Considerations in Establishing Cannabinoid Limits for Hemp Products

Rationale for Rulemaking

Oregon Liquor and Cannabis Commission

December 27, 2021

Impetus for Rulemaking

In 2021, the Oregon Legislature passed House Bill 3000 (Oregon Laws 2021, Chapter 542) to address several issues related to cannabis, including:

- Directing the Oregon Liquor and Cannabis Commission (OLCC) to establish cannabinoid limits above which an industrial hemp commodity or product becomes an "adult use cannabis item." Products that exceed these limits can continue to be sold on the general market for hemp products in Oregon (outside the OLCC-regulated marijuana market), but cannot be sold to minors.
- Directing OLCC to establish cannabinoid limits for industrial hemp commodities or products generally. Products that exceed these limits cannot be sold to consumers under Oregon law.

These issues are related, but distinct. The language about "adult use cannabis items" addresses the concern that minors could purchase hemp products containing potentially-intoxicating quantities of tetrahydrocannabinol (THC[1]), the substance primarily responsible for the "high" that marijuana produces. The language about hemp items generally addresses the concern that hemp products are currently legally allowed to contain larger quantities of THC than are permitted in Oregon's adult use marijuana and medical marijuana programs based on a limit of 0.3% total THC:

Table 1.

What does 0.3% look like?		
	Hemp Potency Limit	**Adult-Use Marijuana Limit[2]**
20 g pack of gummies:	60 mg Δ^9-THC	50 mg Δ^9-THC
85 g bar of chocolate:	255 mg Δ^9-THC	50 mg Δ^9-THC
12 oz beverage:	>1,000 mg Δ^9-THC	50 mg Δ^9-THC

Any limits that OLCC establishes will only apply to sales to minors and sales to consumers under Oregon law. These limits have minimal impact on an Oregon hemp business's ability to compete in the hemp market in other states. The only cannabinoid limit on industrial hemp products and commodities exported from Oregon is that they cannot exceed 0.3% total THC, in accordance with the limit in federal law.

Current Regulatory Landscape

The term "cannabis" refers broadly to plants in the genus *Cannabis*, family Cannabaceae. Cannabis regulations generally distinguish between low-THC plants or products made from low-THC plants ("hemp") and high-THC plants or products made from high-THC plants ("marijuana").

[1] Throughout these rules, "THC" generally refers to "total Δ^9-THC," which is calculated by adding the concentration of Δ^9-THC and 0.877× Δ^9-THCA. Much of the THC in the cannabis plant occurs in the form of Δ^9-THCA, a generally non-intoxicating substance, which converts to the more intoxicating Δ^9-THC when exposed to heat.

[2] This table is based on the limits that are currently in effect. OLCC draft rules propose to increase the THC limit for marijuana edibles to 100 mg per container in 2022.

In 2018, hemp was removed from the United States federal schedule of controlled substances by the Agriculture Improvement Act of 2018, also referred to as the "2018 Farm Bill" (Public Law 115–334). This represented a significant expansion of privileges that were implemented through the Agricultural Act of 2014, which allowed the establishment of agricultural pilot programs for the cultivation of industrial hemp (Public Law 113–79).

The 2018 Farm Bill defines hemp as including "all derivatives, extracts, cannabinoids, isomers, acids, salts, and salts of isomers, whether growing or not, with a delta-9 tetrahydrocannabinol concentration of not more than 0.3 percent on a dry weight basis." This means that products and commodities made from hemp are also removed from the schedule of controlled substances. Many hemp businesses have interpreted "derivatives" to also include substances created synthetically from hemp extracts, which has led to a proliferation of semisynthetic cannabinoids ("artificially derived cannabinoids") being incorporated into products sold to consumers. The range of artificially derived cannabinoids currently being sold include semisynthetic versions of naturally-occurring cannabinoids as well as novel cannabinoids that have no history of human use. Some artificially derived cannabinoids are marketed for their intoxicating effects, while others are marketed as health and wellness products.

In the context of hemp plants and flower, hemp industry advocates have argued that the federal limit of 0.3% THC is not adequately based in science. The number comes from a study of a wide variety of cannabis plants grown in Canada under less-than-ideal conditions (Small & Beckstead 1973a; Small & Beckstead 1973b), and one of the authors of that study has come out in support of increasing the THC limit for hemp plants (Israel 2018). But if the 0.3% THC limit for plants is inadequately scientific, a 0.3% THC limit for consumer products is even less so. As shown in Table 1, above, allowing 0.3% THC in foods or supplements allows these products to contain extremely impairing amounts of THC. Scientifically-grounded assessments of the acceptable non-impairing concentration of THC in foods, presented below, result in concentrations that are orders of magnitude smaller than 0.3%. In establishing 0.3% THC as the limit for hemp products generally, rather than the limit for THC in hemp plants, it is not clear that any consideration was given to the quantities of THC that consumers might be exposed to.

