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DELTA-8 TETRAHYDROCANNABINOL WHITEPAPER

SEPTEMBER 2018

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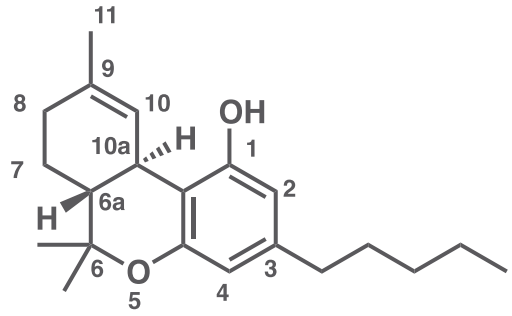
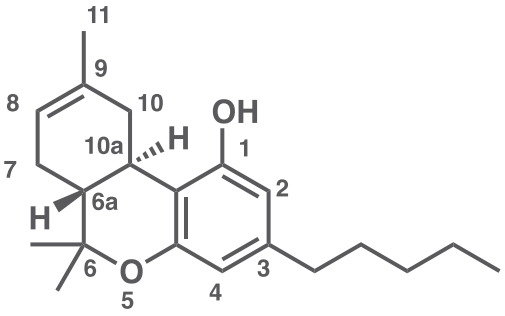
1 WHAT IS DELTA-8 THC?

Delta-8 tetrahydrocannabinol (**Delta-8**; CAS #: 5957-75-5) is a positional isomer of delta-9 tetrahydrocannabinol (**Delta-9**; CAS #: 1972-08-3), the compound typically referred to as "THC." As geometric isomers, Delta-8 and Delta-9 possess the same molecular mass and formula. The only difference is a double bond located between the 8 and 9 carbons (Delta-8) instead of between the 9 and 10 carbons (Delta-9).



Δ9-Tetrahydrocannabinol (Delta-9)



Δ8-Tetrahydrocannabinol (Delta-8)

Figure 1: Delta-9 and Delta-8 Chemical Structures and Numbering

Many people describe Delta-9 as the only psychoactive cannabinoid, particularly in contrast to cannabidiol (CBD). However, there are other native cannabinoids that exhibit physiological activity that can be characterized as psychoactive. Cannabinol (**CBN**), an oxidative degradation product of THC that is commonly found in small quantities on cannabis inflorescences, is one example. CBN is often reported to have 1/10th the psychotropic effect of Delta-9, but CBN clearly has a different mechanism of action.[1]

2 COMPARISON OF ACTIVITY TO DELTA-9 THC

There is less available literature describing the physiological effects of Delta-8 than CBN, but hints of its activity are present. Interestingly, in the few publications that describe administering Delta-8 to humans there appear to be conflicting reports about its psychotropic effects. Delta-8 also appears to have been overlooked in a recent review of native cannabis cannabinoids and terpenoids.[2]

2A CB1 & CB2 RECEPTOR ACTIVITY

In 2015, Radwan et al. reported the binding affinity of Delta-8 to both CB1 and CB2 receptors. The experimentally determined values were 78 ± 5 nM at CB1 and 12 ± 2 nM at CB2. In comparison, Delta-9 exhibits 18 ± 4 nM at CB1 and 42 ± 9 nM at CB2. CB1 receptors are predominantly found in the central nervous system (CNS) and peripheral tissue, while CB2 receptors are typically expressed outside the central nervous system and often associated with immune system regulation.[3,4] Relative to Delta-9, Delta-8 demonstrates tighter binding at CB2 receptors. Furthermore, Delta-8 demonstrated similar but muted patterns of cannabimimetic activity in the mouse tetrad assay.[5] The stronger binding of Delta-9 at CB1 suggests that it will produce a greater psychoactive effect than Delta-8, assuming CB1 mediated effects are wholly responsible for psychoactivity.

