlike foamy macrophages commonly caused by tobacco smoking, were a common feature which led to the suspicion that EVALI was a type of lipoid pneumonia induced by lipophilic ingredients in CEC.[107] However, other histological markers of lipoid pneumonia were lacking, which led Butt *et al.* (2020) to conclude the acute lung injury was a type chemical pneumonitis induced by some unknown toxic ingredient or a degradation product thereof.[107] More recent research showed that LLM are a common feature in healthy adult smokers and nicotine e-cigarette users, and do not serve as a specific marker for EVALI.[108]

Toxicological explanations for VEA pulmonary toxicity are conflicting, and a clear indication to this compound's proinflammatory action on bronchial epithelial cells and pulmonary macrophages is not clear.[11, 109] VEA has been shown to generate ketene, a highly toxic gas, when vaped, but due to the instability of this compound in the presence of water it is not clear if this molecule would persist in the aerosol long enough to cause a toxic response, as it may rapidly decompose to acetic acid in the humid respiratory tract before contacting tissue.[110] It has also been suggested that VEA can disrupt the

natural respiratory compression/decompression cycle of the alveoli by increasing the surface viscosity of pulmonary surfactant, potentially impairing oxygen diffusion leading to tissue hypoxia and inflammation.[111] Inflammation may be further exacerbated by CB_1R-dependent phospholipid/sphingolipid peroxidation[79] that may synergistically add to lipid peroxidation caused reactive oxygen species generated by macrophage respiratory bursts,[112] and CB_2R-dependent attenuation of epithelial cell chemotaxis may prevent clearance of the inhaled toxicants leading to accumulation of redox cycling molecules such as terpenes in an inflammatory feedback loop. Continued lipid peroxidation can further impact alveolar compression/decompression, and also lead to tissue permeability that may result in pneumonia.

Conclusion

Despite the recent deadly outbreak of EVALI, cannabis vaping has continued to proliferate and novel products are introduced at a daunting rate. Compounds already with little safety data at low concentrations are now present at concentrations that, in some cases, are orders of magnitude higher than any previously reported literature. It must be stressed that novel cannabis inhalation formats share so little in common with cannabis smoking that the pool of relevant literature with which consumers and regulators can use to assess their safety is lacking in appropriately relevant data. In order to address these deficits, research on CEC chronic and acute respiratory toxicity/acute lung injuries along with biomarkers of EVALI must use realistic devices and cannabis oil compositions that simplify any internal and external variables. In order to work around academia's inability to access state-level legal CECs, researchers must self-manufacture products that match their experimental requirements. In any case, dedicated attention to cannabis industry trends and user habits is necessary to design meaningful and relevant studies.

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Biography

Jiries Meehan-Atrash short biography

Dr. Jiries Meehan-Atrash graduated from the State University of New York at New Paltz with a Bachelor of Science in Chemistry in May 2014 and in June 2021 received his PhD in Chemistry from Portland State University with a dissertation titled *Chemical Characterization of Toxicologically Relevant Molecules in Cannabis Concentrates and Vaporizer Aerosols* under the mentorship of Dr. Robert M. Strongin. Jiries is currently as postdoctoral fellow at the University of Rochester Medical Center in the laboratory of Dr. Irfan Rahman.

Dr. Irfan Rahman short biography

Irfan Rahman, PhD is a Dean's Professor of Environmental Medicine, Medicine (Pulmonary), and Public Health Sciences at the University of Rochester Medical Center, NY and Director of Flavoring Inhalation Toxicology Center. His research interests include oxidative stress, inflammation, molecular clock, mitochondrial dysfunction, epigenetics, and cellular senescence by tobacco smoke/tobacco products (cigarette smoke, e-cigarettes, waterpipe/hookah, and cigars). Dr. Rahman is an author of over three hundred (300) publications in peer-reviewed journals with an 'H impact factor of 105. He is the author/editor of a book on 'Inflammation, Aging, Diet and Nutrition', and awarded as Highly Cited Researchers by Thomson Reuters.

