

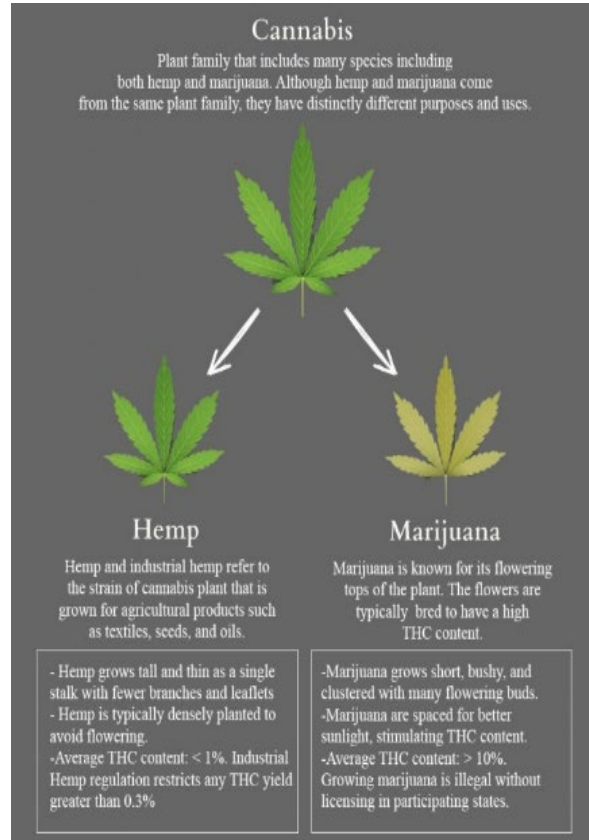
Marijuana, CBD, and Hemp: Understanding the Current Regulatory Landscape and How it Might Change

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What is the Difference Between Cannabis, Hemp, and Marijuana?



Source: gocureco.com

Marihuana? Marijuana? Let's Call the Whole Thing Off.

- The Controlled Substances Act (CSA) adopted the same definition of *Cannabis sativa* that appeared in the 1937 Marihuana Tax Act. The definition of “marihuana” in the CSA (21 U.S.C. § 802(16)) reads:

The term “marihuana” means all parts of the plant *Cannabis sativa* L., whether growing or not; the seeds thereof; the resin extracted from any part of such plant; and every compound, manufacture, salt, derivative, mixture, or preparation of such plant, its seeds or resin. Such term **does not include** the mature stalks of such plant, fiber produced from such stalks, oil or cake made from the seeds of such plant, any other compound, manufacture, salt, derivative, mixture, or preparation of such mature stalks (except the resin extracted therefrom), fiber, oil, or cake, or the sterilized seed of such plant which is incapable of germination.

(emphasis added).

2018 Farm Bill Amendment to CSA Regarding “Hemp”

- Defined “hemp” to mean “the plant *Cannabis sativa* L. and any part of that plant, including the seeds thereof and all derivatives, extracts, cannabinoids, isomers, acids, salts, and salts of isomers, whether growing or not, with a delta-9 tetrahydrocannabinol concentration of not more than 0.3 percent on a dry weight basis.”
- Excluded “hemp” from the CSA definition of marihuana
- Significantly, the marihuana definition now excludes cannabinoids, including CBD

What is the Legal Framework for Cannabis? Who Regulates What?

- Background:
 - Marijuana is a Schedule I (*i.e.*, no currently accepted medical use and a high potential for abuse) controlled substance under the CSA.
 - However, many people grow, process, transport, dispense, study, and/or consume cannabis or cannabis-derived products. How is this so? In short, the legal framework is incredibly complicated and involves a confusing web of conflicting federal and state laws, regulations, and policies.
- U.S. Drug Enforcement Administration (DEA):
 - A federal agency under the Department of Justice (DOJ) that enforces the CSA.
 - DEA issues registrations for growing and processing marijuana for medicinal research.
 - Proceedings to add, delete, or change the schedule of a drug or other substance may be initiated by DEA, the Department of Health and Human Services (HHS), or by petition from any interested party.

What is the Legal Framework for Cannabis? Who Regulates What? (continued)

- U.S. Food and Drug Administration (FDA):
 - Before conducting human testing of any drug (including marijuana), an investigator needs to submit to FDA an investigational new drug application (IND).
 - The Agency also reviews marketing applications to determine whether the proposed drug products are safe and effective for their intended indications.
 - Finally, FDA evaluates and, if appropriate, takes enforcement action against marketers of conventional foods and dietary supplements to which tetrahydrocannabinol (THC) and/or cannabidiol (CBD) have been added.
 - More on this in a few minutes.

