

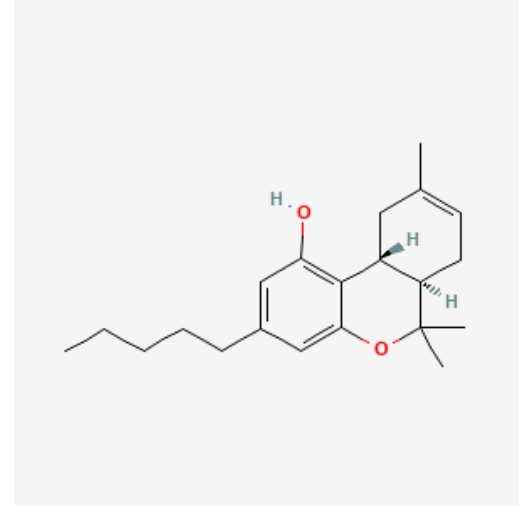


The Legal Status of Synthetic Cannabinoids

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Delta-8-Tetrahydrocannabinol

- An analogue of THC
- A psychoactive cannabinoid usually derived from, but not found in large quantities in *Cannabis sativa*
- Similar activity to Delta-9-THC, the main cannabinoid in cannabis
- Can be synthesized from non-cannabis sources, but Delta-8 is typically manufactured from hemp-derived CBD



Historical Background Surrounding the Legality of Delta-8

- 2018 Farm Bill amends the Controlled Substances Act to remove “tetrahydrocannabinols in hemp” from control.
- Hemp is defined as “the plant cannabis sativa L. and any part of that plant, including the seeds thereof and including the seeds thereof and 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.”
 - 7 USC § 1639o(1)
- DEA enforces the Controlled Substances Act and has responded to inquiries about Delta-8.
 - DEA September 2021 letter to the Alabama Board of Pharmacy
 - Delta-8 synthetically produced from non-cannabis materials is a controlled substance under the CSA.
 - Cannabinoids extracted from the cannabis plant that meet the definition of hemp are not controlled under the CSA.

FDA Jurisdiction

- 2018 Farm Bill preserved FDA's authority over hemp products.
- Where a Delta-8 product meets the “hemp” criteria, FDA jurisdiction will depend on the type of product.
 - Gummies or other edibles, as a food or dietary supplement
 - Pure oil
 - Vapes
- CBD may be a similar comparison as to how FDA may regulate.

Drug Preclusion

- Products that are the active ingredient in a drug product or are a drug for which substantial clinical investigations have been instituted and for which the existence of such investigations has been made public are excluded from the dietary supplement definition and cannot be added to food.
 - Dietary supplements: section 201(ff)(3)(B) of the FD&C Act
 - Foods: section 301(ll) of the FD&C Act
- Prevents THC or CBD products from being regulated by FDA as dietary supplements or foods.
- FDA notes that “ingredients derived from cannabis that do not contain CBD or THC might be able to be used in foods and dietary supplements if all other FD&C requirements are met.”

Regulation as a Dietary Supplement

- A potential Delta-8 product regulated as a dietary supplement would need to notify FDA about a new dietary ingredient.
 - Section 413(d) of the FD&C Act
- The new dietary ingredient notification (NDIN) process identifies:
 - Dietary supplement category
 - Manufacturing process
 - Physical properties, chemical/molecular structure
 - Critical identity and safety attributes of the NDI
- CBD has not found success in the NDIN process
 - FDA has been concerned with safety of CBD, also views CBD as not a dietary supplement
 - Industry disagrees with FDA's assessment

Regulation as a Food or Supplement Additive

- To be acceptable as a food additive, Delta-8 products would need to satisfy the generally recognized as safe (GRAS) standard. For dietary supplements, under the standard for New Dietary Ingredient Notifications, a supplement must be reasonably be expected to be safe.
- In practice, FDA worries more about food additives than new dietary supplements.