While the 2018 Farm Bill removed hemp from the federal schedule of controlled substances, it also "explicitly preserved" the authority of the U.S. Food and Drug Administration (FDA) "to regulate products containing cannabis or cannabis-derived compounds under the Federal Food, Drug, and Cosmetic Act (FD&C Act) and section 351 of the Public Health Service Act" (Gottlieb 2018). In a written response to the passage of the 2018 Farm Bill, FDA Commissioner Scott Gottlieb noted:

> "Additionally, **it's unlawful under the FD&C Act to introduce food containing added CBD or THC into interstate commerce, or to market CBD or THC products as, or in, dietary supplements, regardless of whether the substances are hemp-derived.** This is because both CBD and THC are active ingredients in FDA-approved drugs and were the subject of substantial clinical investigations before they were marketed as foods or dietary supplements. Under the FD&C Act, it's illegal to introduce drug ingredients like these into the food supply, or to market them as dietary supplements. This is a requirement that we apply across the board to food products that contain substances that are active ingredients in any drug." (Gottlieb 2018; emphasis added)

This means that all foods and supplements containing CBD or THC are federally illegal, even when derived from legally-grown hemp. The only exception to this is foods that are derived from parts of the hemp plant that may not contain CBD or THC. The FDA has evaluated Generally Recognized as Safe (GRAS) notices for certain products derived from hemp seed and had no questions regarding the conclusion that the use of the products as described in the notices is safe (FDA 2021a; Gottlieb 2018). The notices specified that THC was present in the food products only as a trace contaminant at very low levels: No more than 4 mg/kg (0.0004%) in hulled hemp seeds and no more than 10 mg/kg (0.001%) in hemp seed oil (Keefe 2018a; Keefe 2018b).

The FDA has reiterated their position that foods and supplements containing CBD or THC are unlawful several times, however, businesses that manufacture or sell these prohibited products have generally not faced any consequences. The FDA appears to be restricting its enforcement action to sending warning letters to companies that sell CBD products with claims that the product can prevent, diagnose, treat, or cure serious diseases (FDA 2019; FDA 2021a; FDA 2021b).

It is important to note that the FDA's position on this is specific to CBD and THC, because they are active ingredients in drugs. It does not apply to hemp derivatives and products generally. Other hemp-derived substances may be eligible for use in foods or dietary supplements if they have a GRAS determination, or if the FDA responds favorably to a new dietary ingredient (NDI) notification. OLCC staff are not aware of any GRAS determinations or NDI notifications related to any other hemp cannabinoids. It seems that the only thing preventing the FDA from evaluating other hemp cannabinoids as dietary ingredients is the fact that no manufacturer has yet submitted notifications for these ingredients.

While foods and supplements containing CBD, THC, or other hemp-derived cannabinoids currently violate federal law, Oregon's laws are less restrictive. With the proliferation of hemp in Oregon prior to the passage of the 2018 Farm Bill, Oregon law was crafted with the intent that hemp-derived ingredients would not be prohibited in foods. Oregon Revised Statutes (ORS) 571.272(2) declares that "For purposes of ORS chapter 616 [laws pertaining to food and other commodities], the [Oregon Department of Agriculture (ODA)] may not consider industrial hemp or industrial hemp commodities or products to be an adulterant." With the passage of House Bill 3000 in 2021, this statute was amended to give ODA the authority to consider artificially derived cannabinoids to be an adulterant. To date, ODA has not yet exercised that authority.

This is the context in which OLCC entered rulemaking: There are a wide variety of cannabinoid hemp commodities and products available to consumers, including minors, that are subject to regulation by the FDA under the FD&C Act and the Public Health Service Act. These products are almost universally not in compliance with those regulations. Currently, the only limit on cannabinoid content for these products under Oregon law is that they may not exceed 3 mg/g (0.3%) total Δ^9-THC, which allows hemp products to contain quantities of THC that far exceed the levels permitted in Oregon's adult use marijuana program.

Rationale for Differentiating Sales to Minors and Adults

As mentioned above, there were two related but distinct motivations for directing OLCC to set cannabinoid content limits for minors and for hemp products generally:

- Minors should not be able to purchase products that contain an intoxicating quantity of THC.

- Considering Oregon's robustly-regulated market for high-THC cannabis products, hemp products sold to consumers should not have quantities of THC that are on par with or exceed Oregon's limits on THC in adult use marijuana products.

In addressing products sold to minors, it is important that THC should not be present in the products in a quantity that may be intoxicating. In addressing products sold to adults, who may purchase high-THC marijuana products through a licensed adult use marijuana retailer, it is not necessarily critical to limit the products to a non-intoxicating amount of THC.

When considering cannabinoid limits for sale to adults, it is important to bear in mind that a significant share of the cannabinoid hemp product market consists of "full-spectrum" products – products that contain CBD, THC, other cannabinoids, and other naturally-occurring substances from hemp in approximately the same proportion that they occur in the hemp plant. CBD and THC in hemp exist in proportion to one another. Even high-CBD low-THC plants may produce THC in proportion to CBD at approximately a 1:20 ratio (Zirpel *et al.* 2018). That means full-spectrum hemp products that contain large concentrations of CBD will also have elevated levels of THC.

