Non-Cannabis Additives in Inhalable Cannabinoid Products:

Rationale for Rulemaking

Oregon Liquor Control Commission

October 29, 2020

The Oregon Liquor Control Commission ("OLCC") is engaging in rulemaking to create robust regulations for non-cannabis ingredients in vaping products. In 2019, all 50 states saw an unprecedented outbreak of a vaping induced lung injury associated with cannabis vaping. To date, the precise cause is unknown; however, it appears that certain non-cannabis ingredients are wholly or partially responsible. While this rulemaking process is being undertaken in the aftermath of the acute lung injury outbreak, the OLCC's concerns regarding additives apply to both the potential for acute and chronic harm associated with unknown ingredients, and these concerns pre-date the outbreak. Once OLCC licensees began using additives, it became apparent that the companies providing them were at best loosely regulated. Most did not disclose the ingredients in their products (or were untruthful in doing so), used misleading language about the ingredients being food safe, and disclaimed their use for inhalation and vaporization, while at the same time, marketing the products to the cannabis industry for use in inhalable products.

For cannabis products that are vaporized or inhaled, OLCC's proposed rulemaking will require that all the components of non-cannabis additives be disclosed to OLCC, licensees, and consumers. Manufacturers will also be required to explicitly state their products are meant for human inhalation. They also prohibit the inclusion of particularly problematic ingredients that pose a risk to public health. Lastly, the OLCC's packaging and labeling rules have been updated to make it clearer to consumers that products contain additives and specifically what those additives are so that they can make an informed decision about what they are consuming.

Cannabis Oil:

Oregon law divides material extracted from cannabis into two categories: cannabinoid concentrate and cannabinoid extract (collectively, "Cannabis Oil"),[1] which are differentiated based on the manner in which cannabinoids are separated from cannabis. Cannabinoid extracts include material where cannabinoids have been separated from cannabis by a process using hydrocarbons as a solvent or by using carbon dioxide in a liquid or supercritical fluid phase as a solvent. Cannabinoid concentrates include material where cannabinoids have been separated from cannabis by a mechanical extraction process such as sifting through a mesh or screen, or by a solvent extraction process that does not use hydrocarbons or carbon dioxide as a solvent.

The chemical composition and tetrahydrocannabinol ("THC") potency of the initial cannabinoid concentrate or extract can vary dramatically depending on the starting material and the extraction methods and conditions. Cannabinoid concentrates or extracts may undergo further refinement. "THC distillate" is a product commonly refined from "crude" cannabinoid concentrates or extracts. The crude concentrate or extract is gradually heated to separate compounds based on their boiling points via short-path distillation. If the crude concentrate or extract contains cannabis aroma compounds (e.g. terpenes) that distill at a lower temperature than THC, this lower boiling point fraction may be collected prior to increasing the temperature to distill the THC-containing fraction. The THC-containing fraction is typically a highly viscous colorless liquid.

[1] While imprecise, for the purposes of this paper, the term "cannabis" will refer to both marijuana and hemp (as those terms are defined in Oregon law).

Inhalable Cannabinoid Products:

The OLCC's rulemaking is directed at products that combine marijuana or hemp items that are meant for inhalation (predominantly Cannabis Oil) with processed non-cannabis substances. These products include bulk Cannabis Oil (e.g. as a viscous liquid in jars or in a solid form such as "shatter"), vape cartridges, syringes used to refill vape cartridges, and infused pre-rolls that are combined with processed non-cannabis ingredients (collectively, "Inhalable Cannabinoid Products"). Under the OLCC's cannabis definitions, "cannabinoid products" generally encompass inhalable or ingestible products that combine a form of cannabis (e.g. extract, concentrate, or flower) with non-cannabis substances.[2] OLCC's proposed rules would not affect ingestible cannabinoid products because more robust standards and a greater body of literature exist with regard to the safety of ingredients delivered via ingestion.

Vape cartridges are the primary product to which non-cannabis substances are added. The vaping process involves attaching a pre-filled cartridge to a battery, which can operate between 300 degrees and 800 degrees, and inhaling an aerosolized mixture into the lungs.[3] The OLCC's seed-to-sale tracking system tracks broad categories of items (e.g. concentrates, extracts, and cannabinoid products), but does not differentiate between specific subcategories (e.g. vape cartridges versus other forms of concentrate and extract). However, the proposed rules would create additional tracking requirements in the seed-to-sale tracking system, including providing manufacturer and ingredient information. This added information will allow OLCC to quickly take action should problematic ingredients be discovered.

[2] Or. Admin. R. 845-025-1015(11) (2020).
[3] Michael Preciado, "The Future of Vape Litigation: Temperature Control," Cannabis Industry Journal (Cannabis Industry Journal, July 3, 2020), https://cannabisindustryjournal.com/column/the-future-of-vape-litigation-temperature-control/.

Cannabis Oil Additives – Terpenes and Flavorings:

The cannabis plant contains a wide variety of chemical compounds; the most relevant to the discussion of cannabis flavoring are terpenes and terpenoids, which will collectively be referred to as "terpenes."[4] Terpenes are not exclusive to cannabis. They can be found in other plants, animals, and can be synthesized. In addition to other compounds present in cannabis, terpenes can contribute to the flavor and fragrance of cannabis.[5] The majority of terpenes found in cannabis are hydrocarbons and common examples include: myrcene, β-caryophyllene, α-humulene, α-pinene, linalool, limonene, and bisabolol.[6] It is also theorized that terpenes contribute to the "entourage effect" in cannabis, which has driven consumer perception and awareness of these compounds.[7] The definition of the "entourage effect" is somewhat vague, but can be described as a "synergy – a net benefit resulting from a combination of plant components that is greater than the sum of its parts…"[8] It should be noted that the entourage effect is a theory and at this time is unproven.[9] Of relevance, the cannabis plant also contains alcohols, aldehydes, ketones, acids, esters, flavonoids, and lactones which may also contribute to its characteristic aroma.[10]

[4] *See, e.g.*, Ethan B Russo, "Taming THC: Potential Cannabis Synergy and Phytocannabinoid-Terpenoid Entourage Effects," *British Journal of Pharmacology* 163, no. 7 (December 2011): pp. 1344-1364, https://doi.org/10.1111/j.1476-5381.2011.01238.x.
[5] Russo, "Taming THC: Potential Cannabis Synergy," 1344.
[6] Judith K. Booth and Jörg Bohlmann, "Terpenes in Cannabis Sativa – From Plant Genome to Humans," *Plant Science* 284 (2019): 68, https://doi.org/10.1016/j.plantsci.2019.03.022.
[7] Russo, "Taming THC: Potential Cannabis Synergy," 1344.
[8] Cogan, Peter S, "The 'Entourage Effect' or 'Hodge-Podge Hashish': the Questionable Rebranding, Marketing, and Expectations of Cannabis Polypharmacy," *Expert Review of Clinical Pharmacology* (2020): 2, https://doi.org/10.1080/17512433.2020.1721281.
[9] Cogan, "The 'Entourage Effect' or 'Hodge-Podge Hashish'," 8.
[10] Grotenhermen, Franjo, Ethan Russo, and Mahmoud ElSohly, "Chemical Constituents of Cannabis," Essay. In *Cannabis and Cannabinoids: Pharmacology, Toxicology, and Therapeutic Potential*, 28. Binghamton, NY: Haworth Press, 2002, https://doi.org/10.4324/9780203479506.

The majority of Cannabis Oil in the Oregon marketplace contains only terpenes derived from cannabis. Terpenes can occur in the cannabis product naturally or be removed through a "first pass process" (e.g. steam distillation, short path distillation, or sub-critical CO_2) and reintroduced later. However, some OLCC licensees prefer to add terpenes and other flavoring compounds from non-cannabis sources. This is done due to cost and scalability (e.g. suitability for multi-state operators). Specific terpenes and ratios differ from batch to batch of usable cannabis and can vary "substantially based on genetic, environmental, and developmental factors."[11] Processors who wish to create a more cost effective and consistent product rely on purchasing non-cannabis products from third-party companies (collectively, the "Companies").

The Companies provide a wide variety of products, ranging from singular non-cannabis terpene isolates to more exotic blends of terpenes and other chemicals (e.g. flavonoids, esters, aldehydes, and ketones) that are meant to mimic the flavor and effects of certain cannabis cultivars (e.g. "Blue Dream" or "OG Kush"), or non-cannabis specific flavors like watermelon, cotton candy, bubble gum, or grape (collectively, "Flavor Additives"). Based on OLCC's observations, most OLCC licensees prefer to use pre-mixed blends (as opposed to singular terpene isolates), which may contain non-cannabis terpenes and other chemicals. Some of the pre-mixed blends contain diluents like medium chain triglyceride ("MCT") oil, propylene glycol ("PG"), or ethyl alcohol.

It is important to note that the Companies are not regulated by any government or third-party body to provide products meant for human inhalation. Some of them are regulated under

[11] Booth, Judith K., Macaire M.s. Yuen, Sharon Jancsik, Lina Madilao, Jonathan Page, and Joerg Bohlmann, "Terpene Synthases and Terpene Variation in Cannabis Sativa," *Plant Physiology*, 2020: 3, https://doi.org/10.1104/pp.20.00593.

food handling laws and may receive accreditation for food safety or good manufacturing practices (e.g. ISO 9001: 2015 and FSSC 22000). Neither of these accreditations address the underlying safety of the products when vaporized and inhaled.