2B ANIMAL DATA

In the early 1980's, Watanabe and coworkers published pharmacological data in which mice were administered Delta-8, 11-OH-delta-8 THC (**11-OH-Delta-8**; CAS #: 28646-40-4), and 11-oxo-delta-8 THC. Sleep time was prolonged for each of the three at 5 mg/kg versus control by 3.4, 4.9, and 5.7 times, respectively. The mechanism of this action is not understood.[6]

Watanabe and coworkers subsequently reported the metabolic distribution of Delta-8, 11-OH-Delta-8, and 11-oxo-delta-8 THC in mouse blood, liver, and brain. Both of the Delta-8 metabolites were more readily transported from blood to brain than Delta-8 itself. This is interesting because Delta-8 is more lipophilic than its metabolites, which normally leads to better blood-brain barrier passage. The researchers hypothesized that this could explain their comparatively stronger CNS effects. In addition, 11-OH-Delta-8 partitioned into the brain over blood and liver at a significantly greater ratio than the other two compounds. Finally, it was found that Delta-8 was eliminated more slowly from the brain suggesting that it is not metabolized in brain tissue.[7]

In a separate line of study, researchers investigated the effects of very low doses (1.0 µg/kg) of Delta-8 on food consumption, neurotransmitter levels, and cognitive function in mice for nine or fifty days. Those fed Delta-8 for nine days exhibited a 16 % increase in food intake compared with controls ($P<.001$), whereas the fifty-day group exhibited a 22 % increase in intake ($P<.05$). Furthermore, the Delta-8 groups showed significantly greater intake than those mice fed the same quantity of Delta-9 ($P<.05$) with similar activity and performance scores. Changes to dopamine, serotonin, and norepinephrine levels were reported in the hypothalamus and hippocampus of the Delta-8 group relative to control. The researchers also reported an increase in cognitive function in the Delta-8 group.[8] It is unclear whether these effects were caused by action downstream of CB1 activity or through some entirely different mechanism.

2C HUMAN DATA

In one of the earliest literature references of Delta-8 administration to humans, Delta-8 was reported to have 2/3 the psychoactive potency of Delta-9 via both oral and intravenous routes.[9] A separate study published in 1995 evaluated the efficacy of Delta-8 for treating nausea in juvenile cancer patients via oral administration, and also found reduced psychoactivity relative to Delta-9.[10] Literature reports of inhaled Delta-8 appear to be non-existent.

ANECDOTAL USER REPORTS

Users inhaling vaporized Delta-8 in low and high doses report little discernible "high" relative to similar inhaled dosages of Delta-9. Some users report a feeling of well-being or mental stimulation, but physical impairment is not commonly reported. This is similar to reports by those who have inhaled CBD. More research is required to validate the reliability of these effects across populations, especially in Delta-8 naive individuals.

ORAL VS. INHALED

Users consuming oral Delta-8 at a dosage of 25 mg (bolus), report a discernible feeling of well-being mixed with stimulating, but non-assertive psychoactivity. The psychotropic effect was commonly described as distinct from the familiar activity of ingested Delta-9, across various doses. The effects reported by a majority of users at relatively low doses are particularly interesting given that larger inhaled doses, upwards of 100 mg, have little discernible psychoactive effect. This result is surprising because inhalation normally leads to higher blood (C_{max}) and brain levels than ingestion. As such, a greater magnitude of effect via inhalation at the same dose would be expected and even more so at a comparatively elevated dose.

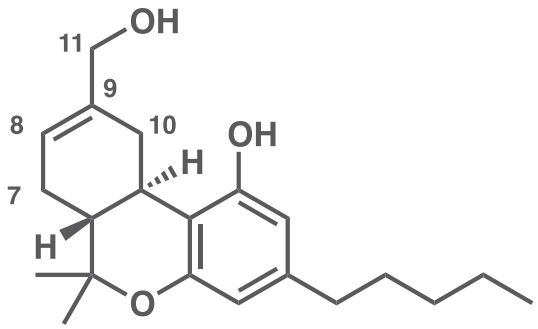
In a group of non-naive subjects, a solid oral formulation (tablet) of Delta-8 and Delta-9 (both 10 mg) resulted in restful and sustained sleep. This sleep was described as unlike any other cannabis product, oral or inhaled. In addition, there are sporadic reports that the effects 8 hours post-ingestion are less like the cannabis "hangover" associated with Delta-9. We are optimistic that continued research and data will further substantiate these reports with respect to Delta-8 use, benefits, and applicability.

