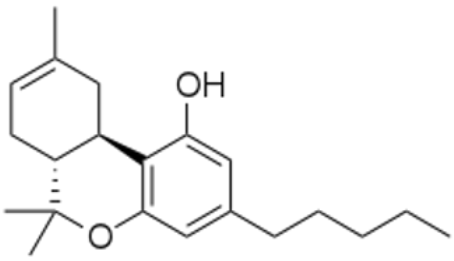
It's time to hold cannabinoid products to the highest standard:

USP Cannabis Panel statement on delta8-THC

The recent reports of products marketed as cannabis / hemp plant material being adulterated with synthetic delta-8-tetrahydrocannabinol (Δ^8-THC), an intoxicating cannabinoid, raise significant public health concerns.[1] The serious risk to public health from these products prompted the Food and Drug Administration (FDA) and the Centers for Disease Control and Prevention (CDC) to release advisories to inform consumers about the these risks and adverse event reports and concerns regarding products containing Δ^8-THC.[2,3] Depending on the method of extraction and isolation, or depending on the method of synthesis, Δ^8-THC products may contain cannabinoid contaminants or unknown impurities and synthetic cannabinoid analogs that are not naturally occurring in cannabis/hemp plants. Information on the quality attributes of cannabis/hemp materials in terms of identity, composition, and purity, and the scientific information to test for these, can help prevent patient and consumer harm resulting from exposure to substandard, contaminated, or adulterated cannabis products. In addition, systematic and properly controlled clinical investigations on Δ^8-THC, and other THC isomers, are needed to mitigate risks to public health prior to their release to the market. Availability of suitable analytical methods will help ensure high quality materials are used in such studies, resulting in the increased reproducibility and applicability of preclinical and clinical data[4].

Background:

The Agriculture Improvement Act (AIA) of 2018 (commonly known as the 2018 Farm Bill) defined the term "hemp" to mean "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% on a dry weight basis" (emphasis added). The AIA also amended the Controlled Substances Act to exclude hemp from the definition of marihuana and to remove it from Schedule I status, thereby providing for regulated cultivation of hemp as an agricultural commodity. Following the descheduling of hemp, several U.S. States provided legal pathways for hemp-derived products to enter the market in their jurisdictions, and several hemp-based products are now being marketed as dietary or food ingredients. While the AIA limits the Δ^9-THC content of hemp to be not more than (NMT) 0.3% on dry weight basis, the content of other cannabinoids or their isomers, such as Δ^8-THC, are not restricted. The limit on Δ^9-THC included in the AIA definition was established to ensure that risks to public health and public safety from this intoxicating cannabinoid were controlled. However, since Δ^8-THC is also an intoxicating substance, some members of industry are attempting to utilize a potential loophole to bring intoxicating products to the market. In order to address this perceived gap, some U.S. state regulatory bodies have created limits and/or definitions for THC that include the delta-8 isomer or otherwise have found means to limit the amount of Δ^8-THC in cannabis or hemp products.



Δ^8-THC

REFERENCES: 1. Delta-8-THC craze concerns chemists (acs.org) **2.** 5 Things to Know about Delta-8 Tetrahydrocannabinol – Delta-8 THC | FDA **3.** HAN Archive - 00451 | Health Alert Network (HAN) (cdc.gov) **4.** www.usp.org/cannabis

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The Issues:

Some products containing amounts of Δ^8-THC at levels that are unlikely to be naturally-occurring are marketed as hemp products. These products may be within the limit for the maximum amount of Δ^9-THC allowed in hemp, but they could present risks to public health due to the intoxicating effects of Δ^8-THC at high levels of exposure and potential product quality issues. Based on extensive data analysis, USP noted in a recent paper that Δ^8-THC typically occurs at very low to insignificant natural levels in the cannabis flower as a degradation by-product of Δ^9-THC Acid.[5] Products labeled as containing Δ^8-THC have a high probability of being synthetically derived, because it is not generally thought to be economically feasible to extract naturally occurring Δ^8-THC, given the low concentrations present in cannabis and hemp. A common way that Δ^8-THC is being obtained is through synthetic or semi-synthetic conversion from hemp-derived cannabidiol (CBD). This process normally involves use of strong acids and catalysts, which tend to be harsh reaction conditions conducive to the formation of other reaction by-products and impurities[6]. Depending on the reaction conditions and purification processes, synthetic Δ^8-THC may be associated with unknown impurities, different degradants, and synthetic cannabinoid analogs that are not naturally produced in cannabis/hemp plant material, and for which there may be little or no safety or toxicity data. This raises safety and product quality concerns for consumers – given the unknown and untested nature of Δ^8-THC, other synthetic analogs, and any other impurities present.

