U.S. FOOD & DRUG ADMINISTRATION

Meeting of the Science Board to the U.S. Food and Drug Administration

Challenges in regulatory oversight for substances with predicted pharmacological activity, marketed in foods and dietary supplements, using cannabinoids as a case study

June 14, 2022

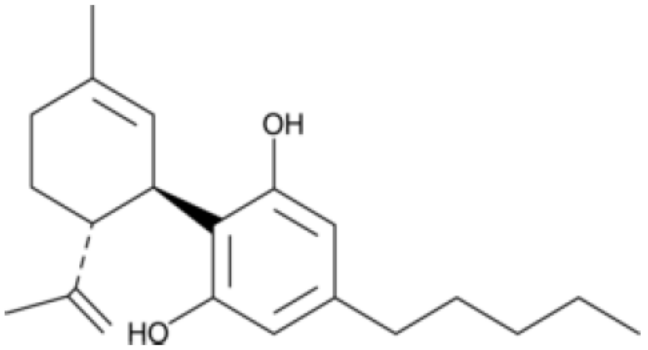
Janet Woodcock, MD
Principal Deputy Commissioner
Chair, Cannabis Product Committee

Patrick Cournoyer, PhD
Acting Science and Policy Coordinator
Cannabis Product Committee

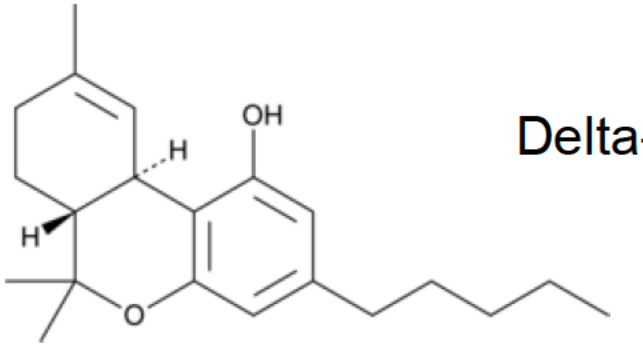
The cannabis plant contains bioactive compounds known as cannabinoids

Cannabis sativa L.

THC and CBD are the most prevalent cannabinoids in most varieties of cannabis.



Cannabidiol
(CBD)



Delta-9 Tetrahydrocannabinol
(THC)

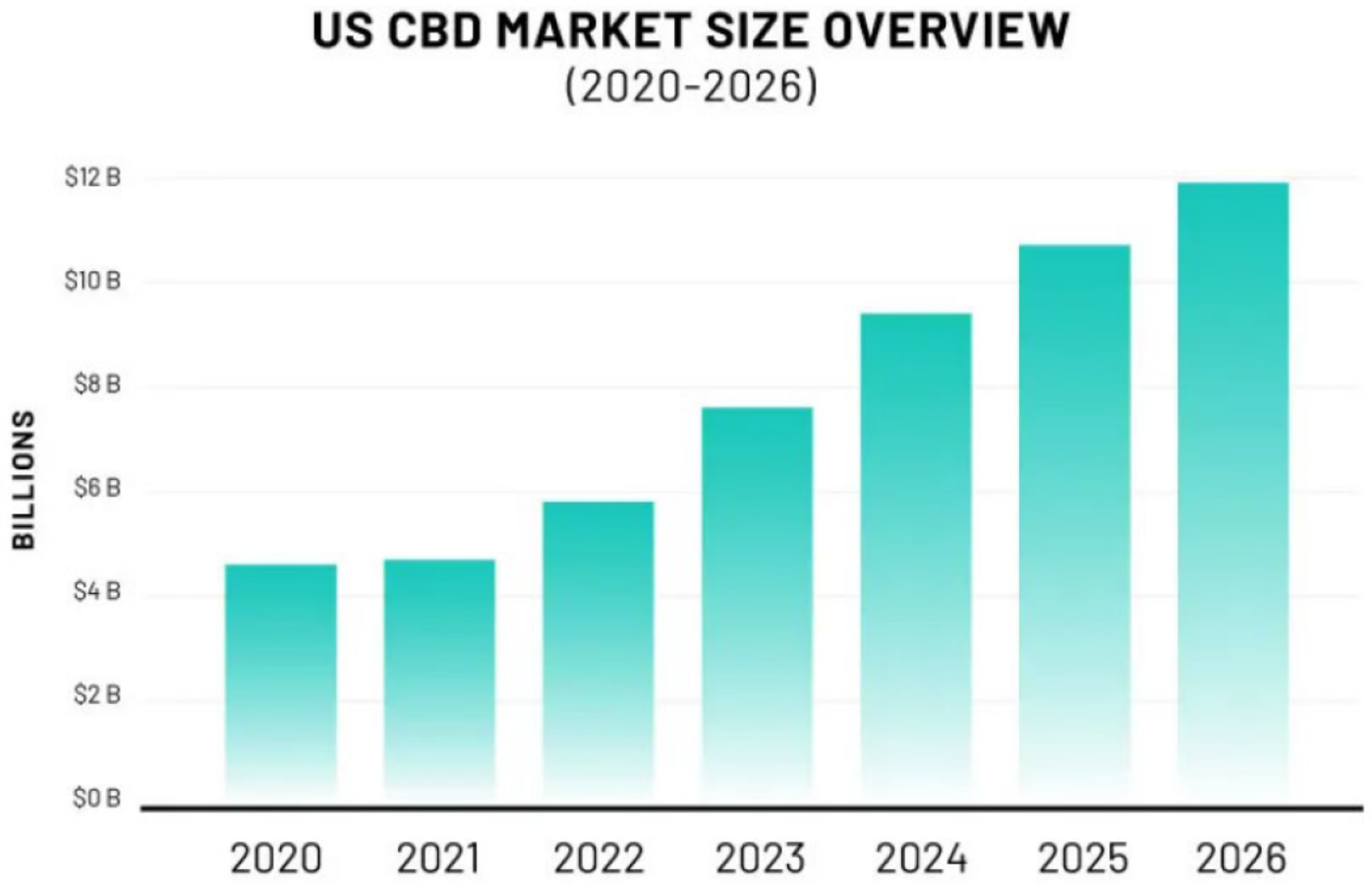
The 2018 Farm Bill removed hemp from regulation under the CSA

- The Agriculture Improvement Act (Farm Bill) of 2018 removed hemp from regulation by the Drug Enforcement Administration (DEA) under schedule 1 of the CSA

- The Farm Bill defined hemp as *Cannabis sativa* L. with delta-9 THC concentration not more than 0.3 percent (on a dry weight basis)
  - Includes hemp derivatives, e.g. CBD
  - Hemp can have high concentrations of CBD

- **Hemp products remain subject to regulation under the Federal Food Drug & Cosmetic Act (FD&C Act), when applicable:**
  - As drugs, foods, dietary supplements, cosmetics, veterinary products

CBD is a $4B+ market that is predicted to grow



Source: Brightfield Group 2021

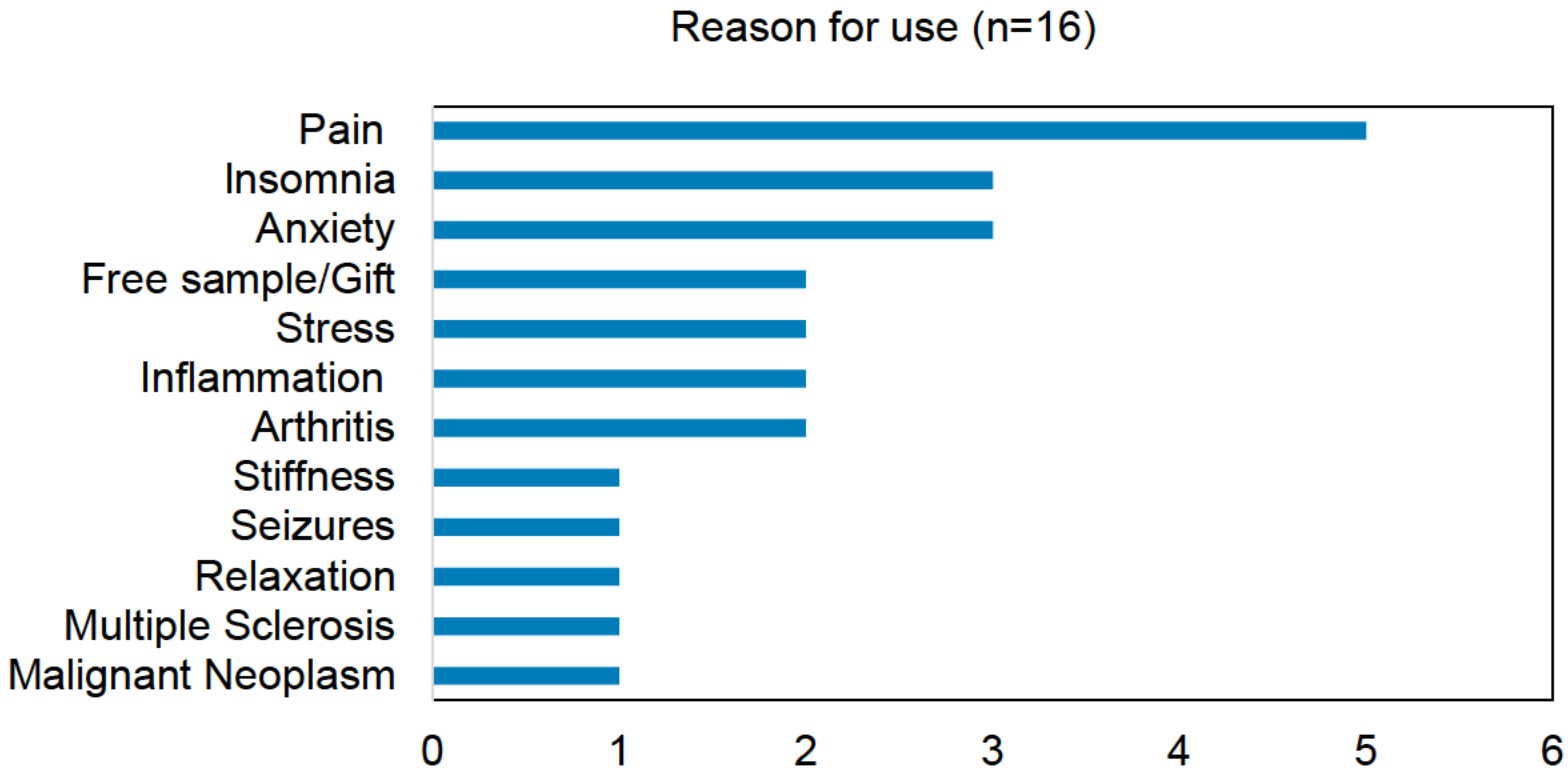
CBD products come in a wide variety of formats

- Tinctures
- Capsules
- Topicals
- Beauty and Personal Care
- Vape Oil and Cartridges
- Combustible/Flower
- For Pets
- Gummies
- Beverages
- Other “Edibles”
- Approved Drug

Consumers use CBD products for a variety of reasons

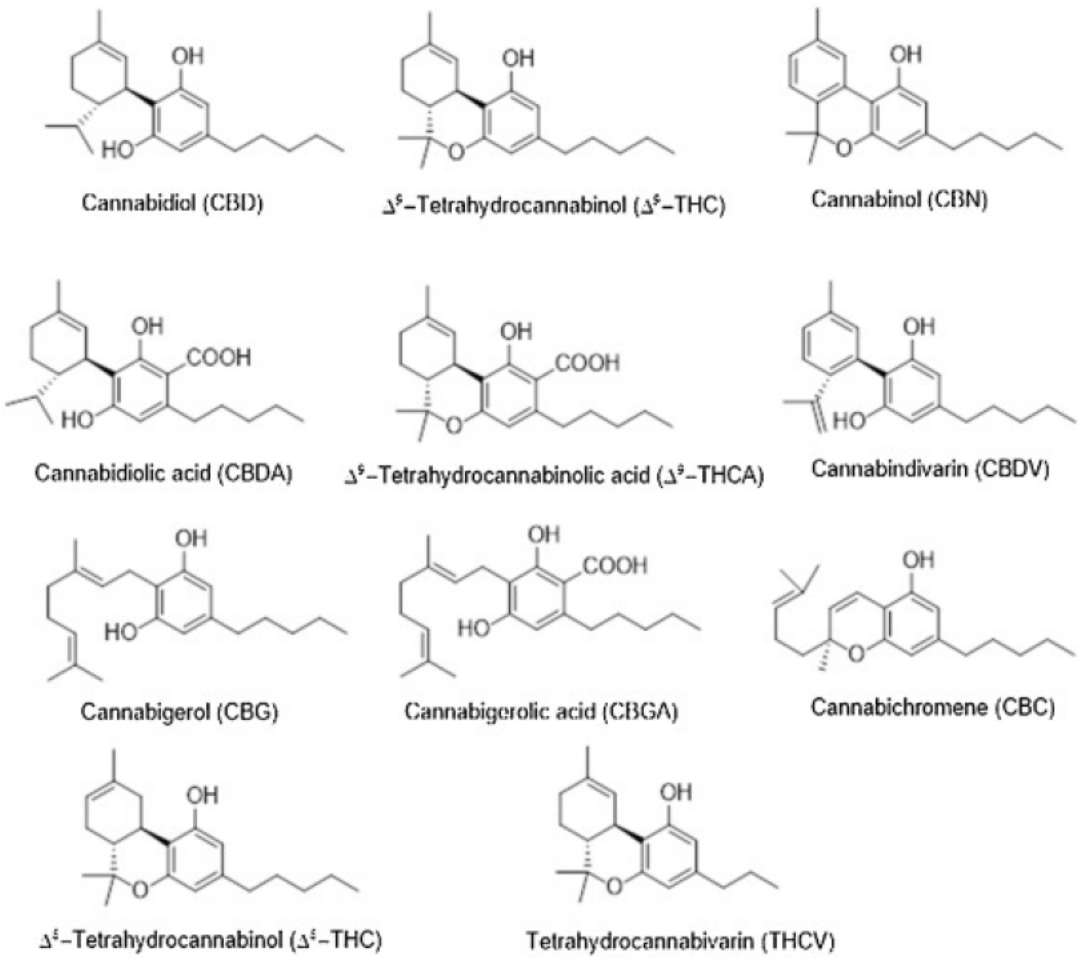
- In an FDA analysis of CBD-related adverse event reports received in 2020, the top three self-reported conditions for using CBD products were **pain, anxiety, and insomnia.**

