ASTM INTERNATIONAL
Helping our world work better

White Paper

Delta-8-Tetrahydrocannabinol and the Need to Develop Standards to Protect Safety of Consumers

Introduction

The rapid rise of products, typically marketed as hemp-based products containing delta-8-tetrahydrocannabinol (Δ^8-THC, pronounced "delta-8-THC") has raised significant concerns surrounding the impacts on public health and safety of these unregulated products. Because Δ^8-THC typically occurs at very low to insignificant levels in nature in the cannabis flower, it is currently not economically feasible to extract natural Δ^8-THC. Thus, products containing Δ^8-THC are synthetically derived and thus the crux of the issue. Some estimate the synthetic cannabinoid market to be $10 billion by 2025[1], amplifying the need for standardization and regulation of not just Δ^8-THC, but synthetic cannabinoids in general and the control of the processes before allowing unabated public consumption.

The issue is multi-faceted:

- Products containing Δ^8-THC are being marketed and sold as safe and legal hemp-based products to consumers and lack any formal or informal oversight by public health agencies.
- Unlike hemp-based products, containing CBD, a non-psychoactive cannabinoid, Δ^8-THC is moderately psychoactive.
- There is uncertainty regarding the legality of these products based on the language in the Agricultural Improvement Act of 2018, the Controlled Substances Act, the US Drug Enforcement Agency (DEA) Analogues Act, and others.
- The process to derive Δ^8-THC for addition into products begins with cannabidiol (CBD) and is a synthetic process utilizing harsh and toxic chemicals that are not safe for human consumption
- The process not only creates Δ^8-THC but also other cannabinoids including delta-9- tetrahydrocannabinol (Δ^9-THC) as well as many impurities that are not well characterized.

Why Did the Δ^8-THC Marketplace Develop So Rapidly?

Products containing can be found in gas stations, convenience stores, and even some cannabis dispensaries throughout the United States and beyond. They are in gummies, vaporizer cartridges, tinctures, and more. Its rise is largely attributed to the oversupply of CBD shortly after the passage of the Agricultural Improvement Act of 2018 (commonly known as the Farm Bill). The Farm Bill defined the term "hemp" as "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-tetrahydrocannabinoid (Δ^9-THC) concentration of not more than 0.3% on a dry weight basis". Additionally, it removed hemp from the definition of marihuana from the Controlled Substances Act, resulting in "hemp" no longer being a Schedule I controlled substance.

The following year, 2019, saw a four-fold increase in the amount of hemp acreage licensed for growing, resulting in a flood of biomass for the creation of hemp-based products, including commonly found CBD products that are marketed and sold as wellness products for human consumption. Not surprisingly, prices of both the biomass (hemp flower) and bulk CBD oil fell over 80% during 2019[2] causing a flurry of bankruptcy filings and pushing struggling producers to seek to innovate and discover alternative products that could be profitable. The synthesis of Δ^8-THC from CBD extracted from hemp biomass quickly became a key part of that solution.

1. https://www.businessinsider.com/biotechs-racing-to-capture-115-billion-market-for-synthetic-cannabis-2021-7#
2. https://www.politico.com/news/2020/05/25/hemp-farmers-275046

A Void in Oversight Grows

While the Farm Bill created a legal framework for hemp as defined within, a void was created in oversight of final products – particularly those destined for human consumption. Oversight of cannabis products (including hemp) has been largely left to the States.

Legal clarity remains controversial, and, likely, the issue will not be resolved anytime soon at a federal level. Given this conundrum, there is no shortage of opinions from legal experts, trade organizations, and state agencies to steer the industry in a manner that protects businesses and influences the creation of critical safeguards needed to protect consumers.

This is demonstrated by the number of state agencies that have already enacted regulations or issued guidelines related to Δ^8-THC over the last several months. For example:

- Colorado's Department of Public Health and Environment (CDPHE) announced a ban on May 14th, 2021 on delta-8 THC as well as "any process that converts an industrial hemp cannabinoid ... into Δ^9-THC, Δ^8-THC, Δ^{10}-THC, or other tetrahydrocannabinol isomers or functional analogues"
- Kentucky's Department of Agriculture released a letter in April stating that Δ^8-THC is illegal under both federal and Kentucky law.
- Michigan's Governor signed legislation that places Δ^8-THC and all cannabis-derived products under the oversight of the Michigan Marijuana Regulatory Agency effective October 2021[3].
- New York's Department of Health updated its regulations[4] to ban Δ^8-THC and similar isomers.
- Oregon passed House Bill 3000[5] in July of 2021 which was signed by Governor Brown enabled the Oregon Liquor Control Commission, the agency regulating the state cannabis market to establish and enforce limits for Δ^8-THC and other analogous compounds.