This makes it impossible to set a THC limit that prohibits the sale of intoxicating hemp products without also prohibiting the sale of full-spectrum hemp products. Conversely, allowing full-spectrum hemp products necessarily means setting a THC limit that is high enough for some intoxicating hemp products to also be sold.

Differentiating between cannabinoid limits for sales to minors and sales to adults recognizes the importance of continuing to allow full-spectrum hemp products to be sold to adults without also allowing the sale of large amounts of THC to minors.

THC Limits for Sales to Minors

During the rulemaking process, OLCC heard concerns that minors should not be purchasing *any* quantity of THC. One major drawback to setting the threshold at zero is that it would be impractical to enforce. With a limit of zero, a testing lab might use a method with a relatively high threshold for detection or quantification of THC and consequently "not find" THC even when a significant amount might be present.

Setting a specific limit, either on a percentage basis or a milligram-per-container basis, and requiring a certificate of analysis to show the laboratory can detect at that level, provides more assurance that adult use cannabis items will not be sold to minors.

In order to establish a non-intoxicating THC threshold, it is instructive to consider the limits that are currently in place for alcohol in products sold to minors, as well as work that has been done internationally to establish safe thresholds for the presence of THC in foods.

Comparison to Alcohol

Alcohol may be present in small quantities in foods and beverages other than alcoholic beverages. In order to be considered "non-alcoholic," a food or beverage can contain no more than 0.5% alcohol by volume. A minor may purchase non-alcoholic foods and beverages that contain this small amount of alcohol.

This 0.5% threshold for alcohol is not at all comparable with the 0.3% threshold for THC in hemp products because alcohol is much less potent than THC on a weight-to-weight basis. One standard unit of alcohol – a typical 12 fl oz beer, 5 fl oz glass of wine, or 1.5 fl oz portion of distilled spirits – contains 14 g or 14000 mg of alcohol (National Institute on Alcohol Abuse and Alcoholism [NIAAA] 2021). By contrast, a standard unit of THC is only 5 mg (National Institute on Drug Abuse [NIDA] 2021). There is nearly a 3000-fold difference between the weights of these standard units.

The relevant limiting factor with consumption of alcohol from non-alcoholic beverages is the amount of liquid that a person can reasonably drink at one time. A person would have to consume approximately one gallon of liquid at 0.5% to consume one standard unit of alcohol. By contrast, a person would only have to drink one-third of a teaspoon (1.7 ml) of liquid at 0.3% to consume one standard unit of THC.

A threshold for THC equivalent to the non-alcoholic threshold can be derived on a percentage basis, or on a per-container basis by comparison to a typical unit of a non-alcoholic beverage:

- **Percentage equivalence:** 0.5% alcohol × (5 mg THC ÷ 14000 mg alcohol) = 0.0002% THC.[3]
- **Per-container equivalence:** Taking 12 fl oz to be a typical container size for a non-alcoholic beverage, 12 fl oz × 0.5% alcohol × 29.5735 ml/fl oz × 0.789 g/ml = 1.4 g alcohol[4]. Since a standard unit of alcohol is 14 g, this means a typical container of a non-alcoholic beverage can contain one-tenth of a unit of alcohol. A standard unit of THC is 5 mg, so one-tenth of a standard unit of THC would be 0.5 mg THC.

Most hemp products have smaller weights than typical non-alcoholic products, which makes a simple percentage limit on THC significantly more restrictive than a milligram-per-container limit for the vast majority of products. For example, under this percent limit, a 1 oz tincture would be limited to approximately 0.06 mg THC.

Comparison to International Standards

As hemp seed and products derived from hemp seed have become more prevalent in foods, significant work has been done internationally to establish safe levels for residual THC in these foods. While the seeds of hemp do not naturally contain any THC, they are contained within a part of the plant called the calyx, which does contain THC. Some amount of THC transfers from the plant to the seeds in the course of processing (Food Standards Australia New Zealand [FSANZ] 2002). Consequently, several countries that allow hemp seeds and hemp seed oil to be used in foods have established limits or guidance values on the amount of trace THC contamination that may be present in hemp seeds or hemp seed-derived food products to ensure

[3] The equation is $[\text{limit of alcohol by volume}] \times \frac{[\text{standard unit of THC}]}{[\text{standard unit of alcohol}]}$

[4] Using the density of pure ethanol in order to convert from volume to mass.

that THC exposure through hemp foods does not pose a risk of intoxication or other adverse consequences. Significantly, these analyses consider exposure for the entire population, not only exposure for adults.

General guidelines for THC exposure

Several efforts have been made to evaluate appropriate levels of exposure to THC originating from hemp in the food supply.