The Companies also market their products in a manner that suggest they are meant for inhalation and "[w]hile companies may be marketing pharmaceutical-grade reagents that are approved for other purposes such as ingestion, their safety in [the] vaping scenario is unknown."[12] Most of the Companies disclaim their use for inhalation, and some go so far as to put the onus on the consumer to conduct their own safety testing on the products.[13] The picture of where the Companies source their products from is not entirely clear due to the secretive and unregulated nature of the Companies. Some purchase products from other companies and further refine them, while others purchase them from large chemical suppliers like Sigma Aldrich or "flavor houses," which make products meant for ingestion (i.e. culinary use), and blend them.

The cannabis industry colloquially refers to these products as "botanical terpenes." However, the term "botanical terpene" does not have a legal definition in this context, and by and large the Companies do not use this term, which renders it essentially meaningless. In fact, to the extent that it is ascertainable, most of the blends used by OLCC licensees contain other ingredients in addition to terpenes. Flavoring Additives can be derived from natural sources or can be produced synthetically.[14] The use of this term obfuscates the reality that many of the products are synthetic or contain a mixture of natural and synthetically derived compounds. As

[12] Bryan Duffy, Lingyun Li, Shijun Lu, Lorie Durocher, Mark Dittmar, Emily Delaney-Baldwin, Deepika Panawennage, David Lemaster, Kristen Navarette, and David Spink, "Analysis of Cannabinoid-Containing Fluids in Illicit Vaping Cartridges Recovered from Pulmonary Injury Patients: Identification of Vitamin E Acetate as a Major Diluent," *Toxics* 8, no. 1 (2020): 15, https://doi.org/10.3390/toxics8010008.
[13] *See e.g.* "Safety Data Sheet – Forbidden Fruit Infused," True Terpenes, Accessed July 16, 2020, https://trueterpenes.com/certificates/sds/Forbidden_Fruit_ID_SDS_True_Terpenes.pdf.
[14] John B. Hallagan, "The Use of Diacetyl (2,3-Butanedione) and Related Flavoring Substances as Flavorings Added to Foods—Workplace Safety Issues," *Toxicology* 388 (2017): 1, https://doi.org/10.1016/j.tox.2017.05.010.

part of the OLCC's packaging and labeling program, licensees must submit documentation that shows whether the ingredients are natural or artificial flavors as those terms are defined by FDA food labeling laws.[15] The term "natural flavor" generally means the flavor is derived from a plant, but can also mean it was derived from edible yeast, animals, animal byproducts, or fermentation products.[16] An "artificial flavor" is anything that is not derived from one of these sources, i.e. is synthesized.[17] It is estimated that roughly half of the Flavor Additives used by OLCC licensees contain at least some artificial ingredients. Whether the source of the ingredients makes any difference from a health standpoint is unclear.[18] Consumers prefer the term "natural" on food and cosmetic labeling.[19] The terminology "botanical terpenes" is generally inaccurate and is likely used to mislead consumers about the complex mixture of substances they are vaporizing and inhaling.

Some OLCC licensees use flavorings that are also present in the e-cigarette marketplace. These primarily consist of products that do not contain terpenes and by and large are not cannabis specific, e.g. cinnamon bun, bubble gum, grape pie, vanilla, or raspberry punch. The OLCC prohibits flavors that are considered attractive to minors such as bubble gum, root beer, and cotton candy.[20] These types of products are the minority in the Oregon marketplace.

---

[15] "Recreational Marijuana Program Compliance Education Bulletin CE2018-09," Oregon Liquor Control Commission (November 28, 2018), https://www.oregon.gov/olcc/marijuana/Documents/Bulletins/Compliance_1809.pdf.
[16] 21 C.F.R. § 101.22(a)(3) (2019).
[17] 21 C.F.R. § 101.22(a)(1) (2019).
[18] Hallagan, "The Use of Diacetyl (2,3-Butanedione)," 3.
[19] *See, e.g.*, Ferreira, Denise. "How Are Changes in Consumer Preferences for Natural Products Driving Market Disruption?" Web log. *CAS. A Division of the American Chemical Society* (blog), March 9, 2018, https://www.cas.org/blog/how-are-changes-consumer-preferences-natural-products-driving-market-disruption.
[20] Or. Admin. R. 845-025-3220(2)(a) (2017).

Cannabis Diluents:

The commonly known diluents used with Cannabis Oil include: MCT, PG, and polyethylene glycol ("PEG").[21] The word "known" is used because it is likely that unknown diluents are being used by some of the cannabis industry. In addition to Flavoring Additives, many of the Companies also provide "thickeners," "cuts," "diluent blends," or "odorless and flavorless terpene diluents." Little is known about these products, as the Companies tend to keep their ingredients secret.[22]

Diluents are used for a variety of reasons, including overcoming hardware limitations of cheaper cartridges and increasing profit margins. Innovations in vape cart technology are beginning to overcome hardware limitations in regards to thicker Cannabis Oils. In Oregon, "diluent terpenes" are predominately used and it is common to see phytol and α-bisabolol being used as diluent terpenes.[23] Both of these terpenes are found in cannabis, however, the health effects of their elevated use is unknown, particularly phytol which naturally appears in low levels in the cannabis plant. MCT oil appears to be used sparingly in the OLCC marketplace.

Vaping Induced Lung Injury – Searching for a Cause:

During 2019, an outbreak of what the Centers for Disease Control ("CDC") dubbed e-cigarette, or vaping, product use-associated lung injury ("EVALI" or "VALI") began. As of February 18, 2020, a total of 2,807 hospitalized VALI cases were reported to the CDC from all

[21] The OLCC explicitly prohibits the use of PEG in any cannabis product, *see* Or. Admin. R. 845-025-3220(3) (2017).
[22] *See, e.g.*, "Safety Data Sheet – High Viscosity Diluent," Floraplex Terpenes, Accessed July 16, 2020, https://www.buyterpenesonline.com/wp-content/uploads/FLPX-LLC-High-Viscosity-Diluent-v1.1.pdf.
[23] *See, e.g.*, "Viscosity" from True Terpenes, "Buy Viscosity," True Terpenes, Accessed July 16, 2020, https://trueterpenes.com/shop/flavorless-terpenes/. *See also*, The Werc Shop, LLC, "The Werc Shop Announces Latest Innovation in Vaping Technology," PR Newswire: news distribution, targeting and monitoring, February 20, 2019, https://www.prnewswire.com/news-releases/the-werc-shop-announces-latest-innovation-in-vaping-technology-300799242.html.

50 states, the District of Columbia, and two U.S. territories (Puerto Rico and U.S. Virgin Islands).[24] In Oregon, as of March 12, 2020, 23 cases of VALI were reported, 2 of which were fatal.[25] Persons with VALI experience the following symptoms: cough, chest pain, shortness of breath, abdominal pain, nausea, vomiting, stomach pain, diarrhea, fever, chills, and weight loss.[26] The onset of these symptoms can be rapid.[27] Reported cases of VALI have lessened, as both the Oregon Health Authority ("OHA")[28] and the CDC have generally stopped accepting reports.[29] However, the CDC recently reported nineteen confirmed cases in California.[30] The decrease in reported cases is likely due in part to COVID-19, which necessitated a shift of resources and displays symptoms similar in nature to VALI[31] (as part of a VALI diagnosis, COVID-19 must be determinatively ruled out).[32]

As of October 2020, no singular substance has been determined to be the causative agent of VALI. However, it does appear that THC containing vaping products and vitamin E acetate ("VEA") are strongly linked to the VALI outbreak in some states, particularly the Midwest.[33]

---

[24] "Outbreak of Lung Injury Associated with the Use of E-Cigarette, or Vaping, Products," Centers for Disease Control and Prevention, Accessed July 16, 2020, https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease.html.
[25] "Oregon Vaping Illness Investigation," Oregon Health Authority: Oregon Vaping Illness Investigation: Acute and Communicable Disease: State of Oregon, Accessed July 16, 2020, https://www.oregon.gov/oha/PH/DISEASESCONDITIONS/COMMUNICABLEDISEASE/Pages/vaping-illness.aspx.
[26] "For Healthcare Providers," Centers for Disease Control and Prevention (Centers for Disease Control and Prevention, March 17, 2020), Accessed July 16, 2020, https://www.cdc.gov/tobacco/basic_information/e-cigarettes/severe-lung-disease/healthcare-providers/index.html.
[27] "For Healthcare Providers."
[28] "Oregon Vaping Illness Investigation."
[29] "Outbreak of Lung Injury Associated with the Use of E-Cigarette, or Vaping, Products."
[30] Christina Armatas, Amy Heinzerling, and Jason A Wilken, "Notes from the Field: E-Cigarette, or Vaping, Product Use–Associated Lung Injury Cases During the COVID-19 Response - California, 2020," Centers for Disease Control and Prevention (Centers for Disease Control and Prevention, June 25, 2020), https://www.cdc.gov/mmwr/volumes/69/wr/mm6925a5.htm.
[31] "Symptoms of Coronavirus," Centers for Disease Control and Prevention, Accessed October 26, 2020, https://www.cdc.gov/coronavirus/2019-ncov/symptoms-testing/symptoms.html.
[32] "Notes from the Field: E-Cigarette, or Vaping, Product Use-Associated Lung Injury."
[33] "Outbreak of Lung Injury Associated with the Use of E-Cigarette, or Vaping, Products."

