Current State of the Science: Toxicology of Cannabidiol and Other Cannabinoids

May 8, 2024
Welcome from FDA

Namandjé Bumpus, PhD
Principal Deputy Commissioner
US FDA
Silver Spring, MD
SOT FDA Colloquium Series

- Partnership of US FDA Center for Food Safety and Applied Nutrition (CFSAN) and the Society of Toxicology (SOT)
- Colloquium series established in 2014
  - 31st installment
- **Goal:** To stimulate dialogue among leading toxicology experts on future-oriented toxicological science relevant to food and food ingredient safety assessment
- Forum to discuss the latest toxicological science in the context of food chemical safety
- Not for soliciting regulatory advice or for discussing food or food ingredient regulatory issues
Colloquium Series

- Open to the public via webcast at no cost.
- General audience from all employment sectors.
- Recording and slides for all colloquia are available at www.toxicology.org.
Society of Toxicology 2024-2027 Strategic Plan

CENTRAL CHALLENGE:
Enhance the Scientific Influence of Toxicology

Relevant Objectives

- Effectively communicate scientific advances.
- Proactively pursue impactful scientific content.
- Foster connectivity across scientific disciplines.
- Provide training and education that reflects the needs of members.
- Leverage member expertise and connections to address human and environmental health concerns.
SOT FDA Organizing Committee Leadership
2023-2025

- **David C. Dorman**, DVM, PhD, DABT, DABVT, ATS, Colloquium Series Chair 2023-2024, North Carolina State University, Raleigh, NC

- **Jason R. Richardson**, PhD, DABT, ATS, Colloquium Series Chair 2024-2025, University of Georgia, Athens, GA

- **Esther Haugabrooks**, PhD, Colloquium Series Co-chair 2024-2025, The Coca-Cola Company, Atlanta, GA

- **Jason L. Aungst**, PhD, US FDA Liaison, College Park, MD

- **Omari Bandele**, PhD, US FDA Liaison, College Park, MD
SOT FDA Organizing Committee Members 2023-2025

- Patrick Crittenden, PhD, US FDA, Rockville, MD
- Alex Eapen, PhD, Cargill Inc, Wayzata, MN
- Suzanne C. Fitzpatrick, PhD, DABT, US FDA, College Park, MD
- Rayetta Henderson, PhD, ToxStrategies Inc, Katy, TX
- Alexandra Lobach, PhD, Givaudan, Mississauga, ON, Canada
- Willie McKinney, PhD, DABT, McKinney Regulatory Science Advisors, LLC, Henrico, VA
- Jeffrey J. Yourick, PhD, DABT, ATS, US FDA, Laurel, MD
- Chidozie Amuzie, DVM, PhD, DACVP, DABT, SOT Council Contact, Johnson and Johnson, Toronto, Canada
The Cannabis Plant contains Bioactive Compounds Known as Cannabinoids

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

Delta-9 Tetrahydrocannabinol (THC)

Cannabidiol (CBD)
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
  - Hemp can have high concentrations of CBD

- Hemp and CBD products have become prevalent.
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
- Insomnia

These findings are consistent with other sources.
FDA Statement: January 2023

- Existing regulatory frameworks for foods and supplements are not appropriate for CBD.

- Given the available evidence, it is not apparent how CBD products could meet safety standards for dietary supplements or food additives.

- FDA has concluded that a new regulatory pathway for CBD is needed.

- Today’s colloquium is not for discussing regulatory policy, but rather is a forum for scientific discourse about cannabinoid toxicology.
People Could Be Exposed to CBD in Multiple Ways, Including:

- CBD Products
  - E.g.: Ingestible, inhaled, and topical

- Cannabis (THC) Products
  - E.g.: Inhaled and ingestible

- Approved Drug
  - Epidiolex

- Hemp-derived food
  - E.g.: Hemp seeds and hempseed-derived food ingredients

Given the widespread use of CBD-containing products, it is critical to understand both its pharmacological and toxicological effects.
In 2020, FDA 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

FDA Is Monitoring Scientific Literature on Cannabinoid Toxicology

https://www.fda.gov/media/152317/download
https://doi.org/10.1016/j.fct.2023.113799
FDA is Conducting Toxicological Studies on Cannabinoids

Ongoing FDA Toxicological Studies

- **In vitro** evaluation of male reproductive toxicities induced by cannabidiol and its main metabolites
- Developmental and reproductive toxicity studies on CBD in rats
- Pharmacokinetics of cannabidiol upon dermal exposure in rats
- **In silico** binding prediction between cannabinoids and biological targets
- Physiologically based pharmacokinetic modeling and simulation of cannabinoids in human plasma and tissues
- Additional studies
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https://doi.org/10.1002/jat.4478
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https://doi.org/10.1002/jat.4409
Colloquium Co-Chairs

Luísa Camacho, PhD
US FDA NCTR

Barbara Kaplan, PhD
Mississippi State University
Colloquium Objectives

- Describe cannabidiol (CBD) in the context of marijuana, hemp, and other cannabinoids
- Understand the pharmacokinetics of CBD across species and routes of exposure
- Overview of potential target organs/systems of CBD
  - Central nervous system
  - Male reproductive system
- Summarize potential exposures and biological activities of other, “minor” cannabinoids
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<tr>
<th>Time</th>
<th>Session</th>
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<tbody>
<tr>
<td>9:10 AM</td>
<td><strong>Cannabidiol Overview: Clinical Considerations, Regulatory Status, and Marketplace Concerns</strong>&lt;br&gt;Robert Welch, PharmD, University of Mississippi, Oxford, MS</td>
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<tr>
<td>9:40 AM</td>
<td><strong>Pharmacokinetics of Cannabidiol</strong>&lt;br&gt;Ryan Vandrey, PhD, Johns Hopkins University, Baltimore, MD</td>
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<td>10:10 AM</td>
<td><strong>Central Nervous System Effects of Cannabidiol</strong>&lt;br&gt;Ethan Russo, MD, CReDO Science, Vashon, WA</td>
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<td>10:40 AM</td>
<td>Break (20 min)</td>
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<td>11:00 AM</td>
<td><strong>Effects of Cannabidiol on the Male Reproductive System</strong>&lt;br&gt;Renata Mazaro-Costa, PhD, Federal University of Goias, Goiânia, Brazil</td>
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<td>11:30 AM</td>
<td><strong>Beyond CBD: Exposure, Chemistry, and Toxicity of “Minor” Cannabinoids</strong>&lt;br&gt;Michael Santillo, PhD, US FDA/CFSAN/OARSA, Laurel, MD</td>
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<td>12:00 Noon</td>
<td><strong>Roundtable Discussion</strong>&lt;br&gt;Moderators: Luisa Camacho and Barbara Kaplan</td>
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