Hemp-Derived CBD: Health Impacts, Safety Concerns, and Research Gaps

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CBD Is One of Many Different Cannabinoids in Cannabis

- Eleven general types of cannabinoids
- Total cannabinoids (120)
  - Δ^9-Type (23)
  - Δ^8-Type (5)
  - Cannabigerol (CBG) Type (16)
  - Cannabichromene (CBC) Type (9)
  - Cannabidiol (CBD) Type (7)
  - Cannabinodiol (CBND) Type (2)
  - Cannabielsoin (CBE) Type (5)
  - Cannabicyclol (CBL) Type (3)
  - Cannabinol (CBN) Type (11)
  - Cannabitrol (CBT) Type (9)
  - Miscellaneous Types (30)
- Total non-cannabinoids (445)

Background: Farm Bill

- Reduces limitations on cultivation of hemp in U.S.
  - 2018 Farm Bill explicitly allows commercial sale of hemp and hemp-derived products
- 2018 Farm Bill allows states to decide whether to take primary regulatory authority over cultivation of hemp in that state
- “Nothing in this title or an amendment made by this title prohibits the interstate commerce of hemp (as defined in Section 297A of the Agricultural Marketing Act)…or hemp products.”

Background: Several Hemp Derived Ingredients are GRAS

- In 2018, three GRAS Notifications for a Hemp-derived products (Hemp Seed Oil, Hemp Seed Protein, Dehulled Hemp Seed) were filed with the FDA and received “no questions” letters.
  - Hemp seeds contain trace amounts of THC.
  - The ingredients are intended to be a source of protein and fats.
  - Intended uses are conventional foods.
  - **CBD cumulative exposure from finished ingredients is estimated at 722.6 micrograms/day.**

Hemp-Derived Ingredients

- GRAS Notified Ingredients (contains trace levels of THC and CBD)
  - Hemp seed (de-hulled)
  - Hemp seed protein powder
  - Hemp seed oil
- Non-GRAS or NDI-Notified Ingredients
  - Hemp oil extracted from the entire hemp plant (or portions of the hemp plant other than seeds)
  - CBD isolate—the isolated and purified form of CBD extracted from the whole hemp plant

2018 Farm Bill Does Not Amend FDA's Authority

- 2018 Farm Bill contains a provision that nothing in the law affects or amends FDA's authority under the Federal Food, Drug, and Cosmetic Act (FFDCA).
- To the extent that hemp or hemp-derived ingredients are used in an FDA-regulated product, they are subject to FDA's regulatory authority, which is unchanged by 2018 Farm Bill.

Background: Public Hearing on CBD (5/19)

- Key questions about product safety need to be addressed for CBD intake from foods.
  - Data are needed to determine safety thresholds for CBD.
  - Datasets/information should be objective, of adequate quality and available for transparent review.
  - Lab testing and data analyses need to be replicable.

FDA Warning Letters

- FDA issued warning letters to companies for illegally selling products containing CBD in ways that violate the FD&C Act*:
  - Based on the lack of scientific information supporting the safety of CBD in food, the FDA is also indicating today that it cannot conclude that CBD is generally recognized as safe (GRAS) among qualified experts for its use in human or animal food.
  - Many unanswered questions and data gaps about CBD toxicity exist, and some of the available data raise serious concerns about potential harm from CBD.

* https://www.fda.gov/news-events/press-announcements/fda-warns-15-companies-illegally-selling-various-products-containing-cannabidiol-agency-details (November 25, 2019)