What Is Δ^8-THC and How Is It Made?

Δ^8-THC is an isomer of Δ^9-THC, the most common cannabinoid that produces psychoactive effects and remains listed as a Schedule I drug on the United States Controlled Substance Act as well as being controlled by the United Nation's Single Convention on Narcotic Drugs (SCND)[6]. The only difference between Δ^8-THC and Δ^9-THC from a physical perspective is the location of the double bond between two carbons **(Table 1)**. Δ^8-THC is also a moderately psychoactive cannabinoid, producing similar but milder effects than Δ^9-THC.

A common method to convert CBD to delta-8-THC was patented in 2001[7] and utilizes solvents such as toluene sulphonic acid as a catalyst. The result is an impure oil that needs further clean-up to minimize the byproducts to an acceptable level – a level at which there is scant or no evidence.

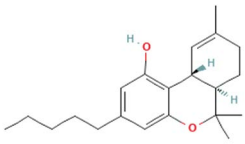
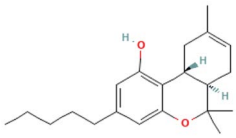
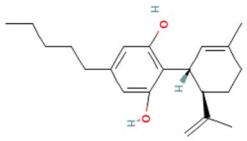
	Cannabinoid		
	CAS# 1972-08-3[8]	**CAS# 5957-75-5[9]**	**CAS# 13956-29-1[10]**
Select Properties	Δ^9-THC	Δ^8-THC	CBD
Intoxicating	Yes	Yes, moderately	No
Naturally produced by cannabis plant	Yes	Trace[11]	Yes
Chemical formula	$C_{21}H_{30}O_2$	$C_{21}H_{30}O_2$	$C_{21}H_{30}O_2$
Molecular weight (g/mol)	314.5	314.5	314.5
2-D Structure			

Table 1: Comparison of the properties of commonly known cannabinoids discussed within, summarized from the National Library of Medicine. Note the visual similarity between Δ^9-THC and Δ8-THC (2-D structure) with the location of the double bond on the top right being the only difference, while CBD, which Δ8-THC is synthesized from, has a more markedly different structure, despite identical chemical formula and weight.

3. https://www.michigan.gov/mra/0,9306,7-386-90056-563487--,00.html
4. https://regs.health.ny.gov/sites/default/files/proposed-regulations/Cannabinoid%20Hemp_0.pdf
5. https://olis.oregonlegislature.gov/liz/2021R1/Measures/Overview/HB3000
6. https://www.unodc.org/unodc/en/treaties/single-convention.html?ref=menuside
7. US Patent Pub US 2004/0143126 A1

Analytical testing laboratories that routinely analyze products containing CBD and Δ^8-THC for producers are in broad agreement that products labeled as containing Δ^8-THC are far from legitimate and pure. Many report Δ^9-THC levels above the federal limit of 0.3% in addition to unidentified peaks in the chromatogram that reiterate the lack of purity in the process[12]. This highlights an additional unintended consequence that regulatory agencies will need to grapple with – are we prepared for the next set of synthetically produced cannabinoids that may take the marketplace by storm such as Δ^{10}-THC (CAS Number 95588-87-7) and THC-O-acetate (CAS Number 23132-17-4)?

The Problem Lies Deeper – The Wave of Synthetic Cannabinoids

Δ^8-THC is one of many isomers that can be created in a laboratory thanks to the principles of synthetic chemistry. It is becoming easier to find marketed products with other synthetic cannabinoids on the internet and even in storefront, such as Δ^{10}-THC and THC-O-Acetate. These cannabinoids are also intoxicating inducing psychotropic effects on humans, with THC-O-Acetate reportedly having stronger psychotropic effects than even Δ^9-THC. **Simply banning delta-8-THC does nothing to address the next wave of synthetic cannabinoids.** We have seen this before, with the rise of K2 and Spice, a mixture of synthetically created cannabinoids that have varying levels of psychotropic effects. Sold through illicit channels, adverse events from consumption of K2 products flooded emergency rooms in 2018, leading to over 300 suspected deaths in just 2 weeks.[13]

Simply banning delta-8-THC does nothing to address the next wave of synthetic cannabinoids.