List of Abbreviations

Δ^9-THC
Δ^9-tetrahydrocannabinol

Δ^8-tetrahydrocannabinol

Δ^{10}-THC
Δ^{10}-tetrahydrocannabinol

CBD
cannabidiol

ENDS
electronic nicotine delivery systems

CEC
cannabis e-cigarette

EVALI
e-cigarette or vaping product use-associated lung injury

HHC
hexahydrocannabinol

CBC
cannabichromene

CBL
cannabicylol

CBT
cannabicitran

MCT
medium chain triglyceride

PG
propylene glycol

GL
glycerol

VEA
vitamin E acetate

BAL
bronchoalveolar lavage

AM
alveolar macrophage

LPS
lipopolysaccharide

LLM
lipid-laden macrophage

VOC
volatile organic compound

ALI
acute lung injury

CT
computed tomography

BHO
butane hash oil

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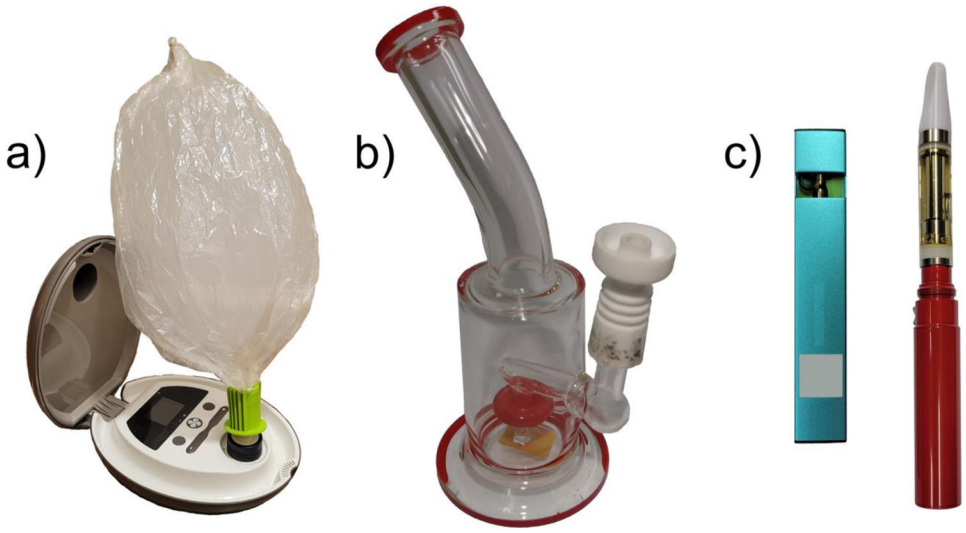

Figure 1.

Cannabis vaping modalities: a) is a tabletop flower vaporizer equipped with a balloon which traps the aerosol for inhalation, b) is a small “dab rig” which consists of a water pipe with a ceramic “nail” which is heated with a blow torch prior to administration of cannabis extract, and c) displays two types of CECs, a pod type (left) and cartridge type (right).