CBD: What We Don’t Know

The Safety of Food Ingredients is Determined Using Risk Assessments

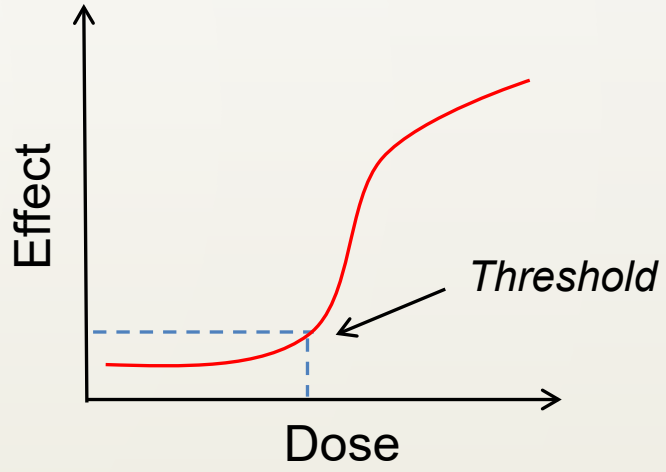
- Risk assessment = the systematic process of evaluating the potential for adverse effects to hazardous agents or activities
- Toxic responses increase in incidence, severity, and sometimes both, as the dose increases
- The four elements of a risk assessment:
    1. Hazard Identification
    2. Hazard Characterization
    3. Exposure Assessment
    4. Risk Characterization

Hazard Identification

- Is the evaluation of whether a particular chemical can cause an adverse health effect
- Involves identifying the potential for exposure, as well as the nature of the adverse effect expected
- Methods used to identify hazards:
  - Computational toxicology studies (i.e., structure-activity relationships)
  - *In vitro* tests
  - Short-term and long-term toxicology studies
  - Human studies (i.e., clinical trials, occupational exposure, epidemiological studies, post-marketing surveillance)

Hazard Characterization

- Is the quantitative characterization of chemical potency
- It is the relationship between exposure and effect.
  - What is the dose response?
  - Is there a threshold for the toxic effects (NOAEL/LOAEL)?



Exposure Assessment

- Exposure is defined as the concentration or amount of a particular agent that reaches a target organism, system, or (sub)population in a specific frequency for a defined duration (WHO, 2004).
- Key elements to assessing exposure:
  - Dose administered
  - Frequency
  - Duration
  - Route of exposure
  - The amount absorbed/amount reaching target

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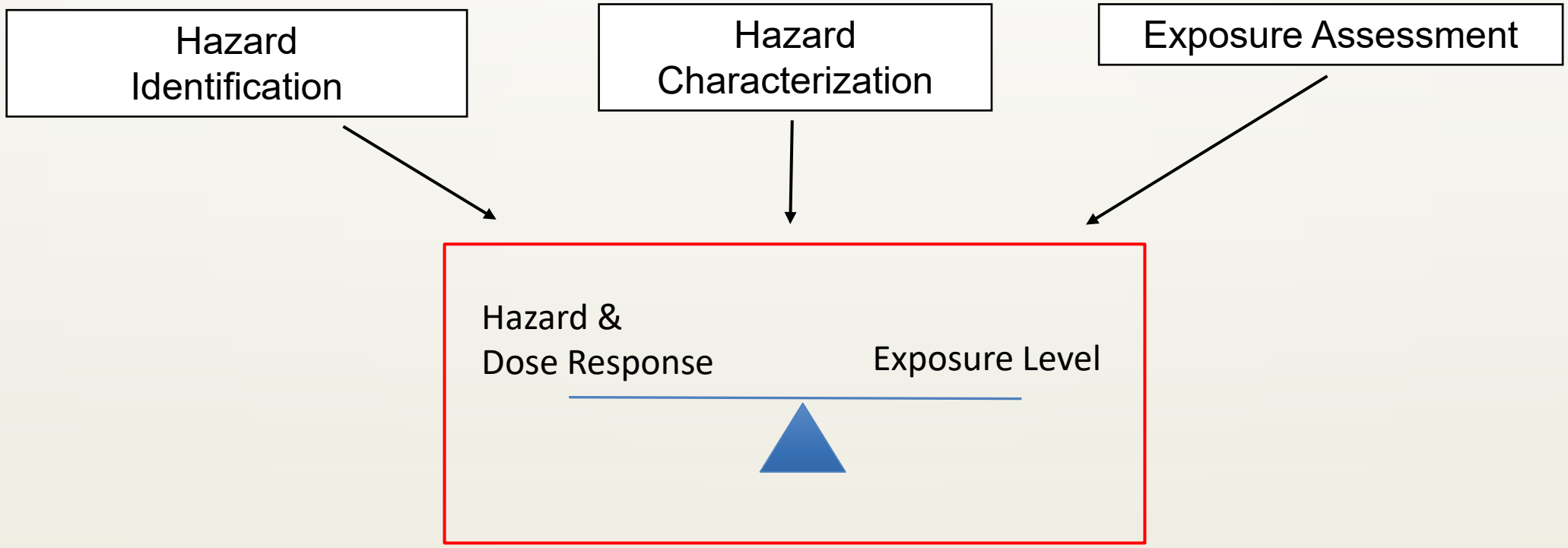
Risk Characterization

