Memorandum

From CFSAN Office of Food Additive Safety _ [redacted] _

CVM Office of Surveillance and Compliance _ [redacted]

Subject Regulatory status and review of available information pertaining to cannabidiol: lack of general recognition of safety for its use in conventional foods.

To CBD Policy Working Group

The Division of Food Ingredients' toxicology review team in CFSAN's Office of Food Additive Safety and the Division of Animal Feeds in CVM's Office of Surveillance and Compliance were asked to review whether any food use of cannabidiol (CBD) meets the statutory criteria for general recognition of safety. This memorandum considers the pertinent scientific information and concludes that the use of CBD in food does not meet the criteria for general recognition of safety because there is inadequate scientific data and information supporting the safety of consumption of CBD in food for humans or animals, and the information that is available indicates that CBD use in food may be harmful.

Food Additives and the GRAS Provision

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 its becoming a component of any food, unless the substance is generally recognized as safe (GRAS) among qualified experts under the conditions of its intended use (or unless the substance meets a listed exception, none of which is relevant here). Under section 409(a) of the FD&C Act [21 U.S.C. § 348(a)], a food additive that is directly added to food is considered unsafe unless it is used in conformity with an existing food additive regulation that prescribes the conditions of safe use for the additive. As there is no food additive regulation establishing safe conditions of use for CBD in food for humans or animals, CBD is an unsafe food additive unless it is GRAS for its intended use. This memorandum will therefore consider the applicability of the GRAS criteria for the use of CBD as an ingredient in food for humans or animals.

GRAS Criteria

FDA's regulations in 21 CFR Part 170 and 570 describe the eligibility criteria for classification of a substance added to food as GRAS. A conclusion that a particular use of a substance is GRAS under the conditions of its intended use requires both evidence of safety and general recognition.

A demonstration of safety under the GRAS criteria requires that information about the substance establish that the intended use of the substance is safe. FDA has defined "safe" (21 CFR 170.3(i)) and 570.3(i))[1] as a reasonable certainty in the minds of competent scientists that the substance is not harmful under its intended conditions of use.

A demonstration of general recognition under the GRAS criteria must be based on the views of qualified food safety experts. 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 and 570 define "scientific procedures" and establish eligibility criteria for classification as GRAS through scientific procedures. Under 21 CFR 170.3(h) and 570.3(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) and 570.30(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) and 570.30(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.

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. This standard is discussed in the GRAS final rule, which took effect on October 17, 2016 (81 Federal Register (FR) 54960; August 17, 2016).

General recognition of safety through common use in food must be based on the views of experts qualified by scientific training and experience to evaluate the safety of substances added to food, and the experts' views must be founded on experience based on the ingredient's common use in food prior to January 1, 1958 (21 CFR 170.30(a) and (c)). Under 21 CFR 170.3(f), regarding human food uses, common use in food means, "a substantial history of consumption of a substance for food use by a significant number of consumers." Under 21 CFR 570.3(f), regarding animal food uses, common use in food means, "a substantial history of consumption of a substance by a significant number of animals of the species to which the substance is intended to be fed (and, for food-producing animals fed with such substance, also means a substantial history of consumption by humans consuming human foods derived from those food-producing animals)." The fact that a substance may have been used in food prior to 1958 does not, in itself, demonstrate that such use is safe. The use prior to 1958 must be sufficiently broad to demonstrate safety to qualified experts.

Overview of CBD

Compounds that act on cannabinoid receptors are collectively referred to as cannabinoids. Cannabinoids can be broadly classified into three groups: (1) phytocannabinoids or plant-derived cannabinoids, (2)

[1] The definitions of 'food' and 'food additive' in the Federal Food Drug and Cosmetic Act are inclusive of substances intended for man and other animals. Citations in this memo to §170 and §570 of 21 CFR reflect that the implementing regulations are published separately to reflect differences between human and animal food, but the same safety standard is maintained.

synthetic cannabinoids, and (3) endocannabinoids or endogenous cannabinoids (Kelly and Nappe, 2019). The two best-known endocannabinoids are anandamide (AEA) and 2-arachidonoylglycerol (2-AG). The body produces these endocannabinoids in response to physiological demand, such as stress (Pacher et al., 2006).

The primary source of phytocannabinoids is the plant *Cannabis sativa* L. (marijuana, hemp, or cannabis). The predominant cannabinoids in cannabis are delta-9 tetrahydrocannabinol (THC), cannabidiol (CBD), and cannabinol (CBN). THC is the major psychoactive component of marijuana. It is 4-20 times more potent than endocannabinoids and has a significantly longer duration of action (Brutlag and Hommerding, 2018). Unlike THC, CBD is not known to induce euphoria, but has anticonvulsant and barbiturate-induced sleep prolonging effects (Yamamoto et al., 1995). The THC and CBD content of cannabis can vary widely, with CBD constituting up to 40% of plant extracts (Bergamaschi et al., 2011).

Cannabinoids act on cannabinoid receptors. Cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2) are the two best characterized cannabinoid receptors in humans. Cannabinoid receptors are widely distributed in the brain, peripheral nervous system, and in most glands and organs in the body. In vitro studies demonstrated that CBD can act as a cannabinoid receptor antagonist (CB1 and CB2) (Thomas et al., 2007). In addition to CB1 and CB2, other receptor candidates have been identified. However, our knowledge of the potential of additional cannabinoid receptors, as well as the functioning of the cannabinoid receptor system, is limited.

Phytocannabinoids and synthetic cannabinoids can cause cannabinoid toxicity. In recent years, particularly since the legalization of medical and/or recreational use of marijuana under the laws of some states (though not under federal law), there have been many reports of cannabis toxicity (Atakan, 2012; Zou and Kuman, 2018; Kelly and Nappe, 2019).

Regulatory Status of CBD

Evidence of Safety Based on Common Use in Food Prior to 1958

FDA is unaware of CBD's use in foods for humans or animals prior to 1958. To find evidence of use of CBD in food prior to 1958, a search was conducted in two databases: the PubMed database and *FDA's Scientific Terminology and Regulatory Information (STARI)*[2] *database*, on July 31 and August 3, 2019. The PubMed database has literature dating back to about 1951, and in some cases, even earlier literature is available. A search in PubMed using the search terms "cannabidiol and food", "cannabidiol as food", "cannabidiol in food", and "food use of cannabidiol" using the "Most Recent" filter retrieved articles dating as far back as 1975. These articles were retrieved based on the presence of the two terms, "cannabidiol" and "food", and not necessarily because they discuss the use of CBD as food. For example, Sofia and Knobloch (1976) published on the effect of intraperitoneal injection of THC, CBN, and CBD on food, sucrose, and water consumption by rats. The search in both PubMed and STARI failed to retrieve any record that CBD was commonly used in food for humans or animals before 1958.