FDA Enforcement on CBD

- Warning letters on disease cure claims
- Cite other violations
- No other enforcement

FDA NEWS RELEASE

FDA Warns Companies Illegally Selling CBD Products

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For Immediate Release: December 22, 2020

Today, the U.S. Food and Drug Administration issued five warning letters to companies for selling products containing cannabidiol (CBD) in ways that violate the Federal Food, Drug, and Cosmetic Act (FD&C Act). All five warning letters address the illegal marketing of unapproved CBD products claiming to treat medical conditions. The warning letters include CBD products that are especially concerning from a public health perspective due to the route of administration, including nasal, ophthalmic and inhalation. In addition, they address violations relating to the addition of CBD to food, and the impermissible marketing of CBD products as dietary supplements. Two of the letters also address CBD products illegally marketed for pets, including a product for use in the eye.

“The FDA’s first priority is to protect the health and safety of Americans. Many questions remain regarding the science, safety, effectiveness and quality of products containing CBD.” said FDA Principal Deputy

Delta-8 vs. CBD

- Unlike CBD, Delta-8 does not contain an active ingredient of an approved drug.
 - FDA does not appear to have accepted the argument that the purified isolates used in the approved CBD drug product (Epidiolex) differ from that in CBD product, but Delta-8 is a sufficiently different “article” than CBD.
 - Refer to section 201(ff)(3)(B) of the FD&C Act: dietary supplement exclusion
- To date, Delta-8-THC is listed in one clinical trial at clinicaltrials.gov.
- Would Delta-8 be considered a constituent of CBD?
 - A constituent of another dietary supplement is a dietary ingredient.
 - A constituent is an article that is part of the whole and can be isolated from the whole.
 - A synthetic copy, however, is not part of the botanical and does not qualify as a constituent, even if chemically identical.

FDA's Current Stance on Delta-8

- FDA has posted a warning page on Delta-8.

- Not evaluated by FDA
- Adverse event reports
- Psychoactive and intoxicating effects
- Harmful chemicals in the manufacturing process
- Keep out of the reach of children and pets



Summary Conclusions

- DEA indicates that cannabinoids , such as Delta-8, “extracted from the cannabis plant” are not controlled substances if they otherwise meet the definition of hemp. But Delta-8 that is “synthetically produced from non-cannabis materials” is a controlled substance.
- FDA’s jurisdiction may depend on the form of the Delta-8 product.
 - Regulation as a dietary supplement or as a food, could be possible.
 - FDA’s drug preclusion could come into play.
- FDA’s current enforcement on CBD may be an indication of how FDA will regulate.
 - Currently focused on products making disease cure claims.
- Delta-8, however, could be seen by FDA as a more serious health risk than CBD.



What is a “Synthetic” Cannabinoid?

The Regulatory Status of $\Delta 8$ -THC
and Other Hemp-Derivatives Cannabinoids

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Definitions & Regulatory Status

- Hemp: "...the plant *Cannabis sativa* L. and any part of that plant, including the seeds thereof and 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." (7 U.S.C. 1639o, **emphasis** added).
- Hemp-Derived Tetrahydrocannabinols (THC): The Agricultural Improvement Act of 2018 ("The Farm Bill") amended the CSA so that tetrahydrocannabinols derived from hemp are longer controlled under Schedule I so long as it contains a $\Delta 9$ - THC concentration of nom ore than 0.3% on a dry weight basis. (Pub. L. 115-334, § 12619)
- Isomer: one of two of more compounds, radicals or ions that contain the same number of atoms of the same element but differ in structural arrangement and properties
- Cannabidiol (CBD): A cannabinoid found in *Cannabis sativa* L

Isomers of Hemp??

