FDA U.S. FOOD & DRUG ADMINISTRATION
CENTER FOR FOOD SAFETY & APPLIED NUTRITION

Memorandum

Date December 2, 2021

From [redacted] Ph.D. (HFS-255)

Through

[redacted], Ph.D. (HFS-255) _____

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Subject Regulatory status and review of available information pertaining to delta(8) tetrahydrocannabinol: a lack of general recognition of safety for its use in food.

To [redacted], Ph.D.
Office Deputy Director, OFAS, CFSAN, HFS-200 _____

Keywords: delta(8) *trans*-tetrahydrocannabinol, delta(8) tetrahydrocannabinol, delta(8) THC

The Division of Food Ingredients (DFI) was asked to review whether delta(8) *trans*-tetrahydrocannabinol (hereinafter referred to as delta(8) THC) meets the statutory criteria for general recognition of safety for any use in food. This memorandum considers the pertinent scientific information and concludes that the use of delta(8) THC in food does not meet the criteria for general recognition of safety. There is inadequate scientific data and information on the safety of its consumption, and the information that is available indicates that the use of delta(8) THC in food may be harmful to the general population.

GRAS Provision in Defining a Food Additive

As defined in section 201(s) of the Federal Food, Drug, and Cosmetic Act (FD&C Act) [21 U.S.C. § 321(s)], the term "food additive" refers to any substance the intended use of which results in it becoming a component of any food, unless the substance is the subject of a prior sanction or is generally recognized as safe (GRAS) among qualified experts under the conditions of its intended use. Furthermore, under section 201(s) of the FD&C Act, a substance is exempt from the definition of a food additive and thus, from premarket approval requirements, if its safety is generally recognized by qualified experts.

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As there is no food additive regulation or prior sanction establishing safe conditions of use for delta(8) THC as an ingredient in foods, this memorandum will consider the applicability of the GRAS criteria for the use of delta(8) THC as an ingredient in food.

GRAS Criteria

A conclusion that a particular use of a substance is GRAS under the conditions of its intended use requires both general recognition and evidence of safety. FDA has issued a guidance document to advise stakeholders on laws and regulations applicable to substances added to foods, the GRAS notification procedure, and information and other criteria relevant to a GRAS conclusion.[1]

General recognition of safety requires common knowledge, throughout the expert scientific community knowledgeable about the safety of substances added to food, that there is reasonable certainty that the substance is not harmful under the conditions of its intended use. General recognition of safety through scientific procedures must be based upon the application of generally available and accepted scientific data, information, or methods, which ordinarily are published, as well as the application of scientific principles, and may be corroborated by the application of unpublished scientific data, information, or methods. The usual mechanism to establish that scientific information is generally available is to show that the information is published in a peer-reviewed scientific journal. Mechanisms to establish the basis for concluding that there is common knowledge throughout the expert scientific community about the safety of a substance are more varied. Most often, publications in peer-reviewed scientific journals for data on a test substance have been used to establish common knowledge throughout the expert scientific community in addition to general availability. These criteria are discussed in the GRAS final rule, which took effect on October 17, 2016 (81 Federal Register (FR) 54960; August 17, 2016).

A demonstration of safety under GRAS criteria requires information establishing that the intended use of the substance is safe. FDA has defined "safe" (21 CFR 170.3(i)) as a reasonable certainty in the minds of competent scientists that the substance is not harmful under its intended conditions of use. FDA's regulations in 21 CFR Part 170 describe the eligibility criteria for classification of a substance added to food as GRAS. Under 21 CFR 170.30(a)-(c), general recognition of safety must be based on the views of experts qualified by scientific training and experience to evaluate the safety of substances directly or indirectly added to food. The basis of such views may be either through: (1) scientific procedures; or, (2) in the case of a substance used in food prior to January 1, 1958, experience based on common use in food.

FDA's regulations in 21 CFR Part 170 define "common use in food" and establish eligibility criteria for classification as GRAS through experience based on common use in food. Under 21 CFR 170.3(f), common use in food means "a substantial history of consumption of a substance for food use by a significant number of consumers."