In general, these evaluations are based on establishing a "lowest observed adverse effect level" (LOAEL) or a "no observed adverse effect level" (NOAEL) for THC, then adjusting that number for safety or uncertainty factors. This provides an estimate the amount of THC that can be consumed in a short period of time without significant health risks to the consumer (Liu & Chen 2003). This may be expressed as an "acceptable daily intake" (ADI), "acute reference dose" (ARfD), "health based guidance value" (HBGV) or "tolerable daily intake" (TDI). The following is a summary of these values from a variety of sources:

- Croatian Food Agency (Hrvatska agencija za hranu [HAH]): 0.5 mg/day ADI[5] (HAH 2011)
- European Food Safety Authority Panel on Contaminants in the Food Chain (EFSA CONTAM Panel): 1 µg/kg bw, equivalent to 0.08 mg for an 80 kg person (EFSA CONTAM Panel 2015; Bundesinstitut für Risikobewertung[6] [BfR] 2018)
- European Industrial Hemp Association (EIHA): 7 µg/kg bw HBGV, equivalent to 0.56 mg for an 80 kg person (EIHA 2021)
- Food Standards Australia New Zealand (FSANZ): 6 µg/kg bw TDI, equivalent to 0.48 mg/day for an 80 kg person (FSANZ 2002; FSANZ 2012)
- Leson Environmental Consulting, in an analysis commissioned by Dr. Bronner's Magic Soaps and the North American Industrial Hemp Council (NAIHC): 0.5 mg/day ADI (Grotenhermen *et al.* 2001)

The majority of these values are in good agreement, being equivalent to approximately 0.5 mg THC. The EFSA evaluation is an outlier, proposing an ARfD equivalent to less than 0.1 mg THC for an 80 kg person. However, the German BfR supports the EFSA analysis, stating that "exceeding [the ARfD of 1 µg/kg bw] is undesirable from a toxicological point of view, since adverse health effects can no longer be ruled out with the required degree of certainty" (BfR 2021).

It is also worthwhile to consider the data that these analyses used to establish an LOAEL or NOAEL for THC. The following is a non-exhaustive selection of literature that addresses oral THC dosage, impairment, and adverse events:

- A study on the effects of oral THC in 16 healthy human subjects evaluated doses of 0, 5, 10, 15, and 20 mg/person. A dose of 5 mg THC was sufficient to affect the skill performance measures, but subjective intoxication based on self-reporting was indistinguishable from placebo. (FSANZ 2002, citing Chesher *et al.* 1990)

[5] The English language summary contains a typo, specifying the ADI as 500 mg per day. In the original Croatian text, the correct figure is twice stated as 500 µg/day (e.g. "izračunat je ADI za THC putem hrane i iznosi 500 µg/dan.").
[6] German Federal Institute for Risk Assessment.

- A study on treatment of anorexia associated with weight loss in patients with AIDS receiving placebo or 2.5 mg THC twice daily orally. Treatment-related adverse events were noted in 43% of patients receiving THC, compared with 13% of patients receiving placebo; 8.3% of patients receiving THC discontinued due to perceived drug toxicity, compared with 4.5% of patients receiving placebo. "Most patients who required dose reduction were able to tolerate the half-dose (one 2.5-mg capsule in the evening)." (Beal *et al.* 1995)
- A follow-up 12 month study involving patients from the previous study (Beal *et al.* 1995) starting with 2.5 mg THC once or twice daily orally and adjusting dosage up or down "based on patient response and side effects." Dosage was adjusted in 38% of patients, with half of those reducing to 2.5 mg THC once daily and half increasing to between 7.5 and 20 mg daily. 15% of patients discontinued due to perceived drug toxicity. "Adverse events were primarily related to the central nervous system (for example, anxiety, confusion, depersonalization, dizziness, euphoria, somnolence, and thinking abnormality) and occurred in 35 of 93 patients (38%) enrolled in the study. In 19 patients, treatment-related adverse events were the primary or secondary reason for early study discontinuation." (Beal *et al.* 1997)
- A study on treatment of spasticity in 57 patients with multiple sclerosis using oral cannabis extract with a THC:CBD ratio of 1:0.36. Five patients discontinued due to persistent side effects. "The maximally tolerated THC dose exhibited a bimodal distribution" with the largest numbers of patients consuming 27.5 mg THC daily, 7.5 mg THC daily, or 10 mg THC daily. (Vaney *et al.* 2004)
- A study on appetite and weight in 243 patients with cancer receiving placebo, 2.5 mg THC twice daily orally, or cannabis extract containing 2.5 mg THC and 1 mg CBD twice daily orally. Dose reductions due to adverse events were necessary in 33% of patients receiving THC or cannabis extract (Strasser *et al.* 2006)
- A randomized, double-blind study of the effects of "very-low-dose" oral THC and ethanol in 11 healthy human subjects. Participants did not report feeling any drug effects following administration of 2.5mg THC without any ethanol, but this dose produced "modest effects on subjective ratings, measures of cognitive performance, and physiological measures." (Ballard & de Wit 2011)