What is the Legal Framework for Cannabis? Who Regulates What? (continued)

- FDA and DEA interplay:
 - FDA reviews the IND application and the research protocol submitted by the applicant.
 - DEA reviews the registration application filed by the researcher.
 - The National Institute on Drug Abuse (NIDA) provides research-grade marijuana for scientific study. DEA also may allow additional growers to register with the DEA to produce and distribute marijuana for research purposes.
 - If FDA approves an NDA for a cannabis-derived product, DEA will issue a scheduling order for the same.
- State Cannabis Commissions:
 - These agencies, which are sometimes part of state departments of health, promulgate and enforce regulations on a range of topics, including growing, processing, dispensing, and consuming cannabis (medical, and in some states, also adult use). Some states allow edibles, but many do not.

USDA's Role in Regulating Hemp

- The 2018 Farm Bill directs the U.S. Department of Agriculture (USDA) to develop federal hemp regulations “as expeditiously as practicable.” Without a specific timetable attached to this responsibility, promulgation of regulations could take a year or more.
- While the law will allow states to be the primary regulators of hemp, this will only occur if a state can demonstrate to USDA that it can properly monitor cultivation and production.
- If states are unable or unwilling to create their own regulatory plans, USDA would maintain oversight. Until USDA issues its regulations, hemp cultivators and processors will continue to be subject to state pilot programs.
- Eventually, states will submit to USDA their plans to regulate hemp. While there is not a deadline for states to do so, once a state submits a plan to USDA, the agency will have 60 days to approve it or reject it.

Current FDA Position on CBD

- CBD (whether from marijuana or hemp) may not be sold as or in a dietary supplement or food in the United States; the 2018 Farm Bill has no effect on existing FDCA requirements.
- The FDCA excludes from dietary supplements (FDCA § 201(ff)(3)(B)(ii)) or food (FDCA § 201(ff)) any article approved as a new drug or authorized for investigation for which “substantial clinical investigations have been instituted and for which the existence of such investigations has been made public,” *unless* the article was first marketed as a dietary supplement or a food.
 - FDA authorized substantial clinical investigations for CBD drugs, and approved Epidiolex.
 - FDA believes CBD was not marketed as a dietary supplement or food first.
- FDA can issue a regulation finding the article to be lawful.
- FDA may ask Congress for legislative change to allow CBD in foods and dietary supplements.
- CBD in cosmetic/topical products is not precluded by FDA’s restrictions on CBD in dietary supplements or foods (but these would still be subject to DEA restrictions).

Current FDA Position on CBD (continued)

- Even if exclusionary clauses could be overcome, CBD and products containing it must comply with all other applicable regulatory requirements
- Dietary ingredient requirements:
 - must be a “dietary ingredient” as defined in FDCA § 201(ff)
 - if a “new dietary ingredient,” may need an NDI notification to FDA
- Food ingredient requirements:
 - must be an FDA-approved food additive or GRAS substance
 - must contribute taste, aroma, or nutritive value, or technical/functional effect
- Must comply with applicable cGMPs, FSMA requirements, etc.
- Must bear only lawful claims, if any

Current FDA Activities Regarding CBD and Hemp

- Recognizing that the proponents of the 2018 Farm Bill intended to create a pathway for CBD in foods and supplements, FDA is actively considering the issues
- Formed an internal CBD working group
 - Aims to provide recommendations possibly as early as this summer
 - Recommendations may include suggestions to Congress for a legislative pathway
- Enforcement stance: enforcing (by warning letters) where products bear egregious disease claims or may present safety concerns
- FDA accepted 3 GRAS notices for three Generally Recognized as Safe (GRAS) notices related to hulled hemp seeds, hemp seed protein, and hemp seed oil

FDA Public Hearing, “Scientific Data and Information About Products Containing Cannabis or Cannabis-Derived Compounds”

- Hearing will be May 31, 2019; FDA accepting written comments until July 2, 2019
- FDA solicits input on:
 - Health and safety risks
 - FDA believes questions remain regarding safety of widespread use of cannabis-derived products
 - Asks for data on levels that may cause safety concerns, anticipated cumulative exposure
 - Manufacturing and product quality
 - Asks whether there are any particular standards or processes needed to address safety or ensure quality and consistency
 - Asks about the functional purposes of adding cannabis-derived compounds to foods (e.g., nutritive value, technical effect)
 - Marketing/labeling/sales
 - Warnings required/appropriate?
 - FDA also asks about potential impact on incentives for drug research