[2] The data in STARI goes back to the 1970s. It includes primarily chemical substances (including substances/organisms used as chemicals) and associated identifying and regulatory information, but also any scientific term that may have been of interest to CFSAN. There are currently over 342,000 terms accessed through STARI, including over 66,000 "preferred terms", over 115,000 synonyms, nearly 50,000 CAS numbers, over 37,400 CERES IDs, over 13,600 UNII codes, and over 1,400 regulations (primarily 21 CFR 73-189 and 40 CFR 180-186) with over 10,200 connections to specific substances. Additional regulatory information and reference source information is contained within STARI's notes and comments fields, which are also searchable.

If some evidence of use of CBD in food prior to 1958 were to be found, meeting the eligibility criteria for general recognition of safety of CBD based on common use in food is not expected. Use in food prior to 1958 would have to be sufficiently broad to demonstrate safety to qualified experts. Furthermore, history of use prior to 1958 is not sufficient to support GRAS status if new evidence demonstrates that there is no consensus that the ingredient is safe (See 80 FR 34650, 34653 (June 17, 2015)). This memorandum shows, below, a lack of scientific evidence supporting safety and shows evidence that CBD may be harmful.

Evidence of Safety Based on Scientific Procedures

The following discussion focuses on the current status of knowledge on the toxicity potential of CBD in humans, emphasizing data on orally consumed CBD in mammalian species.

1. **Literature search strategy:** The search targeted published, peer-reviewed scientific literature, because GRAS conclusions based on scientific procedures must be based on data and information that are generally available and accepted. The literature search was conducted in PubMed, because PubMed is the primary bibliographic source of peer-reviewed biomedical literature. Initially, a parallel literature search was also performed using TOXNET, the Web of Science, and Google Scholar. The relevant results returned by these sources were also identified in PubMed. Therefore, the final literature search was performed in PubMed.

   A literature search with the search term 'cannabidiol' retrieved 2531 references using the 'Best Match' filter, and 2498 references using the 'Most Recent' filter, as of July 31, 2019. *It should be recognized that the number of references retrieved changes almost on a weekly basis as new publications on CBD appear in PubMed. This was verified by performing several searches at various times beginning from the third week of July 2019.* Most articles retrieved with this search were not strictly relevant to the potential for oral toxicity of CBD. Many assert therapeutic and beneficial effects of CBD, alone or in combination with THC or other medications. Other articles discuss other aspects of CBD use, such as (1) opinions and recommendations on what is needed for CBD to be used safely as a drug; (2) summaries of the available literature on cannabinoid use, with a specific focus on use of CBD as a drug to treat specific diseases, such as its utility in reducing pain during chemotherapy, inflammatory pain etc.; (3) pharmacological comparisons of CBD and other potential therapeutic molecules; and (4) use of CBD in protecting against various toxicities (e.g., cadmium hepatotoxicity).

   A more targeted literature search was performed with the following search terms; "cannabidiol and toxicity", "cannabidiol toxicity", and "toxicity of cannabidiol", using the 'Most Recent' filter, as of July 31, 2019. The search using all three terms retrieved 150 references. The retrieval was clearly based on the presence of one or both the words, "cannabidiol" and "toxicity" in the references that were retrieved. Again, most of these articles assert therapeutic and purported beneficial applications of CBD. Many articles also mention that CBD might alleviate or reverse certain toxicities, such as cocaine toxicity, alcohol toxicity, and certain drug toxicity. Therefore, these articles are not directly useful for this memorandum as they do not pertain to food ingredient toxicity. However, many articles discussing CBD's toxicity/potential toxicity on various *in vivo* and *in vitro* models were also retrieved. These articles were used to write this memorandum. These references also include several review articles that summarize a large number of studies. These articles are cited in APPENDIX I.

In order to find comprehensive review articles, another literature search was conducted in PubMed with the search term "cannabidiol and toxicity and review" using the 'Most Recent' filter as of July 31, 2019. The search retrieved 28 articles. The majority of these articles included reviews on the use of CBD as a therapeutic agent. However, a few reviews on the side effects of CBD were also retrieved. These are listed in APPENDIX II.

Additional rounds of literature search were conducted using the search term "cannabidiol metabolism" using the 'Most Recent' filter as of July 31, 2019. A total of 945 references were retrieved. The retrieval was clearly based on the presence of the word, "cannabidiol." Therefore, a more targeted search of CBD metabolism was performed using the search term "cannabidiol metabolism by P450" using the 'Most Recent' filter as of July 31, 2019. The search retrieved 30 references. Using the search term "cannabidiol metabolism by conjugation" applying the 'Most Recent' filter as of July 31, 2019 retrieved 2 references. References useful for this memorandum were obtained from these retrieved articles. These references are listed in APPENDIX III. Finally, using the references already obtained, additional relevant references were identified through cross-referencing.

During the drafting of this memorandum, a PubMed search was conducted on August 3, 2019 with the search term "cannabidiol and DNA damage" using the "Most Recent" filter. The search retrieved 12 articles, of which one was relevant for this memorandum (Russo et al., 2019). An additional search on the same day with the search term "cannabidiol and chromosome abnormality" using the "Most Recent" filter retrieved 7 articles, of which two were found relevant for this memorandum (Zimmerman and Raj, 1980; Zimmerman and Zimmerman, 1990). These two articles were not retrieved by previous searches.

The analysis in this memorandum is based on published, peer-reviewed scientific literature. A summary posted online of information evaluated by FDA's Center for Drug Evaluation and Research (CDER) from GW Pharmaceuticals pertaining to the drug Epidiolex was also taken into account.[3] CBD is the active ingredient in Epidiolex. Information in this summary was used to corroborate some findings from published, peer-reviewed scientific literature discussed in this memorandum.