[1] Guidance for Industry: Regulatory Framework for Substances Intended for Use in Human Food or Animal Food on the Basis of the Generally Recognized as Safe (GRAS) Provision of the Federal Food, Drug, and Cosmetic Act. FDA. November 2017. https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-industry-regulatory-framework-substances-intended-use-human-food-or-animal-food-basis.

Similarly, FDA's regulations in 21 CFR Part 170 define "scientific procedures" and establish eligibility criteria for classification as GRAS through scientific procedures. Under 21 CFR 170.3(h), scientific procedures "include the application of scientific data (including, as appropriate, data from human, animal, analytical, or other scientific studies), information, and methods, whether published or unpublished, as well as the application of scientific principles, appropriate to establish the safety of a substance under the conditions of its intended use." Under 21 CFR 170.30(b), general recognition of safety based upon scientific procedures "shall require the same quantity and quality of scientific evidence as is required to obtain approval of a food additive." Section 170.30(b) further states that general recognition of safety through scientific procedures is ordinarily based upon published studies, which may be corroborated by unpublished scientific data, information, or methods.

Overview of Delta(8) THC

Delta(8) THC (CAS#: 5957-75-5) is one of at least 105 different cannabinoids known to be produced by the plant *Cannabis sativa* (ElSohly and Gul, 2014), and is a structural isomer of delta(9) tetrahydrocannabinol (hereinafter referred to as delta(9) THC). Both delta(8) THC and delta(9) THC have comparatively similar physiological functions after oral exposure in humans (Hollister and Gillespie, 1973).

The Controlled Substances Act (CSA) of 1970 established constituents of the *Cannabis sativa* plant to be classified as "Marihuana" (commonly referred to as "marijuana") under 21 U.S.C. § 802(16). This classification refers to all parts of the *Cannabis sativa* plant, 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. "Marihuana" is listed as a Schedule I controlled substance under 21 U.S.C. § 812(c) due to its high potential for abuse. This abuse potential is primarily attributed to the delta(9) THC content in "Marihuana". The Agriculture Improvement Act of 2018 (commonly referred to as the Farm Bill) removed "hemp," a term referring to *Cannabis sativa* plants containing no more than 0.3% delta(9) THC, from Schedule I status under the CSA.

Regulatory Status of Delta(8) THC

Evidence based on common use in food prior to 1958

FDA is unaware of any evidence that delta(8) THC was intentionally added to food prior to 1958. In order to determine if delta(8) THC was used in food prior to 1958, a search was conducted in three databases– PubMed[2], Web of Science Core Collection[3], and *FDA's Scientific Terminology and Regulatory Information (STARI)*[4] database. The PubMed database has

[2] Pubmed, https://pubmed.ncbi.nlm.nih.gov/, accessed between September 13, 2021 and September 30, 2021, and on December 1, 2021.
[3] Web of Science, http://www.webofknowledge.com/, accessed between September 13, 2021 and September 30, 2021, and on December 1, 2021.
[4] The data contained within STARI dates back to the 1970s. It includes primarily chemical substances (including substances/organisms used as chemicals) and associated identifying and regulatory information, but also any

literature dating back to about 1951, and in some cases, even earlier literature is available. The Web of Science Core Collection consists of six online databases with indexing coverage from the year 1900 to the present.

All databases were searched using the search term "("delta(8) THC" or "delta(8) tetrahydrocannabinol") AND ("food" or "food ingredient")." The searches yielded no records pertaining to the intentional addition of delta(8) THC to food prior to 1958. Therefore, delta(8) THC does not meet the "common use in food" criteria and its eligibility for classification as GRAS can only be established on the basis of "scientific procedures." In other words, adequate technical evidence of safety must exist, and this technical evidence must be generally known and accepted by qualified experts to demonstrate the safety of the intended use.

Evidence based on scientific procedures (technical evidence of safety)
A search of the published literature was conducted on September 13, 2021 and continued through September 30, 2021. An updated literature search was performed December 1, 2021. The results from PubMed and Web of Science Core Collection databases are summarized in Table 1. A comparison of available publications across database queries identified 51 and 69 records unique to PubMed and Web of Science Core Collection searches, respectively, and 65 shared records.

Table 1: Summary of literature search terms and results.