Specific limits on the concentration of THC in foods

Several countries have established limits or guidance values on the concentration of THC that is allowed in hemp-derived foods:

Belgium

Cannabis sativa is included on a list of plants that are prohibited from being used in foods. This regulation dates back at least to 1997, and was updated as recently as August 2021 (Arrêté Royal 2017; Arrêté Royal 2021). Belgium's Federal Agency for the Safety of the Foodchain has clarified that this prohibition includes legally-grown hemp, but notes that "a derogation from the prohibition on the manufacture and marketing of these plants as foodstuffs or as components incorporated into foodstuffs may sometimes be requested. The assessment is made on a case-by-case basis, taking into account the THC content of each batch and the other characteristics of the product." (Federal Agency for the Safety of the Food Chain [FASFC] 2018)

Canada

Canada allows hemp containing no more than 10 mg/kg THC (0.001%) in natural health products that are subject to the Natural Health Products Regulation rather than the Cannabis Act. Products with more than 10 mg/kg THC are regulated under Canada's federally-legal cannabis framework (Health Canada 2021). Prior to the passage of the Cannabis Act, hemp products containing no more than 10 mg/kg THC were similarly except from the Controlled Drugs and Substances Act (Health Canada 2020).

Germany

Germany has not established formal limits on THC content in hemp-derived foods, however the German Federal Institute for Consumer Health Protection and Veterinary Medicine (BgVV[7]) established "guidance values" for THC content in hemp-derived foods in 2000 (BgVV 2000):

- 0.005 mg/kg THC (0.0000005%) for non-alcoholic and alcoholic beverages
- 5 mg/kg THC (0.0005%) for edible oils
- 0.15 mg/kg THC (0.000015%) for all other foods

More recently, the German Federal Institute for Risk Assessment (BfR) reconsidered the previously-published guidance values and recommended that they be lowered because it is possible that a person consuming foods with THC content in accordance with the guidance values could ingest a dose of more than 2.5 mg THC per day. Only the guidance value for beverages was considered to be sufficiently conservative. (BfR 2018, BfR 2021)

Italy

In 2020, Italy published the following limits on the concentration of "total THC," defined as the sum of Δ^9-THC and Δ^9-THCA (Gazzetta Ufficiale 2020):

- 2 mg/kg THC (0.0002%) for hemp seed and hemp seed flour (or other shredded, chopped, or ground preparations)
- 5 mg/kg THC (0.0005%) for hemp seed oil
- 2 mg/kg THC (0.0002%) for foods containing hemp-derived ingredients

New Zealand

In 2012, Food Standards Australia New Zealand (FSANZ) approved an application for low-THC hemp as a food, establishing the following limits on the concentration of THC (FSANZ 2012):

- 5 mg/kg THC (0.0005%) in hemp seed
- 10 mg/kg THC (0.001%) in hemp seed oil
- 0.2 mg/kg THC (0.00002%) in beverages made from hemp seed
- 5 mg/kg THC (0.0005%) in any other hemp seed-derived product

Switzerland

[7] Bundesinstitut für Gesundheitlichen Verbraucherschutz Und Veterinärmedizin.

Switzerland has established THC limits for foods that include hemp seed since at least 1995 (Das Eidgenössische Departement des Innern[8] [EDI] 1995), although those limits have since been reduced. As of 2016, Switzerland imposes the following limits on THC concentration (EDI 2016):

- 20 mg/kg THC (0.002%) in hemp seed oil
- 10 mg/kg THC (0.001%) in hemp seed
- 5 mg/L THC (approximately 0.00063% by weight based on pure alcohol) in spirits
- 2 mg/kg THC (0.0002%) in baked goods
- 2 mg/kg THC (0.0002%) in pasta
- 1 mg/kg THC (0.0001%) in plant-based foods
- 0.2 mg/kg THC (0.00002%) in alcoholic beverages other than spirits
- 0.2 mg/kg THC (0.00002%) in non-alcoholic beverages
- 0.2 mg/kg THC (0.00002%) in herbal and fruit teas (based on a preparation of 15 g plant material per k kg water; boiling water poured over plant material and temperature held above 85 °C for 30 minutes)

Unites States

The FDA has not yet established any formal limits for THC in hemp-based foods, however FDA has evaluated GRAS notices for hemp seeds and hemp seed oil and concluded that "these products can be legally marketed in human foods for the uses described in the notices, provided they comply with all other requirements. […] The GRAS conclusions can apply to ingredients for human food marketed by other companies, if they are manufactured in a way that is consistent with the notices and they meet the listed specifications" (FDA 2021a). The GRAS notices for hulled hemp seed and hemp seed oil specify that the products contain THC below the following concentrations (Keefe 2018a; Keefe 2018b):

- 4 mg/kg THC (0.0004%) in hulled hemp seed
- 10 mg/kg THC (0.001%) in hemp seed oil

Conclusion

On balance, a percentage limit by weight on THC content is likely to be significantly more restrictive than a milligram-per-container limit. In order to minimize the impact on segments of the industry selling products containing minimal amounts of THC while still prohibiting the sale of intoxicating quantities of THC to minors, a milligram-per-serving limit is preferable.