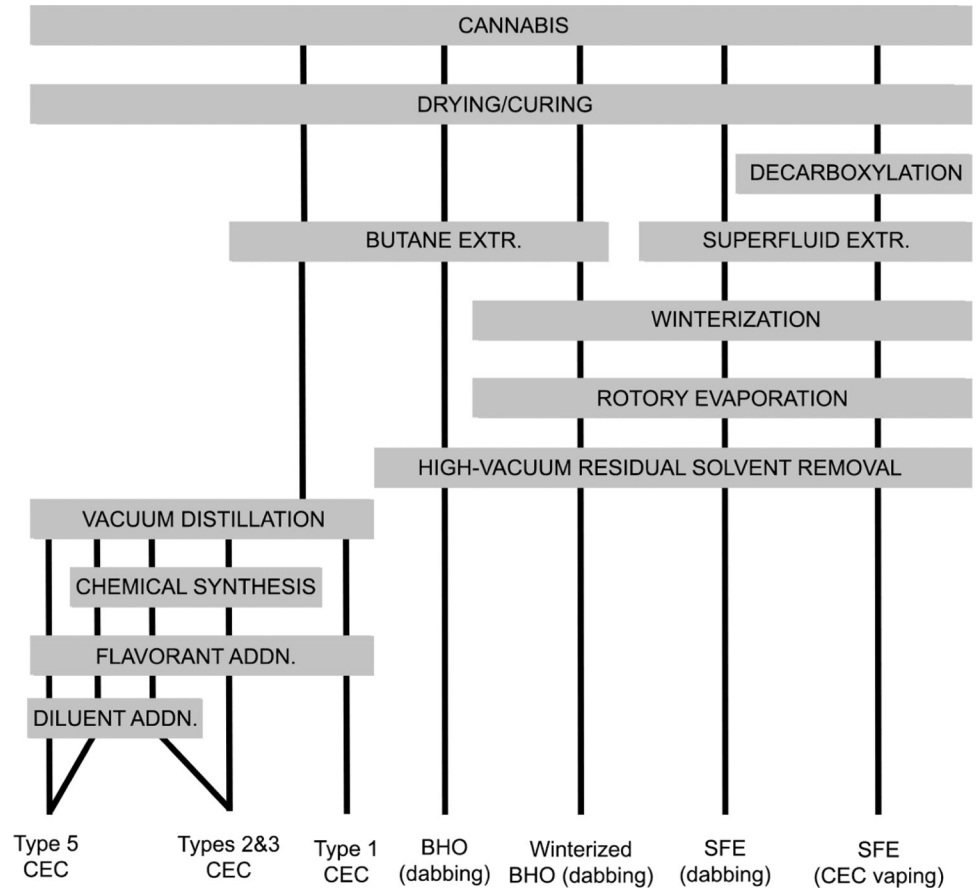

Figure 2.
Common cannabis extraction and processing methods for vaping and dabbing.

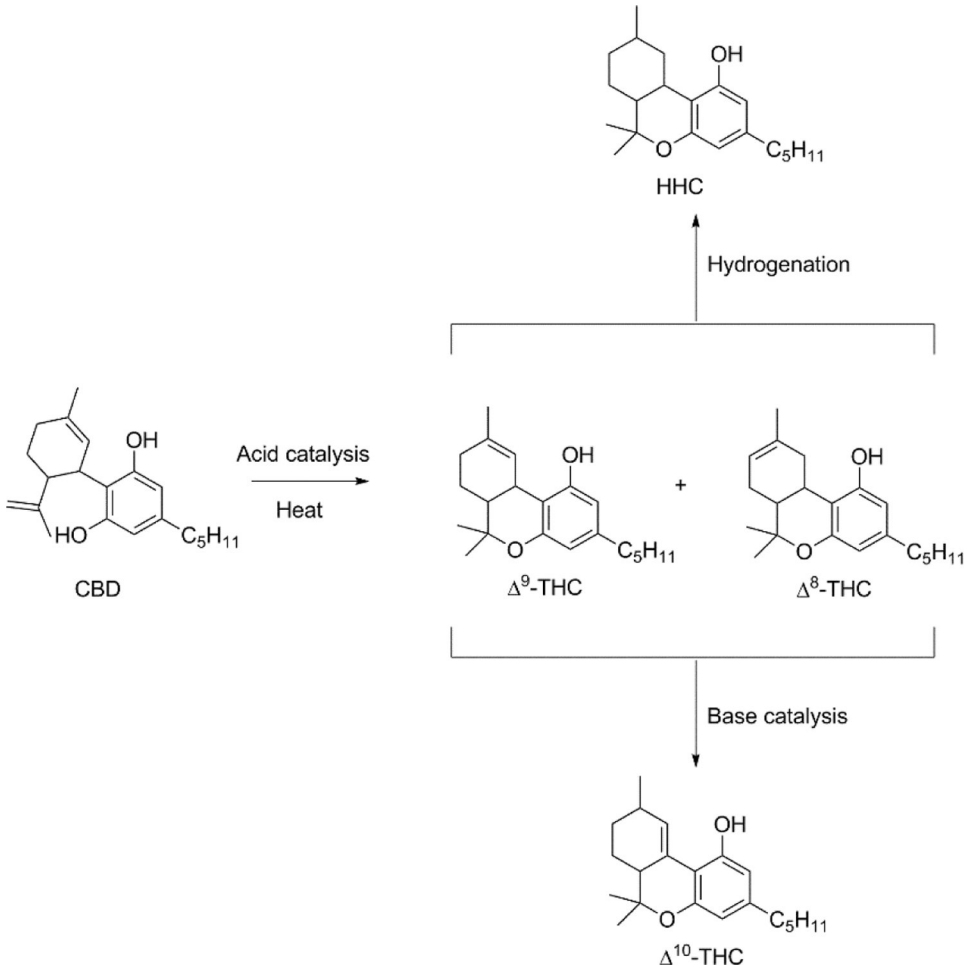

Figure 3.
Synthetic pathways used for manufacturing alternative cannabinoids for CECs.

