CANNABIS PUBLIC POLICY CONSULTING

Response to Congress Regarding Approaches for Regulating CBD

August 18, 2023

Prepared For:
Congress of the United States of America
Washington, D.C. 20515

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Background

In January 2023, FDA announced that it would like to work with Congress to craft a legislative approach to the regulation of CBD products. On July 27, 2023, Congress of the United States issued a Request for Information from stakeholders to aid in their assessment of the potential for a regulatory pathway for hemp-derived CBD products that prioritizes consumer safety and provides certainty to the U.S. market.

Cannabis Public Policy Consulting has prepared the following document of responses to select questions using our novel, in-house data as well as external sources where appropriate.

About Cannabis Public Policy Consulting

Cannabis Public Policy Consulting is the leading original cannabis research to practice consulting and research firm in the United States. We offer a multidisciplinary approach to data-informed policymaking. Our mission is to embed advanced data and our implementation science expertise in cannabis policymaking to protect public health and safety, promote equity, and increase the regulated cannabis industry sustainability.

Internal Data Sets Analyzed in this Response Document

The primary data source used to answer the select questions in this document is the *Regulatory Determinants of Cannabis Outcomes Survey* (RDCOS)[1]. The RDCOS is the largest and most frequently issued cannabis-related consumption and outcomes survey in the nation. The RDCOS is an internally funded product of CPPC and is issued to all 50 states quarterly in an effort to collect data on cannabis consumption, related behaviors, and outcomes in real time.

A total of 59,505 survey responses were collected between March and June of 2023 from our *Regulatory Determinants of Cannabis Outcomes Survey* (RDCOS). We sampled participants from states in a manner that reflected state populations [2]. Of these, 55% (n = 32,931) said that they have used some form of cannabinoid other than *delta*^{9}-THC in the past year, and 40% of survey respondents indicated using at least one alternative or synthetic cannabinoid within the past month.

Results of the survey are presented below per topic category, as delineated in the Request for Information from Congress. Not all categories are immediately addressable with our available data, so we have limited our description to (I) current market dynamics, and (II) safety. The RDCOS assessed seven different synthetic and alternative cannabinoids, these being: *delta*^{8}-THC, *delta*^{8}-THCO, *delta*^{10}-THC, THCP, THCV, HHC, and CBD.

[1] For more information on the RDCOS methodology, questions, and accessibility of data, please contact RDCOS Principal Investigator, Michael Sofis, PhD at msofis@cannabispublicpolicyconsulting.com. To cite this document, please use the following: "Sofis, M. et al. Regulatory Determinants of Cannabis Outcomes 2023, Response to Congress. Cannabis Public Policy Consulting. https://www.cannabispublicpolicyconsulting.com/research/reports/)"

[2] State populations from the 2022 National Census report correlated with samples from each state in our survey ($r = 0.77$, $p < 0.05$), which yielded a mean of 20.31 completed surveys per 100,000 residents.

Current Market Dynamics

1. *What does the current market for CBD products look like? Please describe the types and forms of products available, manufacturing practices within the industry, market supply chain, how products are marketed and sold, the types of cannabinoids used in products, the marketed effects of CBD products, and the range of CBD doses currently found in the market.*

- CBD use is not more common, nor uncommon across states relative to *delta*^{9}-THC legal status.
- Relative to other forms for synthetic and alternative cannabinoids, CBD is used more exclusively for *medicinal* rather than *recreational* purposes.
- HHC (hexahydrocannabinol) is used equally for both recreational and medicinal purposes.
- All other forms of cannabinoid alternatives to *delta*^{9}-THC are used for recreational purposes more explicitly, and each is known to produce intoxicating effects (*i.e.,* "intoxicating variants" in **Table 1**).
- Use of these is highly correlated with *delta*^{9}-THC use ($\rho = 0.23$, $p < 0.001$), which suggests that cannabis consumers are *supplementing*, rather than replacing, their use of *delta*^{9}-THC with these intoxicating variants.
- Use of intoxicating variants is more common among states in which *delta*^{9}-THC is prohibited compared to those in which there is some form of regulated market ($p < 0.001$).