To date, the cannabis and hemp marketplace and regulations have largely been focused on products containing CBD and Δ^9-THC, as it is these two cannabinoids, technically in their acidic forms, that naturally occur in the largest concentrations in the flowers of the cannabis plant (e.g. Sarma et al., 2020[14]). But, as the market continues to evolve and businesses are challenged to find new ways to differentiate their products, the safety concerns surrounding delta-8 are an indicator of what is to come.

The consequences are numerous:

1. The ability to purchase products like Δ^8-THC at brick and mortar establishments such as convenience stores and gas stations result in a false public perception that the products are safe.
2. From marketing and consumer-facing perspectives – Δ^8-THC is being hyped as a safe and legal alternative to Δ^9-THC. This is a fine line, as much of the marketing tactics also promote Δ^8-THC as a hemp-derived product, aligning it with the CBD and wellness camp. This could not be further from the truth.
3. The chemical similarity of these products (Table 1) and the process in which they degrade in our bodies can result in failed drug tests that look for metabolites of Δ^9-THC. Unknowing consumers can jeopardize their careers, child custody battles, and other scenarios where drug tests may be required, all because they purchased a product advertised as safe and available at nationally recognized retail stores. Even CBD products that claim to be safe and "free of THC" have been linked to failed drug tests with significant legal consequences [15].
4. Direct and almost immediate human health is at risk every day that products continue to be available in an unregulated marketplace. There are existing reports from poison control centers showing hospitalizations that have been directly linked to consuming Δ^8-THC products as well as reports of amateur producers obtaining battery acid and pool chemicals to create these products [16].

In the eyes of the US Drug Enforcement Agency (DEA) as stated in their late 2020 Interim Final Rule, "all synthetically derived tetrahydrocannabinols remain schedule I controlled substances."[17] While the definition of synthetic is not clearly defined, there are approximately 20 years of precedent from the DEA on this matter including references within the DEA's "Orange Book"[18]. Further discussion on the legality of this matter is outside the scope of this article.

8. https://pubchem.ncbi.nlm.nih.gov/compound/16078
9. https://pubchem.ncbi.nlm.nih.gov/compound/638026
10. https://pubchem.ncbi.nlm.nih.gov/compound/644019
11. E.g. Hollister, Leo E., Gillespie, H. K., (1973), Delta-8- and delta-9-tetrahydrocannabinol; Comparison in man by oral and intravenous administration, Clinical Pharmacology & Therapeutics, 14, doi: 10.1002/cpt1973143353
12. https://cen.acs.org/biological-chemistry/natural-products/Delta-8-THC-craze-concerns-chemists/99/i31
13. https://www.npr.org/2018/07/27/632261920/d-c-has-had-more-than-300-suspected-k2-overdoses-in-2-weeks
14. Sarma, N. D.; Waye, A.; ElSohly, M. A.; Brown, P. N.; Elzinga, S.; Johnson, H. E.; Marles, R. J.; Melanson, J. E.; Russo, E.; Deyton, L.; Hudalla, C.; Vrdoljak, G. A.; Wurzer, J. H.; Khan, I. A.; Kim, N.-C.; Giancaspro, G. I. Cannabis Inflorescence for Medical Purposes: USP Considerations for Quality Attributes. J. Nat. Prod. 2020, acs.jnatprod.9b01200. https://doi.org/10.1021/acs.jnatprod.9b01200.
15. https://www.nytimes.com/2019/10/15/science/cbd-thc-cannabis-cannabidiol.html
16. https://www.bloomberg.com/news/articles/2021-06-02/a-pot-knockoff-sometimes-made-with-household-acid-draws-scrutiny
17. https://www.federalregister.gov/documents/2020/08/21/2020-17356/implementation-of-the-agriculture-improvement-act-of-2018
18. https://www.deadiversion.usdoj.gov/schedules/orangebook/orangebook.pdf