Search Term	Database	Search Results (Number)
("delta(8) THC" or "delta(8) tetrahydrocannabinol") AND ("toxi*" or "oral" or "food" or "chronic" or "subchronic" or "acute")	PubMed	85
	Web of Science (Core Collection)	127
("delta8 THC" or "delta8 tetrahydrocannabinol") AND ("toxi*" or "oral" or "food" or "chronic" or "subchronic" or "acute")	PubMed	40
	Web of Science (Core Collection)	14

Twenty-six of these publications reported the use of delta(8) THC for its purported beneficial properties or pharmacological potential. Purported efficacy or health benefits from delta(8) THC are outside the purview of DFI and such effects are not considered supportive of a GRAS conclusion for use in foods.

Fifty-six of these publications pertained to delta(8) THC analogs, metabolites, or other cannabinoids; twenty-five pertained to analysis or analytical methods for delta(8) THC; sixteen discussed delta(9) THC; four discussed interconversion of cannabidiol and delta(8) THC;

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scientific term that may have been of interest to CFSAN. There are currently over 198,000 terms (preferred terms, synonyms) accessed through STARI, including over 50,000 CAS numbers, over 44,000 CERES IDs, over 17,600 UNII codes, and over 1500 Regulations (primarily 21 CFR 73-189 and 40 CFR 180-186) with over 11,000 connections to specific substances. Accessed on September 13, 2021.

eleven pertained to delta(8) THC metabolism or analysis of metabolites; twelve reported methods for synthesis of delta(8) THC or its analogs. As none of these articles were pertinent technical evidence of safety for delta(8) THC, they are not further discussed.

Ten of these publications report toxicokinetic or toxicodynamic data for delta(8) THC. Such data include cannabinoid receptor binding affinity profiles (Compton et al., 1993), distribution of delta(8) THC with phospholipids in serum (Capelle et al., 1976), activity of metabolites (Kimura et al., 1996; Yamamoto et al., 1998), effects on hemodynamic activity (Sultan et al., 2018), transfer of delta(8) THC through breast milk (Baker et al., 2018), and toxicokinetic profiles following intramuscular injection of delta(8) THC in rats (Nahas et al., 1981). Importantly, three publications have drawn conclusions suggesting delta(8) THC has similar physiological functions as delta(9) THC in humans and primates (Babalonis et al., 2021; Hollister and Gillespie, 1973; Wiley et al., 1995).

Sixteen publications identified adverse effects following delta(8) THC administration. Eight of which evaluate effects after exposure via intraperitoneal injection and report effects such as increased food intake (Avraham et al., 2004), decreased body weight (Jarbe and Henriksson, 1973), decreased pubertal growth (Gupta and Elbracht, 1983), decreased circulating androgens (Gupta and Elbracht, 1983), hypothermia (Hine et al., 1977; MacLean and Littleton, 1977), hyper-reactivity (MacLean and Littleton, 1977), sleep prolongation (Rating et al., 1972), and increased spontaneous yawning (Nakamura-Palacios et al., 2002). Hypothermia was also demonstrated in mice following acute intravenous exposure to delta(8) THC (Watanabe et al., 1980). Four publications reported effects following *in vitro* testing of delta(8) THC, including increased hepatic liver enzyme activity (Watanabe et al., 1987), cytotoxicity in neuroblastoma cells (Klegeris et al., 2003) and in macrophages (Yamaori et al., 2013), and decreased mitochondrial respiration in spermatozoa (Badawy et al., 2009). Four articles, discussed in detail below, that evaluated effects of delta(8) THC following oral exposure were considered the most relevant (Akpunonu et al., 2021; Gong et al., 1984; Hollister and Gillespie, 1973; Walters and Carr, 1988).

Lack of Sufficient Data to Establish Safety in Food Use

The scientific literature available in the public domain presented no evidence that delta(8) THC has been used in foods. Findings in the literature that raise concerns regarding the safety of delta(8) THC are discussed below. Studies which utilized an oral route of exposure for administration of delta(8) THC are of increased relevance in our weight-of-evidence approach. Non-oral routes of exposure may have different absorption, distribution, metabolism, and excretion profiles, and correspondingly different physiological effects, which may not be pertinent to general recognition of safety for use as a food ingredient.