VEA is commonly used as a vitamin supplement and in skincare products.[34] However, the CDC states that "[e]vidence is not sufficient to rule out the contribution of other chemicals of concern…."[35] A study analyzed the bronchoalveolar-lavage fluid ("BAL") of 51 VALI patients (none of whom were from Oregon) for "vitamin E acetate, plant oils, medium-chain triglyceride oil, coconut oil, petroleum distillates, and diluent terpenes."[36] The study found VEA in the BAL fluids for 94% of the case patients and one patient had coconut oil and limonene in their BAL fluid.[37]

Acute lung injuries are common among all VALI cases.[38] To date, it is unclear whether there is a singular type of lung injury associated with VALI, which may be due to the many complex variables involved. Hospitalized VALI patients "manifested a variety of radiological imaging patterns consistent with lipoid pneumonia, eosinophilic pneumonia, and chemical damage to the lung tissue."[39] Some VALI cases have been diagnosed with lipoid pneumonia.[40] However, more recently, "histopathological reports showed the presence of burnt/blackened

[34] Grady, Denise, "Vaping Illnesses Are Linked to Vitamin E Acetate, C.D.C. Says," The New York Times, November 8, 2019, https://www.nytimes.com/2019/11/08/health/vaping-illness-cdc.html.
[35] "For Healthcare Providers."
[36] Blount, Benjamin, Mateusz Karwowski, Peter Shields, Maria Morel-Espinosa, Liza Valentin-Blasini, Michael Gardner, Martha Braselton, et al, "Vitamin E Acetate in Bronchoalveolar-Lavage Fluid Associated with EVALI," *The New England Journal of Medicine*, February 20, 2020, 697–705, https://doi.org/DOI: 10.1056/NEJMoa1916433.
[37] Blount *et al.*, "Vitamin E Acetate in Bronchoalveolar-Lavage Fluid."
[38] Layden, Jennifer E., Isaac Ghinai, Ian Pray, Anne Kimball, Mark Layer, Mark W. Tenforde, Livia Navon, et al, "Pulmonary Illness Related to E-Cigarette Use in Illinois and Wisconsin — Final Report," *New England Journal of Medicine* 382, no. 10 (2020): 903–16, https://doi.org/10.1056/nejmoa1911614.
[39] Muthumalage, Thivanka, Michelle R. Friedman, Matthew D. Mcgraw, Alan E. Friedman, and Irfan Rahman, "Chemical Constituents Involved in e-Cigarette, or Vaping Product Use-Associated Lung Injury (EVALI)," 2020, 1, https://doi.org/10.1101/2020.01.14.905539.
[40] *See, e.g.*, Bryno Gay, Zachary Field, Sachin Patel, Rodrigo Murillo Alvarez, Wael Nasser, Mario Maduga, and S.J. Carlan, "Vaping-Induced Lung Injury: A Case of Lipoid Pneumonia Associated with E-Cigarettes Containing Cannabis," *Case Reports in Pulmonology*, April 3, 2020, https://doi.org/10.1155/2020/7151834. *See also,* Kevin Davidson, Alison Brancato, Peter Heetderks, Wissam Mansour, Edward Matheis, Myra Nario, Shrinivas Rajagopalan, et al, "Outbreak of Electronic-Cigarette-Associated Acute Lipoid Pneumonia – North Carolina, July-August 2019," Centers for Disease Control and Prevention (Centers for Disease Control and Prevention, September 13, 2019), https://doi.org/DOI:10.15585/mmwr.mm6836e1.

lungs, suggesting that aromatic/volatile hydrocarbons, including terpenes (diluent) and oils, are involved in EVALI."[41] These results are "more consistent with airway-centered chemical pneumonitis from inhaled toxic substance(s) rather than exogenous lipoid pneumonia."[42] Wu and O'Shea recently found that when VEA is heated and vaporized, it has the potential to produce "exceptionally toxic ketene gas, which may be a contributing factor to the upsurge in pulmonary injuries associated with using e-cigarette/vaping products."[43] The researchers also found that vaporizing VEA created "carcinogen alkenes and benzene for which the negative long-term medical effects are well recognized."[44] Similar findings were reported by Narimani and da Silva.[45]

The production of toxic ketene gas is particularly relevant, and Dr. Robert Strongin of Portland State University commented in PNAS: "[s]ome vaping proponents have been dismissive of the relevance of nonclinical chemical investigations of e-cigarette aerosol chemical toxins, positing that vapers can effectively self-regulate any elevated toxin intake simply by sensorial perception. Sadly, the EVALI outbreak has shown self-regulation by vapers to be unreliable at best and deadly at worst."[46] These results suggest harmful substances are created during the heating and vaporization process and that users do not immediately recognize them as harmful. On July 24th, 2020, Ali Hammade, Deputy State Epidemiologist for OHA, testified at an

[41] Chand, Hitendra S., Thivanka Muthumalage, Wasim Maziak, and Irfan Rahman, "Pulmonary Toxicity and the Pathophysiology of Electronic Cigarette, or Vaping Product, Use Associated Lung Injury," *Frontiers in Pharmacology* 10 (2020): 2, https://doi.org/10.3389/fphar.2019.01619.
[42] Dan Wu and Donal O'Shea, "Potential for Release of Pulmonary Toxic Ketene from Vaping Pyrolysis of Vitamin E Acetate," 2019, 6349, https://doi.org/10.26434/chemrxiv.10058168.
[43] Wu and O'Shea, "Potential for Release of Pulmonary Toxic Ketene," 6349.
[44] Wu and O'Shea, "Potential for Release of Pulmonary Toxic Ketene," 6349.
[45] Narimani, Milad, and Gabriel da Silva, "Does 'Dry Hit' Vaping of Vitamin E Acetate Contribute to EVALI? Simulating Toxic Ketene Formation During E-Cigarette Use," 2020, https://doi.org/10.26434/chemrxiv.11889828.
[46] Strongin, Robert M., "Toxic Ketene Gas Forms on Vaping Vitamin E Acetate Prompting Interest in Its Possible Role in the EVALI Outbreak," *Proceedings of the National Academy of Sciences* 117, no. 14 (2020): 7553, https://doi.org/10.1073/pnas.2003384117.

OLCC rules advisory committee ("Experts RAC") that persons exposed to toxicants may take years, if not decades, to manifest symptoms.[47] At the Experts RAC, Tom Jeanne, Deputy State Epidemiologist for OHA, testified that the precise causative agent of VALI in Oregon is still unknown and stressed the scientific limitations of relying on after-the-fact public health investigations (i.e. many people have to harmed and/or killed).[48] While searching for a cause to VALI in Oregon is of great importance, OLCC is concerned that consumers and patients are being exposed to toxic substances for which they may not immediately manifest symptoms.

The CDC has reported that most of the VALI cases used THC containing products and were purchased via the illicit market.[49] However, Oregon appears to be an outlier – to date there is no evidence any Oregon case purchased products from the illicit market. At the Experts RAC, Dr. Jeanne testified that the Food and Drug Administration ("FDA") tested liquids of products from three Oregon cases and found, among other things, cannabinoids, terpenes, and squalene.[50] The CDC tested aerosols from seven cannabis vaping products from Oregon cases and found squalene in all the cannabis product aerosols. Of note, neither the FDA nor CDC found VEA in any Oregon products.[51]

Prior to these preliminary results, the OLCC was unaware of any licensee using squalene or squalane in Inhalable Cannabinoid Products. Squalene is a terpene that can be derived from

[47] "2020-07-24 Additives Rules Advisory Committee - Expert Presentations.mp3," Oregon Liquor Control Commission, July 24, 2020: 2:22, https://ecm.olcc.state.or.us/share/s/iOu-w-EVQ0eEZixDcY5FkQ.
[48] "2020-07-24 Additives Rules Advisory Committee - Expert Presentations.mp3," 1:49.
[49] "Outbreak of Lung Injury Associated with the Use of E-Cigarette, or Vaping, Products."
[50] Hamade, Ali and Jeanne, Tom, "Public Health Aspects of Vaping Toxicology," Oregon Health Authority (2020): 16, https://www.oregon.gov/olcc/marijuana/Documents/Rules/Marijuana-Additives/Hamade-and-Jeanne-OHA-Presentation.pdf.
[51] Hamade and Jeanne, "Public Health Aspects of Vaping Toxicology," 16.

plants (e.g. olives, sugar cane, and amaranth), including in very low amounts in cannabis,[52] or animal sources (i.e. shark livers). Squalane is the hydrogenated version of squalene. Squalene is known to cause exogenous lipoid pneumonia[53] and when heated to "decomposition" emits carbon monoxide and carbon dioxide.[54] Squalane creates toxic degradation products when exposed to vaping conditions[55] and is similar to VEA in that it is used in the cosmetics industry.[56] It is also known that at least some commercially available non-cannabis diluents contain or contained squalane.[57] Squalane is readily soluble in oil, colorless, and odorless – making it an ideal candidate to be used as a diluent in Cannabis Oils.[58] Recently, through audit testing, the OLCC has found squalane in a commercially available diluent used by at least one OLCC licensee to formulate Inhalable Cannabinoid Products. The presence of squalane in the diluent was not disclosed by the manufacturer.