The Recommendations:

The public health issues associated with synthesized Δ^8-THC and its different isomers demand appropriate mitigation strategies, which could include the following:

1. Scientifically-valid analytical methods: Besides CBD and Δ^9- THC, the cannabis plant contains several other phytochemicals that may contribute to the bioactivity of cannabis.[7,8] Analytical methods should be able to characterize the content of minor cannabinoids such as Δ^8-THC, among others, in any cannabis that is being used to study the various biological activities of cannabis. This is particularly important, as new varieties of cannabis may contain elevated levels of these other cannabinoids or their degradation products, such as Δ^8-THC. Further, the products labeled as "Δ^8-THC" should be tested for synthetic impurities, and novel cannabinoid analogs and isomers, and the levels of these impurities should be controlled unless they have been demonstrated as safe for the conditions of use.

    - The recent USP publication and the supplementary information[9] illustrates approaches to connect the name of a substance with its quality specifications for identity, purity or composition, and limits on contaminants. The publication provides liquid chromatography (LC)- and gas chromatography (GC)-based analytical methods and relevant USP Reference Standards for determination of Δ^8-THC and its resolution from other cannabinoids, including Δ^9-THC. The publication also provides data-based acceptance criteria, and labeling recommendations to indicate the content of any cannabinoid above 1% w/w.

2. Need for systematic clinical investigations supported by quality research materials and methods: The USP publication identified the lack of systematic clinical investigation of minor cannabinoids, such as Δ^8-THC, as a research gap. The understanding of how additional cannabis constituents modulate the activity of major cannabinoids on endogenous receptors continues to be a developing area of science.[10,11] FDA's draft guidance[12] and other resources, such as USP general chapters, could be used to help ensure the quality of research materials in order to facilitate addressing the critical need for systematic clinical research on cannabis-derived compounds, including minor cannabinoids, such as Δ^8-THC. USP also provided public comments in response to the FDA draft guidance on the importance of quality in conducting clinical research related to the development of drugs containing cannabis-derived compounds.[13]

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3 Recognize emerging concerns from novel substances: The concerns related to synthetic cannabinoids are not limited to Δ^8-THC. Several synthetic modifications of cannabinoids such as Δ^{10}-THC and Δ^8-THC-O-acetate, hexahydrocannabinol (HHC), and tetrahydrocannabiphorol (Δ^9-THCP) are being introduced into the market with no safety or toxicity data, or data on metabolic fate to support their use, in both ingestible and inhalable forms, and marketed as hemp derivatives. The emerging use of minor cannabinoids and the cannabinoid analogs should be subjected to systematic preclinical and clinical investigations before they are released to the market to help ensure their safety and to characterize and identify any potential toxicities.

4 Scientifically valid analytical methods can separate Δ^8-THC from other cannabinoids and synthetic impurities, and can serve as analytical tools to regulators and industry to address growing concern regarding Δ^8-THC.[14,15] The approaches to address public health concerns from the use of minor cannabinoids and synthetically produced cannabinoids, including Δ^8-THC, should recognize that:

- Natural origin does not necessarily mean that these cannabinoids are safe at any level. While USP is not aware of safety concerns that have been reported from the use of hemp containing naturally occurring levels of Δ^8-THC, the same substance could present safety concerns at a high amount of exposure, or from prolonged periods of exposure, especially if it contains impurities from the synthesis, extraction, and/or purification process.

- Synthetically-derived cannabinoids are not inherently unsafe if they are quality-controlled and shown through systematic studies to be safe. Substances that are chemically identical will exhibit the same biological properties, irrespective of whether the source is natural or synthetic. Use of public quality standards can help in controlling the quality of synthetically derived or cannabis-derived constituents, including setting appropriate limits for impurities. USP standards could help demonstrate that the quality of two ingredients that are obtained using different processes are indeed similar in terms of their identity, strength, and limits on contaminants.

The USP publication on cannabis highlights the lack of systematic clinical investigation of minor cannabinoids, such as Δ^8-THC, as a research gap.[16] The firms that conduct clinical research should consider the FDA's draft guidance which focuses on quality considerations for clinical research using cannabis-derived compounds.[17,18] Furthermore, the USP Cannabis Expert Panel recommends additional considerations to mitigate risks to public health through suitable analytical methods to help ensure that high quality materials are used in such studies, resulting in the increased reproducibility and applicability of preclinical and clinical data.

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