OLCC staff recommend maintaining the limit of 0.5 mg THC per container that was established through temporary rulemaking following the passage of 2021 House Bill 3000. This limit is very well-aligned with limits on the sale of non-alcoholic beverages to minors and with the majority of recommendations on acceptable daily exposure to THC through foods.

[8] Switzerland's Federal Department of Home Affairs.

THC Limits for Sales to Adults

As discussed above, it is not necessarily critical to establish limits such that a product cannot contain an intoxicating quantity of THC when establishing cannabinoid limits for hemp products that are offered for sale to adults. In fact, limiting THC to a non-intoxicating level would effectively prohibit the sale of full-spectrum hemp products to consumers. Full-spectrum products constitute a significant portion of cannabinoid hemp products currently sold in Oregon, so prohibiting these products is not a desirable outcome.

Instead, the primary objectives in limiting THC content in hemp products for sale to adults are:

1. Establishing THC-per-serving limits such that a single serving is relatively unlikely to produce significant impairment in a typical adult consumer.
2. Establishing THC-per-container limits such that a hemp product contains substantially less THC than is permitted in Oregon's adult use marijuana system.

Per-serving limits

Based on the data evaluated by various countries and other organizations in establishing safe limits of residual THC in hemp food products, the consensus appears to be that the LOAEL is 2.5 mg THC. This is partly because oral doses of THC below 2.5 mg have not been well-studied; it is possible that future studies could establish an LOAEL below 2.5 mg. However, not all studies that involved 2.5 mg found the dose to have an intoxicating effect. In the studies where adverse events related to administration of THC occurred at 2.5 mg, the incidence of adverse events was relatively low. Dr. Ethan Russo, former Director of Research and Development of the International Cannabis and Cannabinoids Institute, has described 2.5 mg THC as "a threshold dose for most people without tolerance" (Skodzinski 2021).

There is evidence that CBD may reduce the impairing effects of THC, although the data are not unanimous on this, and the effect may be dependent on the dose of CBD relative to THC (Ganesh *et al.* 2021; Petitet *et al.*1998; Solowij *et.al.* 2019). If CBD does reduce the effects of THC, full-spectrum products containing both THC and CBD could be better-tolerated than THC alone.

It may also be worthwhile to consider the effect on sensitive persons. There is significant individual variation in sensitivity to THC. In particular, elderly persons have been noted as being potentially more sensitive to the psychoactive effects of THC (Abbot Laboratories 2011).

Whatever per-serving limit is set for THC will ultimately have an impact on the amount of CBD that can be present in a serving of the product. As discussed above, high-CBD low-THC plants will typically contain THC in a ratio of around 1:20 with CBD. In other words, a full-spectrum product will typically contain 20 mg CBD for each milligram of THC that is present. There are many hemp products that aim to provide greater than 20 mg CBD per serving. If THC were limited to 1 mg per serving, doses above 20 mg CBD in full-spectrum hemp products would no longer be viable.

A per-serving limit of 2 mg THC balances the available data on the effects of THC with the concerns of established industry participants making full-spectrum THC products. Available data indicate that a typical adult consumer is relatively unlikely to be significantly impaired in this range. However, it is important that

consumers be adequately informed of the amount of THC they are consuming when using cannabinoid hemp products. OLCC staff are concerned about the lack of clear or consistent labeling standards for hemp products. The risk of accidental overconsumption of THC is significantly higher when a consumer is not able to quickly and easily determine how much THC is present in the product they are consuming.

Per-container limits

At present, the only state that has established THC limits per-container for hemp products is Alaska, which limits THC content in a hemp product to no more than 50 mg under 11 Alaska Administrative Code (AAC) §40.415. This is identical with the current limit for THC in adult use marijuana edibles in Oregon, but significantly lower than Oregon's limit for THC in adult use tinctures. In order to effectively accomplish the objective of establishing THC-per-container limits such that a hemp product contains substantially less THC than is permitted in Oregon's adult use marijuana system, it seems necessary to differentiate per-container limits for different categories of products, analogous to the THC limits for adult use marijuana products.

One basis for comparing the relative amounts of THC in hemp and marijuana products is to consider the amount of THC present in the plants. Hemp is limited by definition to no more than 0.3% total THC. By contrast, approximately 90% of marijuana in Oregon's adult use market contains 15% total THC or greater. This means that, for flower products, marijuana is typically at least 50 times more potent than legal hemp flower.