***Table 1**. How products are sold, by alternative-cannabinoid type.*

	CBD	Intoxicating variants of *delta*^{9}-THC
Source		
Legal Dispensary	52%	37%
Gas station or grocery store	7%	17%
Smoke shop	16%	24%
Another type of store	1%	3%
Online	7%	7%
Illicit dealer	4%	6%
Friends & family	10%	5%
Methods of consumption		
Smoke	30%	45%
Eat	43%	30%
Vape	14%	19%
Dabbing	5%	4%

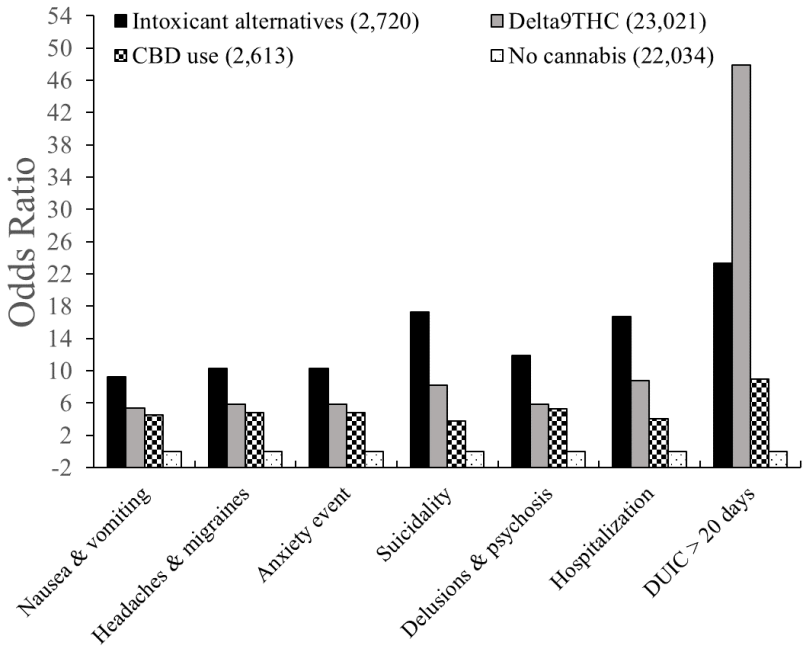
**Note: typical concentrations of CBD and the specific ailments it is used to alleviate can be addressed in the next RDCOS survey in Fall of 2023. Those indicating topical application or "other" form of consumption for CBD was < 8%.*

Safety

11. What is currently known about the safety and risk-benefit profile of CBD and other hemp derived cannabinoids? What safety and toxicity data are available to support this knowledge. Please include in your answer any relevant information about safety with regard to specific populations, such as children and pregnant individuals.

- Among those who use CBD exclusively, the risk of developing cannabis-use disorder (*i.e.,* CUD) [3] does not differ from non-cannabis users; however, those who reported using *any* intoxicating-cannabinoid variant are more likely to reach diagnostic criteria for CUD than those who use *delta*^{9}-THC on a daily basis ($p < 0.001$).
- Those using intoxicating variants were statistically more likely to report numerous mental-health diagnoses compared to those using *delta*^{9}-THC on a *daily basis*, CBD, or non-users (*p's* < 0.001).
- Moreover, those using intoxicating variants believe that the risks associated with cannabis use during pregnancy, and use before the age of 16, are significantly less substantial compared to CBD users ($p < 0.001$).

***Figure 1**. Odds ratio of reporting each adverse event relative to their exclusive use of each product listed. Those in delta9-THC group reported daily use; figure includes (n's per group). Driving under-the-influence of cannabis (DUIC) is listed as days*



- The health consequences associated with the use of intoxicating variants is extremely negative and surpasses the risks of *daily use* of *delta*^{9}-THC (see **Fig 1**). Toxicological evidence from poison control centers supports this, but our data suggest that adverse reactions to these are not uncommon.
- Even those who use CBD (exclusively) report adverse reactions which they directly attribute to the consumption of CBD; unclear at this time is whether these adverse

[3] Cannabis-use disorder was assessed in the survey using the validated measure (CUD-IT, taken from Loflin *et al.* 2018 https://doi.org/10.1080/00952990.2017.1376677)

reactions depicted in **Fig 1** are caused by CBD or are related to the variety of chemical compounds known to contaminate CBD products [4].

12. What actions, if any, should the Federal government take to better understand the potential benefits or harms of CBD products and other cannabinoids?

To our knowledge there are fewer than three survey studies examining the prevalence or risks of using cannabinoids other than *delta*^{9}-THC, CBD, *delta*^{8}-THC. Although we have gleaned insights into findings suggesting that *delta*^{8}-THC, *delta*^{8} -THCO, Delta-10, THCV, THCP, CBD, CBN, and HHC each carry additional risks of chronic and acute cannabis-related harms above and beyond that of *delta*^{9}-THC use, repeatedly assessing national samples with different survey participants (i.e., repeated cross-sectional design) will never be sufficient to untangle the extent to which each of these cannabinoids elevates risk of harms. **The Federal government's funding of a longitudinal cohort study is an imperative requisite to understand the prevalence of risks of such cannabinoid use.**

Longitudinal cohort designs involve recruiting a single, very large sample of participants who regularly take the same general survey repeatedly (e.g., once a quarter). Longitudinal cohort designs are generally used to provide the closest proxy to a causal analysis of the impacts of a given variable on outcomes (here it is initiation of cannabinoid use on risk of negative health outcomes or harms). This approach would address many of the overarching limitations of current research that extend past a simple dearth of available data:

(i) First, to establish any degree of causality, it is necessary to examine initiation and maintained cannabinoid use patterns across different cannabinoid profiles differentially add risk to acute and chronic health outcomes. Such an approach is necessary to isolate the potential confounding role of individual differences in personality which may explain cross-sectional relationships between cannabis use and risk of harms instead of the potential role of each drug's behavioral pharmacology.