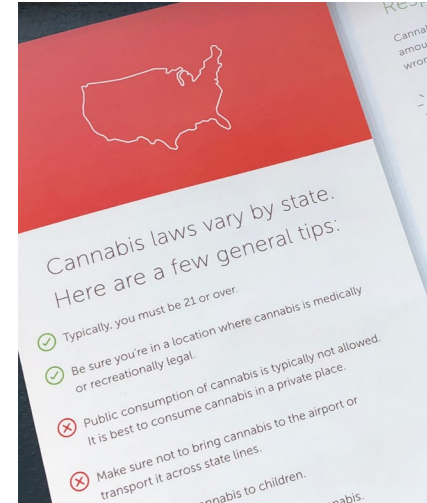
FDA Resources Regarding Marijuana, CBD and Hemp

- FDA and Marijuana: Questions and Answers:
<http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm421168.htm#enforcement>.
- Marijuana Research with Human Subjects:
<http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm421173.htm>.
- FDA and Marijuana:
<http://www.fda.gov/NewsEvents/PublicHealthFocus/ucm421163.htm>.
- CBD Warning Letters, e.g.:
<http://www.fda.gov/ICECI/EnforcementActions/WarningLetters/2017/ucm549298.htm> (2017);
<http://www.fda.gov/newsevents/publichealthfocus/ucm484109.htm> (2016).

What's happening at the state level?

- CSA does not preempt state law. Many states automatically follow the federal CSA, but many don't. A number of states are moving to conform their CSA's with federal law, so hemp is being descheduled at the state level in many states.
- At the same time, as FDA has become quite vocal that CBD is not a lawful food/supplement ingredient, many states and even local governments are banning it, even if not a controlled substance.
- Some state and local authorities have taken or threatened enforcement action against CBD products

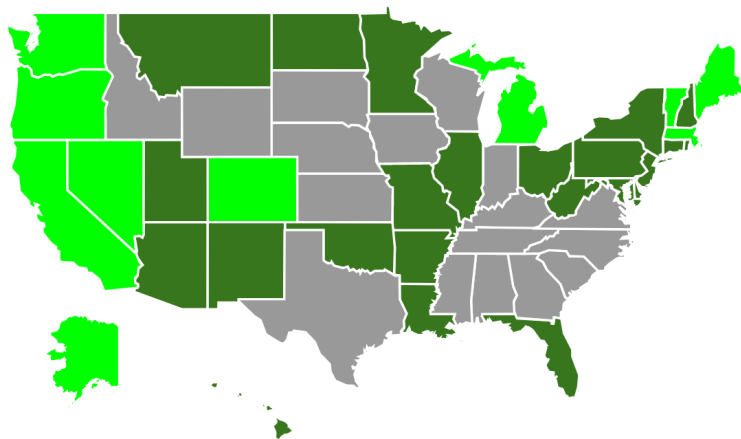
Public Health Considerations: Cannabinoid Legalization



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Information is current as of Nov. 7, 2018.

State Marijuana Regulation



Marijuana Legalization Status

- Medical marijuana broadly legalized
- Marijuana legalized for recreational use
- No broad laws legalizing marijuana

- Medical legal in 31 states
- Recreational legal in 10 states and DC (But retail sales not authorized in DC, Michigan, Maine, Vermont)

<https://www.governing.com/gov-data/safety-justice/state-marijuana-laws-map-medical-recreational.html>

Investment in Edibles

- Edibles' market share grown from 5.4 % in 2011 to 12% in 2018.
- Edibles sales projected to reach \$4.1 billion by 2022.
- Dec 2017, private equity firm Privateer Holdings purchased Goodship, which sells edibles in Washington state.
- Jun 2018, Heineken brand Lagunitas launched "IPA-inspired, THC-infused sparkling water" in California.
- Incredibles is based in Colorado and currently expanding to 4 new jurisdictions, with plans for 6 more.



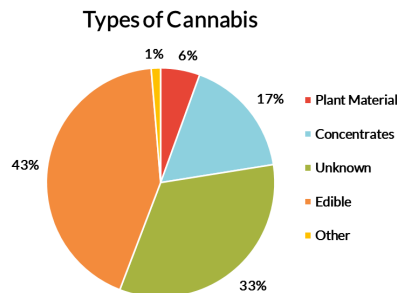
Impact of Legalization on Cannabis Poison Control Center Calls in Washington State