VALI Specific Scientific Research - an Overview:

Since the 2019 VALI outbreak, several scientific papers have been published that examined the liquids inside a variety of vape cartridges (including illicit and medical products) and what chemicals are produced when they are heated and vaporized. Unfortunately, "[t]he

[52] It should be noted that no firm data exists on how much squalene is present in cannabis flower and extracts, as most cannabis labs are not required to test for this analyte as part of any state mandated testing. However, the data that is available suggests it appears in very low (i.e. trace) amounts.
[53] Lee, Jin Seong, Gyungyub Gong, and Tae Hwan Lim, "Squalene Aspiration Pneumonia: Thin-Section CT and Histopathologic Findings," *Journal of the Korean Radiological Society* 38, no. 3 (1998): 453, https://doi.org/10.3348/jkrs.1998.38.3.453.
[54] NOAA Office of Response and Restoration, US GOV. "Chemical Datasheet," NOAA - Cameo Chemicals, Accessed October 25, 2020, https://cameochemicals.noaa.gov/chemical/21030.
[55] Jiang, Huanhuan, C. M. Sabbir Ahmed, Thomas J. Martin, Alexa Canchola, Iain W. H. Oswald, Jose Andres Garcia, Jin Y Chen, et al, "Chemical and Toxicological Characterization of Vaping Emission Products from Commonly Used Vape Juice Diluents," *Chemical Research in Toxicology*, 2020, https://doi.org/10.1021/acs.chemrestox.0c00174.
[56] *See, e.g.*, Fiume, Monice, "Final Report on the Safety Assessment of Squalane and Squalene," *Journal of the American College of Toxicology* 1, no. 2 (1990): 37–56, https://doi.org/10.3109/10915818209013146.
[57] Duffy *et al*., "Analysis of Cannabinoid-Containing Fluids in Illicit Vaping Cartridges," 13-16.
[58] Fiume, Monice, "Final Report on the Safety Assessment of Squalane and Squalene," 38.

legal restrictions on cannabis products limit research avenues to study the effects of these e-cig vaping products using surrogate models. Thus, there is a paucity of risk assessment and toxicological data on THC/cannabis containing products."[59] Due to the federal illegality of cannabis, researchers have an incredibly difficult job in studying cannabis containing products. From a regulator's perspective, it made the OLCC and OHA's reactive investigation into the causative agent(s) of VALI in Oregon incredibly burdensome as well.

Despite the research hurdles that make it difficult, if not impossible, to pinpoint all possible causes of lung injury, a general consensus has begun to form. VEA is one contributing cause, but is not unique in its ability to harm. Other additives and similar ingredients show the same physical properties (e.g. high molecular weight and boiling point)[60] and pose similar risks to consumers, and many of these ingredients continue to be detected in commercially available Flavor Additives and diluents.[61]

Duffy et al. analyzed 38 illicit vape cartridges from confirmed VALI patients and six commercially available diluents.[62] Notably, the researchers found VEA in 23 of the 36 cartridges and MCT in 15 of the 36 cartridges.[63] They also analyzed commercially available "diluents" and "thickeners" and found the following substances: VEA, squalane, MCT, triethyl citrate, α-bisabolol, and isophytol (an isomer of phytol).[64] The authors offer this stark conclusion: "[t]here is little scientific knowledge of the long-term health effects of vaping any material, and the cannabis-oil vaporizer diluent industry appears to be operating with minimal oversight….[T]here

[59] Muthumalage *et al*., "Chemical Constituents Involved in EVALI," 10.
[60] *See e.g.,* Fiume, Monice, "Final Report on the Safety Assessment of Squalane and Squalene," 39 (Squalane boiling point of 350°C and squalene at 335°C)
[61] *See, e.g.*, Duffy *et al*., "Analysis of Cannabinoid-Containing Fluids in Illicit Vaping Cartridges."
[62] Duffy *et al*., "Analysis of Cannabinoid-Containing Fluids in Illicit Vaping Cartridges."
[63] Duffy *et al*., "Analysis of Cannabinoid-Containing Fluids in Illicit Vaping Cartridges," 9-10.
[64] Duffy *et al*., "Analysis of Cannabinoid-Containing Fluids in Illicit Vaping Cartridge," 14.

appears to have been no testing for or evaluation of the potential toxic effects of these products in the vaping process. There is no evidence that vaping large amounts of compounds such as VEA, squalane, or other chemicals present in diluent products on the market is safe."[65]

Duffy et al.'s findings on the diluents and thickeners are particularly relevant. As previously mentioned, many of the Companies that provide these products do not disclose their ingredients. In September 2019, the New York Department of Health subpoenaed Honey Cut Labs LLC, Floraplex Terpenes, and Mass Terpenes to assist the department in its VALI investigation.[66] This is notable because Floraplex and Mass Terpenes continue to supply products to the cannabis industry, including "Terp Liquefy" by Mass Terpenes (an "all-in-one blend of terpenes, flavor, and medium chains")[67] and "Terpene Diluent" by Floraplex (an "all natural, nearly flavorless and odorless terpene diluent!").[68] Neither of these companies makes the ingredients in these products available on their website (Floraplex states that 100% of the chemical makeup is proprietary).[69]

Muthumalage et al. examined the liquids found in illicit, CBD, and medical grade cannabis containing cartridges.[70] The researchers analyzed both CBD and medical grade cartridges (obtained via New York's medical system) because they were not known to be

[65] Duffy *et al*., "Analysis of Cannabinoid-Containing Fluids in Illicit Vaping Cartridge," 16.
[66] "Governor Cuomo Takes Aggressive Action to Protect New Yorkers from Harmful and Addictive Vaping Products Following Rise in Vaping-Associated Illnesses Nationwide," Governor Andrew M. Cuomo, September 18, 2019, https://www.governor.ny.gov/news/governor-cuomo-takes-aggressive-action-protect-new-yorkers-harmful-and-addictive-vaping.
[67] "Terp Liquefy Collection: Extract Liquidizers," Mass Terpenes, Accessed July 16, 2020, https://www.massterpenes.com/collections/terp-liquefy.
[68] "Terpene Diluent and Liquefier: Flavorless & Odorless," Floraplex Terpenes, Accessed July 16, 2020, https://www.buyterpenesonline.com/terpenes-for-sale/terpene-diluent/.
[69] "Safety Data Sheet – Terpene Diluent," Floraplex Terpenes, Accessed October 26, 2020, https://cdn.buyterpenesonline.com/wp-content/uploads/20201006223744/FLPX-LLC-Terpenes-Diluent-SDS-v1.pdf
[70] Muthumalage *et al*., "Chemical Constituents Involved in EVALI."

associated with VALI.[71] The illicit cartridges contained an alarming number of substances, and notably they found terpenes that are present in cannabis (e.g. myrcene, limonene, β-pinene, phytol, and caryophyllene), as well as squalene and VEA.[72] The medical grade cartridges contained far fewer non-cannabis substances; however, retinol (Vitamin A), acetyl chloride, benzene, and aflatoxin b_1 were found, all of which are likely harmful when heated and vaporized.[73] These results suggest products from a regulated marketplace contain far less contaminants than those from the illicit market. However, it is clear that even regulated products can contain harmful substances. More recently, Muthumalage et al. published a study where the health effects of VEA and MCT were evaluated *in vitro* and *in vivo*.[74] Their results strongly suggest both substances have negative health implications.

A recent study by Jiang et al. examined changes in the chemical composition between vaped and unvaped PG, MCT, VEA, and squalane.[75] Jiang et al. compared the toxicity of these diluents on cells by exposing cells to the unvaped diluents and vaping emission condensates produced by them. The "results revealed significant changes in chemical composition and a shift of cellular toxicity in cells exposed to vaping emission condensates compared to the unvaped liquid diluents, supporting our hypothesis that toxic byproducts formed during the vaping process are important to induce vaping-associated health effects."[76] The researchers also found "the chemical compositions of vaping emission products are very different from their parent

[71] Muthumalage *et al*., "Chemical Constituents Involved in EVALI," 2.
[72] Muthumalage *et al*., "Chemical Constituents Involved in EVALI," 4-7.
[73] Muthumalage *et al*., "Chemical Constituents Involved in EVALI," 9.
[74] Muthumalage, Thivanka, Joseph H. Lucas, Qixin Wang, Thomas Lamb, Matthew D. Mcgraw, and Irfan Rahman, "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," *Toxics* 8, no. 3 (2020): 46, https://doi.org/10.3390/toxics8030046.
[75] Huanhuan *et al*., "Chemical and Toxicological Characterization of Vaping Emission Products," 4.
[76] Huanhuan *et al*., "Chemical and Toxicological Characterization of Vaping Emission Products," 10.

liquid diluents, showing formation of new products in vaping emissions. The detected new products include carbonyls, alkyl alcohols, esters, carboxylic acids and short chain alkanes, likely resulting from thermal decomposition and oxidation of liquid diluents."[77]

Under vaping conditions, squalane and MCT oil both produced short chain esters, alkanes, and carbonyls.[78] The researchers noted that esters and carbonyls generated under vaping conditions "may contribute to the observed decrease in cell viability…"[79] Notably, under vaping conditions, both produced alkyl alcohols which are "surfactant-like" and "[i]t has been reported that alkyl alcohols can elicit a number of cellular responses that are potentially cytotoxic and can affect membrane structure and compromise cell function."[80] Vaped VEA, among other compounds, produced acetone and "quinone-like compounds."[81] These results suggest that these diluents are relatively safe in their intended use scenarios, but when heated, a variety of chemical reactions occur, some resulting in the formation of toxic chemicals.

OLCC's proposed rules would also prohibit the inclusion of triglycerides from Inhalable Cannabinoid Products. This includes a wide variety of non-cannabis substances, including, but not limited to vegetable (e.g. MCT) and animal fats. It is well documented that the inhalation of oils causes lipoid pneumonia.[82] In the occupational setting, it is also documented that inhalation

[77] Huanhuan *et al*., "Chemical and Toxicological Characterization of Vaping Emission Products," 10.
[78] Huanhuan *et al*., "Chemical and Toxicological Characterization of Vaping Emission Products," 11-12.
[79] Huanhuan *et al*., "Chemical and Toxicological Characterization of Vaping Emission Products," 12.
[80] Huanhuan *et al*., "Chemical and Toxicological Characterization of Vaping Emission Products," 12.
[81] Huanhuan *et al*., "Chemical and Toxicological Characterization of Vaping Emission Products," 12-13.
[82] *See, e.g.*, Beck, Lauren R, "Lipoid Pneumonia," StatPearls [Internet], U.S. National Library of Medicine, June 22, 2020, https://www.ncbi.nlm.nih.gov/books/NBK554577/.

of oils causes both short-term[83] and long-term health effects.[84] Given the high molecular weight of most triglycerides, it is highly conceivable cannabis vapers would be inhaling some amount of triglycerides into their lungs during the vaping process.