“Hemp” =

- the plant (*Cannabis sativa* L)
- and any part of the plant
- derivatives
- extracts
- cannabinoids
- isomers thereof
- salts thereof
- salts of isomers thereof

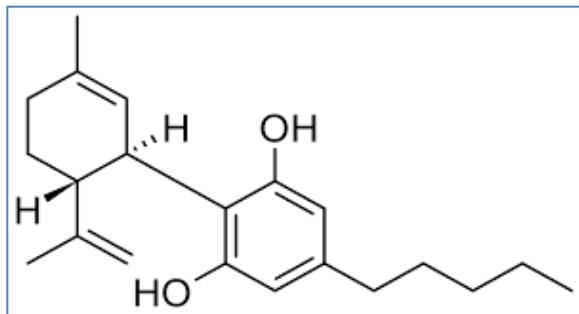
Cannabinoids =

- isomers thereof
- salts thereof
- salts of isomers thereof

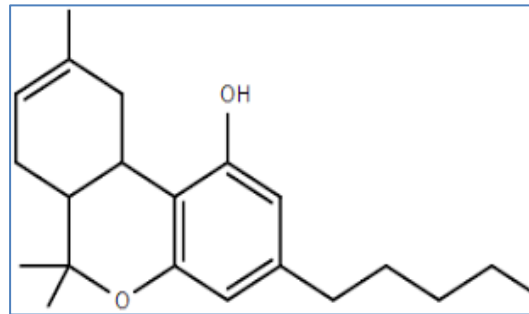
Cannabidiol (“CBD”) = -Isomer thereof
(a cannabinoid)

Isomers

Cannabidiol (CBD)



Δ 8-Tetrahydrocannabidiol (Δ 8-THC)



NOTE: Both phytocompounds contain 21 carbons (“C”), 30 hydrogens (“H”) and 2 oxygens (“O”) and are therefore **isomers**.

Synthetic Cannabinoid are Schedule I Controlled Substances

- Farm Bill: “The AIA does not impact the control status of synthetically derived tetrahydrocannabinols (for Controlled Substance Code Number 7370) because the statutory definition of “hemp” is limited to materials that are derived from the plant Cannabis sativa L. For synthetically derived tetrahydrocannabinols, the concentration of Δ^9 -THC is not a determining factor in whether the material is a controlled substance. All synthetically derived tetrahydrocannabinols remain schedule I controlled substances.” (85 CFR 51639)
- DEA Letter to Alabama Board of Pharmacy: “...only tetrahydrocannabinol in or in or derived from the cannabis plant – not synthetic tetrahydrocannabinol – is subject to being excluded from control as a “tetrahydrocannabinol” in hemp.
- Source of $\Delta 8$ -THC: While hemp naturally contains $\Delta 8$ -THC in minor quantities, most $\Delta 8$ -THC-containing products currently marketed in the U.S. use $\Delta 8$ -THC made from hemp derived CBD through a simple isomerization using acid reagents.

Is Δ^8 -THC a Synthetic Cannabinoid?

- Synthetic: “...of, relating to, or produced by chemical or biochemical synthesis especially produced artificially”.
- DEA: Has typically focused on “designer drug” synthetic cannabinoids derived from laboratory chemicals and not from hemp-derived compounds. DEA described the following compounds in its 2017 publication “*Drugs of Abuse: A DEA Resource Guide*” (2017):
 - Bath Salts or Designer Cathinones – Synthetic stimulants manufactured in East Asia
 - K2/Spice – Synthetic cannabinoids created in the laboratory and intended to mimic THC; primarily manufactured in Asia without manufacturing standards or quality control standards.

Is Δ^8 -THC a Synthetic Cannabinoid?

NDI Revised Draft Guidance (2016)

Defines “chemical alteration” of a food ingredient requiring an NDI Notification as:

- A process that **makes or breaks chemical bonds**, unless the bonds created by the process are reversed when the ingredient is dissolved in water (e.g., creation of a soluble salt) or during ingestion. Example: hydrolysis. (Emphasis added)
- Use of solvents other than water or aqueous ethanol to make an extract or tincture.

Is $\Delta 8$ -THC a Synthetic Cannabinoid?

9th Circuit Court of Appeals

*“True, that term [synthetic cannabinoids] is not used in everyday conversation, but that does not render the condition unconstitutionally vague. The first part — the modifier “synthetic” — has a readily discernible meaning. It refers to **man-made (as opposed to naturally occurring) chemical compounds**, a concept familiar enough from the distinction between, say, **synthetic fibers like polyester** and **natural fibers like cotton**....The court then clarified the definition of “synthetic cannabinoid” by providing specific examples of what the term is intended to cover: “**synthetic marijuana**,” “**K2**,” and “**Spice**.”*

(U.S v Sims, 849 F. 3d 1295; Court of Appeals, 9th Circuit, 2017)

Is $\Delta 8$ -THC a Synthetic Cannabinoid?