Cannabidiol (CBD)-Related Adverse Events Reports from the FDA CFSAN Adverse Event Reporting System (CAERS), 2020



https://www.fda.gov/science-research/fda-science-forum/cannabidiol-cbd-related-adverse-events-reports-fda-cfsan-adverse-event-reporting-system-caers-2020

Consumer interest in other cannabinoids is growing



https://doi.org/10.1016/j.jfca.2020.103800

Statutory barriers prevent marketing of CBD in foods and supplements

- CBD is the active ingredient in an FDA-approved drug and was the subject of substantial clinical investigations before it was marketed as a food or dietary supplement.
  - FD&C Act §301(ll): Food prohibition (human and animal food)
  - FD&C Act §201(ff)(3)(B): Dietary supplement exclusion

- FDA has authority to issue a regulation allowing the use of a pharmaceutical ingredient in a food or dietary supplement

- Commissioner Gottlieb stated in 2018 that, "FDA would only consider doing so if the agency were able to determine that all other requirements in the FD&C Act are met, including those required for food additives or new dietary ingredients"

- Commissioner Gottlieb established the CBD Policy Working Group (now the Cannabis Product Committee, CPC)

- **Can CBD meet the safety standards for ingredients in foods and dietary supplements?**

Since 2018 we have collected information

- May 2019 public meeting
- Open public docket
- Analytical sampling study of CBD products
- Collecting information on market and usage
- FDA-led toxicological studies on CBD
- Monitoring adverse event reports
- Scientific literature review
- Established cooperation with external research groups
- Studies as a part of drug development, including post-market studies
- Issued Cannabis-Derived Products Data Acceleration Plan

We held a public meeting in May 2019

- To obtain scientific data and other information about products containing cannabis and cannabis-derived compounds to inform FDA regulatory oversight
- Over 100 speakers presented
- Over 4500 comments submitted to the docket

PUBLIC HEARING

Scientific Data and Information about Products Containing Cannabis or Cannabis-Derived Compounds; Public Hearing

MAY 31, 2019

Share Tweet LinkedIn Email Print

Date: May 31, 2019
Time: 8:00 AM - 6:00 PM ET
Location: White Oak Campus: The Great Room
Conference Center
10903 New Hampshire Ave
Building 31, Room 1503
Silver Spring, MD 20993
United States

Organized By: Food and Drug Administration

Content current as of: 07/03/2019

Background

The Food and Drug Administration held a public hearing to obtain scientific data and information about the safety, manufacturing, product quality, marketing, labeling, and sale of products containing cannabis or cannabis-derived compounds. See the *Federal Register* notice for more information.

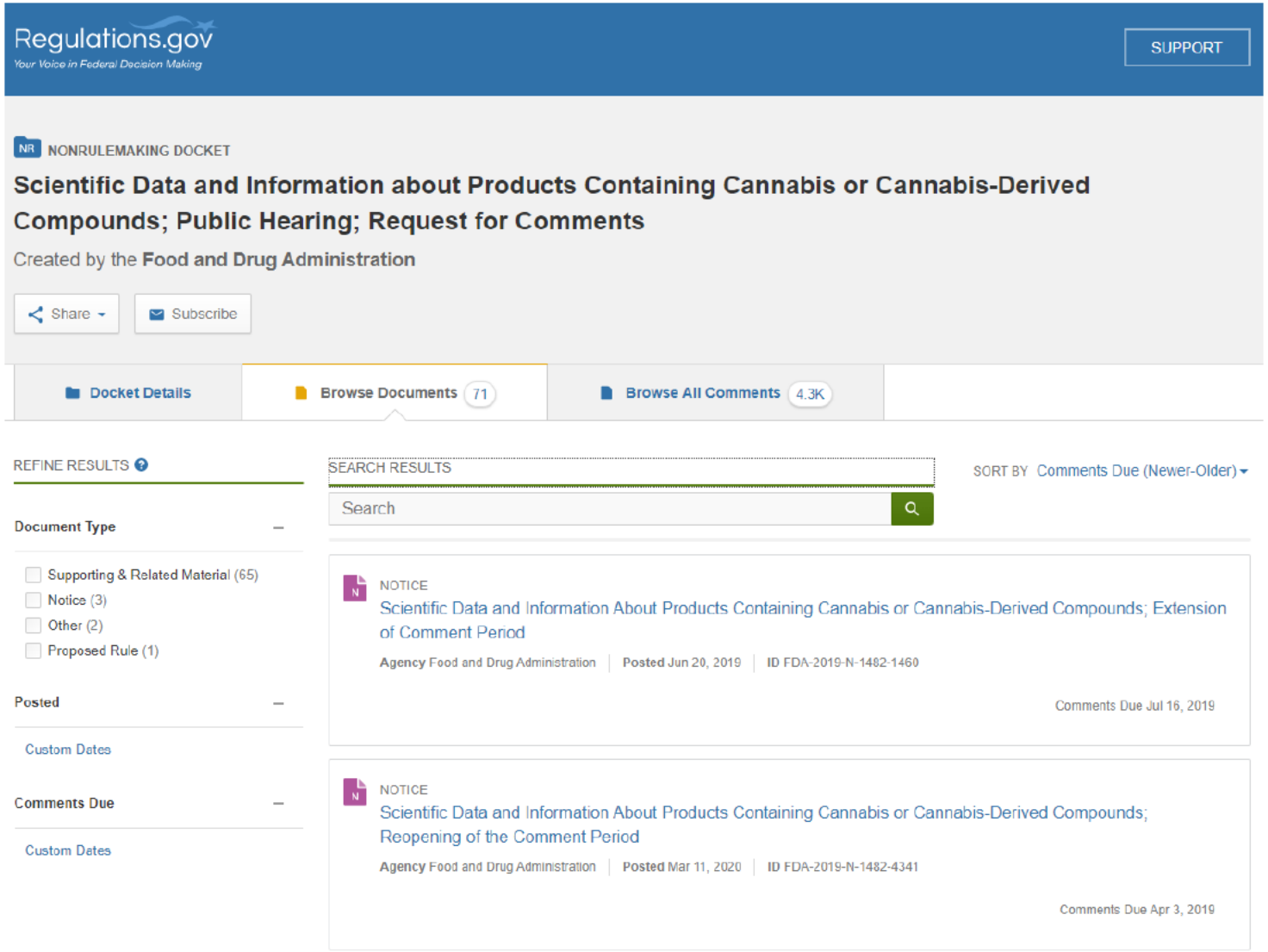
Opening Remarks

Dr. Sharpless' opening remarks are now available.

Presentations

- Presentations made by members of the public

A public docket to receive information remains open

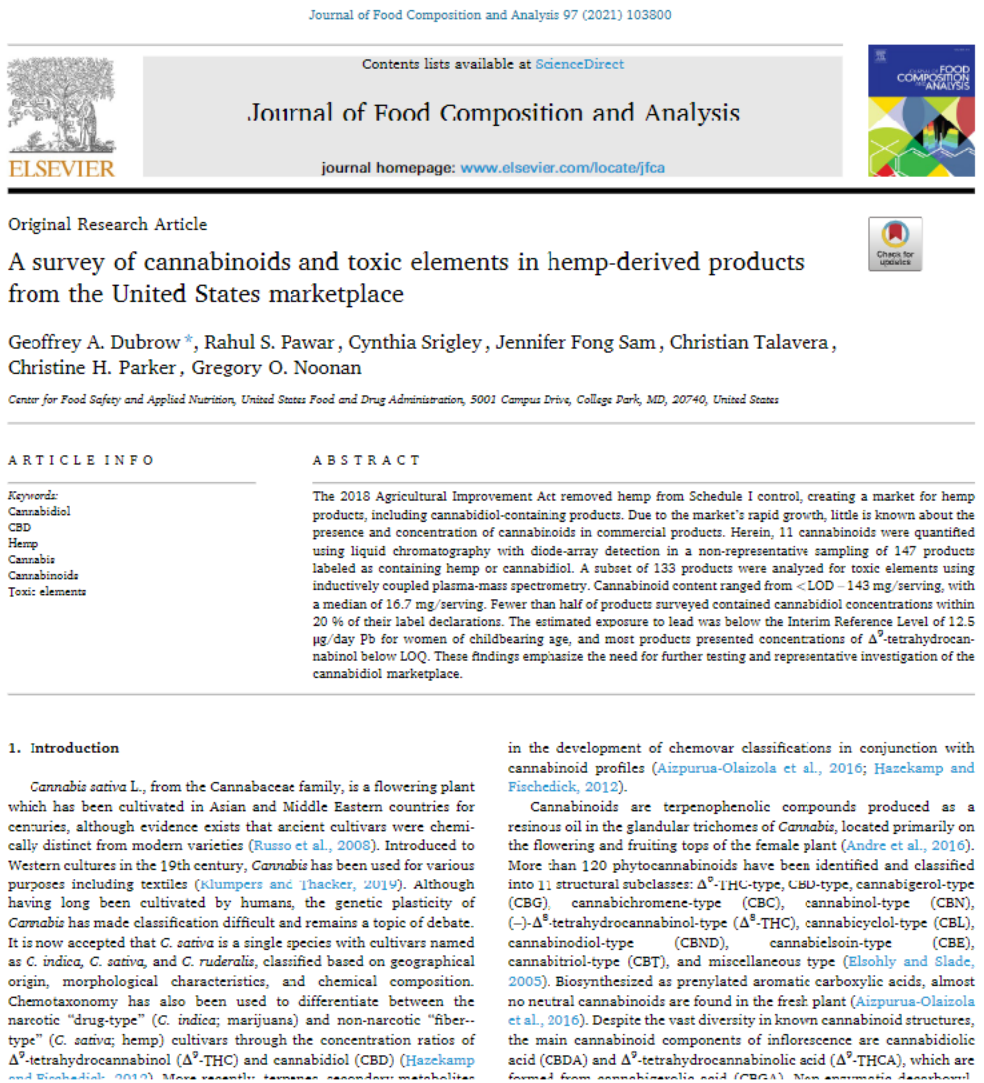


We posted scientific questions about CBD safety related to:

- The risk of liver injury
- Toxicities of active metabolites, e.g. 7-COOH-CBD
- Impact on the male reproductive system
- Effect of co-administration with other substances
- Impact on neurological development
- Sedative effects, including effects on driving and operating heavy machinery
- Transdermal penetration and pharmacokinetics
- Long-term (chronic) repeated dose toxicity studies
- Effect of different routes of administration (e.g., oral, topical, inhaled)
- Effect on pets and food-producing animals
- The potential for bioaccumulation of CBD
- Effect on the eye

We are sampling and testing products on the market

- We analyzed 147 hemp and/or cannabidiol-containing products for 11 cannabinoids
- We analyzed 133 products for toxic elements content
- Products included beverages, edibles, gummies, pet products, tinctures, and oils
- Second phase is underway, targeting approx. 1400 samples for 11 cannabinoids and toxic elements
  - Analyzing a subset for: pesticides, residual solvents, microbes



Journal of Food Composition and Analysis 97 (2021) 103800

Contents lists available at ScienceDirect

Journal of Food Composition and Analysis

journal homepage: www.elsevier.com/locate/jfca

Original Research Article

A survey of cannabinoids and toxic elements in hemp-derived products from the United States marketplace

Geoffrey A. Dubrow *, Rahul S. Pawar, Cynthia Srigley, Jennifer Fong Sam, Christian Talavera, Christine H. Parker, Gregory O. Noonan

Center for Food Safety and Applied Nutrition, United States Food and Drug Administration, 5001 Campus Drive, College Park, MD, 20740, United States

ARTICLE INFO

Keywords:
Cannabidiol
CBD
Hemp
Cannabis
Cannabinoids
Toxic elements

ABSTRACT

The 2018 Agricultural Improvement Act removed hemp from Schedule I control, creating a market for hemp products, including cannabidiol-containing products. Due to the market's rapid growth, little is known about the presence and concentration of cannabinoids in commercial products. Herein, 11 cannabinoids were quantified using liquid chromatography with diode-array detection in a non-representative sampling of 147 products labeled as containing hemp or cannabidiol. A subset of 133 products were analyzed for toxic elements using inductively coupled plasma-mass spectrometry. Cannabinoid content ranged from <LOD – 143 mg/serving, with a median of 16.7 mg/serving. Fewer than half of products surveyed contained cannabidiol concentrations within 20 % of their label declarations. The estimated exposure to lead was below the Interim Reference Level of 12.5 μg/day Pb for women of childbearing age, and most products presented concentrations of Δ^9-tetrahydrocannabinol below LOQ. These findings emphasize the need for further testing and representative investigation of the cannabidiol marketplace.