Hollister and Gillespie (1973) performed an oral exposure study in humans to compare the effects of delta(8) THC and delta(9) THC, both orally administered at doses of 20 and 40 mg per person to separate groups of volunteers. Subjects were blinded to the treatment material and dose. Delta(8) THC at 40 mg per person produced the greatest undesirable effects among subjects, and included: dizziness, drying of mucous membranes, paresthesia (tingling and pricking sensation on the skin), tinnitus (ringing noise in one or both ears), increased body awareness, muscle weakness, tension or tremors, incoordination, and sleepiness. These data

suggest delta(8) THC negatively affects the central nervous system. Importantly, post-exposure outcomes noted by the subjects were similar between delta(8) THC and delta(9) THC.

Walters and Carr (1988) performed a gestational exposure study in rats using three cannabinoids, including delta(8) THC. Maternal exposure occurred via daily oral gavage of delta(8) THC at 1 mg/kg BW/day, beginning two-weeks prior to mating and continuing through lactation. Offspring were weaned and humanely euthanized on postpartum day 20. Evaluation of the offspring brain showed that delta(8) THC exposure resulted in a decrease in tyrosine hydroxylase activity, an enzyme used in the biosynthesis of dopamine. Results from this study suggest that gestational exposure to delta(8) THC could negatively affect offspring neurodevelopment.

Gong et al. (1984) performed a double-blind study in humans comparing effects of oral exposure to three cannabinoids, including delta(8) THC. When administered at 75 mg per person, delta(8) THC induced bronchodilation and tachycardia, suggesting that an acute exposure to delta(8) THC may trigger an adverse cardiopulmonary reaction/event in humans.

Akpunonu et al. (2021) discuss a case report of a previously healthy 2-year-old girl who presented with acute encephalopathy—being in a sedate state with minimal responsiveness to external stimuli—following ingestion of approximately 225 mg delta(8) THC (or 14.7 mg/kg BW) and required intubation for 10 hours out of concern that her breathing was compromised. The patient's mental impairment resolved after 24 hours and was eventually discharged.

FDA notes that the aforementioned published findings raise safety concerns and are not considered consistent with general recognition of safety for use as food ingredients.

Overall Conclusions

The available data on delta(8) THC are insufficient to support its safety for use as a food ingredient that will be consumed by the general population. It should be emphasized that because a substance added to food may be consumed by the entire population over a lifetime, assurance of safety requires an evaluation of potential effects of long-term use within various segments of the population, with consideration for vulnerable subpopulations such as pregnant women, conceptus/fetus, infants, and young children.

Due to the lack of adequate data and information in the scientific literature to support the safe use of delta(8) THC in food, DFI is unable to conclude that the addition of delta(8) THC to food meets the statutory criteria for classification as GRAS. Additionally, the available data raise safety concerns as there are potential adverse effects of delta(8) THC on the nervous, respiratory, circulatory, reproductive, and endocrine systems, as well as on neurodevelopment in gestationally exposed individuals. Based on the available data and information, delta(8) THC does not meet the experience based on common use in food (prior to 1958) criterion or the technical evidence of safety and the general recognition of safety necessary for GRAS designation for use in food. Accordingly, the use of delta(8) THC in food constitutes use of an unsafe food additive within the meaning of Section 409 of the FD&C Act, rendering the food product to which delta(8) THC is added adulterated within the meaning of Section 402(a)(2)(C) of the FD&C Act.

References

Akpunonu P, Baum RA, Reckers A, Davidson B, Ellison R, Riley M, Trecki J, Gerona R. Sedation and Acute Encephalopathy in a Pediatric Patient Following Ingestion of Delta-8-Tetrahydrocannabinol Gummies. Am J Case Rep. 2021 Nov 11;22:e933488. doi: 10.12659/AJCR.933488. PMID: 34762615.

Avraham Y, Ben-Shushan D, Breuer A, Zolotarev O, Okon A, Fink N, Katz V, Berry EM. Very low doses of delta 8-THC increase food consumption and alter neurotransmitter levels following weight loss. Pharmacol Biochem Behav. 2004 Apr;77(4):675-84. doi: 10.1016/j.pbb.2004.01.015. PMID: 15099912.

