Testimony in Support of Senate Bill 86

Chris Lindsey, Director of State Advocacy and Public Policy
American Trade Association for Cannabis and Hemp

Chair Roegner, Vice Chair Gavarone, and Ranking Member Blackshear, and members of the Ohio Senate General Government Committee, thank you for the opportunity to testify as a proponent to Senate Bill 86.

My name is Chris Lindsey and I am the Director of State Advocacy and Public Policy for the American Trade Association for Cannabis and Hemp (ATACH). ATACH is a 501c(6) trade association registered in Washington, DC, that represents state-regulated cannabis and hemp businesses around the US. We were founded 10 years ago to advocate for consumer safety for marijuana and hemp products, and we support businesses engaged in state-licensed medical and adult-use production and sale. Our organization serves as a founding member and remains a board member of the ASTM International's D37 committee, which is focused on cannabis and hemp standards. I am proud to say ATACH remains on the forefront because of its advocacy for better regulations, and we often serve as a bridge between the regulated cannabis industries and regulators and policymakers. ATACH has taken a leading role in responding to the sudden rise of unregulated hemp intoxicants including products such as delta-8 similar products.

As some of you may recall, I appeared before this committee last year regarding last session's bill. At that time, I visited smoke shops in the area and purchased a variety of hemp intoxicant products that were readily available in Ohio's unregulated market. I presented those products during the hearing and later had them tested. The test results were shared with the committee, and they really highlight the fact that these are essentially the same thing as marijuana products, except they showed presence of contaminants, THC levels above advertised, unlisted synthetic compounds. So basically the same products, except no rules and you can see the result.

My goal today is to provide some context on how we got here, discuss what these products are, and from my experience dealing with this issue across the country discuss the concerns with synthetic THC. Mr. Chairman, to respect the committee's time please note I have attached additional information, resources, and studies to my testimony, however I will not read those but will be available to discuss these as follow questions or at a later time if the committee deems appropriate.

1. How We Got Here: Congressional Intent and the Rise of Synthetic THC

Congressional Intent
The 2018 Farm Bill was a landmark piece of legislation aimed at legalizing hemp for industrial purposes, such as fiber, rope, and other non-intoxicating uses. The removal of hemp and its derivatives from the Controlled Substances Act (CSA) was intended to encourage agricultural development. Instead it has introduced synthetic intoxicants into the marketplace. The law never envisioned the rise of synthetic THC derivatives or the proliferation of finished consumer products derived from hemp.

Unintended Consequences
The lack of a clear regulatory framework for consumer products created a significant loophole. Chemists began manipulating non-intoxicating compounds like CBD which is plentiful in hemp into intoxicants such as Delta-8 THC, effectively undermining congressional intent. Misleading marketing terms like "Farm Bill compliant" have perpetuated the false notion that these products are legal under federal law. However, "Farm Bill compliant" does not mean "federally legal."

Regulatory Gaps and Challenges
If these products were genuinely removed from the CSA (which we think is not clear), they would fall under FDA jurisdiction. The FDA has consistently deemed them unsafe and unapproved, issuing dozens of warning letters to manufacturers for producing and selling these products in violation of federal law. Yet, this regulatory gap has enabled a booming market for unregulated intoxicants, often sold in convenience stores, gas stations and bars and restaurants under the guise of legality.

Escalating Weight Function
The legal framework for hemp was designed with plants in the field in mind, using weight-based limits like "less than 0.3% THC." However, this standard is now being applied to finished consumer products, such as gummies and candy, creating a massive regulatory disconnect. No other U.S. product regulation applies such a weight-based standard to consumer goods. This misuse of the law further demonstrates that these intoxicating products were never intended to fall under the 2018 Farm Bill. The upshot is a wide range of consumer goods including candy, beverages, and inhaled products that are many times more potent than anything allowed in regulated cannabis programs.

2. What These Products Are

First, What These Products Are <u>Not</u>
These products are not coming from U.S.-grown, USDA-regulated hemp farms. For context, hemp farming in the U.S. has sharply declined since passage of the 2018 Farm Bill, with acreage dropping from 160,000 in 2019 to just 22,000 acres in 2023. In Ohio, for example, farmers planted only 170 acres of hemp in 2023, harvesting a mere 120 acres. Compare this to the state's 4.75 million acres of soybeans, 3.6 million acres of corn, and 650,000 acres of wheat harvested the same year.

In fact, the U.S. now operates at a significant trade deficit for hemp, importing many times more than we produce. Most of the hemp used in synthetic THC production comes from countries like China, India, and Eastern Europe. The reality is that much of the hemp used for synthetic THC production comes from countries like China, India, and Eastern Europe, where U.S. regulators have no oversight. This raises serious concerns about product quality and safety, especially when compared to the rigorous standards applied to state-licensed cannabis businesses. Consumers should be pretty careful about consuming products made from Chinese hemp without some pretty careful tests.

The Synthetic Process

In labs, imported CBD is chemically altered using acids and solvents. This process—essentially boiling the CBD in battery acid for 24 hours—strips the molecule down to its core structure, which is then rebuilt into synthetic cannabinoids like Delta-8 THC and a host of other chemicals. Some are intoxicating, while others are contaminants with unknown effects on human health. They all go into a broad range of consumer goods from there – these are the gummies, vapes and beverages that we now see in stores.

I brought you some examples of the kinds of products we are talking about. These were purchased by myself when I got here to Columbus at area convenience stores. We are testing these products from a lab that specializes in synthetic THC testing to see what is actually in them and how that compares to the label and will share the results with this committee.

We are very concerned about these products because to most people, there is no real difference between these products and ours. And frankly, many of these products are very questionable, and nobody should be putting them in their bodies, much less kids. And that is devastating to the highly regulated industry trying to follow all the rules and regulations Ohio is just now in the process of setting up. This is the exact opposite of what our program is about and it shouldn’t be tolerated.

Comparison to Marijuana

The reason why state marijuana programs are so heavily regulated is to ensure consumer safety through rigorous testing and oversight. Tax revenue is an additional benefit, but the primary purpose of regulation is to protect public health. Unlike regulated marijuana, synthetic THC products lack the extensive safety measures built into state marijuana programs. These programs mandate rigorous testing for potency, contaminants, and consistency to ensure consumer safety. Synthetic THC products, by contrast, evade all oversight. They are marketed as substitutes for regulated marijuana even though they are synthetic, but offer none of the safeguards designed to protect consumers and prevent diversion even from marijuana products, much less lab-created drugs, and often they are marketed directly to children.

3. Concerns About Synthetic THC

Health and Safety Risks

There is a false equivalency that gets thrown around in these debates. As if the cannabis industry and the hemp industry were really just fighting over who gets to sell products. That misses a big difference that is often overlooked. Natural cannabis and synthetic THC are not the same thing. The production of synthetic THC is a laboratory process that introduces a range of unknown chemicals and byproducts, posing significant risks to public health that we know little about. Studies have repeatedly highlighted the dangers of these products, including the potential for serious health effects from long-term exposure.

These products are often aimed at consumers unable to access legal cannabis - they are a marijuana substitute. In states where legal cannabis is available, synthetic THC products are increasingly marketed to children, often in the form of candy-like edibles. Unlike state-regulated marijuana programs, which impose strict safeguards to ensure safety and prevent diversion, synthetic THC operates without any regulatory guardrails. While no child should ever consume intoxicating cannabis products outside the supervision of a doctor, in reality, no consumer—including adults—are safe consuming unregulated synthetic THC products.

Potency levels in these products are often extremely high, with no safeguards for dosage or contaminants. Moreover, the rapid creation of new synthetic cannabinoids outpaces regulatory efforts, leaving consumers vulnerable to unpredictable risks.

A New "Flavored Vape" Crisis

Synthetic THC products represent the latest in a series of gray-market substances that have emerged in convenience stores and smoke shops, following the paths of ephedrine, bath salts, and flavored vapes. Like all these others, these products show up because they are cheap to produce, difficult to enforce against, and marketed in a legal gray area to convenience store consumers.

It is worth noting that these products did not exist five years ago, and convenience stores, smoke shops and other retail outlets thrived without them. Claims that banning synthetic THC would harm retail outlets are unfounded and misleading. These types of stores bounced back when rules were imposed around ephedrine, then bath salts and then flavored vapes, they can weather this storm. And frankly that should be no excuse for selling products like this that are so clearly harmful.

These products are not marijuana lite—in fact they often aren't real cannabis at all—and they aren't feeding Ohio farmers. These are modern designer drugs that go by the name hemp. The bottom line is, if folks in that industry want to sell intoxicants from this plant, then they need to get a license through DCC.

Chair Roegner and members of the committee, it is for these reasons we support Senate Bill 86. Ohio has an opportunity to lead by closing this loophole, ensuring that all intoxicating THC

products are subject to appropriate oversight. I urge the committee to advance SB 86 and establish a responsible, enforceable regulatory framework.

Thank you Chair Roegner and the members of the Ohio Senate General Government Committee, at this time I would be happy to answer any questions that you may have.

Chris Lindsey

VP of State Advocacy and Public Policy

Encl:

Geci, M., et al. "The Dark Side of Cannabidiol: The Unanticipated Social and Clinical Implications of Synthetic Δ8-THC." *Cannabis and Cannabinoid Research*, vol. 8, no. 2, 2023, pp. 270–282. DOI: 10.1089/can.2022.0126(Dark side of delta 8).

News Article Compilation. "Hemp Intoxicants News Stories," including reports on delta-8 THC overdoses and FDA enforcement actions. Examples:

- WBIR, "Dozens of Young TN Children Hospitalized in 2021 Due to Accidental Delta-8 THC Overdoses," February 14, 2022.
- FDA, "FDA Issues Warning Letters to Companies Illegally Selling CBD and Delta-8 THC Products," May 4, 2022.
- University of Michigan News, "Delta-8 THC Use Reported by 11% of 12th Graders," March 12, 2024. For the full set of articles, see [Hemp Intoxicants News Stories Document](241002 -- Hemp Intoxica…)(Delta-8-THC use reporte…).

National Poison Data System. Graph of Poison Control Center Incidents (2016–2022), with emphasis on cannabis edibles exposure in children aged 0–12. Available through National Poison Center data(05. Graph - Poison Cont…).

University of Michigan News. "Delta-8 THC Use Reported by 11% of 12th Graders." Monitoring the Future Study, published in *Journal of the American Medical Association*, March 12, 2024. DOI: 10.1001/jama.2024.0865(Delta-8-THC use reporte…).

Congressional Research Service. "Hemp Provisions in the House Farm Bill and FY2025 Agriculture Appropriations Bill." CRS Insight, June 17, 2024. Available: https://crsreports.congress.gov:contentReference[oaicite:0]{index=0}.

Gorbenko, A. A., et al. "Cannabidiol Increases Psychotropic Effects and Plasma Concentrations of Δ9-Tetrahydrocannabinol Without Improving Its Analgesic Properties." *Clinical Pharmacology & Therapeutics*, vol. 116, no. 5, 2024, pp. 1289–1303. DOI: 10.1002/cpt.3381(CBD potency study).

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REVIEW

The Dark Side of Cannabidiol: The Unanticipated Social and Clinical Implications of Synthetic Δ^8-THC

Michael Geci,[1] Mark Scialdone,[2,*,†] and Jordan Tishler[3]

Abstract

Introduction: The explosive growth of the cannabis industry in the United States over the past decade has spurred a multitude of products derived from phytocannabinoids produced by *Cannabis sativa* L. Decades of cannabis prohibition coupled with the more recent 2018 Farm Bill have lead to several unanticipated consequences and the widespread availability of synthetic cannabinoids derived from hemp CBD, including Δ^8-THC, Δ^{10}-THC and HHC.

Methods: Herein, we review the available literature of the complexity of the chemistry of its current manufacture, namely, the acid-catalyzed ring closure of cannabidiol (ACRCC), the myriad of issues involving the unsolved technical problems with quality control of ACRCC-Δ^8-THC and the multitude of isomerized byproducts, and the lack of consistent regulation regarding consumer safety and labeling.

Results: We provide what we believe is the first comprehensive listing of all the documented ACRCC-Δ^8-THC byproducts. Perhaps, most importantly, we highlight the growing concern that, other than Δ^8-THC itself, the compounds in ACRCC-Δ^8-THC product mixtures have not been subjected to any human toxicological evaluation. This is especially troubling as ACRCC-Δ^8-THC products relate to vaping, and their contribution to a growing and lethal epidemic of electronic cigarette, or vaping, product use–associated lung injury (EVALI).

Conclusions: Quality control is totally inadequate in the newly emerging Δ^8-THC industry. American consumers are ingesting products that are mislabeled with many compounds that have never received any toxicological testing. EVALI cases continue to be reported with a fatality rate approaching 2% (in California).

Keywords: CBD; 2018 Farm Bill; Δ^8-THC; synthetic cannabinoids; chemical conversion

Introduction

The explosive growth of the cannabis industry in the United States over the past decade has spurred a multitude of new and innovative products derived from the naturally occurring phytocannabinoids produced by *Cannabis sativa* L. Entrepreneurs have incorporated CBD (Table 1), the wunderkind of cannabinoids, into nearly everything imaginable, from chocolates to pet treats to massage oils to bed sheets, marketing CBD as the cure-all for nearly every conceivable ailment and condition.[1]

The 2018 Farm Bill[2] expressly removed industrial hemp from the definition of marihuana,

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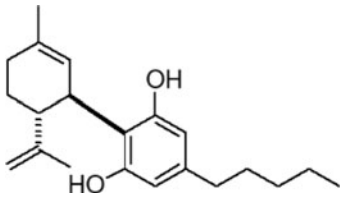
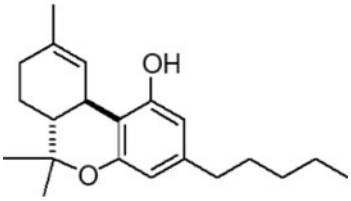
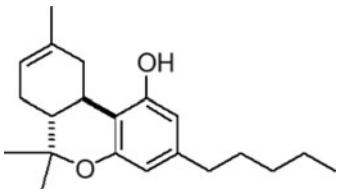
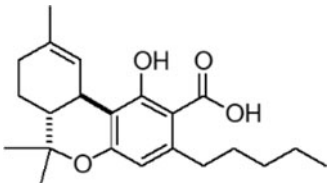
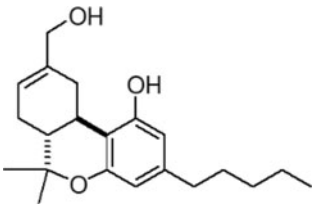
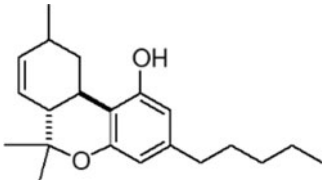
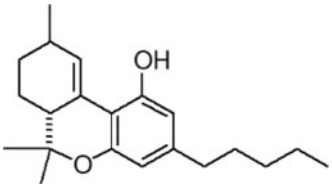
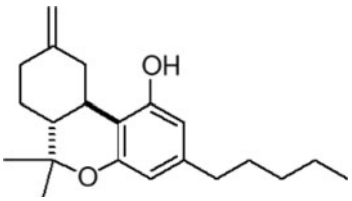
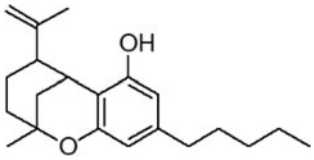
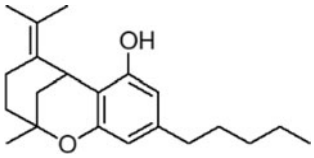
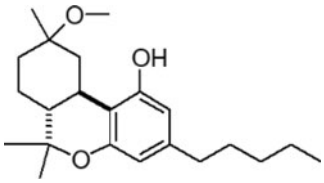
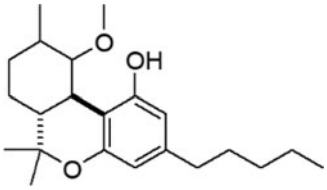
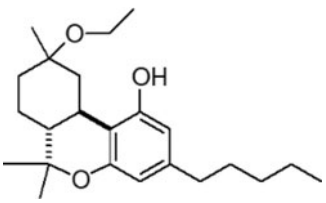
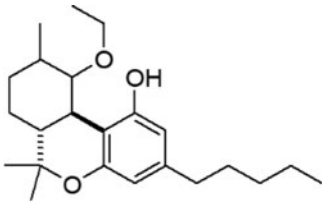
Table 1. Chemical Structures