1. Introduction

Cannabis sativa L., from the Cannabaceae family, is a flowering plant which has been cultivated in Asian and Middle Eastern countries for centuries, although evidence exists that ancient cultivars were chemically distinct from modern varieties (Russo et al., 2008). Introduced to Western cultures in the 19th century, *Cannabis* has been used for various purposes including textiles (Klumpers and Thacker, 2019). Although having long been cultivated by humans, the genetic plasticity of *Cannabis* has made classification difficult and remains a topic of debate. It is now accepted that *C. sativa* is a single species with cultivars named as *C. indica*, *C. sativa*, and *C. ruderalis*, classified based on geographical origin, morphological characteristics, and chemical composition. Chemotaxonomy has also been used to differentiate between the narcotic "drug-type" (*C. indica*; marijuana) and non-narcotic "fiber-type" (*C. sativa*; hemp) cultivars through the concentration ratios of Δ^9-tetrahydrocannabinol (Δ^9-THC) and cannabidiol (CBD) (Hazekamp and Fischedick, 2012). More recently, terpenes, secondary metabolites in the development of chemovar classifications in conjunction with cannabinoid profiles (Aizpurua-Olaizola et al., 2016; Hazekamp and Fischedick, 2012).

Cannabinoids are terpenophenolic compounds produced as a resinous oil in the glandular trichomes of *Cannabis*, located primarily on the flowering and fruiting tops of the female plant (Andre et al., 2016). More than 120 phytocannabinoids have been identified and classified into 11 structural subclasses: Δ^9-THC-type, CBD-type, cannabigerol-type (CBG), cannabichromene-type (CBC), cannabinol-type (CBN), (–)-Δ^8-tetrahydrocannabinol-type (Δ^8-THC), cannabicyclol-type (CBL), cannabinodiol-type (CBND), cannabielsoin-type (CBE), cannabitriol-type (CBT), and miscellaneous type (Elsohly and Slade, 2005). Biosynthesized as prenylated aromatic carboxylic acids, almost no neutral cannabinoids are found in the fresh plant (Aizpurua-Olaizola et al., 2016). Despite the vast diversity in known cannabinoid structures, the main cannabinoid components of inflorescence are cannabidiolic acid (CBDA) and Δ^9-tetrahydrocannabinolic acid (Δ^9-THCA), which are formed from cannabigerolic acid (CBGA). Non-enzymatic decarboxyl-

https://doi.org/10.1016/j.jfca.2020.103800

We are obtaining information on market and usage

Third party market research

Scientific Literature

Cannabis and Cannabinoid Research
Volume X, Number X, 2020
© Mary Ann Liebert, Inc.
DOI: 10.1089/can.2020.0093

Use and Perceptions of Cannabidiol Products in Canada and in the United States

Samantha Goodman,[1,*] Elle Wadsworth,[1] Gillian Schauer,[2] and David Hammond[1]

Abstract
Objectives: This
Materials and M
completed meas
2019 Internation
Results: Past 12
States (26.1%) th
CBD products, ir
vs. 17.6%), vape
most commonly
both countries r
Conclusions: Us
reported health
regarding the th
Keywords: cann

Moltke and Hindocha *Journal of Cannabis Research* (2021) 3:5
https://doi.org/10.1186/s42238-021-00061-5

Journal of Cannabis Research

ORIGINAL RESEARCH Open Access

Reasons for cannabidiol use: a cross-sectional study of CBD users, focusing on self-pe
proble

Julie Moltke[1*]

Abstract
Background: various source
have been sca
self-perceived
Methods: The
survey was ser
demographics
Results: The s

JAMA Network Open

Original Investigation | Public Health

Self-reported Cannabidiol (CBD) Use for Conditions With Proven Therapies

Eric C. Leas, PhD, MPH; Erik M. Hendrickson, MPH, MA; Alicia L. Nobles, PhD, MS; Rory Todd, BA; Davey M. Smith, MD, MAS; Mark Dredze, PhD; John W. Ayers, PhD, MA

Abstract

IMPORTANCE Use of cannabidiol (CBD) has markedly increased in the past 5 years, concurrent with marketing claims that over-the-counter CBD can be used to treat almost any health condition. However, the reasons why individuals use CBD remain unclear.

OBJECTIVE To assess whether individuals are using CBD for diagnosable conditions that have evidence-based therapies.

DESIGN, SETTING, AND PARTICIPANTS This case series assessed claimed treatment applications reported by CBD users in public testimonials shared on the Reddit forum r/CBD. The r/CBD forum was selected because it includes a large, naturally occurring sample of 104 917 registered individuals who publicly discuss their experiences using CBD. All r/CBD posts were obtained from January 1, 2014, through August 31, 2019. A random sample of posts was drawn (n = 3000) and filtered to include posts in which self-identified CBD users testified why they take CBD (n = 376).

Key Points

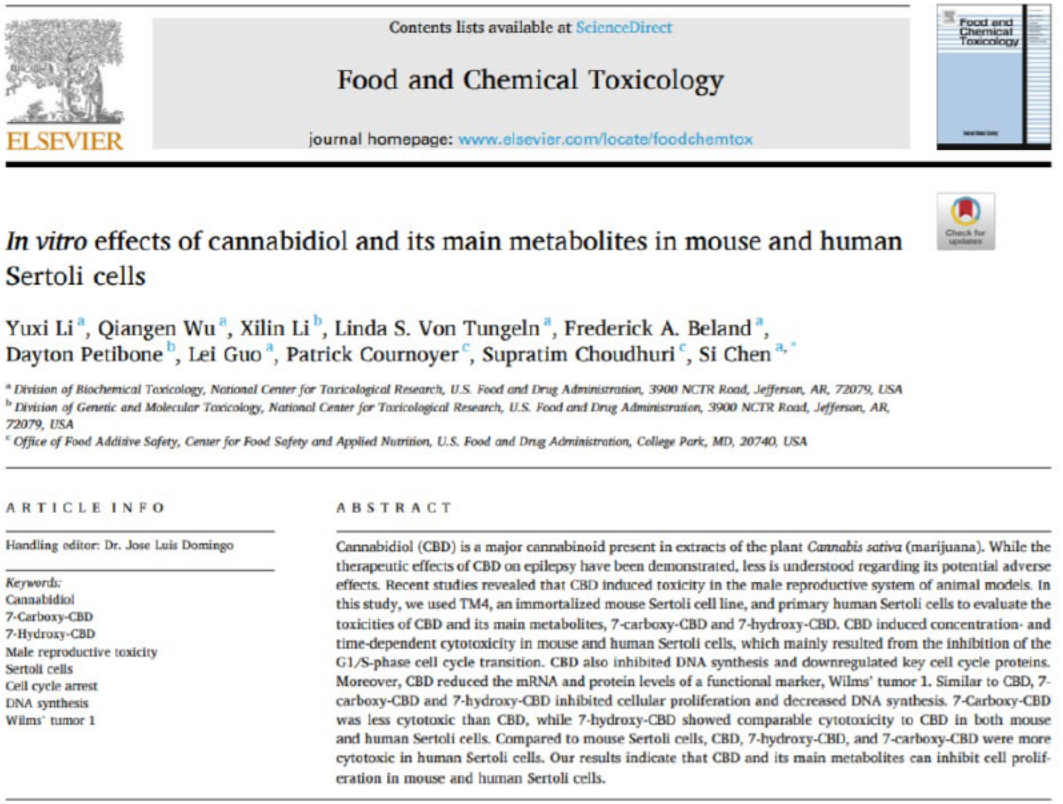
Question Is the public using cannabidiol (CBD) to treat diagnosable conditions that have evidence-based therapies?

Findings In this case series of 376 posts on a CBD forum on Reddit, most users reported taking CBD as a therapeutic for diagnosable conditions, including mental health, cardiological, dermatological, gastroenterological, ophthalmological, oral health, and sexual health conditions, many of which have other evidence-based treatment regimens.

We are conducting toxicological studies

Ongoing FDA Toxicological Studies

- In vitro evaluation of male reproductive toxicities induced by cannabidiol and its main metabolites
- Assessing the developmental neurotoxicity of cannabidiol (CBD) exposure in Sprague Dawley rats
- Examining the immune modulating effects of perinatal cannabidiol (CBD) exposure in Sprague-Dawley rats
- Pharmacokinetics of cannabidiol and its major metabolites in pregnant Sprague-Dawley rats and their pups exposed orally to cannabidiol
- Assessment of the male reproductive system in Sprague-Dawley rats dosed orally with cannabidiol from gestation day 6 to postnatal day 21
- Pharmacokinetics of cannabidiol upon dermal exposure in rats
- Additional studies



Contents lists available at ScienceDirect

Food and Chemical Toxicology

journal homepage: www.elsevier.com/locate/foodchemtox

***In vitro* effects of cannabidiol and its main metabolites in mouse and human Sertoli cells**

Yuxi Li [a], Qiangen Wu [a], Xilin Li [b], Linda S. Von Tungeln [a], Frederick A. Beland [a], Dayton Petibone [b], Lei Guo [a], Patrick Cournoyer [c], Supratim Choudhuri [c], Si Chen [a,*]

[a] Division of Biochemical Toxicology, National Center for Toxicological Research, U.S. Food and Drug Administration, 3900 NCTR Road, Jefferson, AR, 72079, USA
[b] Division of Genetic and Molecular Toxicology, National Center for Toxicological Research, U.S. Food and Drug Administration, 3900 NCTR Road, Jefferson, AR, 72079, USA
[c] Office of Food Additive Safety, Center for Food Safety and Applied Nutrition, U.S. Food and Drug Administration, College Park, MD, 20740, USA

ARTICLE INFO

Handling editor: Dr. Jose Luis Domingo

Keywords:
Cannabidiol
7-Carboxy-CBD
7-Hydroxy-CBD
Male reproductive toxicity
Sertoli cells
Cell cycle arrest
DNA synthesis
Wilms' tumor 1

ABSTRACT

Cannabidiol (CBD) is a major cannabinoid present in extracts of the plant *Cannabis sativa* (marijuana). While the therapeutic effects of CBD on epilepsy have been demonstrated, less is understood regarding its potential adverse effects. Recent studies revealed that CBD induced toxicity in the male reproductive system of animal models. In this study, we used TM4, an immortalized mouse Sertoli cell line, and primary human Sertoli cells to evaluate the toxicities of CBD and its main metabolites, 7-carboxy-CBD and 7-hydroxy-CBD. CBD induced concentration- and time-dependent cytotoxicity in mouse and human Sertoli cells, which mainly resulted from the inhibition of the G1/S-phase cell cycle transition. CBD also inhibited DNA synthesis and downregulated key cell cycle proteins. Moreover, CBD reduced the mRNA and protein levels of a functional marker, Wilms' tumor 1. Similar to CBD, 7-carboxy-CBD and 7-hydroxy-CBD inhibited cellular proliferation and decreased DNA synthesis. 7-Carboxy-CBD was less cytotoxic than CBD, while 7-hydroxy-CBD showed comparable cytotoxicity to CBD in both mouse and human Sertoli cells. Compared to mouse Sertoli cells, CBD, 7-hydroxy-CBD, and 7-carboxy-CBD were more cytotoxic in human Sertoli cells. Our results indicate that CBD and its main metabolites can inhibit cell proliferation in mouse and human Sertoli cells.

DOI: 10.1016/j.fct.2021.112722

We are monitoring adverse event data

Figure 1. Number of exposure calls involving cannabidiol to U.S. Poison Control Centers by year: National Poison Data System 2014-2019

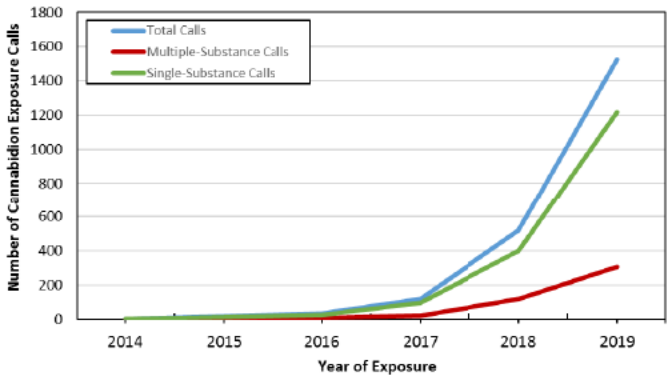
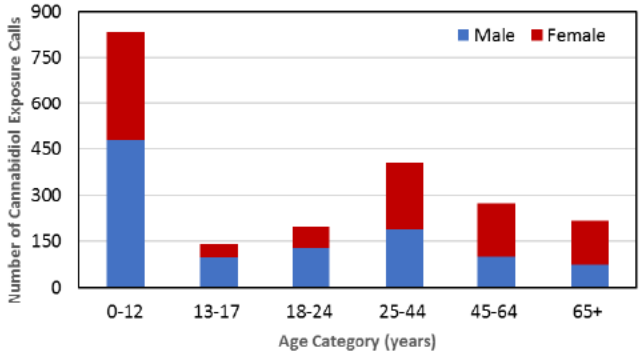


Figure 2. Exposure calls involving cannabidiol to U.S. Poison Control Centers by sex and age category: National Poison Data System 2014-2019



Dara on sex and/or age unknown for n=149 cannabidiol exposure calls

Figure 3. Formulation in exposure calls involving cannabidiol to U.S. Poison Control Centers: National Poison Data System 2014-2019