On April 3, 2019, FDA announced the opening of a public docket to obtain scientific data and information about the safety, manufacturing, product quality, marketing, labeling, and sale of products containing cannabis or cannabis-derived compounds (Docket No. FDA-2019-N-1482; see 84 FR 12969, April 3, 2019). The comment period for the docket ended on July 16, 2019. (See 84 FR 28822, June 20, 2019.) Comments to the docket were evaluated for relevance to this memorandum. No additional scientific information warranting inclusion in this memorandum, beyond the information already identified in the literature search, was identified in the comments.

Articles cited in the text of this memorandum are listed under bibliography. It is likely that some articles about CBD have been published in sources that are not indexed in PubMed or were published too recently to appear in PubMed. Such articles would not have been recovered in this search. However, the rationale for the use of PubMed as a search engine is justified above, and

[3] This memorandum took into account information in the publicly available summary from CDER and did not take into account any data that may be considered confidential commercial information. The CDER review is accessible at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2018/210365Orig1s000PharmR.pdf

the articles identified by this search and used in this memorandum are adequate to conclude that the weight of existing evidence does not provide a basis for CBD to be GRAS for use in food.

2. **Evidence from animal studies demonstrate that CBD is not GRAS for use in food:** In the following discussion, animal studies in which CBD was administered orally are emphasized. Results of animal studies conducted using non-oral routes and results from *in vitro* studies are discussed to underscore an effect observed in animal studies using the oral route, or to underscore a potentially important adverse effect of CBD.

   (a) ***Several toxicology studies in different mammalian models demonstrate that orally administered CBD can cause male reproductive toxicity, hepatotoxicity, organ weight change, and drug metabolism interactions*:** Rosenkrantz et al. (1981) conducted three types of studies on Rhesus monkeys: (1) acute intravenous toxicity studies of CBD and cannabichromene (CBCH); (2) a 90-day subchronic oral toxicity study of CBD; and (3) an acute and a 5-day subacute intravenous toxicity studies of hashish oil containing high concentrations of CBD and CBCH. The authors stated that the CBD used in these studies was 99% pure. In the acute intravenous toxicity study, the doses used were 0, 150, 200, 225, 250, 300 mg/kg body weight (mg/kg bw). The LD50 of CBD was estimated to be 212 mg/kg bw with 95% confidence limits of 199-225 mg/kg bw. At the 200 mg/kg bw dose, there was a marked (57%) decrease in relative testicular weight and a 33% increase in ovarian weight. The 90-day subchronic oral toxicity study of CBD is discussed here in detail. In the 90-day oral toxicity study, the orally administered doses of CBD were 0, 30, 100, and 300 mg/kg bw. Although not strictly dose-related, marked changes in organ weights were seen in all CBD dose groups in both sexes. For example, relative liver weights were increased 13-56%, and relative kidney weights were increased 16-22%, compared to controls. Relative heart weight was increased 16-22% in the highest dose group. Marked decreases were observed in several other relative organ weights, including a 10-50% decrease in thyroid and thymic relative weights, and a 10-30% decrease in female spleen and pancreas relative weights. Changes in gonadal weight occurred in both sexes to different degrees. For example, a 25-75% decrease in relative weights of ovaries was observed, whereas testicular weight tended to be lower at the low and high doses. However, the testicular size (length x width) showed a dose-dependent decrease (8-25%) at 90 days. *After a 30-day recovery period, the weight of most organs returned to normal, suggesting that the changes in relative weights were CBD treatment-related. However, the liver weights remained slightly elevated and gonadal and associated reproductive organ weights continued to be depressed. Testicular size remained depressed by 20-25% after the 30-day recovery period*. The authors also stated that changes in organ weights were not associated with any observed functional impairment for most organs, except for the testes. In the testes, inhibition of spermatogenesis was observed in 2 of 4; 3 of 4; and 4 of 4 monkeys given 30, 100 and 300 mg/kg bw of CBD, respectively. There were no changes in spermatogenesis in vehicle controls. Functional impairment of testes was accompanied by histological changes, such as smaller seminiferous tubules, lower mitotic index, fewer germ cells per tubule, decreased number of spermatocytes (both primary and secondary), spermatids, and spermatozoa. The effects of orally administered CBD on the testes of Rhesus monkeys (an Old World monkey; hence evolutionarily more closely related to humans than rodents), such as seminiferous tubule degeneration and inhibition of sperm maturation, were also observed when CBD was administered by inhalation to rats (Rosenkrantz and Hayden, 1979). Therefore, the data strongly suggest that CBD exerts toxic effects on the male reproductive system.

Subsequent work by other authors in rats demonstrated that CBD may disrupt the sex hormone homeostasis in mammals, at least in part, through selective inhibition of male-specific cytochromes P-450 in the liver (Narimatsu et al., 1988; Watanabe et al., 2005). The exposure of hCG-stimulated Leydig cell suspensions to CBN, CBD, and THC resulted in the inhibition of testosterone production in the incubation medium, with CBN and CBD being more potent inhibitors than THC (Jakubovic et al., 1979; Gorzalka et al., 2010). CBD metabolism and CBD-P450 interactions are discussed in more detail in the next section.

Dalterio and deRooij (1986) studied the impact of perinatal exposure to THC, CBN or CBD on testicular function and fertility in mice. The strain of mice was not specified in this article. However, previous articles by the same first author with the same institutional affiliation stated that the mice were derived from two inbred strains, Dw/Wf and YS/Ch WF-dw, and from a randomly bred stock, CD-1 (Dalterio et al., 1982; Dalterio et al., 1986). The article did not specify the source or purity of the THC, CBN and CBD used. In the following text, the results associated with CBD exposure are described. One group of females received a single oral dose of 50 mg/kg bw of CBD on day 12 of gestation, and another group of females received a single oral dose of 50 mg/kg bw of CBD within 12 h of parturition so that the suckling pups are exposed to CBD through mother's milk. The authors observed that female mice receiving an oral dose of 50 mg CBD/kg bw on day 12 of gestation produced male offspring with a significant reduction in testicular weight. The doses were selected based on previous studies using maternal cannabinoid exposure (Dalterio 1980; 1984a, b). These doses do not produce overt maternal toxicity or pup mortality. Testicular weight was significantly reduced in male mice born to CBD-treated females exposed to CBD on day 12 of gestation. The adult male offspring exposed to CBD postnatally had a reduced rate of successful impregnations compared to controls, and the number of live pups born to these males was significantly reduced. In these rats (exposed to CBD postnatally), the number of spermatids was about 20% less than in controls. The authors stated that their findings are consistent with earlier findings that cannabinoids can disrupt testicular function in laboratory animals as well as in man (Bloch et al. 1978). Dalterio et al. (1982) had also shown that exposure of adult male mice to CBD altered the spermatogenic function of the testes, caused reduced fertility,and there were significantly more prenatal and postnatal deaths from impregnation by CBD-exposed males.