Washington Poison Center

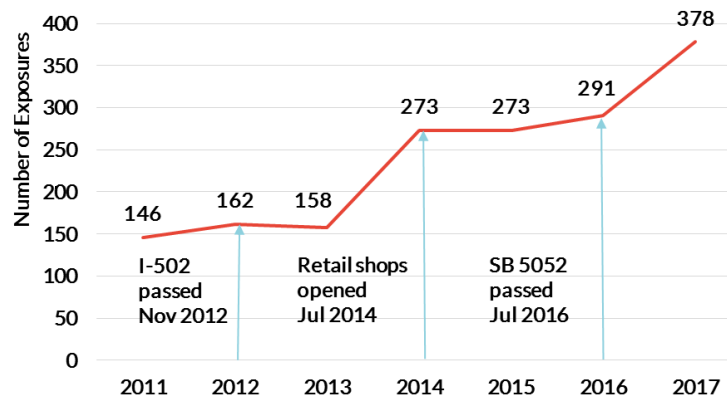
2017 Annual Toxic Trend Report:
Cannabis

Among the 0-5 year age group, WAPC reports a 57.7% increase (n=82) in exposures compared to 2016 (n=52).

Of those cases followed to a known medical outcome, 23.2% of individuals exposed developed moderate or life-threatening symptoms.



Cannabis Exposures 2011-2017



Washington State requires:

- Child-resistant packaging
- Ban on lollipops, gummies
- 10mg THC per serving/100 per product



Public Health Risks: Cannabis

National Academies 2017 Report on the Health Effects of Cannabis and Cannabinoids

“Substantial Evidence” of harms:

- Worse respiratory symptoms more frequent chronic bronchitis episodes (long-term cannabis smoking)
- Increased risk of motor vehicle crashes (cannabis use)
- Lower birth weight of the offspring (cannabis smoking in pregnancy)
- The development of schizophrenia or other psychoses, with the highest risk among the most frequent users (cannabis use)



Public Health Concerns: CBD Legalization

- Liver injury risk identified during Epidiolex approval
- Cumulative exposure to CBD across a broad range of consumer products
- May discourage investment in clinical trials for additional new drug approvals, impeding development of an evidence base for safe and effective use.
- Deceptive marketing may deter use of appropriate, FDA-approved therapies to treat serious and even fatal diseases.



Good Manufacturing Practices (cGMP)

- Potency problems:
 - Sample of 84 CBD extract products (oil, tincture, and vaporization liquid) sold online found 70% were inaccurately labeled with high/low CBD concentrations, and 20% had THC levels over the limit of quantification (up to 6.4 mg/mL). (Bonn-Miller 2017)
- Other major hazards:

Aflatoxins (mold), chemical residues (lead), pathogenic contamination (*Salmonella*, *E coli*).

 - In Washington State, >12 percent of marijuana products fail mold, *Salmonella*, and *E coli* requirements following launch of testing program.
 - Massachusetts testing revealed max lead levels in marijuana to be >300x the maximum lead levels found in spinach and 96x higher than the legal lead limit for marijuana in Massachusetts
- Hurdles to effective enforcement of state testing programs:
 - Developing and validating multiple analytical methods to verify dosing/test for contaminants in diverse food and plant matrices
 - 2016 Seattle Times investigation found that four state-certified pot labs failed 0 percent of samples

Public Health Concerns: Edibles

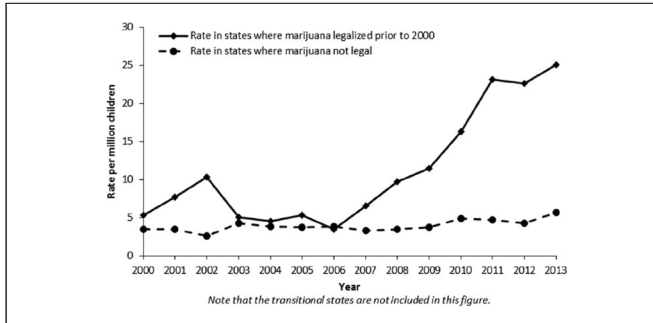


Figure 2. Annual rate of marijuana exposures among children younger than 6 years by marijuana legalization status of state (National Poison Data System 2000-2013).



Levy Thamba Pongi

- Dosing/titration challenges: onset in 30min – 4 hours versus minutes, variable effects, slower dissipation.
- Pediatric exposures: Ingestion the most common route of unintentional pediatric exposure (78 % of all incidents). (Onders *et al.* 2016)
- Edibles account for only 0.32% of total cannabis sales in Colorado, but 10.7 % of cannabis-related emergency room visits. Edibles more likely to involve acute psychiatric and cardiovascular symptoms than inhaled cannabis. (Monte *et al.* 2019)
- Several reported deaths associated with edibles, including suicide by 19-yr-old Levy Thamba Ponai in 2014.

So what happens now? Let's discuss.

- Potential pathways forward in light of exclusionary clauses
- Safety considerations
- Meeting other requirements for food/dietary ingredients
- State law considerations