(ii) The dynamic and ever-changing status of the diverse array of cannabinoids will likely continue to outpace existing research as new and hybrid categories of cannabinoids increasingly become discovered and available to the public in an unregulated fashion. However, a longitudinal cohort design would allow for new cohorts to be introduced and followed across time that could include survey items regarding different types of cannabinoids and different preferences, attitudes, perceptions, and outcomes.

(iii) Similar to the above point, adding new cohorts would enable researchers to differentiate between age, trend, and cohort effects to produce robust insights on the extent to which cannabinoid prevalence and harms associated with its use are increasing, decreasing, or staying the same.

(iv) Conducting a longitudinal cohort design would also facilitate much more methodology rigorous analyses on the impacts of specific legal cannabinoid policies on the prevalence and risks of cannabinoid use by type, frequency, dose, and reasons for use, thus further informing the federal government and individual states on the relative impacts of policies on risky cannabinoid patterns of use.

(v) Another limitation that could be addressed using this study design is the inclusion of physical sites to annually test for long-term impacts of CBD and other cannabinoids on

[4] Substance Abuse and Mental Health Services Administration (2023): Cannabidiol (CBD) – Potential Harms, Side Effects, and Unknowns. Publication No. PEP22- 06-04-003. Rockville, MD: National Mental Health and Substance Use Policy Laboratory.

physical health such as liver toxicity, elevated blood pressure, heart palpitations, cancer, and many other indicators, outcomes, or diagnoses.

If pursued, such a project should rapidly recruit, collect, and analyze data from large U.S. samples to provide the findings within a two- or three-month period after data collection to ensure outcomes do not outpace policymaking. This timeframe contrasts sharply with the existing Federally funded surveillance such as the BRFSS, the NSDUH, and the NESARC. Given the rapid and dynamic trends observed in the prevalence and policies surrounding diverse cannabinoids, the timely administration and analysis of national data on this topic will be paramount to providing meaningful data to Federal and State regulators alike and can be employed prior to national and regional crises in health.

13. Some stakeholders have raised concerns that CBD products have inherent risks. What are those inherent risks, and at what levels of CBD do those risks present themselves? What data and other evidence support the existence of such risks, and from which products are such data and evidence derived?

At least four studies (two non-human animal and two human) have demonstrated an association between *particularly high levels of CBD use and potential issues with liver toxicity*[5]. In a recent study conducted with European residents, the authors found data that led them to recommend any dosages above 10mg/day be considered "unsafe for consumption"[6]. However, some study results have been mixed, with some studies showing null effects of CBD consumption on liver toxicity[7], and it is unknown whether liver toxicity outcomes (or other physical health outcomes) are a product of individual differences that increased the odds that certain individuals would initiate and maintain CBD use, or whether the CBD use itself is responsible for the findings. In one rat study, within-subject reversal effects were found such that risky liver toxicity levels returned to normal after a 28-day washout period, which provides additional evidence that bio pharmacological exposure to CBD itself may be pivotal in increasing the risk of liver toxicity.

Similar to our suggestions on how the Federal government can better understand the potential benefits or harms of CBD products and other cannabinoids, funding and conducting multiple cohorts of a longitudinal cohort study with a physical health center element would provide at least five methodological improvements that would dramatically improve our understanding of the extent to which:

(i) Perceptions, behavior, and attitudes towards CBD impact risks,

(ii) The inherent bio pharmacological nature of the cannabinoid impacts risks, and

(iii) How these findings differentiate from other specific cannabinoids and combinations of cannabinoids that include and do not include CBD.

[5] Therapeutic Efficacy of Cannabidiol (CBD): a Review of the Evidence From Clinical Trials and Human Laboratory Studies | SpringerLink
[6] Psychoactives | Free Full-Text | Does Cannabidiol (CBD) in Food Supplements Pose a Serious Health Risk? Consequences of the European Food Safety Authority (EFSA) Clock Stop Regarding Novel Food Authorisation (mdpi.com)
[7] Nanochannel delivery system for CBD: Sustained low level plasma levels without liver toxicity - ScienceDirect