Consistent with these earlier findings on the male reproductive toxicity of CBD, Carvalho et al. (2018a, b) observed that CBD administered orally to male mice at doses of 15 or 30 mg/kg bw produced reproductive toxicity. The purity of the CBD powder used in these two studies was approximately 99.9%, and was purchased from THC Pharm GmbH (Frankfurt, Germany). Male Swiss mice were administered CBD by gavage for 34 consecutive days at doses of either 0 (control), 15, or 30 mg/kg bw. Controls received sunflower oil. Sexual behavior was analyzed using parameters such as the first mount, intromission, ejaculation latencies, and postejaculatory mount. The observation of sexual behavior lasted for 10 days. Chronic administration of 15 mg/kg bw CBD reduced the frequency of mounts, and the number of intromission and ejaculations. The CBD 30 mg/kg bw group showed a statistically significant reduction in fertility rate and the number of litters. The average loss (%) of pre- and post-implantation tended to be higher in the 30 mg/kg bw group, although the difference was not statistically significant (2018a). In another study by the same group (2018b), male Swiss mice were administered CBD by gavage for 34 consecutive days at doses of 0 (control), 15 or 30 mg/kg bw. Mice were allowed to recover for 35 days. After the 35-day recovery period, the weight of testes, epididymides, seminal vesicles, and the concentration of plasma testosterone were determined; spermatogenesis and histomorphometric analysis were perfomed; daily

sperm production and sperm morphology were examined. CBD treatment did not affect body weight or reproductive tissue weight, such as testis, epididymis or seminal vesicle weight. The CBD 30 mg/kg bw group had a significant decrease in total circulating testosterone compared to controls. In the 15 mg/kg group, there was a decrease in total circulating testosterone compared to controls, but the decrease was not statistically significant. CBD treatment resulted in a statistically significant decrease in the number of Sertoli cells in the 30 mg/kg bw group. There were no significant differences in testicular sperm counts in the CBD groups compared to controls. However, in both 15 and 30 mg/kg bw CBD groups, spermatozoa had head and tail abnormalities, and a large number of cytoplasmic droplets. The number of spermatozoa in the epididymis tail was also reduced, and cytoplasmic droplets were observed in the medial region of flagellum. These results indicated that chronic CBD exposure in males was associated with abnormalities of spermatozoa and reproductive toxicity. The authors stated that CBD blood levels at the steady state for the doses used in the study, i.e., 15 and 30 mg/kg bw administered orally, would be about 80–160 ng/ml.

Carvalho et al. (2019) also reviewed studies cited in PubMed that analyzed the effects of CBD on the male reproductive system and the development of vertebrates and invertebrates. A total of thirty-two citations covering *in vivo* and *in vitro* studies were retrieved. Among mammals, studies were carried out in men, monkeys, rats, and mice. The CBD treatment periods included mostly acute and subacute evaluations (35 days or less); only the study by Rosenkrantz et al. (1981) was subchronic. The route of administration included oral as well as non-oral routes, such as intraperitoneal and inhalation. Collectively, the results from these studies clearly demonstrate that exposure to CBD is associated with a reduction in mammalian testis size, spermatogenesis, and fertilization rate. There is a reduction in the number of Sertoli cells, as well as germ cells from various stages of spermatogenesis, that is, spermatocytes (primary and secondary), spermatids and mature spermatozoa. Abnormalities in sperm morphology were also reported. CBD treatment was associated with reduced plasma concentrations of gonadotropins and androgens. Chronic exposure to CBD in mice resulted in impaired sexual behavior. CBD-induced male reproductive toxicity as well as developmental toxicity discussed in the review showed that the trend holds true even in phylogenetically distant organisms, such as zebra fish and even in sea urchin (an invertebrate). In sea urchin, preincubation of spermatozoa with CBD inhibited acrosome reaction, which is necessary for fertilization (Schuel et al., 1991). Zebrafish exposed from blastula through larval stage (96 hr post-fertilization) to THC or CBD produced developmental toxicity as revealed by edemas, curved axis, eye/snout/jaw/trunk/fin deformities, swim bladder distention, and behavioral abnormalities; however, CBD was found to be a more potent developmental toxicant than THC (LC50 for CBD = 0.53 mg/L; LC50 of THC = 3.65 mg/L) (Carty et al., 2018). The THC and CBD used in this study were provided by the NIDA Drug Supply Program (Research Triangle Park, NC) (suggesting that the CBD was most likely highly pure). The authors stated that the mechanism of CBD-mediated adverse effects on the male reproductive system is yet to be understood, and further research is needed.

Ewing et al. (2019a) showed that orally administered CBD resulted in clear signs of hepatotoxicity in mice gavaged with allometrically scaled[4] mouse equivalent doses (MED) of the maximum recommended human dose of CBD in Epidiolex (20 mg/kg). The CBD was

[4] Allometric scaling approach considers the differences in body surface area, which is associated with animal size and weight. Using allometric scaling, the dose in one species is extrapolated to another species, such as a human equivalent dose from the dose in mouse or vice versa.

about 58% pure. Doses of the CBD extract were calculated based on the CBD content to deliver the required dose of CBD. An acute toxicity study and a 10-day (Mon-Fri per week) subacute toxicity study was conducted. In the acute toxicity study, mice were gavaged with a single dose of 0, 246, 738, or 2460 mg/kg bw of CBD. The authors chose the 246 mg/kg bw dose because it is the MED of the human CBD dose of 20 mg/kg bw. In the subacute toxicity study, mice were gavaged with CBD extract for ten days at doses of 61.5, 184.5, and 615 mg/kg bw. The authors chose the 61.5 mg/kg bw dose because it is the MED of the human CBD dose of 5 mg/kg bw. In the acute toxicity study, there was a dose-dependent, statistically significant increase in both aspartate aminotransferase (AST) and alanine aminotransferase (ALT), and there was a marked elevation of total bilirubin at the highest dose, indicating that CBD can cause a dose-dependent increase in hepatotoxicity. Gene expression analysis revealed a dose-dependent increase in several P450 and UDP-glucuronosyltransferase (UGT) isoforms. In the subacute study, histopathological evaluation revealed pan-hepatic cytoplasmic swelling in the 615 mg/kg bw dose group, foci of cytoplasmic swelling were clearly present in the 184.5 mg/kg bw dose group, but not in the livers of mice gavaged with 61.5 mg/kg dose group. There was an increase in the relative weight of liver and kidney, an increase in the ALT, AST as well as serum bilirubin. Gene expression analysis revealed the same trend seen in the acute toxicity study. The authors concluded that CBD treatment showed clear signs of hepatotoxicity.