QUESTION

Is $\Delta 8$ -THC more POLYESTER or COTTON?

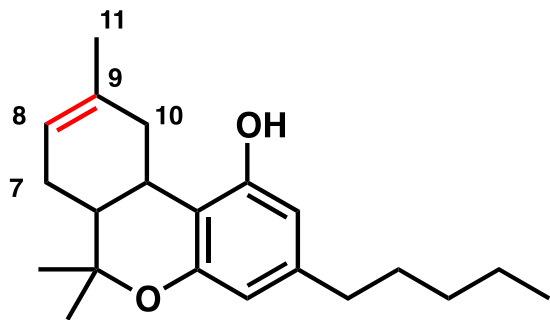
The Hazy Legal Status of Synthetic Cannabinoids

Brad Douglass, Ph.D.

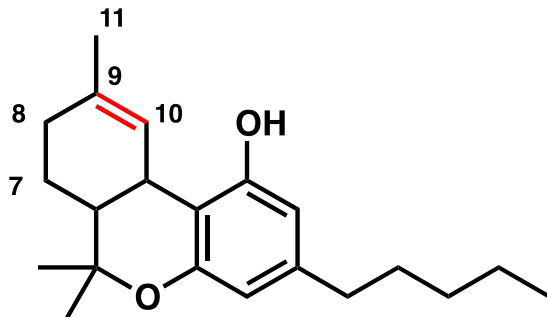
December 2nd 2021

WHAT ARE DELTA-8 THC and DELTA-10 THC?

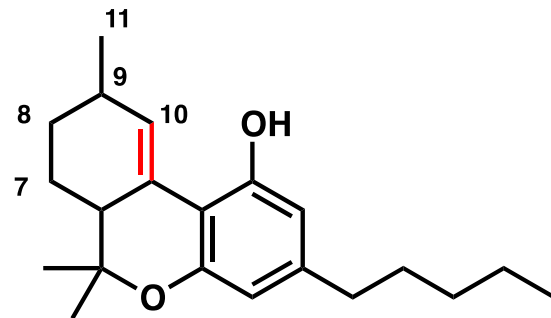
Answer: Constitutional isomers of delta-9 THC



$\Delta 8$ -Tetrahydrocannabinol (Delta-9 THC)



$\Delta 9$ -Tetrahydrocannabinol (Delta-9 THC)

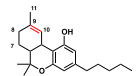


$\Delta 10$ -Tetrahydrocannabinol (Delta-10 THC)

WHAT IS AN ISOMER?

Answer: Compounds possessing the same molecular formula

“Isomer” Definition

Any chemical compound that has the same molecular formula (e.g. $C_{21}H_{30}O_2$) as another chemical compound but a different chemical structure (e.g. ). Isomers can exhibit different physical, chemical and biological activities.

WHAT IS DELTA-8 THC?

Answer: A psychotropic cannabinoid with medicinal properties

- Marketed as “THC Lite”
 - Roughly 40% of the potency of Delta-9 THC from user reports
 - Not a 1-to-1 replacement for Delta-9 THC
- Binds Cannabinoid Receptors *similar to but not the same as* Delta-9 THC
 - CB1 Receptor: Delta-9 has 4X Greater Affinity than **Delta-8** THC
 - CB2 Receptor: **Delta-8** has 4X Greater Affinity than Delta-9 THC
- Clinically-Studied For Reducing Nausea in Juvenile Cancer Patients
- Thermodynamically More Stable Than Delta-9 THC

WHAT IS DELTA-10 THC?