Considering this in the context of edibles, tinctures, and topicals:

- Marijuana edibles will be able to contain up to 100 mg THC in 2022. One-fiftieth of this limit would be 2 mg THC per container, which equates to approximately 40 mg CBD in a full-spectrum edible product. This seems unnecessarily restrictive and could contribute to significant packaging waste for products reformulated to stay below 2 mg THC per container. In this product category, it is more realistic to limit hemp products to one-tenth or one-fifth the amount of THC allowed in marijuana edibles: A limit of 10 mg THC would allow full-spectrum edibles with approximately 200 mg CBD, while a 20 mg THC limit would allow full-spectrum edibles with approximately 400 mg CBD. OLCC staff recommend a limit of 20 mg THC per container for hemp edibles and other cannabinoid hemp products (excluding tinctures and topicals).
- Marijuana tinctures can contain up to 1,000 mg THC. One-fiftieth of this limit would be 20 mg THC per container, which equates to approximately 400 mg CBD in a full-spectrum tincture product. This seems unnecessarily restrictive and could contribute to significant packaging waste for products reformulated to stay below 20 mg THC per container. In this product category, it is more realistic to limit hemp products to one-tenth the amount of THC allowed in marijuana tinctures: A limit of 100 mg THC would allow full-spectrum hemp tinctures with approximately 2,000 mg CBD. OLCC staff recommend a limit of 100 mg THC per container for hemp tinctures.
- Marijuana topicals can contain up to 6% THC by weight. One-fiftieth of this limit would be 0.12% THC. However, considering the low central bioavailability of THC when applied topically, there does not appear to be a compelling reason to limit hemp topicals beyond the statutory limit of 0.3% total THC by weight. The 0.3% THC limit is one-twentieth of the limit for THC in marijuana topicals. OLCC staff recommend no specific limit on the number of milligrams per container for hemp topicals.

Regardless of the maximum per-container limits established by OLCC, ORS 475B.254 (as amended by 2021 House Bill 3000) limits hemp products to no more than 0.3% total THC. In cases where the 0.3% limit is more restrictive than the milligram-per-container limit, the 0.3% total THC limit applies. For example, a 1 fl oz tincture weighing 25 g is limited to no more than 75 mg THC, even if OLCC establishes a limit of 100 mg THC per container for tincture products.

Artificially Derived Cannabinoids

In House Bill 3000, the Oregon Legislature defined "artificially derived cannabinoids" explicitly in terms of how they are created: "a chemical substance that is created by a chemical reaction that changes the molecular structure of any chemical substance derived from the plant Cannabis family Cannabaceae." There is no reference in the definition to whether the artificially derived cannabinoid has an intoxicating effect. Other parts of the bill, such as the definition of "adult use cannabinoid" specifically delineate when they are referring to the subset of artificially derived cannabinoids which are intoxicating[9]. From this, it can be inferred that the entire set of artificially derived cannabinoids includes all cannabinoids made through the methods described in the definition, not just the subset of those substances that may have an intoxicating effect.

Intoxicating artificially derived cannabinoids were included in the definition of "adult use cannabinoid" out of concern that they might be legally included in products sold to minors or used to circumvent the potency limits that apply to Δ^9-THC in marijuana products. However, there are broader concerns applicable to all artificially derived cannabinoids, and it is the understanding of OLCC staff that these broader concerns are the reason that Section 17 of House Bill 3000 directs OLCC to establish limits on the cannabinoid content of hemp products, including: "The maximum concentration of any other cannabinoid, adult use cannabinoid **or artificially derived cannabinoid** that is permitted in a single serving of an industrial hemp product" (emphasis added). For these reasons, OLCC has considered both intoxicating and non-intoxicating artificially derived cannabinoids in the context of this rulemaking.

Entirely separate from any concerns about dosage, toxicity, or intoxicating potential, there is cause for concern related to impurities that may result from the manufacturing process by which an artificially derived cannabinoid is made:

- The process of synthesizing an artificially derived cannabinoid can employ a wide range of solvents and reagents. If adequate steps are not taken to remove residual solvents or reagents from the reaction product, a consumer could be exposed to the residual solvents or reagents. Marijuana and hemp products are subject to certain required compliance testing under Oregon law, but this compliance testing does not encompass all solvents that may be used in the production of an artificially derived cannabinoid, and they do not encompass any reagents at all. Further, it is impractical to generate a comprehensive list of solvents and reagents of concern because of the wide variety of synthetic routes that may be used to generate any number of artificially derived cannabinoids from a cannabis starting material.

[9] E.g. "any artificially derived cannabinoid that is reasonably determined to have an intoxicating effect."

- No chemical reaction is 100% efficient. In nearly every chemical reaction, some amount of side-reaction products[10] will also be created. The side-reaction products will differ depending on the specific reaction conditions, including the reagents, solvents, temperature, pressure, and atmosphere. The required compliance testing for hemp and marijuana in Oregon is based on the concerns presented by cannabis itself and processes that may be used to extract cannabinoids from cannabis. They do not encompass any side-reaction products that result from synthetic manipulation of a cannabis-derived starting material, nor is it practical to encompass side-reaction products of concern that could be generated by all possible syntheses that might use a cannabis-derived starting material.