The same group (Ewing et al., 2019b) conducted another study to determine whether CBD-rich cannabis extract (CRCE) could interact with acetaminophen (APAP) in mice. APAP is a common over-the-counter drug known to cause liver injury through glutathione depletion and oxidative stress. The CBD was approximately 58% pure. Doses of the CBD extract were calculated based on the CBD content to deliver the required dose of CBD. In this study, female CD-1 mice were orally administered clinically relevant CBD doses in CRCE (116 mg/kg bw or 290 mg/kg bw) for three consecutive days, followed by an intraperitoneal challenge with APAP. The 116 mg/kg bw is the MED of 10 mg/kg bw, and 290 mg/kg bw is the MED of 25 mg/kg bw of CBD in humans. The lower dose (116 mg/kg bw + APAP) produced liver injury (sinusoidal obstruction) and mortality. These effects were not observed in the Vehicle + APAP group. Paradoxically, in the higher dose group (290 mg/kg bw + APAP), liver injury was seen in two out of eight mice. APAP hepatotoxicity is known to involve glutathione (GSH) depletion and a consequent massive oxidative stress. The lower incidence of hepatotoxicity in the 290 mg/kg bw group was associated with a rapid re-synthesis of glutathione so that the total glutathione level was similar to that in controls. The authors concluded that these findings highlight the potential for CBD/drug interactions and reveal an interesting paradoxical effect of CBD/APAP-induced hepatotoxicity. Further studies are needed to investigate the mechanism of the paradoxical effect. The authors also stated that their observations were consistent with the emerging evidence suggesting that CBD is involved in significant drug interaction that could lead to serious adverse health effects, including liver injury. In support of their claim, the authors referred to a clinical study that combined CBD with valproic acid. This study showed a more robust elevation in liver enzymes in 17% of patients, which suggests hepatotoxicity (Devinsky et al., 2019). The authors cautioned against casual, non-medically supervised usage of CBD with potentially hepatotoxic medications.

(b) ***CBD could be genotoxic and clastogenic*****:** In the literature, there are some controversies over whether CBD could be genotoxic and cause cytogenetic abnormalities. For example, Zimmerman and Raj (1980) observed that intraperitoneal administration of 10 mg/kg bw of CBD to mice for 5 consecutive days produced statistically significant increases in the percentage of micronuclei in bone marrow polychromatic erythrocytes compared to controls.

There were increased incidence of chromosomal abnormalities, such as deletions. However, in a double-blind placebo-controlled study Matsuyama and Fu (1981) failed to detect statistically significant increases in chromosome damage after feeding 27 volunteers 1200 mg CBD/day for 20 consecutive days in a 26-day study (days 1-4 was a cleansing period to determine the baseline; CBD was administered orally from days 5-24; days 25 and 26 was for post-drug testing). Some of the conflicting reports on CBD's potential genotoxicity and clastogenicity have been reviewed by Zimmerman and Zimmerman (1990-1991). Russo et al. (2019) reported that CBD treatment of human-derived HepG2 and TR146 cells resulted in single and double-stranded DNA breaks. The purity of the CBD used in these experiments was 99.95%. To emphasize the importance of the finding, the authors stated that the effects were seen at concentrations that could be found in the blood of cannabis users. For example, the highest plasma concentrations of CBD detected after smoking were between 0.25 and 2.18 μM (Russo et al., 2019).

(c) ***CBD can act as a substrate, an inhibitor and an inducer of certain drug metabolizing enzymes and transporters; therefore, CBD's effects on drug disposition raise safety concerns for its use in food*****:** In animal models, CBD is known to be an inhibitor of hepatic microsomal drug metabolism because of the inhibition of specific P450 enzymes. The potential inhibitory action of CBD on microsomal enzymes was proposed by Paton and Pertwee as early as 1972. Their opinion was based on the observation that pentobarbitone-induced sleep in mice was significantly prolonged by CBD treatment in a dose-dependent manner. This suggested that CBD-induced inhibition of microsomal enzymes prevented pentobarbitone metabolism, resulting in the prolongation of pentobarbitone-induced sleep time. Microsomal enzyme inhibition by CBD was confirmed by the inhibition of phenazone metabolism by hepatic microsomes prepared from CBD-treated mice. The CBD used in this study was a gift from Prof. R. Mechoulam (an experienced researcher on CBD). Subsequent investigations by other authors further characterized the individual P450 enzymes that are inhibited by CBD.

Work by Watanabe and colleagues using human liver microsomes showed that CBD is a potent inhibitor of human cytochromes (CYP) P450, such as CYP1A1, 2B6, 2C9, 2C19, 2D6, 3A4 and 3A5 (see Jiang et al., 2013, and references therein). The CBD used in these studies were purified from cannabis leaves and the purity was greater than 97%. It was also shown that treatment of animals with CBD affects CYP2C11 in male rats, as indicated by CBD-induced competitive inhibition of 2α- and 16α-hydroxylation of testosterone. In mouse, CBD treatment showed a decrease in testosterone 6β-hydroxylation and erythromycin *N*-demethylation, both reactions are markers of CYP3A (Narimatsu et al., 1988; see Yamamoto et al., 1995 and references therein).