3A 11-OH DELTA-8 THC: THE DIFFERENCE BETWEEN INGESTED AND INHALED DELTA-8?

Not much is known about the human pharmacological action of 11-OH-Delta-8, the first metabolite of Delta-8. However, 11-OH-Delta-8 is metabolized from Delta-8 by the same oxidative pathway that transforms Delta-9 to 11-OH-delta-9 THC in humans.[11] The work of Watanabe and coworkers with mice in the early 1980s provides some clues about what may be true in humans.

Based upon user reports, there appears to be a difference in experiential effects between inhaled Delta-8 (no pronounced psychoactivity) and ingested Delta-8 (a definite psychoactive effect) that is different than reported between inhaled and ingested Delta-9. Due to first-pass metabolism that impacts ingested compounds to a much greater degree than inhaled compounds, it is possible that Delta-8 is either non-psychoactive or does not effectively cross the blood-brain barrier. Since pharmacological research clearly demonstrates the presence of Delta-8 in the brain, we can eliminate the latter possibility. Evidence does show that 11-OH-Delta-8 passes the blood-brain barrier better than Delta-8 itself, however. The lack of true Delta-8 psychoactivity is still a possibility, even though the sleep prolongation data suggests that Delta-8 itself possesses some sort of CNS activity.

Delta-8 non-psychoactivity would be unexpected due to the incontrovertible psychoactivity of Delta-9. Nevertheless, 11-OH-delta-9 THC has been reported to possess two times the subjective psychoactivity of Delta-9.[12] It is conceivable that inhalation leads to a large percentage of Delta-8 passing quickly into the brain where it cannot be metabolized. Upon slow elimination from the brain into the blood, it would be metabolized into 11-OH-Delta-8, but the concentration may never be high enough to induce noticeable effects.



11-Hydroxy-Δ8-Tetrahydrocannabinol (11-OH-Delta-8)

Figure 2: 11-OH-Delta-8 Chemical Structure and Numbering

HU-210 (CAS #: 112830-95-2) and HU-211 (Dexanabinol, CAS #: 112924-45-5) are enantiomers and can be considered structural analogues of 11-OH-Delta-8. However, HU-210 and HU-211 are distinctly different from 11-OH-Delta-8 and Delta-8 in that they are not produced by native cannabis biosynthetic machinery, not found on/in native cannabis due to natural degradative forces, and not human metabolites of native cannabinoids. As such, HU-210 and HU-211 are classified as "synthetic cannabinoids. The unnatural aliphatic tail present in HU-210 and HU-211 ensures that these compounds will never be made by a non-bioengineered cannabis plant.