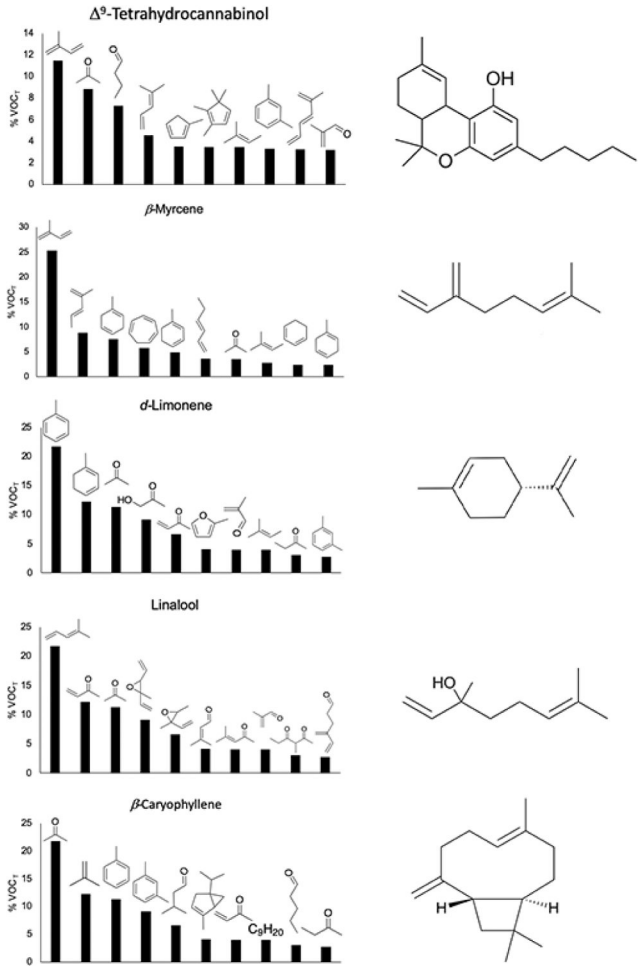

Figure 4.

Relative levels of VOCs emitted by Δ^9-THC and four high abundance terpene flavorants present in many CECs. Data derived from Meehan-Atrash (2021).[33]

Table 1.

Physical properties of some common cannabis extract components at standard temperature and pressure.

Compound	Melting point (°C)	Boiling point (°C)	Vapor pressure (Pa)
Δ^9-THCA	70 (with decomposition)[37]	decomposes	NA
Δ^9-THC	<25[38]	417.25[35]	2.57E-05[35]
CBDA	45–48[37]	decomposes	NA
CBD	62–63[39]	421.95[35]	2.73E-06[35]
β-Myrcene	<25	167[40]	265[41]
d-Limonene	<25	176[42]	196[43]
Linalool	<25	198.6[44]	24.6[43]
α-Pinene	<25	155[45]	576[43]

Table 2.

Classes of CECs by active ingredients, additives, legal statuses, and presence in the scientific literature.

Type	Active ingredients, (% composition)	Other ingredients, (% composition)	Legal status	Relevant literature
1	Δ^9-THC, (70 −90%)	Terpenes/ flavorants (10–30%)	Legal in states with recreational and medical cannabis programs.	Oregon Liquor Control Commission (2020), Meehan-Atrash *et al.* (2021)
2	Δ^8-THC, Δ^{10}-THC, HHC, (60 −90%)	Terpenes/ flavorants (10–30%), cutting agents/ viscosity modifiers (NA)	Federally legal under 2018 Farm Bill. Regulated or banned in some states.	US Cannabis Council (2021)
3	CBD, CBC, CBL, CBT, etc. (60 −90%)	Terpenes/ flavorants (10–30%)	Federally legal under 2018 Farm Bill. Regulated in some states.	NA
4	Δ^9-THC, CBD. (10 −60%)	Terpenes/ flavorants (10–30%), cutting agents/ viscosity modifiers (20–60%)	MCT oil, VEA, and polyethylene glycol banned in CO; squalene, squalane, MCT oil, VEA, PG banned in OR; VEA banned in WA and requires labelling for non-cannabis additives.	Peace *et al.* (2016a), Muthumalage *et al.* (2020b), Duffy *et al.* (2020)
5	CBD (1 −3%)	Flavorants (NA), PG, GL (<90%)	Federally legal under 2018 Farm Bill. Regulated in some states.	Peace *et al.* (2016b)