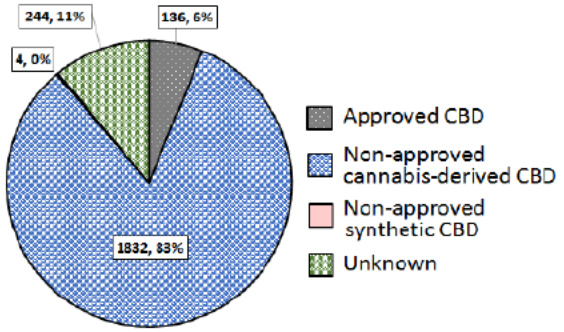
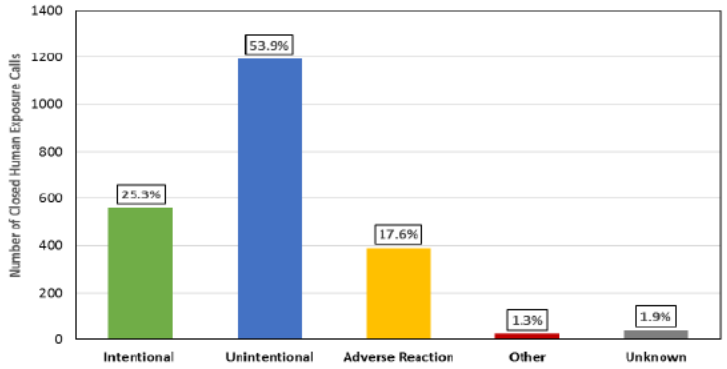
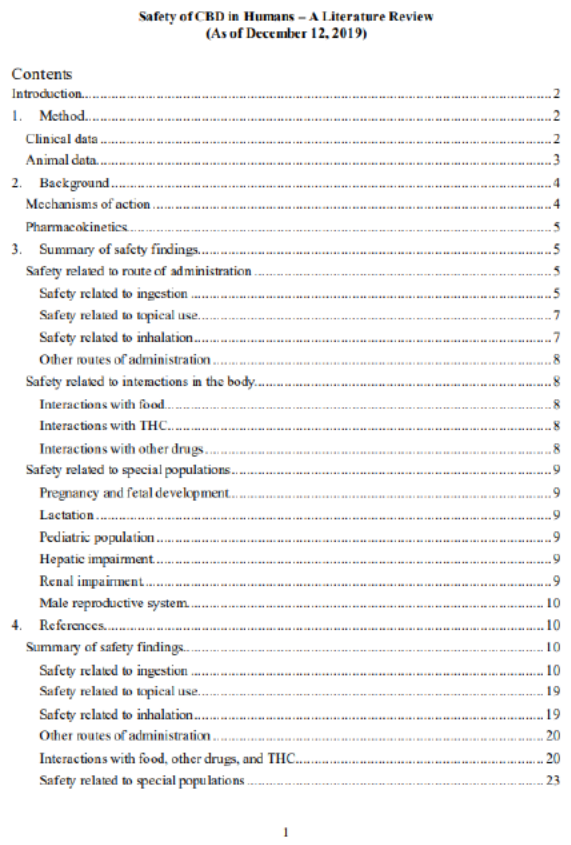


Figure 4. Reasons for exposure among U.S. Poison Control Center calls involving cannabidiol: National Poison Data System 2014-2019



Cannabidiol Exposure Calls to U.S. Poison Control Centers https://onlinelibrary.wiley.com/doi/10.1002/pds.5114

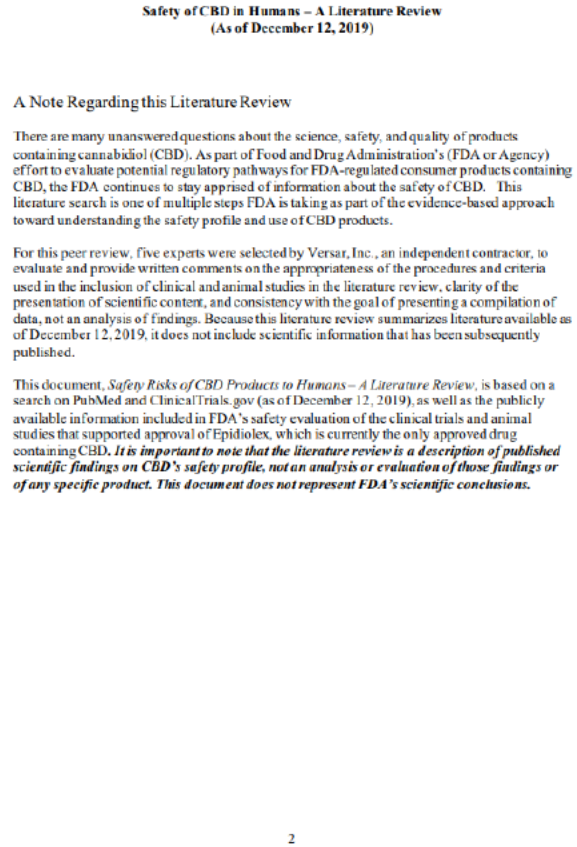
We are monitoring scientific literature



Safety of CBD in Humans – A Literature Review
(As of December 12, 2019)

Contents

1



Safety of CBD in Humans – A Literature Review
(As of December 12, 2019)

A Note Regarding this Literature Review

There are many unanswered questions about the science, safety, and quality of products containing cannabidiol (CBD). As part of Food and Drug Administration's (FDA or Agency) effort to evaluate potential regulatory pathways for FDA-regulated consumer products containing CBD, the FDA continues to stay apprised of information about the safety of CBD. This literature search is one of multiple steps FDA is taking as part of the evidence-based approach toward understanding the safety profile and use of CBD products.

For this peer review, five experts were selected by Versar, Inc., an independent contractor, to evaluate and provide written comments on the appropriateness of the procedures and criteria used in the inclusion of clinical and animal studies in the literature review, clarity of the presentation of scientific content, and consistency with the goal of presenting a compilation of data, not an analysis of findings. Because this literature review summarizes literature available as of December 12, 2019, it does not include scientific information that has been subsequently published.

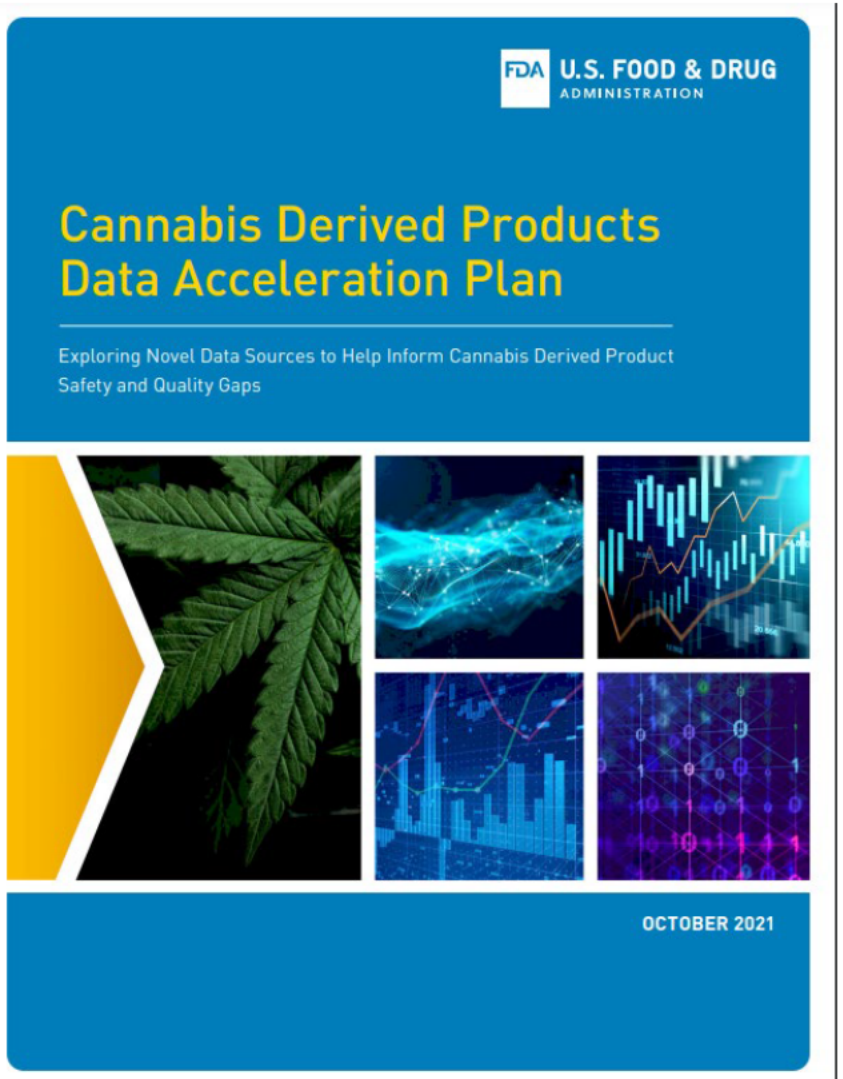
This document, *Safety Risks of CBD Products to Humans – A Literature Review*, is based on a search on PubMed and ClinicalTrials.gov (as of December 12, 2019), as well as the publicly available information included in FDA's safety evaluation of the clinical trials and animal studies that supported approval of Epidiolex, which is currently the only approved drug containing CBD. ***It is important to note that the literature review is a description of published scientific findings on CBD's safety profile, not an analysis or evaluation of those findings or of any specific product. This document does not represent FDA's scientific conclusions.***

2

https://www.fda.gov/media/152317/download

We issued the Cannabis-Derived Products Data Acceleration Plan

- The DAP is a portfolio of pilot initiatives and partnerships focused on advancing data-driven safety signal detection and building advanced technology capabilities.
- The primary goal is to leverage novel data sources and advanced data analytics to identify current and emerging safety vulnerabilities in the CDP market.
- The plan also aims to forge government data partnerships and champion scientific research to evaluate safety and consumer vulnerabilities.



https://www.fda.gov/news-events/public-health-focus/cannabis-derived-products-data-acceleration-plan

We know CBD raises important safety concerns

What You Need to Know (And What We're Working to Find Out) About Products Containing Cannabis or Cannabis-derived Compounds, Including CBD

The FDA is working to answer questions about the science, safety, and quality of products containing cannabis and cannabis-derived compounds, particularly CBD.

Subscribe to Email Updates | Share | Tweet | LinkedIn | Email | Print

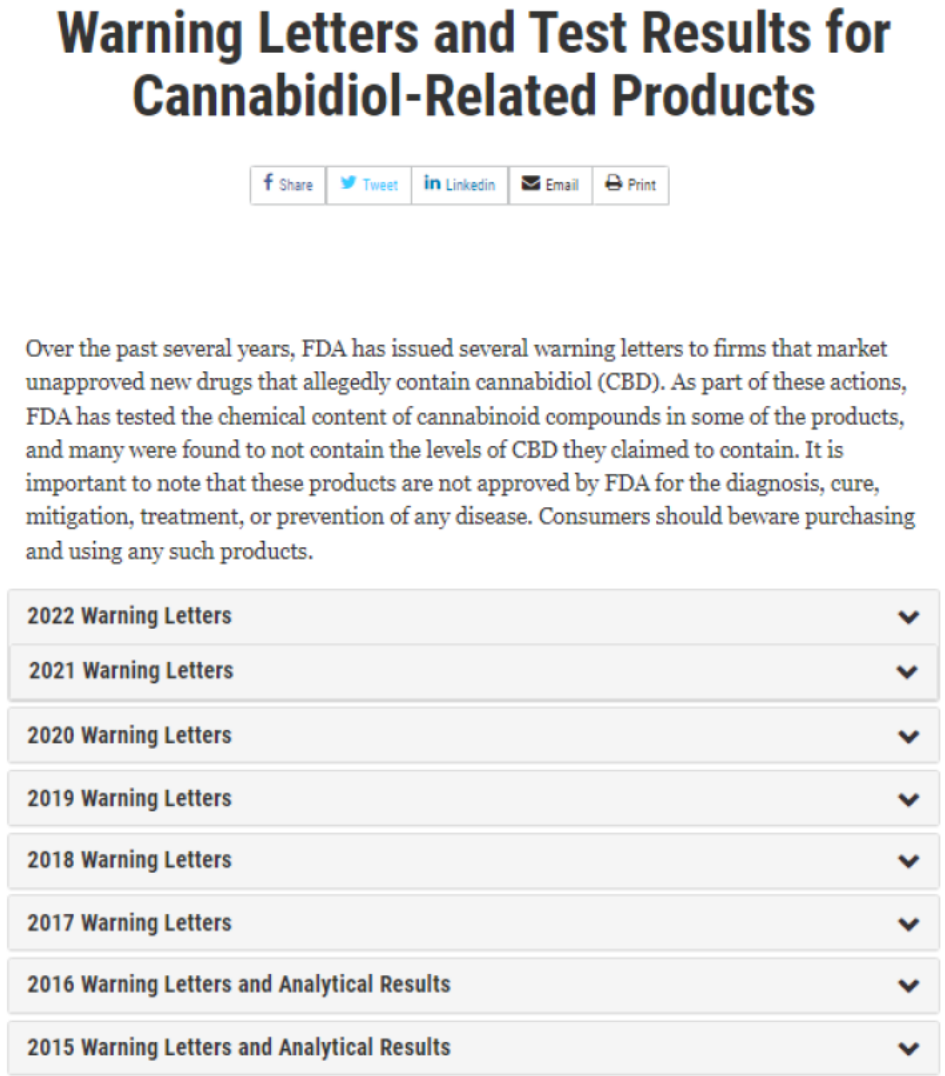
Potential harm, side effects and unknowns

1. CBD has the potential to harm you, and harm can happen even before you become aware of it.
    - CBD can cause liver injury.
    - CBD can affect how other drugs you are taking work, potentially causing serious side effects.
    - Use of CBD with alcohol or other drugs that slow brain activity, such as those used to treat anxiety, panic, stress, or sleep disorders, increases the risk of sedation and drowsiness, which can lead to injuries.
    - Male reproductive toxicity, or damage to fertility in males or male offspring of women who have been exposed, has been reported in studies of animals exposed to CBD.

https://www.fda.gov/consumers/consumer-updates/what-you-need-know-and-what-were-working-find-out-about-products-containing-cannabis-or-cannabis

We have taken targeted actions to protect public health

- Prioritizing products with greatest public health risks
- We have issued warning letters to firms marketing:
  - CBD products marketed to treat diseases or for other therapeutic uses for humans and/or animals
  - CBD products for food producing animals
  - Foods for humans and animals with added CBD (FDA cannot conclude that CBD is generally recognized as safe for use in food)
  - CBD products with concerning routes of administration, including nasal, ophthalmic, and inhalation
  - Delta-8 THC products



Warning Letters and Test Results for Cannabidiol-Related Products

Share Tweet Linkedin Email Print

Over the past several years, FDA has issued several warning letters to firms that market unapproved new drugs that allegedly contain cannabidiol (CBD). As part of these actions, FDA has tested the chemical content of cannabinoid compounds in some of the products, and many were found to not contain the levels of CBD they claimed to contain. It is important to note that these products are not approved by FDA for the diagnosis, cure, mitigation, treatment, or prevention of any disease. Consumers should beware purchasing and using any such products.