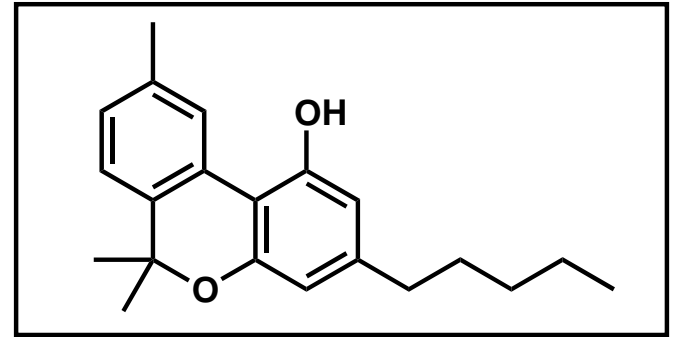
Answer: A psychotropic cannabinoid with mostly unknown properties

- Marketed as the Next Hemp Cannabinoid (Post-D8)
 - Reported to have less psychotropic potency than Delta-8 THC
 - Not found in chemically pure form in commerce
- Unclear How It Binds Cannabinoid Receptors
 - CB1 Receptor: ?
 - CB2 Receptor: ?
- No Published Clinical Data
- Thermodynamically Less Stable Than Delta-9 THC and Delta-8 THC

WHAT IS CANNABINOL (CBN)?

Answer: A cannabinoid found naturally-occurring on *Cannabis sativa* L.

- Oxidative Degradation Product of Delta-9 THC
 - Not produced by *Cannabis sativa* L.
- Not an Isomer of THC
 - Similar chemical backbone
 - Not a human metabolite either
- Binds Cannabinoid Receptors...
 - CB1 Receptor: K_i (nm) > 200
 - CB2 Receptor: K_i (nm) > 100
- Often a Byproduct of Remediating “Hot” Hemp
 - See “T-free” full-spectrum hemp extract



Cannabinol (CBN)

WHAT ARE STATES DOING?

Answer: Experiencing challenges with chemistry & complexity

- Trying to understand the intended meaning of “hemp-derived” and “cannabis-derived”
- Grappling with “chemical alteration” and potential impact on product hazards
- Deciding if and under what conditions to permit “synthetically-derived” constituents and to future-proof
- Contemplating policy and regulatory bright-lines between “impairing” and non-impairing [cannabinoids]

HOW ARE STATES DEFINING “IMPAIRING”?

Answer: Considering addressing structurally AND functionally

The Duck Strategy

If something...

Looks like a duck

-AND-

Quacks like a duck

...it must be a duck



HOW ARE STATES DEFINING “IMPAIRING”?

Answer: Considering addressing structurally AND functionally

The Duck Strategy

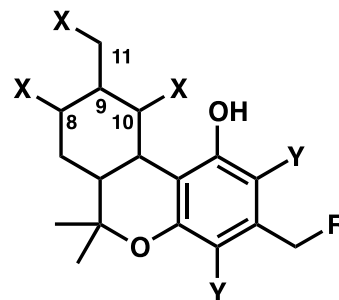
1) Has the structural backbone shown here (to the right)

-AND-

2) Possesses significant CB1 agonist activity as demonstrable by binding affinity (K_i) to CB1 receptors at less than 200 nM.

-AND-

3) Results in positive effects for all four components of the Tetrad Test in rodents OR reliably causes functional impairment in humans as assayed by a method possessing scientific consensus.



X = H, O
Y = H, COOR
R = H, alkyl

WHAT DOES “CHEMICALLY-ALTERED” MEAN?

Answer: Depends on context and who you ask

One “Chemically Altered” Definition

Does not include the following physical modifications: minor loss of volatile components, dehydration, lyophilization, milling, tincture or solution in water, slurry, a powder, or solid in suspension.*

-Congressional Statement of Agreement, 1994

*FDA states that this is not necessarily a complete list (NDI Draft Guidance, p. 26)