AN IMPURE PROCESS AMPLIFIES THE RISK TO PUBLIC HEALTH

Unlike the extraction and isolation of CBD and Δ^9-THC from the cannabis plant, the process required to derive Δ^8-THC involves significantly more advanced chemistry. Nearly anyone with access to the internet can find videos online showing how to synthesize Δ^8-THC using acetic acid available in your kitchen, alluding to a simple process that is ridden with unintended consequences. There must be an understanding and characterization of the composition and purity of the outputs of this process, as Δ^8-THC is just one of many compounds found during analytical testing. The lack of controls on these processes, including taking appropriate safety precautions and consistency and quality of raw materials (such as the purity of the toxic reagents used in the process), with proper oversight from trained synthetic chemists amplifies the risk to the end consumer. The level of complexity is more akin to the creation of pharmaceutical active pharmaceutical ingredients (or APIs) which for good reason, requires appropriate characterization of toxicological and safety risks, and extensive data collection during the development of the process to sufficiently validate. This includes the adherence to federally and internationally recognized Good Manufacturing Practices (or GMPs) of which very few if any producers in the marketplace have demonstrated their ability to conform to.

The evidence is irrefutable from testing labs across the nation – the majority of products marketed as containing Δ^8-THC have quantities of Δ^8-THC that not only do not meet what is claimed on their labels but also contain many unidentified compounds as well as Δ^9-THC in quantities above 0.3%. We are currently using consumers as lab rats to test out these novel products with varying levels of unidentified and unsafe contaminants.

DOCUMENTED ADVERSE EVENTS HIGHLIGHT THE NEED FOR A SCIENTIFIC AND DATA-DRIVEN APPROACH

There needs to be a scientific and data-driven approach to the policies surrounding the regulation of cannabinoids, especially ones synthetically derived. As well as regulation, a systematic reporting process of adverse events would be beneficial. There have been several Δ^8-THC poisoning case reports reported across the nation resulting in Δ^8-THC regulation in some states. At a recent cannabis conference, researchers presented data using the FDA adverse event reporting system (FAERS) which showed a total of 748 cases as of December 31, 2020, where a cannabis-derived product was listed as the suspect agent responsible for the adverse effect. The case distribution was as follows: cannabis sativa (N=580), Δ^8-THC (N=135), and Δ^9-THC (N=33). Respiratory events were the most commonly reported adverse event in cases listing Δ^8-THC as the suspect drug. Toxicity to various agents was the most common event for both Δ^9-THC and cannabis sativa. There was a doubling of respiratory events when Δ^8-THC cases were compared to cannabis sativa. The FAERS data is known to have an underreporting of adverse events associated with a product, thus the gravity of the problem is unknown but likely to be significantly more than the data present.

Can we learn from history? We have an opportunity to learn from the past 200 years and follow established best practices to prevent the next public health crisis.

A scientific and data-driven approach needs to include consideration of the route of administration, intended use, and the processes and ingredients used to create the final product. Failure to take a holistic approach to address synthetically derived cannabinoids creates near certainty of the next massive public health crisis.

Can we learn from history? It was the lack of control and consistency in creating and dispensing of botanical drugs that catalyzed the formation of the United States Pharmacopeia in 1820[19]. Today, the nonprofit United States Pharmacopeia is recognized and referenced globally by health agencies as the trusted source of public quality standards for medicines, food ingredients, dietary supplement products, and ingredients.

Less than a century later, public outcry following Upton Sinclair's *The Jungle* prompted Congress to enact the Pure Food and Drug Act[20] which would prevent "the manufacture, sale, or transportation of adulterated or misbranded or poisonous or deleterious foods, drugs or medicines, or liquors". **We have an opportunity to learn from the past 200 years and follow established best practices to prevent the next public health crisis.**

Solving a Complex Problem

Producers, retailers, and regulators alike are all grappling with how to best navigate this murky area of Δ^8-THC and synthetic cannabinoids. We must first understand the true root cause and extent of the problem – the process of changing a naturally derived product from its originally intended purpose and the risks associated with the new final product. By understanding the scientifically established risks and considering a risk-based approach to both regulating and producing chemically synthesized products from the cannabis plant, our decisions will be informed through a science-based approach to protecting consumers, businesses, and others in the supply chain from the farmers to retailers.