Babalonis S, Raup-Konsavage WM, Akpunonu PD, Balla A, Vrana KE. Δ8-THC: Legal Status, Widespread Availability, and Safety Concerns. Cannabis Cannabinoid Res. 2021 Oct;6(5):362-365. doi: 10.1089/can.2021.0097. PMID: 34662224.

Badawy ZS, Chohan KR, Whyte DA, Penefsky HS, Brown OM, Souid AK. Cannabinoids inhibit the respiration of human sperm. Fertil Steril. 2009 Jun;91(6):2471-6. doi: 10.1016/j.fertnstert.2008.03.075. Epub 2008 Jun 18. PMID: 18565513.

Baker T, Datta P, Rewers-Felkins K, Thompson H, Kallem RR, Hale TW. Transfer of Inhaled Cannabis Into Human Breast Milk. Obstet Gynecol. 2018 May;131(5):783-788. doi: 10.1097/AOG.0000000000002575. PMID: 29630019.

Capelle N, Treich I, Ayrault-Jarrier M, Hoellinger H, Scherrmann JM. Liaison du delta8-THC aux protéines sériques humaines: étude de sa fixation en fonction de la composition lipoprotéinique [Binding of delta-8-THC to human serum proteins: binding as a function of lipoprotein composition]. Eur J Toxicol Environ Hyg. 1976 Jan-Feb;9(1):5-9. French. PMID: 176039.

Compton DR, Rice KC, De Costa BR, Razdan RK, Melvin LS, Johnson MR, Martin BR. Cannabinoid structure-activity relationships: correlation of receptor binding and in vivo activities. J Pharmacol Exp Ther. 1993 Apr;265(1):218-26. PMID: 8474008.

ElSohly, M., & Gul, W. (2014-08-21). Constituents of Cannabis Sativa. In Handbook of Cannabis. : Oxford University Press. Retrieved 14 Sep. 2021, from https://oxford.universitypressscholarship.com/view/10.1093/acprof:oso/9780199662685.001.0001/acprof-9780199662685-chapter-1.

Gong H Jr, Tashkin DP, Simmons MS, Calvarese B, Shapiro BJ. Acute and subacute bronchial effects of oral cannabinoids. Clin Pharmacol Ther. 1984 Jan;35(1):26-32. doi: 10.1038/clpt.1984.4. PMID: 6690168.

Gupta D, Elbracht C. Effect of tetrahydrocannabinols on pubertal body weight spurt and sex hormones in developing male rats. Res Exp Med (Berl). 1983;182(2):95-104. doi: 10.1007/BF01851115. PMID: 6306747.

Hazekamp A, Ruhaak R, Zuurman L, van Gerven J, Verpoorte R. Evaluation of a vaporizing device (Volcano) for the pulmonary administration of tetrahydrocannabinol. J Pharm Sci. 2006 Jun;95(6):1308-17. doi: 10.1002/jps.20574. PMID: 16637053.

Hine B, Toreelio M, Gershon S. Analgesic, heart rate, and temperature effects of delta8-THC during acute and chronic administration to conscious rats. Pharmacology. 1977;15(1):63-72. PMID: 14347.

Hollister LE, Gillespie HK. Delta-8- and delta-9-tetrahydrocannabinol comparison in man by oral and intravenous administration. Clin Pharmacol Ther. 1973 May-Jun;14(3):353-7. doi: 10.1002/cpt1973143353. PMID: 4698563.

Järbe TU, Henriksson BG. Acute effects of two tetrahydrocannabinols (delta9-THC and delta8-THC) on water intake in water deprived rats: implications for behavioral studies on marijuana compounds. Psychopharmacologia. 1973 Jun 29;30(4):315-22. doi: 10.1007/BF00429190. PMID: 4722202.

Kimura T, Yamamoto I, Ohta T, Yoshida H, Watanabe K, Ho IK, Yoshimura H (1996) Changes in 5-HT receptor binding induced by tetrahydrocannabinol metabolites in bovine cerebral cortex. Res Commun Alcohol Subst Abuse 17:57–69.