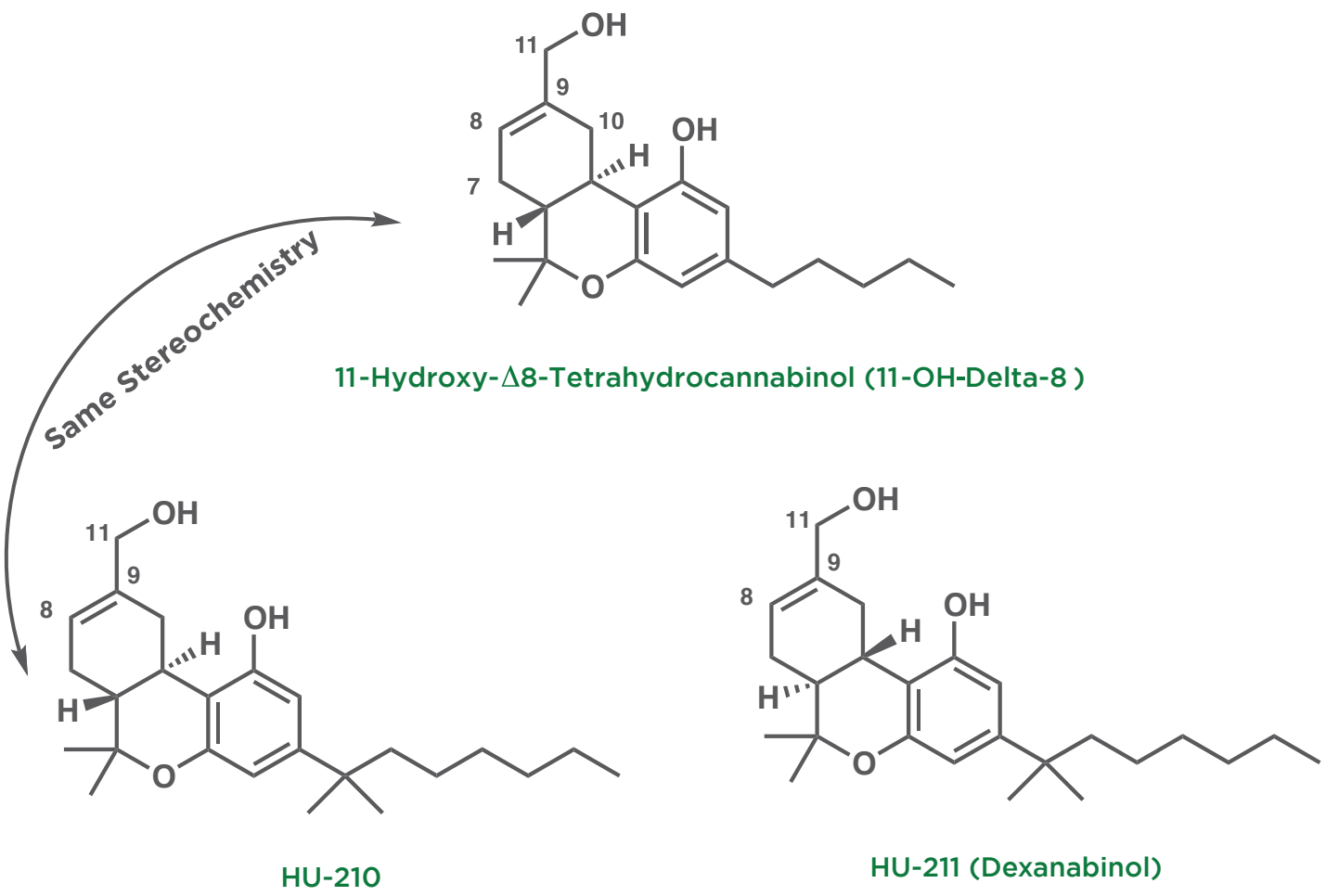


Figure 3: Comparison of 11-OH-Delta-8 to Two Synthetic Cannabinoids Containing the 11-OH Delta-8 Motif

HU-210 has been reported to be 80-100 times more psychoactive than Delta-9.[13] Dexanabinol, the chemical mirror image of HU-210, has been reported to be devoid of cannabinoid receptor agonist activity and any attendant psychotropic effects. Yet, it demonstrates NMDA antagonism and neuroprotective activity.[14, 15]

