Memorandum

Date January 19, 2022

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Office of Food Additive Safety, CFSAN, HFS-200

Subject Updated literature search and GRAS evaluation on Cannabidiol

To Cannabis Product Committee

Keywords:
Cannabidiol, CBD, *Cannabis sativa*, CAS RN: 13956-29-1

This is an addendum to the November 13, 2019 memorandum that discusses the regulatory status and review of available information pertaining to cannabidiol (hereinafter referred to as CBD). That memorandum concluded that the use of CBD in food for humans or animals does not meet the criteria for GRAS due to inadequate safety data. Additionally, the available data from animal studies, such as evidence of male reproductive toxicity in monkeys and rodents, suggests CBD consumption may be harmful. As such, the use of CBD in food constitutes use of an unapproved food additive, rendering it an unsafe food additive within the meaning of Section 409(a) of the FD&C Act [21 U.S.C. § 348(a)], and therefore adulterating the food to which it is added within the meaning of Section 402(a)(2)(C)(i) of the FD&C Act [21 U.S.C. § 342(a)(2)(C)(i)]. This addendum summarizes the findings of an updated literature search of publicly available information since the original review and determines whether the new information continues to corroborate the previous conclusion.

Following the methodology described in the original review, PubMed literature searches were performed for the terms “cannabidiol and food”, “cannabidiol as food”, “cannabidiol in food”, “food use of cannabidiol”, “cannabidiol and toxicity”, “cannabidiol toxicity”, “toxicity of cannabidiol”, “cannabidiol and toxicity and review”, “cannabidiol and DNA damage”, and “cannabidiol and chromosome abnormality,” and conducted to cover the date of the original literature search (July 31, 2019) through December 3, 2021. Results from these searches are summarized in Table 1.

Table 1: Articles from July 31, 2019 to December 3, 2021 retrieved in PubMed searches

Search term:	*Articles retrieved:*
cannabidiol and food	212
cannabidiol as food	212
cannabidiol in food	212
food use of cannabidiol	212
cannabidiol and toxicity	115
cannabidiol toxicity	115
toxicity of cannabidiol	115
cannabidiol and toxicity and review	25
cannabidiol and DNA damage	7
cannabidiol and chromosome abnormality	3
Total (non-redundant)	322

These searches recovered 322 unique articles. The majority of articles retrieved from these searches were not relevant to the potential for oral toxicity of CBD. Many of these articles discuss studies that were designed to investigate potential purported therapeutic and/or beneficial effects of CBD alone or in combination with tetrahydrocannabinol (THC) or other medications. Eight articles were deemed relevant to the general recognition of safety of CBD for use in food. These articles are cited and discussed below. None these articles address concerns for safety or refute the conclusion of the prior memorandum.

In vitro, CBD interferes with cellular processes involved in human placental development and function (Alves et al., 2021), endometrial stromal cell differentiation (Almada et al., 2020), and trophoblast-endometrial crosstalk (Neradugomma et al., 2019); processes necessary for uterine receptivity, implantation, and successful pregnancy. These new data suggest that the reproductive toxicity of CBD is not limited to male fertility parameters as previously concluded but could also include effects on female fertility and pregnancy outcomes.

Prenatal CBD exposure (20 mg CBD/kg BW/day) in mice, occurring via maternal oral exposure 2-weeks prior to mating and continuing through gestation and lactation, resulted in increased anxiety-like behavior in F_1 female offspring (Wanner et al., 2021). Additionally, differentially methylated loci in both the cerebral cortex and hippocampus brain regions were identified. Taken together, these findings suggest that developmental exposure to CBD may be associated with undesirable behavioral outcomes in female offspring and perturbations in the brain epigenome.

In 21-day-old male mice that received CBD (15 or 30 mg CBD/kg BW/day) by oral gavage for 34 consecutive days (Carvalho et al., 2021), marked effects in spermatogenesis and spermatozoa performance were noted at both doses. Such effects included increases in DNA damage and number of abnormal acrosomes in mature spermatozoa, decreases in enzymatic activity of superoxide dismutase and catalase—enzymes which function to protect spermatozoa from oxidative stress—and decreases in spermatozoa straight-line and average pathway velocities. Changes in testicular morphology, like a reduced seminiferous tubule epithelium height, and on spermatogenesis in a stage-specific manner were also noted between control

and CBD-exposed animals. Additionally, the highest dose (30 mg CBD/kg BW/day) resulted in reductions in spermatozoa motility, curvilinear velocity, and number of mature spermatozoa with intact acrosomes. This study adds to the body of literature on CBD's reproductive toxicity potential in males as discussed in the original memorandum.

Other relevant publications include: one review article that discusses the current status of safety and regulation of CBD in consumer products (Li et al., 2021), one review article that addresses previously discussed effects of CBD on the male reproductive system (Carvalho et al., 2020), and one clinical case study where a 56-year-old male presented with depressed respiratory and cardiovascular function after ingesting gummies containing 370 mg of CBD (Bass and Linz, 2020).

Conclusion

Based on the updated literature search, no new information was identified that would change the conclusion as stated in our memorandum dated November 13, 2019.

References:

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