The Hazy Legal Status of Synthetic Cannabinoids

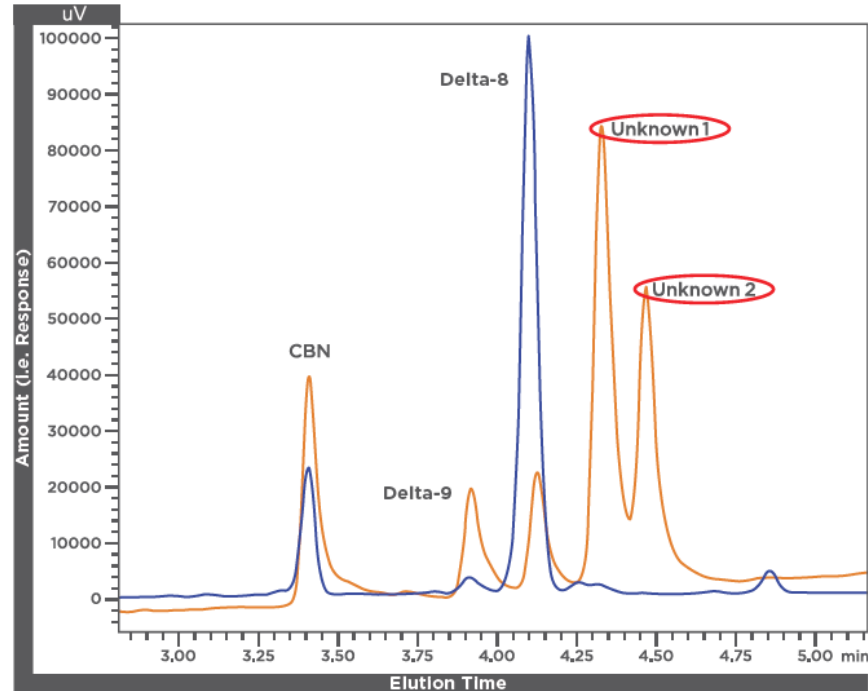
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December 2nd, 2021

WHAT IS DELTA-8 THC?

Answer: An ingredient that requires quality control testing

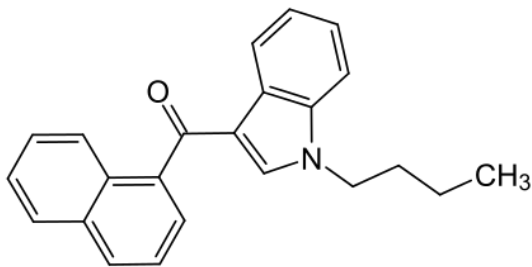
Cannabinoid	Elution Time (min.)
THCV	2.3
CBD	2.4
CBG	2.5
CBDA	2.8
CBGA	3.2
CBN	3.4
Delta-9	3.9
Delta-8	4.1
CBC	4.7
THCA-A	5.6



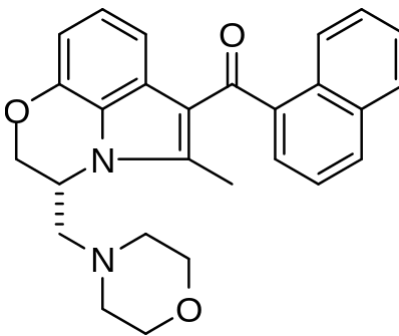
HPLC Chromatogram Overlay of Low Purity and High-Purity Delta-8 Samples

WHAT DELTA-8 THC IS NOT?

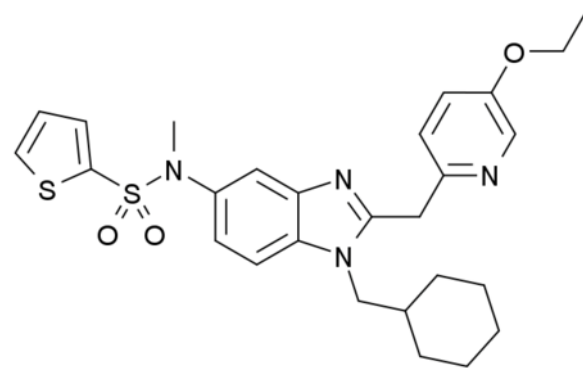
Answer: Not an artificial cannabinoid



JWH-073



WIN 55,212-2



AZ-11713908

These are examples of artificial, non-phytocannabinoids