- 2022 Warning Letters
- 2021 Warning Letters
- 2020 Warning Letters
- 2019 Warning Letters
- 2018 Warning Letters
- 2017 Warning Letters
- 2016 Warning Letters and Analytical Results
- 2015 Warning Letters and Analytical Results

https://www.fda.gov/news-events/public-health-focus/warning-letters-and-test-results-cannabidiol-related-products

CBD and cannabinoids raise scientific and regulatory challenges

- Sufficient information about CBD is available to know that its use outside of the context of an approved drug raises important safety concerns.
  - Long-term use
- Other cannabinoids are poorly understood.
  - Suspected pharmacological activity
  - Limited understanding of toxicity profile
- Our questions to the Science Board relate to challenges in ensuring the safety of substances with predicted pharmacological activity outside the context of an approved drug.

Comparing pathways for drugs, food ingredients, and dietary supplements

	Drugs	Dietary Supplements	Food Ingredients
Typical users:	Those with a medical condition	Those seeking to supplement their diet and maintain health	All people, including vulnerable groups
Summary of safety standard:	*For new drug approval:* Benefit outweighs risk	*Pre-market standard for new dietary ingredients:* Reasonably expected to be safe (benefits not considered)	Reasonable certainty of no harm (benefits not considered)
Common types of data and information:	- Animal pharmacology and toxicology tests - Human clinical studies (many participants, long duration)	- Evidence of history of safe use - Safety narrative - Animal toxicology tests (as needed)	- Safety narrative - Animal toxicology tests (as needed)
Examples of risk management options:	- Labeling with detailed instructions and warnings - Prescription and behind counter - Risk Evaluation and Mitigation Strategy (REMS) program - DEA scheduling - Spontaneous adverse event reporting	- Safety standards - Labeled conditions of use, e.g. recommended serving, duration of use, population - Users can report adverse events	- Primarily through strict pre-market safety standard (not labeled conditions of use) - Users can report adverse events

Pathways for CBD in select foreign jurisdictions

Jurisdiction	Pathway	Status
European Union	Novel Food	Novel food evaluations on hold pending new data. EFSA's scientists cannot currently establish the safety of cannabidiol (CBD) as a novel food due to data gaps and uncertainties about potential hazards related to CBD intake.
United Kingdom	Novel Food	Novel food evaluations ongoing
Australia and New Zealand	Medicine	Not permissible in food Schedule 3 (Pharmacist Only Medicine)
Canada	Cannabis Product (Cannabis Act)	Subject to all of the rules and requirements that apply to cannabis under the Cannabis Act

U.S. FOOD & DRUG ADMINISTRATION

Meeting of the Science Board to the U.S. Food and Drug Administration

Drug Regulation of Cannabis-Containing Products

Cassandra Taylor, PhD
Chemist, Botanical Review Team
Office of Pharmaceutical Quality
CDER, FDA

Regulated Products include:

Human Foods (e.g., conventional foods, dietary supplements, food additives)

Drugs (including prescription and non-prescription)

Biologics (e.g., vaccines, blood and blood products)

Medical Devices (e.g., tongue depressors, pacemakers)

Electronic Products that give off radiation (e.g., microwave oven, X-ray equipment)

Cosmetics (e.g., skin moisturizers, lipsticks, eye and facial make-up, nail polish, cleansing shampoos)

Veterinary Products (e.g., animal foods, animal drugs)

Tobacco Products (e.g., cigarettes, smokeless tobacco)

Picture https //pixabay.com/vectors/us-united-states-russia-map-1907526/

Center for Drug Evaluation and Research (CDER)

- CDER regulates prescription and nonprescription drugs, including generic drugs
- An independent and unbiased multidisciplinary team of physicians, statisticians, chemists, pharmacologists and other scientists review investigators' data and proposed labeling
- Drugs are evaluated for safety, efficacy, and quality
  - If review team establishes that a drug's health benefits outweigh its known risks, CDER considers it safe enough to approve
- CDER works to ensure safe and effective drugs are available to improve the health of consumers
  - Ensures prescription and nonprescription drugs, both brand name and generic, work correctly and that the health benefits outweigh known risks

Overview of FDA Drug Authority

- Under the Food Drug and Cosmetic (FD&C) Act:
  - Any product, including a cannabis product (hemp or otherwise), that is intended for use in the diagnosis, cure, mitigation, treatment, or prevention of disease or is an article (other than food) intended to affect the structure or any function of the body of man or other animals is considered to be a drug.
  - With limited exceptions, a new drug must be approved by the FDA for its intended use before it may be introduced into interstate commerce
- FDA regulations can be found in Title 21 of the Code of Federal Regulations (21 CFR)

Overview of FDA Drug Authority

- Pre-market review (before drug approval)
  - Includes single molecule and botanical drug products
  - Investigational New Drug Application (IND) – Drug development: Phases 1-3
  - New Drug Application (NDA) – Marketing application

- Post-market surveillance (after drug approval)
  - Monitor products references under section 3075 of the 21st Century Cures Act *
    - Section 505 of the FD&C Act
    - Section 351 of the Public Health Services (PHS) Act
  - Over-the-counter monograph products
  - Compounded products
  - Homeopathic products
  - Other unapproved products

* The Act was enacted on December 13, 2016, and has the goal of advancing medical product innovation, as well as ensuring patient access to safe and effective treatments as soon as possible.

Botanical Drugs

- A botanical drug product is intended for use in the diagnosis, cure, mitigation, treatment or prevention of disease in humans
  - A botanical drug product consists of vegetable materials, which may include plant materials, algae, macroscopic fungi, or combinations thereof
  - A botanical drug product may be available as (but not limited to) a solution (e.g., tea), powder, tablet, capsule, elixir, topical, or injection
  - Botanical drug products often have unique features, for example, complex mixtures, lack of a distinct active ingredient, and substantial prior human use. Fermentation products and highly purified or chemically modified botanical substances are not considered botanical drug products
- A botanical drug's special features require consideration and adjustment during the FDA review process
  - ***Botanical Drug Development Guidance for Industry***
  - Issued by CDER in 2016 takes into consideration these features and helps to facilitate development of new therapies from botanical sources

Compounds derived from and related to cannabis

Cannabis-derived compounds

- Compounds occurring naturally in the plant – like **CBD** and **THC**
- These compounds are extracted directly from the plant
- Can be used to manufacture drug products
- Example: highly-purified CBD extracted from the plant
- Agency approved one cannabis-derived drug product: Epidiolex (cannabidiol)

CANNABIS

- *Cannabis sativa* L. is a plant that contains over 80 different naturally occurring compounds called "cannabinoids"
- Two well-known cannabinoids:
  - **Cannabidiol (CBD)**
  - **Tetrahydrocannabinol (THC)**
- Plants are grown to produce varying concentrations of cannabinoids – **THC** or **CBD**
- These plant variations are called cultivars

Cannabis-related compounds

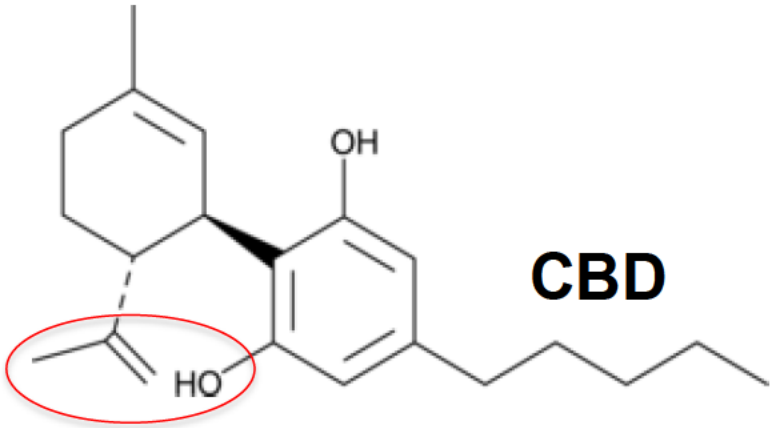
- These synthetic compounds are created in a laboratory
- Can be used to manufacture drug products
- Some synthetic compounds may also occur naturally in the plant and some may not
- Examples: Synthetically-derived dronabinol (also naturally occurring) and nabilone (not naturally occurring)
- Agency approved 3 synthetic cannabis-related drug products: Marinol & Syndros (dronabinol), Cesamet (nabilone)

FDA and Cannabis: Research and Drug Approval Process

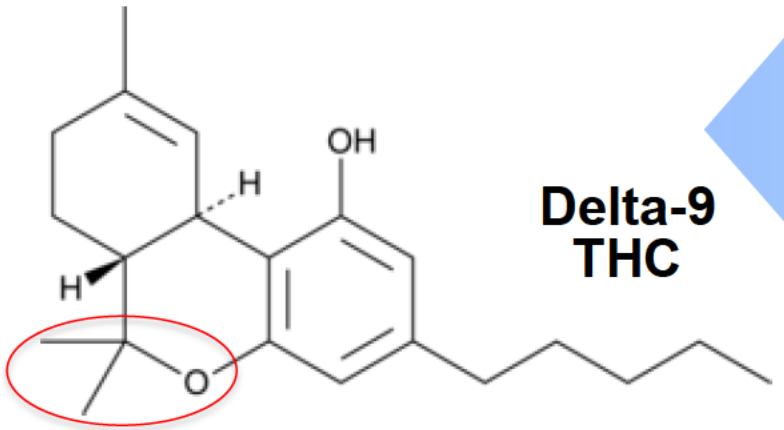
Cannabis-Derived Compounds

Cannabis-derived compounds

- Compounds occurring naturally in the plant – like **CBD** and **THC**
- These compounds are extracted directly from the plant
- Can be used to manufacture drug products
- Example: highly-purified CBD extracted from the plant
- Agency approved one cannabis-derived drug product: Epidiolex (cannabidiol)



CBD



Delta-9 THC

Examples of other cannabis-derived compounds

- **Other Cannabinoids**: CBDA, THCA, CBN, CBDV, CBC, CBG, CBGA, THCV, etc.
- **Terpenes**: Myrcene, Limonene, Linalool, Caryophyllene, Pinene, etc.

[FDA and Cannabis: Research and Drug Approval Process]

Cannabis Drug Development

Four products approved by FDA; with re-scheduling drug control actions upon approval:

1. Marinol (dronabinol) (1985): nausea from cancer chemotherapy; anorexia associated with AIDS → **Schedule III (under the Controlled Substances Act)**
2. Cesamet (nabilone) (1985 (2006)): nausea from cancer chemotherapy → **Schedule II**
3. Syndros (dronabinol) (2016): nausea from cancer chemotherapy; anorexia associated with AIDS → **Schedule II**
4. Epidiolex (CBD) (2018): for childhood seizures & Tuberous Sclerosis Complex → Originally Schedule V but now **No longer controlled**

Photo: https://prescriptiongiant.com/product/cesamet-generic-nabilone/

Photo: https://www.syndros.com/what-is-syndros/how-to-use

Photo: https://www.epidiolex.com/about-epidiolex/story

Cannabis Drug Development

- Cannabis products intended for use under clinical trial with a claim of therapeutic benefit or with any other disease claim **are drugs**
  - Submit an Investigational New Drug Application (IND) or request Pre-IND meeting with clinical division
  - Drug sponsors formally propose that FDA approve a new pharmaceutical via the New Drug Application (NDA)

- When used under clinical trial, cannabis and cannabis-derived compounds must meet all FDA requirements for IND applications, which includes 3 broad areas
  1. Animal Pharmacology and Toxicology Studies
  2. Manufacturing Information
  3. Clinical Protocols and Investigator Information


NIDA Photo: https://www.drugabuse.gov/publications/research-reports/marijuana/letter-director

Cannabis Drug Development

- Draft IND Guidance
  - Investigational New Drug Applications Prepared and Submitted by Sponsor-Investigators

- In each phase of clinical investigation, sponsors **must submit** sufficient information to ensure the identity, quality, purity, and potency or strength of the investigational drug. The amount of information appropriate to meet this expectation **will increase with successive stages of drug development**