No.	Name	Structure
I	CBD	
II	Δ^9-Tetrahydrocannabinol (Δ^9-THC)	
III	Δ^8-Tetrahydrocannabinol (Δ^8-THC)	
IV	Δ^9-Tetrahydrocannabinolic acid (Δ^9-THCA)	
V	11-Hydroxy-Δ^8-tetrahydrocannabinol (11-OH-Δ^8-THC)	
VI	Δ^7-Tetrahydrocannabinol (Δ^7-THC)	
VII	Δ^{10}-Tetrahydrocannabinol (Δ^{10}-THC)	

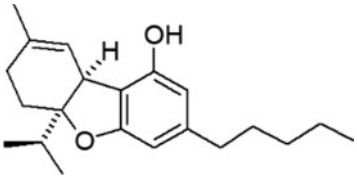
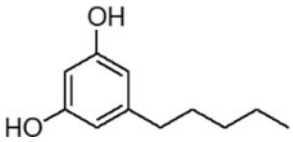
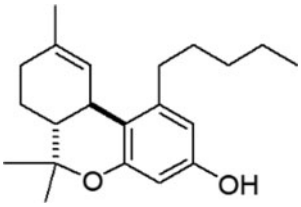
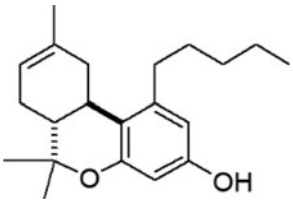
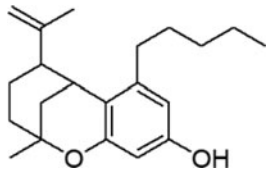
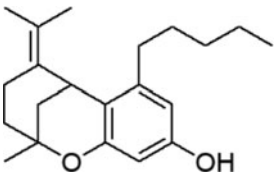
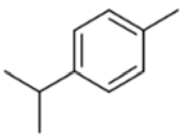
(*continued*)

Table 1. Continued

No.	Name	Structure
VIII	$\Delta^{9,11}$-Tetrahydrocannabinol ($\Delta^{9,11}$-THC)	
IX	Δ^{8}-Iso-tetrahydrocannabinol (Δ^{8}-iso-THC)	
X	$\Delta^{4(8)}$-Iso-tetrahydrocannabinol ($\Delta^{4(8)}$-iso-THC)	
XI	9-Methoxy-hexahydrocannabinol (9-MeO-HHC)	
XII	10-Methoxy-hexahydrocannabinol (10-MeO-HHC)	
XIII	9-Ethoxy-hexahydrocannabinol (9-EtO-HHC)	
XIV	10-Ethoxy-hexahydrocannabinol (10-EtO-HHC)	

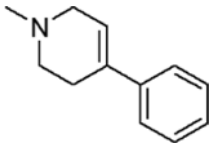
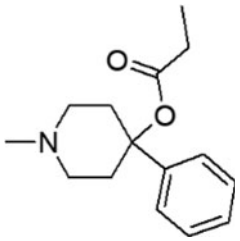
(*continued*)

Table 1. Continued

No.	Name	Structure
XV	Δ^9-Iso-tetrahydrocannabifuran (Δ^9-iso-THCBF)	
XVI	Olivetol (3,5-dihydroxy-pentylbenzene)	
XVII	Ortho-Δ^9-tetrahydrocannabinol (o-Δ^9-THC)	
XVIII	Ortho-Δ^8-tetrahydrocannabinol (o-Δ^8-THC)	
XIX	Ortho-Δ^8-iso-tetrahydrocannabinol (o-Δ^8-iso-THC)	
XX	Ortho-$\Delta^{4(8)}$-iso-tetrahydrocannabinol (o-$\Delta^{4(8)}$-iso-THC)	
XXI	p-Cymene (4-isopropyl toluene)	

(*continued*)

Table 1. Continued

No.	Name	Structure
XXII	MPTP (1-methyl-4-phenyl- 1,2,3,6-tetrahydropyridine)	
XXIII	MPPP—desmethylprodine (1-methyl-4-phenyl-4-propionoxypiperidine)	

defined as cannabis with $<0.3\%$ by weight Δ^9-tetrahydrocannabinol (Δ^9-THC) **II*** and its derivatives, in the 1970 Controlled Substance Act (CSA),[3] resulting in a market glut of CBD. The following year, domestic-licensed hemp cultivation skyrocketed 445%, with about 510,000 acres being cultivated. The subsequent hemp surplus resulted in depressed prices, which motivated producers to consider new markets for the overabundance of CBD.[4] The unanticipated result has been the widespread production and commercial introduction of psychoactive cannabinoid products synthesized by acid-catalyzed ring closure of cannabidiol (ACRCC).

The focus of this article is to highlight the myriad of non-natural THC isomers formed in the ACRCC conversion reaction, including Δ^8-tetrahydrocannabinol, (Δ^8-THC) **III**, the issues related to their accurate identification and quantification, the sale of finished goods in the absence of any human safety data, the without appropriate regulatory oversight mandatory throughout the regulated cannabis industry today, and the clinical implications for a new type of pulmonary pathology that needs to be recognized appropriately, diagnosed and treated in the cannabis vaping population. Although the ACRCC-Δ^8-THC problem is currently isolated to the United States, it is simply a matter of time before this issue becomes problematic throughout the developed world.

The Legal Landscape

Despite the 2018 legislation exempting the hemp plant and its derivatives from the regulatory prohibition of the CSA, all other naturally occurring cannabinoids produced from *C. sativa*, including the psychoactive cannabinoid, Δ^9-THC, are still listed as Schedule 1 substances. According to the CSA,[5] a Schedule 1 substance is a drug that has

(1) no currently accepted medical use
(2) a high potential for abuse or addiction
(3) a lack of accepted safety for use under medical supervision.

By default, Schedule 1 substances like cannabis (marijuana) remain illegal under federal statutes and in the 32 states in which recreational cannabis has not been legalized; it is in these states where the emerging market for Δ^8-THC, which has psychoactivity similar to Δ^9-THC, is most lucrative. Ironically, despite the Schedule 1 designation for the phytocannabinoid Δ^9-THC (and its isomeric derivatives), the U.S. Food and Drug Administration (FDA) has approved a number of pharmaceutically produced Δ^9-THC drugs such as Marinol® and Syndros®, prescribed for the treatment of severe nausea and vomiting,[6] and Epidiolex,® a plant-derived CBD for the treatment of intractable forms of epilepsy.[7]

There is no known biosynthetic pathway that synthesizes Δ^8-THC in *C. sativa*; however, to a small extent, the Δ^9 isomer can isomerize to the more thermodynamically stable Δ^8 isomer.[8] Through the actions of the plant enzyme tetrahydrocannabinolic acid (THCA) synthase, the plant produces the Δ^9 isomer exclusively. Within the glandular trichomes of *C. sativa*, Δ^9-THC is produced as its acidic precursor, namely Δ^9-tetrahydrocannabinolic acid (Δ^9-THCA) **IV**.[9] When cannabis is heated or exposed to light, decarboxylation occurs, whereby the Δ^9-THCA molecule

*The Δ symbol followed by a number indicates the position of a critical carbon-carbon double bond that characterizes different ring isomers of THC. Isomers are related compounds that have identical formulas, but slightly different chemical structures and sometimes have very different physical and pharmacological properties.

loses a carbon dioxide molecule, becoming the psychoactive neutral cannabinoid Δ^9-THC.[10] A certificate of analysis that notes small amounts of Δ^8-THC in aged dried plant material is the result of nominal isomerization from Δ^9-THC.[11]

Through an unforeseen loophole in the 2018 Farm Bill, ACRCC-Δ^8-THC has been construed as legal because it may be produced in a chemical process directly from CBD isolated from industrial hemp. Unfortunately, the Bill's language directly contradicts the CSA, where all tetrahydrocannabinol isomers (code 7370) specifically list Δ^8-THC along with its isomeric cousin Δ^9-THC as a Schedule 1 substance.[12] Further ambiguity regarding the legality of ACRCC-Δ^8-THC comes from a recent September 2021 letter to the Alabama Board of Pharmacy in which the Drug Enforcement Administration (DEA) wrote as follows:

> cannabinoids extracted from the cannabis plant that have a Δ^9-THC concentration of not more than 0.3 percent on a dry weight basis meet the definition of "hemp" and thus are not controlled under the CSA.[13]

Since being introduced to consumer markets, ACRCC-Δ^8-THC products have become a substantial revenue generator in many states where cannabis-derived products containing Δ^9-THC are not legal, either medicinally or recreationally. These ACRCC-Δ^8-THC products, often promoted to consumers as a less potent form of Δ^9-THC, are currently being produced and sold without any regulatory control or quality assurance oversight. ACRCC-Δ^8-THC products are not legally subjected to the same type of third-party testing at certified testing laboratories as required under state cannabis regulations.[14]

Throughout the era of federal cannabis prohibition, illicit products have been, and will continue to be, made available to consumers to meet market demand. The principles of contraband economics dictate that if there's a market for an illegal product, producers will provide that product particularly when substantial profit can be made.

The Chemistry of THC Isomers

Δ^8-THC is an isomer closely resembling Δ^9-THC as seen from their three-dimensional structures (Figs. 1 and 2).[15,16] The sole distinction is the position of the double bond in the methyl-cyclohexene ring between carbons 9 and 10 in Δ^9-THC and 8 and 9 in Δ^8-THC. However, even with this subtle conformational shift, a change in their corresponding pharmacological properties is observed. This includes their respective psychoactivity where Δ^8-THC is reported to be less potent than Δ^9-THC isomer in receptor binding studies.[17,18]

Structurally speaking, CBD and all the THC isomers, including Δ^7, Δ^8, Δ^9, and Δ^{10}, have the identical molecular formula, $C_{21}H_{30}O_2$. It is the subtle variation of how the atoms are three dimensionally arranged that confers major pharmacological differences between isomers. This is classically represented by the tremendous pharmacological differences between CBD and Δ^9-THC. The differences in molecular topologies (shape) and

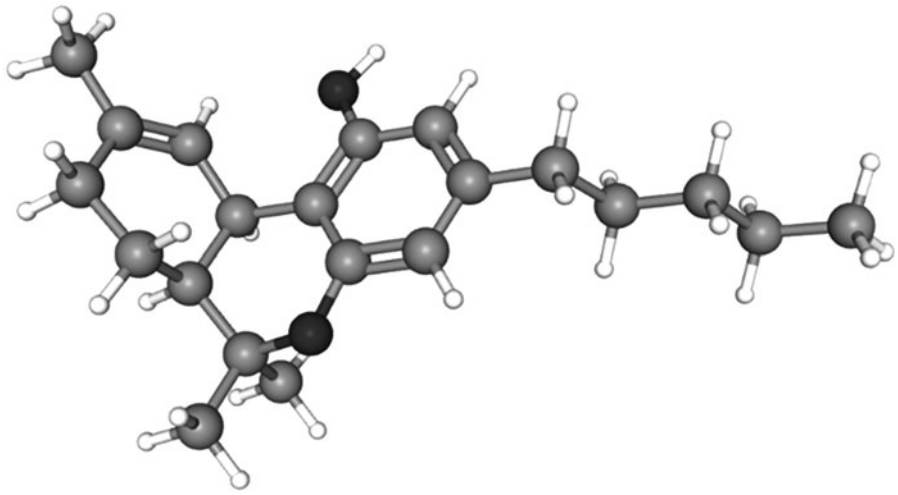


FIG. 1. 3D structure of Δ^9-THC. 3D, three dimensional. Figure adapted with permission from PubChem.[15]

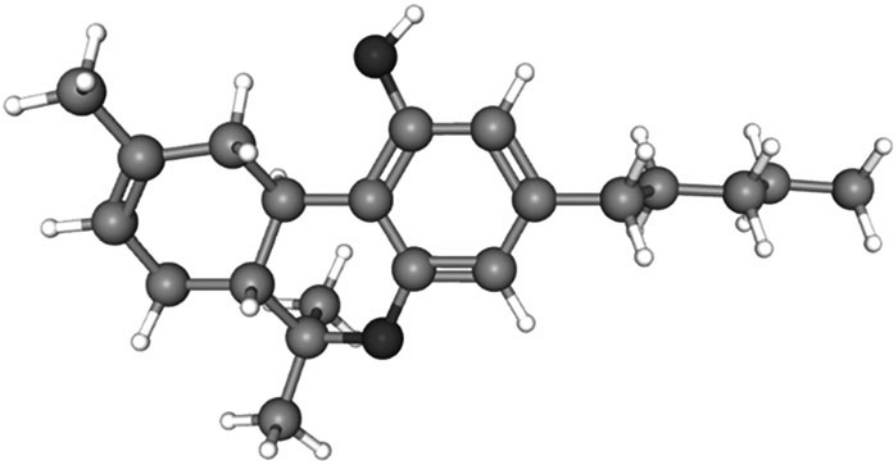


FIG. 2. 3D structure of Δ^8-THC. Figure adapted with permission from PubChem.[16]

spatial flexibility center around the fact that CBD is a constitutional isomer of THC with free rotation of the terpene ring along the axis of the phenyl ring of CBD.

Another way of looking at these differences is that CBD is a resorcinol with two *meta*-phenolic groups, while THC possesses one phenol, which provides for a significantly different and more varied pharmacological action. It is this nuanced difference that affects the isomer's respective receptor binding affinity to cannabinoid receptors. In this case, with both cannabinoid-1 receptor (CB_1R) and cannabinoid-2 receptor (CB_2R), Δ^8-THC acts pharmacologically similar to Δ^9-THC, as a partial agonist, with receptor binding at $CB_1R > CB_2R$. Also similar to Δ^9-THC, the Δ^8-isomer is metabolized in its first pass through the liver by the P450 cytochrome system to 11-hydroxy-Δ8-tetrahydrocannabinol (11-OH-Δ^8-THC) **V**.[19]

When organic compounds are used as reactants in chemical reactions, conducted both at small, research-scale and at larger production-scale facilities, the process chemistry is often complicated. In the case of ACRCC-Δ^8-THC, depending on the reaction conditions, numerous additional THC isomers are formed with unknown pharmacological and safety profiles in humans. The crux of the problem is that ACRCC-Δ^8-THC products are currently being manufactured and sold without any appreciable consideration for customer safety. The concern stems from the complexity of chemical processes involved in the manufacture of ACRCC-Δ^8-THC. The issue in the crosshairs of the safety debate is that ACRCC-Δ^8-THC is a "designer drug" synthesized from hemp-derived CBD and not extracted from naturally grown *C. sativa* material.

Historically, ACRCC-Δ^8-THC products are not the first cannabinoid designer drugs. Professor James W. Huffman, a medicinal chemist at Clemson University, never anticipated that his library of laboratory synthesized CB_1R agonists, such as JWH-018 and JWH-073, would end up on the street as psychoactive synthetic cannabinoids of abuse, namely K2 and Spice.[20] These compounds were designed solely for research purposes to study the pharmacological effects of potent CB_1R full agonists, some exceeding 100 times greater binding affinity than Δ^9-THC. These synthetic cannabinoids carry serious adverse side effects that often require emergent medical attention, including severe cardiovascular, neurological, gastrointestinal, renal, metabolic, and psychiatric sequelae.[21]

The chemical conversion process of CBD to Δ^8-THC was first described in the early 1940s by Professor Roger Adams and published by Drs. Yechiel Gaoni and Raphael Mechoulam in 1966.[22] The technical information describing this acid-catalyzed cyclization reaction can be easily accessed on various internet sites in step-by-step detail.[23] However, minor changes in reaction conditions, including reaction temperature, type of acid, solvent, exposure to atmosphere, the presence of water or alcohol, and duration of the reaction, can significantly affect the yield and mix of reaction by-products.[24] After the passage of the 2018 Farm Bill, professional and inexperienced, amateur chemists began looking at the synthetic possibilities of the surplus of CBD; thus, the race to market new psychoactive products containing laboratory manufactured cannabinoids began.