OLCC staff have heard comments that these risks may be mitigated through implementation of a purity standard, such as requiring that all artificially derived cannabinoids be at least 97% pure. Unfortunately, this is not an adequate solution. Knowing that impurities make up no more than 3% of the product is only reassuring when it is known that the impurities are not harmful when consumed at that level. Without knowing the identity of the side-reaction products, which will vary depending on the specific synthetic route employed by the manufacturer, the potential toxicity of the side-reaction products also remains largely unknown

There are also practical complications to implementing a purity standard: At present, Oregon's OLCC-licensed, ORELAP[11]-accredited laboratories are not necessarily accredited for detection or quantification of any artificially derived cannabinoids, nor are their accredited methods sufficiently sensitive to report a purity level above 97% with a high degree of confidence.

Considering the potential risks, and the current inability to mitigate those risks through required compliance testing, it is appropriate to defer to the ordinary regulatory processes that would apply to any other novel synthetic material being introduced into a food or dietary supplement. The FDA generally regulates the introduction of novel synthetic ingredients into foods or dietary supplements, and provides multiple routes:

- GRAS determination: A business can make the determination that an ingredient is generally recognized as safe (GRAS), meaning that there is a reasonable certainty of no harm under the conditions of its intended use (21 CFR 170.30). The business may voluntarily submit notice of the GRAS determination to the FDA, allowing the FDA to evaluate the manufacturer's basis for making the GRAS determination, but the business is not required to notify FDA when they make a GRAS determination.
- NDI notifications: Prior to including a "new dietary ingredient" in a dietary supplement that will be introduced into interstate commerce, the manufacturer or distributor of the supplement or ingredient is required to submit notification to the FDA, including information about the basis for concluding that there is a reasonable expectation of safety for the use of the ingredient. This requirement does not apply to an ingredient that has been present in the food supply as an article used for food in a form in which the food has not been chemically altered. (21 CFR 190.6)

[10] A product other than the desired product.
[11] Oregon Environmental Accreditation Program, the agency that accredits cannabis testing laboratories in Oregon.

To date, there is no evidence that manufacturers of artificially derived cannabinoids or products containing artificially derived cannabinoids are complying with these requirements prior to including their artificially derived cannabinoids in foods or supplements that enter into interstate commerce. Anecdotally, manufacturers and industry advocates justify this non-compliance by asserting that the FDA will not fairly consider any information about cannabis-derived ingredients. That assertion ignores two important facts: First, that active involvement by the FDA is not necessarily required if the manufacturer has sufficient evidence that there is a reasonable certainty of no harm to make a GRAS determination; and second, that the FDA has not yet been given the opportunity to evaluate a new dietary ingredient notification for an artificially derived cannabinoid because no such notification has been submitted.

The FDA's publicly-stated position is that CBD and THC specifically are excluded from being considered a dietary supplement under 21 USC 321 (ff)(3)(B), which states that the term "dietary supplement" does not include an article approved as a new drug or authorized for investigation as a new drug. It is on this basis that the FDA recently objected to NDI notifications for two dietary supplements containing full-spectrum hemp extracts (Welch 2021a; Welch 2021b). This exclusion does not apply to artificially derived cannabinoids unless they are an approved new drug or authorized for investigation as a new drug. Until an NDI notification is submitted for such an artificially derived cannabinoid, any assertions about the FDA's response to such a notification remains conjecture.

OLCC staff recommend that non-intoxicating artificially derived cannabinoids should not be permitted in products sold to consumers until they meet one of the established regulatory standards for affirming that there is a reasonable expectation of safety or certainty of no harm. Recognizing that products containing the artificially derived cannabinoid cannabinol (CBN) are already prevalent in Oregon's cannabinoid hemp market, staff recommend that these products should continue to remain available, absent evidence of harm to consumers, for a period of 18 months while they work to establish a GRAS determination or complete an NDI notification, but limit these products to Oregon's more closely-regulated marijuana market where clear labeling standards apply and the Cannabis Tracking System provides a mechanism for effectively tracking a product recall should a recall become necessary. Oregon would not be alone in having regulations that effectively prohibit artificially derived cannabinoids in the general market for hemp products; the Colorado Department of Public Health and Environment (CDPHE 2021) has publicly clarified that "chemically modifying or converting any naturally occurring cannabinoids from industrial hemp is non-compliant with the statutory definition of "industrial hemp product."

OLCC staff further recommend that intoxicating artificially derived cannabinoids should not be permitted in products sold to consumers absent evidence of a reasonable expectation of safety or certainty of no harm. Should such evidence become available, OLCC could engage in further rulemaking to establish concentration and serving size limits and allow specific artificially derived cannabinoids to be present in products based on the evidence.

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