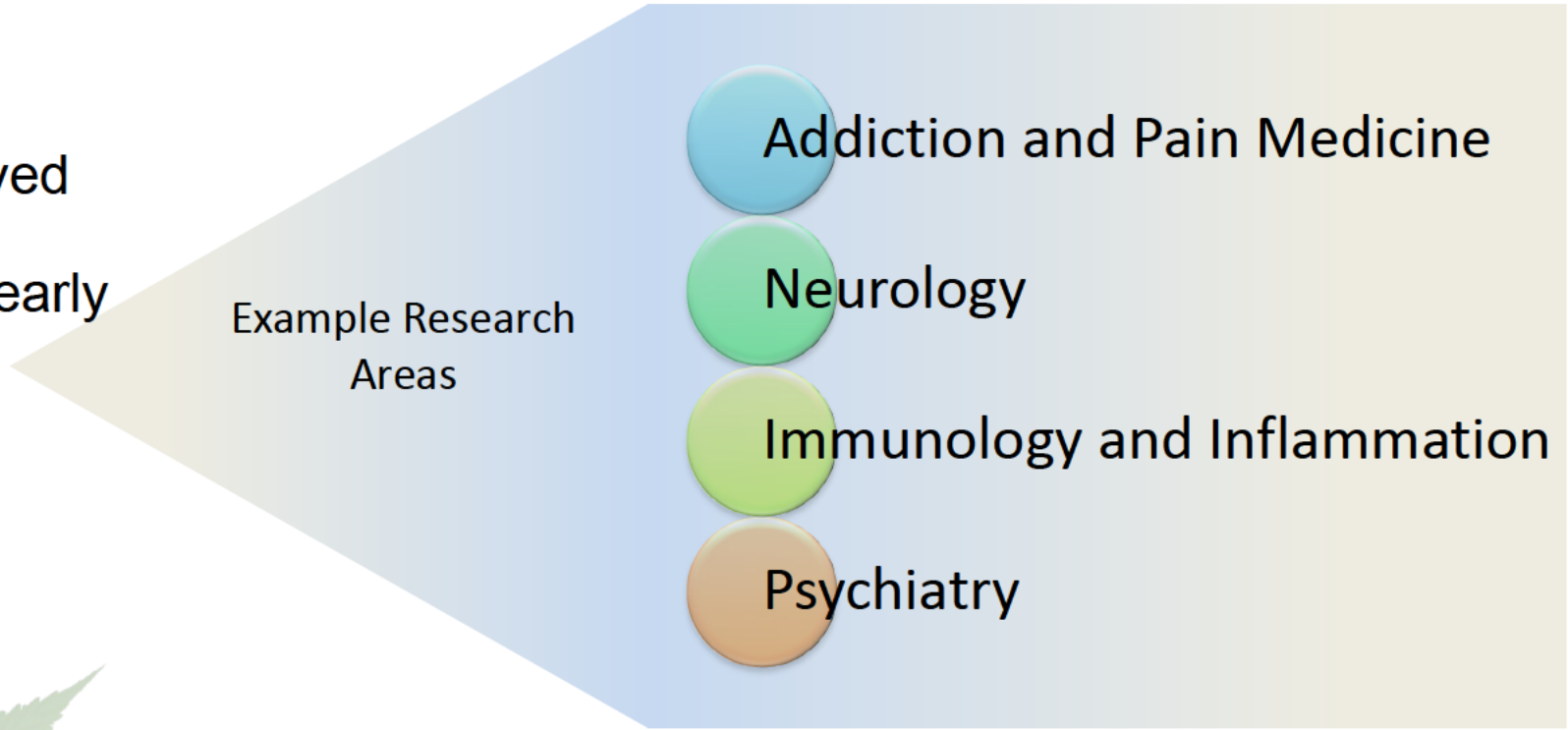
- We treat products containing cannabis or cannabis-derived compounds as we do any other FDA-regulated products
  - Meaning they're subject to same authorities and requirements as FDA-regulated products containing any other substance

- ***Botanical Drug Development Guidance for Industry***
  - Provides Agency's current thinking on botanical drug development
  - Focuses on quality controls
  - Botanical raw material growing conditions

- After the 2018 Farm Bill, on July 21st, 2020 FDA published Draft Guidance ***Cannabis and Cannabis-Derived Compounds: Quality Considerations for Clinical Research***

Cannabis Therapeutic Research Areas

- Over last 50 years, >800 INDs submitted
  - In first 40 years, FDA received over 400 submission
  - In last 10 years, received nearly 400 submission
  - Dramatic increase in submissions
- Nearly 150 active INDs



Summary and Conclusions

- CDER has a well-defined role to play in the **regulation and development of human drug products** containing cannabis and cannabis-derived compounds and will continue to protect and promote the public health with respect to these products.

- CDER continues to focus on supporting scientific and rigorous testing and approval of human drugs derived from cannabis and supporting **robust scientific research** into understanding **human and animal uses and safety** of non-drug cannabis products.

- FDA is **committed to protect and promote the public health** with respect to human drug products containing cannabis and cannabis-derived compounds, including enforcement action when needed.

U.S. FOOD & DRUG ADMINISTRATION

Meeting of the Science Board to the U.S. Food and Drug Administration

Challenges in regulatory oversight for substances with predicted pharmacological activity, marketed in foods and dietary supplements, using cannabinoids as a case study

Gregory Noonan, Ph.D.
Acting Deputy Director
Office of Dietary Supplement Programs

Dietary Supplement Health and Education Act (DSHEA)

- October 1994
- Defined the term “dietary supplement”
  - Exclusion clause
- May not claim to diagnose, mitigate, treat, cure, or prevent a disease
- Established requirements for new dietary ingredients (NDI)
- Dietary supplements are regulated as a category of food

DSHEA Findings (October 1994)

- Almost 50 percent of Americans regularly consumed dietary supplements of vitamins, minerals, or herbs.
- Used products to supplement nutrition, maintain health, reduce risk of chronic disease.
- Estimated 600 supplement manufacturers and 4,000 products.

Consumers and Market in 2022

- Consumers
  - Nearly 75-80% of Americans consume dietary supplements
  - Vitamins/Minerals still most common
  - Increase in targeted intended uses (e.g., improve sleep, increase energy, weight loss, reduce stress)

- Current Market
  - Current estimates of 50,000 to 80,000 different products
  - Greater diversity and complex supply chain
  - Standardized and specialty formulas, purified components with more specific uses

Dietary Supplements are Regulated as Food

- FDA does not approve any dietary supplement product
  - Ingredients marketed prior to 1994: No premarket review
  - New Dietary Ingredients (NDI)
    - No premarket review if in food supply
    - Premarket review only for those NDIs not present in the food supply

Dietary Supplement Safety Standard

Ingredient/Timing	Safety Standard
Pre-DSHEA Ingredients (Postmarket)	Significant or unreasonable risk of illness or injury under recommended (or ordinary) conditions of use
Premarket NDI	Reasonable expectation of safety under recommended conditions of use
Postmarket NDI	Inadequate information to provide reasonable assurance it does not present a significant or unreasonable risk of illness or injury

New Dietary Ingredient Notifications

- Manufacturers or distributors must submit a notification to FDA 75 days prior to introducing certain new dietary ingredients to market
  - Review of the notifier's information and safety determination
- NDI notifications must meet the requirements of 21 CFR 190.6 to be considered complete
- Not an approval
  - In fact, even if FDA identifies identity or safety concerns in our review, the product can still go to market and FDA bears the burden to demonstrate it is adulterated

Requirements for Premarket Notification (21 CFR 190.6)

- Name and address of the manufacturer or distributor
- Name and description of the NDI
- Description of the dietary supplement
- The level of the NDI
- The conditions of use
- The history of use or other evidence of safety
- Made public after 90th day

NDI Characterization and Manufacturing (Identity)

- Description of the identity of the NDI
- Description of the evidence verifying the identity of the NDI
- DI manufacturing
  - Raw materials
  - Formulation ingredients
  - Manufacturing process
  - Specifications
  - Methods of analysis

NDI Safety Standard

The notification must contain “history of use or other evidence of safety establishing that the [NDI], when used under the conditions recommended or suggested in the labeling of the dietary supplement, will reasonably be expected to be safe.”

History of Use Safety Assessment

- Information in history of use safety assessment
  - Description and characterization: comparing the historically consumed material with the NDI
  - Exposure estimates for the historically consumed material and comparison to NDI
  - Size and Characteristics of consuming population
  - Adverse events associated with historically consumed material
- With sufficient history of use data a reasonable expectation of safety can be established

Other Safety Data

- *In vitro* Studies
  - Cannot establish safety, but support other studies
- Animal Studies
  - Specific recommended studies depend heavily on conditions of use
- Clinical Studies
  - Establishing safety, not efficacy
  - Performed on healthy population

Considerations for Additional Safety Data

- Design additional studies based on the ingredient and product use
  - Conditions of Use (e.g., serving size, target population) informs the animal and clinical studies
  - Identity/Source informs the animal studies (e.g., type of extract will influence co-extracts)
- Studies should be performed on the product of commerce
- Safety narrative should summarize data and establish how the notifier determined the product will be reasonably expected to be safe

Major Takeaways

- Dietary supplements are regulated as food
- No approval needed to market dietary supplements
- Premarket review only on limited set of NDI/products
- Specific safety studies are recommendations and not requirements

Thank You!

U.S. FOOD & DRUG ADMINISTRATION

Meeting of the Science Board to the U.S. Food and Drug Administration

Regulation and Safety Evaluation of Food Ingredients

Patrick Cournoyer, PhD
Acting Science and Policy Coordinator
Cannabis Product Committee

Regulatory Scientist
Office of Food Additive Safety, CFSAN, FDA

“Food additives” require FDA approval

Food Additive

“…any substance the intended use of which results or may reasonably be expected to result, directly or indirectly, in its becoming a component or otherwise affecting the characteristics of any food…”

Generally Recognized as Safe (GRAS)

“… [unless the substance is] generally recognized, among experts qualified by scientific training and experience to evaluate its safety, as having been adequately shown . . . to be safe under the conditions of its intended use.”

“Food additives” require FDA approval

Food Additive

Requires pre-market FDA review and approval

Petition to FDA

If approved, results in a regulation

Generally Recognized as Safe (GRAS)

Does not require FDA approval

FDA evaluates GRAS notices

GRAS is a high standard and has two key elements

1. Evidence of Safety

Food additives and substances whose use is GRAS must meet the same, strict safety standard

+

2. General Recognition of Safety

Substances whose use is GRAS must ALSO have essential evidence of safety be:

1. **Generally accepted:** Consensus among qualified experts
2. **Generally available:** Publication in peer-reviewed scientific journals, textbooks, scientific reports *etc.*

The safety standard:

Safety Standard for Substances Added to Food

"reasonable certainty in the minds of competent scientists that the substance is not harmful under the conditions of its intended use"

- Typically accounts for expected use by the general population, including certain vulnerable groups, e.g. those who are young, elderly, or pregnant
- Typically accounts for lifetime consumption
- Normally safety does not depend on special labels, warnings, or arbitrary consumption limits
- The safety standard does not consider benefits

Basic elements of a food ingredient safety assessment

- **What is it?**
  - Identity, properties, and composition
  - Manufacturing process
  - Specifications, limits on impurities/contaminants
- **What are its intended uses?**
  - Purpose or technical effect (why is it added to food/packaging?)
  - Food categories
  - Use levels
- **How much will people consume?**
  - Exposure estimate based on maximum intended use levels and on food consumption data
- **Will amounts consumed be safe?**
  - Data and information supporting safety at estimated exposure levels

How much will people consume?

Define intended food uses (which types of food)

Define intended use level (amount) in each food type

Estimate consumption of foods in which the substance will be used

Account for variation

- High-end (90th percentile) consumers

Calculate estimated exposures (mg/kg/day)

- Include “background” exposure from other foods

How much exposure is safe?

Approaches are case-by-case

- Safety assessment depends on the nature of the substance

No Observed Adverse Effect Level (NOAEL):

- The highest dose in an appropriately designed animal study shown to cause no adverse effects
- The study must assess the most sensitive toxicological endpoint for the substance
- The study must use an appropriate model system
- This approach is most useful for defined chemicals consumed in relatively small amounts
  - Less applicable to macro-ingredients, complex mixtures, substances normally in the diet (e.g. starch, proteins)

Protective safety factors:

- Actual exposure levels should be well below levels shown to cause no adverse effects in test animals
- 100-fold is commonly applied, to account for:
  - Differences between test animals and people
  - Differences between individuals
- Additional safety factors can offer additional protection in the case of specific safety concerns or data gaps

Acceptable Daily Intake (ADI)

- NOAEL / protective safety factor = ADI
- The amount of a substance that can be consumed daily, over a lifetime with reasonable certainty of no harm

How much exposure is safe?