ACRCC-Δ^8-THC production requires the use of flammable reaction solvents (e.g., benzene), highly corrosive acidic reagents such as boron trifluoride, sulfuric acid, and hydrochloric acid, and heat to drive the cyclization reaction to completion. Typically, under most reaction conditions, CBD is converted to Δ^8-THC, as well as several other non-natural isomers of THC, which could include Δ^7-tetrahydrocannabinol **VI**, Δ^{10}-tetrahydrocannabinol **VII**, and Δ^{11}-tetrahydrocannabinol **VIII,** also known as exo-THC, in addition to Δ^9-THC. These isomers represent five of the seven possible double-bond isomers of the THC tricyclic ring structure. In addition, there are two iso-THC isomers that possess a different tricyclic ring structure, namely Δ^8-iso-tetrahydrocannabinol **IX** and $\Delta^{4(8)}$-iso-tetrahydrocannabinol **X**.[25]

Furthermore, it has been demonstrated that even under physiological conditions, CBD may be converted to both Δ^8-THC and Δ^9-THC through this same ACRCC reaction in simulated gastric fluid[26] and in Wistar rats.[27] This may potentially explain reports of many patients reporting somnolence and psychoactivity after oral CBD ingestion. In fairness, the physiological conversion of CBD into THC isomers and derivatives is still being debated.[28–30]

Interestingly, studies have indicated the presence of other oxygenated cannabinoids in CBD vape products.[31] When the conversion reaction is performed using alcohol solvents, such as methanol or ethanol, a mixture of the corresponding 9- and 10-methoxy-hexahydrocannabinols **XI** and **XII** and 9- and 10-ethoxy-hexahydrocannabinols **XIII** and **XIV** is formed in the product.[32] The presence of these ACRCC oxygenated byproducts is the result of carbonium ion intermediates with those oxygen nucleophiles producing ether products when reacted with alcohols, and hydroxylated products when reacted with water.

In another recent report, a full stoichiometric equivalent of an extremely reactive acidic reagent, phosphorus oxychloride ($POCl_3$),[33] produced ACRCC.[34] It was found that, in addition to ACRCC-Δ^8-THC and $\Delta^{4(8)}$-iso-tetrahydrocannabinol **X**, several other hydroxylated derivatives of non-natural THC isomers were formed upon hydrolytic workup of the reaction mixture.

The Quality Control Dilemma

Similar to other aspects of the cannabis industry, serious product quality control issues plague this new ACRCC-Δ^8-THC marketplace.[35] The most important consideration of these products is the current absence of accepted product specifications or proper analytical standards and techniques for testing commercially produced ACRCC-Δ^8-THC products. As this article was completed, a new certified analytical standard was made commercially available for the identification and quantification of Δ^8-iso-tetrahydrocannabinol **IX**.[36]

Traditionally, high-performance liquid chromatography (HPLC) has been the analytical instrumentation utilized by most laboratories to analyze and quantify cannabinoid mixtures.[37] However, the mixtures of THC isomers formed in the ACRCC reaction present unique challenges in their identification, isolation, quantification, and purification, since some isomers co-elute with the other known isomers of THC. In practical terms, because of their similarity in polarity, the ACRCC-Δ^8-THC byproducts may appear as a single unresolved peak in the HPLC chromatogram (Personal communication; Sams R, February 14, 2022).

Simply put, with current methodology, HPLC is unable to separate, identify, and quantify these myriad byproducts present in ACRCC-Δ^8-THC products. Consequently, proper analysis and quantification of the full spectrum of these substances require different and more experienced data analysis, including the utilization of more sophisticated analytical techniques such as gas chromatography/mass spectrometry (GCMS), which have been demonstrated to be fit-for-purpose for the determination of Δ^8-THC.[38]

A recent publication illustrated the necessity for a more sophisticated analytical methodology. Researchers performed detailed chemical analysis of fluid from several commercially available vaporizers (vape pens) containing ACRCC-Δ^8-THC using nuclear magnetic resonance, GCMS, and ion-coupled plasma/mass spectrometry.[39] The authors found that none of the products tested had accurate labeling and significant discrepancies were discovered in actual Δ^8-THC content. Many of the products tested contained known ACRCC-Δ^8-THC byproducts such as $\Delta^{4(8)}$-iso-tetrahydrocannabinol **X** and 9-ethoxy-hexahydrocannabinol **XIV**, as well as reporting the identification and characterization of Δ^9-iso-tetrahydrocannabifuran (Δ^9-iso-THCBF) **XV**, a newly reported THC isomer.

Several of the products contained unlabeled cutting agents used in vape pen fluid formulations such as medium-chain triglycerides (MCT), triethyl citrate, and parts per billion levels of heavy metals such as chromium, nickel, copper, zinc, lead, mercury, and others, which likely leached from the vape pen hardware.

Perhaps most troubling was the finding of olivetol (3,5-dihydroxy-pentylbenzene) **XVI**,[40] in 22 out of 27

samples tested. Olivetol is reported to be a respiratory, eye, and skin irritant. Remember that olivetol is the decarboxylated form of olivetolic acid, which is the immediate upstream precursor in the cannabinoid biosynthetic pathway that creates cannabigerolic acid (CBGA).[41] While olivetol can be used as a precursor to synthesize cannabinoids, its presence in commercial vape products is likely due to a retro-Friedel-Crafts reaction of CBD and subsequent degradation of the limonene cation formed.[42]

The detection of olivetol further supports the formation of abnormally ortho-substituted THC regioisomers such as ortho-Δ^9-tetrahydrocannabinol **XVII**, ortho-Δ^8-tetrahydrocannabinol **XVIII**, ortho-Δ^8-iso-tetrahydrocannabinol **XIX,** and ortho-$\Delta^{4(8)}$-iso-tetrahydrocannabinol **XX**.[†] These olivetol-based regioisomers are formed in the Δ^8-THC, Δ^9-THC, Δ^8-iso- and $\Delta^{4(8)}$-iso-configurations having both *cis* and *trans* isomers present because the recombination of olivetol and the accompanying generated limonene cation is not likely to be stereoselective.[43] Furthermore, residual amounts of the conversion catalysts used may also be present if care is not taken to remove them from the ACRCC reaction products.

The presence of olivetol in the ACRCC-Δ^8-THC products further implies that the recombination of the olivetol and the limonene cation in the reaction leads to the formation of the terpene p-cymene (4-isopropyl toluene) **XXI** as the likely degradant species. Unfortunately, at this time, the toxicological and pharmacological properties of p-cymene are inconsistent. While p-cymene is indeed a naturally occurring terpene found in numerous citrus and aromatic plants and has a plethora of bioactivity, including anticancer and anti-inflammatory properties,[44] the material safety data sheet states that it is harmful if swallowed or absorbed by the skin, considered to be irritating to mucous membranes and the upper respiratory tract.[45] Whether p-cymene, or any of the other dozen or more secondary ACRCC-Δ^8-THC endproducts that have been discussed possess a significant health risk, either acutely or in the long term, is an issue to be further investigated.

Vaping and ACRCC-Δ^8-THC Pathology

A sizable amount of the ACRCC-Δ^8-THC is sold for the vape market with no safety data for inhalation exposures. The FDA considers both polyethylene glycol (PG) and vegetable glycerin (VG) as "Generally Recognized as Safe" (GRAS). However, the GRAS designation applies only to dermal application or oral ingestion and does not address or imply the safety of inhalation exposure to these products. Goods meant to be eaten or swallowed are not necessarily meant to be inhaled deeply into the vast microenvironment of the pulmonary alveoli system. PG/VG-containing e-liquids, when heated, generate pulmonary irritants as well as known and suspected carcinogenic carbonyl compounds such as formaldehyde, acetaldehyde, and acrolein.[46,47]

Since the advent of the commercial availability of ACRCC-Δ^8-THC in 2019, there has been a marked increase in reports of electronic cigarette, or vaping, product use–associated lung injury (EVALI).[48] Patients with EVALI present with a constellation of respiratory, gastrointestinal, and constitutional symptoms, including shortness of breath, cough, chest pain, diarrhea, abdominal pain, fever, and fatigue. To meet the Centers for Disease Control (CDC) criteria for a "confirmed" EVALI case, patients must have vaped within 90 days before symptom onset, have bilateral infiltrates on chest imaging, have a negative evaluation for infection, and have no other plausible alternative diagnosis.[49]

In the current marketplace, ACRCC-Δ^8-THC mixtures are solubilized with a multitude of diluents, including limonene, which individually have been suspected as being problematic for inhalation. Vape pen base fluids such as PG and VG, which when heated can generate pulmonary irritants including carcinogenic carbonyl compounds (formaldehyde, acetaldehyde, and acrolein) in addition to various metals contained within the heating coils and cartridge casings in vaping devices, leach into the inhaled vapor as well.[50] The CDC has postulated that the additive vitamin E acetate (VEA), a tocopherol, is a causative factor for EVALI,[51] as is diacetyl, a common buttery flavoring agent, has well-documented pulmonary toxicity leading to bronchiolitis obliterans, sometimes called "popcorn lung."[52,53]

The role of VEA as a causative factor for EVALI has been postulated to be associated with its long, 16-carbon aliphatic tail that is thought to penetrate into the surfactant layer within the alveoli. Increasing amounts of tocopherols affect the transition of surfactant from a gel to a liquid, which affects its ability to maintain the necessary surface tension within the alveoli, and therefore has been postulated as a mechanism for EVALI lung injury.[54]

[†]Naturally occurring cannabinoids such as Δ^9-THC are para-substituted such that the terpenyl ring and 5-carbon pentyl chain are para (1,4 disubstituted on the benzene ring) to each other. The Razdan article refers to abnormal THC regioisomers that are ortho-substituted where the terpenyl ring and 5-carbon pentyl chain are ortho (1,2 disubstituted on the benzene ring) to each other.

Despite the aliphatic tail of ACRCC-Δ^8-THC and its byproducts being only five carbons in length, we postulate that this may still be long enough to affect the phase state of the phosphatidylcholines acting as a surfactant in the alveoli, although likely not to the same degree as VEA. Regrettably, there are no toxicological data on ACRCC-Δ^8-THC and its byproducts, yet their contributive role in EVALI is circumstantial. Definitive pulmonary vaping studies need to be done to definitively tie ACRCC-Δ^8-THC products to the EVALI epidemic. To ignore the coincidence of the sudden appearance of ACRCC-Δ^8-THC, vaping with the emergence of EVALI seems shortsighted.

A newly published national study reveals the breadth of the EVALI epidemic and its connection to cannabis vaping products, including ACRCC-Δ^8-THC: as of January 2020, a total of 2558 nonfatal hospitalized patients and 60 patients with fatal cases of EVALI have been reported to the CDC.[55] This group observed a direct relationship between the frequency and duration of vaping with patient morbidity and mortality. Of note, secondary to the COVID-19 pandemic, the CDC stopped tracking EVALI cases in February 2020. In addition, because of the novelty of EVALI, the potential pulmonary morbidity seen with ACRCC-Δ^8-THC products substances may be significant, and clinically is oftentimes untested, overlooked, and goes undiagnosed; therefore, the true breadth of the EVALI epidemic remains unknown.

Recently, 13 adolescents were admitted to a large university-teaching hospital for clinical signs consistent with EVALI, 30% of whom necessitated intensive care unit, and one required intubation with prolonged mechanical ventilation. Ninety-two percent of those patients admitted tested positive for Δ^9-THC.[56] What number of those patients were also vaping ACRCC-Δ^8-THC? We will never know as few hospital laboratories test for Δ^8-THC exposure, but considering the large and growing market for ACRCC-Δ^8-THC vape products, we know this number is not likely zero. In a study of computed tomography-diagnosed EVALI, the researchers looked at 160 cases in 14 states, and 133 cases (83%) were found in states where recreational cannabis was not legal.[57] It is in these states where ACRCC-Δ^8-THC vape products are most prevalent.

Consumer Protection Concerns

The purification and isolation of purified ACRCC-Δ^8-THC reaction products are problematic because the byproducts formed are chemically similar to both Δ^8 and Δ^9-THC. The process chemistry expertise needed to develop a suitable purification and analytical method to establish product specifications is not something that most manufacturers currently possess. Any perturbation in the reaction conditions such as reaction temperature, reaction time, concentration, and type of acid catalyst used changes the distribution of the various components in the final end-product mixture.

Consequently, finished consumer goods are being produced using ACRCC-Δ^8-THC, which contain various amounts of the isomeric and degradation byproducts in substantial amounts (more than 30%) and being sold to consumers labeled as solely containing Δ^8-THC (Personal communication; Sams R, February 14, 2022). As emphasized earlier, critical to the quality control and safety issue of these products is the lack of standardization of quality assurance or analytical methods being performed by accredited third-party testing laboratories.

A principal issue with the ACRCC-Δ^8-THC products is the lack of relevant human toxicological data to the numerous isomeric byproducts and degradants found in commercial products today. Although extrapolation of animal data may be misleading, it is an important first step in understanding potential human toxicity. The toxicology data for Δ^8-THC date from 1978 with a relative flurry of studies done in the early 1970's. Perhaps the most interesting finding was the lethal toxicity seen with both Δ^8-THC and Δ^9-THC in rats, dogs, and monkeys, between 225 and 3600 mg/kg.[58] Available data suggest that the bioactivity of Δ^8-THC is similar to that of Δ^9-THC, including euphoria, paranoia, dry mouth, reddened eyes, dizziness, blurred vision, relaxation, and small increases in heart rate.[59]

Adverse Effects of ACRCC-Δ^8-THC Products

Ultimately, consumer safety should drive the need for appropriate quality control and regulation of all products whether they are derived from cannabis or industrial hemp. Notably, health concerns regarding the use of ACRCC-Δ^8-THC products have not been infrequent. From December 2020 through July 2021, the FDA received adverse event reports from both consumers and law enforcement agencies describing 22 patients who consumed ACRCC-Δ^8-THC products; of these, 14 presented to a hospital or emergency room for treatment following its ingestion.[60] Adverse events included vomiting, hallucinations, trouble standing, respiratory distress, and loss of consciousness.

In addition, poison control centers across the United States reported 660 exposure cases of ACRCC-Δ^8-THC products between January 1, 2021, and July 31, 2021. Of these cases, 41% involved unintentional exposure to Δ^8-THC with 77% of those affected being pediatric patients < 18 years of age. Eighteen percent of these patients required hospitalization, including several children who required intensive care unit admission following exposure to these products, and one required emergency intubation and ventilatory support.[61]

On September 14, 2021, the FDA stated that there could be serious health risks to humans who use ACRCC-Δ^8-THC products and CDC issued a health advisory to health care professionals and the public of the

> increased availability of cannabis products containing delta-8 tetrahydrocannabinol (THC) and the potential for adverse events due to insufficient labeling of products containing THC and cannabidiol (CBD).[62]

Although the CDC health advisory was welcomed, there is concern regarding the FDA's lack of enforcement to labeling requirements of ACRCC-Δ^8-THC products from its manufacturers. If the FDA can require both tobacco and alcohol manufacturers to accurately label their products, warning consumers of health risks they accept by consuming their products, surely the FDA should mandate that all product manufacturers do the same. At the very least, consumers should be aware of the potential health risks associated with the use of all ACRCC-Δ^8-THC-containing products.

Currently, a plethora of ACRCC-Δ^8-THC products are being produced without any regulatory oversight, process standardization, product specification, or standardized third-party testing requirement. Without industry-wide regulation and governmental oversight, these companies may be, or may not be, following strict pharmaceutical standards for quality control in this manufacturing process.

Our apprehension centers around the possibility that ACRCC-Δ^8-THC products may potentially parallel the classic example of a designer drug disaster: the story of MPTP (1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) **XXII**. In the summer of 1982, reports emerged from the San Francisco Bay Area of young intravenous heroin addicts suddenly stricken with an acute form of Parkinson's disease, and termed "frozen addicts."[63] The common thread was that all the "frozen addicts" had recently used a new form of synthetic heroin made by an underground chemist who failed to strictly maintain a critical temperature during a chemical reaction. Instead of producing a batch of relatively pure MPPP (desmethylprodine) **XXIII**, it produced a quantity containing the contaminant MPTP in the final product, which produced neurotoxic effects.[64]

The case of the "frozen addicts" represents the potential for serious long-term and unintended health consequences when the steps of a chemical reaction are not strictly followed, resulting in the formation of unforeseen (and unquantifiable) byproducts. The MPTP story clearly demonstrates that even very minor differences in chemical structure may produce radically different pharmacological and toxicological effects in humans. The lesson from MPTP highlights the importance of caution when considering the use of a synthetically produced drug and the potential catastrophic consequences that may occur when drugs are manufactured using nonpharmaceutical quality control standards. Currently, the nonpharmaceutical production and widespread consumer use of cannabinoids like ACRCC-Δ^8-THC exist and should prompt concern among regulators, medical professionals, and consumers alike.