Despite CBD's ability to inhibit various P450 isoforms, CBD is also metabolized by P450 enzymes, in particular CYP2C19 and CYP3A4 (Stout and Cimino, 2014; Zendulka, 2016). Harvey and Mechoulam (1990) analyzed the urine from a dystonic patient chronically treated with 600 mg CBD daily. GC-MS analysis of the urine identified unmetabolized CBD and 33 metabolites that included an *O*-glucuronide metabolite. The authors noted that the main metabolic pathway of CBD in humans may be oxidation and hydroxylation at the C-7 position, producing 7-OH-CBD, which is further oxidized to CBD-7-oic acid (7-COOH-CBD). In another study, Harvey et al. (1991) extracted urinary metabolites of CBD from human, mongrel dog and rat urine. The dogs and the rats were administered CBD intravenously. The human patient was a dystonic patient chronically treated with 600 mg CBD daily. They identified a complex profile of 50 metabolites with considerable species variation. In the human urine,

unmetabolized CBD, *O*-glucuronide metabolite and the derivatives of CBD-7-oic acid were all identified. It is not clear whether the subject in both studies was the same individual. In contrast to humans, the CBD-7-oic acid was a minor metabolite in dog urine. The metabolite profile in rats also differed from humans. Mazur et al. (2009) investigated whether CBD is conjugated by glucuronidation in humans and attempted to identify the specific human UGTs responsible for classic cannabinoid metabolism. CBD was purchased from Cerilliant (Round Rock, TX). Membrane fractions from baculovirus-infected insect cells expressing individual recombinant human UGTs were prepared. The authors found that UGT activity towards CBD was limited and minimal amounts of glucuronidated CBD was produced by UGT1A9, UGT2B7, and UGT2B17. In contrast, animal studies showed that a large portion of the administered CBD is excreted intact or as its glucuronide (Ujvary and Hanus, 2016). It is interesting to note that despite differences in the CBD metabolic profile, the male reproductive toxicity is a common effect of CBD exposure across different species.

More recently, Jiang et al. (2011) studied the metabolism of CBD using human liver microsomes (HLM) and microsomes from baculovirus-infected insect cells individually expressing 14 different human CYPs. The metabolic activity of pooled HLMs were also studied using specific inhibitors for 2C9. 2C19, 2D6, 3A4. HLMs produced eight hydroxylated metabolites of CBD, but the relative abundance of the identified metabolites indicated that 6α-OH, 6β-OH-, 7-OH-, and 4"-OH-CBDs were the predominant metabolites. Inhibition studies suggested that 6β-OH- and 4"-OH-CBDs were mainly formed by CYP3A4 whereas 6α-OH and 7-OH- were mainly formed by CYP2C19. Significant 6α-hydroxylation was also carried out by CYP3A4. The work strongly suggested that CYP2C19 and CYP3A4 play important roles in the metabolism of CBD in humans.

In addition to inhibiting P450 enzymes, CBD also inhibits crucial efflux transporters resulting in cellular accumulation of chemicals that are normally transported out. For example, Feinshtein et al. (2013) performed an *in vitro* study using Choriocarcinoma BeWo and Jar cells as human placental barrier model. These cells express the efflux transporter ABCG2, also known as breast cancer resistance protein (BCRP). Exposure of these cells to 10 and 25 μM CBD resulted in a dose-dependent accumulation of mitoxantrone, a BCRP substrate, inside the BeWo and Jar cells, demonstrating that BCRP-mediated efflux transport of mitoxantrone is inhibited by CBD. CBD was a gift from Prof R. Mechoulam. The authors concluded that the safety of drugs that are BCRP substrates is questionable in cannabis consuming women.

In a recent review of human metabolism of CBD, Ujvary and Hanus (2016) stated that CBD undergoes extensive hydroxylation at multiple sites and further oxidation results in a complex metabolic pattern. The major metabolites are derivatives of CBD-7-oic acid (7-COOH-CBD). Although P450, glucuronosyltransferases (UGTs) and sulfotransferases (SULTs) are all involved in metabolizing CBD in humans, the roles of P450 have been studied the most. The phenolic oxygen of CBD provides the glucuronidation site (Mazur et al., 2009) but hydroxylated metabolites of CBD could also act as substrates for glucuronidation (Ujvary and Hanus, 2016). The route of administration influences the pharmacokinetics of CBD (see Millar et al., 2018 in the next section) and there exists a high intra- and inter-individual variability. Because CBD undergoes significant Phase I metabolism and interindividual differences in the expression of CYP450 enzymes may considerably affect its metabolism, exposure to CBD could influence the therapeutic efficacy of drugs and adverse effects due to drug-drug interactions.

(d) ***Several comprehensive reviews of CBD's safety and side effects concluded that further studies are needed to clarify various reported in vitro and in vivo adverse effects of CBD:*** In a review of the literature on CBD, Bergamaschi et al. (2011) summarized various *in vivo* and *in vitro* reports of CBD administration across a wide range of concentrations, based on reports retrieved from the Web of Science, Scielo and Medline. Although the review summarized certain therapeutic uses of CBD in humans, the review concluded that further studies are needed to clarify various reported *in vitro* and *in vivo* adverse effects of CBD. Some of the highlights of studies that raised questions regarding the proposed safe use of CBD include inhibition of drug transport and metabolism, inhibitory effects on the immune system, and toxicity on the male reproductive system. The observation that CBD is a potent inhibitor of hepatic drug metabolizing enzymes raises the issue that CBD could alter the disposition of various drugs *in vivo*. Tissue accumulation and drug concentration can be further complicated because of CBD's inhibitory effects on P-glycoprotein, multidrug resistance protein 1 (ABCC1/MRP1) and BCRP. For example, CBD (3-100 μM) exerted potent inhibitory effects on P-glycoprotein mediated efflux, leading to an increased intracellular accumulation of P-glycoprotein substrates. Because P-glycoprotein is responsible for the low oral bioavailability and limited brain penetration of many therapeutic drugs and xenobiotics, inhibition of P-glycoprotein could result in greater penetration and accumulation of these chemicals in the brain. The literature also shows that CBD can exert inhibitory effects on the cells of the immune system affecting cytokine production. In a recent review titled, "An Update on Safety and Side Effects of Cannabidiol: A Review of Clinical Data and Relevant Animal Studies", Iffland and Grotenhermen (2017) opined that gaps in our knowledge of the safety of CBD following chronic oral administration continue to exist. Thus, various areas of CBD research should be extended to the study of its side effects after chronic administration.