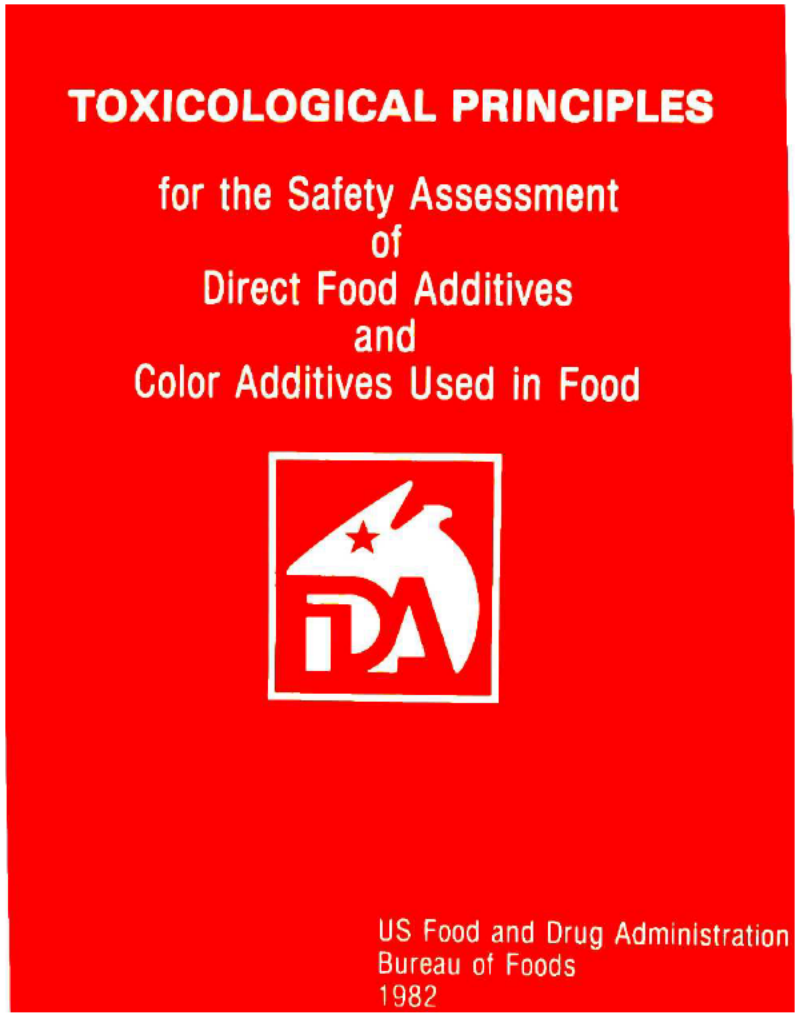
The proposed use of a substance in food can be considered safe if the estimated daily intake (EDI) is less than the acceptable daily intake (ADI).

Both EDI and ADI are conservative to ensure safety.

Human studies are not typically used in food chemical safety assessments.

- Animal studies enable higher dosing and lifetime exposure
- Animals can be examined more thoroughly
- Human studies are advised only in rare cases

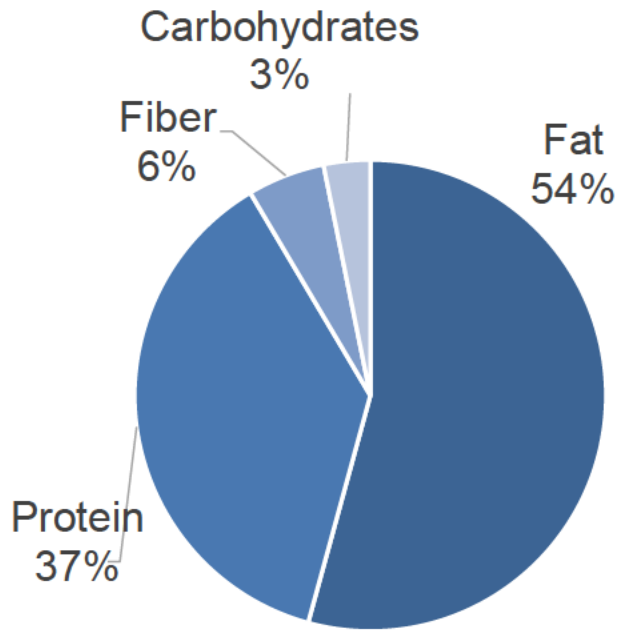
FDA's "Redbook" gives guidelines for toxicity studies



We evaluated three hempseed ingredients for human food use

- FDA evaluated GRAS Notices for:
  - Dehulled hemp seed
  - Hemp seed protein powder
  - Hemp seed oil
- Hemp seeds consist primarily of fat, protein, fiber, and carbohydrates
- Safety narrative:
  - Safety of the fatty acid profile
  - Safety of the protein content
  - Anti-nutrient levels are comparable to nuts and to other seeds
  - THC and CBD contamination levels are adequately low
  - Other info: some history of safe consumption of hemp seeds

Hemp seed composition



We evaluated three hempseed ingredients for human food use

FDA Responds to Three GRAS Notices for Hemp Seed-Derived Ingredients for Use in Human Food

SHARE | TWEET | LINKEDIN | PIN IT | EMAIL | PRINT

Constituent Update

December 20, 2018

The U.S. Food and Drug Administration has completed its evaluation of three generally recognized as safe (GRAS) notices for hemp seed-derived food ingredients. The GRAS notices were submitted by Fresh Hemp Foods, Ltd. The agency has no questions about Fresh Hemp Food's conclusion that the following ingredients are GRAS under their intended conditions of use: hulled hemp seed (GRN765), hemp seed protein powder (GRN771), and hemp seed oil (GRN778).

Foods containing hemp seed and hemp seed-derived ingredients are currently marketed in the US. Hemp seeds are the seeds of the hemp plant, *Cannabis sativa*. Although hemp is from the same species as cannabis (marijuana), the seeds themselves do not naturally contain tetrahydrocannabinol (THC), the main psychoactive ingredient in cannabis. The hemp seed-derived ingredients that are the subject of these GRAS notices contain only trace amounts of THC and CBD, which the seeds may pick up during harvesting and processing when they are in contact with other parts of the plant. Consumption of these hemp seed-derived ingredients is not capable of making consumers "high".

We have issued warning letters to companies selling foods with added CBD

- We cannot conclude that CBD is generally recognized as safe (GRAS) among qualified experts for its use in human or animal food

- Safety concerns include:
  - Potential liver injury
  - Interactions with other drugs
  - Drowsiness, diarrhea, and changes in mood
  - Studies in animals have shown that CBD can interfere with the development and function of testes and sperm, decrease testosterone levels, and impair sexual behavior in males.

- We stated in warning letters:
  - CBD added to a conventional food is a food additive
  - A food additive is deemed unsafe unless it is approved by FDA for its intended use prior to marketing
  - CBD is not approved for use in any conventional food
  - Food containing an unsafe food additive is adulterated

FDA NEWS RELEASE

FDA warns 15 companies for illegally selling various products containing cannabidiol as agency details safety concerns

Violations include marketing unapproved new human and animal drugs, selling CBD products as dietary supplements, and adding CBD to human, animal foods

Share Tweet LinkedIn Email Print

For Immediate Release: November 25, 2019

Today, the U.S. Food and Drug Administration issued warning letters to 15 companies for illegally selling products containing cannabidiol (CBD) in ways that violate the Federal Food, Drug, and Cosmetic Act (FD&C Act). The FDA also published a revised Consumer Update detailing safety concerns about CBD products more broadly. 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.

Today's actions come as the FDA continues to explore potential pathways for various types of CBD products to be lawfully marketed. This includes ongoing work to obtain and evaluate information to address outstanding questions related to the safety of CBD products, while maintaining the agency's rigorous public health standards. The FDA plans to provide an update on its progress regarding the agency's approach to these products in the coming weeks.

We have issued warning letters to companies selling foods with added delta-8 THC

FDA NEWS RELEASE

FDA Issues Warning Letters to Companies Illegally Selling CBD and Delta-8 THC Products

Violations Include Marketing Unapproved New Drugs, Misbranding, Adding Delta-8 THC to Food Products

Share | Tweet | Linkedin | Email | Print

More Press Announcements

For Immediate Release: May 04, 2022

Español

Today, the U.S. Food and Drug Administration issued warning letters to five companies for selling products labeled as containing delta-8 tetrahydrocannabinol (delta-8 THC) in ways that violate the Federal Food, Drug, and Cosmetic Act (FD&C Act). This action is the first time the FDA has issued warning letters for products containing delta-8 THC. Delta-8 THC has psychoactive and intoxicating effects and may be dangerous to consumers. The FDA has received reports of adverse events experienced by patients who have consumed these products.

There are no FDA-approved drugs containing delta-8 THC. Any delta-8 THC product claiming to diagnose, cure, mitigate, treat, or prevent diseases is considered an unapproved new drug. The FDA has not evaluated whether these unapproved drug products are effective for the uses manufacturers claim, what an appropriate dose might be, how they could interact with FDA-approved drugs or other products, or whether they have dangerous side effects or other safety concerns.

Delta-8 THC is one of over 100 cannabinoids produced in the *Cannabis sativa* L. plant but is not found naturally in significant amounts. Concentrated amounts of delta-8 THC are typically manufactured from hemp-derived cannabidiol (CBD) and have psychoactive and intoxicating effects. Products containing delta-8-THC are available in varying forms, including but not limited to candy, cookies, breakfast cereal, chocolate, gummies, vape cartridges (carts), dabs, shatter, smokable hemp sprayed with delta-8-THC extract, distillate, tinctures, and infused beverages.

Content current as of:
05/04/2022

Follow FDA
Follow @US_FDA
Follow FDA
Follow @FDAmedia

We have warned consumers about accidental ingestion of foods containing THC

FDA Warns Consumers About the Accidental Ingestion by Children of Food Products Containing THC

May 13, 2022

Audience

- All consumers

What is the problem?

- Edible products containing tetrahydrocannabinol (THC) can be easily mistaken for commonly consumed foods such as breakfast cereal, candy, and cookies, and accidentally ingested.
- Accidental ingestion of these products can lead to serious adverse events, especially in children.
- Some edible products are designed to mimic the appearance of well-known branded foods by using similar brand names, logos, or pictures on their packaging. These copycats are easily mistaken for popular, well-recognized foods that appeal to children.
- The FDA is aware of reports of copycat products packaged to look like Cap'n Crunch, Cocoa Pebbles, Cocoa Puffs, Froot Loops, Fruity Pebbles, Nerds Ropes, Starbursts, Sour Patch Kids, and Trix, among others.

Examples of Products

Who is at risk?

The FDA is advising consumers about the risk of accidental ingestion, especially by children, of edible products that contain THC. Accidental ingestion of these edible products may cause serious adverse events.

Summary of Problem and Scope

Some manufacturers are packaging and labeling edible products containing THC to look like popular brands of commonly consumed foods, such as breakfast cereal, candy, and cookies. These products appeal to children and may be easily mistaken for popular, well-recognized foods.

The FDA is aware of multiple media reports describing children and adults who accidentally consumed copycat edible products containing THC and experienced adverse events. Additionally, from January 2021 through April 24, 2022, the FDA received over 100 adverse event reports related to children and adults who consumed edible products containing THC. Some individuals who ate these edible products reportedly experienced adverse events such as hallucinations, increased heart rate and vomiting, and many required medical intervention or hospital admission. Seven of the reports specifically mention the edible product to be a copycat of popular foods, such as Cocoa Pebbles, Nerds Rope, Skittles, Sour Patch Kids, and Starburst.

Thank you for your attention

U.S. FOOD & DRUG ADMINISTRATION

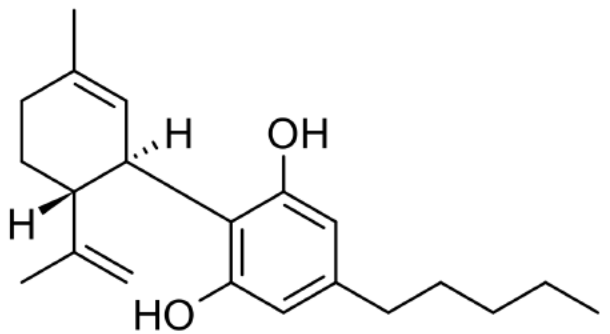
Meeting of the Science Board to the U.S. Food and Drug Administration

Cannabidiol (CBD) Toxicological Profile

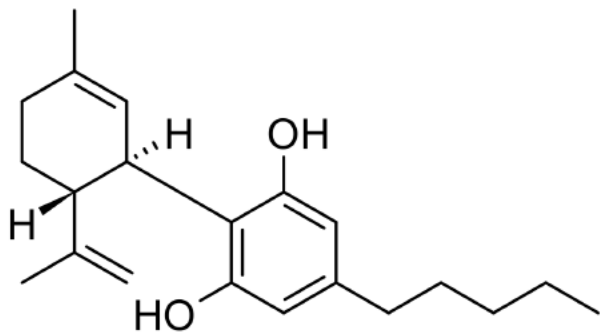
Jeremy Gingrich, PhD
Center for Food Safety and Applied Nutrition
Office of Food Additive Safety
Division of Food Ingredients

Overview

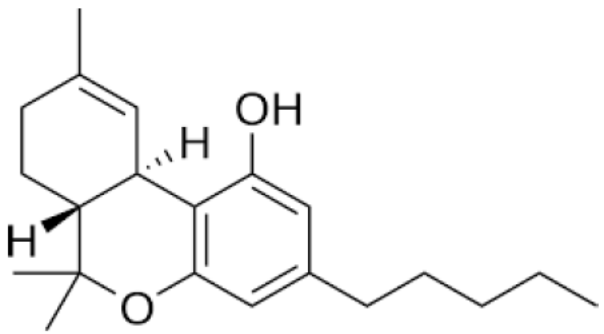
1. CBD & the Endocannabinoid System
2. Receptor Binding Profile
3. Toxicokinetic Studies (ADME)
4. Safety Concerns & Supportive Data
5. Potential Mechanisms of Toxicity
6. Conclusions
7. Beyond CBD