Fortunately, there has been no report in the literature of "frozen vapers" from consumption of products containing ACRCC-Δ^8-THC, but the emergence of EVALI aligns exactly with the appearance of ACRCC-Δ^8-THC. The lesson of the MPTP "frozen addicts" should be that we do not know what could seriously hurt us. There is compelling data to show that these products being sold contain various reaction derivatives formed in the production process, resulting in inaccurate product quality testing and labeling. Introduction of these products into the cannabis consumer marketplace has been done without any thoughtful and empirically driven discussion regarding the issues and possible dangers of these designer cannabinoids. We have no understanding of their potential clinical impact for both the casual and chronic consumer.

We assert that the public deserves a consistent and accurate cannabinoid testing program for all cannabis-based products being sold, within both the recreational and medical marketplaces. These products need to be produced reproducibly with a focus on quality assurance much like that required of over the counter and pharmaceutical ingredients. In addition, these products need to be consistently tested by certified laboratories using standardized methods and accurately labeled, just like other consumer products.

Cannabis consumers are witnessing a large-scale human experiment with the introduction of these synthetically produced ACRCC-Δ^8-THC products. Ultimately, the issues surrounding these products are simply another chapter in the continuing saga of cannabis prohibition, unregulated capitalism, and the political and racially motivated intentions of the CSA.

Instead, we envision a futuristic and enlightened Congress and FDA to implement a well-regulated cannabis industry (both medical and recreational) in which consumer safety and product reliability are paramount over profits.

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Abbreviations Used

3D = three dimensional
ACRCC = acid-catalyzed ring closure of cannabidiol
CB_1R = cannabinoid-1 receptor
CB_2R = cannabinoid-2 receptor
CBD = cannabidiol
CDC = Centers for Disease Control
CSA = Controlled Substance Act
EVALI = electronic cigarette, or vaping, product use–associated lung injury
FDA = U.S. Food and Drug Administration
GCMS = gas chromatography/mass spectrometry
GRAS = Generally Recognized as Safe
HPLC = high performance liquid chromatography
MPTP = 1-methyl-4-phenyl- 1,2,3,6-tetrahydropyridine
PG = polyethylene glycol
THC = tetrahydrocannabinol
THCA = tetrahydrocannabinolic acid
VEA = vitamin E acetate
VG = vegetable glycerin

Sample News Stories on Hemp Intoxicants

"Dozens of Young TN Children Hospitalized in 2021 Due to Accidental Delta-8 THC Overdoses"
WBIR

February 14, 2022
In Tennessee, 115 cases of accidental delta-8 THC overdoses were reported in 2021, with 30% involving children under 5. These incidents highlight the severe effects and regulatory challenges of delta-8 THC products.
https://www.wbir.com/article/news/local/dozens-of-young-tn-children-hospitalized-in-2021-due-to-accidental-delta-8-thc-overdoses/51-948febbb-3258-449f-aa3a-8ee244dacd7b

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

May 4, 2022
The FDA issued warnings to five companies for selling delta-8 THC products illegally. Reports included adverse events like hallucinations and vomiting, with several cases involving children requiring hospitalization. These products were often packaged to appeal to children.
https://www.mcguirewoods.com/client-resources/alerts/2023/12/fda-warning-letter-declares-delta-8-and-cbd-gummies-adulterated-foods/#:~:text=FDA%20goes%20so%20far%20as,products%20treat%20or%20cure%20disease.

"Man Claims Lexington Store Sold Him Delta-8 Instead of CBD Causing Him to Crash into Bus"
WKYT, Kentucky.com, KOLN

October 5, 2022
A man in Lexington, Kentucky is suing a local CBD store after he allegedly bought a product labeled as CBD that actually contained delta-8 THC, causing a car crash.
https://www.wkyt.com/2022/10/05/man-claims-lexington-store-sold-him-delta-8-instead-cbd-causing-him-crash-into-bus/

"Grand Island Woman Arrested After Child Ingests THC Gummy"
News Channel Nebraska, KSNB Local 4, KOLN

April 4, 2023

A woman in Nebraska was arrested after her 4-year-old son ingested a delta-8 THC gummy, highlighting the severe effects on young children and legal consequences for parents.
https://central.newschannelnebraska.com/story/48668832/woman-arrested-after-son-eats-thc-gummy

"Virginia Mother Sentenced to 10 Years After 4-Year-Old Son Dies from Delta-8 THC Gummies" Fox News

June 12, 2023
A Virginia mother was sentenced after her 4-year-old son died from consuming delta-8 THC gummies. The incident highlighted the dangers of children accessing hemp-derived intoxicants.
https://www.foxnews.com/us/virginia-mom-charged-murder-4-year-old-son-eats-large-amount-thc-gummies-police-say

“DEA Considers Delta-8 THC Products Federally Illegal When Synthesized From CBD, Official Says In Newly Revealed Email” Marijuana Moment

August 14, 2023
The Drug Enforcement Administration (DEA) has clarified its position on delta-8 THC, stating that when synthesized from legal CBD, delta-8 THC is considered a prohibited controlled substance. This clarification was revealed in an email from a top DEA official, which has significant implications for the rapidly expanding market for delta-8 products.
https://www.marijuanamoment.net/dea-considers-delta-8-thc-products-federally-illegal-when-synthesized-from-cbd-official-says-in-newly-revealed-email/

“Bus driver blacks out behind wheel, says he didn’t know his gummy snacks included THC” KTTV, Fox News, AP News, US News

December 1, 2023
A bus driver in Connecticut was granted probation after he unknowingly consumed THC-infused gummies, leading to him passing out while driving a bus with passengers. The case underscored the need for clearer labeling of hemp-derived products.
https://www.kktv.com/2022/06/15/bus-driver-blacks-out-behind-wheel-says-he-didnt-know-his-gummy-snacks-included-thc/

"Pickens County 7-Year-Old Hospitalized Over Drug Disguised as Candy"
Fox 5 Atlanta

February 12, 2024
A 7-year-old in Pickens County, Georgia was hospitalized after consuming delta-8 THC gummies mistaken for candy, prompting the school to issue warnings about the dangers of such products.
https://www.fox5atlanta.com/news/pickens-county-candy-thc-delta-8

"Elementary School Students Ate Cannabis Edibles Thought They Were Candy" St. Louis Post-Dispatch, Fox 2 Now

March 16, 2024

Six elementary school students in St. Louis mistakenly consumed delta-8 THC edibles, believing they were regular candy. The incident raised concerns about the regulation and accessibility of hemp-derived intoxicants.
https://www.stltoday.com/news/local/crime-courts/elementary-school-students-ate-cannabis-edibles-thought-they-were-candy/article_1b28969c-e3ba-11ee-99e8-b3be109d3f42.html

"Big Rise in Emergencies Involving Synthetic Weed Among Kids Adults"
US News

May 8, 2024

Calls to U.S. poison centers about synthetic cannabis, including delta-8 THC, increased by 88% between 2021 and 2022, with a significant portion involving young children.
https://www.usnews.com/news/health-news/articles/2024-05-08/big-rise-in-emergencies-involving-synthetic-weed-among-kids-adults

"Attorney General Tong Announces Crackdown on Illegal Sale of Delta-8 THC"
Connecticut Attorney General's Office

February 9, 2023

Connecticut's Attorney General sued five retailers for selling delta-8 THC products resembling popular youth snacks, posing significant risks including accidental ingestion by children and numerous hospitalizations.
https://portal.ct.gov/ag/press-releases/2023-press-releases/attorney-general-tong-announces-crackdown-on-illegal-sale-of-delta8-thc

"NC Looks to Crack Down on Delta-8 THC Cannabis Products"
NC Health News

June 21, 2024

North Carolina is cracking down on delta-8 THC products marketed to children. Increased incidents of minors consuming products resembling snacks have led to seizures of illegal THC products from various shops.
https://www.northcarolinahealthnews.org/2023/08/03/nc-legislators-law-enforcement-want-crack-down-delta-8-thc/

“Texas Has Basically Legalized Marijuana. We Have the Proof.”
Texas Monthly

June 26, 2024

Marijuana masquerades as hemp products and is sold in retail stores throughout Texas, despite state laws prohibiting the production and sale of marijuana.
https://www.texasmonthly.com/news-politics/texas-legalized-marijuana-thc-delta-9/

“In 2018, Republicans accidentally legalized cannabis. Now 22 AGs want them to undo it”

The Hill

March 30, 2024

A coalition of 22 state attorneys general called on Congress to address “the glaring vagueness” that has led to legal cannabis products being sold over the counter across the country — including sometimes from vending machines or online. A letter dated March 20 addresses the consequences of lawmakers’ choice to legalize hemp production in the 2018 omnibus Farm Bill — a decision that inadvertently led to a multibillion-dollar market in intoxicating cannabis products that are arguably federally legal.
https://thehill.com/homenews/4564181-2018-farm-bill-hemp-cannabis-attorneys-general/

A significant number of US 12th-graders report using delta-8 products, study says, and it may be a public health concern
CNN

March 13, 2024

A study published in the Journal of the American Medical Association (JAMA) found that over 1 in 10 12th graders had consumed hemp intoxicants including delta-8 THC within the past year. Based on findings in the study, the authors argue that the number of teens who have reported using delta-8 may be a “potential public health concern.” “What we hadn’t known prior to this study was to what extent are these products reaching teens, which was a concern because they weren’t being comprehensively regulated,” said study author Dr. Adam Leventhal, executive director of the USC Institute for Addiction Science.
https://www.cnn.com/2024/03/12/health/delta-8-use-students/index.html

High on Hemp?
Des Moines Register

October 5, 2023

“We were promised that industrial hemp couldn't be used to mimic the effects of marijuana," **Republican U.S. Sen. Chuck Grassley** said in a statement. "I was skeptical at the time and voiced my concerns. It turns out my skepticism was well-placed.”
https://www.desmoinesregister.com/story/news/health/2023/10/05/consumable-hemp-including-heavy-thc-products-are-gaining-popularity-in-iowa-marijuana-des-moines/70969527007/#:~:text=%E2%80%9CWe%20were%20promised%20that%20industrial,my%20skepticism%20was%20well%2Dplaced.

Ohio Issues Consumer Alert on Delta-8 THC Products and Packaging
Ohio Attorney General's Office

July 10, 2024

The Ohio Attorney General issued a consumer alert regarding delta-8 THC products, highlighting concerns over packaging that resembles candy and other popular snacks,

which poses significant risks for accidental ingestion by children. This alert follows an increase in incidents involving delta-8 THC, urging consumers to exercise caution and report suspicious products.
https://www.ohioattorneygeneral.gov

More Than 90% of Smokable Hemp Samples Test Positive for Delta-8 THC, Federal Study Finds
Marijuana Moment

July 15, 2024
A federal study revealed that over 90% of smokable hemp samples tested positive for delta-8 THC. The study raises significant concerns about the widespread presence of intoxicating cannabinoids in products marketed as hemp.
https://www.marijuanamoment.net/more-than-90-percent-of-smokable-hemp-samples-test-positive-for-delta-8-thc-federal-study-finds

Four Kids Hospitalized After Taking CBD Gummies at Coventry Camp
WPRI

July 20, 2024
Four children were hospitalized in Coventry, Rhode Island after consuming CBD gummies that reportedly contained delta-8 THC. The incident underscores the dangers of mislabeled hemp products and the urgent need for clearer labeling and stricter regulations to prevent such occurrences.
https://www.wpri.com/news/local-news/4-kids-hospitalized-after-taking-cbd-gummies-at-coventry-camp

Feds Warn About Copycat Packaging of Delta-8 THC Edibles

July 2024
The FDA and Federal Trade Commission issued warnings to five companies for selling delta-8 THC edibles in packaging mimicking popular snack brands, raising concerns about accidental ingestion, particularly among children. Products such as “Slizzles” and “Double Stuff Stoneo” were flagged for their close resemblance to Skittles and Oreo cookies. The federal agencies highlighted that inadequate or confusing labeling poses significant health risks, with nearly 10,500 incidents involving THC-laced products reported to national poison control centers, 77% involving consumers under 19. The FDA and FTC emphasized the illegality of marketing such products in this manner and called for immediate corrective actions from the companies.
https://www.painnewsnetwork.org/stories/2024/7/19/feds-warn-about-copycat-packaging-used-to-sell-delta-8-thc-edibles

She used delta-8 from a gas station. Alabama said she couldn’t keep her baby at home

August 16, 2024

An Alabama woman used delta-8 THC purchased from a gas station, to manage her anxiety and insomnia. However, when child welfare services discovered its use, they ruled it as an issue of concern, leading to determination that removed her child from her home. The case highlights uncertainty over legal claims and the legal status of intoxicants, and serious consequences surrounding the consumption of hemp-derived intoxicants in certain states. https://www.al.com/news/2024/08/she-used-delta-8-from-a-gas-station-alabama-said-she-couldnt-keep-her-baby-at-home.html

Those who opened doors for delta-8 in Wisconsin say they had 'no idea'

July 22, 2024

After the 2018 Farm Bill aimed to support farmers by legalizing hemp, products like delta-8 THC have surged in Wisconsin and other states, creating a $28 billion industry largely free of oversight. Interviews suggest that lawmakers and legal experts, including those who crafted the bill, were unaware that intoxicating compounds could be derived from hemp. Jonathan Miller, who helped draft the legislation, and others have expressed surprise at the unintended consequences, with some products now circumventing THC limits by converting to high-potency forms when used. As lawmakers now scramble to regulate these products, proposed amendments could impose stringent bans, which Miller argues would unfairly burden farmers. The call for FDA regulation remains strong amidst these developments.
https://www.jsonline.com/story/news/investigations/2024/07/22/lawmakers-who-opened-doors-to-delta-8-hemp-products-had-no-idea/74269933007/

Young Texas Woman Arrested for Legal Delta-8 Vape Oil Purchase

September 14, 2024

In 2022, a young woman in North Texas named Kendall Reed was arrested and charged with a felony after purchasing what she believed was legal delta-8 THC vape oil from a local store. Despite the product being labeled as containing less than 0.3% delta-9 THC, further testing revealed a concentration above the legal limit. Reed, unaware of the offense, faced months of emotional stress, financial burdens, and the long-term impact of having a felony arrest on her record. Although the case was eventually dismissed, it highlighted the complexities and potential legal pitfalls of purchasing hemp-derived products in Texas, where laws on THC content remain strict and unclear.
https://www.dallasnews.com/news/commentary/2024/09/13/a-young-north-texas-woman-bought-legal-delta-8-vape-oil-and-wound-up-jailed-on-a-felony/

Cannabis Laced with Amphetamines Found at Illegal D.C. Shops Amid Crackdown

September 26, 2024

D.C. police have been cracking down on unlicensed cannabis shops which often include synthetic THC products. Investigators discovered cannabis laced with amphetamines in several of the shuttered locations. Officials warned of the danger to consumers who

might believe they are purchasing regulated products but are instead exposed to harmful substances unrelated to marijuana.
https://www.nbcwashington.com/news/local/cannabis-laced-with-amphetamines-found-at-illegal-dc-shops-amid-crackdown/3444171/:contentReference[oaicite:0]{index=0}

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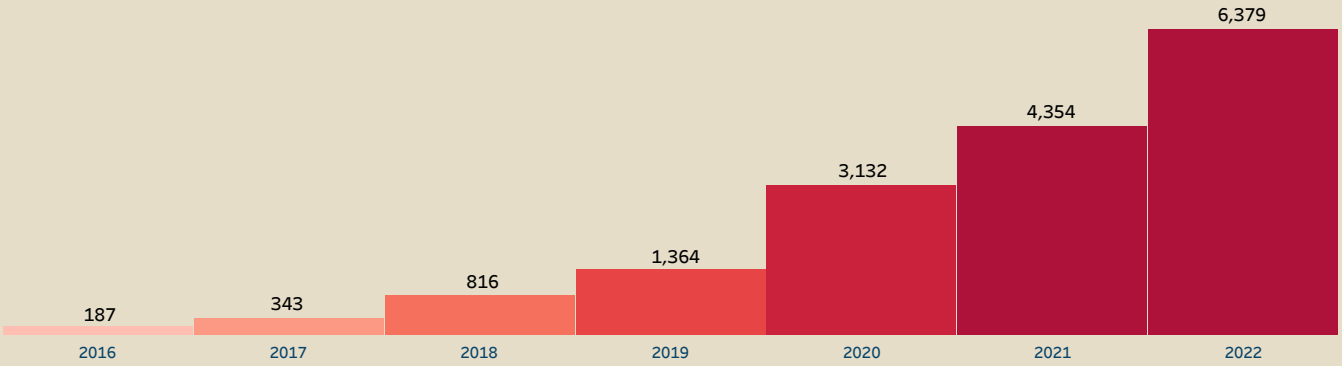

Delta-8-THC use reported by 11% of 12th graders

March 12, 2024Morgan Sherburne

Use of the psychoactive cannabis product is higher in states without existing delta-8 regulations or cannabis legalization, NIH-funded study finds

The first ever national estimates of teen delta-8 use indicate that 11% of 12th grade students across the United States used it in the past year.