Assessing the inhalation safety of Flavor Additives and diluents is incredibly complex. Wu and O'Shea state: "[t]he current worrying trend of increasing vaping-associated lung injuries is due to complex and multifaceted issues encompassing social, physical, and biological, and medical sciences. When viewed from a physical science standpoint, medical complications from vaping a diverse set of substances is perhaps not unexpected as the pyrolytic chemistry of single pure compounds is complex, so what occurs within ill-defined mixtures is a risky venture into the unknown."[85] The authors conclude: "[c]onsidering the continuing evolving and large number of natural and synthetic substances used in recreational vaping and the unknown chemistries that may occur under vaping pyrolysis conditions, urgent research into this topic is now required."[86] While regulators wait for a greater understanding of the health risks consumers may expose themselves to by consuming these products, some sectors of the cannabis industry continue to use Flavoring Additives and advocate for their use with at best unclear evidence of their safety.

[83] *See, e.g.*, Svedahl, Sindre, Kristin Svendsen, Torgunn Qvenild, Ann Sjaastad, and Bjørn Hilt, "Short Term Exposure to Cooking Fumes and Pulmonary Function," *Journal of Occupational Medicine and Toxicology* 4, no. 1 (2009): 9, https://doi.org/10.1186/1745-6673-4-9.
[84] *See, e.g.*, Chen, Huang-Chi, Chia-Fang Wu, Inn-Wen Chong, and Ming-Tsang Wu. "Exposure to Cooking Oil Fumes and Chronic Bronchitis in Nonsmoking Women Aged 40 Years and over: a Health-Care Based Study," *BMC Public Health* 18, no. 1 (2018), https://doi.org/10.1186/s12889-018-5146-x.
[85] Wu and O'Shea, "Potential for Release of Pulmonary Toxic Ketene," 6354.
[86] Wu and O'Shea, "Potential for Release of Pulmonary Toxic Ketene," 6354.

Looking to E-cigarette Regulation:

E-cigarettes were introduced to the market in 2003 and have only increased in popularity.[87] These products include: vapes, vaporizers, vape pens, hookah pens, and electronic cigarettes (collectively, known as electronic nicotine delivery systems or "ENDS").[88] ENDS produce "aerosolized nicotine in vapor form (e-vapor) by heating e-cigarette liquid (or e-liquid), which is typically composed of propylene glycol (PG), vegetable glycerin (VG), nicotine, and flavoring compounds."[89] Generally speaking, ENDS safety is unknown: "[the] long-term health effects are unknown and emerging preclinical and clinical studies suggest that e-cigarettes may not be harmless."[90]

In the United States, the FDA regulates ENDS devices and premarket approval must be given by the FDA starting September 9, 2020 to legally sell ENDS products.[91] ENDS producers must submit to the FDA a premarket tobacco product application ("PMTA"), including scientific data that demonstrates the "product is appropriate for the protection of the public health."[92] To date, only one ENDS product has received premarket approval by the FDA – IQOS by Phillip

[87] Andrey Khlystov and Vera Samburova, "Flavoring Compounds Dominate Toxic Aldehyde Production during E-Cigarette Vaping," *Environmental Science & Technology* 50, no. 23 (2016): 13080, https://doi.org/10.1021/acs.est.6b05145.
[88] Products, Center for Tobacco, "Vaporizers, E-Cigarettes, and Other ENDS," U.S. Food and Drug Administration, Accessed July 17, 2020, https://www.fda.gov/tobacco-products/products-ingredients-components/vaporizers-e-cigarettes-and-other-electronic-nicotine-delivery-systems-ends.
[89] Samburova, Vera, Chiranjivi Bhattarai, Matthew Strickland, Lyndsey Darrow, Jeff Angermann, Yeongkwon Son, and Andrey Khlystov, "Aldehydes in Exhaled Breath during E-Cigarette Vaping: Pilot Study Results," *Toxics* 6, no. 3 (2018): 1, https://doi.org/10.3390/toxics6030046.
[90] Hussein Traboulsi, Mathew Cherian, Mira Abou Rjeili, Matthew Preteroti, Jean Bourbeau, Benjamin M. Smith, David H. Eidelman, and Carolyn J. Baglole, "Inhalation Toxicology of Vaping Products and Implications for Pulmonary Health," *International Journal of Molecular Sciences* 21, no. 10 (2020): 1, https://doi.org/10.3390/ijms21103495.
[91] "Premarket Tobacco Product Applications," U.S. Food and Drug Administration, Accessed July 17, 2020, https://www.fda.gov/tobacco-products/market-and-distribute-tobacco-product/premarket-tobacco-product-applications.
[92] "Premarket Tobacco Product Applications."

Morris.[93] It is unclear what the "protection of the public health," means to the FDA, but a recent article criticized the IQOS approval process and accused the FDA of ignoring evidence that the product was still harmful.[94] While it is too early to see how the PMTA process will proceed, it is clear that the onus is placed on ENDS manufacturers to demonstrate the safety of their products. To the OLCC's knowledge, none of the Companies or OLCC licensees have conducted any kind of safety study of Flavor Additives or diluents. It should also be noted that the FDA is regulating flavors that appeal to minors.[95]

Flavorings & Diluent Research in Nicotine Containing ENDS Products:

By and large, Flavoring Additives and diluents have not been tested for inhalation safety or chronic use. Chronic use should be considered when evaluating these products, as many ENDS users and consumers of Inhalable Cannabinoid Products use them frequently. John Hallagan, general counsel and senior advisor to the Flavor & Extract Manufacturers Association ("FEMA"), states:

> [T]here is little data available on the effects of inhalation exposure of flavoring substances in laboratory animal models. There are two reasons for this. First, for physiological reasons, the rat is an inadequate species for inhalation exposure studies. Second, there is no requirement for the generation of inhalation exposure data as a condition of approval for the use of food ingredients including flavoring substances – the focus of the regulatory programs for food ingredients is ingestion exposure.[96]

[93] "Premarket Tobacco Product Marketing Orders," U.S. Food and Drug Administration, Accessed July 17, 2020, https://www.fda.gov/tobacco-products/premarket-tobacco-product-applications/premarket-tobacco-product-marketing-orders.
[94] Lempert, Lauren Kass, and Stanton Glantz, "Analysis of FDA's IQOS Marketing Authorization and Its Policy Impacts," *Tobacco Control*, 2020, https://doi.org/10.1136/tobaccocontrol-2019-055585.
[95] "FDA Finalizes Enforcement Policy on Unauthorized Flavored Cartridge-Based e-Cigarettes That Appeal to Children, Including Fruit and Mint," U.S. Food and Drug Administration, Accessed July 17, 2020, https://www.fda.gov/news-events/press-announcements/fda-finalizes-enforcement-policy-unauthorized-flavored-cartridge-based-e-cigarettes-appeal-children.
[96] Hallagan, "The Use of Diacetyl (2,3-Butanedione)," 4.

It should also be noted that "flavors are complex mixtures typically containing various amounts of many individual ingredients…."[97] The lack of research is also likely due to the novelty of these products. Prior to the invention of the first e-cigarette, humans were not purposefully heating and inhaling flavoring compounds deeply into their lungs multiple times a day. However, the research that has been conducted on flavorings and diluents in ENDS devices makes it clear that some of these products do cause harm and are not innocuous substances.

Most nicotine-containing ENDS devices use PG or VG as a carrier for the nicotine and flavorings. It is known that both VG and PG produce aldehydes during vaping conditions.[98] Common examples of aldehydes are formaldehyde, acetaldehyde, and propionaldehyde, which are all on the FDA's "Harmful and Potentially Harmful Constituents in Tobacco Products and Tobacco Smoke: Established List."[99] Formaldehyde is a human carcinogen and acetaldehyde is possibly carcinogenic to humans.[100] Inhalation of aldehydes can have negative health consequences.[101] Some use PEG, which produces formaldehyde and acetaldehyde under vaping conditions.[102]

[97] Hallagan and Hall, "FEMA GRAS - A GRAS Assessment Program for Flavor Ingredients," 423.
[98] *See e.g.*, Gillman, I.g., K.a. Kistler, E.w. Stewart, and A.r. Paolantonio, "Effect of Variable Power Levels on the Yield of Total Aerosol Mass and Formation of Aldehydes in e-Cigarette Aerosols," *Regulatory Toxicology and Pharmacology* 75 (2016): 58–65, https://doi.org/10.1016/j.yrtph.2015.12.019. *See also*, Flora, Jason W., Celeste T. Wilkinson, James W. Wilkinson, Peter J. Lipowicz, James A. Skapars, Adam Anderson, and John H. Miller, "Method for the Determination of Carbonyl Compounds in E-Cigarette Aerosols," *Journal of Chromatographic Science* 55, no. 2 (2016): 142–48, https://doi.org/10.1093/chromsci/bmw157.
[99] Products, Center for Tobacco, "Established List of HPHCs in Tobacco Products and Tobacco Smoke," U.S. Food and Drug Administration, Accessed October 21, 2020, https://www.fda.gov/tobacco-products/rules-regulations-and-guidance/harmful-and-potentially-harmful-constituents-tobacco-products-and-tobacco-smoke-established-list.
[100] "Agents Classified by the IARC Monographs, Volumes 1–127," Agents Classified by the IARC Monographs, Volumes 1–127 – IARC Monographs on the Identification of Carcinogenic Hazards to Humans, Accessed October 25, 2020, https://monographs.iarc.fr/agents-classified-by-the-iarc/.
[101] "Final Report: Inhalation of Aldehydes and Effects on Breathing," Environmental Protection Agency, Accessed July 17, 2020, https://cfpub.epa.gov/ncer_abstracts/index.cfm/fuseaction/display.abstractDetail/abstract/2313/report/F.
[102] Samburova *et al*., "Aldehydes in Exhaled Breath," 8.