- Is the quantitative assessment of the likelihood of observing the toxic effect in the population being studied at the exposure level



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What Changes the Sensitivity of a Response to a Dose

- **Interspecies Variation**
  - Animals → Humans
- **Intraspecies Variation: Human variability**
  - Health status
  - Body weight
  - Age
  - Sensitivity

Differences In Sensitivity

- **Species: (interspecies variation)**
  - Not all organisms have same sensitivity to chemicals
  - A human is not a big rat

What Changes the Severity of a Response

- Increase in Dose, Duration, Frequency, of Intake
- Increase in Bioavailability

Extrapolation to Human Safe Dose

- **Safety Factor or Uncertainty Factor:**
  - A multiplier used to account for differences between animals and humans, between differences in humans, and limitations in animal studies that allows us to deal with the uncertainty about the predictive value of the animal data to extrapolate to humans in the context of safety

Identification of NOAEL from an Animal Toxicology Study

- **NOAEL:** the No-Observable-Adverse-Effect Level which is the highest dose that did not elicit an adverse effect in a properly designed and executed toxicology study

Safety Factors

- Intraspecies differences (10 X): (healthy to sick)
- Interspecies extrapolation (10 X): (e.g. rat to human)
- Subchronic exposure to chronic exposure (10 X): (90 day rat toxicology to lifetime human intake)

Derivation of the Acceptable Daily Intake (ADI)

$$ADI = \frac{NOAEL\ (mg/kg/day)}{Safety\ Factors}$$

Background: Drug Approval for Epidiolex®

- In 2018, FDA approved Epidiolex, a CBD-containing drug, for the treatment of Dravet and Lennox-Gastaut Syndrome in patients 2 years of age and older.
  - Is intended for oral administration.
  - Is available in bottles containing 100 ml of a 100 mg/ml solution for oral administration.
  - Recommended starting dosage is 2.5 mg/kg taken twice a day (5 mg/kg/day).
  - Dosage can then be increased to 20 mg/kg/day, based on individual clinical response and tolerability.

FDA Summary of Metabolism for Epidiolex

- CBD exhibits a nonlinear increase in absorption with dose
  - The food effects are large for CBD. With a high-fat meal, the Cmax and AUC of cannabidiol increased by approximately 5-fold and 4-fold respectively.
- CBD is metabolized to two major metabolites in humans:
  - 7-hydroxy-cannabidiol (7-OH-CBD) which is further metabolized by conjugation with glucuronic acid or further oxidation to 7-carboxy-cannabidiol (7-COOH-CBD).
- Compared to humans, rats and dogs do not produce the two major human metabolites to a comparable extent.
  - Although the toxicity evaluation of the parent compound was considered adequate, the assessment of 7-COOH-CBD metabolite was inadequate (at least 90% of all drug-related material in human plasma).
- High plasma protein binding (>94%) was observed for CBD and metabolites
- Mean elimination half-life of CBD ranged from 56 to 61 hours in healthy volunteers.

FDA Summary of Drug-drug Interaction for Epidiolex

- Drug-drug interaction (in vitro)
  - In vitro studies suggest that CBD inhibits (IC50 <10 μM) CYP1A2, CYP2B6, CYP2C8, CYP2C19, and CYP3A4. CBD is also a time-dependent inhibitor of CYP3A4, CYP1A2 in vitro. CBD is a strong inhibitor of UGT1A9 and UGT2B7 in human liver microsomes.
  - Cannabidiol induces CYP1A2, CYP2B6, and CYP3A4 in vitro at clinically relevant concentrations.