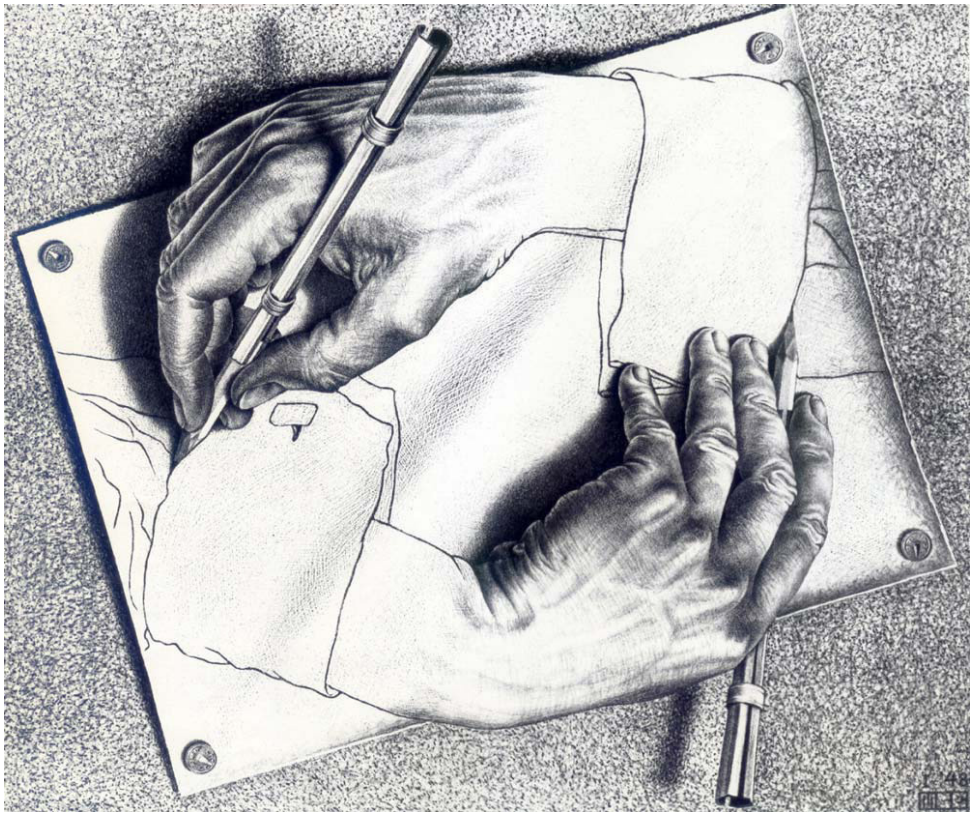


Figure 4: Drawing Hands (courtesy of mcescher.com)

HU-210 possesses the same analgesic and anti-inflammatory activity as Delta-9 and has been implicated in guarding against inflammation caused by beta-amyloid proteins. In addition, HU-210 has been reported to increase proliferation of hippocampal stem cells and, through that activity, to positively modulate anxiety and depressive effects in the central nervous system.[16]

Despite being inactive at CB1 and CB2 receptors, Dexanabinol putatively exhibits neuroprotective and anticonvulsant activity by mediation through NMDA antagonism.[17] Further exploration is underway into the neuroprotective effects with respect to head trauma and stroke.[18, 19] Dexanabinol was determined to be safe with little to no toxicological impact when administered at a dosage of 150 mg in a multi-center Phase III clinical trial.[20] Preliminary Phase I trials have also recently investigated the efficacy of Dexanabinol for various forms of cancer.[21, 22]

The preceding discussion about HU-210 and HU-211 is meant to illustrate the disparate and in some cases complementary activity that similar molecules can exert on the complex and sensitive human biochemistry. Nevertheless, synthetic cannabinoids have distinct and different effects from native cannabinoids and their metabolites, even if also produced by chemical reactions. Although HU-210 and HU-211 share a pharmacophore with 11-OH-Delta-8, neither are native to the cannabis plant or are compounds that result from normal degradative or human metabolic action on native cannabinoids.

4 COMMERCIAL AVAILABILITY

The necessity of obtaining a DEA Schedule 1 license to investigate the pharmacology of new cannabinoids can be an impediment to research. That said, regulated adult-use and medical cannabis systems protect the legal consumption of cannabinoids derived from cannabis enabling research without the necessity of a DEA Schedule 1 license to acquire materials. For example, delta-8 THCA has been found on cannabis and Delta-8 is a derivative of delta-8 THCA.[23] This is analogous to Delta-9 that is produced post-biosynthesis by decarboxylation of the natural product delta-9-THCA.

Delta-8 THCA is usually only present in very small quantities in cannabis. Producing Delta-8 requires a cultivar that produces atypically elevated amounts of Delta-8 THCA, a process that can separate Delta-8 from a mixture containing Delta-9, or a semi-synthetic conversion to create Delta-8 from Delta-9. It is currently unclear whether genetic modification techniques, such as gene deletions, can be used to increase Delta-8 concentration because its presence in cannabis may be due to non-enzymatic isomerization.