This information comes from the Monitoring the Future study, which annually surveys adolescents across the U.S. and is conducted by researchers at the University of Michigan and funded by the National Institute on Drug Abuse of the National Institutes of Health.

Study: Adolescent Delta-8-THC and Marijuana Use in the United States (DOI: 10.1001/jama.2024.0865)

Delta-8 is a cannabis compound that can produce a 'high' similar to marijuana. The term "delta-8" stands for delta-8-THC, which is chemically a close cousin of delta-9-THC, the principal psychoactive compound of marijuana. The purchase of delta-8 products typically has no age restrictions. Most delta-8 is derived from hemp, a variety of the cannabis plant.


Richard Miech

"This is the first national study to report the extent of delta-8 use among young people, which is important to inform research and policy," said Richard Miech, team lead of the Monitoring the Future study at the University of Michigan and co-author of the study. "A prevalence of 11% is appreciable and indicates this drug is quickly making inroads among teens."

The study is published in the Journal of the American Medical Association.

To date, there is no conclusive evidence to suggest delta-8 is safer than marijuana or other THC cannabis products. Given its similarities to delta-9, delta-8 is likely to carry the same risks, the study's authors note. Lack of federal regulation of delta-8 products can also put consumers at high risk of exposure to toxic byproducts.

According to the Food and Drug Administration, because delta-8 content in the cannabis plant is naturally very low, manufacturers often use other, more abundant hemp cannabinoids—namely cannabidiol (CBD)—to make delta-8. The CBD to delta-8 conversion process requires additional chemicals, which can be hazardous. The resulting delta-8 products may contain residual contaminants that are harmful when inhaled or ingested.

Research on cannabis suggests that the developing brain in children and adolescents may be at risk of negative and deleterious effects from cannabis use, including memory loss, cognitive difficulties, brain developmental processes and cannabis use disorder. There are no existing medications to treat cannabis use disorder, and current treatments are primarily through psychosocial interventions, such as cognitive behavioral therapy.

The Monitoring the Future survey is administered annually to students in classrooms in eighth, 10th and 12th grades who self-report their substance use behaviors over various time periods, such as past 30 days, past 12 months and lifetime. From February through June 2023, the Monitoring the Future investigators collected 22,318 surveys from students enrolled across 235 public and private schools in the U.S. In 2023, the survey included questions on delta-8 for the first time, and they were administered to a randomly selected one-third of 12th grade students, resulting in 2,186 12th graders in 27 states. Given the prevalence of use found in the 2023 survey, questions on delta-8 have been added to future surveys for all age groups.

The survey showed approximately 14% of 12th graders in the South and 15% in the Midwest reported delta-8 use, compared to 10% in the Northeast and 5% in the West. Around 14% of 12th graders in states without cannabis legalization reported delta-8 use, compared to 8% in states with legalization. In states without existing delta-8 regulations, 14% reported use compared to 6% in states with delta-8 legislation.

"In states without cannabis legalization, delta-8 might be marketed as a legal alternative to cannabis and be easier for teenagers to access" said Alyssa Harlow, clinical assistant professor of population and public health sciences at the University of Southern California, a member of the USC Institute for Addiction Science and lead author of the study.

"Delta-8 products are out there where teens can easily find and buy them, and there needs to be continued surveillance of its use, as well as policy and public health efforts to help youth and parents stay informed and safe."

Because the survey is taken in school settings, students who were absent, not enrolled or with less engagement in school—a known risk factor for drug use—may have been less likely to participate in the survey, the investigators note. This exclusion may have potentially led to an underestimation of adolescent

use of delta-8. Future work will need to assess delta-8 use in younger teens; include a larger survey sample across a wider range of states; and examine the use of other hemp-derived products, including delta-9 and delta-10.

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INSIGHT

Hemp Provisions in the House Farm Bill and FY2025 Agriculture Appropriations Bill

June 17, 2024

Recent action by the House Agriculture Committee on the next farm bill (Farm, Food, and National Security Act of 2024; H.R. 8467, as amended) and the House Agriculture Appropriations Subcommittee on the FY2025 Agriculture, Rural Development, Food and Drug Administration, and Related Agencies Appropriations bill would amend the Domestic Hemp Production Program (§§1639o-s) administered by the U.S. Department of Agriculture (USDA) to prohibit the commercial production, sale, and distribution of certain intoxicating hemp derivatives and products. Congress is continuing to debate these proposed changes as it proceeds to consider these bills. These provisions have both supporters and detractors.

Existing Hemp-Related Requirements

The 2018 farm bill (Agriculture Improvement Act of 2018; P.L. 115-334, §12619) legalized hemp by establishing a statutory definition for *hemp* (7 U.S.C. §1639o) that excludes hemp from the definition of *marijuana* (21 U.S.C. §802(16)) under the Controlled Substances Act (CSA; 21 U.S.C. §§801 et seq.) and oversight by the U.S. Drug Enforcement Administration (DEA) (botanically, hemp and marijuana are from the same species of plant, *Cannabis sativa* L). The 2018 farm bill (P.L. 115-334, §§10113-10114) established the Domestic Hemp Production Program (§§1639o-s) requiring hemp producers comply with USDA regulations promulgated in consultation with the U.S. Attorney General (7 U.S.C. §1639r(a)(1)(B) and §1639q(c)(3)). USDA issued its final hemp regulations in January 2021. In enacting the 2018 farm bill, Congress preserved the laws and regulations of the Food and Drug Administration (FDA) and the Federal Food, Drug, and Cosmetic Act (FFDCA; 21 U.S.C. §§301 et seq.) regarding hemp-derived products (7 U.S.C. §1639r(c)). FDA continues to assert that products containing cannabis and cannabis-derived compounds, including cannabidiol (CBD), tetrahydrocannabinol (THC) derivatives, and other cannabinoids remain under its jurisdiction and that it is "unlawful" under the FFDCA "to introduce food containing added CBD or THC into interstate commerce, or to market CBD or THC products as, or in, dietary supplements, regardless of whether the substances are hemp-derived."

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House Agriculture Committee's 2024 Farm Bill

The House Agriculture Committee passed a 2024 farm bill (Farm, Food, and National Security Act of 2024; H.R. 8467) on May 23, 2024, and would add new and modify existing statutory definitions related to hemp cultivation and its products, and make certain changes to how hemp is regulated by USDA.

H.R. 8467 (§10006) would add a new statutory definition of *industrial hemp* to mean hemp grown for fiber or for the "whole grain, oil, cake, nut, hull, or any other non-cannabinoid compound, derivative, mixture, preparation, or manufacture of the seeds of such plant," among other related changes. H.R. 8467 would relax certain regulatory requirements for producers of industrial hemp only, including to reduce or eliminate testing requirements and background checks, and take steps to eliminate the existing 10-year period of ineligibility following the date of conviction for a felony related to a controlled substance. Changes related to *industrial hemp* in H.R. 8467 broadly reflect proposed changes in H.R. 3755/S. 980.

In addition, H.R. 8467 as amended in an en bloc amendment (#35) would make changes to clarify the types of hemp cannabinoid products that would be considered lawful under USDA's hemp program. (As of June 17, 2024, text on congress.gov is not updated.) As passed by committee, the bill would redefine the existing statutory definition of *hemp* (7 U.S.C. §1639o) by replacing language basing the legal limits for hemp on its delta-9 tetrahydrocannabinol (delta-9 THC) concentration and instead basing the definition on hemp's "total tetrahydrocannabinol [Total THC] (including tetrahydrocannabinol acid (THCA]) concentration." Other statutory language regarding hemp "derivatives, extracts, cannabinoids, isomers, acids, salts, and salts of isomers, whether growing or not" would remain unchanged. The amendment specifies that *hemp* would exclude non-naturally occurring synthetic and intoxicating products (i.e., allows only naturally occurring or derived nonintoxicating products). While the amendment does not define *intoxicating*, it would prohibit hemp cannabinoid products with "quantifiable amounts" of Total THC (including THCA) or any other cannabinoids that have (or are marketed to have) "similar effects on humans or animals" as THC, as determined by USDA. This would not prohibit all hemp cannabinoid products, such as CBD, but would require determinations by USDA based on available scientific research and quantification methods. This approach recognizes the rapidly evolving landscape of hemp derivatives. The amendment further adds a statutory definition of a *hemp cannabinoid product* that would exclude those derived from *industrial hemp*.

Changing the basis for determining the legal limits for *hemp* on its Total THC (including THCA) concentration is broadly consistent with regulatory practices established by USDA. (USDA's 2021 final hemp regulations provide a rationale for this determination.) The exclusion of synthetic compounds is consistent with an April 2024 determination by DEA regarding the control status of cannabis compound, hexahydrocannabinol (HHC) under DEA laws. In that case, DEA determined that HHC "does not occur naturally in the *Cannabis sativa* L. plant and can only be obtained synthetically, and therefore does not fall under the definition of hemp." Some states have adopted or are considering similar restrictions. These include prohibition of intoxicating hemp cannabinoid products or regulating such products under a state's medical or recreational marijuana regulations, thus limiting access through a licensed state dispensary.

House Subcommittee on FY2025 Agriculture Appropriations

The House Agriculture Appropriations Subcommittee's FY2025 Agriculture Appropriations bill includes a provision (§760) that is nearly identical to the en bloc amendment (#35) discussed above. (As of June 17, 2024, text on congress.gov is not updated.) Accordingly, the bill would clarify that *hemp* include only naturally occurring, non-synthetic, nonintoxicating hemp cannabinoid products and exclude those with "quantifiable amounts" of Total THC (including THCA) that have (or are marketed to have) similar

effects as THC, as determined by USDA in consultation with FDA. (Similar to as described above.) The appropriations provision, however, does not include a definition of *industrial hemp*, although the bill makes allowances for industrial hemp for use in hemp cannabinoid products. This exclusion could create confusion since the term is not defined. Appropriations acts usually do not amend the *U.S. Code*; however, this is possible pending resolution of points of order under House rules.

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Disclaimer

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Cannabidiol Increases Psychotropic Effects and Plasma Concentrations of Δ^9-Tetrahydrocannabinol Without Improving Its Analgesic Properties

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Abstract

Cannabidiol (CBD), the main non-intoxicating compound in cannabis, has been hypothesized to reduce the adverse effects of Δ^9-tetrahydrocannabinol (THC), the main psychoactive and analgesic component of cannabis. This clinical trial investigated the hypothesis that CBD counteracts the adverse effects of THC and thereby potentially improves the tolerability of cannabis as an analgesic. A randomized, double-blind, placebo-controlled, five-way cross-over trial was performed in 37 healthy volunteers. On each visit, a double-placebo, THC 9 mg with placebo CBD, or THC 9 mg with 10, 30, or 450 mg CBD was administered orally. Psychoactive and analgesic effects were quantified using standardized test batteries. Pharmacokinetic sampling was performed. Data were analyzed using mixed-effects model. Co-administration of 450 mg CBD did not reduce, but instead significantly increased subjective, psychomotor, cognitive, and autonomous effects of THC (e.g., VAS "Feeling High" by 60.5% (95% CI: 12.7%, 128.5%, $P < 0.01$)), whereas THC effects with 10 and 30 mg CBD were not significantly different from THC alone. CBD did not significantly enhance THC analgesia at any dose level. Administration of 450 mg CBD significantly increased AUC_{last} of THC (AUC_{last} ratio: 2.18, 95% CI: 1.54, 3.08, $P < 0.0001$) and 11-OH-THC (AUC_{last} ratio: 6.24, 95% CI: 4.27, 9.12, $P < 0.0001$) compared with THC alone, and 30 mg CBD significantly increased AUC_{last} of 11-OH-THC (AUC_{last} ratio: 1.89, 95% CI: 1.30, 2.77, $P = 0.0013$), and of

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Study Highlights

WHAT IS THE CURRENT KNOWLEDGE ON THE TOPIC?

Cannabis and cannabis products are used as an analgesic for chronic neuropathic pain. Cannabidiol (CBD), a non-intoxicating constituent of cannabis, is hypothesized to attenuate the effects of Δ^9-tetrahydrocannabinol (THC), the main psychoactive constituent. However, this effect is not found consistently and its mechanism and the required CBD dose remain unknown.

WHAT QUESTION DID THIS STUDY ADDRESS?

The modulation of acute subjective, cognitive, psychomotor, autonomous, and analgesic effects of THC by three dose levels of CBD was investigated in healthy volunteers and compared with placebo.

WHAT DOES THIS STUDY ADD TO OUR KNOWLEDGE?

This study found no evidence of CBD reducing adverse THC effects. On the contrary, THC effects were significantly increased by 450 mg of CBD, which was most likely explained by CBD inhibiting cytochrome P450-mediated metabolism of THC. Evidence of a pharmacokinetic interaction between CBD and THC was found at both 30 and 450 mg CBD dose levels. CBD did not enhance THC analgesia at any dose level.

HOW MIGHT THIS CHANGE CLINICAL PHARMACOLOGY OR TRANSLATIONAL SCIENCE?

These results provide evidence against the hypothesis that CBD attenuates THC effects, highlight the potential for drug interactions even at low doses of CBD, and add to the understanding of THC analgesia.

Δ^9-Tetrahydrocannabinol (THC) is the main psychoactive component of cannabis plants. Its effects are mediated by partial agonism of the cannabinoid receptor 1 (CB_1) and include feeling high, altered perception, and an elevated heart rate. THC shows promise as an analgesic in patients with chronic neuropathic pain,[1, 2] although its effectiveness is limited to an undefined

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impairment, anxiety, delusions, and hallucinations.[3, 4]

Cannabidiol (CBD), the main non-intoxicating compound in cannabis, has been hypothesized to reduce the adverse effects of THC.[5-7] The purported superior tolerability of CBD-rich cannabis has been the subject of numerous scientific publications[5, 8, 9] and is routinely referenced in popular and commercial publications.[10] The complex pharmacology of CBD includes multiple pathways, which could plausibly contribute to such an effect. For instance, CBD is a negative allosteric modulator (NAM) of the CB_1 receptor,[11] potentially diminishing any CB_1-mediated THC effects. Additionally, CBD acts as an agonist at the serotonin 5-HT_{1a} receptor with potential for anxiolytic properties[12] and as a partial agonist at the dopamine D_{2High} receptors with a suggested potential for antipsychotic action.[13] Furthermore, CBD potentially possesses analgesic effects via its activity at the $TRPV_1$ and 5-HT_{1a} receptors.[14]

The results of clinical research to date are conflicting. Studies have shown CBD to inhibit THC-elicited paranoid and psychotic symptoms and memory impairment,[15] reduce anxiety,[16] and produce a lower degree of subjective intoxication[17, 18] compared with THC alone. However, in other clinical trials, CBD failed to attenuate THC-induced anxiety,[4] subjective intoxication and cognitive task performance[19] as well as acute psychotic and memory-impairing effects of THC.[20]

Drug doses, THC:CBD ratios, and routes of administration varied throughout the studies, further complicating the interpretation of the results. Consequently, there is no consensus on what effects of THC are attenuated by CBD, if any, at which doses or dose ratios, and if different routes of administration alter this.