FDA Summary of Toxicology for Epidiolex

- In the pivotal oral toxicity studies (26-week in Wistar rat; 15, 50 and 150 mg/kg, 39-week in Beagle dog; 10, 50, 100 mg/kg), the primary target organ was the liver in both species at mid and high doses in rat, all doses in dog.
- There was no evidence of genotoxicity with CBD in a standard battery of in vitro and in vivo tests (Ames, in vivo Micronucleus, Comet assay).
- Total litter loss at the high dose (250 mg/kg) was observed in the embryofetal development study in rats.
- In the pre- and postnatal development study in rats (75, 150 and 250 mg/kg), adverse effects were observed on body weight, attainment of developmental landmarks, learning and memory, and reproductive structure and, possibly, function, primarily at the medium and high doses (150 mg/kg and 250 mg/kg).
- A juvenile toxicity study was conducted in rats. Findings included neurobehavioral deficits and delayed sexual maturation in males.

FDA Summary of Clinical Outcomes for Epidiolex

- Results from Clinical Studies
  - The most commonly observed adverse events were: central nervous system (e.g., somnolence and sedation), gastrointestinal (e.g., decreased appetite and diarrhea), hepatic (e.g., transaminase elevations) and infections (e.g., pneumonia). These events were generally mild to moderate in severity.
  - Serious and/or severe adverse events were generally related to transaminase elevations, somnolence and lethargy, and infections.
  - A signal for drug-induced liver toxicity was seen in the frequencies of adverse events of transaminase elevations: 8% in the CBD 10 mg/kg/day group, 16% in the CBD 20 mg/kg/day group, and 3% in the placebo group.

Review of CBD Toxicity in the Context of Drug Use (Huestis et al. 2019)

- CBD is not risk-free.
  - In animals, CBD AEs 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, although at doses higher than recommended for human pharmacotherapies.
  - Human CBD studies for epilepsy and psychiatric disorders reported CBD-induced drug-drug interactions, hepatic abnormalities, diarrhea, fatigue, vomiting, and somnolence.

Discussion

- Epidiolex Summary Basis of Approval indicates the following hazards:
  - Metabolism in humans differs from animal models used in toxicology testing; in addition food matrix effects are large.
  - Potential for CBD-drug interaction.
  - Toxicology studies reveal: primary target organ of toxicity is liver; developmental and reproductive toxicity.
  - Major adverse clinical outcome is liver toxicity.
- Epidiolex composition is undisclosed; maximum dosage is 20 mg/kg/day (Assuming a 12 kg child and a 60 kg adult and the drug product contains 100% CBD), the resulting intake will be approximately 240 mg and 1200 mg CBD/day, respectively.

Discussion

- Approval of Epidiolex based on risk/benefit consideration.
- The risks associated with CBD treatment are acceptable, particularly given the findings of clinical efficacy in LGS and DS, which are serious, debilitating, and life-threatening disorders.
  - Although the risk of liver injury has the potential to be serious, the observed risk can be appropriately managed with inclusion of relevant language in labeling, education of prescribers regarding the risk of transaminase elevation and need for monitoring of liver enzyme levels, and further characterization of the risk in the postmarket setting.
- Risk (Dose-response and threshold) for these effects at lower intakes of CBD from a dietary ingredient needs to be determined.
  - Unlike the approval of new drugs, the law for food additives does not permit FDA to consider ‘benefits’ from the use of the additive in its decision – rather; it is a safety per se standard; no risk/benefit argument can be applied.

Safety Reviews of CBD for Dietary Ingredient Use

The World Health Organization (WHO) 40th Meeting of the Expert Committee on Drug Dependence (June 2018)

- **Cannabidiol (CBD)**
  - The Committee recommended that preparations considered to be pure CBD should not be scheduled within the International Drug Control Conventions. Based on:
    - There are no case reports of abuse or dependence relating to the use of pure CBD. No public health problems have been associated with CBD use;
    - CBD has been found to be generally well tolerated with a good safety profile. Adverse effects of CBD use include loss of appetite, diarrhea and fatigue;
    - CBD is not specifically listed in the schedules of the 1961, 1971 or 1988 United Nations International Drug Control Conventions. However, if prepared as an extract or tincture of cannabis it is controlled in Schedule I of the 1961 Single Convention on Narcotic Drugs;
    - There is no evidence that CBD as a substance is liable to similar abuse and similar ill-effects as the substances in the 1961 or 1971 Conventions such as cannabis or THC, respectively.