One of the most well-known examples of a flavoring substance causing respiratory harm is diacetyl and its substitute, 2,3-pentanedione.[103] When heated, these flavoring chemicals are responsible for workers getting "popcorn lung" or obliterative bronchiolitis.[104] Diacetyl is a permitted food additive and is present in a wide variety of foods, such as butter, milk, cream, and cheese.[105] Neither substance is known to be harmful when ingested,[106] but clearly poses a health risk when heated and inhaled.

It has been documented that "numerous flavorings, e.g. menthol, menthone, maltol, ethyl maltol, vanillin, ethyl vanillin, cinnamaldehyde, ethyl cinnamate, benzyl alcohol, benzaldehyde, eugenol, *p*-anisaldehyde, triacetin, and 2,5-dimethypyrazine…may cause cytotoxicity, mostly to the respiratory system."[107] Cytotoxicity is toxicity caused by chemical agents on living cells.[108] It has been shown that the thermal decomposition of flavoring compounds are "the main source of aldehydes in vapors produced by e-liquids…."[109] A study by Samburova et al. tested the exhaled vapor from nicotine ENDS devices containing PG/VG and flavorings (e.g. bubblegum, watermelon, fruit mix, and menthol) and found elevated levels of formaldehyde, acetaldehyde, and acrolein[110] – all of which are toxic.[111]

---

[103] *See, e.g.*, Mckinley, Jesse, "Flavoring-Factory Illnesses Raise Inquiries," The New York Times, May 6, 2007, https://www.nytimes.com/2007/05/06/us/06butter.html.
[104] "Flavorings-Related Lung Disease - NIOSH Workplace Safety and Health Topic," Centers for Disease Control and Prevention, October 3, 2017, https://www.cdc.gov/niosh/topics/flavorings/default.html.
[105] Hallagan, "The Use of Diacetyl (2,3-Butanedione)," 3.
[106] Hallagan, "The Use of Diacetyl (2,3-Butanedione)," 3.
[107] Ruszkiewicz, Joanna A., Ziyan Zhang, Filipe Marques Gonçalves, Yousef Tizabi, Judith T. Zelikoff, and Michael Aschner, "Neurotoxicity of e-Cigarettes." *Food and Chemical Toxicology* 138 (2020): 7, https://doi.org/10.1016/j.fct.2020.111245.
[108] "Cytotoxicity - an Overview," ScienceDirect, Accessed July 17, 2020, https://www.sciencedirect.com/topics/chemistry/cytotoxicity.
[109] Khlystov and Samburova, "Flavoring Compounds Dominate Toxic Aldehyde Production," 13084.
[110] Samburova *et al*., "Aldehydes in Exhaled Breath," 10.
[111] *See e.g.*, Traboulsi *et al*., "Inhalation Toxicology of Vaping Products and Implications for Pulmonary Health," 8.

It may be argued that in the context of cannabis, these results are irrelevant. However, many of the Companies use these ingredients in their products. As previously mentioned, it is incredibly difficult to gain a clear picture of what ingredients are in most of the Flavoring Additives because there are currently no disclosure requirements; however, some of the Companies do list non-terpene ingredients in their SDS. For example, "Blue Berry" from Extract Consultants lists cinnamaldehyde, vanillin, and ethyl maltol as ingredients[112] and "Mentholated Oil Terpene" blend lists menthol as an ingredient.[113] "Forbidden Fruit" from True Terpenes lists benzaldehyde as an ingredient[114] and "Black Lime Infused" lists pulegone as an ingredient.[115] When administered orally, pulegone is a known carcinogen and likely has similar effects when inhaled.[116] Greater transparency by the Companies would likely result in the discovery of many more potentially harmful flavoring ingredients.

Flavorings and Food Safety – Looking to the FDA and "GRAS" status:

It is relevant to look at federal food safety laws in the context of evaluating Flavor Additive safety. Due to a lack of regulation in the inhalation sphere, many of the Companies mislead consumers into thinking their products are safe for inhalation by stating they are "food safe," "food grade," or "GRAS." Many of the Flavor Additives can be classified as "food additives" under the Federal Food, Drug, and Cosmetic Act ("FFDCA").[117] In 1958, due to

[112] "Blueberry Terpene Blend – Safety Data Sheet," Extract Consultants, LLC, Accessed July 17, 2020, https://cdn.shopify.com/s/files/1/0148/2348/9584/files/TPBS04.SDS.BlueberryTerpeneBlend.pdf?v=252984487345122668.
[113] "Mentholated Oil Terpene Blend – Safety Data Sheet," Extract Consultants, LLC, Accessed July 17, 2020, https://cdn.shopify.com/s/files/1/0148/2348/9584/files/TPBL19.SDS.MentholatedOilSFTF.pdf?v=50801515348982 57244.
[114] "Safety Data Sheet – Forbidden Fruit."
[115] "Safety Data Sheet – Black Lime Infused, True Terpenes, Accessed July 17, 2020, https://trueterpenes.com/certificates/sds/Black_Lime_ID_SDS_True_Terpenes.pdf.
[116] "Risk Analysis for the Carcinogen Pulegone in Mint- and Menthol-Flavored e-Cigarettes and Smokeless Tobacco Products," *JAMA Internal Medicine* 179, no. 12 (2019): 1721, https://doi.org/10.1001/jamainternmed.2019.3649.
[117] Federal Food, Drug, and Cosmetic Act, 21 U.S.C. § 348 (2018).

concerns about flavoring substances being added to food, Congress enacted the Food Additives Amendment ("FAA") to the FFDCA.[118] The FAA "placed squarely on the industry the burden of demonstrating safety and established a new requirement for premarket approval of food additives as defined in the FAA."[119] The FAA mandates premarket approval of all "food additives" unless the ingredient is generally recognized as safe ("GRAS").[120] The FFDCA recognizes that naturally occurring substances in food should be held to a lesser standard and it places a much higher threshold of scrutiny on added substances (e.g. flavorings) and may consider food "adulterated" if it is "injurious to health."[121] This is because humans have a history of self-regulating when it comes to harmful substances naturally present in food.[122]

The statutory requirements of the FFDCA for GRAS conclusions made through scientific procedures require "[a] general recognition of safety by qualified experts, [t]he experts must be qualified by scientific training and experience to evaluate the substance's safety, [t]he experts must base their conclusion of safety on scientific procedures, [and] [t]he conclusion of general recognition of safety must take account of the substance's conditions of intended use."[123] Additionally "GRAS status also depends on whether there is common understanding of a substance's safety. General recognition of safety "requires common knowledge about the substance throughout the scientific community knowledgeable about the safety of

[118] John Hallagan and Richard Hall, "FEMA GRAS - A GRAS Assessment Program for Flavor Ingredients," *Regulatory Toxicology and Pharmacology* 21, no. 3 (1995): 422–30, https://doi.org/10.1006/rtph.1995.1057.
[119] Hallagan and Hall, "FEMA GRAS - A GRAS Assessment Program for Flavor Ingredients," 422.
[120] John Hallagan, Richard L. Hall, and Joanna Drake, "The GRAS Provision - The FEMA GRAS Program and the Safety and Regulation of Flavors in the United States," *Food and Chemical Toxicology* 138 (2020): 2. https://doi.org/10.1016/j.fct.2020.111236.
[121] Smith, R.L., S.M. Cohen, J. Doull, V.J. Feron, J.I. Goodman, L.J. Marnett, P.S. Portoghese, et al, "A Procedure for the Safety Evaluation of Natural Flavor Complexes Used as Ingredients in Food: Essential Oils." *Food and Chemical Toxicology* 43, no. 3 (2005): 350, https://doi.org/10.1016/j.fct.2004.11.007.
[122] Smith *et al*., "A Procedure for the Safety Evaluation of Natural Flavor Complexes Used as Ingredients in Food: Essential Oils," 347.
[123] Hallagan *et al.*, "The GRAS Provision," 4.

substances…added to food."[124] To meet the safety standard set out in the FFDCA, the food ingredient(s) must meet the standard "of a reasonable certainty of no harm."[125] Lastly, it is very important to note that GRAS status *only* applies to the "designated uses of substances and not to the substances themselves."[126]

There are several pathways to "obtain regulatory authority to use flavor ingredients in the U.S.: (1) FDA food additive status; (2) FDA voluntary GRAS notification; (3) private GRAS determination; and (4) FEMA GRAS status."[127] The most common pathway to regulatory approval is FEMA GRAS status.[128]

FEMA is opposed to using flavor ingredients in the vaping context and has issued the following relevant statements:

- "[t]he FEMA Expert Panel evaluates the safety of flavor ingredients only under their conditions of intended use in food and does not evaluate flavor ingredients for use in vaping products, or any other uses that are intended for inhalation. Therefore, FEMA GRAS status for the use of flavor ingredients in food does not provide regulatory authority to use flavor ingredients in vaping products."[129]
- "FEMA does not support the use of flavors in vaping products in the absence of rigorous safety assessments performed by vaping product manufacturers and

[124] Hallagan and Hall, "FEMA GRAS - A GRAS Assessment Program for Flavor Ingredients," 425.
[125] Hallagan *et al.*, "The GRAS Provision," 4.
[126] Hallagan, Hall, and Drake, "The GRAS Provision - The FEMA GRAS Program and the Safety and Regulation of Flavors in the United States," 2.
[127] Hallagan, Hall, and Drake, "The GRAS Provision - The FEMA GRAS Program and the Safety and Regulation of Flavors in the United States," 2.
[128] Hallagan, Hall, and Drake, "The GRAS Provision - The FEMA GRAS Program and the Safety and Regulation of Flavors in the United States," 2.
[129] Hallagan, John, "Safety and Regulatory Authority to Use Flavors – Focus on Vaping Products," FEMA, March 2020, https://www.femaflavor.org/safety-regulatory-authority-use-flavors-focus-vaping-products.