The goal of this study was to assess whether co-administration of CBD could reduce the adverse effects of THC while not compromising, or potentially even enhancing its analgesic properties. Effects of THC alone were therefore compared with the combination of THC with three doses of CBD, controlled with a placebo and a THC + placebo treatment arm. Subjective, cognitive, and psychomotor effects were measured using a validated CNS test battery,[21] and the analgesic effects using a validated pain test battery.[22]

METHODS

Participants and study design

The study was a double-blind, randomized, double-dummy placebo-controlled, five-way cross-over study in which the effects of THC + placebo were compared with the effects of THC in combination with three doses of CBD and double-placebo. The study was conducted at the Center for Human Drug Research in Leiden, the Netherlands. The study was approved by the

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Human Participants (WMO) and in compliance with all International Conference on Harmonization Good Clinical Practice (ICH-GCP) guidelines and the Declaration of Helsinki. This study was registered prospectively with the Netherlands National Trial Register (NTR) under registration number: NL9543.

Each participant provided written informed consent before any screening procedures were performed. All participants were healthy male and female volunteers aged 18–45 years with a body mass index of 18–30 kg/m^2. The participants underwent a full medical screening, including medical history anamnesis, a physical examination, blood chemistry and hematology, urinalysis, and an electrocardiogram (ECG) to assess eligibility. Participants with a clinically significant known medical condition, particularly any psychotic disorder or existing condition affecting cold or pain sensitivity, were excluded. All included participants were cannabis users for at least 1 year prior to screening, with cannabis use not exceeding once per month on average in the 6 months prior to study participation. The participants refrained from cannabis use from at least 3 weeks prior to the first dosing day until the end of the study. Any participant who was a regular user of any illicit drugs other than the casual use of cannabis, or had a history of drug abuse or a positive drug screen at screening, was excluded. Any nutrients known to modulate CYP enzyme activity (e.g., grapefruit or Seville orange-containing products or quinine-containing drinks (tonic water or bitter lemon)) were not permitted from 3 days before each study visit until discharge from the research unit. Smoking and the use of xanthine-containing products were not allowed during dosing days. The full list of inclusion and exclusion criteria is provided in the **Supplementary Materials**.

All females of childbearing potential and all males were required to practice effective contraception during the study and to continue contraception for at least 90 days after the last dosing (detailed contraception requirements provided in the **Supplementary Materials**). Urine pregnancy testing was conducted in female participants on each study day prior to dosing.

Study drugs

On each visit, participants received single doses of one of the five oral treatments: double-placebo, THC 9 mg with placebo, or THC 9 mg with either CBD 10 mg, CBD 30 mg or CBD 450 mg. The doses were chosen based on concentration–effect relationship and receptor occupancy data for three potential mechanistic pathways through which we hypothesized that CBD could attenuate THC effects: (i) negative allosteric modulation of the CB_1 receptor, (ii) partial agonism of the 5-HT_{1a} receptor, and (iii) partial agonism of the $D2_{High}$ receptor (full dose rationale is provided in the **Supplementary Materials**). CBD (or placebo) was always

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THC was administered in oral tablets containing 1.5 mg THC (Namisol®) and CBD in oral tablets containing 20 mg or 150 mg CBD (Arvisol®); 20 mg CBD tablets were halved for the 10 mg CBD treatment. Both formulations, as well as matching placebo, were manufactured by Echo Pharmaceuticals. Namisol® had been previously administered in multiple studies in healthy volunteers and patient populations[23, 24] and Arvisol® in healthy volunteers only (unpublished). Active and placebo tablets contained an identical amount of excipients. The drug substance in both Namisol® and Arvisol® was botanically derived. Release specifications for impurities are provided in the **Supplementary Materials**.

Fasting was required for at least 4 hours prior to every scheduled visit. Shortly after arrival, participants received a semi-standardized light breakfast (contents described in **Supplementary Materials**). Participants remained fasted for at least 2 hours before, and 1.5 hours after study drug administration (water was allowed as required).

Pharmacodynamic assessments

Assessments were performed in “test-blocks,” where for each nominal timepoint (e.g., 1 hour post-dose), vital signs were measured 2 minutes prior to the timepoint, blood sampling for hormones and pharmacokinetics was performed exactly on the timepoint, and subjective, psychomotor, and cognitive tests were performed thereafter, with the analgesic tests performed last. Such a “test-block” ended approximately 45 minutes after the nominal timepoint. Measurements were performed at approximately the same clock time during each visit to account for circadian effects. Within 3 weeks prior to the first study visit, participants had a training session to get acquainted with the pharmacodynamic tests and to minimize learning effects. Brief descriptions of each pharmacodynamic assessment are provided below; detailed descriptions can be found in the **Supplementary Materials**.

Subjective effects

Visual Analogue Scales (VAS) according to Bond and Lader were used for assessment of study participant's subjective state.[25] Three main factors, namely, “alertness,” “mood” and “calmness,” were calculated from 16 bipolar horizontal scales ranging from 0 to 100, where values of 0 and 100 represented opposing subjective states and a value of 50 represented the neutral state.[26] Subjective psychedelic effects including VAS ‘Feeling High’ were evaluated using the 13-item VAS ‘Bowdle’ with unipolar scales ranging from 0 to 100.[27] The VAS scales were performed twice pre-dose and at 1, 2, 3, 4, and 6 hours post-dose. The state-trait anxiety inventory was used to quantify present feelings of anxiety or tension and was performed twice pre-dose and 1, 2, 4, and 6 hours post-dose.[28] Once pre-dose and 6 hours post-dose, participants completed the

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cognitive symptoms, interpersonal sensitivity, depressed mood, anxiety, hostility, phobic anxiety, paranoid thoughts, and psychoticism.

Psychomotor and cognitive effects

A selection of tests from the validated NeuroCart® CNS test battery was performed pre-dose and at 1, 2, 3, 4, and 6 hours post-dose for assessment of THC effects on psychomotor function and cognition. The body sway task measures postural stability.[29] The adaptive tracking test is used to evaluate visuomotor coordination and vigilance.[21] The Stroop task is used to assess attention, perception, and inhibition. Two parameters were derived from the Stroop task: Stroop 1 relates to reaction time and Stroop 2 relates to the number of correct responses. The simple reaction time (SRT) task is designed to measure the attention and speed of information processing of the participant.

Autonomous effects

Measurements of autonomous effects were performed pre-dose (twice for heart rate and once for cortisol and prolactin) and 0.5, 1, 2, 3, 4, 6, and 8 hours post-dose. Heart rate measurements were performed using Dash 3000, Dash 4000, Dynamap 400, or Dynamap ProCare 400 automated devices after 5 minutes in the supine position. Serum prolactin levels were determined as a potential marker of antipsychotic effects of CBD, as antipsychotic drugs consistently increase prolactin levels due to their antidopaminergic properties[30] and CBD has been hypothesized to have potential antipsychotic properties due to its partial agonism of the D_{2High} receptor.[13, 31] Serum cortisol levels have been shown to increase after administration of THC compared with placebo in previous research.[32]

Analgesic effects

During each treatment period, a validated battery of pain tests, the PainCart®, was performed twice pre-dose and at 1, 2, 3, and 6 hours after dosing, consisting of a heat pain test, a pressure pain test, an electrical pain test, and the cold pressor pain test.[33, 34] For all tests (except heat pain) participants were given an electronic visual analogue scale (eVAS) slider to hold, with which they could indicate their current perceived pain intensity. The eVAS had a range of 0–100, with 0 defined as “no pain,” sliding > 0 defined the pain detection threshold (PDT), and 100 defined the pain tolerance threshold (PTT; “worst pain tolerable”). When PTT was reached, the test automatically stopped and immediately relieved participants of their pain. Following the test, the participant was asked to rate the pain experienced during the test using the short form of the McGill pain questionnaire (SF-MPQ), a questionnaire that evaluates the affective and sensory components of pain with four-point Likert-type scales. The SF-MPQ also evaluated the

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The capsaicin 1% solution model was included as a model for thermal and mechanical allodynia by selectively sensitizing the $TRPV_1$ channel.[33, 34] A 3 × 3 cm surface on the dominant volar forearm was used for the application of the 1% capsaicin solution. The nondominant volar forearm served as a control (not treated with capsaicin). The size of the area of secondary mechanical allodynia around the 3 × 3 cm area where capsaicin was applied was assessed using Von Frey filaments. The heat pain test was performed on capsaicin-treated skin as well as the untreated skin.

Pharmacokinetic assessments

Venous blood samples were taken pre-dose and between 0.5, 1, 2, 3, 4, 6, and 8 hours following THC dosing. Approximately 2 mL of blood per sample was collected via a venous catheter in an antecubital vein. Plasma THC and its metabolites 11-OH-THC, 11-COOH-THC, and CBD and its metabolites 6α-OH-CBD, 6β-OH-CBD, 7-OH-CBD, 7-CBD-COOH, and 2'-CBD-Glucuronide concentrations were measured using a validated LC–MS/MS method.[35] The lower limits of quantification (LLOQs), as well as reference material sources and analytical run acceptance criteria, are provided in the **Supplementary Materials**.

R 3.6.1 for Windows (R Foundation for Statistical Computing/R Development Core Team, Vienna, Austria, 2019) was used to calculate pharmacokinetic parameters. When an actual sampling time differed from the protocol time by more than 10% and at least 5 minutes, the concentration was excluded from the descriptive statistics, but not from the non-compartmental analysis. For the calculation of PK parameters, concentration values below the LLOQ (BLQ) were replaced by 0, except when such values could be interpolated from two neighboring concentration values. Metabolite-to-parent ratios (MPRs) were calculated for 11-OH-THC with respect to THC and for 11-COOH-THC with respect to 11-OH-THC using AUC_{last} estimates.

Sample size, randomization, and blinding

VAS "Feeling High" was used for the sample size calculation as this assessment has been shown sensitive to the effects of THC in previous studies, data from which were used to determine variability.[22, 23] A sample size of 24 was calculated to have 81.5% power to detect a reduction of 25% of the VAS "Feeling High," assuming a CV% of 50% (conservative estimate) and using a one-sample *t*-test with a 0.05-sided significance level, presuming a log-normal distribution. To properly balance the cross-over study with five treatment arms, a sample size of $n = 30$ (15 males and 15 females) was chosen. Additional details regarding the sample size are provided in the **Supplementary Materials**.

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statistician. 10 sequences were randomized in 3 blocks of 10, with 10 females in one block, 10 males in the second block, and 5 males and 5 females in the third block. Blinded study staff assigned the randomization numbers to the participants sequentially after medical screening.

Statistical analysis

To establish whether significant treatment effects could be detected, the repeatedly measured pharmacodynamic (PD) parameters were analyzed with a mixed-effects model with fixed factors treatment, period, time and treatment by time, random factors participant, participant by treatment, and participant by time and the average baseline value as covariate. Single measured PD data were compared with a mixed-effects model with fixed factors treatment, period, as random factors participant, and the baseline value as a covariate. PK parameters were compared with a mixed-effects model with treatment and period as fixed factors and subject as random factors on log-transformed data. Post-dose measurements that were performed outside a 10% time window around the scheduled protocol time were excluded from the analysis. The general treatment effect and specific contrasts were reported with the estimated difference and the 95% confidence interval, the least square mean estimates, and the *P*-value. Graphs of the least square mean estimates over time by treatment were presented with 95% confidence intervals as error bars. All calculations were performed using SAS for Windows V9.4 (SAS Institute, Cary, NC, USA). No adjustments for multiple comparisons were employed in accordance with the exploratory nature of this study.[36]

RESULTS

Participants and demographics

The clinical phase of the trial ran from July 2021 to May 2022. A total of 108 participants were screened and 37 participants were enrolled in the study and dosed at least once. **Table S1** contains a summary of the baseline demographics. Of the 37 dosed participants, 8 withdrew from the study and 3 were excluded prior to completion; 26 participants (15 males and 11 females) completed the trial per protocol. Further details are contained in the study flow diagram (**Figure S2**).

Pharmacodynamic outcomes

Pharmacodynamic measurements of all participants (completers and drop-outs) were analyzed. No measurements fell outside the 10% time window around the planned timepoints and had to be excluded from the analysis.

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Statistics of the subjective effects are summarized in **Table 1**. VAS "Alertness" was significantly reduced by THC with 450 mg CBD compared with THC alone (**Figure 1**). VAS "Mood" was not significantly affected by any treatment. VAS "Calmness" did not differ significantly between THC alone and any combination of THC and CBD. VAS "Feeling High," VAS "Internal perception" and VAS "External perception" were significantly increased by THC with 450 mg CBD compared with THC alone. State anxiety did not differ significantly between THC alone and any combination of THC and CBD (**Figure 1**). THC with 450 mg CBD significantly increased the BSI total score compared with THC alone. The statistics of the BSI subscales are provided in the **Table S3**.

Table 1. Overall treatment effects on subjective, psychomotor, cognitive, and autonomous outcome measures (estimated means, estimated mean difference, 95% CI, *P*-value)

Measurement	Treatment	*N*	LSM	Estimated difference vs. placebo (95% CI), *P*-value	Estimated difference vs. THC 9 mg (95% CI), *P*-value
Subjective effects					
VAS Alertness (mm)	Placebo	32	51.0	–	–
	THC 9 mg	27	45.4	**−5.7 (−8.2, −3.1), *P* < 0.0001**	–
	THC + CBD 10 mg	32	45.1	**−5.9 (−8.4, −3.4), *P* < 0.0001**	−0.2 (−2.8, 2.3), *P* = 0.86
	THC + CBD 30 mg	30	43.0	**−8.0 (−10.5, −5.6), *P* < 0.0001**	−2.4 (−5.0, 0.2), *P* = 0.067
	THC + CBD 450 mg	30	41.6	**−9.5 (−11.9, −7.0), *P* < 0.0001**	**−3.8 (−6.4, −1.2), *P* < 0.01**
VAS Mood (mm)	Placebo	32	53.7	–	–
	THC 9 mg	27	53.6	−0.2 (−2.5, 2.2), *P* = 0.88	–
	THC + CBD 10 mg	32	52.9	−0.9 (−3.2, 1.4), *P* = 0.45	−0.7 (−3.1, 1.7), *P* = 0.56
	THC + CBD	30	53.5	−0.2 (−2.5, 2.1), *P* =	−0.0 (−2.4, 2.4), *P* =

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CI, confidence interval; LSM, least square mean; N, number; STAI, state–trait anxiety inventory; THC, Δ^9-tetrahydrocannabinol; VAS, visual analogue scale.