4A CRUDE PREPARATIONS AND MINORITY CONSTITUENTS

Because of the limited commercial availability of high-purity Delta-8, crude preparations of Delta-8 (often with purities of less than 50 %) are available in adult-use retail outlets and medical cannabis dispensaries. Often Delta-8 is present alongside Delta-9 and various unidentified cannabinoid analogues as depicted in the HPLC chromatogram below. These products appear to be the result of uncontrolled processing steps and often have attendant side-products and unidentified cannabinoid derivatives present.

In the cannabis world, we have come to lionize Ensemble Effects—those effects attributed to other compounds in cannabis aside from THC and CBD, such as terpenoids. The Ensemble Effect concept recognizes that single molecules may not be capable of creating the nuanced pharmacological interaction with a complex system of receptors and biochemical cascades that a multicomponent formulation can. Ensemble Effects also offer a referendum on the simplistic lock-and-key paradigm of drug action. But Ensemble Effects do not excuse unnatural impurities. Low-purity preparations of Delta-8 THC, like that depicted in the chromatogram below and purchased from an Oregon cannabis retail store, should be approached with caution. While Delta-8 has reputable safety data as cited, the same cannot be claimed for unidentified cannabinoids, analogues, and degradation products.[24]

Cannabinoid	Elution Time (min.)
THCV	2.3
CBD	2.4
CBG	2.5
CBDA	2.8
CBGA	3.2
CBN	3.4
Delta-9	3.9
Delta-8	4.1
CBC	4.7
THCA-A	5.6

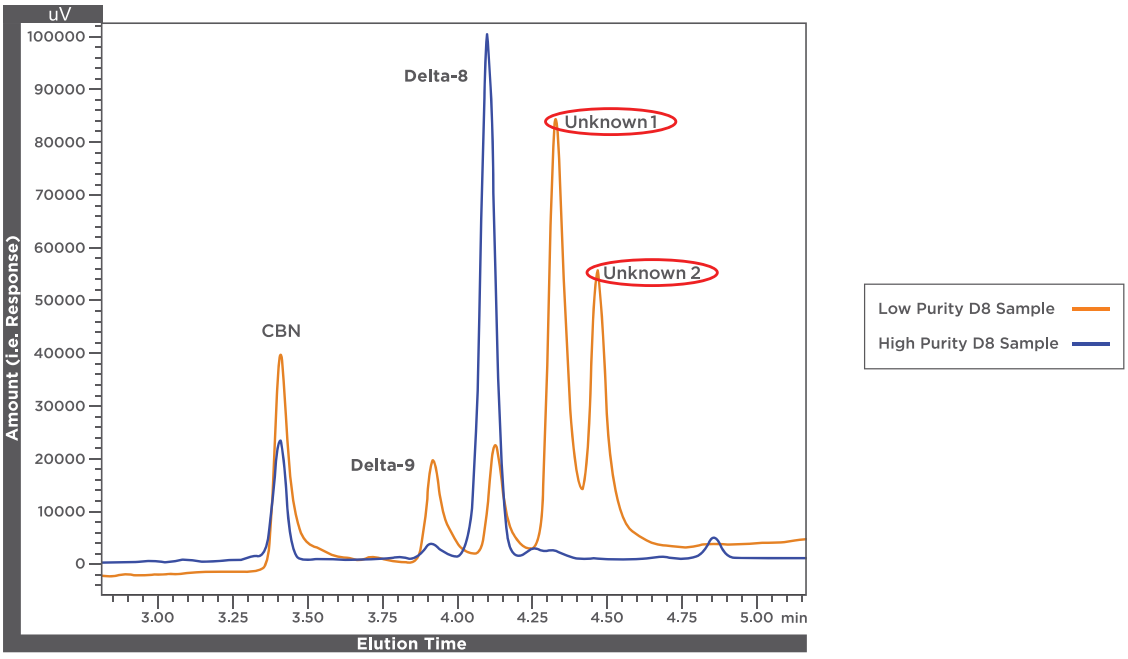


Figure 5: HPLC Chromatogram Overlay of Low Purity and High-Purity Delta-8 Samples

5 LEGAL & REGULATORY CONSIDERATIONS

Marijuana, or "marihuana," is a Schedule 1 controlled substance according to the Federal Controlled Substances Act of 1970. The definition of "marihuana" includes all compounds found in cannabis or derived from those compounds:

> *The term "marihuana" means all parts of the plant* Cannabis sativa L.*, whether growing or not; the seeds thereof; the resin extracted from any part of such plant; and every compound, manufacture, salt, derivative, mixture, or preparation of such plant, its seeds or resin.*[25]

Following suit, states have used this same or similar definitions when legislating controlled substances provisions. Interestingly, as states have begun to control and regulate the use of cannabis, the same definition has been used in reverse. For example, in Washington State, cannabis is defined in RCW 69.50.101 as:

> *(v) "Marijuana" or "marihuana" means all parts of the plant Cannabis, whether growing or not, with a THC concentration greater than 0.3 percent on a dry weight basis; the seeds thereof; the resin extracted from any part of the plant; and every compound, manufacture, salt, derivative, mixture, or preparation of the plant, its seeds or resin.*[26]

A literal reading of this law asserts that all compounds found in/on cannabis and derivatives thereof now fall under the regulatory control of Washington State's cannabis statutes and regulations, and can lawfully be sold in the state provided all other legal requirements are met. This has important implications for controlled-substance analogue and synthetic cannabinoid laws at both the federal and state level.

5A THC SERVING/PACKAGE LIMITS FOR EDIBLES

The Werc Shop monitors cannabis legal and regulatory frameworks in a number of states, including Washington, Oregon and California. In those states, "THC" and/or "THC concentration" are defined in terms of Delta-9 only.[26, 27, 28, 29, 30, 31] In some cases, Delta-9 is unambiguously identified through its Chemical Abstracts Services number (CAS #: 1972-08-3). Technically, that means that serving and package limits of THC only apply to Delta-9 and not any other compound that is not Delta-9. This is salient because our review of the information on ingesting Delta-8 alone suggests that an effective oral dose of Delta-8 may need to be 25 mg or higher.

	WA	OR	CO	CA
THC SERVING LIMITS	10 mg	5 mg (edibles), 10 mg (capsules)	10 mg	10 mg
THC PACKAGE LIMITS	100 mg	50 mg (edibles), 100 mg (capsules)	100 mg	100 mg
SINGLE SERVE WRAPPING	Yes, generally. Does not include tablets, capsules, lozenges upon approval.	No	No. Only physically "demarked" and "easily separable."	No. Only "delin-eated and scored" where applicable.
Defined in terms of Delta-9 only	Yes	Yes	No, defined in terms of "active THC"	Yes

Figure 6: State-By-State THC Serving/Package Limits for Edible Products

In states such as Washington and Colorado, THC blood concentration is used to determine allowable exposure to cannabis products while driving. These statutes explicitly regulate plasma concentrations of Delta-9, not Delta-8.[32, 33]

In addition, some sporting organizations, such as the National Football League, have chosen to define positive tests for marijuana in terms of 11-nor-9-carboxy THC, a secondary metabolite of Delta-9, instead of Delta-9. For example, documents published by the NFL Players Association report that the NFL has a limit of "Delta 9-THC-carboxylic acid (marijuana) ≥ 35 ng/mL."[34]