> marketers that demonstrate safety for this use. The manufacturers and marketers of vaping products…and flavor manufacturers and marketers, should not represent or suggest that the flavor ingredients used in these products are safe because they have FEMA GRAS status for use in food because such statements are false and misleading."[130]

It is important to note that Congress was concerned with flavoring additives people were *ingesting* when they enacted the FFDCA and subsequent FFA. Ingestion and inhalation are vastly different methods of consumption. The digestive system is designed to assist the body in processing toxic substances; the lungs, however, are not and are much more sensitive to toxicants. Because of this, greater care and consideration should be given to substances being heated and inhaled. Neither Congress nor the FDA has shown any appetite for similar GRAS status for inhalable products. However, as discussed previously, the FDA has begun the process of regulating e-cigarettes. It should also be emphasized that neither the Companies nor e-cigarette manufacturers have created an organization like FEMA to address the safety of the products they sell.

As a recognized private partner with the FDA that administers GRAS certification, FEMA's stance on using flavors in vaping products is particularly relevant because many of the Companies suggest their products are "GRAS" or "food safe." This is done because many of the Companies provide vague disclaimers that their products are intended for culinary use. However, they clearly market to the cannabis industry (e.g. creating cannabis cultivar specific strain profiles and appearing at cannabis trade shows) and know that their products will be used in

[130] Hallagan, "Safety and Regulatory Authority to Use Flavors – Focus on Vaping Products."

vaporization applications. Most of the Companies have sections on their websites dedicated for how to mix or use their products. For example, one of the Companies' "Mixing Calculator" asks "How many grams of extract do you want to mix?"[131] Another's "Add Back Statement" states their products are "designed to work directly with CO2 oil or Distillate" and are meant "primarily [for] Vape Pens and Tinctures."[132]

Examples of food safety language by the Companies include:

- "Recommended Use: Concentrated aromatic and flavor ingredients which may be used in flavor and fragrance compounds according to legal and IFRA or FEMA GRAS/FDA guidelines."[133]
- "Are terpenes safe for human consumption? [T]erpenes are generally recognized as safe (GRAS) and common in numerous food products."[134]
- "Rest assured that we only use ingredients that are listed as being generally recognized as safe (GRAS) on a reliable published industry association (FEMA) list…this product is safe for use in food when used properly for its intended purpose."[135]
- "PRODUCT USAGE: The Company only attests to the safety of its products when used within the Codex definition of food(1)."[136]

[131] "Mixing Calculator - Create Your Perfect Mix of Terpenes Here," True Terpenes, Accessed July 17, 2020, https://trueterpenes.com/calculator/.
[132] "Add Back Statement," Extract Consultants, Accessed October 19, 2020, https://cdn.shopify.com/s/files/1/0148/2348/9584/files/AddBackStatement.pdf?v=5209744910441264054.
[133] "Material Safety Data Sheet Gorilla Glue #4," Connoisseur Concentrates, Accessed July 17, 2020, https://www.mrextractor.com/wp-content/uploads/MSDS-01-Gorilla-Glue-4.pdf.
[134] "Questions & Answers: What Are Terpenes and What Are They Used For?" Abstrax Tech., Accessed July 17, 2020, https://abstraxtech.com/pages/faq.
[135] "Food Grade Certificate," DTI Media, Accessed July 17, 2020, https://denverterpenes.mystagingwebsite.com/wp-content/uploads/2019/03/Agent-Orange-FGC.pdf.
[136] "Terms and Conditions Policy • Floraplex Terpenes," Floraplex Terpenes, Accessed July 17, 2020, https://www.buyterpenesonline.com/terms-and-conditions/.

- "Product Use: concentrated flavor mixture for foodstuffs in which added flavoring is permitted"[137]
- "Identified Uses: For use in aromatherapy (requires dilution)" and "[u]ses advised against: No other uses are advised."[138]

What all these examples illustrate is at least some of the Companies rely on misleading statements that provide a false sense of safety and provides them with some legal protection if their products are used in vaping products.

Safety Data Sheets, Trade Secrets, and Unlisted Ingredients:

Federal law requires chemical manufacturers and distributors to provide safety data sheets ("SDS") for products with at least some toxic ingredients to downstream users to inform them of what is in the product, what hazards the ingredients may pose, and what precautions should be taken when handling them in industrial use scenarios.[139] The Companies are subject to these requirements. Through the OLCC's observations, there are a wide variety of SDS provided by the Companies – ranging from fully compliant with federal requirements to completely deficient with those requirements.

An SDS should provide a full list of chemicals present in the product that are *known* to be acutely toxic.[140] If some ingredients are of unknown acute toxicity, the SDS must state so.[141] If the product is a mixture, the SDS must list the exact percentages or ranges of each chemical.[142]

---

[137] "Safety Data Sheet - Gelato," Abstrax Tech, Accessed July 17, 2020, https://cdn.shopify.com/s/files/1/2149/6413/files/GELATO_SDS_2019_FINAL.pdf?3245.
[138] "Safety Data Sheet for Terpene Blend," Mass Terpenes LLC, Accessed July 17, 2020, https://cdn.shopify.com/s/files/1/0092/1783/5065/files/Terpene_Blend_SDS.pdf?1068.
[139] 29 C.F.R. § 1910.1200(g) (2019).
[140] 29 C.F.R. § 1910.1200(c) (2019).
[141] 29 C.F.R. § 1910.1200(g), Appendix D, Table D.1., 2 (2019).
[142] 29 C.F.R. § 1910.1200(g), Appendix D, Table D.1., 3 (2019).

However, if a trade secret is claimed, the manufacturer may withhold the exact composition and percentage by utilizing a disclaimer.[143] Typically, an SDS will list the common name of the chemical and the CAS Registry Number. The CAS number specifically identifies what substance is being referenced. This is important because some common names of substances can refer to multiple variations of that substance (i.e. isomers). In some cases, the variants can have different effects (e.g. Thalidomide).[144]

SDS reviewed by the OLCC differ widely in how much detail is disclosed – sometimes disclosing no ingredients, a partial list of ingredients, the majority of ingredients with a caveat that it may contain other substances, or missing CAS numbers. It is common to see either some or all of the ingredients withheld as a trade secret.

Examples of ingredient lists in SDS include:

- "Agent Orange" by Denver Terpenes lists no ingredients or CAS numbers.[145]
- "King Louie XIII" by Abstrax Tech states: "Specific chemical identities and/or exact percentages of composition are being withheld as a trade secret…"[146]
- "Gorilla Glue 4" by Connoisseur Concentrates lists some ingredients but then states: "This product may contain other natural and artificial

[143] 29 C.F.R. § 1910.1200(g), Appendix D, Table D.1., 3 (2019).
[144] Vargesson, Neil, "Thalidomide-Induced Teratogenesis: History and Mechanisms," *Birth Defects Research Part C: Embryo Today: Reviews* 105, no. 2 (2015): 140–56, https://doi.org/10.1002/bdrc.21096.
[145] "Material Safety Data Sheet – Agent Orange," DTI Media, Accessed July 17, 2020, https://denverterpenes.mystagingwebsite.com/wp-content/uploads/2019/03/Agent-Orange-MSDS-1.pdf.
[146] "Safety Data Sheet – King Louie XIII Gas," Abstrax Tech, Accessed July 17, 2020, 2, https://cdn.shopify.com/s/files/1/2149/6413/files/Abstrax_Tech_King_Louie_XIII_SDS.pdf?25164.

ingredients. Specific chemical identities and/or its exact percentages in use have been withheld as a trade secret."[147]

- "Terpology Focus" by True Terpenes withholds all ingredients as trade secrets.[148]
- "Banana Kush" by Floraplex states: "100% of the composition has been withheld as a trade secret."[149]

One element of trade secret law is that in order to keep a trade secret, the "secret" being protected must not be disclosed or disclosed in a sensitive manner. This is relevant in this context because many of the Companies protect some or all of the ingredients and their concentrations as trade secrets (whether in their SDS or "ingredient decks"). It is possible that some OLCC licensed processors sign non-disclosure agreements ("NDA") with the Companies to obtain full or partial disclosure. However, the disclosure likely does not apply to downstream licensees (e.g. wholesalers and retailers), who are in the dark as to the composition of the products they are selling. Of course, this exposes licensees to a great deal of liability or risk if the products cause harm. It is unclear how widespread the practice of disclosure via NDA is – the OLCC does have many examples of licensees who are unaware of the full ingredient composition of the Flavor Additives they are using.