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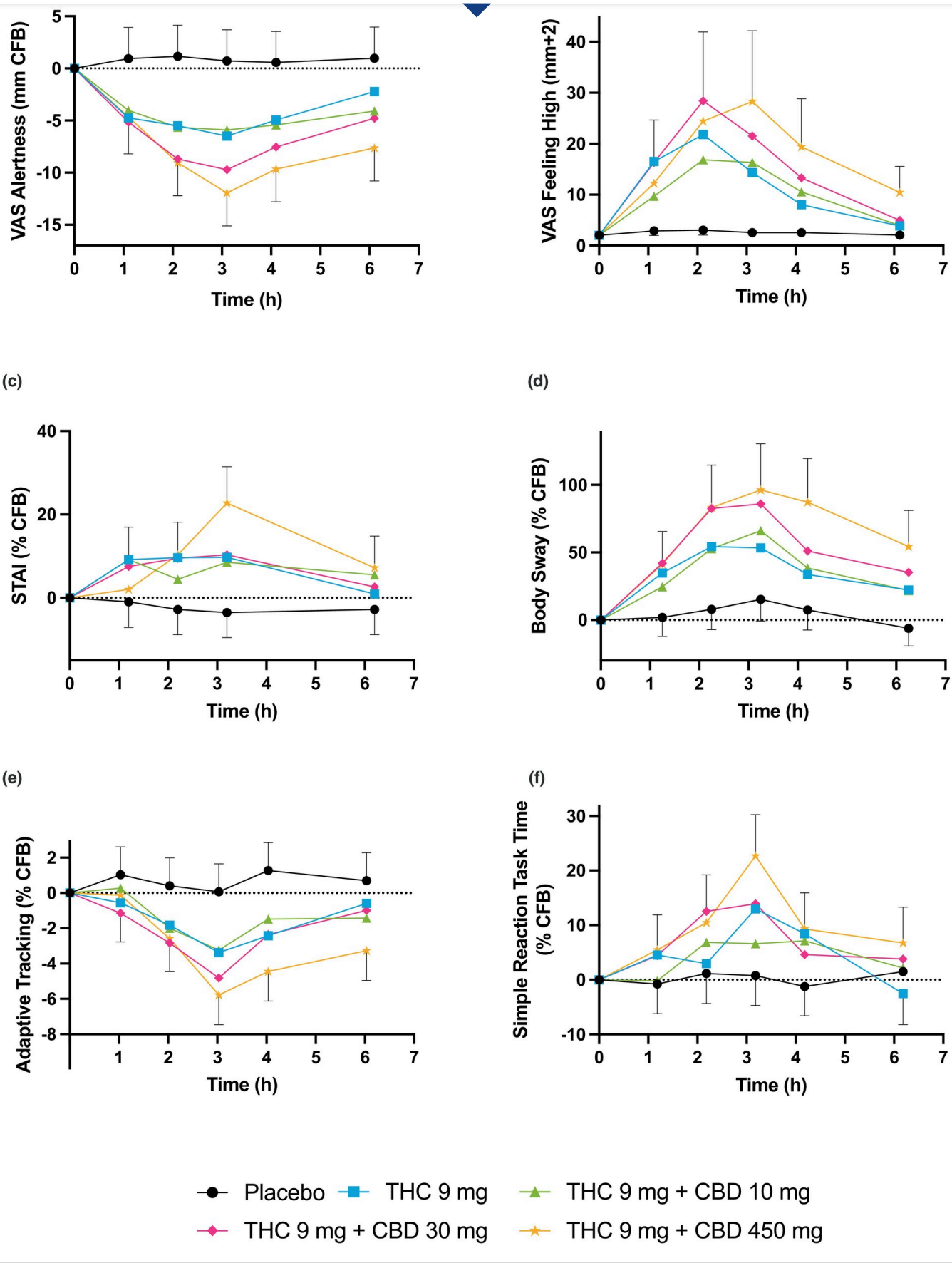
VAS Alertness (mm CFB)
Time (h)
VAS Feeling High (mm+2)
Time (h)
(c)
STAI (% CFB)
Time (h)
(d)
Body Sway (% CFB)
Time (h)
(e)
Adaptive Tracking (% CFB)
Time (h)
(f)
Simple Reaction Task Time (% CFB)
Time (h)
Placebo
THC 9 mg
THC 9 mg + CBD 10 mg
THC 9 mg + CBD 30 mg
THC 9 mg + CBD 450 mg

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Least square means of (**a**) VAS Alertness (displayed as mm change from baseline, (**b**) VAS Feeling High (absolute values in mm + 2), (**c**) State–Trait Anxiety Inventory state scores, (**d**) postural stability, (**e**) Adaptive Tracking performance, and (**f**) reaction time in the Simple Reaction Time Task displayed as % change from baseline. Means are displayed with 95% confidence intervals (for the treatments with the highest and lowest means only; confidence intervals for other treatments omitted for visual clarity).

Psychomotor and cognitive effects

Statistics of the psychomotor and cognitive effects are summarized in **Table** 1. Postural stability was significantly impaired by THC with 450 mg CBD compared with THC alone (**Figure** 1). Adaptive tracking performance did not differ significantly between THC alone and any combination of THC and CBD (**Figure** 1). Scores on the Stroop task (both Stroop 1 and Stroop 2 parameters) were not significantly affected by any treatment. Reaction time was significantly increased by THC with 450 mg CBD compared with THC alone (**Figure** 1).

Autonomous effects

Statistics of the autonomous effects are summarized in **Table** 1. Heart rate was significantly increased by THC with 450 mg CBD compared with THC alone (**Figure** 2). Serum cortisol and prolactin concentrations did not differ significantly between THC alone and any combination of THC and CBD (**Figure** 2).

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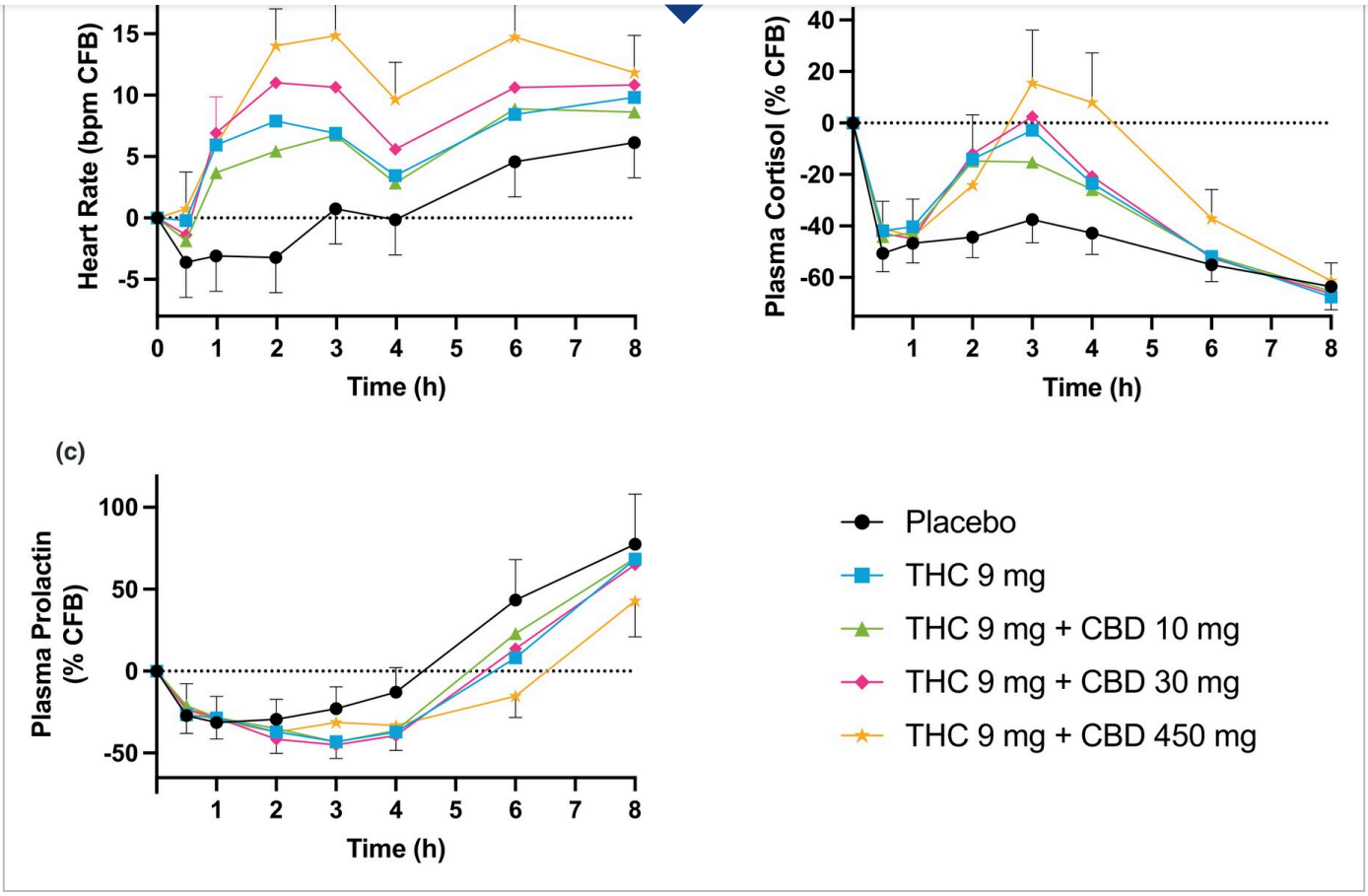

Figure 2

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Least square means of the autonomous outcome measures. (**a**) Heart Rate, displayed as beats per minute change from baseline with 95% confidence intervals, (**b**) Plasma Cortisol concentrations, and (**c**) Plasma Prolactin concentrations, displayed as % change from baseline with 95% confidence intervals (for the treatments with the highest and lowest means only; confidence intervals for other treatments omitted for visual clarity).

Analgesic effects

Statistics of the SF-MPQ VAS scores, PTTs, and the area of secondary allodynia are summarized in **Table** 2, statistics of the SF-MPQ affective, sensory, and PPI scores in **Table S4**, and statistics of the PDTs in **Table S5**.

Table 2. Overall treatment effects on analgesic outcome measures (estimated means, estimated mean difference, 95% CI, *P*-value)

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				P-value	CI), *P*-value
Area of Secondary Allodynia					
Area of Secondary Allodynia (mm^2)	Placebo	32	745.6	–	–
	THC 9 mg	27	587.6	**−158.0 (−313.0, −3.1), *P* = 0.046**	–
	THC + CBD 10 mg	32	647.6	−98.1 (−245.1, 49.0), *P* = 0.19	60.0 (−94.6, 214.5), *P* = 0.44
	THC + CBD 30 mg	30	747.1	1.4 (−148.7, 151.6), *P* = 0.98	**159.5 (3.2, 315.7) *P* = 0.046**
	THC + CBD 450 mg	30	695.6	−50.1 (−201.2, 101.1), *P* = 0.51	108.0 (−49.9, 265.9), *P* = 0.18
SF-MPQ peak pain intensity VAS scores					
SF-MPQ VAS Electrical Pain (mm)	Placebo	32	47.2	–	–
	THC 9 mg	27	42.9	**−4.34 (−7.30, −1.37), *P* < 0.01**	–
	THC + CBD 10 mg	32	42.8	**−4.37 (−7.27, −1.47), *P* < 0.01**	−0.03 (−3.03, 2.97), *P* = 0.99

The figures in bold indicate statistical significance. CBD, cannabidiol; CI, confidence interval; LSM, least square mean; *N*, number; SF-MPQ, Short-Form McGill Pain Questionnaire; THC, Δ^9-tetrahydrocannabinol; VAS, visual analogue scale.

The area of secondary allodynia was significantly reduced by THC alone compared with placebo. Area of secondary allodynia was not significantly reduced by any CBD-containing treatment compared with placebo, and was significantly increased by THC with 30 mg CBD, compared with THC alone (**Figure** 3). The SF-MPQ VAS was significantly reduced by all THC-containing treatments compared with placebo following the electrical pain, pressure pain, cold pain, and heat pain (on capsaicin-treated skin) tests, except THC alone on pressure pain and THC with 10 mg CBD on cold pain (**Figure** 3). SF-MPQ VAS following the heat pain test on control skin was significantly reduced by THC alone compared with placebo (**Figure** 3). SF-MPQ affective and

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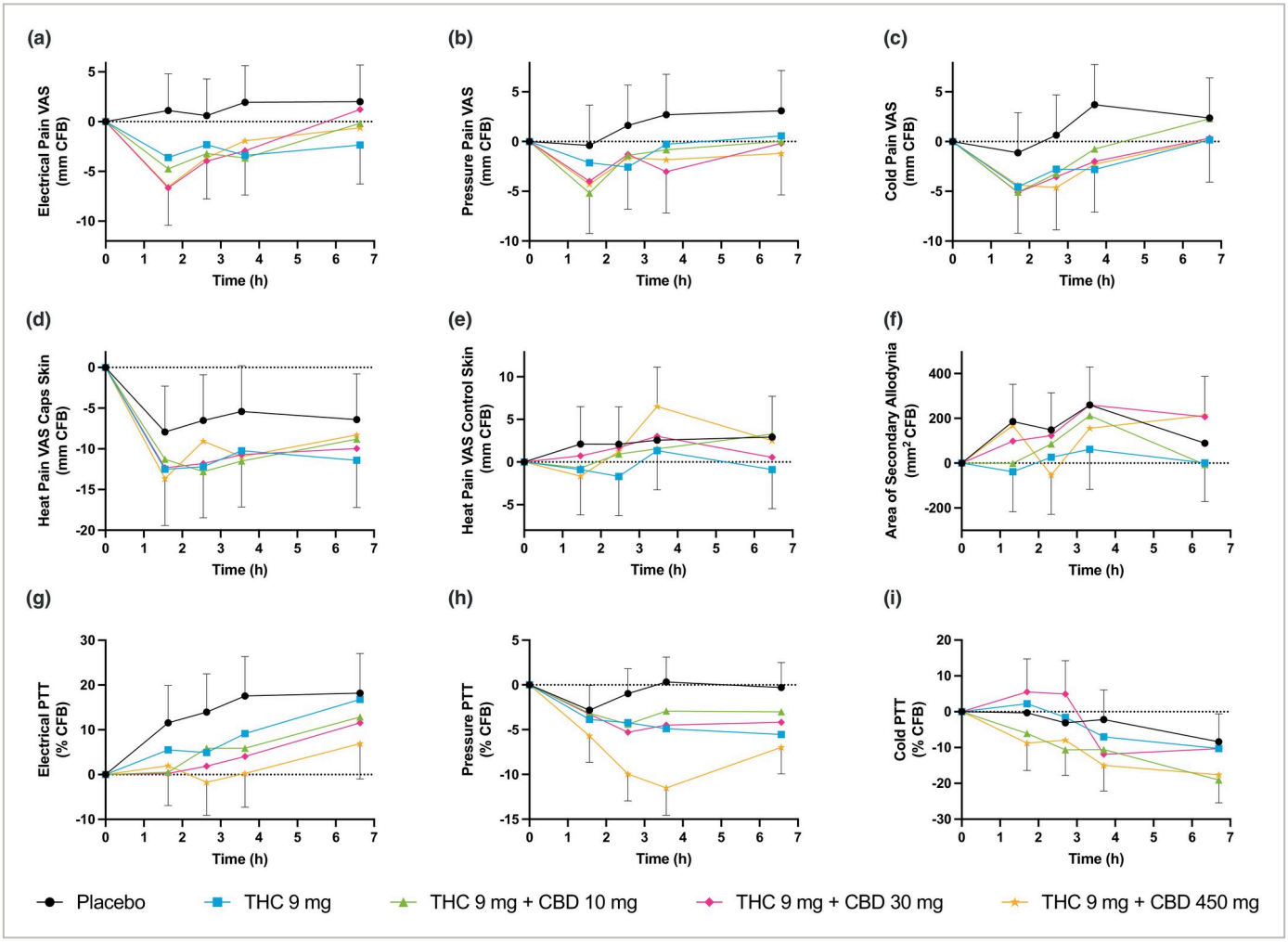

Figure 3

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Least square means of selected measurements of the nociceptive test battery. Short-Form McGill Pain Questionnaire (**a**) VAS Electrical Pain, (**b**) VAS Pressure Pain, (**c**) VAS Cold Pain, (**d**) VAS Heat Pain on capsaicin-treated skin, and (**e**) VAS Heat Pain on control skin, displayed as mm change from baseline with 95% confidence intervals. (**f**) Area of Secondary Allodynia, displayed as mm^2 change from baseline with 95% confidence intervals. (**g**) Electrical Pain Tolerance Threshold, (**h**) Pressure Pain Tolerance Threshold, (**i**) Cold Pain Tolerance Threshold, displayed as % change from baseline with 95% confidence intervals (for the treatments with the highest and lowest means only; confidence intervals for other treatments omitted for visual clarity).

SF-MPQ PPI scores were significantly reduced compared with placebo by some, but not all THC-containing treatments following the electrical pain, cold pain and heat pain (on capsaicin-

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PDTs for electrical pain, pressure pain, cold pain or heat pain (capsaicin-treated skin and control skin) were not increased significantly by any of the study treatments (**Table S5**). PTTs for electrical pain, pressure pain, or cold pain were not increased significantly by any of the study treatments. Conversely, the electrical PTT was significantly reduced by all combinations of THC and CBD compared with placebo. The pressure PTT was reduced significantly by THC alone, as well as THC with 30 and 450 mg CBD compared with placebo, and further reduced significantly by THC with 450 mg CBD compared with THC alone (**Figure 3**). The cold PTT was significantly reduced by THC with 10 mg CBD and THC with 450 mg CBD both compared with placebo and compared with THC alone (**Figure 3**).