19. https://www.herbalgram.org/resources/herbalgram/issues/126/table-of-contents/hg126-feat-usp/
20. https://history.house.gov/Historical-Highlights/1901-1950/Pure-Food-and-Drug-Act/

I AM A RETAILER THAT CARRIES AND IS CONSIDERING CARRYING CBD AND OTHER HEMP-DERIVED PRODUCTS ON MY SHELVES

As a retailer, you are the last line of defense in preventing consumers from consuming products that may be dangerous for their health. What you choose to carry or not carry on your shelves, how you promote such products both directly and indirectly shapes consumer buying behavior. Despite the US Food and Drug Administration (FDA) stance on CBD products not being approved for use as an ingredient in any food or dietary supplement many retailers – both small independently owned and big box stores have chosen to carry products containing CBD. Even many CBD products on retailers' shelves have been found to not contain the quantities of CBD that their labels claim, with more than half of Δ^8-THC products in one study containing sufficient quantities of the psychoactive Δ^9-THC compound[21], placing consumers at risk. Unlike CBD, delta-8-THC and related isomers have psychotropic effects similar to Δ^9-THC. Carrying those products on store shelves increases the risk of underage consumption

To date, the majority of Δ^8-THC products are sold online and in smaller stores – such as gas stations and convenience stores. As with any business decision, it is critical to review your legal obligations and perform adequate due diligence before carrying new products. Requesting Certificates of Analysis and proof of third-party certification to a food or similar quality system (including Good Manufacturing Practices) are best practices in assessing whether to carry a particular product line. Ultimately, extreme caution should be observed.

I AM A PRODUCER OR MANUFACTURER. SHOULD I CONSIDER ADDING Δ^8-THC TO MY PRODUCTION LINE? WHAT IS THE RISK?

There are many operations in the business of extracting hemp biomass and formulating products with CBD and other cannabinoids to meet the growing market demand, despite the US FDA's firm stance through warning letters[22] that any product containing CBD is considered adulterated and not fit for human consumption. The FDA has also made clear that delta-8-THC presents serious health risks. The concerns and actions taken by multiple state agencies, the FDA, and industry groups as summarized within this report should concern manufacturers that are committed to producing safe products and protecting their consumers.[23] Considering that 15 + states have banned Δ^8-THC in not as many months' time should not be taken lightly in assessing the viability of your business model.

Where Does the Industry Currently Stand On Δ^8-THC?

The ball is already in motion within many industry groups and states having taken strong stances.

- Over 15 states have banned delta-8-THC.
- trade organizations have also weighed in with The US Hemp Roundtable being the first group to take a firm stance against delta-8-THC[24] in the marketplace[25].
- the American Herbal Products Association (AHPA) approved a guidance policy[26] discouraging the marketing of goods containing synthesized cannabinoids – including Δ^8-THC. Meanwhile, groups such as the Hemp Industries Association has publicly supported Δ^8-THC as a legal product[27].

Conclusion

Δ^8-THC is a psychotropic cannabinoid that is being synthetically created through the conversion of hemp-derived CBD found in legal hemp and added to a myriad of products that are sold for human consumption across the nation and the world, with virtually zero regulatory oversight. The rapid increase in popularity is generally attributed to the crash of CBD prices shortly after the passage of the Agricultural Improvement Act of 2018 pushing CBD extractors and formulators to seek innovative and profitable ways to produce hemp-derived products for the consumer. Δ^8-THC is just one of many synthetically derived cannabinoids of concern, which, if not addressed by stakeholders from a holistic product safety and risk profile, will just be one of many compounds that businesses will create and market – forcing a continued cat and mouse game between businesses and regulators. Common sense solutions exist in already established frameworks to proactively address how to ensure products are evaluated and regulated to keep consumers safe without adversely impacting businesses and the global supply chain.

Industry stakeholders need to come together – and platforms such as ASTM International, with over 120 years of providing a framework for the development of consensus standards – are ripe to address this issue in a proactive manner. Failure to do so exposes significant unintended consequences – both to consumers, industry, health care, and limited government resources.

21. https://www.leafreport.com/education/delta-8-thc-products-market-report-11339
22. https://www.fda.gov/news-events/public-health-focus/warning-letters-and-test-results-cannabidiol-related-products
23. https://www.fda.gov/consumers/consumer-updates/5-things-know-about-delta-8-tetrahydrocannabinol-delta-8-thc
24. https://hempsupporter.com/news/u-s-hemp-authority-announces-it-will-not-certify-hemp-products-that-are-marketed-for-intoxication
25. https://hempsupporter.com/news/delta-8
26. https://www.ahpa.org/Portals/0/PDFs/Policies/Guidance-Policies/2021_AHPAGuidance_policy_for_cannabinoids_Final.pdf
27. https://thehia.org/the-hia-stands-for-all-parts-of-the-hemp-plant-including-delta-8-thc/