In another review, Huestis et al. (2019) provided a thorough discussion on various studies of the toxicity as well as the beneficial effects of CBD to provide a balanced risk/benefit perspective of exposure to CBD. The adverse effects of CBD in animals discussed by the authors included developmental toxicity, embryo-fetal mortality, central nervous system inhibition and neurotoxicity, hepatocellular injuries, spermatogenesis reduction, organ weight alterations, male reproductive system alterations, and hypotension. A few animal studies discussed by the author had been reviewed by FDA's Center for Drug Evaluation and Research (CDER); and the review is publicly available (see footnote 3). The relevant animal and human studies discussed by Huestis et al. are briefly mentioned here. The authors discussed several human clinical trials, which showed that when patients on anti-epileptic drugs were treated with CBD, the most frequently observed adverse effect was the elevation of liver enzymes (ALT, AST), indicating adverse hepatic effects. In these studies, the CBD dose usually varied from 10 mg/kg bw/day to 50 mg/kg bw/day, and the duration of the studies varied from 3 weeks to 48 weeks. In emphasizing CBD's effects on male reproductive toxicity, the authors discussed *in vivo* reproductive effects of CBD from sea urchin to monkeys, and developmental toxicity of CBD in rats and rabbits. In sea urchin, *in vivo* fertilization was inhibited by 0.1-100 μM CBD because of decreased acrosomal reaction in sperm. Acrosomal reaction is essential to fertilization. Thus, the male reproductive toxicity of CBD observed in monkeys is also seen in sea urchin, an invertebrate, thereby confirming CBD's male reproductive toxicity in a wide spectrum of phylogenetically disparate organisms. A developmental toxicity study, which administered 0 (control), 75, 150, or 250 mg/kg bw/day of CBD in pregnant rats by oral gavage from gestational day 6 through postnatal day 21 (hence, spanning the period of organogenesis), found developmental toxicity of CBD at doses that were not maternally toxic. Developmental

effects included decreased pup body weights at birth and throughout lactation, delays in achieving developmental landmarks (pinna unfolding, eye opening, pupillary reflex, male and female sexual maturation), neurobehavioral changes (decreased locomotor activity), and adverse effects on reproductive system (small testes) and possibly function. There was an increased number of males with small testis in the CBD-dosed groups at all doses; 1 in low-dose, 2 in mid-dose and 3 in high-dose group and none of the males were littermates. In addition, for 2 high-dose males, small prostate and small seminal vesicle was also observed (CDER review of GW Report # GWTX1532; see footnote 3). In a similar embryo-fetal developmental toxicity study, pregnant rabbits were orally administered 0, 50, 80, or 125 mg/kg bw/day of CBD during organogenesis (gestational day 7-19). Decreased fetal body weights (10%) and increased fetal structural abnormalities, such as unossified metacarpal, bulging eyes, and nonerupted incisors, were observed at the high dose (CDER review of GW Report # GWTX1452; see footnote 3).

3. **Conclusion of CBD's adverse effects/toxicity following oral exposure in humans:** The information discussed above indicates that CBD can cause male reproductive toxicity at doses that could be consumed by human adults (e.g., as a drug or when abused). The trend of CBD-induced male reproductive toxicity is ubiquitous and has been observed from sea urchin (an invertebrate) to rhesus monkey (a primate). Rhesus monkeys are Old World monkeys and are evolutionarily closer to humans and apes than rodents. The targets of CBD's male reproductive toxicity have a wide spectrum and may involve the structure, function, as well as the development and abundance of spermatozoa, and it does not involve any outwardly visible injury to the reproductive tissues. The half-life of CBD varies widely depending on the route of administration. For example, the half-life was reported to be 1.4-10.9 hr after oromucosal spray; 2-5 days after chronic oral administration; 24 hr after intravenous administration; and 31 hr after smoking (Millar et al., 2018). Because the half-life seems to be the longest after oral administration, chronic oral consumption of CBD can conceivably result in the accumulation of CBD levels in the body, thereby increasing the possibility of adverse effects on the male reproductive system without overt clinical signs and symptoms of injury to the reproductive tissue. Available evidence also suggests CBD could be hepatotoxic in humans. In addition to the male reproductive toxicity and hepatotoxicity, CBD has been shown to inhibit certain important drug metabolizing enzymes and transporters in humans. The inhibition of drug transport and metabolism does not cause any immediate symptoms of toxicity. However, individuals who have been taking drugs that are normally metabolized by enzymes inhibited by CBD would eventually experience drug-induced toxicity if the drug level in the plasma reaches a toxic level. Likewise, the inhibition of efflux transporters would result in an unwanted level of accumulation of drugs in tissues including brain, which may result in long-term toxicity. To summarize, the weight-of-evidence available in the scientific literature clearly establishes that CBD is not safe for consumption in food. Therefore, CBD is not GRAS for any intended use in food.

The following discussion focuses on the current status of knowledge on the toxicity potential of CBD, emphasizing orally consumed CBD in target species for animal food use.

Data and information in target animal species are generally necessary to assess the safety of a substance for use in animal food due to differences in metabolism across animal species. With respect to CBD, the information in a variety of animal models discussed above indicates the potential for CBD to cause adverse effects -- including but not limited to male reproductive toxicity and hepatoxicity-- across all target animal species. Because these adverse effects have been shown in laboratory species raising safety concerns for

all animal species, studies addressing the safety of CBD in target animal species would need to include appropriate end points to address these potential effects.

Literature searches were conducted to determine if information is available in target animal species, including both food producing species and companion animal species, to address the potential adverse effects observed in laboratory species to affirmatively demonstrate safety in target animal species and human food. With respect to food producing species, we note that the discussion above indicates that chronic oral consumption of CBD can conceivably result in the accumulation of CBD levels in the body. The accumulation of CBD in the body of food producing species raises not only target animal safety questions, but also human food safety questions if this accumulation were to occur in edible tissues. Accordingly, for food producing species the search focused on the availability of data addressing the potential for CBD residues in edible tissues to assess if safety in these target species has been adequately addressed tissues. For companion animal species, the search focused on dogs, cats, and horses as the primary target animal species because the vast majority of CBD products marketed for animals at this time are marketed for these companion animal species

1. **Literature Search Strategy:**
   A literature review was performed using terms related to CBD and residues in edible tissues (e.g., meat, milk, and eggs) after oral administration using the PubMed database and Web of Science. No references were found that address CBD residues in edible tissues after oral administration. With no information available to address the safety of human food produced from these animals, additional searches on target animal safety in these species were not performed.