Pharmacokinetics

Pharmacokinetic parameters of THC, 11-OH-THC, 11-COOH-THC, and CBD are summarized in **Tables S6–S9**, concentration–time profiles are displayed in **Figure 4** (linear *y*-axis), as well as **Figures S10–S13** (logarithmic *y*-axis) and statistical comparisons of PK parameters between treatments are provided in **Table 3**. Administration of 450 mg CBD significantly increased the AUC_{last} of THC, 11-OH-THC, and 11-COOH-THC, as well as the C_{max} of 11-OH-THC and 11-COOH-THC, and significantly increased the metabolite-to-parent ratio for both THC metabolites, when compared with THC alone. Administration of CBD 30 mg significantly increased the AUC_{last} of THC, 11-OH-THC, and 11-COOH-THC, the C_{max} of 11-OH-THC and 11-COOH-THC, and significantly changed the metabolite-to-parent ratio for 11-COOH-THC compared with administration of THC alone. The 10 mg CBD dose did not significantly change any pharmacokinetic parameters compared with THC alone. The pharmacokinetic parameters and concentration–time profiles of CBD metabolites are displayed in **Tables/Figures S14–S26**. The number and percentage of BLQ samples per analyte are provided in **Table S27**.

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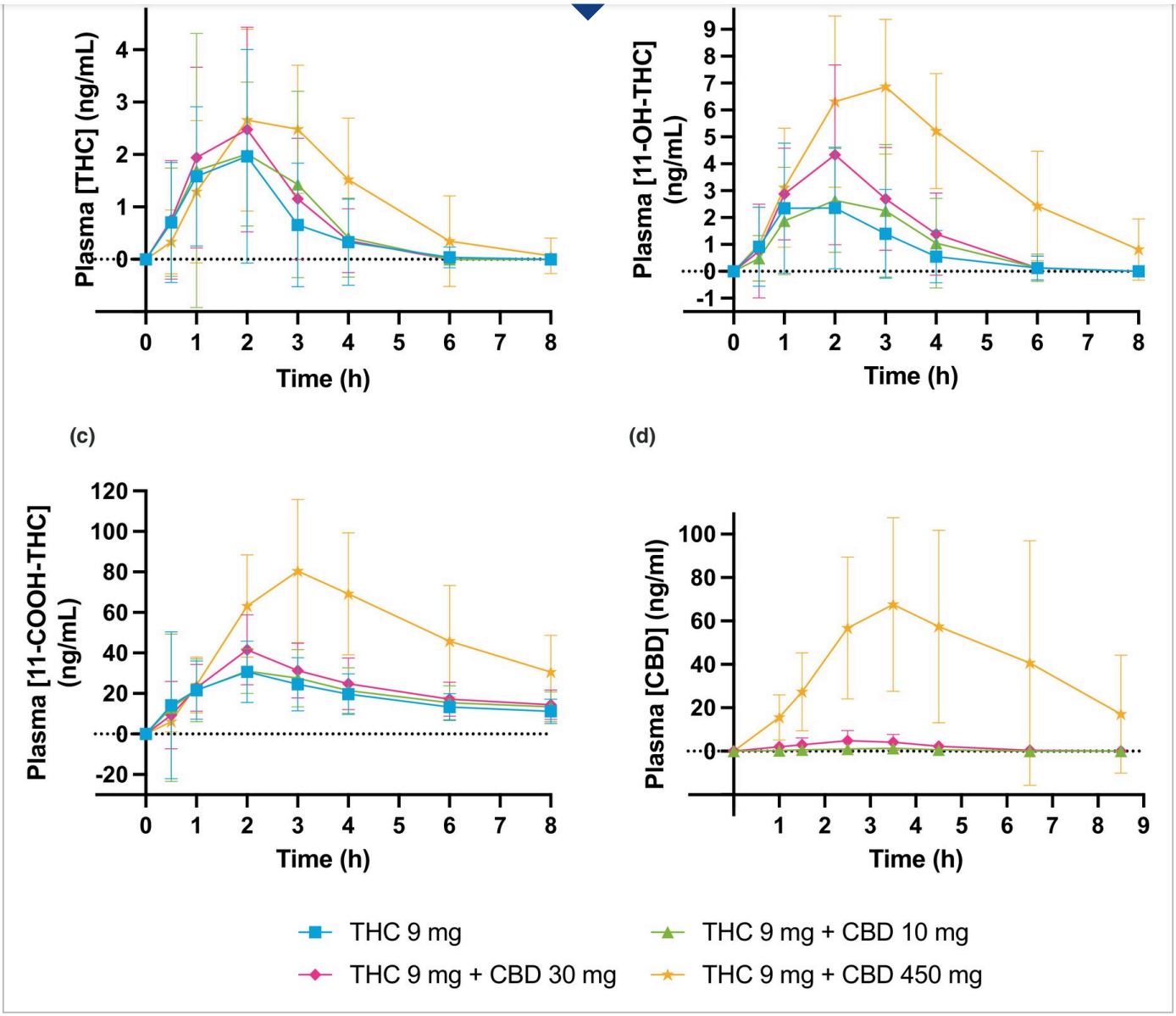

Figure 4

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Concentration–time profiles of (**a**) THC, (**b**) 11-OH-THC, (**c**) 11-COOH-THC, and (**d**) CBD following oral administration, displayed as means with standard deviation.

Table 3. Overall treatment effects on pharmacokinetic parameters (estimated means, estimated mean ratios, 95% CI, *P*-value)

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THC				
AUC_{last}	THC 9 mg	25	3.26	–
	THC + CBD 10 mg	30	3.03	0.93 (0.66, 1.32), *P* = 0.6776
	THC + CBD 30 mg	27	4.68	**1.44 (1.01, 2.04), *P* = 0.0446**
	THC + CBD 450 mg	28	7.09	**2.18 (1.54, 3.08), *P* < 0.0001**
C_{max}	THC 9 mg	25	2.63	–
	THC + CBD 10 mg	30	2.50	0.95 (0.76, 1.19), *P* = 0.6526
	THC + CBD 30 mg	27	2.64	1.00 (0.80, 1.26), *P* = 0.9889
	THC + CBD 450 mg	28	3.25	1.23 (0.98, 1.55), *P* = 0.0687
11-OH-THC				
AUC_{last}	THC 9 mg	25	4.00	–
	THC + CBD 10 mg	29	4.27	1.07 (0.73, 1.56), *P* = 0.7324
	THC + CBD 30 mg	28	7.58	**1.89 (1.30, 2.77), *P* = 0.0013**
	THC + CBD 450 mg	28	24.95	**6.24 (4.27, 9.12), *P* < 0.0001**
C_{max}	THC 9 mg	25	3.18	–

The figures in bold indicate statistical significance. AUC_{last}, area under the concentration–time curve from time zero to time of last measurable concentration; CBD, cannabidiol; CI, confidence interval; C_{max}, maximum concentration; LSM, least square mean; MPR, metabolite-to-parent ratio; *N*, number; THC, Δ^9-tetrahydrocannabinol.

DISCUSSION

In this study, in contrast to what is commonly hypothesized in (popular) literature, CBD did not reduce the adverse effects of THC, and CBD did not enhance the analgesic properties of THC. While the lower doses of 10 and 30 mg of CBD did not significantly influence the subjective (including anxiety), psychomotor, cognitive, or autonomous effects of 9 mg THC, the high dose of 450 mg CBD significantly increased THC effects on most measures. The enhanced THC effects were accompanied, and most plausibly explained by significantly elevated plasma concentrations of THC and its psychoactive metabolite 11-OH-THC.

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study. CBD has been shown to inhibit CYP3A4-, CYP2C9-, CYP2CB6-, and CYP2C19-mediated metabolism *in vitro* and[37-40] in humans,[41] and CYP2C9 is the major enzyme responsible for metabolism of THC.[42] The significant changes in THC metabolite-to-parent ratios observed in this study support the presence of a cytochrome P450-mediated drug–drug interaction. Furthermore, pharmacokinetic interactions have been reported in two recent clinical trials, where CBD was co-administered with THC[43] or with a cytochrome P450 drug cocktail.[41]

Previous studies reporting pharmacokinetic interactions with CBD either administered 640 mg CBD[41, 43] or took place in the context of treatment of rare epilepsy syndromes, where daily doses up to 50 mg/kg were administered.[44-46] Most patient populations or recreational cannabis users are unlikely to use CBD in such high doses. However, our results show that pharmacokinetic drug interactions could be caused by CBD doses as low as 30 mg, which are easily available to consumers in the United States as CBD-containing gummies, oils and tinctures, and other oral formulations referred to as edibles. In fact, some online retailers of such products recommend a starting dose of 20–30 mg CBD,[47] potentially putting consumers at risk for drug interactions. Theoretically, recreational cannabis use could similarly result in sufficient CBD intake to influence CYP450 metabolism, although the risk would depend on the CBD content of the cannabis variety, and the amount of cannabis consumed, both of which are highly variable.

Although the simplest and most obvious explanation for our study results is a PK interaction between oral CBD and THC in the absence of a PD interaction, the study design cannot conclusively rule out the presence of a PD interaction that is distinct from the PK interaction. Such hypothetical PD interaction could either be negative, meaning CBD *reduced* THC effects (as was hypothesized prior to the study) or positive, meaning CBD *increased* THC effects. Both cases contradict the use of CBD to attenuate THC effects. If the negative interaction was present, then its magnitude must have been relatively small, as it was clearly overshadowed by the increased psychotropic effects of increased THC and metabolite exposures. If the positive interaction was present, then the THC effects would be in effect enhanced by *both* PK and PD interactions. What is certain then, is that CBD is not useful for attenuation of adverse THC effects when administered orally.

It is possible that the findings of this study are specific to the oral administration route, and findings in studies with other administration routes differ.[9, 48] To our knowledge, studies with inhaled cannabinoids have not reported PK interactions between CBD and THC, nor increases in THC effects when co-administered with CBD. Possibly, the difference in findings is due to the substantial formation of the active metabolite 11-OH-THC following oral administration of THC,[49] and further elevation of 11-OH-THC levels via CBD-induced CYP inhibition. In contrast,

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attenuating THC effects.[9, 48, 51] Regardless of the administration route, the hypothesis that CBD attenuates THC effects remains contentious, and our results add to a growing body of evidence against it. Besides, alternative explanations have emerged for the purported superior long-term safety of CBD-rich cannabis. For example, CBD-rich cannabis varieties could cause fewer long-term side effects simply by virtue of containing smaller absolute amounts of THC, rather than due to a pharmacological interaction.[48]

A key strength of this study was the wide, and pharmacologically relevant, dose range of CBD administered. The pharmaceutical drug formulations in this study contained low levels of impurities, minimizing the risk of other cannabis constituents biasing the study results. The extensive set of both subjective and objective validated CNS tests, the use of a validated pain test battery, and a dense PK sampling schedule around the T_{max} resulted in a detailed assessment of oral THC/CBD interaction effects over time, both at the level of PK and PD, and the cross-over design allowed for within-participant comparison of effects.

Our study is not without limitations. A larger sample size may have confirmed the presence of increased THC effects at the 30 mg CBD dose level – a possibility which appears plausible due to the confirmed presence of the PK interaction and the consistent, although not statistically significant increases across multiple measures of THC effects at the 30 mg CBD dose level. The administration of CBD 30 minutes prior to THC, while done to align the T_{max} of the study drugs, may have enhanced the PK interaction compared with simultaneous administration, as CYP450 inhibition is a time-dependent process. However, in all likelihood the staggered administration was not a decisive factor in the study outcomes, as simultaneous administration studies have led to similar conclusions.[43] Also, because CBD is a time-dependent inhibitor of many CYPs,[38, 39, 41] the interaction may be more profound in chronic administration compared with single doses administered in this study. Another limitation is that no CBD-only cross-over arms were included. This could obscure the distinction between “pure” CBD effects and THC/CBD interaction effects. However, it is highly likely that the observed increase in THC effects is explained by a THC/CBD interaction, rather than the PD effects of CBD alone, since CBD is not known to cause psychotropic effects on its own.[52] Furthermore, a relatively high proportion of the study participants dropped out of the study due to adverse effects or the study being too burdensome, which may have introduced a selection bias toward participants who are less sensitive to adverse effects of THC. The drop-outs were disproportionately female; although sex differences in sensitivity to THC effects have been described previously,[53] more research is needed on the differences in THC effects between sexes.

A substantial proportion of plasma concentration values for THC and 11-OH-THC fell below the limit of quantification in this study. As BLQ values were replaced by “0” when calculating

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this effect is unknown, but we can deduce that it must have differed between the treatments in this study. The underestimation of the AUC_{last} will be greater when THC was administered alone, as this treatment had the lowest THC and metabolite exposures and the highest proportion of BLQ values – and for the opposite reasons, will be smaller when 450 mg CBD was co-administered. Therefore, some degree of overestimation of the point estimate of the AUC_{last} ratios between treatments will have occurred – although it can be assumed to have been limited. Per definition, plasma concentrations reported as BLQ are relatively low, and therefore would contribute relatively little to the AUC estimate. Most importantly, the presence of a pharmacokinetic drug interaction in this study is not under question. First, a decreasing proportion of BLQ values at an increasing CBD dose is in itself an indication of an increase in concentration and therefore a pharmacokinetic interaction. Second, the drug interaction is also evident from the significant treatment effects on the mean 11-OH-THC C_{max}, a pharmacokinetic parameter which is not meaningfully impacted by varying proportions of BLQ values between treatments.

This is the first study to evaluate the analgesic effects of a wide dose range of CBD when co-administered with THC. We found relatively small, but significant analgesic effects on the peak pain intensity VAS scores of the McGill Pain Questionnaire following the pressure, cold, and electrical pain tests, and after the heat test on capsaicin-sensitized skin, which occurred to a similar extent following all THC-containing treatments, regardless of CBD dose. This points to THC, and not CBD, being the cannabinoid responsible for the analgesia, and to the analgesia not being linearly dependent on plasma THC concentrations, since the magnitude of the analgesia across treatments was similar despite varying THC and 11-OH-THC concentrations. On the other hand, we did not find any analgesic effects on nociceptive thresholds for any treatment regardless of the presence and dose of CBD. In fact, we occasionally found THC-containing treatments had small, but significant *hyperalgesic* effects on cold pressor, pressure, and electrical PTTs. These findings are consistent with previous observations by our group and by others[22, 54] that THC can paradoxically decrease nociceptive thresholds.

The absence of THC analgesia on nociceptive thresholds in our study should not be interpreted as contradictory to earlier evidence of efficacy in patient populations.[2] Pain is a complex subjective phenomenon which, in addition to nociception, also involves cognitive and affective components, and in case of neuropathic pain, additional neurological pathology like central sensitization.[55] Therefore, results obtained with evoked pain tests in healthy volunteers do not lend themselves to a straightforward translation to patients. Rather, our findings provide insights into the mechanisms of cannabinoid-induced analgesia. The absence of THC analgesia on nociceptive thresholds, a measure obtained *during* the administration of the painful stimulus, combined with clear analgetic effects when pain scores were measured shortly *after*

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suggesting that THC may target preferentially the affective qualities of pain, for example, via dissociative effects resulting from reduced sensory-limbic functional connectivity.[56] Furthermore, we found THC to reduce mechanical allodynia, which is a prominent symptom of many neuropathic pain syndromes.[55] This finding may partially explain how THC exerts its analgesic effects in patients with neuropathic pain.[2]

In conclusion, in this study, CBD did not reduce the (adverse) effects of THC, but rather increased them at higher doses, likely by way of a pronounced pharmacokinetic interaction, while not enhancing the analgesic effects of THC. In a future study, we aim to learn more about the potential phenotypical differences between neuropathic pain patients who respond to cannabinoid-induced analgesia vs. patients for whom cannabinoid-based treatments do not work well.

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CONFLICT OF INTEREST

The authors declared no competing interests for this work.

AUTHOR CONTRIBUTIONS

A.A.G., J.A.A.C.H, L.E.K., S.J.V. and G.J.G wrote the manuscript, A.A.G., J.A.A.C.H., L.E.K., G.J.G. designed the research, A.A.G., J.A.A.C.H. and G.J.G. performed the research, M.K. and P.K.S. analyzed the data.

Supporting Information

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Filename	Description
cpt3381-sup-0001-SupinfoS1.docx Word 2007 document , 740.2 KB	**Data S1**
cpt3381-sup-0002-SupinfoS2.docx Word 2007 document , 660.4 KB	**Data S2**

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