Klegeris A, Bissonnette CJ, McGeer PL. Reduction of human monocytic cell neurotoxicity and cytokine secretion by ligands of the cannabinoid-type CB2 receptor. Br J Pharmacol. 2003 Jun;139(4):775-86. doi: 10.1038/sj.bjp.0705304. PMID: 12813001; PMCID: PMC1573900.

MacLean KI, Littleton JM. Environmental stress as a factor in the response of rat brain catecholamine metabolism to delta8-tetrahydrocannabinol. Eur J Pharmacol. 1977 Jan 21;41(2):171-82. doi: 10.1016/0014-2999(77)90206-0. PMID: 832673.

Nahas G, Leger C, Tocque B, Hoellinger H. The kinetics of cannabinoid distribution and storage with special reference to the brain and testis. J Clin Pharmacol. 1981 Aug-Sep;21(S1):208S-214S. doi: 10.1002/j.1552-4604.1981.tb02597.x. PMID: 6271826.

Nakamura-Palacios EM, Amodeo Bueno OF, Takahashi RN, Tufik S. Acute or chronic effects of cannabinoids on spontaneous or pharmacologically induced yawning in rats. Pharmacol Biochem Behav. 2002 Dec;74(1):205-12. doi: 10.1016/s0091-3057(02)00991-7. PMID: 12376169.

Rating D, Broermann I, Honecker H, Kluwe S, Coper H. Effect of subchronic treatment with (-) 8 -trans-tetrahydrocannabinol (8 -THC) on food intake, body temperature, hexobarbital sleeping time and hexobarbital elimination in rats. Psychopharmacologia. 1972;27(4):349-57. doi: 10.1007/BF00429388. PMID: 4648618.

Sultan SR, Millar SA, O'Sullivan SE, England TJ. A Systematic Review and Meta-Analysis of the In Vivo Haemodynamic Effects of Δ⁸-Tetrahydrocannabinol. Pharmaceuticals (Basel). 2018 Jan 31;11(1):13. doi: 10.3390/ph11010013. PMID: 29385080; PMCID: PMC5874709.

Walters DE, Carr LA. Perinatal exposure to cannabinoids alters neurochemical development in rat brain. Pharmacol Biochem Behav. 1988 Jan;29(1):213-6. doi: 10.1016/0091-3057(88)90300-0. PMID: 2895481.

Watanabe K, Arai M, Narimatsu S, Yamamoto I, Yoshimura H. In vivo effects of tetrahydrocannabinols and their eight monooxygenated metabolites of the hepatic microsomal drug-metabolizing enzyme systems of mice. J Pharmacobiodyn. 1987 Oct;10(10):580-6. doi: 10.1248/bpb1978.10.580. PMID: 2831334.

Watanabe K, Yamamoto I, Oguri K, Yoshimura H. Comparison in mice of pharmacological effects of delta 8-tetrahydrocannabinol and its metabolites oxidized at 11-position. Eur J Pharmacol. 1980 Apr 11;63(1):1-6. doi: 10.1016/0014-2999(80)90110-7. PMID: 6247159.

Wiley JL, Huffman JW, Balster RL, Martin BR. Pharmacological specificity of the discriminative stimulus effects of delta 9-tetrahydrocannabinol in rhesus monkeys.

Drug Alcohol Depend. 1995 Nov;40(1):81-6. doi: 10.1016/0376-8716(95)01193-5. PMID: 8746928.

Yamamoto I, Kimura T, Kamei A, Yoshida H, Watanabe K, Ho IK, Yoshimura H. Competitive inhibition of delta8-tetrahydrocannabinol and its active metabolites for cannabinoid receptor binding. Biol Pharm Bull. 1998 Apr;21(4):408-10. doi: 10.1248/bpb.21.408. PMID: 9586583.

Yamaori S, Ishii H, Chiba K, Yamamoto I, Watanabe K. Δ-Tetrahydrocannabinol induces cytotoxicity in macrophage J774-1 cells: involvement of cannabinoid receptor 2 and p38 MAPK. Toxicology. 2013 Dec 15;314(2-3):254-61. doi: 10.1016/j.tox.2013.10.007. Epub 2013 Oct 30. PMID: 24184660.