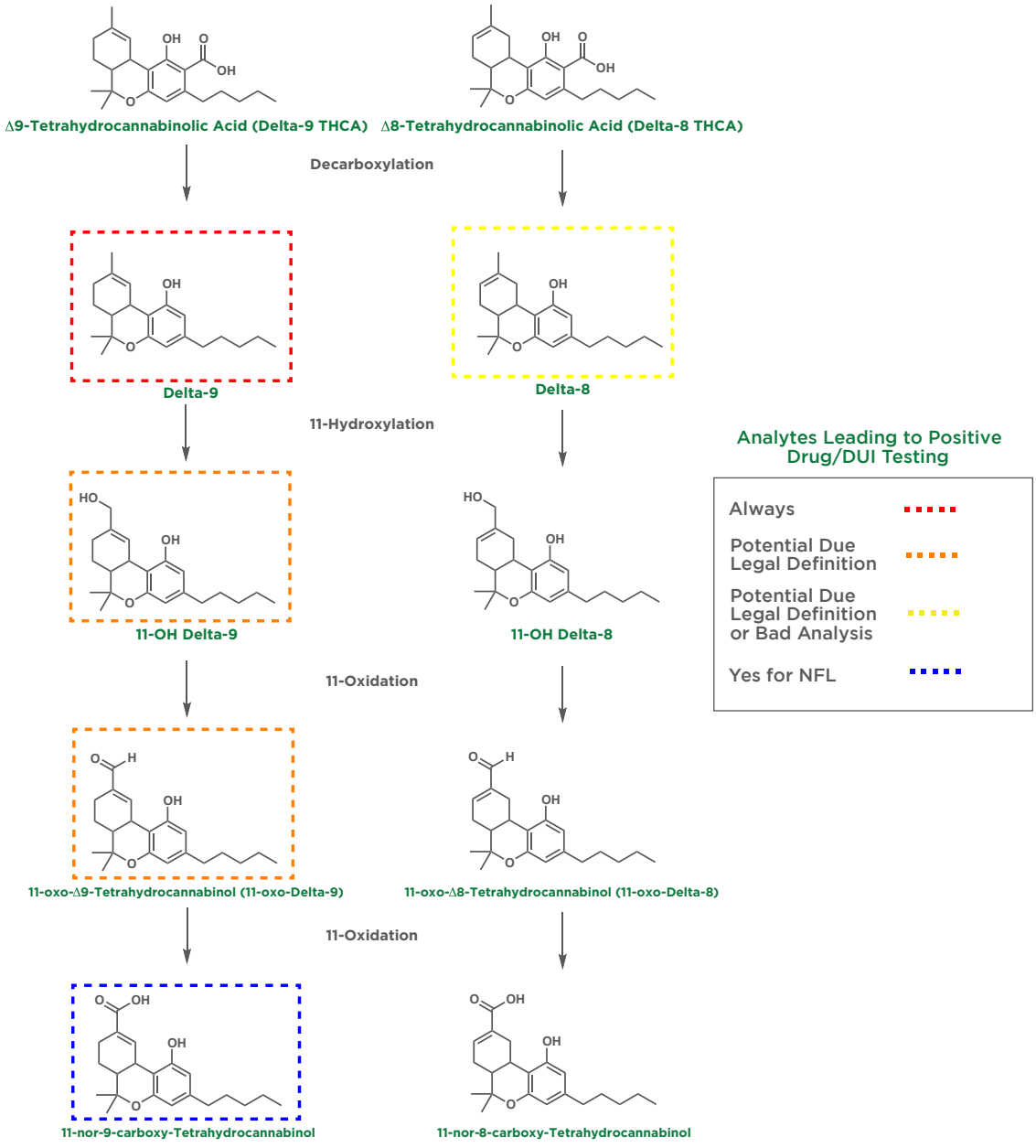


Figure 7: Delta-9, Delta-8, and Metabolic Analytes in Drug Testing

Under these testing regimes, Delta-8 and its metabolites should not cause a positive test for cannabis. Moreover, it is unclear whether metabolites of Delta-9 and Delta-9 THCA, such as 11-OH Delta-9, can legally be used as proxies for assessing Delta-9 blood levels. Strict interpretation of the legal and policy definitions suggest that usually metabolites cannot be used in this way. However, it is not clear how strictly the laws are implemented via analytical methods used by clinical testing laboratories. For example, it is unclear whether common laboratory methods used by clinical labs discriminate between Delta-8 and Delta-9 or their respective metabolites.[35]

6 PRACTICAL RECOMMENDATIONS & SUMMARY

Delta-8 possesses unique bioactivity that distinguishes its effects from the far more common Delta-9. This is promising on multiple levels. For adult users and medical cannabis patients, Delta-8 may provide cannabinoid activity that complements both cannabis plant material and Delta-9. For those interested in creating medicines and therapeutics, Delta-8 may be an example of how the widespread commercial availability of minor phytocannabinoids and their analogues will suggest medical applications not previously explored or expected. It is clear that regulators and legislators must directly confront these issues to continue effective governenance and regulation of this emerging, rapidly changing industry.

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