https://www.who.int/medicines/access/controlled-substances/ecdd_40_meeting/en/

Toxicology Studies

- Genotoxicity and Subchronic Toxicology of Hemp-Derived Oil containing CBD (GLP and OECD compliant) (Marx et al. 2018).
  - No evidence of genotoxicity was found in a bacterial reverse mutation test (Ames), in an in vitro mammalian chromosomal aberration test, or in an in vivo mouse micronucleus study.
  - 14-day range finding rat toxicology study at 1000, 2000, 4000 mg/kg bw/day indicated adverse findings at all doses: clinical signs, decreased body weight gain, adverse macroscopic changes in liver, adrenal, spleen, thymus, seminal vesicle and prostate and testes. Adverse effects on liver thymus, spleen and adrenal gland weights noted. Histologic examination revealed adverse effects in adrenal glands, liver, kidney, thymus, spleen seminal vesicle and prostate. Additionally, lack of mature spermatozoa and spermatids.

Toxicology Studies

- Genotoxicity and Subchronic Toxicology of Hemp-Derived CBD Containing Oil (GLP and OECD compliant) (Marx et al. 2018).
  - A 90-day oral toxicity study in rats of 100, 360, and 720 mg/kg bw/day (product is 25% CBD: findings consistent with FDA summary basis of Epidiolex approval:
    - Adverse effects on clinical signs, body weight, body weight gain, food consumption at mid and high doses.
    - Increases in ALP (statistically significant in high dose females), GGT in mid and high dose males and females.
    - Increased liver and adrenal weights in mid and high dose males and females; Decreased epididymis weight in mid and high dose males and decreased uterus weight in mid and high dose females and decreased spleen weight in low, mid and high dose females.
    - Adverse histopathologic findings in adrenals (high dose male and female).
- The NOAEL was considered by the authors to be 100 mg/kg/day for males and 360 mg/kg/day for females.

Draft Assessment For CRN

- Systematic review of CBD safety including pharmacokinetics, clinical tolerance, safety testing in animal models and potential drug interaction
  - Pharmacokinetic studies show that absorption increased with fatty foods and plasm levels of CBD are increased in people with liver disease
  - CBD may have effects of P-450 enzymes with potential consequences for drug interaction
  - The adverse events reported in Epidiolex clinical studies included an increase in drowsiness, a decrease in appetite, an increase in diarrhea, and an increase in serum levels of liver enzymes
  - Concern from animal studies of adverse effects on embryo-fetal toxicity

Draft Assessment For CRN

- Preliminary suggested cautionary statements for CBD are:
  - decrease the dose of CBD if you have symptoms of liver disease,
  - check with your pharmacist before combining prescription drugs with CBD, and
  - if you are pregnant of breastfeeding consult your doctor before use.
- Information has been obtained from animal studies but as yet there are no human studies. A post-marketing survey of use by women who plan to get pregnant, pregnant women, or are breastfeeding that reports on pregnancy outcomes and adverse events might to considered to supply more information on the subject.

Scoping Paper on the Potential Adverse Effects of CBD Products

- Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment (COT)

COT Meeting Minutes (July 2019)

- Some CBD products would not only contain CBD but also other cannabinoids such as tetrahydrocannabinol (THC), potentially due to different extraction methods.
- There was potential for interactions between the cannabinoids present in CBD products and this in turn, could affect the potential adverse effects of CBD.
- Lack of data on the mechanism of action of CBD and whether it was truly non-psychoactive. In particular, there was a lack of understanding of the potential interactions at CB1 and CB2 receptors.

COT Meeting Minutes

- Lack of data concerning the absorption of CBD from different food matrices. There was also little information on plasma concentrations and the bioavailability of CBD in different products. The extent of inter-individual variation in disposition of CBD was also uncertain.
- CBD could potentially accumulate in adipose tissue (including the brain) as well as other areas of the body due to its lipophilic properties.