CBD



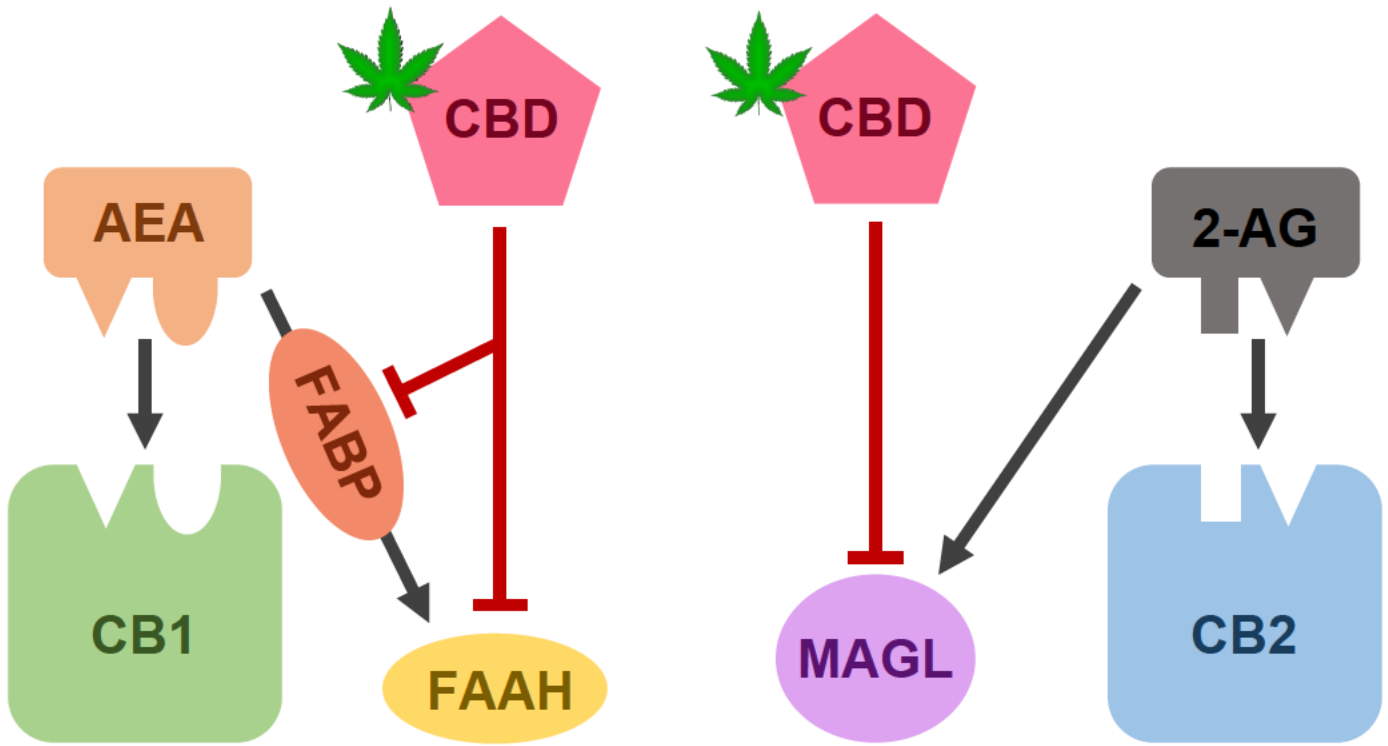
Δ9-THC



The Endocannabinoid System

- Cannabinoid receptors 1 & 2
  - CB1: brain, endocrine, reproductive tissues
  - CB2: GI-tract, kidney, lymphoid tissues
- Endogenous ligands
  - Anandamide (AEA)
  - 2-Arachidonoylglycerol (2-AG)

CBD disrupts endocannabinoid signaling



FABP – Fatty acid binding proteins
FAAH – Fatty acid amide hydrolase

MAGL – Monoacyl glycerol lipase

CBD Receptor Binding Profile

- Weak affinity for CB1 and CB2
  - Non-competitive negative allosteric modulator (NAM)
- Agonist, Vanilloid type 1 receptor (TRPV1)
- NAM for D1-like dopamine receptor and μ- and δ-opioid receptors
- Abundant others…
  - GPR55, 5-HT, D2, PPAR-γ, α1-adrenoceptors, $GABA_A$

Overview

1. CBD & the Endocannabinoid System
2. Receptor Binding Profile
3. Toxicokinetic Studies (ADME)
4. Safety Concerns & Supportive Data
5. Potential Mechanisms of Toxicity
6. Conclusions
7. Beyond CBD

ADME Studies in Humans

- ADME: Absorption, Digestion, Metabolism, and Excretion
- Low oral bioavailability (6%)
  - High-fat diet increases absorption and bioavailability (19%)
- Distributes to adipose tissue
- Elimination half-life
  - 1-2 hr. for single oral (20 mg)
  - 2-5 days for chronic oral
- Excreted in feces (84%) and urine (8%)

ADME Studies in Humans

- Phase 1 & 2 metabolism in humans
  - CYP2C19 & 3A4
  - UGT1A7, 1A9 & 2B7
- 7-COOH-CBD predominant metabolite in humans
- Animal studies similar toxicokinetics, but metabolites vary among animal models
  - 7-OH-CBD predominant in animal models
    - Active metabolite

Safety Concerns

1. Immunotoxicity
2. Hepatotoxicity
3. CBD-drug interactions
4. Developmental and Reproductive Toxicity

Immunotoxicity

- Mouse T and B lymphocyte
  - Decreased function
  - Apoptosis of T lymphocytes
  - Oxidative stress
    - Via reduced intracellular glutathione
- Similar effects in splenic lymphocytes and human leukemia cells

Hepatotoxicity

- Humans – 5-20% elevated liver enzymes in epileptic individuals
  - –Elevated liver enzymes in healthy individuals
- Rats – hepatocellular hypertrophy
- Mice – increased liver weights, liver enzymes
- Dogs – hepatocellular hypertrophy

CBD-Drug Interaction Potential

- Inhibits multiple CYP enzymes *in vitro*
  - Drug metabolism: 1A1, 2B6, 2C9, 2C19, 2D6, 3A4, 3A5
  - Testosterone homeostasis: 2C11

- Inhibits multiple efflux transporters
  - BCRP & P-gp

Developmental and Reproductive Toxicity

- Rodents
  - –Adult exposure in rats and mice (males only)
    - Reduced fertility, increased pre- and postnatal mortality
    - Decreased plasma testosterone

Developmental and Reproductive Toxicity

- Gestational exposure in rats and mice
  - Fewer live pups
  - Shorter gestational length
    - Smaller offspring
  - Reduced testicular weight and size in male offspring
    - Decrease in viable spermatids
    - Reduced pregnancy success
  - Delayed sexual maturity
  - Delayed neurobehavioral development
    - Anxiety-like behavior in female offspring
  - Perturbed skeletal development (rabbits only)

Developmental and Reproductive Toxicity

- Non-human primates
  - 90-day oral toxicity, adult exposure
  - Lower gonadal weights (up to 75% both sexes)
  - After 30-day washout, testes weights remained low
  - Inhibited spermatogenesis at all doses
    - Accompanied by abnormal histopathology

Developmental and Reproductive Toxicity

- DART effects observed across evolutionarily distant organisms
  - Chicken – embryotoxic *in ovo*
  - Sea urchin – decreased reproductive success via inhibition of acrosomal reaction
  - Zebrafish – developmental toxicant

Potential Mechanisms of Toxicity

1. Prolonged or erroneous EC signaling
2. Complex receptor binding profile
3. Perturbation of testosterone steroidogenesis
4. Disruption of normal liver enzyme function
5. Inhibition of normal efflux transporter function
6. Oxidative stress

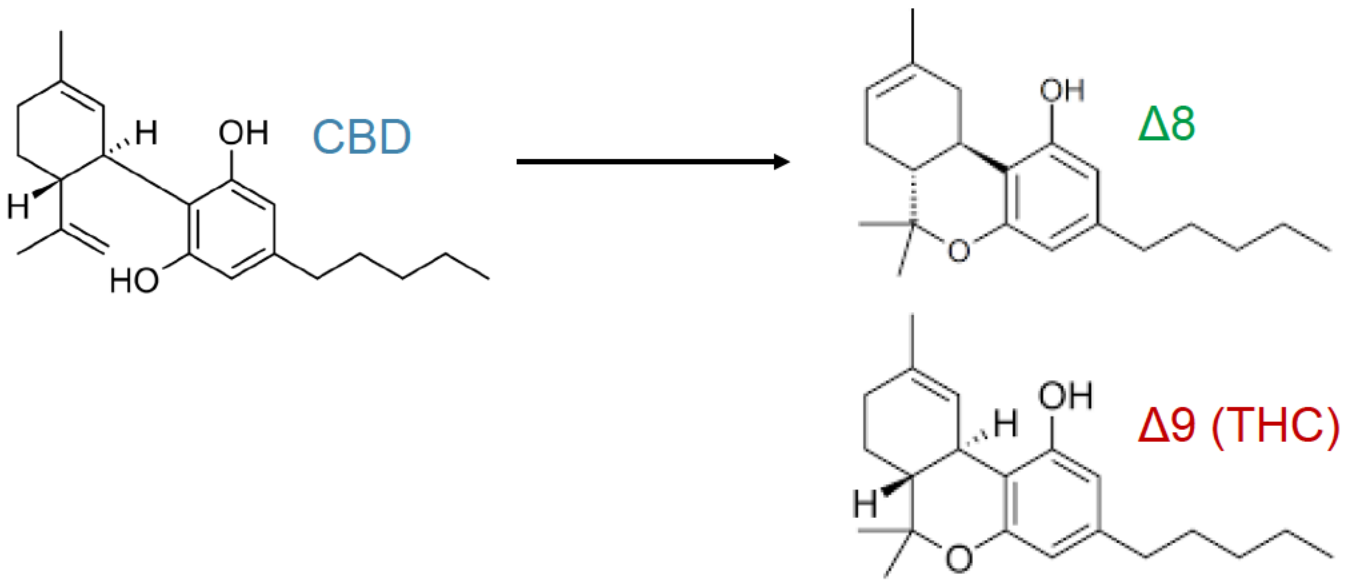
Conclusions

- Studies in animals show oral CBD can cause immune, liver, and/or developmental and reproductive toxicity
- Effects may not be immediately evident by users
  - Undetected liver toxicity
  - Subfertility in the absence of visible damage
  - Complicated post-market monitoring
- FDA has stated in warning letters it cannot conclude that the use of CBD is Generally Recognized as Safe (GRAS) in human or animal food

https://www.fda.gov/news-events/press-announcements/fda-warns-15-companies-illegally-selling-various-products-containing-cannabidiol-agency-details

Beyond CBD

- CBD-derived synthetic cannabinoids



https://www.fda.gov/consumers/consumer-updates/5-things-know-about-delta-8-tetrahydrocannabinol-delta-8-thc

Thank you

Acknowledgements

Supratim Choudhuri, Ph.D.
Patrick Cournoyer, Ph.D.
Jason Downey, Ph.D.
Kristi Muldoon-Jacobs, Ph.D.
Susan Carlson, Ph.D.
Ron Chanderbhan, Ph.D.
Kotaro Kaneko, Ph.D.

References

Silver *et al.*, 2019 – Endocannabinoid system
McPartland *et al.*, 2015 – Receptor binding affinity
WHO, Critical Review Report, 2018 – Toxicokinetics
Harvey *et al.*, 1991 – CBD metabolism in humans
Wu *et al.*, 2008 – Immunotoxicity, oxidative stress
Watkins *et al.*, 2021 – Elevated liver enzymes in healthy users
Ewing *et al.*, 2019 – Hepatocellular injury in animal models
Iffland & Grotenhermen, 2017 – CBD and efflux transporters
Dalterio *et al.*, 1986 – Mouse (adult male) exposure
Dalterio *et al.*, 1980 – Gestational rodent exposures
Rosenkrantz *et al.*, 1981 – Non-human primate (adult) exposure
Gustafsson *et al.*, 2019 – Embryotoxic *in ovo* (chicken)
Schuel *et al.*, 1991 – Sea urchin reproductive toxicant
Carty *et al.*, 2019 – Zebrafish developmental toxicant

U.S. FOOD & DRUG ADMINISTRATION

Meeting of the Science Board to the U.S. Food and Drug Administration

Challenges in regulatory oversight for substances with predicted pharmacological activity, marketed in foods and dietary supplements, using cannabinoids as a case study

June 14, 2022

Steven Musser, PhD
Deputy Director for Scientific Operations
Center for Food Safety and Applied Nutrition

Substances consumed for pharmacological effects pose challenges

1. Substances are consumed with the intent of experiencing a pharmacological (often psychoactive) effect
   - No other function in the product (not a flavor, nutrient, preservative, etc.)
   - Consumers might consume the amount needed to cause the desired effect, regardless of the suggested serving or dose

2. Substances might lack adequate or relevant history of safe use
   - Might not have been historically consumed in our society
   - Historical use context might differ in ways that diminish relevance to safety of new use context

3. Society might prefer access over prohibition
   - Some degree of safeguards/oversight desired

4. An expected route for access (outside of the drug pathway) is the food ingredient or dietary (supplement) ingredient pathways
   - Different pathways exist for tobacco and alcohol

Questions for the Science Board

How might a public health agency assess the unique toxicological safety questions raised by a substance (e.g. cannabinoids), likely used for pharmacological (e.g. psychoactive) effects, outside the context of an approved drug?

Consider the following potential scenarios:

- Known or predicted pharmacological activity that raises toxicological concerns
- Lack of substantial history of safe use directly relevant to the context of use
- Variability in product quality and composition, particularly variability in the concentration of active constituents
- Consumer ability to self-administer without practical limitations to dosage

Questions for the Science Board

If consumers have broad access to a substance (e.g. cannabinoids), likely used for its known or predicted pharmacological (e.g. psychoactive) effects, outside of the context of an approved drug, what approaches might a public health agency use to manage, mitigate, or communicate potential harm?

Consider the following potential scenarios:

- Known or predicted pharmacological activity that raises toxicological concerns
- Lack of substantial history of safe use directly relevant to the context of use
- Variability in product quality and composition, particularly variability in the concentration of active constituents
- Consumer ability to self-administer without practical limitations to dosage

Conclusion

- We thank the members of the Science Board for considering these important questions

- We also thank the public for their comments and attendance at today's meeting.