Preliminary research also shows that commercially available Flavoring Additives provided by the Companies contain undisclosed and unidentified ingredients. ChemHistory, an

[147] "Material Data Safety Sheet," Connoisseur Concentrates, Accessed July 17, 2020, 4, https://www.mrextractor.com/wp-content/uploads/MSDS-01-Gorilla-Glue-4.pdf.
[148] "Safety Data Sheet – Terpology Focus," True Terpenes, Accessed July 17, 2020, 5, https://q2a3q6a8.rocketcdn.me/certificates/sds/Terpology_Focus_SDS_True_Terpenes.pdf.
[149] "Safety Data Sheet – Banana Kush," Floraplex, Accessed July 17, 2020, 2, https://www.buyterpenesonline.com/wp-content/uploads/FLPX-SDS-Banana-Kush-4.pdf.

OLCC licensed lab, tested several commercially available Flavor Additives. In samples of myrcene and geraniol – products that were marketed as pure isolates of those terpenes – other terpenes were present as were unknown compounds.[150] Dr. Robert Strongin also tested similar products and identified PEG; naphthalene, a substance used in mothballs; and methyl anthranilate, a grape flavoring.[151] Due to the COVID-19 pandemic, Dr. Strongin's research was put on hold, but he expects to eventually publish the results. What these results make clear, is that these ingredients may not be what they are purported to be and they may contain substances that are known to be toxic.

To state the obvious, it makes a regulator's job incredibly difficult, if not impossible, to begin to try and assess the safety of the Flavor Additives and diluents when the ingredients are hidden and contradictory statements are included about product composition. Withholding the concentrations is also problematic as well, as it may be found that certain substances in certain concentration ranges or ratios may cause harm. It should be strongly noted that regulators, licensees, and consumers should not rely on the SDS as the sole source of ingredients.

Disclaimers – Passing Liability to Licensees and Consumers:

As previously mentioned, most of the Companies do not explicitly state their products are meant for inhalation, and are rather intended for ingestion. Each Company provides on their website or SDS some kind of disclaimer. Most are fairly explicit about disavowing their usage or safety for inhalation. Several even place the onus on the end user to conduct safety studies when considering whether to use the product. It is unclear whether OLCC licensees understand the

[150] D. Duncan and P. Trujillo, "Independent Testing & Adulterants," (2020): 8-12, https://www.oregon.gov/olcc/marijuana/Documents/Rules/Marijuana-Additives/Duncan-and-Trujillo-Presentation.pdf.
[151] Robert M. Strongin, "Vaping Chemistry and Cannabis Product Additives, (2020): 27-29, https://www.oregon.gov/olcc/marijuana/Documents/Rules/Marijuana-Additives/Strongin-Presentation.pdf.

risks they are accepting by using Flavoring Additives or diluents when the Companies have attempted to absolve themselves of liability.

Examples include:

- "Consumers should determine and conduct their own safety standards and testing…" and "[t]his product has not been evaluated for safe use in e-cigarettes or any vaping application where the product(s) is/are intentionally vaporized and inhaled."[152]
- "No company can make any guarantee that any flavor, terpene, diluent, or aroma chemical is safe for vaporization. Customers are responsible for determining the safety of the finished products they make using anything purchased on this site."[153]
- "It is your responsibility to determine that level of concentration at which terpene additives are safe for your own products or use and the levels set forth herein are put forth merely as examples and not as representations."[154]
- "This product has not been evaluated for safe use in e-cigarettes or any vaping application where the product is vaporized and inhaled."[155]
- "[The Company] has performed no testing on these products in e-cig/vaping applications. It is the sole responsibility of the individual(s) purchasing this product to assess its safety in the final application. It is the responsibility of the

[152] "Safety Data Sheet – Blood Orange Down Terp Flavor," True Terpenes, Accessed July 17, 2020, 1, https://q2a3q6a8.rocketcdn.me/certificates/sds/Blood_Orange_DN_SDS_True_Terpenes.pdf.
[153] "Terpene Safety," Mass Terpenes, Accessed July 17, 2020, https://www.massterpenes.com/pages/safety.
[154] "Terms and Conditions," Extract Consultants, Accessed July 17, 2020, https://extractconsultants.com/pages/terms-and-conditions.
[155] "Material Safety Data Sheet – Sour Diesel," Connoisseur Concentrates, Accessed July 17, 2020, 1, https://www.mrextractor.com/wp-content/uploads/MSDS-02-Sour-Diesel.pdf.

> user to review all safety information about this product and determine its safety and suitability in their own processes and operations."[156]

Many of the Companies engage in double-speak – on one hand, they market and sell their products to the cannabis industry, often with guidance on how to mix them into vaping products, yet on the other hand, completely disavow their use for vaporization and inhalation. This situation is somewhat analogous to "off-label drug use." When FDA approves new medications, they are approved for specific indications (or "on-label" prescribing).[157] Only a *trained medical professional* can prescribe drugs for off-label use and is done under the prescriber's supervision.[158] It is unrealistic for the OLCC to accept that its licensees are using products for which the manufacturers do not advise their use in the vaping scenario. If the Companies will not stand behind the use of their products for inhalation, then consumers should not be subjected to products that aren't being used in their intended manner.

Consumer Right to Know – Ingredient Listings and Allergens

For food products that contain compounds that are solely meant to impart flavor, manufacturers can list the broad category of compounds simply as "natural" or "artificial" flavors on the label. Previously, the OLCC issued guidance allowing its licensees to include Flavoring Additives on the labels' ingredient lists using these terms. However, these terms do not

[156] "Safety Data Sheet – Golden Ticket Terpene Profile," Atlas Technology Manufacturing, LLC, Accessed on October 27, 2020, 8, https://terpenes.net/wp-content/uploads/2020/08/Terpenes.net-SDS-GTH-Ghost-Train-Haze-Terpene-Profile-WAAT.TELGTH0NNZ0.pdf.
[157] Wittich, Christopher M., Christopher M. Burkle, and William L. Lanier, "Ten Common Questions (and Their Answers) About Off-Label Drug Use," *Mayo Clinic Proceedings* 87, no. 10 (2012): 982–90, https://doi.org/10.1016/j.mayocp.2012.04.017.
[158] Wittich *et al*., "Ten Common Questions (and Their Answers) About Off-Label Drug Use."

provide consumers with any meaningful information about the substances they are consuming. This is exacerbated by the secretive nature of ingredient disclosure by the Companies.

As previously mentioned, food additives or flavorings that are being introduced into food must be GRAS, otherwise they are considered adulterants. The GRAS process rigorously assesses the safety of the flavor additives under their intended use. No such evaluation process exists for Flavor Additives that are vaporized and inhaled. Therefore, the OLCC's proposed rules will require all ingredients to be displayed on the label so that consumers may make informed decisions.

Research also shows that food additives can cause allergic reactions both internally[159] and externally (i.e. contact allergens).[160] Watanabe et al. found that in guinea pig models, various aldehydes, including citral, ethyl vanillin, vanillin, and benzaldehyde (present in some Flavoring Additives) induced allergic skin reactions.[161] Some researchers have already called into question the potential for allergic reactions when inhaling flavors in e-cigarettes and e-liquids and stressed toxicological principals guide their selection and inclusion levels.[162] In at least one example, a case report suggests an e-cigarette user suffered hypersensitivity pneumonitis due to their use of e-cigarettes.[163] Because of the possibility of Flavor Additives containing potential allergens, it is even more important to fully disclose the ingredients on a label.

---

[159] *See, e.g.,* Ramirez, Daniel A, and Sami L Bahna,"Food Hypersensitivity by Inhalation," *Clinical and Molecular Allergy* 7, no. 1 (2009), https://doi.org/10.1186/1476-7961-7-4.
[160] *See, e.g.*, Watanabe, Kazuhito, Midori Matsuda, Shizuka Furuhashi, Toshiyuki Kimura, Tamihide Matsunaga, and Ikuo Yamamoto, "Skin Reaction Induced by Aldehydes for Food Flavoring Agents," *Journal Of Health Science* 47, no. 3 (2001): 327–29, https://doi.org/10.1248/jhs.47.327.
[161] Wantanabe *et al.*, "Skin Reaction Induced by Aldehydes for Food Flavoring Agents," 327 – 328.
[162] Costigan, Sandra, and Juan Lopez-Belmonte, "An Approach to Allergy Risk Assessments for e-Liquid Ingredients," *Regulatory Toxicology and Pharmacology* 87 (2017): 1–8, https://doi.org/10.1016/j.yrtph.2017.04.003.
[163] Sommerfeld, Casey G., Daniel J. Weiner, Andrew Nowalk, and Allyson Larkin, "Hypersensitivity Pneumonitis and Acute Respiratory Distress Syndrome From E-Cigarette Use," *Pediatrics* 141, no. 6 (2018), https://doi.org/10.1542/peds.2016-3927.

Conclusion:

Because humans do not have a long history of heating, vaporizing, and inhaling a wide variety of chemicals deeply into their lungs, there is a lack of scientific consensus on what compounds are problematic and what precautionary principals should apply. However, science is beginning to catch up on the creativity of both the e-cigarette and cannabis industries. Furthermore, the FDA is now taking an active role in assessing the safety of Flavoring Additives. It is likely in the coming years, much more will be known about the short-term health effects of vaping various chemical compounds. Unfortunately, the long-term health implications of these products may take many more years to fully understand, similar to tobacco.

OLCC's proposed rulemaking is the first attempt at establishing *minimum* standards for non-cannabis ingredients used in Inhalable Cannabinoid Products within the Oregon cannabis market. These standards would prohibit the ingredients most suspected of causing acute harm, and provide greater clarity both on the contents and intended use of other ingredients. Requiring that the Companies fully disclose their ingredients to OLCC, licensees, and consumers will allow OLCC to more easily evaluate Flavor Additives for adulterants and take quicker action should problematic ingredients arise, and also provide consumers with a more informed choice about the products they are vaporizing and inhaling into their lungs.