COT Meeting Minutes

- Based on the currently available in vitro and in vivo data, CBD appeared to have the following adverse effects:
  - Hepatoxicity, immunotoxicity, reproductive toxicity, changes to organ weights and alterations to drug metabolizing enzymes (P450).
  - Genotoxicity data were conflicting but indicated genotoxic potential in some but not all in vivo studies.
  - Epidiolex® safety data sheet the most common adverse reactions noted were somnolence, decreased appetite, diarrhea, transaminase elevations (hepatocellular injury), fatigue, malaise, asthenia, rash, insomnia, sleep disorder/poor quality sleep and infections.

COT Secretariat Preliminary Background Paper January 2020

- It is important to note that the safety profile of food grade CBD might be different to medical grade products due to differences in composition and production. Products may also be formulated in such a way to enhance uptake.
- In humans, adverse liver effects were observed at 5 mg/kg/day and there may be possible effects at 1 mg/kg/day. As stated on the GW Pharmaceutical statement: “5 mg/kg/day of CBD is not a safe dosage and causes an unacceptable safety signal outside of a clinical setting where there is a benefit risk consideration.”
- Other uncertainties might be the lack of chronic data in humans, the lack of data on lactation, the interaction with other cannabinoids/botanicals as well as other medicines or compounds such as alcohol and the lack of data in some vulnerable groups. CBD has the potential to accumulate due to its lipophilic properties.
- A possible provisional risk assessment has demonstrated that a health-based guidance value of 0.17 mg/kg bw/day (4 mg/day in a 70 kg adult) would be the maximum acceptable daily dose derived from a LOAEL in humans.

Food Standards Agency (UK) CBD Advice

- The CBD safety advice given February 13, 2020 by the FSA advises that vulnerable groups, including pregnant and breastfeeding women, should not take CBD, and healthy adults should take no more than 70mg a day. This doesn't mean that these levels are definitely safe, but that the evidence we have suggests adverse health effects could potentially be seen above this.
  - **70 mg is total intake from ALL sources**
- The FSA is giving the CBD industry a deadline of 31 March 2021 to submit valid novel food authorization applications.
  - After this date, only products which have submitted a valid application will be allowed to remain on the market.
- The reality of getting authorization for a novel food from the FSA is burdensome and involves a dossier of rigorous and comprehensive scientific data

CBD in Jelly Beans

- Spectrum Confections sells the CBD jellybeans in 38 flavors like toasted marshmallow, piña colada and strawberry cheesecake. It also sells sour and sugarless versions.
- Each jellybean has about 10 mg of CBD in it.
- There were 15 billion Jelly Belly jellybeans eaten in 2017.
- How many jellybeans do you consume in a single seating?
- Would you eat more than 7?
- How many dietary sources of CBD are there that would increase cumulative intake (oils, pills, vapes, edibles, beverages…)?

https://www.washingtonpost.com/food/2019/03/19/no-cbd-infused-jelly-beans-definitely-wont-get-you-high-heres-why/ Accessed September 7, 2019

Why Quantitative Risk Assessment May Not Support the FSA Limit of 70 mg CBD/day

- NOAEL in 90-day rat study reported as 100 mg/kg/day (25 mg/kg CBD/day) (Marx et al. 2018) (resulting in 1 mg/kg oil for 70 kg human or 70 mg/day or 17.5 mg CBD/day); 26-week rat study reported as 15 mg/kg/day (Epidiolex) (resulting in 10.5 mg CBD/day); does not account for uncertainty in extrapolation based on combination of: intraspecies, interspecies and subchronic to chronic duration.
- Rat may not be the right model (known pharmacokinetic differences).
- Provisional risk assessment provides a health-based guidance value of 0.17 mg/kg bw/day (4 mg/day in a 70 kg adult) from human data.
- No data is available to predict CBD effects following long-term exposure on hormones, and the immune system. Long term human data is missing.
- Insufficient data to assess and characterize the risk of reproductive and developmental toxicity at relevant levels of exposure.
- We can not yet account for the effects of different foods matrices on the bioavailability and toxicity of CBD? Known effect of fat on increasing Cmax and AUC. We can not yet account for ingestion from multiple sources.
- How do we address the issue of CBD-drug interactions?

Conclusions

- Data gaps must be filled to address the risk of CBD exposure as a dietary ingredient.
- The challenges of dietary ingredient safety can be overcome through carefully designed quantitative risk assessments.

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Thank You!