   To determine if information is available in target animal species to address the potential adverse effects discussed above and affirmatively demonstrate safety, a literature review was performed using terms related to CBD in target animal species using the PubMed database and Web of Science on August 5, 2019. The search focused on dogs, cats, and horses because the vast majority of CBD products marketed for animals at this time are marketed for these companion animal species. The searches were performed using the terms Cannabidiol or CBD in conjunction with the words dog, cat, or horse. A total of 34 references were identified using the search terms listed above. This total included 21 references for dogs and 13 for cats. No references were identified for horses. This total was reduced to 21 after combining the separate searches and removing duplicates. These 21 references are listed in APPENDIX IV.

   Since this review is focused on oral administration of CBD, studies describing *in vitro* assays using cells or tissues were excluded from the search results. Studies that used iv, inhalation or topical administration were not considered unless the oral route was also investigated. Studies that used a combination of THC and CBD were also not considered. The searches were limited to peer-reviewed publications. Of these 21 references, only 3 described oral administration of CBD in target species and are discussed below. However, none of these studies are adequately designed safety studies to address long-term use of CBD in animal food products, and two of the studies focus on clinical effectiveness of parameters that would cause CBD to be regulated as a drug. The studies are discussed below for completeness and raise additional questions about hepatotoxicity potential in target animal species. We also note that only one of the three dog studies available used healthy animals. Data generated in diseased animals, such as those with osteoarthritis or idiopathic epilepsy, would generally not be appropriate for substantiating the target animal safety of a substance intended for use in animal food because the metabolism of these animals may differ from normal, healthy animals that would be expected to consume a food product.

2. Evidence from scientific literature that CBD is not GRAS for use in animal food:

All three of the target animal references that met the criteria were dog studies. The available cat studies did not meet the criteria and no horse studies were identified in the literature search.

a. A study examined the pharmacokinetics following oral and transdermal administered CBD in healthy beagle dogs (Bartner et al., 2018). Dogs (n=30, 10 per group) were assigned to receive oral microencapsulated oil beads, oral CBD-infused oil, or CBD-infused transdermal cream, at a concentration of 75 mg or 150 mg every 12 hours for 6 weeks. Serial CBD plasma concentrations were measured over the first 12 h and repeated at 2, 4, and 6 wk. Higher systemic levels were observed with the oral CBD-infused oil formulation and the half-lives were reported. The study found that the exposure was concentration-proportional, and the oral CBD-infused oil provided the most favorable pharmacokinetic profile but did not assess any safety parameters. Further analysis of this study in a report by McGrath et al. (2018) with a focus on safety parameters reported an increase in serum ALP in some dogs and diarrhea in all dogs that was not associated with formulation or dose of CBD.

b. A study to determine the oral pharmacokinetics and assess safety and analgesic efficacy of a CBD-enriched oil was performed in dogs with osteoarthritis (OA) (Gamble et al., 2018). Single-dose pharmacokinetics was first performed using 4 beagle dogs and two different concentrations of CBD-enriched (2 and 8 mg/kg) oil. Pharmacokinetics revealed an elimination half-life of 4.2 h at both doses and no observable side effects. This was followed by a randomized placebo-controlled, veterinarian, and owner blinded, cross-over study using 22 client owned dogs with clinically and radiographically confirmed OA. Of these, only 16 dogs completed the study. Dogs received CBD-enriched oil (2 mg/kg) or placebo oil every 12 h. Each treatment lasted for 4 weeks with a 2-week washout period. Baseline veterinary assessment and owner questionnaires were completed before initiating each treatment and at weeks 2 and 4. Hematology, serum chemistry and physical examinations were performed at each visit. A mixed model analysis, analyzing the change from enrollment baseline for all other time points was utilized for all variables of interest. Clinically, canine brief pain inventory and Hudson activity scores showed a significant decrease in pain and increase in activity. Veterinary assessment showed decreased pain during CBD treatment. No side effects were reported by owners. However, serum chemistry showed an increase in alkaline phosphatase during CBD treatment. The authors acknowledge that further long-term studies with larger populations are needed. No other safety parameters were reported.

c. A study to assess the effect of oral cannabidiol (CBD) administration in addition to conventional antiepileptic treatment on seizure frequency in dogs with idiopathic epilepsy, randomly assigned 26 client-owned dogs with intractable idiopathic epilepsy to a CBD (n = 12) or placebo (n = 14) group (McGrath et al., 2019). The CBD group received CBD-infused oil (2.5 mg/kg) twice daily for 12 weeks in addition to existing antiepileptic treatments, and the placebo group received noninfused oil under the same conditions. Seizure activity, adverse effects, and plasma CBD concentrations were compared between groups. Dogs in the CBD group had a significant (median change, 33%) reduction in seizure frequency, compared with the placebo group. However, the proportion of dogs considered responders to treatment (≥ 50% decrease in seizure activity) was similar between groups. Plasma CBD concentrations were correlated with reduction in seizure

frequency. Dogs in the CBD group had a significant increase in serum alkaline phosphatase activity. No adverse behavioral effects were reported by owners. No other safety parameters were reported.

3. **Conclusion for animal food:** CBD is not GRAS for any intended use in animal food. Identified safety concerns in laboratory animal species together with no data addressing the potential for formation of CBD residues in edible tissues of food producing species and insufficient published data in the primary target animal species (dogs, cats, and horses) prevents CBD from meeting the GRAS criteria for use in food for any animal species. The increases in alkaline phosphatase observed in dogs during CBD treatment in the published short-term studies that were found, combined with knowledge of hepatoxicity in other species, confirms that the effects of CBD on the liver in target species must be more completely understood before a safety conclusion can be made for any animal species.

General Conclusions

There is no food additive regulation establishing safe conditions of use of CBD. In light of the lack of CBD's use in foods prior to 1958, as well as the lack of published scientific data and information establishing CBD's safe use in food for humans or animals, the use of CBD in food for humans or animals does not meet the criteria for GRAS. There are inadequate safety data; thus, general recognition of safety cannot be established based on generally available data and information. Indeed, the available data from animal studies, such as evidence of male reproductive toxicity in monkeys and rats, are a cause for concern. 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)]. Introducing an adulterated food into interstate commerce is a prohibited act under Section 301(a) of the FD&C Act [21 U.S.C. § 331(a)].

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APPENDIX I

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